Cytokine and Growth Factor Reviews 47 (2019) 1–20

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

Naturally occurring and synthetic constitutive-active cytokine receptors in disease and therapy

Doreen M. Floss*, Jürgen Scheller

Institute of Biochemistry and Molecular Biology II, Medical Faculty, Heinrich-Heine-University, Düsseldorf, Germany

ARTICLE INFO

Keywords:
Constitutive-active receptors
Gain-of-function receptors
Cytokine receptors

ABSTRACT

Cytokines control immune related events and are critically involved in a plethora of patho-physiological processes including autoimmunity and cancer development. Mutations which cause ligand-independent, constitutive activation of cytokine receptors are quite frequently found in diseases. Many constitutive-active cytokine receptor variants have been directly connected to disease development and mechanistically analyzed. Nature's solutions to generate constitutive cytokine receptors has been recently adopted by synthetic cytokine receptor biology, with the goal to optimize immune therapeutics. Here, CAR T cell immmunotherapy represents the first example to combine synthetic biology with genetic engineering during therapy. Hence, constitutive-active cytokine receptors are therapeutic targets, but also emerging tools to improve or modulate immunotherapeutic strategies. This review gives a comprehensive insight into the field of naturally occurring and synthetic constitutive-active cytokine receptors.

1. Introduction into cytokine receptor activation and signaling

Cytokines are important mediators of cell-cell communication and act *via* specific cytokine receptors on the cell surface. They control immune related events and are critically involved in a plethora of pathophysiological processes including autoimmunity and cancer development. In general, cytokines but also the closely related growth factors signal *via* three different and tightly regulated types of transmembrane receptors: receptor tyrosine kinases, receptors with associated kinases, and G-protein coupled receptors. Abnormal activation of cytokine signaling frequently results in development of cancer, chronic inflammatory disorders, and life-threatening diseases. Ligand-independent constitutive activation of cytokine receptors (gain-of-function) leads to activation of intracellular signaling pathways *e.g.* initiating changes in gene expression. Naturally occurring gain-of-function mutants have been identified in patients for a variety of cytokine receptors. In general, four principal mechanisms can induce constitutive activation of cytokine receptors: gain-of-function mutations, genomic amplification, chromosomal rearrangements, and autocrine activation [1]. Here, we focus on gain-of-function mutations in cytokine receptors.

On the basis of common structural features, cytokines and cytokine receptors are subdivided into seven major families (reviewed in [2]) (Fig. 1): **Receptor tyrosine kinase family** and corresponding cytokines such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF) induce mainly the activation of the MAPK/ERK pathway.**Class I cytokine receptors (hematopoietin family)** activated by cytokines such as Interleukin (IL)-2, IL-5, IL-6, IL-7, IL-12, granulocyte macrophage-colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), growth hormone (GH), erythropoietin (EPO), thrombopoietin (THPO), and **class II cytokine receptors (interferon family)** including cytokines such as Interferons (IFNs) and IL-10 mainly induce the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signal transduction pathway.**Tumor necrosis factor (TNF) cytokine and receptor superfamily** including cytokines such as TNF, CD40, and Fas ligand (FasL, CD95 L) signal *via* nuclear factor κB (NFκB) and/or Fas associated protein with death domain (FADD)/Caspase cascades and**Immunglobulin (Ig)-type (IL-1-like) receptors (IL-1/Toll-like receptor family)**, including cytokines such as IL-1, IL-18 and macrophage-colony-stimulating factor (M-CSF), activate also the NFκB pathway. The **IL-17 receptor (IL-17R) family** contains five ubiquitously expressed receptors (IL-17RA-E). Engagement with the appropriate ligands IL-17A to IL-17 F activates mitogen activated protein kinases (MAPKs), the phosphoinositide 3 kinase (PI3K) pathway, and NFκB.**Receptor serine/threonine kinases (Transforming growth factor (TGF)-β) family** and corresponding cytokines such as TGF-β_1 to TGF-β_3 signal *via* SMAD

* Corresponding author.
E-mail address: doreen.floss@uni-duesseldorf.de (D.M. Floss).

https://doi.org/10.1016/j.cytogfr.2019.05.007
Received 12 April 2019; Accepted 15 May 2019
Available online 21 May 2019
1359-6101/ © 2019 Elsevier Ltd. All rights reserved.

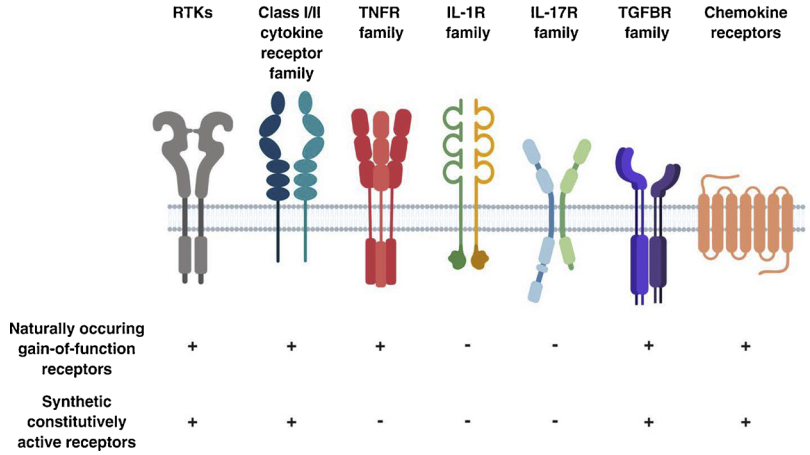

Fig. 1. Schematic representation of prototypical receptors from the seven cytokine receptor subfamilies. The presence (+) or absence (-) of naturally occurring and synthetic constitutively-active receptors is indicated. Images were created with BioRender.

proteins.**Chemokine receptors** including cytokines such as IL-8, rantes, and macrophage inflammatory protein (MIP)-1 signal *via* heterotrimeric G-proteins. Of note, naturally occurring constitutively active cytokine receptors were not found for class II cytokine receptors (interferon family), Ig-type receptors (IL-1/Toll-like receptor family), and IL-17 receptors (Fig. 1).

In addition to naturally occurring constitutive cytokine receptors, also synthetic constitutive-active receptors were developed by genetic engineering for class I cytokine receptors, tyrosine kinase receptors, serine/threonine receptor kinases and chemokine receptors (Fig. 2). The identification and understanding of molecular principles of constitutive-active cytokine receptors is an important part of basic and clinical research to unravel disease development and might also be refined for anti-tumor- or anti-inflammatory immune (-gene) therapies.

With the approval of the first anti-tumor chimeric antigen receptor (CAR) T cell immuno-gene therapy which is based on synthetic receptor biology, further developments are now thinkable. The CAR T cell immunotherapy was approved by the U.S. Food and Drug Administration (FDA) in 2017 for refractory or relapsed B cell precursor acute lymphoblastic leukemia (ALL) and refractory or relapsed diffuse large B cell lymphoma (DLBCL) (reviewed in [3]). CARs are composed of an extracellular single chain Fv (scFv) antibody fragment directed against the tumor associated antigen, CD19 on tumorigenic B cells, followed by a hinge region, the transmembrane domain and intracellular T cell receptor (TCR) activation domains, *i.e.* typically the co-receptor domain from CD3 in a combination with one or two additional activation domains from 4-1BB, CD27, CD28, ICOS or OX40 (reviewed in [4]). For CAR therapy, the patient's peripheral blood mononuclear cells (PBMCs) are collected and T cells are enriched, genetically modified by the addition of the CAR cDNA (retroviral transduction or electroporation), expanded, and returned back to the patient. Once injected, CAR T cells identify tumor cells *via* specific contacts between CAR and the selected tumor antigen. After clustering of many CARs, the CAR T cell gets activated and kills the tumor cell, eventually resulting in tumor remission. Apart from groundbreaking success in this synthetic biology based therapeutic approach, many challenges with respect to efficiency (reviewed in [5]) and side effects have to be overcome [6] for which constitutive-active cytokine receptors might also be suitable.

In this review, we provide a comprehensive overview of naturally occurring and synthetic constitutive-active cytokine receptors of the seven major cytokine receptor families, including mechanism of action, implications in disease development and therapeutic potential.

2. Constitutive activation of Tyrosine kinase receptors

Receptor tyrosine kinases (RTKs) are involved in cellular growth, motility, differentiation and metabolism. All RTKs contain an extracellular ligand-binding domain, a transmembrane domain (TMD) and

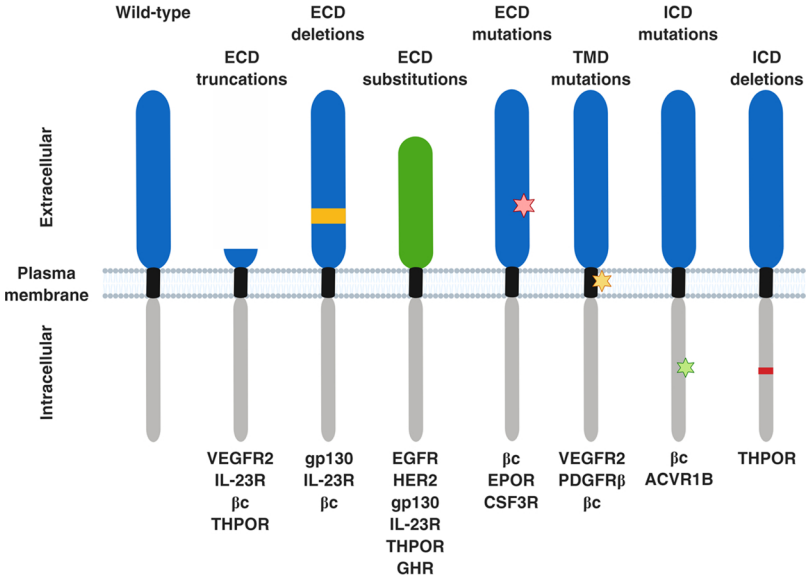

Fig. 2. Molecular principles of ligand-independent cytokine receptor activation. Positions of the mutations are shown schematically. In most cases, the molecular changes of the receptors triggered receptor dimerization and activation (see text for details). ECD, extracellular domain; TMD, transmembrane domain; ICD, intracellular domain. Images were created with BioRender.

Table 1
Naturally occurring and synthetic constitutively active receptor tyrosine kinases.

Cytokine receptor	Mutation	Receptor domain	Human disease	Ref.
EGFR	**Naturally occurring**			
	R108K	ECD (D1)		
	T263P	ECD (D2)	Glioma	[252]
	A289V	ECD (D2)		
	R324L	ECD (D2)	Glioma	[18]
	E330K	ECD (D2)		
	G598V	ECD (D4)	Glioma	[252]
	EGFRvIII	ECD	Glioblastoma	rev. [17]
	G719S	ICD (TKD)	NSCLC	[15]
	V742A	ICD (TKD)		
	Δ747-753insS	ICD (TKD)		
	D761N	ICD (TKD)		
	S768I	ICD (TKD)		
	R776C	ICD (TKD)		
	S784F	ICD (TKD)		
	T790M	ICD (TKD)		
	G810S	ICD (TKD)		
	N826S	ICD (TKD)		
	L838V	ICD (TKD)		
	L858R	ICD (TKD)		
	L861Q	ICD (TKD)		
	A864T	ICD (TKD)		
	ΔELREA	ICD (TKD)	NSCLC	[16]
	ΔLREAT	ICD (TKD)		
	ΔLRE	ICD (TKD)		
	Synthetic			
	LZ-EGFR-GFP	ECD		[19]
	CD3-EGFR	ECD		[20]
HER2	**Naturally occurring**			
	G309A	ECD (D2)	Colon and breast cancer	[26]
	S310F/Y	ECD (D2)		
	p95HER2	ECD	Breast cancer	rev. [22]
	L755S	ICD (TKD)	Breast cancer	[21]
	D769Y/H	ICD (TKD)	Colon and breast cancer	[26]
	A771_Y772insYVMA	ICD (TKD)		
	G776V	ICD (TKD)	Breast cancer	[253]
	V777L	ICD (TKD)	Colon and breast cancer	[26]
	P780_Y781insGSP	ICD (TKD)		
	V842I	ICD (TKD)		
	V862A	ICD (TKD)		
	L869R	ICD (TKD)	Breast cancer	[28]
	$HER2^{YVMA}$	ICD (TKD)	Lung cancer	[27]
	ΔLRENT	ICD (TKD)	Breast cancer	[16]
	Synthetic			
	CD8-HER2	ECD		[29]
HER3	**Naturally occurring**			
	F94L	ECD (D1)	Breast cancer	[35]
	V104M	ECD (D1)	Gastric and colon cancer, NSCLC	[32]
	A232V	ECD (D2)		
	P262H	ECD (D2)		
	G284R	ECD (D2)		
	D297Y	ECD (D2)	Breast cancer	[35]
	T355I	ECD (D3)		
	T389K	ECD (D3)	Gastric and colon cancer, NSCLC	[32]
	V714M	ICD (TKD)		
	Q809R	ICD (TKD)		
	S846I	ICD (TKD)		
	V855A	ICD (TKD)	NSCLC	[34]
	E928G	ICD (TKD)	Gastric and colon cancer, NSCLC	[32]
	E1261A	ICD	Breast cancer	[35]
HER4	**Naturally occurring**			
	E317K	ECD (D2)	Metastatic melanoma	[39]
	E452K	ECD (D3)		
	E542K	ECD (D4)		
	R544W	ECD (D4)		
	E563K	ECD (D4)		
	E836K	ICD (TKD)		
	E872K	ICD (TKD)		
	G1109C	ICD	HNSCC	[40]
VEGFR2	**Naturally occurring**			
	C482A	ECD (D5)	Hemangioma	[46]
	D717V A1065T	ECD (D7) ICD (TKD)	Angiosarcoma	[44]
	A1065T	ICD (TKD)	Hodgkin lymphoma	[45]
	Synthetic			
	ΔECD-VEGFR2	ECD		[51]
	ΔECD-TMD mutants G770E/F777E	ECD/TMD TMD		[50]
	VEGFR2-T771E/F778E	TMD		
VEGFR3	**Naturally occurring**			
	ITD	TMD/ICD (JM)	AML	[48]
	D835H/N I836L + D	ICD (TKD) ICD (TKD)	Leukemia	[49]
PDGFRα	**Naturally occurring**			
	Y288C	ICD (D3)	Breast cancer, melanoma, glioma	[61]
	P345S	ICD (D4)		
	V536E	TMD	Glioblastoma	[58]
	V561D	TMD/ICD (JM)	GIST	[55]
	P577T	TMD/ICD (JM)		[61]
	D842V/Y	ICD (TKD)	GIST	[55]
PDGFRβ	**Naturally occurring**			
	A561C	TMD/ICD (JM)	IM	[66]
	V665A	ICD (TKD)	Premature aging syndrome, Penttinen	[68]
	N666H	ICD (TKD)	*	[62]
	ETV6-PDGFRβ		CMML	[63]
	Synthetic			
	V536A (murine)	TMD/ICD (JM)		[69]
	VVVEVVVins	TMD		[70]

Constitutive activity of listed variants was experimentally verified. *PDGFRβ-related syndromes. ECD, extracellular domain; D, domain; TMD, transmembrane domain, ICD, intracellular domain; JM, juxtamembrane; KD, kinase domain; TKD, tyrosine kinase domain; ITD, internal tandem duplication; NSCLC, non-small-cell lung cancer; HNSCC, head-and-neck squamous cell carcinoma; GIST, gastrointestinal stromal tumors; IM, infantile myofibromatosis; CMML, chronic myelomonocytic leukemia.

an intracellular domain (ICD) comprising a juxtamembrane (JM) regulatory region, a tyrosine kinase domain (TKD) and a C-terminal tail. The RTK family is divided into 20 subfamilies based on the molecular characteristics of the receptor extracellular domain (ECD) and comprises 58 human RTKs (reviewed in [7] and [1]). The main RTK signaling pathways involve the small GTPase Ras, which stimulates the MAPK cascade culminating in activation of ERKs, c-Jun kinases and p38 MAPK resulting in phosphorylation of effectors and further gene regulatory proteins (reviewed in [8]). Protein kinases, including RTKs are frequently mutated in cancer (https://cancer.sanger.ac.uk/cosmic) and these mutated variants are putative therapeutic targets. As stated above, four oncogenic activating mechanisms lead to constitutive RTK activation. In addition, kinase domain duplications represent a unique mechanism of this receptor family [1]. The following chapter focuses on three RTK subfamilies with prominent examples for constitutive activity: class I (EGFR family), class III (PDGFR family) and class IV (VEGFR family) (Table 1). Of note, gain-of-function mutations were also found for other RTKs, including KIT and FGFR which were not covered in this review, but the general activating principles are comparable (reviewed in [1]) [9,10].

2.1. EGFR family

The erbB (avian erythroblastic leukemia virus oncogene homolog)

or human EGF receptor (HER) tyrosine kinase family consists of four members; **EGFR** (also known as ErbB-1/HER1), ErbB-2 (neu, **HER2**), ErbB-3 (**HER3**), and ErbB-4 (**HER4**). Several malignancies are associated with increased expression and/or activity of ErbB family members including glioblastoma, head and neck, lung, breast, stomach, pancreatic and colorectal cancer (reviewed in [11]). The development of effective cancer therapies requires detailed mechanistic and structural studies of gain-of-function mutations because kinase inhibitors are not effective against all constitutive-active receptor variants.

EGFR signaling is important for the regulation of various cellular functions, such as proliferation, motility and differentiation. Accordingly, upregulation of EGFR signaling is associated with cancer. Mutations in EGFR have been identified in patients with non-small-cell lung cancer (NSCLC) and glioblastoma (GBM) (reviewed in [12,13]). Of note, most of the tumors develop resistance against tyrosine kinase inhibitor due to EGFR secondary mutations or bypass signaling activation, so patients show no response to treatment after a while (reviewed in [14]). Mutations and short in-frame deletions (ΔELREA, also referred to as ΔE746-A750, ΔLREAT, ΔLRE) within the EGFR kinase domain of NSCLC patients have been characterized as activating mutations [15,16]. However, sensitivity towards kinase inhibitors varies significantly between different activating EGFR mutations [15]. A specific EGFR mutant in glioblastoma patients (EGFRvIII) with an in-frame deletion of 267 amino acids in the ECD of the receptor is unable to bind the ligand but signals constitutively (reviewed in [17]). EGFR WT might play a role in activation of EGFRvIII due to (a) receptor hetero-dimerization and transphosphorylation of WT EGFR, (b) promoting EGFRvIII dimerization, or (c) transphosphorylation of mutant EGFR by ligand-activated WT EGFR (reviewed in [17]). Glioma specific single point missense mutations (R324L, E330K) in the cysteine rich region of ECD lead to EGFR autoactivation by cysteine disulfide bridge receptor-cross-linking. Transgenic mice with constitutive EGFR activation exhibit enhanced tumorigenicity [18].

Kourouniotis and colleagues designed a synthetic EGFR by replacing the complete extracellular domain by leucine zippers (LZ) and tagged its C-terminus with GFP (LZ-EGFR-GFP), which resulted in constitutive receptor activation, permanent cellular proliferation and enhanced EGFR endocytosis [19]. To identify new therapeutics for targeting EGFR activation and function, constitutively active chimeric EGFRs have been generated. Here, the entire intracellular domain of EGFR was fused to the N-terminus of the CD3ζ component of the T cell receptor signaling complex and stably inserted into murine brain endothelial cells. This initiated the activation of programmed angiogenic responses and constitutive proliferation in these cells, which were susceptible to the small-molecule tyrosine kinase inhibitor PKI166 [20].

Oncogenic activation of **HER2** is mediated by *HER2* gene amplification resulting in HER2 overexpression, or *HER2* gene mutation leading to gain-of-function mutants. Gene amplification of *HER2* is observed in 18–20% of human breast cancers (BCs) with HER2-L755S as the most frequent mutation (24%) (reviewed in [21]). About 40% of HER2-positive tumors express a constitutively active C-terminal fragment of HER2 (p95Her2, 611-CTF) which ligand-independently forms homodimers maintained by intermolecular disulfide bonds (reviewed in [22])[23]. p95HER2 fragments arise through two different mechanisms; shedding of the ECD of the full-length HER2 receptor or translation of *HER2* mRNA from internal initiation codons (reviewed in [24]). Recently, Ruiz and colleagues identified p95HER2 as a *bona fide* tumor specific antigen, because it is not expressed in normal tissue. Accordingly, they developed a p95HER2 T cell bi-specific antibody (TCB) with anti-tumor effects on p95HER2-expressing breast primary cancers and brain lesions. p95HER2-TCB possess a special design which should prevent T cell binding and activation in the absence of p95HER2 binding. The antibody consists of an asymmetric two-armed IgG1 with three binding sites that binds monovalently to CD3ε and bivalently to p95HER2 resulting in recruitment of T cells and subsequent tumor cell lysis [23]. *HER2* gene mutations have been detected in a range of human cancer types and those mutations located in the ECD, TMD or tyrosine kinase domain (TKD) of HER2 are capable of activating HER2 signal transduction (reviewed in [25]). These functionally activating HER2 mutations may drive and maintain cancers in a manner comparable to *HER2* gene amplification. Chmielecki and colleagues analyzed a collection of ~7300 solid tumors and identified 403 tumors from 27 different tissues with an alteration in *HER2* gene. 131 samples harbored a known HER2 mutation (including indels), which lead to constitutive kinase activity and oncogenic cellular transformation (G309A, S310F/Y, D769Y/H, V777L, V842I, T862A). In addition, activating insertions have been identified similar to the previously characterized mutations within the kinase domain (A771_Y772insYVMA and P780_Y781insGSP) [26]. It was already demonstrated that HER2-YVMA was potently auto-phosphorylated and induced trans-phosphorylation of kinase-dead EGFR and HER3 [27]. Short in-frame deletions within HER2 kinase domain (ΔLRENT) have been identified at low frequency in breast cancer patients. HER2-ΔLRENT is an activating deletion through increased phosphorylation of its dimerization partner [16]. HER2 mutant proteins are putative therapeutic targets because they may confer sensitivity to HER2-directed drugs (reviewed in [25]). Recently, Hanker and co-workers analyzed a breast cancer patient with the activating HER2-L869R mutation and the T798I mutation of the gatekeeper residue within the kinase ATP-binding pocket. Cells expressing HER2-L869R exhibited increased phosphorylation of AKT, ERK and S6, which was blocked by neratinib (irreversible EGFR/HER2 tyrosine kinase inhibitor (TKI)), but not lapatinib (reversible HER2/EGFR TKI). However, cells expressing HER2 mutants L869R and T798I showed neratinib resistance. Structural modeling showed that the T798I mutation results in a steric clash with neratinib, which would reduce drug binding affinity [28].

Synthetic constitutively active CD8-HER2 fusion proteins, consisting of the extracellular sequence of the human T cell antigen CD8 α chain and the cytoplasmic sequence of HER2 have been generated. These synthetic receptors form disulfide-mediated homodimers due to intermolecular disulfide bonds within CD8, and have been used for the generation of HER2-dependent tumors in mice which might be helpful for the evaluation of cancer therapeutics [29].

HER3 is a unique member of the HER family because it was considered as kinase inactive receptor (pseudokinase receptor). However, a weak kinase activity was recently reported (reviewed in [30]). HER3 forms heterodimers with other members of the family for signaling, especially HER2. HER2/HER3 heterodimeric complexes are potent activators of the PI3K/AKT pathway due to the HER3 C-terminal part with tyrosine residues for binding of PI3K subunit p85 (reviewed in [30]). Somatic mutations within the HER3 inactive pseudokinase domain might activate the receptor which are rarely found in lung, breast, and colon carcinomas [31]. In 2013, Jaiswal and colleagues identified missense mutations in ~11% of patients with colon and gastric cancer, including several hot spot mutations, which promoted oncogenic signaling in the presence of kinase-active HER2 [32]. The structure of strongly activating HER3 mutations (Q809R, E928G), located in the pseudokinase domain, dimerized with EGFR was almost identical to the structure of EGFR/HER3-WT. This indicated that the HER3 mutations enhanced the allosteric activator function of HER3 by re-designing local interactions at the dimerization interface [33]. An activating HER3-V855A receptor (homologous to EGFR-L858R [15]) was identified in a chemotherapy resistant NSCLC patient. *In silico* modeling predicts that V855A alters the kinase domain and the C-terminus of HER3 [34]. Recently, HER3-T335I was described as activating mutation in estrogen receptor positive (ER+) T47D cells and breast cancer cells lacking HER2 overexpression, indicating that HER3 mutants are oncogenic even in the absence of HER2 overexpression [35]. In addition, several HER3 mutations (F94L, G284R, D297Y, E1261A) with gain-of-function phenotype in HER2 overexpressing cells were found or confirmed respectively. Patients containing HER2 and HER3 mutations have been treated with neratinib, which inhibits the growth of HER2 mutant

tumors but not HER3 mutant tumors (neratinib HER mutation basket study, SUMMIT; clinicaltrials.gov identifier NCT01953926). This study was used to simultaneously evaluate a range of individual HER2 and HER3 variants prior to biological characterization [36].

HER4 (ErbB4) is also unique among the ErbB family because it undergoes proteolytic processing mediated by γ-secretase after ligand binding. The cleaved 80 kDa intracellular domain (containing TKD) translocates into the nucleus and regulates gene expression by modulating the activity of transcription factors (reviewed in [37]). The majority of HER4 mutations are located in exons encoding the extracellular domain of the receptor revealing a unique and substantially different distribution pattern compared to EGFR and HER2 (reviewed in [38]). Somatic HER4 mutations have been identified in melanoma patients and were described as activating mutations due to increased kinase activity and transformation ability [39]. An activating mutation within the C-terminal domain of HER4 (G1109C) was also identified in a cancer cell line that was hypersensitive to HER inhibitors, including the irreversible pan-HER inhibitor afatinib [40]. Downstream signaling pathways from HER4 WT and mutant may be different as shown by Telesco and co-workers. They hypothesized an enrichment of the PI3K/AKT pathway in HER4 mutants which constitutes a cellular shift from differentiation to proliferation [41].

2.2. VEGFR family

Vascular endothelial growth factor receptors (VEGFR1, 2 and 3 (Flt-4)) regulate blood and lymphatic vessel development and homeostasis (reviewed in [42]). VEGFA, B, C, D, and E bind either to one or more types of homo- and heteromeric VEGFRs. Neuropilins (NRP-1 and NRP-2) are co-receptors for VEGFRs which have no intrinsic catalytic activity but enhance the affinity of VEGF to VEGFR and may have additional supporting functions [43]. All VEGF receptors consist of seven Ig-homology domains. VEGF binding to domain 2 and 3 results in receptor dimerization and signal activation of the intrinsic cytoplasmic kinase domain. VEGFR1 has no or only low intrinsic kinase activity and therefore no constitutive-active variant has been described.

Two constitutive-active VEGFR2 variants that were experimentally verified in COS-7 cells were found in patients with angiosarcomas (AS). These mutations were located in the extracellular domain (D717V) and in the kinase domain (A1065T) [44]. The constitutive kinase activity of VEGFR2-A1065T was abrogated after exposure to kinase inhibitors sunitinib and sorafenib [44]. VEGFR2-A1065T was later also found in patients with Hodgkin lymphoma, which is a lymphoproliferative malignancy of B cells [45].

An unusual gain-of-function missense mutation in the VEGFR2 (C482A in Ig-domain 5), that lead to the downregulation of the inhibitory soluble variant of VEGFR1, was identified in juvenile hemangioma, which represents a benign tumor derived from blood vessels or lymphatic vessels in newborns [46]. Interestingly, this mutation does not result in “classical” ligand-independent tyrosine kinase receptor activation, but instead force VEGFR2 in complexes with β1 integrin and TEM8 (ANTRX1, anthrax receptor 1). These complexes reduce β1 integrin-NFAT (nuclear factor of activated T cells)-signaling and expression of the NFAT-target gene VEGFR1 in endothelial cells. Thereby, formation of VEGFR2/β1 integrin/TEM8 complexes induce downregulation of the decoy VEGFR1, which increases the activation of VEGFR2 by VEGF [46].

Internal tandem in-frame duplications of the intracellular juxtamembrane domain (JM) of the VEGFR3 gene (FLT3) were frequently found in acute myeloid leukemia (AML) [47]. All mutants tested were constitutively active due to ligand-independent homo-dimerization [48]. Additionally, gain-of-function missense-mutations in the activation loop of the tyrosine kinase domain, most commonly at D835 were also found in AML patients [49].

Synthetic constitutive-active VEGFR2 variants were obtained by insertion of the polar amino acid residue glutamic acid in the transmembrane domain with (V769E > I767E > L768E) or without (T771E/L778E > G770E/F777E) deletion of the extracellular domain, which conferred a strong dimerization tendency and result in ligand-independent activation of signal transduction [50,51]. Deletion of the extracellular domain was necessary for constitutive activation of the receptor with only one amino acid exchange, given that in the absence of the ligand the ECD acts as an energy barrier that prevents ligand-independent VEGFR2 activation.

2.3. PDGFR family

Platelet derived growth factor receptor (PDGFRα and β) signaling promotes cell proliferation, survival and migration, primarily of cells of mesenchymal origin. All PDGF receptors consist of five Ig-homology domains, a TMD, and an ICD with enzymatic kinase activity. PDGF cytokines act as homo- or heterodimers (AA, AB, BB, CC, DD) and bind either to one or more types of homo- and heteromeric PDGFRs (αα, αβ, ββ) at Ig-like domains 2 and 3. Ligand-independent, constitutive-active PDGFR variants contribute to various pathophysiological conditions, *e.g.* cancer development (reviewed in [52]).

Gastrointestinal stromal tumors (GIST) are mainly characterized by the presence of activating mutations in either of the two receptor tyrosine kinases c-KIT or PDGFRα [53,54]. In contrast to wild-type PDGFRα signal transduction, the activation of STAT factors (STAT1, STAT3, and STAT5) is strongly favored by constitutively active human PDGFRα variants with either juxtamembrane (V561D) or kinase domain (D842V or D842Y) mutations. As has been observed for other cytokine receptor mutants described later, aberrant PDGFRα signaling is also initiated in the endoplasmic reticulum [55]. The PDGFRα-V536E transmembrane mutant was identified in two glioblastoma patients [56,57] and stimulated ligand-independent Ba/F3 cell growth and signaling *via* ERK and STAT5 [58]. The murine pro-B cell line Ba/F3 is commonly used as a cytokine activity reporter, because their proliferation is dependent on cytokine (*e.g.* IL-3) induced pSTAT5 phosphorylation (reviewed in [59]).

An interesting strategy to understand the *in vivo* role of constitutive-active cytokine receptors was demonstrated for PDGFRα. Here, two CRE-inducible mice strains were generated for the human PDGFRα variants V561D and D842V. In general, constitutive PDGFRα signaling led to connective tissue hyperplasia and increased extracellular matrix deposition, resulting in fibrosis reminiscent of the human autoimmune disease systemic sclerosis. Only few sarcomas developed in these mice, suggesting that additional mutations in other genes are needed. Interestingly, the phenotypes of the transgenic mice were similar but differed in severity [60]. In principle, the use of constitutively active cytokine receptors in transgenic mice is an elegant strategy to analyze disease development in a defined genetic background and might be therefore useful to test therapeutic regimens.

The Y288C mutation in PDGFRα is located in the ligand binding Ig-like domain 3, which also leads to ligand-independent constitutive dimerization and activation of signal transduction. Interestingly, PDGFRα-Y288C was mainly localized and activated in the ER/Golgi apparatus. Even though a disulfide bridge was formed between two PDGFRα Y288C molecules, this disulfide bridge was not needed for receptor activation, because PDGFRα-Y288H also induced receptor homo-dimerization and ligand-independent signal transduction [61].

Activating mutations in the PDGFRβ gene contribute to at least four different phenotypes: (1) myeloproliferative disorder with eosinophilia, (2) infantile myofibromatosis, (3) Kosaki overgrowth syndrome, and (4) premature aging syndrome of the Penttinen type [62]. Whereas myeloproliferative disorder with eosinophilia is a result of a fusion of the 154 N-terminal amino acid residues of ETV6 (previously known as TEL (translocation-Ets-leukemia virus)) to the transmembrane and intracellular domains of PDGFRβ, all other diseases are caused by heterozygous germ-line activating mutations in PDGFRβ [62]. Ligand-independent activation of the ETV6-PDGFRβ hybrid receptor is caused by

oligomerization mediated by the pointed (PNT, also called SAM or helix-loop-helix) domain of ETV6 [63]. ETV6-PDGFRβ is not a transmembrane protein and rather located in the cytoplasm. Interestingly, deletion of the original transmembrane domain of PDGFRβ reduces constitutive receptor activity [64]. Importantly, patients with ETV6-PDGFRβ translocations have been successfully treated with the tyrosine kinase inhibitor imatinib [65]. Another successful treatment with imatinib was recently shown for a patient with the constitutive-active PDGFRβ-N666H variant [62]. This N666H mutation is localized in the kinase domain and was originally identified in patients with infantile myofibromatosis [66,67] PDGFRβ-V665A was also constitutively active and found in patients with premature aging syndrome of the Penttinen type [68].

Synthetic constitutive-active PDGFRβ variants were generated by introduction of an amino acid exchange in the cytoplasmic juxtamembrane domain at position V536A of the murine receptor. This mutation also activated a truncated PDGFRβ mutant which was unable to bind PDGF [69]. Alternatively, constitutive-active PDGFRβ variants were generated by insertion of a simplified valine-dominated transmembrane domain with the polar amino acid residue glutamic acid at specific positions (VVVEVVV), which conferred receptor dimerization and activation of signal transduction [70].

In summary, gain-of-function mutations in RTKs have been identified in the ECD, TMD and ICD parts and mainly contribute to cancer development. Mechanistically, most mutations in the ECD and TMD result in ligand-independent receptor homo-dimerization, whereas mutations in the ICD frequently result in constitutive-active kinase domains, which is considered to be independent of receptor dimerization.

3. Constitutive activation of class I and II cytokine receptors

Class I and class II receptors depend on associated tyrosine kinases because they lack intrinsic kinase activity. Accordingly, JAKs play a pivotal role in signal transduction of these cytokine receptors (reviewed in [71]). They are type 1 membrane proteins with extracellular cytokine-binding homology regions (CHR, also called cytokine-binding homology domains (CBD) or cytokine binding module (CBM)) consisting of two fibronectin type III (FNIII) domains. The differences between class I and class II cytokine receptors rely on structural differences within the CHR. Class I receptors contain two disulfide bridges within the first FNIII domain and a highly conserved WSXWS motif in the second FNIII domain. In contrast, class II cytokine receptors have one cysteine pair in each FNIII domain of the CHR and no conserved WSXWS motif (reviewed in [72]).

The largest group among the cytokine receptors are **class I cytokine receptors**, also referred to as hematopoietin receptors (reviewed in [73]). Members of this family are sub-divided based on the shared receptor subunit (reviewed in [2,74]): **glycoprotein (gp) 130 family** (receptors for IL-6, IL-11, IL-12, IL-23, IL-27, IL-31, IL-35, IL-39, cardiotrophin-like cytokine (CLC), ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), oncostatin M (OSM), cardiotrophin 1 (CT-1)), **common γ chain** (γc) **family** (receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21) and **common β chain** (βc) **family** (receptors for IL-3, IL-5 and GM-CSF). Some of the class I cytokine receptors did not belong to these larger families and signal *via* receptor homo-dimerization mediated by classical hormones (EPO, GH, prolactin (PRL), leptin, THPO or G-CSF). Constitutive-active receptors were summarized in Table 2.

On the other hand, **class II cytokine receptors** are mainly executing IFN signaling and IL-10 signal transduction, as well as signaling of IL-10 related cytokines, *e.g.* IL-19, IL-20, IL-22, IL-24 and IL-26 for which no constitutive-active receptors were described so far.

Table 2
Naturally occurring and synthetic constitutively active class I cytokine receptors.

Cytokine receptor	Mutation	Receptor domain	Human disease	Ref.
gp130	**Naturally occurring**			
	K173_D177del	ECD (D2)	IHCA	[78]
	V184_Y186del, S187A	ECD (D2)		
	V184_S187delinsA	ECD (D2)	IHCA	[79]
	Y186_Y190del	ECD (D2)	IHCA	[78]
	S187_Y190del	ECD (D2)		
	V189_V192del	ECD (D2)	IHCA	[79]
	E195_V196del	ECD (D2)		
	D215del	ECD (D2)		
	P216H	ECD (D2)		
	A418_F421del	ECD (D4)		
	Synthetic			
	L-gp130	ECD		[91]
	IL-15-gp130	ECD		[98]
	Δ322-613, SΔ614-616	ECD		[94]
	Y757F (mice)	ICD		[89]
IL-23R	**Synthetic**			
	IL-15-IL-23R (murine)	ECD		[112]
	ΔG24-D353	ECD		
	ΔV319-D353	ECD		
IL-7R	**Naturally occurring**			
	S185C	ECD (D5)	Leukemia	[119]
	L234insPPCL	TMD		
	PILLT240-244RFCPH	TMD	Leukemia	[123]
	IL241-242TC	TMD	Leukemia	[121]
	I241 > ITLYCKT	TMD		
	L242 > DTRVYNSIC	TMD		
	LL242-243 > SPCI	TMD		
	L242-L243insNPC	TMD	Leukemia	[120]
	GCinsL243	TMD	Leukemia	[121]
	T244-I245insCPT	TMD	Leukemia	[120]
	V253 > GFSV	TMD	Leukemia	[121]
	SLILIVPCACELinsA254	TMD		
	V253insGEA	TMD	Leukemia	[122]
	V253insEKV	TMD		
	V253G	TMD		
CRLF2	**Naturally occurring**			
	F232C	ECD/TMD (JM)	Leukemia	[125]
	V244insEIM	TMD	Leukemia	[122]
βc	**Naturally occurring**			
	R461C	TMD/ICD (JM)	Leukemia	[130]
	Synthetic			
	L356P	ECD (D4)		rev. [131]
	W358N	ECD (D4)		
	I374N	ECD (D4)		
	Q375P	ECD (D4)		
	Y376N	ECD (D4)		
	W383R	ECD (D4)		
	L399P	ECD (D4)		
	L445Q	TMD		
	V449E	TMD		
	A459D	TMD		
	H544R	ICD		
	FIΔ	ECD		
	ΔQP	ECD		
	ΔH	ECD		
GHR	**Naturally occurring**			
	P495T**	ICD	Lung cancer	[147]
	Synthetic			
	Fos-GHR (porcine)	ECD		[148]
	Jun-GHR (porcine)	ECD		
	fos-GHRct	ECD/TMD		[150]
	fos-GHRct-fos	ECD/TMD		
	Jun-GHR	ECD		[149]
	C substitutions (E260-L269)	ECD/TMD		
THPOR	**Naturally occurring**			
	P106L	ECD (CRM-1)	HT	[160]

(*continued on next page*)

Table 2 (*continued*)

Cytokine receptor	Mutation	Receptor domain	Human disease	Ref.
	T487A	ECD (CRM-2)	Leukemia	[161]
	S505N	TMD	Thrombocytosis	rev. [152]
	W515A/K/L/R/G/S	TMD/ICD (JM)		
	Synthetic			
	ΔCRM-1	ECD		[154]
	CRM-2/CRM-2	ECD		
	Δ5THPOR	ICD		[156]
	Put3-THPOR	ECD		[164]
EPOR	**Naturally occurring**			
	C338Y	ICD	PFCP	[182]
	T341M	ICD		
	P380A	ICD	PFCP	rev. [173]
	P381Qfs*2	ICD		
	E399*	ICD		
	S407*	ICD	PFCP	[181]
	S412Rfs*41	ICD	PFCP	rev. [173]
	S412*	ICD		
	S415Hfs*18	ICD		
	E417*	ICD		
	G418Pfs*34	ICD		
	F424*	ICD		
	E425*	ICD		
	Y426*	ICD		
	I428Yfs*17	ICD		
	L429Wfs*24	ICD		
	D430Gfs*15	ICD		
	D430Efs*26	ICD		
	Q434*	ICD		
	Q434Cfs*17	ICD		
	Q434Pfs*11	ICD	PFCP	[180]
	R437H	ICD	PFCP	rev. [173]
	P438Mfs*6	ICD		
	W439*	ICD		
	Y454*	ICD	PFCP	[179]
	N487S	ICD	PFCP	rev. [173]
	P488S	ICD		
	Synthetic			
	R129C	ECD		[184]
LepR	**Synthetic**			
	Y985L (murine)	ICD		[190]
CSF3R	**Naturally occurring**			
	W341C	ECD (D4)	Leukemia	[198]
	T618I	ECD (D6)	Leukemia	[194]
	T615A	ECD (D6)	Leukemia	[195]
	T640N	TMD	Leukemia	[197]
	F792X	ICD	Leukemia	[199]
	Q741X	ICD		
	D771fs	ICD		
	L790X	ICD		
	W791X	ICD		
	Q793X	ICD		
	E808X	ICD		
	Q823X	ICD		
	Isoform IV	ICD	Leukemia	[200]
	Synthetic			
	E524G/K	ECD (D5)		[201]
	S581C	ECD (D6)		
	T612A/I	ECD (D6)		

Constitutive activity of listed variants was experimentally verified. **This variant was not constitutively active, but showed significantly enhanced GH-mediated signaling. ECD, extracellular domain; D, domain; TMD, transmembrane domain, ICD, intracellular domain; JM, juxtamembrane; IHCA, inflammatory hepatocellular adenoma; HT, hereditary thrombocythemia; PFCP, primary familial congenital polycythemia; TRAPS, TNF receptor-associated periodic syndrome; NSCLC, non-small-cell lung cancer.

3.1. Naturally occurring and synthetic constitutive-active receptors of the Interleukin 6-family

Cytokines which signal *via* receptors of the gp130 family are generally sub-classified into IL-6 and IL-12 family cytokines, respectively, or even summarized as IL-6/IL-12 type cytokines [75]. Cytokines of the IL-6 family signal *via* gp130 homodimers for IL-6 and IL-11 or gp130 heterodimers with OSM receptor (OSMR), LIF receptor (LIFR) and WSX1 for CNTF, OSM, LIF, CLC, CT-1 and IL-27. Finally, IL-31 signals *via* a heterodimer of IL-31 receptor A (IL-31RA) and OSMR (reviewed in [76]).

Among many immune-related and unrelated functions, IL-6 signaling is important for liver regeneration and acute phase response (reviewed in [77]). Somatic mutations in the gp130 coding exons were found in about 60% of inflammatory hepatocellular adenomas (IHCAs), which are mainly located in the extracellular domain 2 of gp130 [78,79]. The extracellular part of gp130 consists of six domains (D1-D6). The first N-terminal Ig-like domain (D1) is followed by the cytokine-binding module (CBM, comprising D2 and D3) and three fibronectin-like domains (D4-D6). Whereas D1 and CBM each contain one cytokine binding site, D4-D6 are important for correct positioning of the transmembrane and intracellular domains during receptor activation. Twenty distinct in-frame deletions, one-missense substitution, and three in-frame insertion-deletions located in D2 of gp130 have been identified in IHCA patients and resulted in ligand independent constitutive activation of gp130 (reviewed in [80]). Domains D2 and D3 have a common β-sandwich fold, which is mediated by a three-stranded (A, B and E) and a four-stranded (C, C', F and G) β-sheet. The interstrand EF loop in D2 and the interstrand BC loop in D3 form the CBM [81]. Substitution of one of the two critical amino acids N215 (E β-sheet) or C172 (C' β-sheet) both localized in D2 caused a disruption of hydrophobic D2-D3 connectivity. This increased the flexibility of the EF loop and destabilized the inactive state of gp130 resulting in ligand-independent gp130 activation [82]. One in-frame deletion (ΔA418-F421) at the D4-D5 junction was also identified in an IHCA patient, which might favor gp130 homo-dimerization, albeit this has not been experimentally shown [79]. The most frequently occurring IHCAs-associated mutation was the in-frame gp130-deletion ΔY186-Y190 within the EF loop of D2, which led to constitutive ligand-independent phosphorylation of STAT1 and STAT3 but failed to activate the MAPK signaling pathway [78,82–84]. Furthermore, upregulation of the acute phase response gene C-reactive protein (CRP) and the negative feedback inhibitor suppressor of cytokine signaling 3 (SOCS3) was a consequence of constitutive receptor activation [78,79,84]. Although the IHCA-associated gp130 mutant induced the feedback inhibitor SOCS3, this was not sufficient to inhibit constitutive activation of STAT3 [79]. However, SOCS3 expression might explain the missing activation of the MAPK pathway, because SOCS3 binds to the same phosphorylated tyrosine residue Y759 in the intracellular domain of activated gp130 receptors as SHP2 which initiates the MAPK pathway. However, Rinis et al. have presented an alternative explanation based on their finding that SHP2, which is needed for activation of the MAPK/ERK pathway, gets normally phosphorylated by gp130ΔY186-Y190, suggesting that activation of the MAPK/ERK pathway is interrupted due to the limited spatial availability of MAPK cascade compounds at intracellular membranes [84]. Gp130ΔY186-Y190 is incompletely glycosylated, interacts with the ER chaperone calnexin, and is mainly localized in the ER and early endosomes. Consequently, signal transduction of gp130ΔY186-Y190 is mainly initiated from intracellular compartments [84,85].

Constitutive activation of gp130 IHCA-mutants is associated with spontaneous formation of gp130 homodimers which occur through destabilization of the EF loop within D2 and disruption of D2-D3 hydrophobic interactions [79,82]. Ligand-independent activation of mutant gp130ΔY186-Y190 resulted from receptor homo-dimerization which can be competed for by hetero-dimerization with wild-type gp130 [78,79]. Surprisingly, hetero-dimerization of mutant gp130 and OSMR resulted in activation of STAT3 [79]. In the intestine, an interaction between constitutively active gp130 mutants and the transcriptional regulators Yes-associated protein (YAP) of the Hippo signaling pathway and Notch was found, which control tissue growth and

regeneration. The activation of these transcriptional regulators was not induced by STAT3, but by the tyrosine kinases Src and Yes [86].

All of the IHCA-associated gp130 mutants promote constitutive activation of the JAK/STAT pathway, a favorite target for drug development and cancer therapy (reviewed in [87]). Accordingly, blockade of the JAK/STAT pathway is a main focus for development of novel therapeutics. JAK inhibitors such as pyridone 6 (P6, pan-JAK inhibitor) and ruxolitinib (JAK1 and JAK2 inhibitor) blocked constitutive activation of IHCA gp130 mutants, in contrast to the JAK2 inhibitor AG490 [79,82]. Curcumin, Src kinase inhibitors and the neutralizing gp130 antibody B-P4, which targets D4 of gp130 [88], are other potent inhibitors [79,83]. However, blocking signaling activity of mutant gp130 by B-P4 was not confirmed by Rinis et al. [84]. Sommer and co-workers showed that the deletion of the D1 domain of gp130 IHCA mutant, but not anti-gp130 D1 mAbs, abolished constitutive receptor activation. This indicates that D1 might be involved in ligand-independent activation of IHCA-associated gp130 mutants [83]. Rinis and co-workers could down-regulate ligand-independent STAT3 phosphorylation in the context of IHCA-associated gp130 mutant using a dominant-negative STAT3-Y705F mutant [84]. IL-6 induced STAT3 hyper-activation in transgenic mice carrying a phenylalanine knock-in substitution of the cytoplasmic Y757F [89]. This tyrosine provides the competitive docking site for SOCS3 and SHP2, and substitution resulted in exaggerated STAT1 and STAT3 activation due to impairment of negative feedback inhibition by SOCS3 and impaired activation of the MAPK/ERK pathway [90].

To mimic constitutive and ligand-independent activation of gp130, synthetic gp130 variants were generated. The first successful synthetic strategy was the replacement of the complete extracellular domain of gp130 by the 39-amino acid residue long leucine zipper of the transcription factor Jun (L-gp130) [91]. L-gp130 homodimers induced permanent receptor dimerization resulting in STAT3 and MAPK/ERK activation in Ba/F3 cells and maintenance of the undifferentiated state of murine embryonic stem cells [91]. Importantly, proliferation of the cytokine activity reporter Ba/F3 cell line is dependent on Hyper-IL-6 and STAT3 phosphorylation after introduction of the gp130 receptor chain. Hyper IL-6 is a fusion protein of IL-6 and the soluble IL-6R phenocopying IL-6 trans-signaling [92]. Expression of L-gp130 in untransformed telomerase-immortalized human fetal hepatocytes resulted in higher ROS levels, more DNA double strand breaks, enhanced proliferation, higher colony formation, and decreased expression of antioxidant genes resulting in an impaired oxidative stress response [93]. Recently, Lamertz and co-workers reported that deletion of the three FNIII domains D4-D6 plus shortening of the gp130 stalk region to a minimum of three amino acids resulted in ligand independent, constitutive gp130 receptor activation, which was inhibited by the pan-JAK inhibitor P6 [94]. Importantly, constitutive-active gp130 homodimers reproduce signaling of IL-6 and IL-11, since both cytokines signal *via* gp130 homodimers. IL-6 and IL-11 have, however, largely non-overlapping functions in inflammation and regeneration, respectively (reviewed in [95]). Therefore, constitutive IL-6- or IL-11-selective activation of cells expressing wild-type gp130 was achieved by co-expression of membrane-bound Hyper-IL-6 or Hyper-IL-11 variants resulting in autocrine gp130 signaling [96]. In analogy to Hyper-IL-6 (HIL-6), HIL-11 is a fusion protein of IL-11 to its soluble IL-11R [97].

To generate constitutive-active ligand-independent heterodimeric receptor complexes of the IL-6/IL-12 cytokine family, the entire extracellular regions of gp130, LIF, OSMR, WSX1, IL-31RA, IL-12Rβ1, and IL-12Rβ2 were exchanged by the 148-amino acid sequence of IL-15 and/or by the 66-amino acid sequence of the sushi domain of the IL-15Rα [98], (Floss et al. unpublished). The sushi domain of IL-15Rα mainly contributes to the exceptionally high-affinity binding towards IL-15 *via* ionic interactions [99]. The resulting heterodimeric gp130/OSM, gp130/LIFR and gp130/WSX1 receptor complexes showed constitutively ligand-independent signaling that was not blocked by soluble IL-15Rα-sushi domain. Of note, free IL-15 is highly prone to aggregate [100]. Interestingly, only IL-15-gp130 but not IL-15-LIFR, IL-15-OSMR or IL-15-WSX1 was able to form homomeric biologically active receptor complexes that led to sustained activation of STAT3 and ERK1/2 and was inhibited by IL-15Rα-sushi domain [98], suggesting that homodimers of LIFR, OSMR and WSX1 are functionally inactive.

In conclusion, naturally occurring mutations in the extracellular domain of gp130 resulted in constitutive-active gp130 mutant receptors and contributed to the development of IHCA. Moreover, synthetic gp130-type receptors were generated and provided a toolbox of constitutive-active receptors.

3.2. Synthetic constitutive-active receptors of the Interleukin 12-family

The IL-12 cytokine family consists of five members, IL-12, IL-23, IL-27, IL-35 and IL-39 (reviewed in [101]) and is involved in a very broad range of immune functions, including pro- and anti-inflammatory responses.

IL-12 type cytokines are soluble heterodimers containing the cytokine α chains p19, p28 or p35 structurally similar to IL-6 and the cytokine β chains p40 and Epstein-Barr virus induced gene 3 (EBI3), which are structurally related to the sIL-6R. Receptor complexes of these cytokines are also heterodimeric and consist of IL-12Rβ1, IL-12Rβ2, IL-23R, WSX1, and gp130. IL-12 signals *via* IL-12Rβ1 and IL-12Rβ2, and IL-23 signals *via* IL-12Rβ1 and IL-23R, whereas IL-27 and IL-35 shares some receptor subunits with the IL-6 family (gp130/WSX1 and gp130/IL-12Rβ2, gp130/gp130/, IL-12Rβ2/IL-12Rβ2, WSX1/IL-12Rβ2 respectively) (reviewed in [101,102]). The receptor combination for IL-39 (IL-23R/gp130) was postulated and experimentally validated [103,104]. Using IL-6/IL-12 cytokine receptor shuffling of extra- and intracellular domains, Floss and colleagues also demonstrated the functional homodimeric assembly of IL-12Rβ2 [104], which was described as receptor complex for IL-35 [105].

The pro-inflammatory cytokine IL-23 regulates the development of TH17 cells, which are important mediators of antimicrobial and antifungal diseases. In addition, the balance between IL-12 and IL-23 shapes the development of antitumor or protumor immunity (reviewed in [106]). Both cytokines initiate JAK/STAT signaling [107,108]. Based on the structure of the IL-6:IL-6R:gp130 signaling complex models for potential cytokine receptor complexes for IL-12 type cytokines were predicted (reviewed in [109]) [105]. However, a non-canonical topology of the IL-23:IL-23R:IL-12Rβ1 complex was proposed based on experimental validation [110]. Schröder and colleagues demonstrated that the interaction of IL-23 to the IL-12Rβ1 is independent of site II in p19. Recently, it was shown that the low-affinity interaction between IL-23 and IL-12Rβ1 is exclusively mediated *via* p40 [111].

No naturally occurring constitutive-active receptors of the IL-12 cytokine family have been described to date. However, Hummel and co-workers generated synthetic constitutive-active IL-23R variants by deletion of amino acids within the membrane-proximal stalk region of the receptor [112]. In opposite to all other signal transducing receptors of the IL-12 and closely related IL-6 family, the IL-23R lacks the three fibronectin-like domains. Instead of that the cytokine-binding domains (D1-D3) are connected with the transmembrane domain by a 37 amino acid long flexible linker peptide (stalk region) [113]. Interestingly, this composition is reminiscent of the non-signal transducing α-receptors IL-6R, IL-11R, and CNTFR. Surprisingly, extensive deletion of the stalk region (amino acid V319 to D353) and complete deletion of the extracellular domains (G24 to D353) both resulted in constitutive IL-23R homo-dimerization and activation of signal transduction in transduced Ba/F3 cells [112]. The synthetic receptor assembly system based on multimerization of IL-15 was also used to generate constitutive-active IL-23R. Like for gp130, constitutive-active murine IL-23R homodimers were also generated by replacing the ECD of IL-23R by IL-15 and fused to TMD and ICD of IL-23R [112]. Albeit, no mutations have yet been identified that confer constitutive activation of IL-12-type cytokine

receptors, strategies that have been developed and applied to generate constitutive-active IL-6-type receptors were also valid for this receptor family.

3.3. Synthetic and constitutive receptor activation of the common γ chain receptor family

The common gamma chain (γc) cytokine receptor is the shared receptor subunit for IL-2, IL-4, IL-7, IL-9, and IL-21, which all are referred as γc cytokines (reviewed in [114]). The γc and the ligand-specific subunits are mainly expressed in lymphocytes, but can be also found in other hematopoietic cells (reviewed in [2]). IL-2 is the prototypical member of the family and signals *via* the heterotrimeric IL-2R composed of IL-2Rα, IL-2Rβ and γc. IL-2Rα is not a member of the class I cytokine receptor family and does not contain a cytoplasmic signaling subunit, but is pertinent for high affinity binding of IL-2 to its receptor (reviewed in [115]). Furthermore, IL-2Rβ is also part of the heterotrimeric IL-15 receptor together with IL-15Rα and γc. IL-15Rα has a similar structure and function than IL-2Rα. IL-15 signaling is mediated *via* trans-presentation by IL-15Rα (reviewed in [116]). IL-4 signals *via* IL-4Rα in complex with γc or IL-13Rα (reviewed in [2]). IL-7, IL-9, and IL-21 activate cells expressing heterodimeric receptors, IL-7R/γc, IL-9R/γc, or IL-21R/γc, respectively. IL-7 signal transduction is important for normal lymphoid development and excessive IL-7/IL-7R-mediated signaling can drive acute lymphoid leukemia (ALL) of B and T cell origin (reviewed in [117]). In addition, the IL-7 pathway is important for the development and maintenance of the immune system. Mazzucchelli and co-workers summarized genetic variations in the IL-7R gene which are implicated in several severe autoimmune disorders (reviewed in [118]). Somatic gain-of-function mutations in the IL-7R, which led to ligand-independent IL-7R homo-dimerization and activation, were identified in patients with ALL. Most IL-7R-activating mutations coded for an additional cysteine in the transmembrane domain leading to intermolecular disulfide bridges (reviewed in [117]) [119–121]. In addition, also other non-cysteine in-frame point mutations and insertions within the transmembrane domain activate IL-7Rα through ligand-independent receptor homo-dimerization [122]. Functionally, constitutive-active IL-7R promotes induction and development of leukemia [123]. Accordingly, targeting the IL-7R pathway in these ALL patients is a promising therapeutic strategy. Recently, Senkevitch et al. demonstrated that the combination of the JAK1/2 inhibitor ruxolitinib and the BCL-2 inhibitor ventoclax was effective to treat ALL patients with activating IL-7R mutations [124].

Moreover, thymic stromal lymphopoietin (TSLP) signals *via* IL-7Rα and TSLPR (also known as CRLF2), which is a homologue of γc (reviewed in [115]). Activating cysteine insertions and non-cysteine in-frame mutations in TSLPR were also identified in 5–10% B-lineage acute lymphoblastic leukemia (B-ALL) patients [122,125]. Human TSLPR-F232C, carrying an amino acid substitution in the extracellular juxtamembrane region, promotes constitutive receptor dimerization through intermolecular disulfide bridges [125] and signals *via* phosphorylation of Y368, the only intracellular tyrosine in TSLPR [126]. Functionally, TSLPR-F232C expressing PBMCs led to myeloproliferative-like syndrome in a bone marrow transplant mouse model [127].

Moreover, a synthetic IL-7R (T244-I245insCPT) was developed based on the natural variant found in ALL patients, which forms homodimers due to a cysteine in the transmembrane domain and constitutively signals without the need for IL-7 stimulation or the γc receptor subunit [120]. Co-expression of the constitutively active semi-synthetic IL-7R (C7R) with a tumor-directed CAR in T cells increased T cell proliferation, survival, and anti-tumor activity and was effective against metastatic neuroblastoma and orthotopic glioblastoma in xenograft models [128].

Even though cytokines and cytokine receptors are critically involved in T and B cell activation, proliferation and differentiation, constitutively active cytokine receptors were only described for IL-7R and TSLPR, but not for γc, IL-2Rβ, IL-4Rα, IL-13Rα, IL-9R, or IL-21R.

3.4. Constitutive receptor activation of the common β chain receptor family

The common beta chain (βc) is the shared subunit of the receptor complexes for IL-3, IL-5 and GM-CSF. βc bind these cytokines together with the respective α receptors IL-3Rα, IL-5Rα, or GM-CSFRα (reviewed in [73]). All three cytokines are produced by activated T cells and regulate survival, proliferation, differentiation, and activation of hematopoietic cells. Dysregulation of βc cytokine signaling is associated with the development of several diseases including leukemia and inflammatory disorders like arthritis or asthma (reviewed in [129]). βc forms intertwined homodimers that were not observed in other cytokine-receptor systems. For GM-CSF, the cytokine/receptor complex displays a hexameric assembly with two cytokines binding to the homodimeric βc, accompanied by two α receptors on each side of the βc homodimer. Moreover, two hexamers were packed head-to-head, creating a dodecamer. Most likely, IL-3 and IL-5 form comparable receptor compositions (reviewed in [129]).

In 2016, Watanabe-Smith and co-workers described the first heterozygous germline βc mutation (βc-R461C) in a leukemia patient which caused constitutive receptor activation and induced factor-independent growth of transduced Ba/F3 cells. Inhibition of JAK2 by AZD1480 reduced STAT5 phosphorylation in βc-R461C transduced Ba/F3 cells [130]. R461C is most likely localized within the transmembrane domain, but it was not analyzed, if this mutation induced receptor cross-linking by an intermolecular disulfide bridge [130].

Many mutations in the βc which conferred constitutive receptor activation have been identified by mutational screens (summarized by [131]). All of these mutants have oncogenic potential because they converted the murine factor-dependent hematopoietic cell line FDC-P1 to factor-independent growth. However, striking differences between these βc mutants have been demonstrated when analyzed in other hematopoietic cell lines (reviewed in [131]). Some mutations have been further characterized in transgenic mice or primary murine hematopoietic cells. They disrupted hematopoiesis leading to myeloproliferative disorders or acute leukemia [132,133].

The synthetic activation of βc occurs through sequence duplication or amino acid substitutions in the membrane proximal domain 4 (CRD4) [134–136], truncations of the extracellular domains [137], mutations within the transmembrane domain [135,136], the Box 2-JAK binding motif in the cytoplasmic domain [136], or a small deletion in the extracellular domain 3 (reviewed in [131]). Interestingly, certainly not all βc mutants form constitutive-active homodimers. Constitutive activation of human βc-I374 N was dependent on constitutive interaction with GM-CSFRα [138]. Moreover, EPO receptor (EPOR) and most likely also THPO receptor (THPOR) can functionally replace GM-CSFRα and allow factor-independent proliferation and JAK2 activation of Ba/F3 cells expressing βc-I374 N and βc-FIΔ [139]. The 37 amino-acid duplication within CRD4 in βc-FIΔ contains two duplicated conserved motifs (WSEWS and RVRVR) and causes disruption of a preformed βc homodimer and therefore permit spontaneous ligand-independent hetero-dimerization with an α receptor [140].

The cytokine-induced signaling of the βc chain receptor family require tricky hexameric and/or dodecameric cytokine-receptor complexes. Constitutive-active receptors of this family were, however, only described for βc mutants and rely on βc homo-dimerization or hetero-dimerization with GMCSF-R or the non-family members EPOR and THPOR.

3.5. Constitutive and synthetic activation of GHR, THPOR, EPOR, THPOR and LepR and CSF3R

EPO, THPO, GH, PRL, and leptin are classical cytokines/growth factors that also signal *via* homodimeric **class 1 cytokine receptors**

(reviewed in [2]).

Ghr

The GHR was the first cloned class 1 cytokine receptor. The extracellular domain of GHR consists of two fibronectin III-like domains: (1) aa 19–141 involved in GH binding and (2) aa 146–264 involved in receptor dimerization and GH-induced receptor rotation (reviewed in [141,142]). GH binding results in a conversion of parallel receptor transmembrane domains into a rotated crossover orientation, which induces separation of the lower part of the transmembrane helices and of the two associated JAK2 kinases resulting in JAK activation (reviewed in [143]). Until now, many GHR mutations have been described with reduced or loss-of-function of the mutant GHR, which are causing dwarfism (reviewed in [142]). However, GHR deficiency, resulting in insulin like growth factor (IGF)-1 deficiency, facilitates resistance to cancer (reviewed in [144]). Consequently, individuals with prolonged or constitutive activation of GHR should have a higher risk for cancer. The study from Chhabra and colleagues highlights the first identified lung cancer associated GHR-P495T mutant [145,146], which is not constitutively active, but displays significantly enhanced GH-mediated signaling [147]. Chhabra and colleagues demonstrated by co-immunoprecipitation studies that SOCS2 binding to the GHR-P495T mutant was markedly impaired resulting in decreased receptor internalization and degradation. The authors speculate that phosphorylation of T494 supports SOCS2 binding and the new threonine at position 495 (P495T) may also become phosphorylated or interfered with phosphorylation of T494 resulting in impaired SOCS2 binding after receptor activation [147]. At the moment, reports about naturally occurring GHR gain-of-function variants do not exist. Constitutively active synthetic porcine GHR variants have been generated by leucine zipper fusions where almost the entire GHR extracellular domain was replaced by the leucine zipper from either c-Fos or c-Jun. This substitution induces ligand-independent dimerization of the transmembrane and cytoplasmic domains resulting in ligand-independent STAT5 phosphorylation and growth of Ba/F3 cells [148]. Insertion of 3 additional alanine residues between the leucine zipper and the TMD increased constitutive GHR signaling [149]. In addition, a synthetic cytosolic Fos-zippered dimeric GHR variant (fos-GHRct) was generated. JAK2 interaction and activation of fos-GHRct was comparable to the wild-type receptor on the cell membrane [150]. Interestingly, introduction of cysteine residues in the extracellular juxtamembrane domain (JMD) [149] but not within the GHR dimerization domain [151] resulted in constitutively active GHR.

THPOR

Homodimeric THPOR mediated signaling is important for megakaryocyte differentiation and platelet production (reviewed in [152]). The extracellular domain of THPOR is composed of two adjacent pairs of fibronectin-III like domains which are connected *via* the hinge region with two cytokine receptor modules (CRM-1, CRM-2) (reviewed in [153]). Deletion of murine CRM-1 or substitution with CRM-2 diminished binding to THPO but induced factor-independent growth of transduced Ba/F3 cells [154]. Accordingly, CRM-1 is essential for interaction with THPO and likely plays a role in preventing signaling in the absence of THPO (reviewed in [153]). V-mpl is an extracellular truncated, constitutively active form of the murine THPOR found in the murine myeloproliferative leukemia virus (MPLV). In detail, v-mpl is a fusion oncoprotein of 100 aa derived from the friend murine leukemia virus envelope protein and 184 aa of THPOR comprising the TMD and cytosolic region of the receptor [155]. Furthermore, at the junction between the TMD and ICD of THPOR is a unique, amphipathic motif (human: RWQFP (aa 514–518), murine: KWQFP (aa 507–5011)). Synthetic mutation (murine K507A, W508A) or deletion of this motif induced ligand independent activation of murine or human THPOR [156]. Defour and colleagues suggested that the amphipathic motif holds the TMD of THPOR in an inactive conformation in the absence of THPO [157]. Mutations in THPOR were identified in patients with increased platelet numbers, in disorders such as familial thrombocytosis and myeloproliferative neoplasms (MPNs) and were recently reviewed by [152,153]. Gain-of-function mutants were found in the TMD (S505N) and the adjacent juxtamembrane cytoplasmic region (W515A/K/L/R/G/S) of THPOR. S505N induced ligand-independent dimerization and activation of this THPOR variant [158]. Both S505N and W515K induced changes in the tilt angle of the human THPOR transmembrane helix resulting in receptor dimerization [157]. In addition, extracellular H499 close to the N-terminus of the TMD protects the human THPOR against activating mutations such as S505N [159]. Gain-of function mutations have also been identified within the ECD of THPOR. The P106L mutation that was identified in patients with hereditary thrombocythemia (HT) confers cytokine-independent proliferation of Ba/F3 cells [160]. However, THPOR-P106L mutants are not localized on the cell membrane implicating that mutant receptor dimerization also occurs within the ER/Golgi apparatus [160]. The constitutive-active THPOR-T487A mutant was found in a patient with acute megakaryoblastic leukemia (AMKL) [161]. THPOR-T487A induced ligand-independent growth of Ba/F3 cells and constitutive activation of STAT5, ERK1/2, and AKT and induced myeloproliferative disease after mouse bone marrow transplantation of THPOR-T487A transduced bone marrow cells [161]. Functionally, substitution of T487 with valine, *i.e.* with a longer β-branched side-chain than alanine, did not result in constitutive receptor activation, suggesting that the beta-branched side chain structure of the amino acid at position 487 is important to keep the unliganded THPOR in an inactive state.

Calreticulin (CALR) is a chaperone located in the ER which is involved in folding of glycosylated proteins including THPOR. Interestingly, mutations in CALR have been identified in patients with essential thrombocythemia (ET) and primary myelofibrosis (PMF). These mutants obtained a novel C-terminal sequence due to a +1-frameshift resulting in stronger binding to the ECD of THPOR (reviewed in [162]). Mechanistically, mutant CALR homo-multimerization caused then the ligand-independent activation of THPOR [163].

Synthetic dimerization and ligand-independent activation of THPOR was achieved by fusion of the coiled-coil dimerization domain from the yeast transcription factor Put3 to the N-terminal residue of the TMD of THPOR [164]. Staerk and colleagues obtained different orientations of the two intracellular chains by variation of the length of the junctions between coiled-coil and TMD of THPOR. Interestingly, one dimer was inactive whereas the other six dimers induced cell proliferation with different signaling outputs and biological effects [164], which suggests that not only dimerization but also three-dimensional orientation of the receptor dimer is important for activation of signal transduction. THPOR activation resulted in phosphorylation of JAK2 and TYK2 [165] and JAK2 and TYK2 might be differentially induced *via* rotated receptor orientations [164]. In 2014, Brooks and colleagues hypothesized a scissor-like mechanical model for the activation of the GHR dimer [149]. In this model, JAK2 activation occurs through alterations of the JM domain and TMD inducing ICDs splaying and alignment of JAK2 kinase domains leading to transactivation [166]. Matthews and co-workers demonstrated by a combination of cysteine cross-linking, alanine-scanning mutagenesis, and computational simulations that the transmembrane domain of THPOR has a strong intrinsic tendency to form homodimers in a native biological membrane and THPOR dimerization and activation involves rotation of the transmembrane domains [167]. Three stable rotationally related conformations for the transmembrane domain of THPOR corresponding to three specific states of the receptor were suggested, *i.e.* (i) preformed inactive dimer, (ii) active dimer, and (iii) partially active dimer.

EPOR

The binding of EPO to its receptor (EPOR) is important for proliferation and survival of erythroid progenitors and terminal erythroid differentiation. The extracellular region of EPOR consists of two domains (membrane-distal D1 and membrane-proximal D2) which comprise the cytokine receptor homology domain with two binding sites for EPO (reviewed in [168]). EPOR is present as an inactive dimer on the cell surface. Constantinescu and colleagues proposed a model in which TMD-induced dimerization maintained unliganded EPOR in an inactive state. The receptor is switched into an active state after EPO binding [169,170]. EPO binding results in the activation of JAK2 followed by the phosphorylation of STAT5 (reviewed in [171]). However, protective functions in the nervous system and other non-hematopoietic tissues are mediated by alternative EPO receptors, which might be heterodimeric EPOR/βc complexes, homodimeric or multimeric Ephrin B4 (EphB4) complexes, or homodimeric cytokine receptor-like factor 3 (CRLF3) complexes (reviewed in [168]).

Numerous gain-of-function mutations in EPOR were described in patients with congenital erythrocytosis (reviewed in [172]). The majority lead to a cytoplasmic truncated receptor due to frameshifts (by small deletions or insertions) or novel stop-codons (by nonsense mutations) resulting in the loss the C-terminal negative regulatory domain important for binding of the JAK/STAT inhibitory protein cytokine-inducible SH2 protein-3 (CIS3/SOCS3/SSI3) [173,174]. These gain-of-function mutations induced increased EPOR activity and are associated with the development of primary familial congenital polycythemia (PFCP) [173,175] which was supported by development of fetal polycythemia in EPOR knock-in mice coding for a mutation resulting in a truncation after the first tyrosine residue (Y401) of the ICD [176,177]. Additional C-truncation mutations have been identified in patients with BCR-ABL1-like ALL [178], erythrocytosis (by 55 amino acid long deletion) [179], primary polycythemia (alternative ten-amino acid C-terminal tail and a stop codon at position 444 resulting in the truncation of 64 aa of the wild-type receptor) [180], and PFCP (deletion by 102 amino acids) [181]. Moreover, Peroni and colleagues identified two missense EPOR mutations (C338Y, T341M) in female adult sporadic erythrocytotic patients. Both mutations are located in exon 8 encoding the C-terminal negative regulatory domain and replaced a polar amino acid by an aromatic amino acid (C338Y) or a non-polar amino acid (T341M) [182]. These point mutations also resulted in a gain-of-function of EPOR signaling cascades of STAT5 and ERK [182].

Retroviral transduction of EPOR cDNA in IL-3 dependent Ba/F3 cells allows the cells to grow in the presence of EPO. However, spontaneous mutation of the EPOR cDNA during virus production resulted in selection of cytokine-independent Ba/F3-EPOR-R129C cells. The amino acid exchange in EPOR-R129C is located in the ECD of the receptor, which induced disulfide-linked dimeric receptors with constitutive activity [183,184].

LepR

Leptin signaling plays a critical role in regulation of bone turn-over as well as growth and body weight (reviewed in [185]). Six Leptin receptor (LepR) isoforms (LepRa-f) exists due to alternative splicing of the *lepr* gene (reviewed in [186]). LepRb contains an extended intracellular signaling domain with three tyrosine residues (human: Y986, Y1079, Y1141; mouse: Y985, Y1077, Y1138) and plays a key role in leptin signaling by stimulation of associated JAK2s and activation of STAT3, STAT5, ERK, PI3K/Akt and MAPK (reviewed in [187]). The four shorter isoforms (LepRa, LepRc, LepRd, LepRf) have very short cytoplasmic tails of 30–40 amino acids and no intracellular motifs for activation of the JAK-STAT-pathway (reviewed in [188]). The soluble LepRe isoform is directly secreted in mice, but generated by ectodomain shedding in humans, and modulates leptin availability (reviewed in [186]). Leptin binding induces activation of LepR dimers resulting in phosphorylation of the three tyrosine residues located in the intracellular domain of LepRb, which act as docking sites for PTPN11 and SOCS3, STAT5, and STAT3 (reviewed in [185]). Many mutations in the human LepR gene have been identified in patients with extreme-early-onset obesity but based on current knowledge no mutation resulted in a gain-of-function receptor (reviewed in [189]). A mild gain-of-function model for studying leptin action represent the LL mice, carrying a homozygous Y985L mutation in LepR, which abolishes phosphorylation and SOCS3 binding resulting in a leptin hypersensitive mouse [190]. This amino acid substitution protects female mice from high-fat diet-induced obesity. Recently, leptin hypersensitivity for LL mice was confirmed by McCabe and co-workers by analyzing LepRb mutants with regard to sex- and location-dependent bone response to leptin [191].

CSF3R

G-CSF (granulocyte colony-stimulating factor) plays important roles in proliferation and differentiation of myeloid progenitors into neutrophils. Binding of two G-CSF to the CSF3 receptor (CSF3R) causes receptor homo-dimerization (2:2 stoichiometry) and activation of signaling pathways including JAK/STAT, PI3K/Akt and MAPK/ERK (reviewed in [192]) [193]. Activating mutations in CSF3R are found in the extracellular domain, transmembrane proximal and intracellular domain and contribute to the development of myeloid disorders (reviewed in [192]). The gain-of-function mutations T618I and T615A are located in domain 6 of the ECD and have been identified in patients with chronic neutrophilic leukemia (CNL) and atypical (BCR-ABL1-negative) chronic myeloid leukemia (aCML) [194,195]. Activity of these CSF3R mutants was suppressed by the JAK1/2 inhibitor ruxolitinib. These membrane proximal mutations prevent the O-glycosylation of CSF3R and increase the dimerization of the receptor resulting in ligand-independent signaling [196]. Interestingly, the CSF3R mutation (T640N) within the TMD that was identified in patients with CNL or aCML also led to constitutive receptor activation due to a decreased O-glycosylation pattern [197]. In contrast, mutation W341C within ECD 2 induces receptor homo-dimerization *via* intermolecular disulfide bonds. Patient cells and cells transformed with CSF3R-W341C were sensitive to JAK inhibitors [198]. In addition, CSF3R truncation mutations, identified in patients with myeloid disorders, lack a portion of the cytoplasmic part of the receptor containing tyrosine residues, internalization or negative regulatory motifs. These truncations induce CSF3R overexpression and hypersensitivity to G-CSF [199]. CSF3R isoform IV is a naturally occurring splice variant lacking negative regulatory elements in the ICD which is expressed in AML patients and promotes leukemogenic properties [200]. Additional gain-of-function CSF3R mutations have been identified using the Ba/F3 transformation model including cysteine- and disulfide bond interchain dimerization at S581C, introduction of polar, noncharged amino acids at the TMD at T640, increased internalization for E524 substitution that mimics a low G-CSF dose, and introduction of hydrophobic amino acid residues in the ECD/TMD juxtamembrane residues T612, T615, and T618 [201].

In summary, GH, EPO, THPO, leptin and G-CSF signal *via* homodimeric receptor complexes and were intensively studied *in vitro* and *in vivo*. In general, constitutive-active receptors of these cytokines contribute to neoplastic diseases which may explain why so many different mutations have been identified and functionally characterized.

4. Constitutive activation of TNF receptors

Tumor necrosis factor (TNF) and the TNF receptor superfamily (TNFSF/TNFRSF) consists of 29 receptors and 19 ligands in humans (reviewed in [202]). Interactions among these ligands and receptors initiate signaling that controls survival, proliferation, differentiation, and effector functions of immune and non-immune cells. Receptor activation is dependent on trimerization [203]. The proinflammatory properties of the family members mainly rely on the activation of NFκB

pathways but also induce apoptosis and other forms of cell death (reviewed in [204]). Ligands of the TNF receptor superfamily are synthesized in a trimeric membrane-bound form (type II transmembrane proteins) and soluble forms are generated by proteolysis. The TNF receptors superfamily can be further classified into three groups based on downstream interaction partners: death receptors with death domains (DD), receptors with TRAF-interacting motif, and decoy receptors with no intracellular interaction partners. The latter act as TNFSF ligand inhibitors (reviewed in [202]). The shared ligand and receptor usage within this superfamily establishes a tremendous communication network among cell types and tissues which is important for regulation of immunity and homeostasis (reviewed in [204]).

TNF receptor associated periodic syndrome (TRAPS) is an autosomal dominantly inherited systemic autoinflammatory disorder caused by mutations in the type I trans-membrane protein TNF receptor superfamily 1A gene (*TNFRSF1A, TNFR1*). At present 158 *TNFRSF1A* sequence variants have been associated with TRAPS (https://infevers.umai-montpellier.fr). Several hypotheses have been proposed to explain the molecular disease mechanisms, which include constitutively active or hypersensitive TNFR1; among them are decreased levels of circulating inhibitor soluble TNFR1, reduction in TNF-induced apoptosis, intracellular oxidative stress due to misfolding of the receptor in the ER, autophagy, microRNAs and polymorphisms in the promoter (reviewed in [205]). Lobito and colleagues hypothesized that the TRAPS-associated mutations which cause loss of a cysteine residue (C33 or C52) lead to an unpaired cysteine in the ECD of TNFR1 or unfolding of mutant TNFR1 creates free cysteines. These single unpaired cysteines may lead to oligomerization of mutant receptors. In addition, TNFR1 mutant receptors were retained in the ER and induced abnormal ligand-independent signaling [206]. The ligand-independent signaling hypothesis was further demonstrated for the TNFR1-C33Y mutation in inflammatory signaling pathways. Ngem and colleagues analyzed the presence of inflammatory target proteins (*e.g.* pSTAT3, STAT3, p-p65, p65, p-AKT, AKT) in SK-Hep-1 cells transfected with TNFR1-C33Y or WT TNFR1 by Western blotting and reverse phase protein microarray (RPPM), and observed increased expression of the tested markers. This was confirmed by analyzing PBMCs from TRAPS patients carrying the C33Y mutation. Ngem and colleagues provide a model for the inflammatory signaling pathways which are triggered patho-physiologically by constitutive activation of the misfolded TNFR1-C33Y mutant [207]. In addition, three other TRAPS-inducing TNFR1 mutants (S59P, R92Q, and T50M) were transiently transfected into HEK293 cells and TNF-induced cytoplasmic accumulation and constitutive activation was detected [208]. Greco and colleagues also analyzed TNFR1 and inflammasome downstream signaling pathways and confirmed constitutive activation of NFκB for TNFR1-T50M, MAPK and JAK/STAT for TNFR1-S59P, and JAK/STAT for TNFR1-R92Q. The results were confirmed by analyzing PBMCs from TRAPS patients with mutants TNFR1-S59P and TNFR1-R92Q [208].

Despite the many members of the TNF receptor superfamily (TNFSF/TNFRSF), to the best of our knowledge naturally occurring constitutive-active receptors were only described for TNFR1 and no other synthetic constitutively active receptor of the TNF superfamily was described (Table 3). This may at least in part be due to the special requirements of trimeric receptor activation.

Table 3
Naturally occurring constitutively active TNF receptors.

Cytokine receptor	Mutation	Receptor domain	Human disease	Ref.
TNFR1	**Naturally occurring**			
	C33Y	ECD (D1)	TRAPS	[207]
	T50M	ECD (D1)	TRAPS	[208]
	S59P	ECD (D2)		
	R92Q	ECD (D2)		

Constitutive activity of listed variants was experimentally verified. ECD, extracellular domain; D, domain; TRAPS, TNF receptor-associated periodic syndrome.

5. Constitutive activation of serine/threonine kinase receptors

Members of the serine/threonine kinase receptor family are activated by TGF-β cytokines which are in most cases disulfide-linked dimeric molecules, such as TGF-β isoforms (1–3), bone morphogenetic proteins (BMPs), growth and differentiation factors (GDFs) and activins. The cytokines are synthesized with large pro-domains which are required for proper folding and dimerization, and need to be cleaved off to obtain the carboxy-terminal located active cytokine moiety (reviewed in [209]). Signaling occurs *via* heterotetrameric complexes of type I and type II dual specificity kinase receptors which activate the Smad and MAPK pathways. Members of the TGF-β family bind to characteristic receptor combinations. The receptors have small cysteine-rich ECDs, TMDs followed by intracellular juxtamembrane and kinase domains. After ligand binding the constitutively active type II receptor phosphorylates the type I receptor in the glycine serine-rich (GS) domain upstream of the kinase domain (reviewed in [210]). In addition, a third type III group of receptors exists, which does not actively participate in signal transduction but function to present ligands to the signal-transducing receptors (reviewed in [2]). Signaling of TGF-β members is important during embryonic development and for regulation of tissue homeostasis by regulation of cell proliferation, migration, and differentiation (reviewed in [210]).

Here, we focus on constitutive-active cytokine receptors for TGF-β, albeit constitutive-active receptors were also described for other family members, including activin receptor-like kinase 1A (ACVR1A-R206H) [211], BMP receptor 2 (BMPR2-R899P) [212] and ACVR1B (ACVR1B-T206E) [213] (Table 4). TGF-β signals through TGF-β receptors I (TGFBR1) and II (TGFBR2). In early stages of cancer development TGF-β signaling is tumor suppressive, but becomes supportive in later stages of tumor development (reviewed in [214]). A gain-of-function mutation in the TGFBR2 serine/threonine kinase domain (R537P) was found in human head and neck squamous carcinoma cells (HNSCC, A253) which resulted in constitutive trans-activation of TGFBR1 [215]. Another gain-of-function mutation of TGFBR2 was identified in a patient with oral squamous cell carcinoma (TGFBR2-E221V/N238I). This double mutation, located between TMD and kinase domain, promoted TGF-β/Smad signaling due to delayed TGFBR2 internalization leading to a more invasive phenotype of cancer cells [216]. Recently, the expression of TGFBR1*6a, a receptor variant with a deletion of 3 alanine residues in exon 1 resulting in a modified signal peptide with no changes in receptor membrane insertion [217], was shown to activate p38 MAPK and ERK1/2 MAPK pathways in the absence of exogenously added TGF-β in human colorectal cancer SW48 cells [218]. The authors hypothesized that this hypo-morphic variant of TGFBR1 possesses oncogenic properties and may affect the migration and invasion of colorectal cancer cells by an unknown mechanism.

Constitutive activation of TGF-β signaling pathways was achieved in murine Mv1Lu cells, lacking TGFBR1 and TGFRB2, transfected with cDNAs encoding only for the cytoplasmic domains of TGFRB1 and TGFRB2 [219].

6. Constitutive activation of chemokine receptors

Chemoattractant cytokines, also named chemokines, act as drivers for the recruitment of immune cells during inflammation, induce cellular morphological changes, extravasation into inflamed tissue, and chemotaxis (reviewed in [220]). Tumor types have altered chemokine secretion eventually promoting growth, survival and metastasis of the tumor cells (reviewed in [221]). The number and position of conserved cysteines are hallmarks for the classification of chemokines into four

Table 4
Naturally occurring and synthetic constitutively active serine/threonine receptor kinases.

Cytokine receptor	Mutation	Receptor domain	Human disease	Ref.
TGFBR1	**Naturally occurring**			
	*6A	SP	Colorectal cancer	[218]
TGFBR2	**Naturally occurring**			
	E221V/N238I	ICD	OSCC	[216]
	R537P	ICD (KD)	Head and neck cancer	[215]
ACVR1A	**Naturally occurring**			
	R206H	GSD	FOP	[211]
BMPR2	**Naturally occurring**			
	R899P	ICD	PPH	[212]
ACVR1B	**Synthetic**			
	T206E	GSD		[213]

Constitutive activity of listed variants was experimentally verified. D, domain; ICD, intracellular domain; KD, kinase domain; SP, signal peptide; GSD, glycine-serine rich domain; OSCC, oral squamous cell carcinoma; FOP, fibrodysplasia ossificans progressive; PPH, primary pulmonary hypertension.

major groups; CXC, CC, C, and CX3C (reviewed in [222]). Biological activity of chemokines is mediated by G-protein coupled chemokine receptors (GPCR) or atypical chemokine receptors (ACKR). The latter control the chemokine system by shaping chemokine distribution in tissues by means of clearance and transport mechanisms (reviewed in [223]). GPCRs have a characteristic 7-TMD structure with an extracellular amino terminus, an intracellular carboxy terminus, three interhelical loops to the extracellular space, and three interhelical loops facing the cytoplasm. Receptor activation involves the rotation of TMD3 and TMD6 and induces conformational changes of G-protein-interacting cytoplasmic receptor loops resulting in uncovering previously masked G-protein-binding sites on the intracellular loops (review in [224]). A key structural determinant for GPCRs is the highly conserved DRYLAIV motif at the end of TMD3, which is only poorly conserved in ACKRs (reviewed in [225]). GPCRs signal through canonical G-protein pathways or non-canonical GPCR pathways such as β-arrestin (reviewed in [226]). Under specific conditions chemokine receptors may adopt different G-protein or β-arrestin signaling properties and function as biased receptors [227,228]. Structural and biochemical data exist that chemokine receptors act as homo- and heterodimers (reviewed in [229]). Vertebrate chemokine receptors are classified into four subgroups according to the bound chemokine; CXCR1 to CXCR6 (CXC chemokine receptors), CCR1 to CCR10 (CC chemokine receptors), and CX3CR and XCR1. In addition, seven ACKR, which are highly homologous to typical chemokine receptors, have been identified (reviewed in [225]).

Dysfunction of the chemokine receptor system results in various diseases including tumorigenesis and cancer metastasis. Deregulation can occur when constitutively active mutant (CAM) chemokine receptors (Table 5) are locked in the “on” position [230]. In 1984, Cerione et al. first described the existence of a constitutively active GPCR [231]. Since then numerous constitutively active GPCR variants were identified which contribute to human disease development (reviewed in [232]). In general, many constitutively active GPCRs have mutations in the bent region at the cytoplasmic end of TMD6, indicating that this region is important for G-protein coupling and receptor activation [233]. Interestingly, naturally occurring constitutively active chemokine GPCR variants were only described for CCR5 and virally encoded chemokine GPCRs. However, a couple of synthetic chemokine CAMs were developed.

The first constitutively active CXCR1 receptor was generated by site directed mutagenesis of V247 within TMD6 [234]. Additional synthetic CAMs of CXCR1 (V6.40A = V247A), V6.40N = V247N)), CXCR2 (D3.49V = D138V), CXCR3 (N3.35A = N134A, N3.35S = N134S, T2.56P = T105P) and CXCR4 (N3.35A = N119A, N3.35S = N119S) have been described in the absence of ligands and reviewed by [224]. The appropriate single point mutations change the conformational stage of the receptor and mimic the active state of the wild-type receptor. Additionally, amino acid residues in TMD3 (S132, D134) and

Table 5
Naturally occurring and synthetic constitutively active chemokine receptors.

Cytokine receptor	Mutation	Receptor domain	Human disease	Ref.
CXCR1	**Synthetic**			
	M241V	TMD6		[233]
	V247A/N	TMD6		rev. [224]
	F251A/H/Y	TMD6		[233]
CXCR2	**Synthetic**			
	D138V	ICL2		rev. [224]
CXCR3	**Synthetic**			
	T108P	TMD2		rev. [224]
	N134A/S	TMD3		
CXCR4	**Synthetic**			
	N199S/A	TMD3		rev. [224]
CCR2	**Synthetic**			
	T94K	TMD2		[244]
CCR5	**Naturally occurring**			
	R225Q	ICL3	HIV	[241]
	Synthetic			
	T82K/R/H/Y/P	TMD2		[244]
	G286F	TMD7		[245]

Constitutive activity of listed variants was experimentally verified. TMD, transmembrane domain, ICL, intracellular loop; HIV, human immunodeficiency virus.

TMD6 (M241, F251), which might be important for G-protein coupling were mutated in CXCR1. Mutations M241V and F251H induced modest constitutive activation of CXCR1 by coupling to $G_{\alpha 15}$ and $G_{\alpha i}$ proteins [233]. CXCR4 is a multi-facetted receptor which tightly mirrors its ligands CXCL12 functions in homeostasis and disease, and acts as a co-receptor for HIV entry (reviewed in [235]). In 2002, Zhang et al. described the first constitutively active variant of CXCR4 (N119S, N119A) derived by random mutagenesis [236]. CXCR4 CAMs are versatile tools for the high-throughput screening of antagonists which might be useful to block CXCR4 function and are new therapeutics for myeloid malignancies, other tumors, and HIV-1 infection (reviewed in [224]). Furthermore, CXCR4 CAMs are promising candidates to improve hematopoietic stem/progenitor cells (HSPCs) to home and engraft in bone marrow [237]. The wild-type CCR5 receptor is partially constitutively active, which may result from the absence of a “classical ionic lock” mediated by the cytosolic ends of TMD3 and TMD6. In many GPCRs, the basic side chain of R of the highly conserved (D/E)RY motif in TMD3 forms ionic interactions with the acidic side chain of the adjacent D/E and an D/E residue at the cytoplasmic end of TMD6. This interaction maintains the inactive receptor formation (reviewed in [238]). However, CCR5 has a basic R residue at the cytosolic end of TMD3, and mutation resulted in decreased constitutive signaling indicating that CCR5 does not form a classical ionic lock [239]. In addition, mutation L203F in TMD5 controls the level of basal activity in CCR5 [240].

Naturally occurring mutations in CCR5 with different interactions with chemokines and HIV envelope protein have been identified in South African populations [241]. CCR5 is considered the most important co-receptor during the initial transmission and early stages of HIV (reviewed in [238]). Only the CCR5-R225Q mutant, derived from a HIV patient and located in the third cytoplasmic loop of the receptor, showed partial ligand-independent intracellular signaling [241]. Constitutive-active CCR5 mutants act different in HIV envelope-directed membrane fusion [242]. Ligand-independent activation of CCR5 and CCR2 was induced by mutation of T82 in the highly conserved TXP motif in TMD2 [243,244]. Insertion of the steric hindrance mutation G286F in the center of TMD7 resulted in elimination of β-arrestin recruitment but constitutively active $G_{\alpha i}$ mediated signaling. This mutation changes the orientation of W248 in TM6 away from TMD7 resulting in a biased CCR5 conformation [245].

Several naturally occurring viral chemokine receptors are constitutively active and signal ligand-independent by coupling to G-proteins. Six chemokine receptor homologs were identified in human herpesvirus genomes and in some cases ligand-independent constitutive signaling was demonstrated (reviewed in [246]). The Kaposi's sarcoma-associated herpesvirus (KSHV, also known as HHV-8) encodes a GPCR receptor, ORF74 (also known as KSHV vGPCR), which is a constitutively active viral homolog for CXCR2 and contributed to cancer development after KSHV infection. KSHV vGPCRs possess amino acid substitutions at positions which might be involved in stabilization of the inactive state and in agonist-induced conformational changes from the inactive to the active state (reviewed in [247]). The activity of KSHV vGPCR can be modulated by endogenous cytokines (reviewed in [220]). The Epstein-Barr virus (EBV, also known as HHV-4) encodes the GPCR BILF1 which constitutively signals by activating NFκB and cAMP response element-binding protein (CREB). BILF1 forms heterodimeric complexes with human CXCR4 and impairs binding of CXCL12 to CXCR4 in a ligand-independent (constitutive) manner [248]. The HCMV encodes four viral GPCRs (US28, UL33, US27 and UL78). US28 is a constitutive-active homolog of the chemokine receptors CCR1, CCR2 and CX3CR1, engages a variety of ligands and thereby permanently activates PLCβ and NFκB (reviewed in [246]). Recently, nanobodies directed against the extracellular domain of US28 have been developed, which reduced the constitutive signaling and impaired HCMV/US28-mediated tumor growth [249]. Boeck et al. demonstrated for the first time that also US27 is a constitutively active receptor that signals through $G_{\beta\gamma}$, PI3K, and NRF-1 to activate transcription of ARE-regulated genes during HCMV infection [250]. US27, UL33 and UL78 are orphan receptors with up to date no known chemokine ligands. UL33 activates multiple signaling pathways in a ligand-independent manner and the C-terminal cytoplasmic tail of UL33 is responsible for the activation of G_i-proteins [251]. Constitutive activity for UL78 was not described so far [246].

The chemokine receptors are a smaller group within the huge family of GPCRs. Albeit many chemokines are known, only a comparably low number of constitutively active GPCRs have been identified to date.

7. Conclusion and future prospects

This review has summarized current knowledge about constitutively active cytokine receptors. Naturally occurring constitutive-active cytokine receptors were mainly identified in patients due to direct contribution to disease development. Therefore, the understanding of the molecular principles of constitutive receptor activation is an important prerequisite to develop effective therapies. Importantly, most therapeutics also act on the wild-type receptors, *e.g.* by targeting the kinase domain and are therefore not specific for the constitutive-active cytokine receptor. Interestingly, for some constitutive-active receptors, receptor activation from intracellular compartments was described. It is tempting to speculate that more constitutive-active receptors than these rare examples signal from intracellular compartments. This is an important aspect, because intracellular signaling is most likely less efficiently inhibited by antibodies and variants thereof, such as Fab-fragments, scFvs, or nanobodies. Intracellular signaling is only inhibited by small molecules that are able to cross the plasma membrane and in most cases are directed against the intracellular kinase domains. It will be interesting to see, if intracellular signaling holds true for more constitutively active cytokine receptors and if location of signaling is a reason for differences seen between wild-type receptor signaling and constitutively active cytokine receptors. On the other hand, also wild-type receptor signaling is not exclusively executed at the plasma membrane and not automatically terminated by receptor-endocytosis.

Apart from naturally occurring constitutively active cytokine receptors, synthetic biology approaches resulted in constitutive-active cytokine receptors by a variety of approaches. Some of these synthetic cytokine receptors might also be useful as therapeutics, *e.g.* in combination with chimeric antigen receptors, to improve CAR T cell therapy. Whether constitutive-active cytokine receptors are a valid approach in therapy remains to be seen because the inability to control receptor function is critical.

In conclusion, constitutive cytokine receptor activation has revealed that just a fine line exists between desirable and uncontrollable cytokine/cytokine receptor activity. Only a single cytokine receptor mutation has the power to release the brakes of cytokine receptor signaling and decide between health and disease.

References

[1] Z. Du, C.M. Lovly, Mechanisms of receptor tyrosine kinase activation in cancer, Mol. Cancer 17 (2018) 58.
[2] J. O'Shea, M. Gadina, R.M. Siegel, Cytokines and cytokine receptors, in: R.R. Rich, T.A. Fleisher, W.T. Shearer, H.W. Schroeder, A.J. Frew, C.M. Weyand (Eds.), Clinical Immunology, Elsevier, 2018, pp. 127–155.
[3] J. Xu, J.J. Melenhorst, J.A. Fraietta, Toward precision manufacturing of immunogene T-cell therapies, Cytotherapy 20 (2018) 623–638.
[4] W. Si, C. Li, P. Wei, Synthetic immunology: T-cell engineering and adoptive immunotherapy, Synth. Syst. Biotechnol. 3 (2018) 179–185.
[5] D. Gomes-Silva, C.A. Ramos, Cancer immunotherapy using CAR-T cells: from the research bench to the assembly line, Biotechnol. J. 13 (2018).
[6] M. Ruella, J. Xu, D.M. Barrett, J.A. Fraietta, T.J. Reich, D.E. Ambrose, M. Klichinsky, O. Shestova, P.R. Patel, I. Kulikovskaya, F. Nazimuddin, V.G. Bhoj, E.J. Orlando, T.J. Fry, H. Bitter, S.L. Maude, B.L. Levine, C.L. Nobles, F.D. Bushman, R.M. Young, J. Scholler, S.I. Gill, C.H. June, S.A. Grupp, S.F. Lacey, J.J. Melenhorst, Induction of resistance to chimeric antigen receptor T cell therapy by transduction of a single leukemic B cell, Nat. Med. 24 (2018) 1499–1503.
[7] A.I. Segaliny, M. Tellez-Gabriel, M.F. Heymann, D. Heymann, Receptor tyrosine kinases: characterisation, mechanism of action and therapeutic interests for bone cancers, J. Bone Oncol. 4 (2015) 1–12.
[8] V. Di Liberto, G. Mudo, N. Belluardo, Crosstalk between receptor tyrosine kinases (RTKs) and G protein-coupled receptors (GPCR) in the brain: focus on heteroreceptor complexes and related functional neurotrophic effects, Neuropharmacology (2018).
[9] L. Martin, N. Kaci, V. Estibals, N. Goudin, M. Garfa-Traore, C. Benoist-Lasselin, E. Dambroise, L. Legeai-Mallet, Constitutively-active FGFR3 disrupts primary cilium length and IFT20 trafficking in various chondrocyte models of achondroplasia, Hum. Mol. Genet. 27 (2018) 1–13.
[10] J.D. Karkera, G.M. Cardona, K. Bell, D. Gaffney, J.C. Portale, A. Santiago-Walker, C.H. Moy, P. King, M. Sharp, R. Bahleda, F.R. Luo, J.D. Alvarez, M.V. Lorenzi, S.J. Platero, Oncogenic characterization and pharmacologic sensitivity of activating fibroblast growth factor receptor (FGFR) genetic alterations to the selective FGFR inhibitor erdafitinib, Mol. Cancer Ther. 16 (2017) 1717–1726.
[11] R. Roskoski Jr, The ErbB/HER family of protein-tyrosine kinases and cancer, Pharmacol. Res. 79 (2014) 34–74.
[12] M.D. Siegelin, A.C. Borczuk, Epidermal growth factor receptor mutations in lung adenocarcinoma, Lab. Invest. 94 (2014) 129–137.
[13] P.H. Huang, A.M. Xu, F.M. White, Oncogenic EGFR signaling networks in glioma, Sci. Signal. 2 (2009) re6.
[14] Q. Liu, S. Yu, W. Zhao, S. Qin, Q. Chu, K. Wu, EGFR-TKIs resistance via EGFR-independent signaling pathways, Mol. Cancer 17 (2018) 53.
[15] R.K. Kancha, N. von Bubnoff, C. Peschel, J. Duyster, Functional analysis of epidermal growth factor receptor (EGFR) mutations and potential implications for EGFR targeted therapy, Clin. Cancer Res. 15 (2009) 460–467.
[16] S.A. Foster, D.M. Whalen, A. Ozen, M.J. Wongchenko, J. Yin, I. Yen, G. Schaefer, J.D. Mayfield, J. Chmielecki, P.J. Stephens, L.A. Albacker, Y. Yan, K. Song, G. Hatzivassiliou, C. Eigenbrot, C. Yu, A.S. Shaw, G. Manning, N.J. Skelton, S.G. Hymowitz, S. Malek, Activation mechanism of oncogenic deletion mutations in BRAF, EGFR, and HER2, Cancer Cell 29 (2016) 477–493.
[17] G. Guo, K. Gong, B. Wohlfeld, K.J. Hatanpaa, D. Zhao, A.A. Habib, Ligand-

independent EGFR signaling, Cancer Res. 75 (2015) 3436–3441.
[18] S.I. Ymer, S.A. Greenall, A. Cvrljevic, D.X. Cao, J.F. Donoghue, V.C. Epa, A.M. Scott, T.E. Adams, T.G. Johns, Glioma specific extracellular missense mutations in the frst cysteine rich region of epidermal growth factor receptor (EGFR) initiate ligand independent activation, Cancers (Basel) 3 (2011) 2032–2049.
[19] G. Kourouniotis, Y. Wang, S. Pennock, X. Chen, Z. Wang, Non-ligand-induced dimerization is sufficient to initiate the signalling and endocytosis of EGF receptor, Int. J. Mol. Sci. 17 (2016).
[20] H. Cheng, R.R. Langley, Q. Wu, W. Wu, J. Feng, R. Tsan, D. Fan, I.J. Fidler, Construction of a novel constitutively active chimeric EGFR to identify new targets for therapy, Neoplasia 7 (2005) 1065–1072.
[21] F. Petrelli, G. Tomasello, S. Barni, V. Lonati, R. Passalacqua, M. Ghidini, Clinical and pathological characterization of HER2 mutations in human breast cancer: a systematic review of the literature, Breast Cancer Res. Treat. 166 (2017) 339–349.
[22] J. Arribas, J. Baselga, K. Pedersen, J.L. Parra-Palau, p95HER2 and breast cancer, Cancer Res. 71 (2011) 1515–1519.
[23] I. Rius Ruiz, R. Vicario, B. Morancho, C.B. Morales, E.J. Arenas, S. Herter, A. Freimoser-Grundschober, J. Somandin, J. Sam, O. Ast, A.M. Barriocanal, A. Luque, M. Escorihuela, I. Varela, I. Cuartas, P. Nuciforo, R. Fasani, V. Peg, I. Rubio, J. Cortes, V. Serra, S. Escriva-de-Romani, J. Sperinde, A. Chenna, W. Huang, J. Winslow, J. Albanell, J. Seoane, M. Scaltriti, J. Baselga, J. Tabernero, P. Umana, M. Bacac, C. Saura, C. Klein, J. Arribas, p95HER2-T cell bispecific antibody for breast cancer treatment, Sci. Transl. Med. 10 (2018).
[24] D. Tural, E. Akar, H. Mutlu, S. Kilickap, P95 HER2 fragments and breast cancer outcome, Expert Rev. Anticancer Ther. 14 (2014) 1089–1096.
[25] C.M. Connell, G.J. Doherty, Activating HER2 mutations as emerging targets in multiple solid cancers, ESMO Open 2 (2017) e000279.
[26] J. Chmielecki, J.S. Ross, K. Wang, G.M. Frampton, G.A. Palmer, S.M. Ali, N. Palma, D. Morosini, V.A. Miller, R. Yelensky, D. Lipson, P.J. Stephens, Oncogenic alterations in ERBB2/HER2 represent potential therapeutic targets across tumors from diverse anatomic sites of origin, Oncologist 20 (2015) 7–12.
[27] S.E. Wang, A. Narasanna, M. Perez-Torres, B. Xiang, F.Y. Wu, S. Yang, G. Carpenter, A.F. Gazdar, S.K. Muthuswamy, C.L. Arteaga, HER2 kinase domain mutation results in constitutive phosphorylation and activation of HER2 and EGFR and resistance to EGFR tyrosine kinase inhibitors, Cancer Cell 10 (2006) 25–38.
[28] A.B. Hanker, M.R. Brewer, J.H. Sheehan, J.P. Koch, G.R. Sliwoski, R. Nagy, R. Lanman, M.F. Berger, D.M. Hyman, D.B. Solit, J. He, V. Miller, R.E. Cutler Jr., A.S. Lalani, D. Cross, C.M. Lovly, J. Meiler, C.L. Arteaga, An acquired HER2(T798I) gatekeeper mutation induces resistance to neratinib in a patient with HER2 mutant-driven breast cancer, Cancer Discov. 7 (2017) 575–585.
[29] K.A. Kellar, M.V. Lorenzi, C.P. Ho, D. You, M.L. Wen, R.P. Ryseck, S. Oppenheimer, B.E. Fink, G.D. Vite, B.R. Rowley, C. Yu, D.K. Bol, F.Y. Lee, T.W. Wong, Constitutively active receptor tyrosine kinases as oncogenes in preclinical models for cancer therapeutics, Mol. Cancer Ther. 5 (2006) 1571–1576.
[30] H. Lyu, A. Han, E. Polsdofer, S. Liu, B. Liu, Understanding the biology of HER3 receptor as a therapeutic target in human cancer, Acta Pharm. Sin. B 8 (2018) 503–510.
[31] E.G. Jeong, Y.H. Soung, J.W. Lee, S.H. Lee, S.W. Nam, J.Y. Lee, N.J. Yoo, S.H. Lee, ERBB3 kinase domain mutations are rare in lung, breast and colon carcinomas, Int. J. Cancer 119 (2006) 2986–2987.
[32] B.S. Jaiswal, N.M. Kljavin, E.W. Stawiski, E. Chan, C. Parikh, S. Durinck, S. Chaudhuri, K. Pujara, J. Guillory, K.A. Edgar, V. Janakiraman, R.P. Scholz, K.K. Bowman, M. Lorenzo, H. Li, J. Wu, W. Yuan, B.A. Peters, Z. Kan, J. Stinson, M. Mak, Z. Modrusan, C. Eigenbrot, R. Firestein, H.M. Stern, K. Rajalingam, G. Schaefer, M.A. Merchant, M.X. Sliwkowski, F.J. de Sauvage, S. Seshagiri, Oncogenic ERBB3 mutations in human cancers, Cancer Cell 23 (2013) 603–617.
[33] P. Littlefield, L. Liu, V. Mysore, Y. Shan, D.E. Shaw, N. Jura, Structural analysis of the EGFR/HER3 heterodimer reveals the molecular basis for activating HER3 mutations, Sci. Signal. 7 (2014) ra114.
[34] I. Umelo, A. Noeparast, G. Chen, M. Renard, C. Geers, J. Vansteenkiste, P. Giron, O. De Wever, E. Teugels, J. De Greve, Identification of a novel HER3 activating mutation homologous to EGFR-L858R in lung cancer, Oncotarget 7 (2016) 3068–3083.
[35] R. Mishra, S. Alanazi, L. Yuan, T. Solomon, T.M. Thaker, N. Jura, J.T. Garrett, Activating HER3 mutations in breast cancer, Oncotarget 9 (2018) 27773–27788.
[36] D.M. Hyman, S.A. Piha-Paul, H. Won, J. Rodon, C. Saura, G.I. Shapiro, D. Juric, D.I. Quinn, V. Moreno, B. Doger, I.A. Mayer, V. Boni, E. Calvo, S. Loi, A.C. Lockhart, J.P. Erinjeri, M. Scaltriti, G.A. Ulaner, J. Patel, J. Tang, H. Beer, S.D. Selcuklu, A.J. Hanrahan, N. Bouvier, M. Melcer, R. Murali, A.M. Schram, L.M. Smyth, K. Jhaveri, B.T. Li, A. Drilon, J.J. Harding, G. Iyer, B.S. Taylor, M.F. Berger, R.E. Cutler Jr., F. Xu, A. Butturini, L.D. Eli, G. Mann, C. Farrell, A.S. Lalani, R.P. Bryce, C.L. Arteaga, F. Meric-Bernstam, J. Baselga, D.B. Solit, HER kinase inhibition in patients with HER2- and HER3-mutant cancers, Nature 554 (2018) 189–194.
[37] Z. Wang, ErbB receptors and cancer, Methods Mol. Biol. 1652 (2017) 3–35.
[38] C. Lau, K.J. Killian, Y. Samuels, U. Rudloff, ERBB4 mutation analysis: emerging molecular target for melanoma treatment, Methods Mol. Biol. 1102 (2014) 461–480.
[39] T.D. Prickett, N.S. Agrawal, X. Wei, K.E. Yates, J.C. Lin, J.R. Wunderlich, J.C. Cronin, P. Cruz, S.A. Rosenberg, Y. Samuels, Analysis of the tyrosine kinome in melanoma reveals recurrent mutations in ERBB4, Nat. Genet. 41 (2009) 1127–1132.
[40] Y. Nakamura, Y. Togashi, H. Nakahara, S. Tomida, E. Banno, M. Terashima, H. Hayashi, M.A. de Velasco, K. Sakai, Y. Fujita, T. Okegawa, K. Nutahara, S. Hamada, K. Nishio, Afatinib against esophageal or head-and-neck squamous cell carcinoma: significance of activating oncogenic HER4 mutations in HNSCC, Mol. Cancer Ther. 15 (2016) 1988–1997.
[41] S.E. Telesco, R. Vadigepalli, R. Radhakrishnan, Molecular modeling of ErbB4/HER4 kinase in the context of the HER4 signaling network helps rationalize the effects of clinically identified HER4 somatic mutations on the cell phenotype, Biotechnol. J. 8 (2013) 1452–1464.
[42] R. Roskoski Jr., VEGF receptor protein-tyrosine kinases: structure and regulation, Biochem. Biophys. Res. Commun. 375 (2008) 287–291.
[43] G. Neufeld, O. Kessler, Y. Herzog, The interaction of Neuropilin-1 and Neuropilin-2 with tyrosine-kinase receptors for VEGF, Adv. Exp. Med. Biol. 515 (2002) 81–90.
[44] C.R. Antonescu, A. Yoshida, T. Guo, N.E. Chang, L. Zhang, N.P. Agaram, L.X. Qin, M.F. Brennan, S. Singer, R.G. Maki, KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors, Cancer Res. 69 (2009) 7175–7179.
[45] M. Rotunno, M.L. McMaster, J. Boland, S. Bass, X. Zhang, L. Burdett, B. Hicks, S. Ravichandran, B.T. Luke, M. Yeager, L. Fontaine, P.L. Hyland, A.M. Goldstein, N.D.C.S.W. Group, N.D.C.G.R. Laboratory, S.J. Chanock, N.E. Caporaso, M.A. Tucker, L.R. Goldin, Whole exome sequencing in families at high risk for Hodgkin lymphoma: identification of a predisposing mutation in the KDR gene, Haematologica 101 (2016) 853–860.
[46] M. Jinnin, D. Medici, L. Park, N. Limaye, Y. Liu, E. Boscolo, J. Bischoff, M. Vikkula, E. Boye, B.R. Olsen, Suppressed NFAT-dependent VEGFR1 expression and constitutive VEGFR2 signaling in infantile hemangioma, Nat. Med. 14 (2008) 1236–12346.
[47] M. Nakao, S. Yokota, T. Iwai, H. Kaneko, S. Horiike, K. Kashima, Y. Sonoda, T. Fujimoto, S. Misawa, Internal tandem duplication of the flt3 gene found in acute myeloid leukemia, Leukemia 10 (1996) 1911–1918.
[48] H. Kiyoi, M. Towatari, S. Yokota, M. Hamaguchi, R. Ohno, H. Saito, T. Naoe, Internal tandem duplication of the FLT3 gene is a novel modality of elongation mutation which causes constitutive activation of the product, Leukemia 12 (1998) 1333–1337.
[49] Y. Yamamoto, H. Kiyoi, Y. Nakano, R. Suzuki, Y. Kodera, S. Miyawaki, N. Asou, K. Kuriyama, F. Yagasaki, C. Shimazaki, H. Akiyama, K. Saito, M. Nishimura, T. Motoji, K. Shinagawa, A. Takeshita, H. Saito, R. Ueda, R. Ohno, T. Naoe, Activating mutation of D835 within the activation loop of FLT3 in human hematologic malignancies, Blood 97 (2001) 2434–2439.
[50] S. Manni, K.S. Mineev, D. Usmanova, E.N. Lyukmanova, M.A. Shulepko, M.P. Kirpichnikov, J. Winter, M. Matkovic, X. Deupi, A.S. Arseniev, K. Ballmer-Hofer, Structural and functional characterization of alternative transmembrane domain conformations in VEGF receptor 2 activation, Structure 22 (2014) 1077–1089.
[51] D.D. Dosch, K. Ballmer-Hofer, Transmembrane domain-mediated orientation of receptor monomers in active VEGFR-2 dimers, FASEB J. 24 (2010) 32–38.
[52] J.B. Demoulin, A. Essaghir, PDGF receptor signaling networks in normal and cancer cells, Cytokine Growth Factor Rev. 25 (2014) 273–283.
[53] S. Hirota, A. Ohashi, T. Nishida, K. Isozaki, K. Kinoshita, Y. Shinomura, Y. Kitamura, Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors, Gastroenterology 125 (2003) 660–667.
[54] M.C. Heinrich, C.L. Corless, A. Duensing, L. McGreevey, C.J. Chen, N. Joseph, S. Singer, D.J. Griffith, A. Haley, A. Town, G.D. Demetri, C.D. Fletcher, J.A. Fletcher, PDGFRA activating mutations in gastrointestinal stromal tumors, Science 299 (2003) 708–710.
[55] C. Bahlawane, R. Eulenfeld, M.Y. Wiesinger, J. Wang, A. Muller, A. Girod, P.V. Nazarov, K. Felsch, L. Vallar, T. Sauter, V.P. Satagopam, S. Haan, Constitutive activation of oncogenic PDGFRalpha-mutant proteins occurring in GIST patients induces receptor mislocalisation and alters PDGFRalpha signalling characteristics, Cell Commun. Signal 13 (2015) 1–21.
[56] R.G. Verhaak, K.A. Hoadley, E. Purdom, V. Wang, Y. Qi, M.D. Wilkerson, C.R. Miller, L. Ding, T. Golub, J.P. Mesirov, G. Alexe, M. Lawrence, M. O'Kelly, P. Tamayo, B.A. Weir, S. Gabriel, W. Winckler, S. Gupta, L. Jakkula, H.S. Feiler, J.G. Hodgson, C.D. James, J.N. Sarkaria, C. Brennan, A. Kahn, P.T. Spellman, R.K. Wilson, T.P. Speed, J.W. Gray, M. Meyerson, G. Getz, C.M. Perou, D.N. Hayes, N. Cancer Genome Atlas Research, Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1, Cancer Cell 17 (2010) 98–110.
[57] A. Alentorn, Y. Marie, C. Carpentier, B. Boisselier, M. Giry, M. Labussiere, K. Mokhtari, K. Hoang-Xuan, M. Sanson, J.Y. Delattre, A. Idbaih, Prevalence, clinico-pathological value, and co-occurrence of PDGFRA abnormalities in diffuse gliomas, Neuro. Oncol. 14 (2012) 1393–1403.
[58] A.I. Velghe, S. Van Cauwenberghe, A.A. Polyansky, D. Chand, C.P. Montano-Almendras, S. Charni, B. Hallberg, A. Essaghir, J.B. Demoulin, PDGFRA alterations in cancer: characterization of a gain-of-function V536E transmembrane mutant as well as loss-of-function and passenger mutations, Oncogene 33 (2014) 2568–2576.
[59] M. Warmuth, S. Kim, X.J. Gu, G. Xia, F. Adrian, Ba/F3 cells and their use in kinase drug discovery, Curr. Opin. Oncol. 19 (2007) 55–60.
[60] L.E. Olson, P. Soriano, Increased PDGFRalpha activation disrupts connective tissue development and drives systemic fibrosis, Dev. Cell 16 (2009) 303–313.
[61] C.K.M. Ip, P.K.S. Ng, K.J. Jeong, S.H. Shao, Z. Ju, P.G. Leonard, X. Hua, C.P. Vellano, R. Woessner, N. Sahni, K.L. Scott, G.B. Mills, Neomorphic PDGFRA extracellular domain driver mutations are resistant to PDGFRA targeted therapies, Nat. Commun. 9 (2018) 4583.
[62] D. Pond, F.A. Arts, N.J. Mendelsohn, J.B. Demoulin, G. Scharer, Y. Messinger, A patient with germ-line gain-of-function PDGFRB p.N666H mutation and marked clinical response to imatinib, Genet. Med. 20 (2018) 142–150.
[63] M. Carroll, M.H. Tomasson, G.F. Barker, T.R. Golub, D.G. Gilliland, The TEL/platelet-derived growth factor beta receptor (PDGF beta R) fusion in chronic

myelomonocytic leukemia is a transforming protein that self-associates and activates PDGF beta R kinase-dependent signaling pathways, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 14845–14850.
[64] F. Toffalini, C. Hellberg, J.B. Demoulin, Critical role of the platelet-derived growth factor receptor (PDGFR) beta transmembrane domain in the TEL-PDGFRbeta cytosolic oncoprotein, J. Biol. Chem. 285 (2010) 12268–12278.
[65] J.F. Apperley, M. Gardembas, J.V. Melo, R. Russell-Jones, B.J. Bain, E.J. Baxter, A. Chase, J.M. Chessells, M. Colombat, C.E. Dearden, S. Dimitrijevic, F.X. Mahon, D. Marin, Z. Nikolova, E. Olavarria, S. Silberman, B. Schultheis, N.C. Cross, J.M. Goldman, Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta, N. Engl. J. Med. 347 (2002) 481–487.
[66] Y.H. Cheung, T. Gayden, P.M. Campeau, C.A. LeDuc, D. Russo, V.H. Nguyen, J. Guo, M. Qi, Y. Guan, S. Albrecht, B. Moroz, K.W. Eldin, J.T. Lu, J. Schwartzentruber, D. Malkin, A.M. Berghuis, S. Emil, R.A. Gibbs, D.L. Burk, M. Vanstone, B.H. Lee, D. Orchard, K.M. Boycott, W.K. Chung, N. Jabado, A recurrent PDGFRB mutation causes familial infantile myofibromatosis, Am. J. Hum. Genet. 92 (2013) 996–1000.
[67] F.A. Arts, D. Chand, C. Pecquet, A.I. Velghe, S. Constantinescu, B. Hallberg, J.B. Demoulin, PDGFRB mutants found in patients with familial infantile myofibromatosis or overgrowth syndrome are oncogenic and sensitive to imatinib, Oncogene 35 (2016) 3239–3248.
[68] J.J. Johnston, M.Y. Sanchez-Contreras, K.M. Keppler-Noreuil, J. Sapp, M. Crenshaw, N.A. Finch, V. Cormier-Daire, R. Rademakers, V.P. Sybert, L.G. Biesecker, A point mutation in PDGFRB causes autosomal-dominant Penttinen syndrome, Am. J. Hum. Genet. 97 (2015) 465–474.
[69] P.M. Irusta, D. DiMaio, A single amino acid substitution in a WW-like domain of diverse members of the PDGF receptor subfamily of tyrosine kinases causes constitutive receptor activation, EMBO J. 17 (1998) 6912–6923.
[70] C.A. Bell, J.A. Tynan, K.C. Hart, A.N. Meyer, S.C. Robertson, D.J. Donoghue, Rotational coupling of the transmembrane and kinase domains of the Neu receptor tyrosine kinase, Mol. Biol. Cell 11 (2000) 3589–3599.
[71] D.M. Schwartz, M. Bonelli, M. Gadina, J.J. O'Shea, Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases, Nat. Rev. Rheumatol. 12 (2016) 25–36.
[72] C. Liongue, R. Sertori, A.C. Ward, Evolution of cytokine receptor signaling, J. Immunol. 197 (2016) 11–18.
[73] X. Wang, P. Lupardus, S.L. Laporte, K.C. Garcia, Structural biology of shared cytokine receptors, Annu. Rev. Immunol. 27 (2009) 29–60.
[74] J.B. Spangler, I. Moraga, J.L. Mendoza, K.C. Garcia, Insights into cytokine-receptor interactions from cytokine engineering, Annu. Rev. Immunol. 33 (2015) 139–167.
[75] S. Rose-John, J. Scheller, F. Schaper, Family reunion"–A structured view on the composition of the receptor complexes of interleukin-6-type and interleukin-12-type cytokines, Cytokine Growth Factor Rev. 26 (2015) 471–474.
[76] S.A. Jones, B.J. Jenkins, Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer, Nat. Rev. Immunol. 18 (2018) 773–789.
[77] C. Drucker, J. Gewiese, S. Malchow, J. Scheller, S. Rose-John, Impact of interleukin-6 classic- and trans-signaling on liver damage and regeneration, J. Autoimmun. 34 (2010) 29–37.
[78] S. Rebouissou, M. Amessou, G. Couchy, K. Poussin, S. Imbeaud, C. Pilati, T. Izard, C. Balabaud, P. Bioulac-Sage, J. Zucman-Rossi, Frequent in-frame somatic deletions activate gp130 in inflammatory hepatocellular tumours, Nature 457 (2009) 200–204.
[79] K. Poussin, C. Pilati, G. Couchy, J. Calderaro, P. Bioulac-Sage, Y. Bacq, V. Paradis, E. Leteurtre, N. Sturm, J. Ramos, C. Guettier, A. Bardier-Dupas, A. Boulai, D. Wendum, J. Selves, T. Izard, J.C. Nault, J. Zucman-Rossi, Biochemical and functional analyses of gp130 mutants unveil JAK1 as a novel therapeutic target in human inflammatory hepatocellular adenoma, Oncoimmunology 2 (2013) e27090.
[80] C. Pilati, J. Zucman-Rossi, Mutations leading to constitutive active gp130/JAK1/STAT3 pathway, Cytokine Growth Factor Rev. 26 (2015) 499–506.
[81] J. Bravo, D. Staunton, J.K. Heath, E.Y. Jones, Crystal structure of a cytokine-binding region of gp130, EMBO J. 17 (1998) 1665–1674.
[82] A. Schutt, M. Zacharias, N. Schneider, S. Horn, J. Grotzinger, S. Rose-John, D. Schmidt-Arras, gp130 activation is regulated by D2-D3 interdomain connectivity, Biochem. J. 450 (2013) 487–496.
[83] J. Sommer, T. Effenberger, E. Volpi, G.H. Waetzig, M. Bernhardt, J. Suthaus, C. Garbers, S. Rose-John, D.M. Floss, J. Scheller, Constitutively active mutant gp130 receptor protein from inflammatory hepatocellular adenoma is inhibited by an anti-gp130 antibody that specifically neutralizes interleukin 11 signaling, J. Biol. Chem. 287 (2012) 13743–13751.
[84] N. Rinis, A. Kuster, H. Schmitz-Van de Leur, A. Mohr, G. Muller-Newen, Intracellular signaling prevents effective blockade of oncogenic gp130 mutants by neutralizing antibodies, Cell Commun. Signal 12 (2014) 14.
[85] D. Schmidt-Arras, M. Muller, M. Stevanovic, S. Horn, A. Schutt, J. Bergmann, R. Wilkens, A. Lickert, S. Rose-John, Oncogenic deletion mutants of gp130 signal from intracellular compartments, J. Cell. Sci. 127 (2014) 341–353.
[86] K. Taniguchi, L.W. Wu, S.I. Grivennikov, P.R. de Jong, I. Lian, F.X. Yu, K. Wang, S.B. Ho, B.S. Boland, J.T. Chang, W.J. Sandborn, G. Hardiman, E. Raz, Y. Maehara, A. Yoshimura, J. Zucman-Rossi, K.L. Guan, M. Karin, A gp130-Src-YAP module links inflammation to epithelial regeneration, Nature 519 (2015) 57–62.
[87] B. Groner, V. von Manstein, Jak Stat signaling and cancer: opportunities, benefits and side effects of targeted inhibition, Mol. Cell. Endocrinol. 451 (2017) 1–14.
[88] Z.J. Gu, J. Wijdenes, X.G. Zhang, M.M. Hallet, C. Clement, B. Klein, Anti-gp130 transducer monoclonal antibodies specifically inhibiting ciliary neurotrophic factor, interleukin-6, interleukin-11, leukemia inhibitory factor or oncostatin M, J. Immunol. Methods 190 (1996) 21–27.
[89] N.C. Tebbutt, A.S. Giraud, M. Inglese, B. Jenkins, P. Waring, F.J. Clay, S. Malki, B.M. Alderman, D. Grail, F. Hollande, J.K. Heath, M. Ernst, Reciprocal regulation of gastrointestinal homeostasis by SHP2 and STAT-mediated trefoil gene activation in gp130 mutant mice, Nat. Med. 8 (2002) 1089–1097.
[90] B.J. Jenkins, D. Grail, T. Nheu, M. Najdovska, B. Wang, P. Waring, M. Inglese, R.M. McLoughlin, S.A. Jones, N. Topley, H. Baumann, L.M. Judd, A.S. Giraud, A. Boussioutas, H.J. Zhu, M. Ernst, Hyperactivation of Stat3 in gp130 mutant mice promotes gastric hyperproliferation and desensitizes TGF-beta signaling, Nat. Med. 11 (2005) 845–852.
[91] C. Stuhlmann-Laeisz, S. Lang, A. Chalaris, P. Krzysztof, S. Enge, J. Eichler, U. Klingmuller, M. Samuel, M. Ernst, S. Rose-John, J. Scheller, Forced dimerization of gp130 leads to constitutive STAT3 activation, cytokine-independent growth, and blockade of differentiation of embryonic stem cells, Mol. Biol. Cell 17 (2006) 2986–2995.
[92] M. Fischer, J. Goldschmitt, C. Peschel, J.P. Brakenhoff, K.J. Kallen, A. Wollmer, J. Grotzinger, S. Rose-John, I. A bioactive designer cytokine for human hematopoietic progenitor cell expansion, Nat. Biotechnol. 15 (1997) 142–145.
[93] D. Heim, I. Gil-Ibanez, J. Herden, A.C. Parplys, K. Borgmann, D. Schmidt-Arras, A.W. Lohse, S. Rose-John, H. Wege, Constitutive gp130 activation rapidly accelerates the transformation of human hepatocytes via an impaired oxidative stress response, Oncotarget 7 (2016) 55639–55648.
[94] L. Lamertz, D.M. Floss, J. Scheller, Combined deletion of the fibronectin-type III domains and the stalk region results in ligand-independent, constitutive activation of the Interleukin 6 signal-transducing receptor gp130, Cytokine 110 (2018) 428–434.
[95] C. Garbers, J. Scheller, Interleukin-6 and interleukin-11: same same but different, Biol. Chem. 394 (2013) 1145–1161.
[96] L. Lamertz, F. Rummel, R. Polz, P. Baran, S. Hansen, G.H. Waetzig, J.M. Moll, D.M. Floss, J. Scheller, Soluble gp130 prevents interleukin-6 and interleukin-11 cluster signaling but not intracellular autocrine responses, Sci. Signal. 11 (2018).
[97] H. Dams-Kozlowska, K. Gryska, E. Kwiatkowska-Borowczyk, D. Izycki, S. Rose-John, A. Mackiewicz, A designer hyper interleukin 11 (H11) is a biologically active cytokine, BMC Biotechnol. 12 (2012) 8.
[98] J. Suthaus, A. Tillmann, I. Lorenzen, E. Bulanova, S. Rose-John, J. Scheller, Forced homo- and heterodimerization of all gp130-type receptor complexes leads to constitutive ligand-independent signaling and cytokine-independent growth, Mol. Biol. Cell 21 (2010) 2797–2807.
[99] I. Lorenzen, A.J. Dingley, Y. Jacques, J. Grotzinger, The structure of the interleukin-15 alpha receptor and its implications for ligand binding, J. Biol. Chem. 281 (2006) 6642–6647.
[100] N.A. Hanick, M. Rickert, L. Varani, A.J. Bankovich, J.R. Cochran, D.M. Kim, C.D. Surh, K.C. Garcia, Elucidation of the interleukin-15 binding site on its alpha receptor by NMR, Biochemistry 46 (2007) 9453–9461.
[101] H. Hasegawa, I. Mizoguchi, Y. Chiba, M. Ohashi, M. Xu, T. Yoshimoto, Expanding diversity in molecular structures and functions of the IL-6/IL-12 heterodimeric cytokine family, Front. Immunol. 7 (2016) 479.
[102] D.M. Floss, J. Schroder, M. Franke, J. Scheller, Insights into IL-23 biology: from structure to function, Cytokine Growth Factor Rev. 26 (2015) 569–578.
[103] X. Wang, Y. Wei, H. Xiao, X. Liu, Y. Zhang, G. Han, G. Chen, C. Hou, N. Ma, B. Shen, Y. Li, C.E. Egwuagu, R. Wang, A novel IL-23p19/Ebi3 (IL-39) cytokine mediates inflammation in Lupus-like mice, Eur. J. Immunol. 46 (2016) 1343–1350.
[104] D.M. Floss, M. Schonberg, M. Franke, F.C. Horstmeier, E. Engelowski, A. Schneider, E.M. Rosenfeldt, J. Scheller, IL-6/IL-12 cytokine receptor shuffling of extra- and intracellular domains reveals canonical STAT activation via synthetic IL-35 and IL-39 signaling, Sci. Rep. 7 (2017) 15172.
[105] L.W. Collison, G.M. Delgoffe, C.S. Guy, K.M. Vignali, V. Chaturvedi, D. Fairweather, A.R. Satoskar, K.C. Garcia, C.A. Hunter, C.G. Drake, P.J. Murray, D.A. Vignali, The composition and signaling of the IL-35 receptor are unconventional, Nat. Immunol. 13 (2012) 290–299.
[106] J. Yan, M.J. Smyth, M.W.L. Teng, Interleukin (IL)-12 and IL-23 and their conflicting roles in cancer, Cold Spring Harb, Perspect. Biol. Med. 10 (2018).
[107] D.M. Floss, S. Mrotzek, T. Klocker, J. Schroder, J. Grotzinger, S. Rose-John, J. Scheller, Identification of canonical tyrosine-dependent and non-canonical tyrosine-independent STAT3 activation sites in the intracellular domain of the interleukin 23 receptor, J. Biol. Chem. 288 (2013) 19386–19400.
[108] D.M. Floss, T. Klocker, J. Schroder, L. Lamertz, S. Mrotzek, B. Strobl, H. Hermanns, J. Scheller, Defining the functional binding sites of interleukin 12 receptor beta1 and interleukin 23 receptor to Janus kinases, Mol. Biol. Cell 27 (2016) 2301–2316.
[109] D.A. Vignali, V.K. Kuchroo, IL-12 family cytokines: immunological playmakers, Nat. Immunol. 13 (2012) 722–728.
[110] J. Schroder, J.M. Moll, P. Baran, J. Grotzinger, J. Scheller, D.M. Floss, Non-canonical interleukin 23 receptor complex assembly: p40 protein recruits interleukin 12 receptor beta1 via site II and induces p19/interleukin 23 receptor interaction via site III, J. Biol. Chem. 290 (2015) 359–370.
[111] Y. Bloch, L. Bouchareychas, R. Merceron, K. Skladanowska, L. Van den Bossche, S. Detry, S. Govindarajan, D. Elewaut, F. Haerynck, M. Dullaers, I.E. Adamopoulos, S.N. Savvides, Structural activation of pro-inflammatory human cytokine IL-23 by cognate IL-23 receptor enables recruitment of the shared receptor IL-12Rbeta1, Immunity 48 (2018) 45–58 e6.
[112] T.M. Hummel, T. Ackfeld, M. Schonberg, G. Ciupka, F. Schulz, A. Oberdoerster, J. Grotzinger, J. Scheller, D.M. Floss, Synthetic deletion of the Interleukin 23 receptor (IL-23R) stalk region led to autonomous IL-23R homodimerization and activation, Mol. Cell. Biol. 37 (2017).
[113] C. Parham, M. Chirica, J. Timans, E. Vaisberg, M. Travis, J. Cheung, S. Pflanz,

R. Zhang, K.P. Singh, F. Vega, W. To, J. Wagner, A.M. O'Farrell, T. McClanahan, S. Zurawski, C. Hannum, D. Gorman, D.M. Rennick, R.A. Kastelein, R. de Waal Malefyt, K.W. Moore, A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R, J. Immunol. 168 (2002) 5699–5708.
[114] A.T. Waickman, J.Y. Park, J.H. Park, The common gamma-chain cytokine receptor: tricks-and-treats for T cells, Cell. Mol. Life Sci. 73 (2016) 253–269.
[115] Y. Rochman, R. Spolski, W.J. Leonard, New insights into the regulation of T cells by gamma(c) family cytokines, Nat. Rev. Immunol. 9 (2009) 480–490.
[116] S.R. Pulliam, R.V. Uzhachenko, S.E. Adunyah, A. Shanker, Common gamma chain cytokines in combinatorial immune strategies against cancer, Immunol. Lett. 169 (2016) 61–72.
[117] M.L. Oliveira, P. Akkapeddi, D. Ribeiro, A. Melao, J.T. Barata, IL-7R-mediated signaling in T-cell acute lymphoblastic leukemia: an update, Adv. Biol. Regul. 71 (2019) 88–96.
[118] R.I. Mazzucchelli, A. Riva, S.K. Durum, The human IL-7 receptor gene: deletions, polymorphisms and mutations, Semin. Immunol. 24 (2012) 225–230.
[119] C. Shochat, N. Tal, O.R. Bandapalli, C. Palmi, I. Ganmore, G. te Kronnie, G. Cario, G. Cazzaniga, A.E. Kulozik, M. Stanulla, M. Schrappe, A. Biondi, G. Basso, D. Bercovich, M.U. Muckenthaler, S. Izraeli, Gain-of-function mutations in interleukin-7 receptor-alpha (IL7R) in childhood acute lymphoblastic leukemias, J. Exp. Med. 208 (2011) 901–908.
[120] P.P. Zenatti, D. Ribeiro, W. Li, L. Zuurbier, M.C. Silva, M. Paganin, J. Tritapoe, J.A. Hixon, A.B. Silveira, B.A. Cardoso, L.M. Sarmento, N. Correia, M.L. Toribio, J. Kobarg, M. Horstmann, R. Pieters, S.R. Brandalise, A.A. Ferrando, J.P. Meijerink, S.K. Durum, J.A. Yunes, J.T. Barata, Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia, Nat. Genet. 43 (2011) 932–939.
[121] J. Zhang, L. Ding, L. Holmfeldt, G. Wu, S.L. Heatley, D. Payne-Turner, J. Easton, X. Chen, J. Wang, M. Rusch, C. Lu, S.C. Chen, L. Wei, J.R. Collins-Underwood, J. Ma, K.G. Roberts, S.B. Pounds, A. Ulyanov, J. Becksfort, P. Gupta, R. Huether, R.W. Kriwacki, M. Parker, D.J. McGoldrick, D. Zhao, D. Alford, S. Espy, K.C. Bobba, G. Song, D. Pei, C. Cheng, S. Roberts, M.I. Barbato, D. Campana, E. Coustan-Smith, S.A. Shurtleff, S.C. Raimondi, M. Kleppe, J. Cools, K.A. Shimano, M.L. Hermiston, S. Doulatov, K. Eppert, E. Laurenti, F. Notta, J.E. Dick, G. Basso, S.P. Hunger, M.L. Loh, M. Devidas, B. Wood, S. Winter, K.P. Dunsmore, R.S. Fulton, L.L. Fulton, X. Hong, C.C. Harris, D.J. Dooling, K. Ochoa, K.J. Johnson, J.C. Obenauer, W.E. Evans, C.H. Pui, C.W. Naeve, T.J. Ley, E.R. Mardis, R.K. Wilson, J.R. Downing, C.G. Mullighan, The genetic basis of early T-cell precursor acute lymphoblastic leukaemia, Nature 481 (2012) 157–163.
[122] C. Shochat, N. Tal, V. Gryshkova, Y. Birger, O.R. Bandapalli, G. Cazzaniga, N. Gershman, A.E. Kulozik, A. Biondi, M.R. Mansour, J.C. Twizere, M.U. Muckenthaler, N. Ben-Tal, S.N. Constantinescu, D. Bercovich, S. Izraeli, Novel activating mutations lacking cysteine in type I cytokine receptors in acute lymphoblastic leukemia, Blood 124 (2014) 106–110.
[123] K. Cante-Barrett, J.A. Spijkers-Hagelstein, J.G. Buijs-Gladdines, J.C. Uitdehaag, W.K. Smits, J. van der Zwet, R.C. Buijsman, G.J. Zaman, R. Pieters, J.P. Meijerink, MEK and PI3K-AKT inhibitors synergistically block activated IL7 receptor signaling in T-cell acute lymphoblastic leukemia, Leukemia 30 (2016) 1832–1843.
[124] E. Senkevitch, W. Li, J.A. Hixon, C. Andrews, S.D. Cramer, G.T. Pauly, T. Back, K. Czarra, S.K. Durum, Inhibiting Janus Kinase 1 and BCL-2 to treat T cell acute lymphoblastic leukemia with IL7-Ralpha mutations, Oncotarget 9 (2018) 22605–22617.
[125] A. Yoda, Y. Yoda, S. Chiaretti, M. Bar-Natan, K. Mani, S.J. Rodig, N. West, Y. Xiao, J.R. Brown, C. Mitsiades, M. Sattler, J.L. Kutok, D.J. DeAngelo, M. Wadleigh, A. Piciocchi, P. Dal Cin, J.E. Bradner, J.D. Griffin, K.C. Anderson, R.M. Stone, J. Ritz, R. Foa, J.C. Aster, D.A. Frank, D.M. Weinstock, Functional screening identifies CRLF2 in precursor B-cell acute lymphoblastic leukemia, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 252–257.
[126] D. van Bodegom, J. Zhong, N. Kopp, C. Dutta, M.S. Kim, L. Bird, O. Weigert, J. Tyner, A. Pandey, A. Yoda, D.M. Weinstock, Differences in signaling through the B-cell leukemia oncoprotein CRLF2 in response to TSLP and through mutant JAK2, Blood 120 (2012) 2853–2863.
[127] E. Chapiro, L. Russell, E. Lainey, S. Kaltenbach, C. Ragu, V. Della-Valle, K. Hanssens, E.A. Macintyre, I. Radford-Weiss, E. Delabesse, H. Cave, T. Mercher, C.J. Harrison, F. Nguyen-Khac, P. Dubreuil, O.A. Bernard, Activating mutation in the TSLPR gene in B-cell precursor lymphoblastic leukemia, Leukemia 24 (2010) 642–645.
[128] T. Shum, B. Omer, H. Tashiro, R.L. Kruse, D.L. Wagner, K. Parikh, Z. Yi, T. Sauer, D. Liu, R. Parihar, P. Castillo, H. Liu, M.K. Brenner, L.S. Metelitsa, S. Gottschalk, C.M. Rooney, Constitutive signaling from an engineered IL7 receptor promotes durable tumor elimination by tumor-redirected T cells, Cancer Discov. 7 (2017) 1238–1247.
[129] S.E. Broughton, T.L. Nero, U. Dhagat, W.L. Kan, T.R. Hercus, D. Tvorogov, A.F. Lopez, M.W. Parker, The betac receptor family - Structural insights and their functional implications, Cytokine 74 (2015) 247–258.
[130] K. Watanabe-Smith, C. Tognon, J.W. Tyner, J.P. Meijerink, B.J. Druker, A. Agarwal, Discovery and functional characterization of a germline, CSF2RB-activating mutation in leukemia, Leukemia 30 (2016) 1950–1953.
[131] R.J. D'Andrea, T.J. Gonda, A model for assembly and activation of the GM-CSF, IL-3 and IL-5 receptors: insights from activated mutants of the common beta subunit, Exp. Hematol. 28 (2000) 231–243.
[132] M.P. McCormack, T.J. Gonda, Expression of activated mutants of the human interleukin-3/interleukin-5/granulocyte-macrophage colony-stimulating factor receptor common beta subunit in primary hematopoietic cells induces factor-independent proliferation and differentiation, Blood 90 (1997) 1471–1481.
[133] R.J. D'Andrea, D. Harrison-Findik, C.M. Butcher, J. Finnie, P. Blumbergs, P. Bartley, M. McCormack, K. Jones, R. Rowland, T.J. Gonda, M.A. Vadas, Dysregulated hematopoiesis and a progressive neurological disorder induced by expression of an activated form of the human common beta chain in transgenic mice, J. Clin. Invest. 102 (1998) 1951–1960.
[134] R. D'Andrea, J. Rayner, P. Moretti, A. Lopez, G.J. Goodall, T.J. Gonda, M. Vadas, A mutation of the common receptor subunit for interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor, and IL-5 that leads to ligand independence and tumorigenicity, Blood 83 (1994) 2802–2808.
[135] B.J. Jenkins, R. D'Andrea, T.J. Gonda, Activating point mutations in the common beta subunit of the human GM-CSF, IL-3 and IL-5 receptors suggest the involvement of beta subunit dimerization and cell type-specific molecules in signalling, EMBO J. 14 (1995) 4276–4287.
[136] B.J. Jenkins, T.J. Blake, T.J. Gonda, Saturation mutagenesis of the beta subunit of the human granulocyte-macrophage colony-stimulating factor receptor shows clustering of constitutive mutations, activation of ERK MAP kinase and STAT pathways, and differential beta subunit tyrosine phosphorylation, Blood 92 (1998) 1989–2002.
[137] R.J. D'Andrea, S.C. Barry, P.A. Moretti, K. Jones, S. Ellis, M.A. Vadas, G.J. Goodall, Extracellular truncations of h beta c, the common signaling subunit for interleukin-3 (IL-3), granulocyte-macrophage colony-stimulating factor (GM-CSF), and IL-5, lead to ligand-independent activation, Blood 87 (1996) 2641–2648.
[138] B.J. Jenkins, F. Le, T.J. Gonda, A cell type-specific constitutive point mutant of the common beta-subunit of the human granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-3, and IL-5 receptors requires the GM-CSF receptor alpha-subunit for activation, J. Biol. Chem. 274 (1999) 8669–8677.
[139] T.J. Blake, B.J. Jenkins, R.J. D'Andrea, T.J. Gonda, Functional cross-talk between cytokine receptors revealed by activating mutations in the extracellular domain of the beta-subunit of the GM-CSF receptor, J. Leukoc. Biol. 72 (2002) 1246–1255.
[140] K.L. Jones, C.J. Bagley, C. Butcher, S.C. Barry, M.A. Vadas, R.J. D'Andrea, Peptide insertions in domain 4 of hbeta(c), the shared signalling receptor subunit for GM-CSF, IL3 and IL5, induce ligand-independent activation, Cytokine 14 (2001) 303–315.
[141] M. Wojcik, A. Krawczynska, H. Antushevich, A.P. Herman, Post-receptor inhibitors of the GHR-JAK2-STAT pathway in the growth hormone signal transduction, Int. J. Mol. Sci. 19 (2018).
[142] S. Lin, C. Li, C. Li, X. Zhang, Growth hormone receptor mutations related to individual dwarfism, Int. J. Mol. Sci. 19 (2018).
[143] M.J. Waters, The growth hormone receptor, growth horm, Growth Horm. IGF Res. 28 (2016) 6–10.
[144] J. Guevara-Aguirre, A.L. Rosenbloom, Obesity, diabetes and cancer: insight into the relationship from a cohort with growth hormone receptor deficiency, Diabetologia 58 (2015) 37–42.
[145] M.F. Rudd, E.L. Webb, A. Matakidou, G.S. Sellick, R.D. Williams, H. Bridle, T. Eisen, R.S. Houlston, G. Consortium, Variants in the GH-IGF axis confer susceptibility to lung cancer, Genome Res. 16 (2006) 693–701.
[146] G. Cao, H. Lu, J. Feng, J. Shu, D. Zheng, Y. Hou, Lung cancer risk associated with Thr495Pro polymorphism of GHR in Chinese population, Jpn. J. Clin. Oncol. 38 (2008) 308–316.
[147] Y. Chhabra, H.Y. Wong, L.F. Nikolajsen, H. Steinocher, A. Papadopulos, K.A. Tunny, F.A. Meunier, A.G. Smith, B.B. Kragelund, A.J. Brooks, M.J. Waters, A growth hormone receptor SNP promotes lung cancer by impairment of SOCS2-mediated degradation, Oncogene 37 (2018) 489–501.
[148] S.N. Behncken, N. Billestrup, R. Brown, J. Amstrup, B. Conway-Campbell, M.J. Waters, Growth hormone (GH)-independent dimerization of GH receptor by a leucine zipper results in constitutive activation, J. Biol. Chem. 275 (2000) 17000–17007.
[149] A.J. Brooks, W. Dai, M.L. O'Mara, D. Abankwa, Y. Chhabra, R.A. Pelekanos, O. Gardon, K.A. Tunny, K.M. Blucher, C.J. Morton, M.W. Parker, E. Sierecki, Y. Gambin, G.A. Gomez, K. Alexandrov, I.A. Wilson, M. Doxastakis, A.E. Mark, M.J. Waters, Mechanism of activation of protein kinase JAK2 by the growth hormone receptor, Science 344 (2014) 1249783.
[150] T. Nespital, L.M. van der Velden, A. Mensinga, E.D. van der Vaart, G.J. Strous, Fos-zippered GH receptor cytosolic tails act as Jak2 substrates and signal transducers, Mol. Endocrinol. 30 (2016) 290–301.
[151] C. Chen, R. Brinkworth, M.J. Waters, The role of receptor dimerization domain residues in growth hormone signaling, J. Biol. Chem. 272 (1997) 5133–5140.
[152] I. Plo, C. Bellanne-Chantelot, M. Mosca, S. Mazzi, C. Marty, W. Vainchenker, Genetic alterations of the thrombopoietin/MPL/JAK2 axis impacting megakaryopoiesis, Front. Endocrinol. (Lausanne) 8 (2017) 234.
[153] L.N. Varghese, J.P. Defour, C. Pecquet, S.N. Constantinescu, The thrombopoietin receptor: structural basis of traffic and activation by ligand, mutations, agonists, and mutated Calreticulin, Front. Endocrinol. (Lausanne) 8 (2017) 59.
[154] D.F. Sabath, K. Kaushansky, V.C. Broudy, Deletion of the extracellular membrane-distal cytokine receptor homology module of Mpl results in constitutive cell growth and loss of thrombopoietin binding, Blood 94 (1999) 365–367.
[155] M. Souyri, I. Vigon, J.F. Penciolelli, J.M. Heard, P. Tambourin, F. Wendling, A putative truncated cytokine receptor gene transduced by the myeloproliferative leukemia virus immortalizes hematopoietic progenitors, Cell 63 (1990) 1137–1147.
[156] J. Staerk, C. Lacout, T. Sato, S.O. Smith, W. Vainchenker, S.N. Constantinescu, An amphipathic motif at the transmembrane-cytoplasmic junction prevents autonomous activation of the thrombopoietin receptor, Blood 107 (2006) 1864–1871.
[157] J.P. Defour, M. Itaya, V. Gryshkova, I.C. Brett, C. Pecquet, T. Sato, S.O. Smith, S.N. Constantinescu, Tryptophan at the transmembrane-cytosolic junction modulates thrombopoietin receptor dimerization and activation, Proc. Natl. Acad. Sci.

U. S. A. 110 (2013) 2540–2555.
[158] J. Ding, H. Komatsu, S. Iida, H. Yano, S. Kusumoto, A. Inagaki, F. Mori, M. Ri, A. Ito, A. Wakita, T. Ishida, M. Nitta, R. Ueda, The Asn505 mutation of the c-MPL gene, which causes familial essential thrombocythemia, induces autonomous homodimerization of the c-Mpl protein due to strong amino acid polarity, Blood 114 (2009) 3325–3328.
[159] E. Leroy, J.P. Defour, T. Sato, S. Dass, V. Gryshkova, M.M. Shwe, J. Staerk, S.N. Constantinescu, S.O. Smith, His499 regulates dimerization and prevents oncogenic activation by asparagine mutations of the human thrombopoietin receptor, J. Biol. Chem. 291 (2016) 297429–297487.
[160] C. Stockklausner, A.C. Klotter, N. Dickemann, I.N. Kuhlee, C.M. Duffert, C. Kerber, N.H. Gehring, A.E. Kulozik, The thrombopoietin receptor P106L mutation functionally separates receptor signaling activity from thrombopoietin homeostasis, Blood 125 (2015) 1159–1169.
[161] S. Malinge, C. Ragu, V. Della-Valle, D. Pisani, S.N. Constantinescu, C. Perez, J.L. Villeval, D. Reinhardt, J. Landman-Parker, L. Michaux, N. Dastugue, A. Baruchel, W. Vainchenker, J.P. Bourquin, V. Penard-Lacronique, O.A. Bernard, Activating mutations in human acute megakaryoblastic leukemia, Blood 112 (2008) 4220–4426.
[162] M. Araki, N. Komatsu, Novel molecular mechanism of cellular transformation by a mutant molecular chaperone in myeloproliferative neoplasms, Cancer Sci. 108 (2017) 1907–1912.
[163] M. Araki, Y. Yang, M. Imai, Y. Mizukami, Y. Kihara, Y. Sunami, N. Masubuchi, Y. Edahiro, Y. Hironaka, S. Osaga, A. Ohsaka, N. Komatsu, Homomultimerization of mutant calreticulin is a prerequisite for MPL binding and activation, Leukemia 33 (2019) 122–131.
[164] J. Staerk, J.P. Defour, C. Pecquet, E. Leroy, H. Antoine-Poirel, I. Brett, M. Itaya, S.O. Smith, W. Vainchenker, S.N. Constantinescu, Orientation-specific signalling by thrombopoietin receptor dimers, EMBO J. 30 (2011) 4398–4413.
[165] Y. Royer, J. Staerk, M. Costuleanu, P.J. Courtoy, S.N. Constantinescu, Janus kinases affect thrombopoietin receptor cell surface localization and stability, J. Biol. Chem. 280 (2005) 27251–27261.
[166] J.A. Wells, A.A. Kossiakoff, Cell biology. New tricks for an old dimer, Science 344 (2014) 703–704.
[167] E.E. Matthews, D. Thevenin, J.M. Rogers, L. Gotow, P.D. Lira, L.A. Reiter, W.H. Brissette, D.M. Engelman, Thrombopoietin receptor activation: transmembrane helix dimerization, rotation, and allosteric modulation, FASEB J. 25 (2011) 2234–2244.
[168] D. Ostrowski, R. Heinrich, Alternative erythropoietin receptors in the nervous system, J. Clin. Med. 7 (2018).
[169] S.N. Constantinescu, T. Keren, M. Socolovsky, H. Nam, Y.I. Henis, H.F. Lodish, Ligand-independent oligomerization of cell-surface erythropoietin receptor is mediated by the transmembrane domain, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 4379–4384.
[170] R.D. Ferrao, H.J. Wallweber, P.J. Lupardus, Receptor-mediated dimerization of JAK2 FERM domains is required for JAK2 activation, Elife 7 (2018).
[171] S.S. Watowich, The erythropoietin receptor: molecular structure and hematopoietic signaling pathways, J. Investig. Med. 59 (2011) 1067–1072.
[172] C. Bento, Genetic basis of congenital erythrocytosis, Int. J. Lab. Hematol. 40 (Suppl 1) (2018) 62–67.
[173] C. Bento, M.J. Percy, B. Gardie, T.M. Maia, R. van Wijk, S. Perrotta, F. Della Ragione, H. Almeida, C. Rossi, F. Girodon, M. Astrom, D. Neumann, S. Schnittger, B. Landin, M. Minkov, M.L. Randi, S. Richard, N. Casadevall, W. Vainchenker, S. Rives, S. Hermouet, M.L. Ribeiro, M.F. McMullin, H. Cario, E.C.E. Consortium, A. Chauveau, A.P. Gimenez-Roqueplo, B. Bressac-de-Paillerets, D. Altindirek, F. Lorenzo, F. Lambert, H. Dan, S. Gad-Lapiteau, A. Catarina Oliveira, C. Rossi, C. Fraga, G. Taradin, G. Martin-Nunez, H. Vitoria, H. Diaz Aguado, J. Palmblad, J. Vidan, L. Relvas, M.L. Ribeiro, M. Luigi Larocca, M. Luigia Randi, M. Pedro Silveira, M. Percy, M. Gross, R. Marques da Costa, S. Beshara, T. Ben-Ami, V. Ugo, E.C.E. Consortium, Genetic basis of congenital erythrocytosis: mutation update and online databases, Hum. Mutat. 35 (2014) 15–26.
[174] A. Sasaki, H. Yasukawa, T. Shouda, T. Kitamura, I. Dikic, A. Yoshimura, CIS3/SOCS-3 suppresses erythropoietin (EPO) signaling by binding the EPO receptor and JAK2, J. Biol. Chem. 275 (2000) 29338–29347.
[175] M. Gross, N. Ben-Califa, M.F. McMullin, M.J. Percy, C. Bento, H. Cario, M. Minkov, D. Neumann, Polycythaemia-inducing mutations in the erythropoietin receptor (EPOR): mechanism and function as elucidated by epidermal growth factor receptor-EPOR chimeras, Br. J. Haematol. 165 (2014) 519–528.
[176] V. Divoky, Z. Liu, T.M. Ryan, J.F. Prchal, T.M. Townes, J.T. Prchal, Mouse model of congenital polycythemia: homologous replacement of murine gene by mutant human erythropoietin receptor gene, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 986–991.
[177] V. Divoky, J. Song, M. Horvathova, B. Kralova, H. Votavova, J.T. Prchal, D. Yoon, Delayed hemoglobin switching and perinatal neocytolysis in mice with gain-of-function erythropoietin receptor, J. Mol. Med. (Berl) 94 (2016) 597–608.
[178] I. Iacobucci, Y. Li, K.G. Roberts, S.M. Dobson, J.C. Kim, D. Payne-Turner, R.C. Harvey, M. Valentine, K. McCastlain, J. Easton, D. Yergeau, L.J. Janke, Y. Shao, I.M. Chen, M. Rusch, S. Zandi, S.M. Kornblau, M. Konopleva, E. Jabbour, E.M. Paietta, J.M. Rowe, C.H. Pui, J. Gastier-Foster, Z. Gu, S. Reshmi, M.L. Loh, J. Racevskis, M.S. Tallman, P.H. Wiernik, M.R. Litzow, C.L. Willman, J.D. McPherson, J.R. Downing, J. Zhang, J.E. Dick, S.P. Hunger, C.G. Mullighan, Truncating erythropoietin receptor rearrangements in acute lymphoblastic leukemia, Cancer Cell 29 (2016) 186–200.
[179] A. Chauveau, D. Luque Paz, L. Lecucq, G. Le Gac, C. Le Marechal, P. Gueguen, C. Berthou, V. Ugo, A new point mutation in EPOR inducing a short deletion in congenital erythrocytosis, Br. J. Haematol. 172 (2016) 475–477.
[180] F. Pasquier, C. Marty, T. Balligand, F. Verdier, S. Grosjean, V. Gryshkova, H. Raslova, S.N. Constantinescu, N. Casadevall, W. Vainchenker, C. Bellanne-Chantelot, I. Plo, New pathogenic mechanisms induced by germline erythropoietin receptor mutations in primary erythrocytosis, Haematologica 103 (2018) 575–586.
[181] N. Toriumi, M. Kaneda, N. Hatakeyama, H. Manabe, K. Okajima, Y. Sakurai, M. Yamamoto, T. Sarashina, K. Ikuta, H. Azuma, A case of primary familial congenital polycythemia with a novel EPOR mutation: possible spontaneous remission/alleviation by menstrual bleeding, Int. J. Hematol. 108 (2018) 339–343.
[182] E. Peroni, I. Bertozzi, F. Gherlinzoni, P.M. Stefani, A. Lombardi, G. Biagetti, F. Fabris, M.L. Randi, Two novel missense mutations in EPOR gene causes erythrocytosis in two unrelated patients, Br. J. Haematol. 180 (2018) 908–911.
[183] S.S. Watowich, A. Yoshimura, G.D. Longmore, D.J. Hilton, Y. Yoshimura, H.F. Lodish, Homodimerization and constitutive activation of the erythropoietin receptor, Proc. Natl. Acad. Sci. U. S. A. 89 (1992) 2140–2144.
[184] A. Yoshimura, G. Longmore, H.F. Lodish, Point mutation in the exoplasmic domain of the erythropoietin receptor resulting in hormone-independent activation and tumorigenicity, Nature 348 (1990) 647–649.
[185] W.W. Pan, M.G. Myers Jr, Leptin and the maintenance of elevated body weight, Nat. Rev. Neurosci. 19 (2018) 95–105.
[186] J. Wauman, L. Zabeau, J. Tavernier, The leptin receptor complex: Heavier than expected? Front. Endocrinol. (Lausanne) 8 (2017) 30.
[187] J. Liu, X. Yang, S. Yu, R. Zheng, The leptin signaling, Adv. Exp. Med. Biol. 1090 (2018) 123–144.
[188] R.S. Ahima, S.Y. Osei, Leptin signaling, Physiol. Behav. 81 (2004) 223–241.
[189] A. Nunziata, J.B. Funcke, G. Borck, J. von Schnurbein, S. Brandt, B. Lennerz, B. Moepps, P. Gierschik, P. Fischer-Posovszky, M. Wabitsch, Functional and phenotypic characteristics of human leptin receptor mutations, J. Endocr. Soc. 3 (2019) 27–41.
[190] M. Bjornholm, H. Munzberg, R.L. Leshan, E.C. Villanueva, S.H. Bates, G.W. Louis, J.C. Jones, R. Ishida-Takahashi, C. Bjorbaek, M.G. Myers Jr., Mice lacking inhibitory leptin receptor signals are lean with normal endocrine function, J. Clin. Invest. 117 (2007) 1354–1360.
[191] I.C. McCabe, A. Fedorko, M.G. Myers Jr., G. Leinninger, E. Scheller, L.R. McCabe, Novel leptin receptor signaling mutants identify location and sex-dependent modulation of bone density, adiposity, and growth, J. Cell. Biochem. 120 (2019) 4398–4408.
[192] P. Dwivedi, K.D. Greis, Granulocyte colony-stimulating factor receptor signaling in severe congenital neutropenia, chronic neutrophilic leukemia, and related malignancies, Exp. Hematol. 46 (2017) 9–20.
[193] T. Tamada, E. Honjo, Y. Maeda, T. Okamoto, M. Ishibashi, M. Tokunaga, R. Kuroki, Homodimeric cross-over structure of the human granulocyte colony-stimulating factor (GCSF) receptor signaling complex, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 3135–3140.
[194] H.M. Mehta, T. Glaubach, A. Long, H. Lu, B. Przychodzen, H. Makishima, M.A. McDevitt, N.C. Cross, J. Maciejewski, S.J. Corey, Granulocyte colony-stimulating factor receptor T595I (T618I) mutation confers ligand independence and enhanced signaling, Leukemia 27 (2013) 2407–2410.
[195] J.E. Maxson, J. Gotlib, D.A. Pollyea, A.G. Fleischman, A. Agarwal, C.A. Eide, D. Bottomly, B. Wilmot, S.K. McWeeney, C.E. Tognon, J.B. Pond, R.H. Collins, B. Goueli, S.T. Oh, M.W. Deininger, B.H. Chang, M.M. Loriaux, B.J. Druker, J.W. Tyner, Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML, N. Engl. J. Med. 368 (2013) 1781–1790.
[196] J.E. Maxson, S.B. Luty, J.D. MacManiman, M.L. Abel, B.J. Druker, J.W. Tyner, Ligand independence of the T618I mutation in the colony-stimulating factor 3 receptor (CSF3R) protein results from loss of O-linked glycosylation and increased receptor dimerization, J. Biol. Chem. 289 (2014) 5820–5827.
[197] J.E. Maxson, S.B. Luty, J.D. MacManiman, J.C. Paik, J. Gotlib, P. Greenberg, S. Bahamadi, S.L. Savage, M.L. Abel, C.A. Eide, M.M. Loriaux, E.A. Stevens, J.W. Tyner, The colony-stimulating factor 3 receptor T640N mutation is oncogenic, sensitive to JAK inhibition, and mimics T618I, Clin. Cancer Res. 22 (2016) 757–764.
[198] H. Zhang, S. Means, A.R. Schultz, K. Watanabe-Smith, B.C. Medeiros, D. Bottomly, B. Wilmot, S.K. McWeeney, T. Kukenshoner, O. Hantschel, J.W. Tyner, Unpaired extracellular cysteine mutations of CSF3R mediate gain or loss of function, Cancer Res. 77 (2017) 4258–4267.
[199] H. Zhang, A. Reister Schultz, S. Luty, A. Rofelty, Y. Su, S. Means, D. Bottomly, B. Wilmot, S.K. McWeeney, J.W. Tyner, Characterization of the leukemogenic potential of distal cytoplasmic CSF3R truncation and missense mutations, Leukemia 31 (2017) 2752–2760.
[200] H.M. Mehta, M. Futami, T. Glaubach, D.W. Lee, J.R. Andolina, Q. Yang, Z. Whichard, M. Quinn, H.F. Lu, W.M. Kao, B. Przychodzen, C.A. Sarkar, A. Minella, J.P. Maciejewski, S.J. Corey, Alternatively spliced, truncated GCSF receptor promotes leukemogenic properties and sensitivity to JAK inhibition, Leukemia 28 (2014) 1041–1051.
[201] H. Zhang, C. Coblentz, K. Watanabe-Smith, S. Means, J. Means, J.E. Maxson, J.W. Tyner, Gain-of-function mutations in granulocyte colony-stimulating factor receptor (CSF3R) reveal distinct mechanisms of CSF3R activation, J. Biol. Chem. 293 (2018) 7387–7396.
[202] E.S. Vanamee, D.L. Faustman, Structural principles of tumor necrosis factor superfamily signaling, Sci. Signal. 11 (2018).
[203] R. Fischer, J. Marsal, C. Gutta, S.A. Eisler, N. Peters, J.R. Bethea, K. Pfizenmaier, R.E. Kontermann, Novel strategies to mimic transmembrane tumor necrosis factor-dependent activation of tumor necrosis factor receptor 2, Sci. Rep. 7 (2017) 6607.
[204] C. Dostert, M. Grusdat, E. Letellier, D. Brenner, The TNF family of ligands and receptors: communication modules in the immune system and beyond, Physiol.

Rev. 99 (2019) 115–160.
[205] D. Rigante, G. Lopalco, A. Vitale, O.M. Lucherini, C. De Clemente, F. Caso, G. Emmi, L. Costa, E. Silvestri, L. Andreozzi, F. Iannone, M. Galeazzi, L. Cantarini, Key facts and hot spots on tumor necrosis factor receptor-associated periodic syndrome, Clin. Rheumatol. 33 (2014) 1197–1207.
[206] A.A. Lobito, F.C. Kimberley, J.R. Muppidi, H. Komarow, A.J. Jackson, K.M. Hull, D.L. Kastner, G.R. Screaton, R.M. Siegel, Abnormal disulfide-linked oligomerization results in ER retention and altered signaling by TNFR1 mutants in TNFR1-associated periodic fever syndrome (TRAPS), Blood 108 (2006) 1320–1327.
[207] O.H. Negm, H.A. Mannsperger, E.M. McDermott, E. Drewe, R.J. Powell, I. Todd, L.C. Fairclough, P.J. Tighe, A pro-inflammatory signalome is constitutively activated by C33Y mutant TNF receptor 1 in TNF receptor-associated periodic syndrome (TRAPS), Eur. J. Immunol. 44 (2014) 2096–2110.
[208] E. Greco, A. Aita, P. Galozzi, A. Gava, P. Sfriso, O.H. Negm, P. Tighe, F. Caso, F. Navaglia, E. Dazzo, M. De Bortoli, A. Rampazzo, L. Obici, S. Donadei, G. Merlini, M. Plebani, I. Todd, D. Basso, L. Punzi, The novel S59P mutation in the TNFRSF1A gene identified in an adult onset TNF receptor associated periodic syndrome (TRAPS) constitutively activates NF-kappaB pathway, Arthritis Res. Ther. 17 (2015) 93.
[209] A.P. Hinck, T.D. Mueller, T.A. Springer, Structural biology and evolution of the TGF-beta family, Cold Spring Harb, Perspect. Biol. Med. 8 (2016).
[210] C.H. Heldin, A. Moustakas, Signaling receptors for TGF-beta family members, cold spring Harb, Perspect. Biol. Med. 8 (2016).
[211] M. van Dinther, N. Visser, D.J. de Gorter, J. Doorn, M.J. Goumans, J. de Boer, P. Ten Dijke, ALK2 R206H mutation linked to fibrodysplasia ossificans progressiva confers constitutive activity to the BMP type I receptor and sensitizes mesenchymal cells to BMP-induced osteoblast differentiation and bone formation, J. Bone Miner. Res. 25 (2010) 1208–1215.
[212] M. Sankelo, J.A. Flanagan, R. Machado, R. Harrison, N. Rudarakanchana, N. Morrell, M. Dixon, M. Halme, H. Puolijoki, J. Kere, O. Elomaa, M. Kupari, A. Raisanen-Sokolowski, R.C. Trembath, T. Laitinen, BMPR2 mutations have short lifetime expectancy in primary pulmonary hypertension, Hum. Mutat. 26 (2005) 119–124.
[213] S.A. Willis, C.M. Zimmerman, L.I. Li, L.S. Mathews, Formation and activation by phosphorylation of activin receptor complexes, Mol. Endocrinol. 10 (1996) 367–379.
[214] J. Seoane, R.R. Gomis, TGF-beta family signaling in tumor suppression and cancer progression, Cold Spring Harb, Perspect. Biol. Med. 9 (2017).
[215] L. Garrigue-Antar, T. Munoz-Antonia, S.J. Antonia, J. Gesmonde, V.F. Vellucci, M. Reiss, Missense mutations of the transforming growth factor beta type II receptor in human head and neck squamous carcinoma cells, Cancer Res. 55 (1995) 3982–3987.
[216] I. Park, H.K. Son, Z.M. Che, J. Kim, A novel gain-of-function mutation of TGF-beta receptor II promotes cancer progression via delayed receptor internalization in oral squamous cell carcinoma, Cancer Lett. 315 (2012) 161–169.
[217] M.A. Schirmer, A.O. Hoffmann, R. Campean, J.H. Janke, L.M. Zidek, M. Hoffmann, M. Kruse, D. Sehrt, M.V. Tzvetkov, M. Rave-Frank, J. Brockmoller, Bioinformatic and functional analysis of TGFBR1 polymorphisms, Pharmacogenet. Genomics 19 (2009) 249–259.
[218] R. Zhou, Y. Huang, B. Cheng, Y. Wang, B. Xiong, TGFBR1*6A is a potential modifier of migration and invasion in colorectal cancer cells, Oncol. Lett. 15 (2018) 3971–3976.
[219] X.H. Feng, R. Derynck, Ligand-independent activation of transforming growth factor (TGF) beta signaling pathways by heteromeric cytoplasmic domains of TGF-beta receptors, J. Biol. Chem. 271 (1996) 13123–13129.
[220] M.J. Stone, J.A. Hayward, C. Huang, E.H. Z, J. Sanchez, Mechanisms of regulation of the chemokine-receptor network, Int. J. Mol. Sci. 18 (2017).
[221] K.H. Susek, M. Karvouni, E. Alici, A. Lundqvist, The role of CXC chemokine receptors 1-4 on immune cells in the tumor microenvironment, Front. Immunol. 9 (2018) 2159.
[222] P.M. Murphy, M. Baggiolini, I.F. Charo, C.A. Hebert, R. Horuk, K. Matsushima, L.H. Miller, J.J. Oppenheim, C.A. Power, International union of pharmacology. XXII. Nomenclature for chemokine receptors, Pharmacol. Rev. 52 (2000) 145–176.
[223] E.M. Borroni, B. Savino, R. Bonecchi, M. Locati, Chemokines sound the alarmin: the role of atypical chemokine in inflammation and cancer, Semin. Immunol. 38 (2018) 63–71.
[224] X. Han, Constitutively active chemokine CXC receptors, Adv. Pharmacol. 70 (2014) 265–301.
[225] F. Bachelerie, A. Ben-Baruch, A.M. Burkhardt, C. Combadiere, J.M. Farber, G.J. Graham, R. Horuk, A.H. Sparre-Ulrich, M. Locati, A.D. Luster, A. Mantovani, K. Matsushima, P.M. Murphy, R. Nibbs, H. Nomiyama, C.A. Power, A.E. Proudfoot, M.M. Rosenkilde, A. Rot, S. Sozzani, M. Thelen, O. Yoshie, A. Zlotnik, International Union of Basic and Clinical Pharmacology. [corrected]. LXXXIX. Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors, Pharmacol. Rev. 66 (2014) 1–79.
[226] E.C. Hsiao, S.M. Millard, R.A. Nissenson, Gs/Gi regulation of bone cell differentiation: review and insights from engineered receptors, Horm. Metab. Res. 48 (2016) 689–699.
[227] V. Odemis, J. Lipfert, R. Kraft, P. Hajek, G. Abraham, K. Hattermann, R. Mentlein, J. Engele, The presumed atypical chemokine receptor CXCR7 signals through G(i/o) proteins in primary rodent astrocytes and human glioma cells, Glia 60 (2012) 372–381.
[228] J. Corbisier, C. Gales, A. Huszagh, M. Parmentier, J.Y. Springael, Biased signaling at chemokine receptors, J. Biol. Chem. 290 (2015) 9542–9554.
[229] P.M. Murphy, Chemokines and chemokine receptors, in: R.R. Rich, T.A. Fleisher, W.T. Shearer, H.W. Schroeder, A.J. Frew, C.M. Weyand (Eds.), Clinical Immunology, Elsevier, 2018, pp. 157–170.
[230] G. Park, T. Masi, C.K. Choi, H. Kim, J.M. Becker, T.E. Sparer, Screening for novel constitutively active CXCR2 mutants and their cellular effects, Methods Enzymol. 485 (2010) 481–497.
[231] R.A. Cerione, J. Codina, J.L. Benovic, R.J. Lefkowitz, L. Birnbaumer, M.G. Caron, The mammalian beta 2-adrenergic receptor: reconstitution of functional interactions between pure receptor and pure stimulatory nucleotide binding protein of the adenylate cyclase system, Biochemistry 23 (1984) 4519–4525.
[232] Y.X. Tao, Constitutive activation of G protein-coupled receptors and diseases: insights into mechanisms of activation and therapeutics, Pharmacol. Ther. 120 (2008) 129–148.
[233] X. Han, Y. Feng, X. Chen, C. Gerard, W.A. Boisvert, Characterization of G protein coupling mediated by the conserved D134(3.49) of DRY motif, M241(6.34), and F251(6.44) residues on human CXCR1, FEBS Open Bio 5 (2015) 182–190.
[234] X. Han, S.D. Tachado, H. Koziel, W.A. Boisvert, Leu128(3.43) (l128) and Val247(6.40) (V247) of CXCR1 are critical amino acid residues for g protein coupling and receptor activation, PLoS One 7 (2012) e42765.
[235] J. Teixido, M. Martinez-Moreno, M. Diaz-Martinez, S. Sevilla-Movilla, The good and bad faces of the CXCR4 chemokine receptor, Int. J. Biochem. Cell Biol. 95 (2018) 121–131.
[236] W.B. Zhang, J.M. Navenot, B. Haribabu, H. Tamamura, K. Hiramatu, A. Omagari, G. Pei, J.P. Manfredi, N. Fujii, J.R. Broach, S.C. Peiper, A point mutation that confers constitutive activity to CXCR4 reveals that T140 is an inverse agonist and that AMD3100 and ALX40-4C are weak partial agonists, J. Biol. Chem. 277 (2002) 24515-14521.
[237] M. Sharma, F. Afrin, R.P. Tripathi, G. Gangenahalli, Transgene expression study of CXCR4 active mutants. Potential prospects in up-modulation of homing and engraftment efficiency of hematopoietic stem/progenitor cells, Cell Adh. Migr. 8 (2014) 384–388.
[238] C.A. Flanagan, Receptor conformation and constitutive activity in CCR5 chemokine receptor function and HIV infection, Adv. Pharmacol. 70 (2014) 215–263.
[239] J.Y. Springael, C. de Poorter, X. Deupi, J. Van Durme, L. Pardo, M. Parmentier, The activation mechanism of chemokine receptor CCR5 involves common structural changes but a different network of interhelical interactions relative to rhodopsin, Cell. Signal. 19 (2007) 1446–1456.
[240] A. Steen, A.H. Sparre-Ulrich, S. Thiele, D. Guo, T.M. Frimurer, M.M. Rosenkilde, Gating function of isoleucine-116 in TM-3 (position III:16/3.40) for the activity state of the CC-chemokine receptor 5 (CCR5), Br. J. Pharmacol. 171 (2014) 1566–1579.
[241] A.T. Folefoc, B.J. Fromme, A.A. Katz, C.A. Flanagan, South African mutations of the CCR5 coreceptor for HIV modify interaction with chemokines and HIV Envelope protein, J. Acquir. Immune Defic. Syndr. 54 (2010) 352–359.
[242] A. de Voux, M.C. Chan, A.T. Folefoc, M.T. Madziva, C.A. Flanagan, Constitutively active CCR5 chemokine receptors differ in mediating HIV envelope-dependent fusion, PLoS One 8 (2013) e54532.
[243] C. Govaerts, C. Blanpain, X. Deupi, S. Ballet, J.A. Ballesteros, S.J. Wodak, G. Vassart, L. Pardo, M. Parmentier, The TXP motif in the second transmembrane helix of CCR5. A structural determinant of chemokine-induced activation, J. Biol. Chem. 276 (2001) 13217–13225.
[244] D. Alvarez Arias, J.M. Navenot, W.B. Zhang, J. Broach, S.C. Peiper, Constitutive activation of CCR5 and CCR2 induced by conformational changes in the conserved TXP motif in transmembrane helix 2, J. Biol. Chem. 278 (2003) 36513–36521.
[245] A. Steen, S. Thiele, D. Guo, L.S. Hansen, T.M. Frimurer, M.M. Rosenkilde, Biased and constitutive signaling in the CC-chemokine receptor CCR5 by manipulating the interface between transmembrane helices 6 and 7, J. Biol. Chem. 288 (2013) 12511–12521.
[246] S. Lee, Y.H. Chung, C. Lee, US28, a virally-encoded GPCR as an antiviral target for human cytomegalovirus infection, Biomol. Ther. (Seoul) 25 (2017) 69–79.
[247] S. Montaner, I. Kufareva, R. Abagyan, J.S. Gutkind, Molecular mechanisms deployed by virally encoded G protein-coupled receptors in human diseases, Annu. Rev. Pharmacol. Toxicol. 53 (2013) 331–354.
[248] S. Nijmeijer, R. Leurs, M.J. Smit, H.F. Vischer, The Epstein-Barr virus-encoded G protein-coupled receptor BILF1 hetero-oligomerizes with human CXCR4, scavenges Galphai proteins, and constitutively impairs CXCR4 functioning, J. Biol. Chem. 285 (2010) 29632–29641.
[249] R. Heukers, T.S. Fan, R.H. de Wit, J.R. van Senten, T.W.M. De Groof, M.P. Bebelman, T. Lagerweij, J. Vieira, S.M. de Munnik, L. Smits-de Vries, J. van Offenbeek, A. Rahbar, D. van Hoorick, C. Soderberg-Naucler, T. Wurdinger, R. Leurs, M. Siderius, H.F. Vischer, M.J. Smit, The constitutive activity of the virally encoded chemokine receptor US28 accelerates glioblastoma growth, Oncogene 37 (2018) 4110–4121.
[250] J.M. Boeck, G.A. Stowell, C.M. O'Connor, J.V. Spencer, The human cytomegalovirus US27 gene product constitutively activates antioxidant response element-mediated transcription through Gbetagamma, phosphoinositide 3-kinase, and nuclear respiratory factor 1, J. Virol. 92 (2018).
[251] P. Casarosa, Y.K. Gruijthuijsen, D. Michel, P.S. Beisser, J. Holl, C.P. Fitzsimons, D. Verzijl, C.A. Bruggeman, T. Mertens, R. Leurs, C. Vink, M.J. Smit, Constitutive signaling of the human cytomegalovirus-encoded receptor UL33 differs from that of its rat cytomegalovirus homolog R33 by promiscuous activation of G proteins of the Gq, Gi, and Gs classes, J. Biol. Chem. 278 (2003) 50010–50023.
[252] J.C. Lee, I. Vivanco, R. Beroukhim, J.H. Huang, W.L. Feng, R.M. DeBiasi, K. Yoshimoto, J.C. King, P. Nghiemphu, Y. Yuza, Q. Xu, H. Greulich, R.K. Thomas, J.G. Paez, T.C. Peck, D.J. Linhart, K.A. Glatt, G. Getz, R. Onofrio, L. Ziaugra, R.L. Levine, S. Gabriel, T. Kawaguchi, K. O'Neill, H. Khan, L.M. Liau, S.F. Nelson, P.N. Rao, P. Mischel, R.O. Pieper, T. Cloughesy, D.J. Leahy, W.R. Sellers, C.L. Sawyers, M. Meyerson, I.K. Mellinghoff, Epidermal growth factor receptor

activation in glioblastoma through novel missense mutations in the extracellular domain, PLoS Med. 3 (2006) e485.
[253] J.S. Ross, L.M. Gay, K. Wang, S.M. Ali, S. Chumsri, J.A. Elvin, R. Bose, J.A. Vergilio, J. Suh, R. Yelensky, D. Lipson, J. Chmielecki, S. Waintraub, B. Leyland-Jones, V.A. Miller, P.J. Stephens, Nonamplification ERBB2 genomic alterations in 5605 cases of recurrent and metastatic breast cancer: An emerging opportunity for anti-HER2 targeted therapies, Cancer 122 (2016) 2654–2662.

Doreen M. Floss finished her diploma study for Agricultural Sciences in 2003 at the Martin-Luther-University Halle-Wittenberg, Germany. In 2004 she joined the "Phytoantibodies" group at the Leibniz Institute of Plant Genetics and Crop Plant Research (IPK), Gatersleben, Germany and obtained her Dr. rer. nat. (Ph.D.) in 2008. In 2009 she moved to the Institute of Biochemistry of the University of Kiel and started to study the biology of IL-23 signal transduction. Since 2011 she works as a postdoctoral research associate at the Institute of Biochemistry and Molecular Biology II at the Heinrich-Heine-University Düsseldorf. Here, she studies the biology of IL-6 and IL-12-type cytokines.

Jürgen Scheller finished his diploma study of Biology in 1997 at the Georg-August University of Göttingen, Germany and obtained his Dr. rer. nat. (Ph.D.) in 1999. He joined the group "Phytoantibodies" at the Leibniz-Institut IPK in Gatersleben, Germany in 1999. From 1999–2002 he works on spider silk proteins from transgenic plants. In 2002 he became assistant professor in the Biochemical Institute at Christian-Albrechts-Universität of Kiel, Germany. In 2008 he became W2-Professor for "Cytokine Signaling" within the Cluster of Excellence "Inflammation at Interfaces" at Christian-Albrechts-Universität of Kiel, Germany. In 2010 he moved to the Heinrich-Heine-University and became the director of the Institute of Biochemistry and Molecular Biology II as a W3-Professor. His present interests are focused on *in vitro* and *in vivo* studies of IL-6- and IL-12-type cytokines.