Cytokine 118 (2019) 27–34

Contents lists available at ScienceDirect

Cytokine

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

Review article

STAT3 isoforms: Alternative fates in cancer?

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ABSTRACT

Signal transducer and activator of transcription (STAT) 3 is the main mediator of IL-6-type cytokine signaling and an important transcriptional regulator of cell proliferation, maturation and survival. It has been described as a key player in cancer development and progression. However, under certain circumstances, STAT3 is also considered a potent tumor suppressor. This heterogeneity partially depends on its expression as different isoforms. Alternative splicing gives rise to two STAT3 isoforms, STAT3α and its truncated version STAT3β. Both isoforms are transcriptionally active and display distinct functions under physiological and pathological conditions. In fact, while STAT3α is widely described as an oncogene, STAT3β has gained attention as a potential tumor suppressor. This review provides a concise overview of the current knowledge on STAT3 during tumorigenesis, with special emphasis on the unique and complex roles of its alternatively spliced isoforms.

1. Introduction

STAT3 is the key mediator of IL-6-type cytokine signal transduction and acts as a multifunctional transcription factor downstream of various cytokines, interferons, hormones, growth factors and colony stimulating factors [1–6]. It is one of the seven STAT family members identified in mammalian cells and was first described in 1993 as acute phase response factor (APRF) [1]. Like all STAT proteins STAT3 consists of six domains: a conserved amino-terminus, a coiled coil domain, the DNA binding domain, a linker domain, the Src Homology 2 (SH2) domain for receptor binding and dimerization, and a carboxy-terminal transactivation domain for co-factor recruitment. Activation of STAT3 depends on phosphorylation of tyrosine (Tyr^{705}) or serine (Ser^{727}) residues within the C-terminus. Extracellular ligand binding to their cognate receptors leads to receptor oligomerization and activation of Janus family tyrosine kinases (JAKs), which thereupon recruit and phosphorylate STAT3. Upon Tyr^{705} phosphorylation, STAT3 can form homo- or heterodimers via the SH2 domain and translocate into the nucleus. In cooperation with nuclear co-factors, phosphorylated STAT3 (pSTAT3) binds directly to gamma interferon activation site (GAS) elements in DNA promoter regions and activates gene expression [7–9]. In contrast to knock-out mice of other STAT family members, loss of STAT3 in mice leads to embryonic lethality due to severe defects in the visceral endoderm [10]. Thus, STAT3 plays an essential role in mammalian development. Further studies using tissue-specific knock-out mice demonstrated the importance of STAT3 in cell survival, proliferation, migration and cancer [7,11–14]. Similar to other *STAT* family members (*STAT1* and *STAT4*), *STAT3* gives rise to two alternatively spliced isoforms. STAT3α and truncated STAT3β are generated via alternative splicing of exon 23 in mice and men. Both isoforms have distinct functions and are essential for the wide spectrum of STAT3-dependent regulations [15–18]. This review focuses on the specific relevance of STAT3 isoforms in cancer and how they might influence the role of STAT3 in tumorigenesis.

2. STAT3 and its isoforms

STAT3 is expressed and present in all cell types in several different isoforms, derived from alternative splicing and proteolytic processing. Altogether, there have been four isoforms identified for STAT3, STAT3α

Abbreviations: AML, acute myeloid leukemia; APRF, acute phase response factor; Bcl, B cell lymphoma; bFGF, basic fibroblast growth factor; Cten, C-terminal tensin-like; DC, dendritic cells; DNA-BD, DNA-binding domain; EGF, epidermal growth factor; ESCC, esophageal squamous cell carcinoma; GAS, gamma interferon activation site; G-CSF, granulocyte-colony stimulating factor; Gpr65, G protein-coupled receptor 65; HGF, hepatocyte growth factor; IL, interleukin; JAK, Janus family tyrosine kinase; LEDGF, lens-epithelium-derived growth factor; MEF, mouse embryonic fibroblast; MMPs, matrix metalloproteinases; morpholinos, phosphorodiamidate morpholino oligomers; NF-κB, nuclear factor κB; PEX1, peroxisomal biogenesis factor 1; PKCδ/ε, protein kinase C delta/epsilon; PLK-1, polo like kinase 1; pSTAT3, phosphorylated STAT3; SH2, Src Homology 2; Slc28a2, solute carrier family 28 member 2; STAT, Signal transducer and activator of transcription; TAD, transactivation domain; TAM, tumor-associated macrophage; TRAIL, TNF-related apoptosis inducing ligand; VEGF, vascular endothelial growth factor

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https://doi.org/10.1016/j.cyto.2018.07.014
Received 15 January 2018; Received in revised form 10 July 2018; Accepted 11 July 2018
Available online 18 July 2018

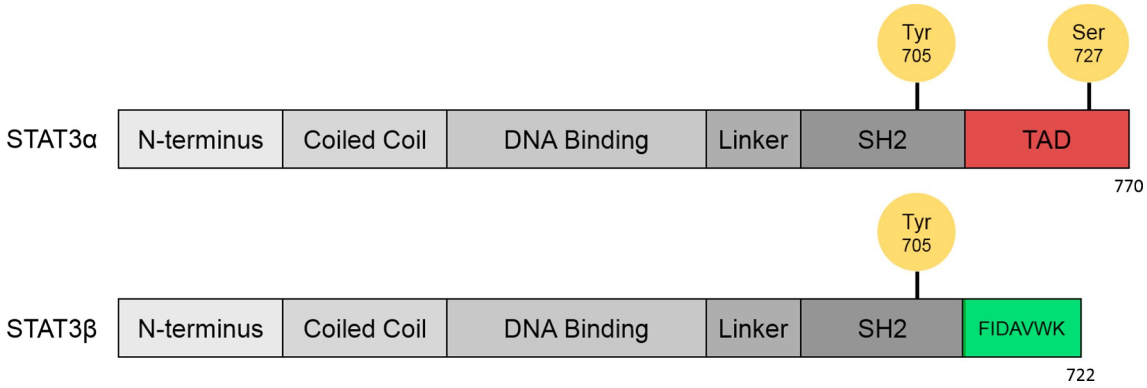

Fig. 1. Schematic overview showing the two alternatively spliced STAT3 isoforms STAT3α and STAT3β. They both share the N-terminal domain; the coiled coil domain that enables protein-protein interactions; the gene-regulating DNA binding domain (DNA-BD); a linker; the Src homology 2 (SH2) domain, that is responsible for STAT3 dimerization; and the activation domain with the tyrosine 705 residue, that is phosphorylated by JAKs. STAT3β lacks the transactivation domain (TAD), responsible for nuclear cofactor recruitment and instead carries seven unique amino acids.

(92 kDa), STAT3β (83 kDa), STAT3γ (72 kDa) and STAT3δ (64 kDa) [9,19–21]. Alternative splicing generates the isoforms STAT3α and STAT3β via a highly conserved acceptor site in exon 23, causing a frameshift, which introduces seven new amino acids and a stop codon. Therefore, in comparison to full-length STAT3α, STAT3β lacks the C-terminal transactivation domain of STAT3, including the Ser^{727} phosphorylation site. It instead carries a unique seven amino acid tail (Fig. 1) [16]. While the loss of *Stat3α* is lethal in mice, *Stat3β* is not required for viability [18]. Consequently, STAT3β was originally postulated as a dominant-negative regulator of STAT3 [16,22,23]. Later, it has been shown that STAT3β indeed has distinct regulatory and transcriptional functions, which will be outlined below [18,24]. Proteolytic processing of STAT3 is responsible for generating the other two STAT3 isoforms, STAT3γ and STAT3δ [19,25,26].

Limited proteolysis, also known as proteolytic processing, can induce biological activity by limited degradation, for instance post-translational limited proteolysis of STAT3α was reported to produce STAT3γ, a C-terminal truncated form of full-length STAT3 [19,21,27]. Proteolytic cleavage by serine proteases results in the loss of the C-terminal transactivation domain, without the addition of novel amino acids [26]. Thus, STAT3γ carries a different C-terminus in comparison to STAT3β and has been shown to act as a dominant-negative variant of STAT3 [27]. STAT3γ is rapidly generated during granulocytic differentiation in human neutrophils [27] and could not be detected in neutrophils lacking granules, indicating that granules are required for proteolysis [28]. Proteolytic processing of STAT3 has further been found in myeloid progenitors, mast cells and peripheral T cells [19,26]. In acute myeloid leukemia (AML) patients, an increased expression of truncated STAT3 proteins has been described after relapse, suggesting that STAT3γ has a certain pathological relevance and may contribute adversely to AML progression [26,29,30]. In addition to serine proteases, STAT3 in platelets can also be cleaved by the calcium-dependent cysteine protease calpain, however its physiological significance is yet unknown [31]. The second truncated isoform resulting from proteolysis, STAT3δ, has been found to be expressed in early stages of granulocytic differentiation, however its exact function remains elusive [19]. Like STAT3γ, STAT3δ cannot actively mediate transcription, so it might serve as a negative regulator as well [26]. However, little is known about the specificity and mechanism of proteolytic conversion of STAT3 at present.

2.1. Differences between STAT3α and STAT3β

In contrast to STAT3γ and STAT3δ, STAT3α and STAT3β are co-expressed in all cell types, with STAT3α generally expressed at higher levels than STAT3β [23]. However, the ratio of STAT3α to STAT3β can drastically change, for instance, in hepatocytes after endotoxic shock [17], upon cytokine stimulation, and during myeloid differentiation [19,32,33]. STAT3α and STAT3β are both capable of forming homo- and heterodimers with each other as well as other STAT family members [15,34]. Huang et al. demonstrated a prolonged phosphorylation and nuclear retention of STAT3β homodimers in comparison to STAT3α, and its dependence on the unique C-terminal amino acid tail [35]. A comparison of the basal nuclear import rates for STAT3α, STAT3β and a C-terminal truncation derivative STAT3ΔC revealed that both truncated STAT3 versions translocate faster into the nucleus [36]. Thus, STAT3β homodimers exhibit increased nuclear import and retention rates. In addition, STAT3β has been found to have a higher DNA-binding affinity compared to STAT3α in serum-starved COS-7 cells [37]. Park et al. confirmed that C-terminal deletions of STAT3α increase dimer stability as well as DNA-binding activity [34]. Taken together, STAT3β homodimers show an enhanced dimer stability and superior DNA-binding affinity due to the truncated and unique C-terminal tail.

First functional differences between both STAT3 isoforms have already been described in 1997, showing an enhanced activity of STAT3β in the absence of growth factor stimulation [37]. However, little was known about its specific functions. In 2004 the research group of Valeria Poli investigated the unique and specific functions of STAT3α and STAT3β, by generating mice that only express either one of the two isoforms. They obtained mouse embryonic fibroblasts (MEFs) from $Stat3^{\Delta\alpha/\Delta\alpha}$ and $Stat3^{\Delta\beta/\Delta\beta}$ mice, and determined that STAT3β has several transcriptional functions and genetic targets [18]. Yoo et al. further demonstrated that, although the expression and phosphorylation of STAT3α remains intact in *Stat3β*-deficient MEFs, overall STAT3 activity and differential gene expression are significantly altered [17]. Ng et al. studied the different functions of STAT3 splice forms in $Stat3^{\Delta/\Delta}$ MEFs with inducible *Stat3α* or *Stat3β* expression [24]. They demonstrated a regulatory effect of STAT3β on STAT3α, prolonging phosphorylation and nuclear retention of STAT3α. This co-regulatory effect depends on the heterodimer formation of STAT3β and STAT3α. The ability of STAT3β to form heterodimers with STAT3α and thus influence its function is one important role for STAT3β and led to the conclusion that all STAT3β–specific actions rely on STAT3α regulation. However, in total absence of STAT3, reintroduced STAT3β can compensate for the loss of STAT3α in hepatocytes and induce acute phase response genes [38]. Moreover, *Stat3β* has been demonstrated to avert embryonic lethality in total *Stat3* knock-out mice [18]. These findings suggest that instead of acting exclusively as a dominant-negative regulator of STAT3α, STAT3β can also act as an active transcriptional modulator. Accordingly, excessive expression of STAT3β failed to inhibit the functionality of STAT3α, neither in embryos nor in adult mice [18].

Furthermore, transcriptome profiling of *Stat3*$^{\Delta/\Delta}$ MEFs expressing only one STAT3 isoform revealed a large number of target genes specifically regulated by STAT3α or STAT3β under basal and stimulated conditions. Interestingly, it was further shown that significantly more genes are specifically regulated by STAT3β than by STAT3α. The most prominent STAT3β-specific target genes were classified in metabolism, protein metabolism, transport, and cell organization, emphasizing the importance of STAT3β as an active transcription factor [24].

3. The roles of STAT3 in cancer

3.1. STAT3 as a tumor promoter

Constitutive activation of STAT3 can induce malignant transformation and promote tumor cell proliferation, resistance to apoptosis, immune evasion, angiogenesis and metastasis [11,39–41]. In cancer patients, abnormal activation of STAT3 often correlates with a poor prognosis and accelerated disease progression [42–49]. Nevertheless, somatic *STAT3* mutations are relatively rare in cancer. Thus, the constitutive activation of STAT3 depends on several complex mechanisms, such as the loss of negative regulation, excessive cytokine stimulation and the activation of positive feedback loops [11]. Most prominently, STAT3 is constitutively activated in tumor cells with a hyperactivation of receptors for pro-oncogenic cytokines and growth factors, such as IL-6, epidermal growth factor (EGF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF). Furthermore, STAT3 acts downstream of several described oncoproteins, for instance Src kinases [39,50]. Prominent oncogenic targets of STAT3 are: *cyclin D1*, *c-myc*, *polo like kinase 1* (*PLK-1*) and *Pim1/2* for proliferation [51,52]; *survivin*, B cell lymphoma 2 (*Bcl-2)* and *c-Jun* for survival and evasion of apoptosis; VEGF and basic fibroblast growth factor (bFGF) for angiogenesis; and matrix metalloproteinases (MMPs) and C-terminal tensin-like (*Cten*) for metastasis [11,51,52].

STAT3 signaling is further active during chronic and cancer-associated inflammation and mediates tumor progression in inflammation-induced gastric, colon, liver and breast cancer [53,54]. In general, STAT3 is regarded an important promoter of pro-carcinogenic inflammation, often in correlation with the inflammation-promoting transcription factor nuclear factor κB (NF-κB). For instance, STAT3 has been reported to promote tumorigenesis in chronic inflammation-driven colorectal and intestinal cancer [55,56] and pharmacological inhibition effectively reduced colon cancer growth in xenografts [57]. High levels of phosphorylated STAT3 correlate with poor clinical outcome in hepatocellular carcinoma patients. Accordingly, hepatocellular tumor growth in *Stat3* knock-out mice was reduced while overall survival was increased [58–60]. In breast cancer patients, STAT3 is frequently found to be constitutively activated [51], and associated with metastasis as well as poor clinical outcome [61]. Likewise, *in vivo* mouse models revealed that STAT3 mediates the invasiveness and metastasis of murine mammary tumor cells via the upregulation of *Cten* [62]. In gastric cancer, the aberrant activation of STAT3 plays a central role in IL-11-driven tumorigenesis [63–65] and tumor growth [66–68] as well as in motility and invasion [69]. Thus, STAT3 is well-established as a potent tumor promoter in cancer and cancer-associated inflammation and therefore the ablation or pharmacological inhibition of STAT3 can be favorable for cancer treatment [70–72].

3.2. STAT3 as a tumor suppressor

While the vast majority of reports on STAT3 and cancer deal with its role as a tumor promoter, STAT3 has also been proposed as a tumor suppressor. For example, STAT3 has been demonstrated to have a suppressive effect on glioblastoma development in combination with decreased PTEN levels [73]. Similarly, in a *Pten*-deficient mouse model for prostate cancer, additional inactivation of STAT3 increased cancer progression and metastasis via p19^{ARF} [74]. In RAS-transformed hepatocytes from *p19*^{ARF} knock-out mice, constitutively active STAT3 induced an anti-tumorigenic effect upon transplantation, whereas an inactive mutant of STAT3 aggravated tumor growth [75]. Hence, it seems that the ability of STAT3 to act as a tumor suppressor is correlated to PTEN and p19^{ARF} expression levels. The hepatoprotective effect of STAT3 during liver carcinogenesis has been confirmed in hepatocyte-specific *Stat3* knock-out mice, where drug-induced tumor formation was shown to be enhanced [76]. Regarding intestinal cancer, Musteanu et al. described STAT3 as a negative regulator of cancer progression using *Apc(Min)* mice and demonstrating that STAT3 loss promoted tumor progression at later stages [77]. Furthermore, STAT3 has been attributed a tumor-suppressive role in K-RAS-mutated lung cancer, as decreased *STAT3* expression levels correlated with decreased survival in mice and patients [78]. An inverse relationship between levels of pSTAT3(Tyr^{705}), tumor size and metastasis was also described in thyroid carcinoma models and patients [79]. In patients with head and neck cancer, high nuclear STAT3 levels were linked to a more favorable prognosis and longer disease-free survival [80]. A similar correlation has been identified in a large cohort of patients suffering from salivary gland tumors [81] and in two separate studies involving low-grade breast cancer patients [82,83]. Hence, STAT3 is also a critical tumor suppressor in certain cancers, correlating with decreased cancer progression and prolonged survival.

These opposing roles of STAT3 in cancer, acting as an oncogene as well as an anti-tumorigenic molecule, and the resulting consequences for STAT3-dependent cancer treatments have gained more and more attention over the last decades [11,40,84–88]. There are several possible explanations for the heterogeneity of STAT3, for instance the wide variety of stimulating cytokines and growth factors or the versatile post-translational modifications of STAT3. However, one of the most important and yet widely neglected explanations is the existence of alternatively spliced STAT3 isoforms and their specific functions under physiological and pathological conditions. Therefore, the subsequent focus of this review will be the scope of STAT3α and STAT3β in cancerogenesis.

3.3. STAT3α in development and cancer

As previously mentioned, STAT3α, being the full-length version of STAT3, is an essential transcription factor for embryonic and perinatal development. Its loss can only be partially compensated by STAT3β or other STAT family members, as *Stat3α*-deficient mice still die perinatally [18]. Thus, most essential STAT3-specific regulatory functions depend on STAT3α activity. STAT3 is highly regulated by post-translational modifications, which are of utmost importance during early human development. For instance, Mehta et al. studied cardiogenesis in human pluripotent stem cells and found two distinct STAT3α forms, one phosphorylated and one acetylated, which displayed different regulatory functions. Phosphorylated STAT3α acts as a classical canonical activator of transcription, while acetylated STAT3α undergoes Caspase-3-mediated cleavage and controls cardiomyocyte formation [89]. This shows that, due to post-translational modifications, STAT3α can serve as a versatile mediator of gene transcription during early development.

The role of STAT3 isoforms in myeloid differentiation was investigated using conditional overexpression in the murine myeloid cell line 32D. The overexpression of STAT3α, but not STAT3β, triggered differentiation in the neutrophilic compartment and promoted apoptosis resistance in response to granulocyte-colony stimulating factor (G-CSF). The authors further identified new STAT3α-specific target genes, such as solute carrier family 28 member 2 (*Slc28a2*) and G protein-coupled receptor 65 (*Gpr65*), which are important for the generation of neutrophils [90].

Not surprisingly, most of STAT3′s oncogenic functions have also been associated with constitutively active STAT3α. Therefore, it is widely assumed that STAT3α is the key player during STAT3-

accelerated cancerogenesis. For instance, expression of constitutively active STAT3α in endometrial carcinoma cells has been shown to enhance proliferation, xenograft growth and metastasis. Furthermore, inhibition of STAT3α in the same model gravely impaired human growth hormone-stimulated oncogenicity [91]. Another study demonstrated the constitutive activation of STAT3α and VEGFR-2 in tumor endothelial cells of glioma and medulloblastoma [92]. Thus, constitutively active STAT3α is capable of promoting angiogenesis and favors metastasis in solid tumors. In a human ovarian cancer cell line (SKOV-3) treated with cisplatin, an upregulation of STAT3α and STAT3α-targets, such as *survivin* and *Bcl-XL*, was observed at early time points. However, treatments with other platinum-based antineoplastic therapeutics, such as oxaliplatin and nedaplatin, showed an opposite effect. The authors concluded, that this specific change in STAT3 regulation could be one of the underlying mechanisms of cisplatin resistance in ovarian cancer [93]. In addition, STAT3α is activated during cancer migration and invasion via protein kinase C δ (PKCδ) and Wnt-1 pathways, causing an upregulation of β-catenin and fascin-1 [94]. Likewise, protein kinase C ε (PKCε) has been shown to specifically interact with STAT3α, but not STAT3β, due to the lack of the Ser^{727} phosphorylation site. The interaction of PKCε and STAT3α plays an important role in various cancers, namely squamous cell carcinomas, prostate cancer, melanoma, glioma, as well as bladder, colon, lung, pancreatic and breast cancer [95]. Finally, STAT3α has been found to be upregulated in AML cell lines as well as AML patient samples stimulated with G-CSF, where it enhanced proliferation and suppressed differentiation [33].

In conclusion, STAT3α is an important transcription factor during development that regulates essential STAT3 target genes involved in cell proliferation, migration, and survival. However, constitutively active STAT3α can drive tumorigenesis and accelerates cancer progression. Therefore, it is tempting to speculate that STAT3-associated oncogenic functions originate from STAT3α activity.

3.4. The role of STAT3β

In comparison to STAT3α, the specific role of STAT3β remained elusive for a long time, presumably because of its low expression levels and its perceived status as a dominant-negative variant of STAT3. However, as outlined above, STAT3β has distinct regulatory and transcriptional functions. In line, STAT3β has been reported to be specifically active during myeloid differentiation, whereas STAT3α is more prominently expressed during proliferation and oncogenic transformation [9,27,33]. STAT3β can also functionally compensate the loss of STAT3 during astrocyte differentiation, which is highly dependent on STAT3 activity [96].

In the context of cancer development, earlier studies demonstrated that STAT3β can act as a repressor of STAT3. For instance, the administration of a STAT3β plasmid inhibited invasion of gastric cancer cells and reduced chemoresistance [97]. In response to Src stimulation, STAT3β can impair the STAT3α-driven activation of *Bcl-XL*, *p21* and *cyclin D1,* and consequently reduce proliferation [15,98–100]. In murine B16 melanoma cells, STAT3β is capable of inhibiting the constitutive activation of STAT3α and therefore suppresses tumor growth. Moreover, it has been shown to cause tumor regression *in vivo* [9,101,102]. STAT3β was shown to promote apoptosis in IL-6-dependent myeloma cells [103] and impaired proliferation of ovarian, breast and colon cancer cells [104,105]. Thus, STAT3β can efficiently inhibit cancer progression *in vivo* by regulating STAT3α, which is also of relevance in patients. Bharadwaj et al. developed a monoclonal antibody specific for the C-terminal amino acids of STAT3β. By using those antibodies for immunoblotting of breast cancer cell lines they revealed an increased expression of STAT3β and pSTAT3(Tyr^{705}), indicating that STAT3β and constitutive STAT3 phosphorylation play a role in breast cancer [106]. Xia et al. analyzed the levels of constitutively active STAT3α and STAT3β in seventeen AML patients at diagnosis and after relapse. The authors could show that STAT3 is constitutively active in thirteen out of seventeen patients at diagnosis but only in four patients at relapse. In contrast, STAT3β was expressed in twelve AML samples at diagnosis and sixteen at relapse, suggesting that STAT3β may play a role in AML progression regardless of the level of constitutive activity [30]. Taken together, these findings propose STAT3β as an important repressor of STAT3α and a potent anti-tumorigenic factor. In addition, STAT3β could be a potential diagnostic tool in cancer patients.

Besides its function as a negative regulator of STAT3α, STAT3β can also regulate STAT3α-independent processes in cancer. Niu et al. found that STAT3β-transfected cells start producing and secreting TNF-related apoptosis inducing ligand (TRAIL), which triggers apoptosis in transfected and non-transfected surrounding cells [101]. Likewise, STAT3β-dependent upregulation of TRAIL receptor 2 on tumor cells in human melanoma xenografts resulted in tumor cell apoptosis and consequently reduced tumor growth [107]. Together with c-Jun, STAT3β can induce Fas expression and therefore favor Fas ligand-induced apoptosis in cancer cells [108,109]. Furthermore, STAT3β has been reported to be involved in the upregulation of pro-inflammatory cytokines, as the supernatants of STAT3β-transfected cells can activate dendritic cells (DCs), granulocytes and macrophages [110].

Correlating with the latter findings, STAT3β has gained growing attention as a tumor suppressor in various cancers, including breast cancer, esophageal squamous cell carcinoma (ESCC), melanoma and lung cancer [101,102,107,109,111–113]. Zammarchi et al. exploited phosphorodiamidate morpholino oligomers (morpholinos) to manipulate the splicing of *STAT3* in favor of *STAT3β*, causing an upregulation of endogenous *STAT3β* in human mammary gland and breast cancer cells [112]. This splicing switch from predominantly *STAT3α* to predominantly *STAT3β* caused an increase in apoptosis and cell-cycle arrest accompanied with a persistent phosphorylation of Tyr^{705} in comparison to a STAT3 knock-down. Furthermore, the authors observed tumor regression in a xenograft model and downregulation of STAT3β target genes, such as lens-epithelium-derived growth factor (*LEDGF*), *cyclin C*, *STAT1β*, p300/CBP-associated factor and peroxisomal biogenesis factor 1 (*PEX1*) [112]. Therefore, manipulation of the splicing from predominantly STAT3α to prevalently STAT3β demonstrates a distinct favorable effect in breast cancer xenografts in contrast to a classical STAT3 knock-down.

Dang et al. overexpressed *STAT3β* in tumor-associated macrophages (TAMs) to analyze the impact of STAT3β on breast cancer progression and metastasis [114]. Their results indicate that STAT3β in TAMs significantly impairs motility and invasiveness of co-cultured breast cancer cells. Further, it prolonged survival and slowed the growth of breast tumors *in vivo* by inhibiting angiogenesis and metastasis [114]. This strongly suggests an important role for STAT3β in the regulation of TAMs and tumor-associated cells during breast cancer progression.

Interestingly, in patients with ESCC, STAT3β has been shown to serve as an independent protective prognostic marker, correlating with longer and recurrence-free survival [111]. In tumor xenografts, expression of *STAT3β* sensitized ESCC cells to chemotherapeutics and decreased the number of cancer stem cells. The authors of this study claimed that the tumor-suppressive effect of STAT3β arises from its heterodimerization with STAT3α, thus impairing its transcriptional activity [111]. However, pSTAT3(Tyr^{705}) was found to be upregulated in presence of STAT3β, as STAT3β also enhances phosphorylation of STAT3α [24,111].

Most mouse models for chronic inflammation-induced tumor formation focus on the pro-oncogenic role of STAT3 without considering the specific effects of its two different isoforms. However, Marino et al. demonstrated that a deletion of STAT3β in chemically-induced inflammation models accelerated the acute phase response and the subsequent inflammation *in vivo* [115]. Moreover, enhanced inflammation has been shown to correlate with a premature tumor onset in both the epidermis and intestine of mice lacking the STAT3β isoform. Regardless, final tumor burden and overall survival remained unaffected.

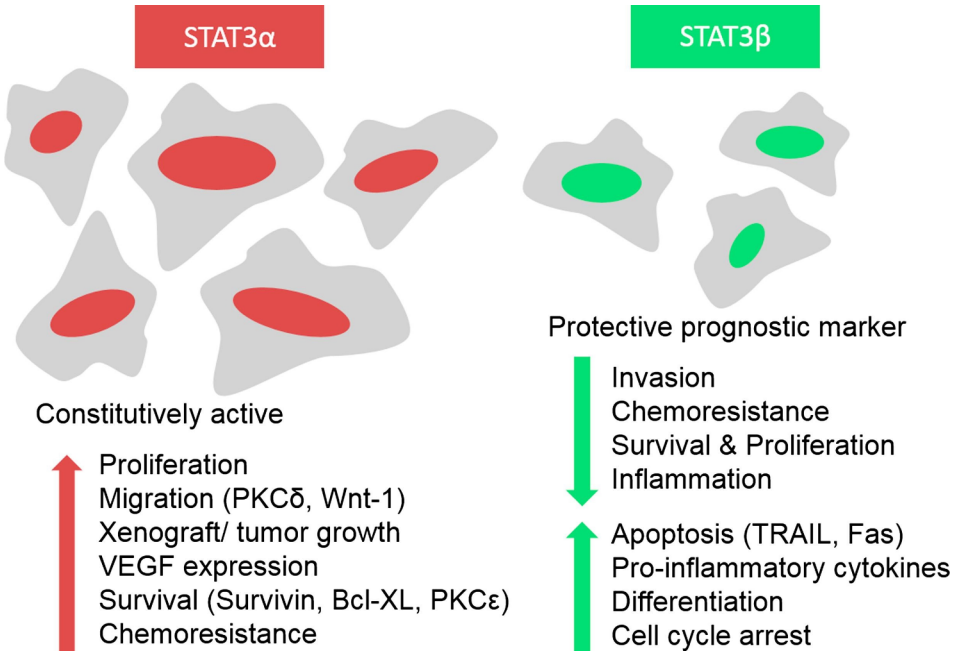

Fig. 2. Schematic overview of the specific roles of STAT3α and STAT3β in cancer. While STAT3α is found to be over-activated and to promote cancerogenesis, cancer progression and metastasis, STAT3β is described as an anti-tumorigenic factor in various tumor types. STAT3β has been shown to induce apoptosis, reduce metastasis and proliferation, diminish inflammation and decrease chemoresistance in cancer. It can further serve as a protective prognostic marker. These controversial functions of both STAT3 isoforms might be one major mechanism behind the heterogeneity of STAT3 in cancer.

These results demonstrate a protective role of STAT3β against inflammation and early stage inflammation-induced tumorigenesis. This further suggests that the previously observed pro-oncogenic effect of STAT3 in inflammation-induced cancers mainly depends on STAT3α activity [115]. The suppressive function of STAT3β in chronic inflammation was also demonstrated in an *in vivo* model for atherosclerosis. The authors of this study observed that *Stat3β*-deficient mice displayed higher expression levels of systemic inflammatory genes and were hypersensitive to lipopolysaccharides. In combination with a deletion of apolipoprotein E, the lack of *Stat3β* significantly enhanced atherosclerotic plaque formation, along with increased numbers of pro-inflammatory Th17 cells [116]. Another study reported that mice deficient for *Stat3β* suffered from more severe anti-glomerular basement membrane autoantibody-induced renal injury, similar to *IL-17* knockout mice [117]. At last, liver regeneration after endotoxic shock has been shown to be gravely impaired in *Stat3β*-deficient mice [17]. In summary, these results demonstrate that STAT3β has a protective role during inflammation and inflammation-induced tumorigenesis.

4. Summary

STAT3 is one of the most complex and versatile regulators of transcription. It is a key player during inflammation and cancerogenesis, where it mainly acts as an oncogene. However, several findings suggest an additional tumor-suppressive role for STAT3. This might be dictated by various mechanisms, one of which is alternative splicing of *STAT3* into two distinct isoforms, STAT3α and STAT3β. While STAT3α is crucial during embryonic and postnatal development, it was also demonstrated as an important oncogenic driver (Fig. 2). On the other hand, STAT3β is capable of negatively regulating STAT3α and thus impairing cancer progression. Recent studies postulate an additional, STAT3α-independent role for STAT3β, as they identified a large number of STAT3β-specific target genes. It has been shown that STAT3β can prolong phosphorylation and nuclear retention of STAT3α, without impairing its transcriptional activities. Moreover, STAT3β gained attention as a potent tumor suppressor and independent favorable prognostic marker in cancer (Fig. 2). Therefore, paying attention to both STAT3 isoforms rather than to only full-length STAT3 might be important in cancer research and treatment. However, the mechanisms underlying the pro-tumorigenic activity of STAT3α and the anti-tumorigenic function of STAT3β remain incompletely understood. Further investigations of the regulatory functions of both STAT3 isoforms in cancer will undoubtedly lead to significant insights into STAT3 biology and may impact future cancer therapies.

5. Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This review was inspired by the scientific discussions that arose during the 2nd International Aegean Conference on Cytokines and Cancer (May/June 2017, Crete, Greece). We thank Emilio Casanova, Eva Maria Zebedin-Brandl, Xavier Monforte Vila and Omar Sharif for critical reading of the manuscript. Financial support was provided by the St. Anna Children's Cancer Research Institute, Vienna, Austria, financing the position of PA.

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