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KIT as a therapeutic target for non-oncological diseases

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ABSTRACT

KIT is a receptor tyrosine kinase that after binding to its ligand stem cell factor activates signaling cascades linked to biological processes such as proliferation, differentiation, migration and cell survival. Based on studies performed on SCF and/or KIT mutant animals that presented anemia, sterility, and/or pigmentation disorders, KIT signaling was mainly considered to be involved in the regulation of hematopoiesis, gametogenesis, and melanogenesis. More recently, novel animal models and ameliorated cellular and molecular techniques have led to the discovery of a widen repertoire of tissue compartments and functions that are being modulated by KIT. This is the case for the lung, heart, nervous system, gastrointestinal tract, pancreas, kidney, liver, and bone. For this reason, the tyrosine kinase inhibitors that were originally developed for the treatment of hemato-oncological diseases are being currently investigated for the treatment of non-oncological disorders such as asthma, rheumatoid arthritis, and alzheimer's disease, among others. The beneficial effects of some of these tyrosine kinase inhibitors have been proven to depend on KIT inhibition. This review will focus on KIT expression and regulation in healthy and pathologic conditions other than cancer. Moreover, advances in the development of anti-KIT therapies, including tyrosine kinase inhibitors, and their application will be discussed.

Contents

Abbreviations: aa, aminoacid; AD, alzheimer's disease; ALS, amyotrophic lateral sclerosis; BCR-ABL, BCR-Abelson fusion protein; BM, bone marrow; CNV, corneal neovascularisation; CSC, cardiac stem cell; DC, dendritic cell; ERK, extracellular signal-regulated kinase; FLT3, fms related tyrosine kinase 3; GI, gastrointestinal tract; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSC, hematopoietic stem cell; HSPC, hematopoietic stem/progenitor cell; ICC, interstitial cell of Cajal; KIT, cellular homolog of the feline sarcoma viral oncogene v-KIT; MAPK, mitogen-activated protein kinase; MC, mast cells; MIFT, microphtalmia-associated transcription factor; miR, microRNA; MMP9, matrix metallopeptidase 9; MS, multiple sclerosis; MSC, mesenchymal stem cell; mSCF, membrane stem cell factor; mTOR, mechanistic target of rapamycin kinase; NK, natural killer cells; NSC, neuronal stem cell; PAH, pulmonary arterial hypertension; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PGM, primordial germ cells; PKC, protein kinase C; RA, rheumatoid arthritis; RAc, retinoic acid; SCF, stem cell factor; SDF-1α, stromal cell-derived factor 1α; Sl, steel; SOHLH, spermatogenesis and oogenesis HLH; SOX, sex determining region Y-box; SS, systemic sclerosis/scleroderma; sSCF, soluble stem cell factor; STAT, signal transducer and activator of transcription; T1D, type 1 diabetes; TKI, tyrosine kinase inhibitor; tr-KIT, truncated KIT; UV, ultraviolet; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; W, white spotting.

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1. Introduction

Tyrosine kinases are critical enzymes in signal transduction pathways that transfer a phosphate group from ATP to a target protein's tyrosine residue (Cohen, 2000). This protein phosphorylation acts as an on/off switch for a variety of cellular activities including the regulation of cell growth, differentiation, apoptosis, migration, immune responses, adhesion, and metabolism (Manning, 2002). Tyrosine kinases are further subclassified in receptor tyrosine kinases and non-receptor tyrosine kinases and both subclasses are involved in the activation of intracellular protein kinases that amplify and propagate the signal by further activating downstream enzymes and transcription factors, which ultimately will modulate gene expression.

KIT (CD117) is a tyrosine kinase receptor belonging to subclass III of receptor tyrosine kinases, which also includes platelet-derived growth factor receptor (PDGFR) and macrophage colony stimulating factor (M-CSF) receptor (André, 1992). The KIT specific ligand is stem cell factor (SCF), and after binding, they induce multiple signaling cascades found to be essential for biological processes including cell proliferation, differentiation, migration, and survival (Lennartsson and Ronnstrand, 2012). KIT and SCF are respectively encoded in the white spotting (W) and the steel (Sl) locus in both human and mice (Geissler, 1988; Zsebo, 1990; Huang, 1990). Mice with loss-of-funtion mutations in any of these loci present defects in pigmentation, anemia and sterility, highlighting the importance of SCF/KIT signaling in melanogenesis, hematopoiesis, and gametogenesis (Russell, 1979). Moreover, expression data for both SCF and KIT suggest important roles for KIT signaling in the nervous system, gastrointestinal (GI) tract, heart, lung, kidney, pancreas, and bones.

The discovery of dysregulated levels of KIT signaling in several types of cancer stimulated studies on the structure and molecular function of this receptor, as well as on its downstream signaling pathways. In fact, most of the publications dealing with KIT function are related to tumoral processes and potential KIT-targeted therapies for cancer (reviewed in Lennartsson and Ronnstrand, 2012; Roskoski, 2018). In this regard, the relevance of tyrosine kinase therapies in the treatment of oncologic diseases has been extensively proven. More recently, these agents are being widely investigated for their potential therapeutic use in non-oncologic diseases that involve inflammatory and/or autoimmune processes. In diseases presenting increased numbers of and/or overactivated mast cells (MC), cells that depend on KIT signaling for their development, proliferation, activation, and survival, the use of KIT inhibitors as a therapeutic option can be easily envisioned. In this line, several publications endorse the utilization of tyrosine kinase inhibitors (TKI) targeting multiple tyrosine kinases, including KIT, for the treatment of diseases such as asthma (Humbert, 2009; Cahill, 2017), rheumatoid arthritis (Eklund, 2008; Tebib, 2009), systemic sclerosis (Spiera, 2011a; Fraticelli, 2014), and Alzheimer's disease (Piette, 2011), among others.

In recent years, new regulators of the SCF/KIT signaling pathway, including cytokines, growth factors, transcription factors, epigenetic factors, and microRNAs, have been unveiled. The latter have contributed valuable insight into the pathophysiological processes known to be regulated by SCF/KIT, but have also unraveled new processes regulated by their signaling.

This review will focus on recent findings regarding KIT expression and regulation in healthy and pathologic conditions other than cancer. Advances in the development of anti-KIT therapies directed against diseases such as asthma, rheumatoid arthritis, and neurobiological disorders, as well as completed or ongoing clinical trials, will be discussed.

2. Molecular biology of KIT

The v-KIT oncogene was first identified in 1986 as the transforming gene of the Hardy-Zuckerman 4 feline sarcoma virus, and the cellular counterpart KIT soon after (Besmer, 1986). It is encoded in the W locus on human chromosome 4q11-q12 and murine chromosome 5 (Yarden, 1987; Grissler, 1988). The *KIT* gene is composed of 21 exons: exon 1 encodes the 5′-untranslated region and the signal peptide; exons 2-9 encode the extracellular domain; exon 10 encodes the transmembrane domain and the remaining exons encode the intracellular domain (Chu and Besmer, 1995). The extracellular region consists of five immunoglobulin (Ig)-like domains involved in ligand binding and receptor dimerization, while the transmembrane domain allows KIT anchoring in the plasma membrane. The cytoplasmic region is composed of a tyrosine kinase domain split in two by an interkinase domain and it is responsible for SCF/KIT signaling.

Different isoforms of KIT have been identified as a consequence of alternative splicing of *KIT* RNA. Two of these isoforms, in both humans and mice, differ by the presence or absence of the tetrapeptide sequence GNNK in the juxtamembrane region, with the $GNNK^-$ isoform being the predominant one (Hayashi, 1991; Zhu, 1994). Additional splice variants, found only in humans, result in the presence or absence of a serine residue in the interkinase domain. In addition, the use of an alternative intronic promoter produces a truncated version of KIT (tr-KIT) consisting of the second part of the kinase domain and the C-terminal tail (Rossi, 1992). This tr-KIT lacks kinase activity, but is able to induce signaling through adapter proteins. Finally, the KIT receptor can be cleaved by proteolysis, generating a soluble isoform composed by the extracellular domain. The latter is probably involved in the modulation of SCF bioactivity (Fig. 1A).

3. Molecular biology of SCF

SCF, also known as KIT ligand, is encoded in the steel (Sl) locus in human chromosome 12q22-q24 and murine chromosome 10 (Zsebo, 1990; Huang, 1990). The SCF gene consists of 9 exons: Exon 1 encodes the 5'-unstranslated region and signal peptide; exons 2-7 encode the extracellular domain and exon 7 also encodes a transmembrane domain; exon 8 encodes a short intracellular domain (Martin, 1990). Alternative splicing of the sixth exon of SCF RNA gives rise to two isoforms (Andersson, 1991; Flanangan, 1991). Both isoforms encode membrane-bound proteins containing extracellular, transmembrane and intracellular domains. The longer SCF isoform [248 aminoacids (aa)] is rapidly cleaved to generate a 165 aa soluble protein. The shorter SCF isoform (220 aa) lacks exon 6 and remains membrane-bound, but might also be cleaved by proteases to generate a soluble form (Fig. 1B). SCF exists as a non-covalent homodimeric conformation. Both mSCF and sSCF bind and activate KIT. However, mSCF induces persistent activation and prolonged KIT lifespan, whereas sSCF induces KIT transient activation and faster degradation. The sSCF/mSCF ratio varies between cells and tissues and both isoforms trigger different downstream KIT signaling cascades.

4. SCF/KIT expression

Loss-of-function studies involving the W and Sl loci have revealed critical roles for SCF/KIT in the migration and differentiation of hematopoietic, germ cell and melanoblast lineages. In this line, KIT is expressed by hematopoietic progenitors as well as committed hematopoietic cells such as mast cells (Galli, 1995; Kitamura, 2006) (they also express SCF), eosinophils (Oliveria, 2002), dendritic cells (DC)(Krishnamoorthy, 2008) and some subsets of natural killer cells (Matos, 1993). Epidermal melanocytes, oocytes in primary follicles and spermatogonia complete the array of SCF/KIT-expressing cells which correspond to the phenotype of SCF/KIT mutated animals (Matsui, 1990; Keshet, 1991). However, SCF and KIT expression patterns have been shown to go beyond these specific compartments. In humans, KIT and SCF immunohistochemical staining have been detected in specific cell types of the breast, uterus, prostate, salivary gland, gastrointestinal tract smooth muscle and interstitial cells of Cajal, heart muscle and cardiac progenitor cells, endothelial cells, lung, sweat glands, the central nervous system, and

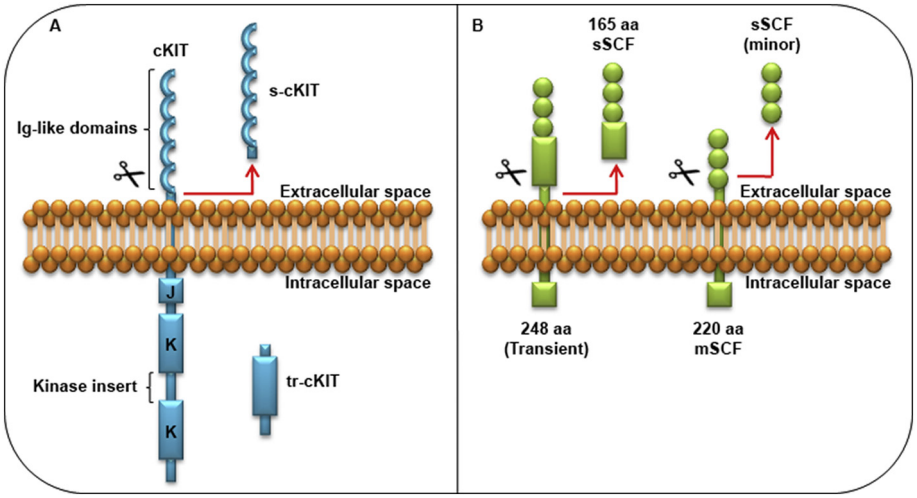

Fig. 1. Structural organization of KIT (A) and SCF (B) proteins and their isoforms. A, KIT protein is composed of an extracellular region consisting of 5 immunoglobulin (Ig)-like domains, a transmembrane domain, a juxtamembrane (j) domain, and two kinase (K) domains connected by an interkinase domain. KIT can be cleaved, generating a soluble isoform (s-KIT) composed of the extracellular region. A truncated version of KIT (tr-KIT) is obtained after using an alternative promoter. B, SCF is composed of extracellular, transmembrane and intracellular domains. SCF RNA can be alternatively spliced and give rise to 2 different membrane isoforms: one transiently expressed and cleaved to give rise to the major soluble SCF isoform (sSCF), and the other that represents the main membrane SCF form (mSCF). The latter can be cleaved and give rise to a minor sSCF isoform.

placenta. In mice, a similar distribution has been reported at both the RNA and protein levels (Bernex, 1996). The overlapping of KIT and SCF expressions in multiple tissues suggest the existence of autocrine mechanisms for KIT activation, confirmed in several cancer conditions.

5. SCF/KIT signal transduction

SCF homodimers bind to KIT inducing receptor homodimerization, autophosphorylation, and subsequent initiation of multiple signal transduction pathways. Only the first three Ig-like domains are strictly involved in SCF binding (Lemmon, 1997). Ligand binding promotes a conformational change that enables homotypic interactions between Ig-like domains 4 and 5 in two adjacent KIT molecules, thus stabilizing the ligand-receptor union. In addition, this conformational change potentiates the juxtaposition of both transmembrane and intracellular adjacent domains, facilitating tyrosine kinase domain activation and subsequent transphosphorylation (Yuzawa, 2007). The main phosphorylation sites found *in vivo* are tyrosine (Tyr)-568, -570, -703, -721, -730, -823, -900, and -936, while tyr-547 and -553 are two additional sites identified in *in vitro* activated kinase domain (DiNitto, 2010). Once KIT is activated, the phosphorylation of these sites has been demonstrated to happen in an orderly manner. Seven of these tyrosine residues, once phosphorylated, act as docking sites for signaling molecules with Src homology 2 (SH2) domains, which in turn initiate intracellular signaling pathways. The main signaling cascades activated by the SCF/KIT system are the mitogen activated protein kinase (MAPK) pathway; the phosphatidyl-inositol-3 kinase (PI3K) pathway; the phospholipase C-γ pathway; the Src pathway; and the janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway (Fig. 2). Each of these pathways has been extensively studied in normal and pathological conditions. A detailed description is out of the scope of this review, but the latter pathways have been nicely presented by others (Reber, 2006; Lennarstsson and Ronnstrand, 2012).

The downregulation of KIT signaling is important for controling the intensity and duration of signal transduction appropriate to each biological response. There are three main ways to modulate KIT signaling: 1) receptor internalization and degradation, 2) inactivation of kinase domain by serine phosphorylation, and 3) tyrosine dephosphorylation. Cbl protein recruitment after SCF stimulation leads to its phosphorylation, which mediates KIT ubiquitination and degradation occurring in both proteasomes and lysosomes (Zeng, 2005). Suppressor of cytokine signaling (SOCS)-1 and 6 are also involved in KIT signaling downregulation (De Sepulveda, 1999). Inactivation of the KIT protein kinase domain by serine phosphorylation is mediated by protein kinase C (PKC) activity in a negative regulatory feedback loop (Yei, 1993). Finally, the tyrosine protein phosphatase SHP1 is able to bind and attenuate KIT signaling by dephosphorylation of its kinase domain.

6. Function of KIT in different biological processes

6.1. Hematopoiesis

Hematopoiesis is the process that leads to the formation of blood cells. This biological process is finely regulated by a myriad of cytokines (including SCF) which cause survival, proliferation and differentiation of hematopoietic stem/progenitor cells (HSPCs) (Broudy, 1997). KIT expression has been found in hematopoietic stem cells and progenitor cells, but decreases with differentiation (Ogawa, 1991; Okada, 1991). A few exceptions exist, such as mast cells, dendritic cells, eosinophils, and certain sets of natural killer cells and lineage committed hematopoietic cells, which maintain variable levels of KIT (Matos, 1993; Oliveira, 2002; Kitamura, 2006; Krishnamoorthy, 2008). Mutations at the W locus in mice are linked to defects in erythrocyte, megakaryocyte and mast cell development, and lethality in these mice is due to anemia (Lev, 1994; Russell, 1979).

Embryonic hematopoiesis takes place in a range of different locations that change according to the developmental stage of the embryo or fetus and the formation of supportive niches (Al-Dres, 2015). During embryonic and fetal development, KIT^{+}-HSPCs have been found in different compartments with a gradual increase on day 8 of the embryonic period up to day 15, after which they decrease. A recent study has shown that SCF, and not interleukin (IL)-3, is the key factor for the maturation of a specific type of HSPC precursor (pro-HSPC) during the embryonic period (Rybstov 2014), confirming SCF-KIT signaling as a key element for embryonic hematopoiesis regulation.

In adult hematopoiesis, basically restricted to the bone marrow, KIT is expressed in both HSC and hematopoietic progenitors without stem cell activity (Fig. 3). The duality of KIT in preserving the quiescence and self-renewal activity of HSC and promoting proliferation in hematopoietic progenitors that are programmed to differentiate is still not clearly understood. Shin and co-workers have recently described two populations of HSPC, one presenting high (KIT^{hi}) levels of KIT expression and signaling and the other low (KIT^{lo}) levels. While the KIT^{lo} subset exhibited enhanced self-renewal and long-term reconstitution

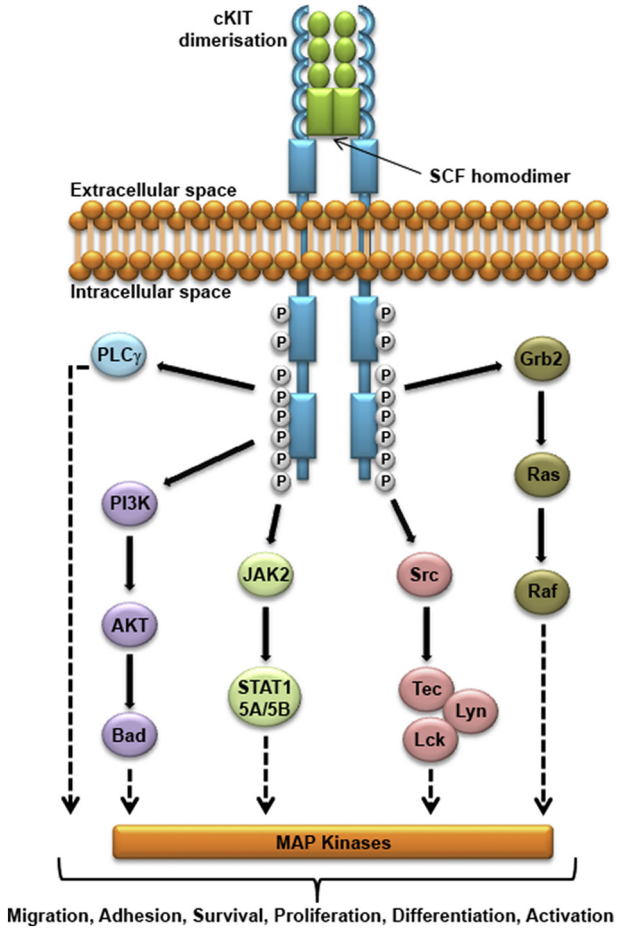

Fig. 2. KIT signaling pathways. A SCF homodimer binds to KIT and induces KIT homodimerisation and autophosphorylation, consequently activating different signaling pathways, including phospholipase C γ (PLCγ), phosphatidyl-inositol-3 kinase (PI3K), janus kinase 2 (JAK2), growth factor receptor-bound protein 2 (Grb2), and Src signaling. Some of these pathways will lead to the induction of the mitogen activated protein (MAP) kinase signaling, promoting regulatory effects on biological processes such as migration, adhesion, survival, proliferation, differentiation, and activation. AKT, alpha serine/threonine kinase; STAT, signal transducer and activator of transcription.

potential, the KIT^{hi} subset favored the megakaryocyte lineage commitment (Shin, 2014). Moreover, a positive feedback loop has been recently described for KIT and protein-tyrosine phosphatase non-receptor type 11 (PTPN11), as well as for KIT and stem cell leukemia (Scl), proteins controlling HSC quiescence, survival, and/or self-renewal activity (Zhu, 2011; Lacombe, 2013).

High-throughput data analysis studies have led to a better characterization of the subpopulations of HSC and progenitor cells and their relationship with specific gene expression programs and regulatory networks involved in stem cell fate choices (Moignard-2013; Wilson, 2015). However, it remains to be elucidated how KIT expression is regulated in HSPCs. Two transcription factors have been recently involved in KIT regulation in HSPCs. Signal transducer and activator of transcription 5 (STAT5)-induced microRNA (miR)-193b expression restricted uncontrolled murine HSPC expansion by inhibiting KIT expression in these cells (Haetscher, 2015). GATA transcription factor (GATA)-2 maintained KIT expression in HSPCs, thus sustaining myelopoiesis and avoiding bone marrow failure (Li, 2015). Zinc finger protein 16 binds and inhibits KIT expression in order to control erythroid and megakaryocytic differentiation in both K562 cells and human HSPCs (Chen, 2014). Other molecules control KIT expression at a translational level, including proviral insertion in murine lymphoma 1 (Pim-1) and RanBPM (An, 2016, Puverel, 2016).

Among the mature hematopoietic cells expressing KIT, mast cells represent the lineage where the SCF-KIT axis functions have been better characterized. It is well known that mast cells depend on SCF for their proliferation, differentiation, survival and function (Galli, 1995; Linnekin, 1999; Kitamura, 2006). Although MC activation by SCF was always thought to depend on prior IgE-priming, a recent study reported that high concentrations of SCF were able to activate human pulmonary MC for the secretion of histamine, cysteine leukotriens and prostaglandin D2 (PGD2), independently of IgE-priming (Lewis, 2013). Silencing of the adaptor protein 3BP2, a positive regulator in MC FcεRI-dependent signaling, decreases KIT expression and stimulates apoptosis in human MC, while establishing a positive regulatory loop (Ainsua-Enrich, 2015). Other molecules recently reported as controlling MC survival are GATA2 and STAT5 (Li, 2015). On the contrary, activation of KIT by means of SCF or via KIT-activating mutations promoted TNF-related apoptosis-inducing ligand receptors (TRAILR) activation on human MC, inducing their apoptosis (Förster, 2015). The SCF-KIT axis also plays an important role in MC migration and tissue distribution via ADAM-10 (a disintegrin and metalloprotease domain) both in *in vivo* and *in vitro* murine models (Faber, 2014).

SCF has a number of effects on eosinophils, in addition to promoting their generation from bone marrow progenitors, a process that is enhanced by granulocyte colony stimulating factor (G-CSF) (Metcalf, 2002). In this line, eosinophil adhesion to integrins and consequent tissue distribution depends on the expression of a functional KIT receptor (Yuan, 1997). Moreover, SCF promotes eosinophil activation and release of eosinophil peroxidase (EPO), leukotriene C4, and several chemokines (Oliveira, 2002).

Although KIT expression seems to be limited on mature dendritic cells, different stimuli are able to induce and activate this receptor. Cholera toxin and house dust mite (HDM), Th2 and Th17 inducing stimuli, were able to induce KIT expression and IL-6 production in dendritic cells, leading to an immune skewing towards Th2 and Th17 responses (Kryshnamoorthy, 2008). A similar effect is observed in humans, where KIT silencing on monocyte-derived DC enhanced Th1 response inducing interferon (IFN)-γ and reducing IL-4 production (Yang, 2014). The KIT rise induced by HDM on DC seems to be mediated via toll-like receptor (TLR)-2 since its inhibition produces a decrease in KIT expression and IL-6 production (Wu, 2015). Another publication demonstrated that the induction of a Th17 response by DC via IL-23 production in murine lungs depended on KIT and mSCF (Oriss, 2014). A recent study demonstrated that granulocyte-macrophage colony-stimulating factor (GM-CSF) added for the *in vitro* culture of bone marrow-derived dendritic cells (BMdDC) downregulated both SCF and KIT expression and that SCF silencing produced a small but significant decrease in BMdDC survival (Barroeta Seijas, 2017). The authors speculated that *in vivo,* DC may more markedly rely on SCF signaling and that this effect might have been overlooked due to the extensive use of GM-CSF in DC cultures *in vitro*.

A small subset of CD56^{bright} natural killer (NK) cells express KIT receptor, and SCF alone or combined with other cytokines (ie. IL-2, IL-15) have been involved in the regulation of survival, expansion, and maturation of natural killer cells (Matos, 1993; Colucci, 2000; Benson, 2009). While human CD56^{bright} NK cells in peripheral blood express low levels of KIT receptor, *in vitro*, they presented an augmentation of this receptor and became responsive to SCF stimulation, in association with increased degranulation. Moreover, KIT increase promoted the tight adhesion of NK cells to COS cells transfected with the membrane form of SCF. The authors suggested that KIT receptor might be decreased in peripheral blood NK cells to render these cells unresponsive to the SCF therein (Pradier, 2014).

6.2. Gametopoiesis

In the early stages of prenatal life, the undifferentiated human gonad is composed of different types of somatic cells and primordial germ cells

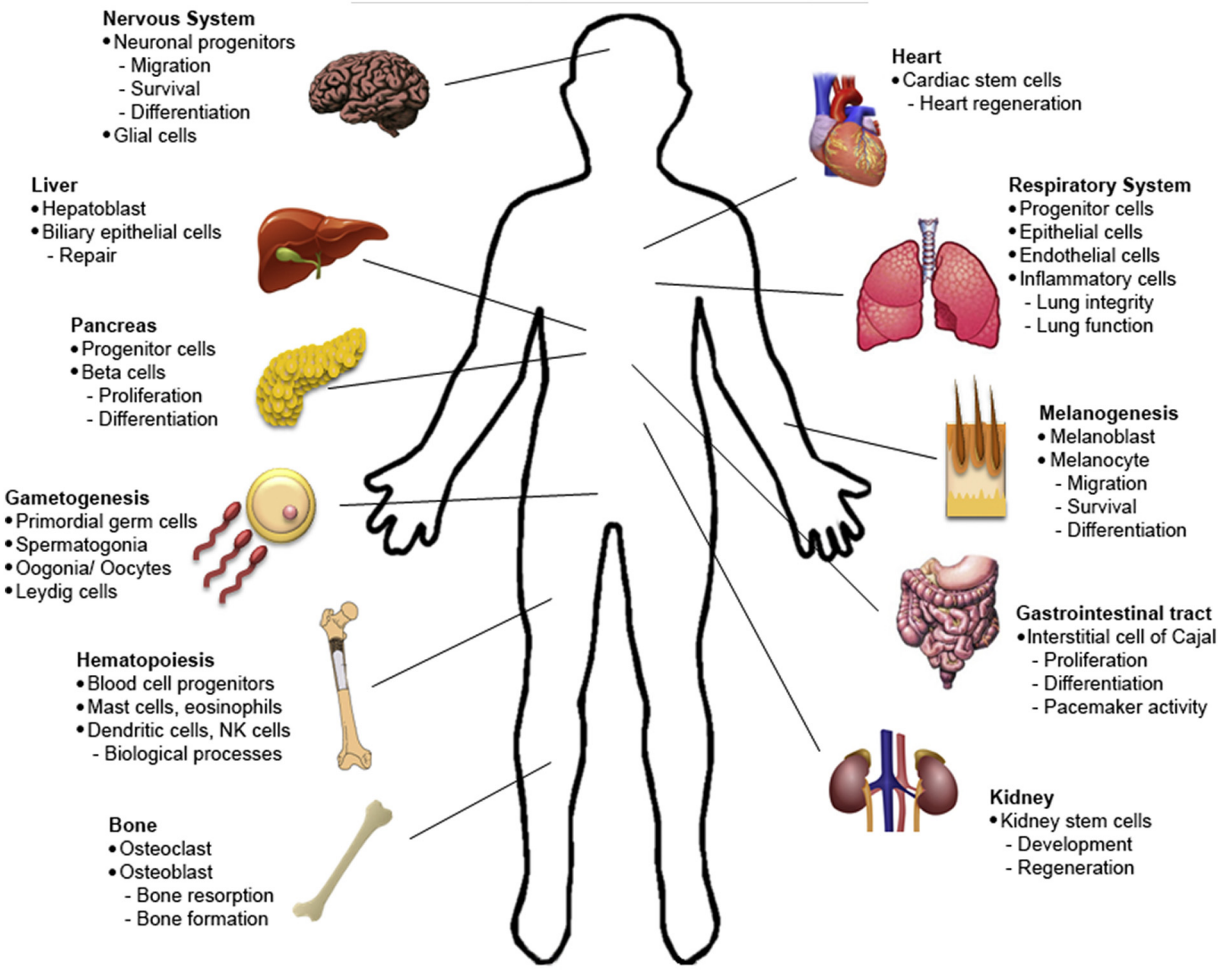

Fig. 3. Overview of KIT expression and main functions. KIT is expressed in stem/progenitor cells of the brain, heart, lung, hematopoietic compartment, reproductive tract, pancreas and kidneys. It plays a role in biological processes such as cellular migration, survival, proliferation, and differentiation, and in physiological functions such as development, tissue repair/regeneration and pacemaker activities. NK, natural killer. For detailed explanations refer to the main text.

(PGC). PGCs migrate to the genital ridges from the base of the allantoid and begin to actively proliferate in coincidence with the expression of KIT (Manova and Bachvarova, 1991). After this stage, PGC enter in a differentiation phase which ultimately leads to the formation of mature gametes. The involvement of the SCF-KIT system in the development and/or physiology of the male and female reproductive systems was first identified in W and Sl mutants, which presented with different degrees of sterility (Besmer, 1993). These loss-of-function mutations affect the survival, migration and proliferation of primordial germ cells and result in a severe decrease of PGC and consequent defects on different steps of spermatogenesis and oogenesis.

6.2.1. SCF and KIT expression

KIT has been proposed as a good marker for the isolation of a pure germ-cell population (Izadyar, 2011; Sa, 2013). In adult rat, mouse and human testis, and during the different phases of spermatogenesis (proliferation, meiosis, differentiation), KIT presents a dynamic expression pattern (Hess and Renato de Franca, 2008). It is mainly expressed in type A spermatogonia but it is also found in early spermatocytes. In the latest stages of spermatogenesis, KIT is replaced by its truncated form, which becomes predominant in round spermatids and spermatozoa (Sette, 2000; Muciaccia, 2010). In both humans and mice, the expression of the truncated form in spermatids depends on the activation of a developmental stage-specific promoter in the *KIT* gene (Albanesi, 1996; Paronetto, 2010; Muciaccia, 2010). Leydig cells, the testosterone producing cells, also express KIT in a consistent manner (Unni, 2009; Tsikolia, 2009). In human fetal ovaries, as well as in mouse and sheep ovaries, KIT expression is highly detected in proliferating oogonia and ceases by initiation of meiosis. However, KIT expression is resumed as soon as oocytes are enclosed in primordial follicles and continues at all the stages of post-natal development (Hoyer, 2005; Driancourt, 2000) (Fig. 3).

SCF expression in the male gonad has been mainly detected in Sertoli cells, which represent the support niche for developing germ cells in the seminiferous tubules (Mruk and Chen, 2004). In rat postnatal testis, SCF-positive staining was also found in gonocytes and spermatogonia (Unni, 2009; Muciaccia, 2010). In ovaries, the granulosa cells surrounding the oocytes are the main source of SCF (Manova, 1993), but SCF expression has also been reported in gonocytes/oogonia of the early fetal human ovary (Hoyer, 2005).

6.2.2. Role of SCF-KIT system

Decreased expression of SCF or KIT and aberrant SCF-KIT signaling in human testis have been associated with male infertility (Sandlow, 1997; Feng, 1999; Malcher, 2013). In this regard, the interaction of mSCF from Sertoli cells with KIT in germ cells has been considered essential for the survival of germ cells, causing this effect by apoptosis suppression (Tu, 2007). In fact, mice unable to produce mSCF and rats haplodeficient for KIT present different degrees of sterility, linked to increased rates of germ-cell apoptosis (Sato, 2012; Guerif, 2002). By contrast, administration of SCF to rat seminiferous tubule cultures *in vitro* renders protection against apoptosis to spermatogonia, spermatocytes, and

spermatids (Yan, 2000). SCF/KIT signaling is also involved in the maintenance of Leydig cells and their testosterone production (Unni, 2009; Tsikolia, 2009; Rothschild, 2003).

Tr-KIT has been found to be involved in the activation and fertilization of oocytes and seems to be a good marker of sperm quality. Although lacking kinase activity, tr-KIT seems to retain signal transduction capabilities (Sette, 1997; Sette, 2002; Muciaccia, 2010).

SCF-KIT signaling has an important role in the migration of germ cells during the developing genital ridge (Packer, 1994; Orth, 1997). It has also been shown to have an anti-apoptotic effect on PGC, oogonia and oocyte, and to be involved in the initiation of primordial follicle growth and the progression beyond the primary follicle stage (Driancourt, 2000). Moreover, the SCF-KIT system in post-natal oocytes seems to be important for their growth and maturation (Klinger and DeFelici, 2002; Hutt, 2006). Recent publications support the idea that germline stem cells, identified among others by KIT expression, are found in the adult ovaries of several mammals (Parte, 2011; White, 2012; Bui, 2014).

Besides its role in gametogenesis, KIT has recently been reported to play a role in the development of male gonads. In this line, a small population of KIT positive cells, also positive for CD140a and F4/80, was critical for *in vivo* testicular reconstitution in a mouse model in which the technique of testicular cell-derived tissue was used (Zhang, 2014).

6.2.3. Regulation of SCF-KIT system

Several reports dealt with the specific regulatory mechanisms acting upstream or downstream of the SCF-KIT system and at different stages of gametogenesis. SCF via KIT activates the PI3K/AKT/mechanistic target of rapamycin kinase (mTOR)/p70 S6 kinase pathway, leading to spermatogonial differentiation (Feng, 2000; Dolci, 2001). In fact, a point mutation (Y719F) in the PI3K binding site on the KIT receptor rendered mice sterile due to a block in spermatogenesis (Blume-Jensen, 2000). In a similar model, where the KIT binding site for the regulatory subunit (p85) of PI3K was mutated, these results were confirmed and extended to females, in which follicle development was impaired and resulted in reduced fertility (Kissel, 2000). Two other publications focused on the inactivation of the PI3K-p110β isoform to prove its involvement in the KIT-mediated male infertility phenotype (Ciraolo, 2010; Guillermet-Guibert, 2015).

Retinoic acid (RAc) has long been known to induce spermatogonial differentiation by stimulating KIT expression in undifferentiated spermatogonia (Pellegrini, 2003; Pellegrini, 2008; Zhou, 2008). Recently, the PI3K/AKT/mTOR signaling pathway has been implicated in this effect (Busada, 2015). The induction of the SALL4A and the inhibition of the promyelocytic leukemia zinc finger (PLZF) transcription factors have been involved in the KIT-mediated spermatogonial differentiation upon RAc stimulation (Gely-Pernot, 2015; Filipponi, 2007; Dann, 2008; Pellegrini, 2008).

Elevated levels of 17β-estradiol, similar to that found in sterile patients, were found to reduce KIT expression in rat testis, resulting in more apoptosis and less proliferation of germ cells (Correia, 2014). Phosphatase of regenerating liver 2 $(PRL2)^{-/-}$ mice showed increased levels of the tumor suppressor PTEN (phosphatase and tensin homologue deleted on chromosome 10) in the testis that lead to attenuated KIT/PI3K/AKT signaling, finally inducing an increase in germ cell apoptosis and a decrease in spermatozoa production (Dong, 2014). In relation to the pro-survival effect of the SCF-KIT signaling in spermatogonial cells, it has been reported that the inhibition of this pathway in testicular cells promoted a decrease in the anti-apoptotic BCL-w protein levels and an increase in the pro-apoptotic Bcl-2-associated X protein (BAX) and Bcl-2 homologous antagonist killer (BAK) proteins (Yang, 2000). Moreover, survival was found to increase in response to SCF in Leydig cells and germ cell cultures (Wang, 2004).

The transcription factors SOHLH1 (spermatogenesis and oogenesis HLH1) and SOHLH2, specifically expressed in germ cells, have been involved in spermatogonia and oocyte differentiation. In males, the deletion of these transcription factors abrogates KIT-expressing spermatogonia in prepuberal testis, while in females, oocyte loss is detected in the neonatal ovary (Pangas, 2006; Toyoda, 2009; Suzuki, 2012). Both transcription factors directly bind to *KIT* (Barrios, 2012; Suzuki, 2012) and the double sex-related transcription factor (DMRT1) seems to play a role in SOHLH1-mediated function (Matson, 2010). SOX2 regulated murine PGC proliferation via KIT *in vivo,* whereas it presented no such effect on oocytes (Campolo, 2013).

A recent publication reported that miR-221 was able to decrease KIT protein expression in testis-derived cell line cultures (Smorag, 2012) and, *in vivo*, the miR-221-222 cluster seems to play a crucial role in maintaining the undifferentiated state of mammalian spermatogonia through repression of KIT expression (Yang, 2013). Moreover, a disruption of the miR17-92 cluster in mice testis produced severe testicular atrophy and decreased sperm production; the authors suggested a direct association with the elevated KIT levels found in the testis of these animals (Xie, 2016).

6.3. Melanogenesis

Melanogenesis is the process by which melanocytes produce melanin pigment in the skin, hair and eyes. Melanoblasts, the precursor cells of melanocytes, originate from the embryonic neural crest (Sviderskaya, 2001; Lei, 2002) and migrate to the basal layer of skin epidermis and hair follicles (Gibbs, 2000; Cichorek, 2013). Melanocytes will proliferate, migrate, produce melanine-containing melanosomes, and transfer them to the surrounding keratinocytes (Lin, 2007; Delevoye, 2014). Melanin absorbs ultraviolet light (UV) and serves as a protection against UV radiation from sunlight (Anderson, 1981). In mammalian skin, the SCF-KIT axis has been found to modulate melanocyte migration, differentiation, melanogenesis, and melanocyte survival/apoptosis (Wehrle-Haller, 1995; Luo, 1995; Costa, 1996; Kunisada, 1998; Botchkareva, 2001). In fact, the heterozygous mutation of *KIT* in humans, results in the pigmentation disorder piebaldism (Giebeld, 1991). Moreover, different mutations in the SCF gene are responsible for familial progressive hyper- and hypopigmentation (FHHP) and familial progressive hyperpigmentation (FPH) disorders (Amyere, 2011; Wang, 2009). *KIT* mutations cause dominant white spotting in pigs (Fontanesi, 2010), and white coat color in horses and mice (Geissler, 1988; Haase, 2007).

6.3.1. SCF and KIT expression

Bernex *et al.* used heterozygous ($W^{lacZ}/+$) and null mutant (W^{lacZ}/W^{lacZ}) mice embryos to show KIT expression in melanoblasts as early as embryonic day (E) 10.5, the moment at which melanoblast migration begins. Melanoblast migration was severely impaired from E15.5 in heterozygous embryos and from E10.5 onwards in the complete absence of KIT (Bernex, 1996). SCF expression is found from E12.5 in a continuous wide layer adjacent to the sites of melanocyte migration (Matsui, 1990). In contrast to the mouse, SCF is expressed in the adult human epidermis where it plays an important role in the homeostasis of epidermal KIT-expressing melanocytes (Grichnik, 1998). Although mouse melanocytes are not found in the interfollicular epidermis as is the case for human melanocytes, they can be rescued by forced expression of cytokines (such as endothelin-3, SCF, or hepatocyte growth factor) by basal keratinocytes (Hirobe, 2005; Saldana-Caboverde and Kos, 2010). In regards to KIT expression in mice hair follicles, Peters *et al.* showed that most of the intraepithelial KIT immunoreactivity found in developing murine back skin corresponded to melanoblasts undergoing migration into the developing hair follicle epithelium (Peters, 2002).

6.3.2. The role of SCF-KIT system

Different groups have modulated SCF and/or KIT expression in order to demonstrate the importance of the SCF-KIT signaling pathway in regulating mammal skin color (Fig. 3). Blocking KIT expression by using the ACK2 antibody showed a reduction in melanoblast differentiation and

melanocyte proliferation (Nishimura, 2002). Similarly, administration of small molecules inhibiting KIT demonstrated inhibition of melanogenesis in mice, guinea pigs, and human beings (Brazzelli, 2007; Na, 2007). The injection of KIT or SCF blocking antibodies into human skin explants grafted on nude mice, also resulted in the loss of melanocytes, whereas sSCF injection led to hyperpigmentation of the explanted skin tissue (Spritz, 1994; Grichnick, 1998). During melanocyte development, sSCF and mSCF have been found to be critical for migration and survival, respectively (Werhler-Haller, 1995), mSCF acting in a synergistic way with integrins to promote the anchoring of melanocytes within intraepithelial niches (Tabone-Eglinger, 2012). In human melanocytes, soluble KIT has been found to decrease SCF-induced melanogenesis by inhibiting the phosphorylation of its membrane counterpart (Kasamatsu, 2008).

Interestingly, generalized skin hypopigmentation is a benign side effect found after administration of imatinib mesylate (Leong, 2004; Brazzelli, 2007; Aleem, 2009), a potent tyrosine kinase inhibitor used for the treatment of multiple types of cancer. In human primary epidermal melanocytes, Wang and colleagues found that imatinib inhibited melanocyte proliferation, survival, and melanogenesis by suppressing the expression of tyrosinase and microphtalmia-associated transcription factor (MITF). Moreover, they found that SCF-stimulated KIT activation and melanocyte proliferation was completely abrogated by imatinib (Wang, 2014b).

Both, SCF and endothelin-1 pathways are crucial during embryonic and postnatal melanocyte function (Grichnick, 1998; Hachiya, 2001; Aoki, 2005). Additionally, they have been suggested to play roles in senile lentigo, the benign hyperpigmentation macules that are commonly found in photo-aged skin (Kadono, 2001; Hattori, 2004). Sriwiriyanont *et al.* studied pigmentation of human skin xenografts on mice after SCF and/or ET-1 and found an additive effect on tyrosinase gene expression and subsequent enhancement of melanin content and skin pigmentation (Sriwiriyanont, 2006). A critical role of SCF-KIT in the pigmentary unit during hair follicle regeneration has also been suggested (Botchkereva, 2001). In this line, Hachiya *et al.* demonstrated that administration of a KIT-neutralizing antibody abolished MITF and tyrosinase expression, resulting in a reversible hair depigmentation in murine regenerated hair and human hair organ culture (Hachiya, 2009), suggesting a causal role for SCF-KIT in hair greying.

As stated before, melanin plays an essential role in protection from UV radiation. In the course of UVB-induced pigmentation, melanocytes in the basal layer of the epidermis are stimulated to proliferate, a process found to be modulated by SCF/KIT signaling in humans, mice and guinea pigs (Hachiya, 2001; Hosaka, 2004; Tobiishi, 2005). Additionally, the UV-induced tanning process was found to be blocked with anti-KIT antibodies in guinea pigs (Hachiya, 2001). Exposure to UV or SCF treatment increased the number of melanocytes in the dermis, mainly via the KIT-mediated signaling cascade (Kawaguchi, 2001).

Different mechanisms have been proposed for the achievement of SCF-KIT-mediated effects on melanogenesis. Tyrosine residues in the juxtamembrane region of KIT (positions 568 and 570), known to be involved in binding and activation of Src family kinases, were shown to be required for normal pigmentation (Kimura, 2004). *In vitro*, MAPK-ERK activated by KIT signaling cascade, phosphorylated MITF at Ser 73 or Ser 409, upregulating the transactivation activity of MITF and melanogenesis (Hemesath, 1998; Wu, 2000). More recently, by using a transgenic mouse model, Baver *et al.* demonstrated that additional phosphorylation sites might be involved in MITF activation (Bauer, 2009). On the other side, miR-137 has been found to regulate melanogenesis in mouse skin melanocytes by repressing KIT and tyrosine-related protein 2 (Tyrp2) expression (Jiang, 2016).

Based on this knowledge, potential therapeutic agents for the treatment of hypo- or hyperpigmentation disorders could focus on the modulation of the SCF-KIT signaling cascade. In this line, several agents of vegetal origin have been found to regulate melanogenesis by modulating this pathway. Glyceollins inhibited melanin synthesis, the expression and activity of tyrosinase and SCF, and the SCF-induced KIT and AKT posphorylation in melanoma cells (Shin, 2013). A platycodon root extract was able to reduce the hyperpigmentation induced by UVB irradiation by suppressing KIT expression in melanocytes and consequently reducing melanogenesis in *in vitro* and *in vivo* human skin (Kasamatsu, 2014). Similarly, Americanin A was identified as an effective inhibitor of melanin synthesis by downregulating the expression of KIT, SOX10, MITF and TYR expression in murine melanocyte cultures and in an *in vivo* murine model (Shin, 2016). Finally, diosmetin attenuated SCF-induced proliferation of human primary melanocytes and suppressed UVB irradiation-mediated melanin synthesis (Lee, 2014).

6.4. Gastrointestinal tract (interstitial cell of Cajal)

Interstitial cells of Cajal (ICC) are dendritic-shaped mesenchymal cells located around the myenteric plexus (the region between the longitudinal and circular muscle layers) from the esophagus to the anus. In some parts of the gastrointestinal tract they are also found inside the muscular layers (Bernex, 1996). Interstitial cells serve as pacemaker cells, forming gap junctions with each other and with neighboring smooth muscle cells. They are thought to be responsible for autonomic intestinal motility, characterized by a continuous slow-wave activity (Langton, 1989). ICC have come into prominence because remodeling or loss of these cells led to a variety of motor disorders (Sanders, 2016). In fact, loss-of-function mutations at the murine white dominant W locus led to the absence of the ICC network in the intestinal myenteric plexus and of pacemaker activity in the small intestine, demonstrating and essential role of ICC cells in gut pacemaker activity (Ward, 1995; Huizinga, 1995; Sanders, 2014). The absence of these cells in W mutant mice also reflects a direct role of KIT in the development of ICC. Similarly, mice with loss-of-function mutations in the Sl locus display abnormalities in the gut similar to those found in the W mutant (Ward, 1995). After all these findings, immunolabeling with antibodies against KIT became a standard means for identification of ICC in a variety of organs (Ward, 1995; Sanders, 2014). Recently, a controversy on the use of KIT as the best candidate for ICC detection has emerged since recent papers advocate for anoctamine 1 (ANO-1) as a more reliable marker for these cells, based on comparative results in human and murine models (Hwang, 2009; Gomez-Pinilla, 2009; Wang, 2014a).

6.4.1. SCF and KIT expression

In embryonic mice, KIT expression was detected from E12.5 onwards in all the digestive tract sections. However, it was found that KIT was not essential for ICC migration, proliferation and/or survival at that developmental stage (Bernex, 1996) (Fig. 3). By contrast, in adults, SCF-KIT signaling is crucial for the maintenance of ICC phenotypes, proliferation and differentiation (Lorincz, 2008; Lin, 2010). Early in human development (7 weeks), KIT^+ cells can be found along the entire length of the esophagus in the region of the myenteric plexus, but this distribution changes with age from proximal to distal esophagus, and from the skeletal to the smooth muscle portion of the esophagus (Radenkovic, 2010). Similar development can be found in the stomach (Radenkovic, 2010). By week 20, ICC can be found in all of the adult niches: the myenteric plexus, intramuscular, and septal layers (Rømert and Mikkelsen, 1998). While KIT is expressed in ICC, its ligand SCF is found expressed in enteric neurons and smooth muscle cells surrounding ICC (Torihashi, 1996; Horvath, 2006).

ICCs have been studied in great detail in the gastrointestinal tract, but it should be noted that all smooth muscles display some types of interstitial cell populations (Sanders, 2016). In this regard, ICC-like cells (KIT^+) have been claimed to occur in other organs such as the urinary and reproductive tracts, blood vessels and lymphatics, and the pancreas (Popescu, 2005), although their function is less established than for their GI counterparts.

6.4.2. The role of SCF-KIT system

To study the role of ICC as intestinal pacemakers and the implication of the SCF-KIT axis in this function, KIT neutralizing antibodies and/or mutant animal models have been used (Ward, 1995; Huizinga, 1995; Torihashi, 1995). The administration of ACK2, a KIT neutralizing antibody, to neonatal BALB/c mice resulted in a lack of normal phasic contractile activity in ileal muscles that produced paralytic ileus (Maeda, 1992). In addition, reduced neural responses in the small bowel and colon were also observed (Torihashi, 1995). Similar contractile patterns were found in W/W^{v} mice, accompanied by a decrease in KIT^{+} cells in the intestinal myenteric plexus (Maeda, 1992; Ward, 1995; Huizinga, 1995). SCF mutants, such as Sl/Sl^{d} mice, also displayed loss of ICC in the myenteric plexus but not in the deep muscular plexus, and loss of pacemaker activity. By contrast, neural inputs were intact in Sl/Sl^{d} animals (Ward, 1995; Mikkelsen, 1998). ICC are also reduced in the colons of Ws/Ws mutants in rats, and this reduction is accompanied by altered pacemaker and motor activities in the colon (Albertí, 2007). Murine cell cultures composed of single or networks of KIT^{+} cells were able to generate spontaneous inward currents under voltage-clamp conditions (Thomsen, 1998).

Similar animal models and/or neutralizing antibodies have served to prove the involvement of KIT^{+} ICC in muscle neurotransmission. Nitrergic and cholinergic junction potentials were significantly reduced in the muscles of W/W^{v} mice presenting reduced ICC in intramuscular layers (Ward, 2000; Suzuki, 2003). Excitatory junction potentials were also reduced in muscles of Sl/Sl^{d} mutants, which lack mSCF (Ward, 1995). More recently, Klein *et al.* generated KIT^{CreERT2} mice that target and reduce ICC populations in adult mice, when crossing them with a strain with inducible expression of diphtheria toxin A. They showed that slow wave activity was disrupted and gastric emptying and intestinal transit were significantly reduced. Additionally, mice with reduced ICC presented neither excitatory nor inhibitory junction potentials in the small intestine (Klein, 2013). In these mice, mast cells are also depleted. By reconstituting them with wild type MC, the authors further demonstrated that the observed effects on gastric activities were not MC-mediated (Klein, 2013). These studies suggest that the loss of ICC in the intramuscular layers results in reduced connectivity between enteric motor neurons and smooth muscle cells.

It was speculated that KIT signaling through PI3K might be responsible for ICC loss and lack of intestinal pacemaker activity. Blocking PI3K signaling with wortmannin and LY294002 in neonatal mice or murine muscle organotypic cultures caused loss of ICC and blocked slow waves within a few days (Ward, 1997; Ward, 1999). In adult muscles, similar effects were observed, but a month of exposure to PI3K inhibitors was needed. By contrast, another study used a transgenic mouse with a tyrosine 719 to phenylalanine (Y719F) mutation in KIT, the tyrosine needed for PI3K activation, and showed no loss of ICC function (Gibbons, 2003). Southwell *et al.* suggested PKC involvement, as a KIT-downstream signaling mechanism, in the regulation of ICC function, after finding it co-expressed with KIT all over the guinea pig GI tract (Southwell, 2003).

Severe reduction of ICC has been related to the gastroparesis observed in diabetic patients. These patients presented worse symptoms and less improvement after gastric electrical stimulation compared to the ones with less reduced or normal ICC levels (Forster, 2005). Another study confirmed this relationship in mice and showed that loss of KIT was the most consistent correlate for defects in gastric emptying in non-obese diabetic mice (Choi, 2008). Heme oxigenase (HO-1) induction reduced reactive oxygen species and increased KIT expression, which led to normalized gastric emptying, and the inverse effect was observed when inhibiting HO-1 activity. A study using the same mouse model found a similar correlation between ICC loss and gastroparesis and SCF expression levels in gastric smooth muscle cells (Horvath, 2006). Homozygous mice for a type II diabetes model presented with diminished KIT and SCF expression in different regions of the GI tract accompanied by delayed gastric emptying and prolonged gut transit times (Yamamoto, 2008). In a mouse model of streptozotocin-induced diabetes, the levels of mSCF and KIT were reduced in gastric smooth muscle cells and Angiotensin II was able to increase mSCF expression and ICC cell proliferation via PI3K/AKT signaling (Zhang, 2016). In obese, hyperglycemic, hyperinsulinemic female (Lepr$^{db/db}$) mice, hyperglycemia was found to increase ICC via MAPK1- and MAPK3 and increased expression of KIT, ultimately causing rapid gastric emptying (Hayashi, 2017). Several studies in murine models of diabetic gastroparesis have proved the beneficial effects of electroacupuncture in reverting KIT- and SCF-decreased expression, and consequently ICC numbers (Tian, 2017; Lin, 2016).

Other diseases have also been associated with KIT and/or ICC decreased levels and gastrointestinal motility disorders. For instance, gastrointestinal disorders are frequently found in patients suffering from depression (North, 2007). In this regard, Lin *et al.* showed that SCF and KIT were decreased in gastric smooth muscle layers in depressed rats. Additionally, they demonstrated that natriuretic peptides, via their receptors, which are involved in the modulation of gastric smooth muscle relaxation (Cai, 2009; Sogawa, 2010), were able to downregulate SCF expression in cultured gastric smooth muscles (Lin, 2016). In humans, patients with gallstones were shown to have reduced levels of SCF and KIT expression and ICC numbers in gallbladder tissue and reduced gallbladder contractility compared to healthy subjects (Tan, 2014). In a rat model of slow transit constipation, glucosides extracted from the root of Paeonia lactiflora, were found to increase fecal volume and moisture content and intestinal transit rate as well as SCF and KIT expression and ICC abundance (Zhu, 2016). Imatinib mesylate, a multitargeted KIT inhibitor, has been found to damage ICC networks in cultured neonatal murine instestinal muscles (Bekett, 2007). In adult guinea pigs, imatinib caused a time-dependent reduction in ICC numbers and this effect was reverted after ending the KIT blockade, i.e. the moment at which bromodeoxyuridine (BrU) incorporation was observed at the intestinal myenteric plexus (Mei, 2009). Similar results have been found in the intramuscular layer ICC numbers of rat bladder after imatinib treatment (Gevaeart, 2014).

6.5. Nervous system

Neurogenesis is the process by which the neurons of the central and peripheral nervous systems develop from neural stem cells and progenitors. Although a longstanding demonstration exist for non-primate mammals (Altman and Das, 1967; Caveness, 1973; Gueneau, 1982; Kuhn, 1996), it has long been debated whether adult neurogenesis decreased during primate evolution and whether there is sufficient generation of neurons in adult humans to contribute to brain function (Kempermann, 2012; Rakic, 1985). Currently, it is widely accepted that neurogenesis occurs in the human adult brain as physiological turnover as well as in response to brain injury (Eriksson, 1998; Magavi, 2000; Yoshimura, 2001; Spalding, 2013; Ernst, 2014). In humans, alterations in both embryonic and/or adult neurogenesis have been associated with more or less severe disabilities in cognition (Paul, 2007; Guerrini, 2010) and with psychiatric disorders (Eisch and Petrik, 2012; Kheirbek, 2012). In murine animal models, only one neurological defect has been attributed to Sl/W mutants, that is reduced performance in hippocampal learning (Motro, 1996; Katafuchi, 2000). However, it is possible that more lethal phenotypes in other organs have masked other unknown neural defects. SCF and KIT are expressed in both the peripheral and central nervous system neurons, and it is thought that the SCF-KIT axis is involved in survival, development, migration, and maturation of these cells (Matsui, 1991; Hirata, 1992; Zang and Federoof, 1998; McLaughlin, 2000; Jin, 2002; Guijarro, 2013) (Fig. 3).

6.5.1. SCF and KIT expression

During embryonic development, SCF is expressed by the floor plate cells of the neural tube, while *KIT* transcripts appear on the dorsal aspect

of the neural tube (Keshet, 1991). Moreover, KIT is expressed in the dorsal root ganglia in mouse embryos, the hippocampus, cortex and olfactory bulb in the adult murine brain, and on neural progenitors (Motro, 1991; Erlandsson, 2004; Guijarro, 2013). KIT has also been suggested to be expressed by some glial cells (Motro, 1991; Ida, 1993). Although SCF is expressed in the embryonic neural stem cell niche (Keshet, 1991), it is not found in the adult neural stem cell niche under baseline conditions (Sun, 2004). Globally, SCF presents complementary or overlapping expression with KIT (Keshet, 1991; Motro, 1991; Erlandsson, 2004; Guijarro, 2013) in the murine brain. This complementary expression suggests that SCF-KIT signaling might be involved in neuron-neuron and neuron-glial interactions. In human brain, neither SCF nor KIT expression has been detected in the hippocampus (Lammie, 1994), and some controversy exists in relation to the olfactory bulb (Motro, 1991; Hirota, 1992).

6.5.2. Role of the SCF-KIT system

As mentioned above, Sl/Sl^{d} mutant mice and Ws/Ws mutant rats were reported to present a deficit in spatial learning (Motro,1996; Katafuchi, 2000) and memory (Katafuchi, 2000), supporting a crucial role of SCF/KIT signaling in the hippocampal region responsible for these cognitive functions. By using mouse embryonic neuronal stem cell-derived primitive (pNSC) and definitive neuronal stem cells (dNSC), Reeve *et al.* showed that KIT inhibition by siRNA or by the use of Imatinib caused a significant increase on pNSC- over dNSC-derived neurospheres. In contrast, SCF administration induced the opposite effect. The same group showed similar results *in vivo* by injecting imatinib directly into the brain lateral ventricles of mice (Reeve, 2016), suggesting that short infusion of pharmacological inhibitors can activate neuronal regeneration by activating pNSC. Sachevsky *et al.* showed that stromal-cell-derived factor-1α (SDF-1α) and SCF, common embryonic factors promoting embryonic NSC survival, were able to induce this same effect in adult NSC (aNSC). In fact, SDF-1α induced neuronal nitric oxide synthase (nNOS) and NO production, which in turn upregulated KIT levels, that in the presence of embryonic neuronal SCF enhanced aNSC survival. They thus proved, that aNSC retain their capacity to respond to embryonic-derived cues into adulthood (Sachevsky and Morshead, 2014).

Besides the importance of neuronal proliferation and differentiation on neuronal development, the migration of neural cells to their final destination and network establishment are also crucial events for the correct development of the nervous system. In this line, SCF was proved to induce chemotaxis of neural stem cells obtained from embryonic rat cortex, and SCF inhibitors or multitargeted TKI targeting KIT abolished the migratory response in these cells (Erlandsson, 2004). Moreover, embryonic knockdown of KIT expression in the rat cortex delayed radial migration of cortical neurons, whereas KIT overexpression in the same region caused accelerated radial migration (Guijarro, 2013). By using cultures of dorsal root ganglia of mouse embryos from wild type and KIT mutants, Hirata *et al.* demonstrated the involvement of the SCF/KIT axis in the development of neuronal networks (Hirata, 1992). Su *et al.* showed that SCF and G-CSF acted synergistically to enhance neurite extention in rat cortical neurons via PI3K/AKT/NFKB signaling pathway (Su, 2013).

By means of injury animal models, other groups have revealed the involvement of SCF/KIT signaling in multiple neuronal protective/repairing processes, suggesting that SCF/KIT might be a plausible target for brain injury therapies. Cerebral cortical cultures obtained from a mouse model of cerebral ischemia presented an increase in SCF expression. SCF administration enhanced proliferation in normoxic cultures *in vitro*, and *in vivo* it enhanced BrdU labeling of immature neurons in neuroproliferative zones of the adult brain, in which KIT expression was prominent (Jin, 2002). An increased expression of KIT was also observed in neural stem/progenitor cells (NSPC) in a mouse model of brain injury accompanied by enhanced SCF expression in neurons within the injured zone. SCF induced potent NSPC migration to sites of brain injury through activation of KIT (Sun, 2004). In the olfactory epithelium, experimentally induced injury activated a KIT^{+} progenitor population to reconstitute the neuronal population, and selective deletion of this population resulted in failure of neurogenesis after experimental injury (Goldstein, 2015).

The combination of SCF and G-CSF proved to be beneficial for the improvement of neurological function and diminution of brain atrophy in a model of neonatal hypoxia-ischemia (Doycheva, 2013), as well as for the reestablishment of neuronal networks after chronic stroke in an aged brain animal model (Cui, 2013). In a model of ischemic stroke rats, masitinib, a multitargeted KIT inhibitor, was found to significantly reduce the infarct size (Kocic, 2015). Maraldi *et al.* proposed KIT^{+}/OCT-4^{+} human amniotic fluid stem cells as a potential source of neural cells as a treatment strategy for neurodegenerative diseases. They showed that these cells were able to survive after post-implantation in newborn rat brains, where they integrated into various areas of the CNS, and migrated away from the graft giving rise to mature neurons and oligodendrocytes (Maraldi, 2014).

6.6. Respiratory system

Over the last two decades, several publications have highlighted the crucial role of the SCF-KIT axis in lung integrity maintenance (Reinhard, 2005; Lindsey, 2011; Spaziano, 2016) and its involvement in respiratory diseases (Oliveira, 2001; Al-Muhsen, 2004; Da Silva, 2006; Makowska, 2009; Young, 2016). These functions can be achieved by means of local SCF production and either KIT signaling from respiratory tract structural cells or KIT^{+} inflammatory cells. Additionally, a role for BM-derived KIT^{+} cells has more recently been reported in the context of lung injury (Dolgachev, 2009; Ding, 2013; Nakashima, 2013; Ramachandran, 2015; Aliotta, 2017).

6.6.1. SCF and KIT expression

Bernex *et al.* showed KIT expression in the epithelial cells of the olfactory epithelium in mouse embryos from E10.5 onwards. After E15.5, expression was found in all cells of nasopharynx, few cells of the trachea and bronchi, and most cells of the lungs. This expression pattern persisted until birth (Bernex, 1996). In human airways, not many data exist in this regard. KIT was found expressed in bronchial epithelium and subepithelium at low levels, the subepithelial expression probably corresponding to inflammatory cells (Al-Muhsen, 2004) (Fig. 3). In the same study, SCF was highly expressed in the epithelial layer. Other studies have reported SCF expression in bronchial myofibroblasts *in vitro* (Zhang, 1996) and nasal epithelial cells and fibroblast *ex vivo* (Wen, 1996; Otsuka, 1998).

6.6.2. Role of the SCF-KIT system

Serum and airway SCF concentrations have been shown to correlate with asthma severity and airway mast cell localization in humans (Makowska, 2009; Da Silva, 2006). KIT was also increased in bronchial biopsies from asthmatic patients (Al-Muhsen, 2004) and alveolar epithelial cells of chronic obstructive pulmonary disease (COPD) patients (Yuan, 2014). Moreover, SCF together with IL-31 were suggested as valuable markers for the diagnosis of allergic asthma (Lei, 2007). In the upper airways, SCF expression was found increased in nasal polyps and nasal epithelial brushings of allergic rhinitis patients compared to controls (Kim, 1997). Additionally, both SCF and KIT were found increased in bronchial biopsies and serum (SCF) of patients following lung transplantation, suggesting a role of this pathway in tissue repair (Da Silva, 2006). These publications suggest an important role of the SCF-KIT signaling pathway in the pathophysiology of the respiratory system.

A region on mouse chromosome 5 was found to be associated with susceptibility to airspace enlargement and abnormal pulmonary function (Reinhard, 2005). One potential candidate gene in this chromosome is *KIT*. Based on that, Lindsey *et al.* used W^{sh}/W^{sh} mutant mice to

prove that KIT was essential for maintaining normal alveolar architecture in mouse lungs. They also showed that KIT inhibition attenuated *in vitro* proliferation of cells expressing epithelial cell adhesion molecule (Lindsey, 2011). By contrast, two groups have proposed KIT$^+$ cells to exclusively contribute to the development of lung endothelial compartment. In a recent study Liu and coworkers proved by inducible genetic lineage tracing in mice that KIT$^+$ cells did not contribute to lung epithelium during homeostasis and repair, and instead maintain a vascular endothelial cell fate (Liu, 2015). In support of the latter, another study on human fetal and postnatal lungs showed that KIT$^+$ cells in the lungs also presented CD34, vascular endothelial growth factor receptor (VEGFR)2, and Tie-2 expression, indicating their endothelial lineage. These cells appeared to continuously proliferate until final development of lung capillary plexus (Suzuki, 2014). These discrepancies might be due to the different technical approaches and animal models used in the different studies.

Other types of KIT$^+$ cells, including the ones derived from bone marrow, have been implicated in different aspects of lung pathophysiology, presenting a dual role towards disease development or disease resolution. On the beneficial side, Spaziano *et al.* showed an improvement of airway remodeling and pulmonary function in an ovalbumin (OVA)-mouse model of asthma after intratracheal administration of KIT$^+$ cells isolated from murine lungs (Spaziano, 2016). SCF, probably by recruiting BM-derived KIT$^+$ cells to the lung, seemed to improve angiogenesis in a neonatal rat model of hyperoxia-induced lung injury (Miranda, 2013; Ramachandran, 2015). Finally, induced pluripotent stem cells-derived mesenchymal stem cells (MSC) attenuated cigarette smoke-induced airway injury in rats via SCF by decreasing apoptosis and promoting cell proliferation (Li, 2017). By contrast, in mouse models of bleomycin-induced pulmonary fibrosis and cockroach-induced allergic asthma, several authors found BM-derived KIT$^+$ cells to be the cause of enhanced pulmonary fibrosis (Ding, 2013; Nakashima, 2013; Dolgachev, 2009). Moreover, BM-derived KIT$^+$ endothelial progenitor cells were found to induce pulmonary hypertensive effects in a mouse model for pulmonary hypertension (Aliotta, 2017). In another model of pulmonary hypertension, SCF/KIT signaling was found to potentiate chronic hypoxia-induced vascular remodeling via ERK activation (Young, 2016).

6.7. Other organs

6.7.1. Heart

Ischemic heart disease is the number one cause of morbidity and mortality in the developed world due to the inability of the heart to replace lost cardiomyocytes (Mozaffarian-2015). Although advances in medicine and surgery have decreased cardiovascular disease mortality, a lot remains to be done to stop the progressive disease process that carries significant morbidity (McMurray, 2005). Two decades ago, the accepted dogma in cardiac biology considered the adult mammalian heart to be an organ without regenerative capacity, by contrast to the neonatal heart. Later on, the discovery of mitotic myocytes in murine and human hearts (Beltrami, 2003; Bergmann, 2009; Senyo, 2013) opened a new line of intense investigation on the potential use of adult cardiac stem cells to regenerate the infarcted heart. In 2003, cardiac stem cells were identified as lin$^-$KIT$^+$ cells and proved to be capable of reconstituting well-differentiated myocardium when injected into an ischemic murine heart (Beltrami, 2003) (Fig. 3). In the same line, genetically mutant mice deficient in KIT signaling (W/W^v) showed a worsened cardiac remodeling after myocardial infarction (Cimini, 2007). Conversely, transgenic mice overexpressing SCF in the heart exhibited an improved myocardial repair compared with their wild-type littermates (Ayach, 2006; Ishikawa, 2015).

Multiple KIT$^+$ stem/progenitor cells derived from the heart and bone marrow have been identified, isolated, and characterized and their role in cardiac repair has been studied in different animal models (Suzuki, 2011; Williams, 2013; Kazakov, 2015; Karantalis, 2015; Ishikawa, 2015). In this regard, Kazakov *et al.* showed an increase in a resident population of KIT$^+$ cardiac stem cells after heart injury and demonstrated that the injection of this population in a cardiac ischemic injury mouse model promoted pro-angiogenic mediators and decreased cardiac fibrosis as well as cardiomyocyte apoptosis (Kazakov, 2015). An additional beneficial effect has been reported when using a combination of BM-derived meshenchymal stem cells and KIT$^+$ CSC cells compared to each of these cell types alone. In fact, an enhanced decrease in the infarct size, an enhanced increase in cardiomyocyte proliferation and an improved cardiac functionality have been observed in these two swine models of myocardiac infarction when using cell combination (Karantalis, 2015; Williams, 2013). One possible explanation for the improved effect might be due to the ability of MSC to induce the recruitment of circulating KIT$^+$CD133$^+$-bone marrow progenitor cells and the increase of KIT$^+$CD133$^+$ resident stem cells (Suzuki, 2011). Forced induction of SCF in a myocardial infarction swine model also promoted KIT$^+$ cell recruitment at the infarct border area and that was associated with decreased cell apoptosis, increased capillary density, and improved cardiac function (Ishikawa, 2015).

Despite this set of publications, there still exists a controversy on the contribution of resident KIT$^+$ stem/progenitor cells to cardiomyocyte regeneration in adulthood. Several studies carried out in murine models demonstrated a minimal cardiomyogenic ability of these cells compared to their large vasculogenic potential, questioning their relevance for myocardial repair from a physiological perspective (VanBerlo and Molkentin, 2016; Liu, 2016; Sultana, 2015). On the contrary, other investigators have reported a multipotent nature of KIT$^+$ cardiac stem cells giving rise to the myocyte, endothelial and/or smooth muscle compartments (Beltrami, 2003; Wu, 2006) or even a specificity to exclusively produce cardiomyocytes (Hatzistergos, 2015). Hatzistergos *et al.* claimed that the limited contribution of KIT$^+$ cells in cardiomyocytes is not a function of deficient cardiomyogenic capacity, but rather reflects a nonpermissive milieu after injury (Hatzistergos, 2016). Globally, all the authors agree on the potential of cardiac progenitor cells for the treatment of the injured heart by combining these cells with other stem cells, or by changing the injured cardiac environment by means of repressing or inducing factors that would modulate KIT$^+$ CSC cardiomyogenic potential. In humans, CSC have also been found increased in human hearts from patients who suffered an infarct (Urbanek, 2005), and the injection of human KIT$^+$ CSC into the infarcted myocardium of immunodeficient rodents caused the regeneration of dead myocardium (Bearzi, 2007). All these findings have promoted several clinical trials to test the safety and efficacy of KIT$^+$ stem/progenitor cells for the treatment of human heart disease (Chugh, 2012; Malliaras, 2014; Bolli, 2018).

Some of the pathways found to be involved in different aspects of cardiac repairing and related to the induction of the SCF/KIT axis include: 1) the PI3K-AKT-MMP2/9 pathway for the survival and/or migration of both human and murine KIT$^+$ cardiac and BM stem cells (Fazel, 2008; Guo, 2014; Vajravelu, 2015); and 2) the SDF-1α/CXCR4 pathway by which MSC induce migration, proliferation and differentiation of CSC in association with SCF/KIT activation (Chen, 2014b; Hatzistergos, 2016).

6.7.2. Bone

KIT has been found expressed in human osteoclast and osteoblast, the cells in charge of bone resorption and bone formation, respectively (Gattei, 1996; Bilbe, 1996) (Fig. 3). Conversely, SCF was found expressed in osteoblast and bone marrow stromal cells, which interact with osteoclasts in the bone microenvironment (Rodan, 1987; Gattei, 1996). Both, Sl/Sl^d and W/W^v mutant mice present osteopenia, probably due to an imbalance in bone turnover (Lotinun, 2005; Iwaniec, 2013). Since W/W^v mice are sterile, the observed skeletal phenotype was thought to be potentially due to a deficiency in sex hormone production. For this reason, W^{sh}/W^{sh} mutant mice which are fertile, have been recently used to prove that disrupted KIT expression is responsible for

the altered bone resorption/formation rate in homeostasis as well as for the compromised healing capacity after bone injury (Lotinun and Krishnamra, 2016; Behrends, 2014). The defective healing capacity is attributed to abnormal catabolic activity and impaired re-vascularization (Behrends, 2014) in these mice. In this respect, it has been shown that patients suffering from chronic myeloid leukemia (CML) and receiving imatinib as a therapy, present an imbalance between bone formation and resorption, resulting in increased bone mineralization and trabecular bone volume (Berman, 2006; Fitter, 2008). However, the exact mechanism behind this side effect has not been elucidated yet.

The SCF/KIT axis has been found to exert protective effects against oxidative stress-induced osteonecrosis via AKT activation in mice (Yang, 2014). Moreover, in a rabbit model of glucocorticoid-induced osteonecrosis, G-CSF and SCF were able to decrease osteonecrosis by inducing bone rate formation and decreasing osteocyte apoptosis (Wu, 2013). Both cytokines were previously found to induce BM-derived stem cell mobilization to the necrotic zone, thus probably contributing to tissue regeneration (Wu, 2008). Czekanska *et al.* found SCF to enhance the expression of proteins involved in proliferation, chondrogenesis and extracellular matrix regulation by human MSC. Hence, they proposed SCF as one potential regulatory factor of the human MSC secretome in order to promote a favorable environment for the regeneration of damaged skeletal tissue (Czekanska, 2014). The adaptor protein Lnk has been identified as an essential inhibitor of SCF/KIT signaling during stem cell self-renewal (Takaki, 2002). In this regard, Matsumoto *et al.* showed that Lnk-deficient mice presented accelerated fracture healing compared to wild-type mice. Specifically, vasculogenesis and osteogenesis was promoted in these mice by the mobilization and recruitment of HSPC/endothelial progenitor cells (EPCs) via SCF-KIT signaling pathway activation in the perifracture zone (Matsumoto, 2010). The same group showed that BM $KIT^+Sca1^+Lin^-$ cells were significantly increased and recruited to the fracture site after bone fracture in mice (Matsumoto, 2008).

6.7.3. Pancreas

In rodents, KIT mRNA and protein expression was detected in the pancreatic ducts from E13 and E18, respectively (Oberg, 1994; Yashpal, 2004) but KIT^+ cells progressively decreased in postnatal pancreas (Yashpal, 2004). 40% of beta cells expresses KIT, and KIT^+ cells co-express markers related to islet differentiation, including pancreatic and duodenal homeobox 1 (PDX-1) and neurogenin 3 (NGN3) (Ma, 2012). In humans, KIT expression was detectable at 8 weeks of fetal age, not only within the ductal epithelium but also in small islet clusters (Li, 2006; Li, 2007). As in murine models, KIT co-expressed transcription factors associated with islet differentiation and this co-expression decreased along with fetal age progression (Li, 2006). SCF was scattered throughout the developing human pancreas (Li, 2006) (Fig. 3).

The SCF-KIT axis has been found to be involved in beta cell proliferation and differentiation in multiple species. Induction of this pathway promoted gene transcription and proliferation in INS-1 rat insulinoma cells *in vitro* and in mice beta cells *in vivo* (Feng, 2012). Moreover, exogenous SCF induced islet-like cluster differentiation from human pancreatic carcinoma, epithelial-like cells (PANC-1) (Wu, 2010) and accelerated the differentiation and maturation of neonatal porcine islets *in vitro* (Mancuso, 2010). SCF enhanced the differentiation of KIT-expressing immature endocrine cells in the human fetal pancreas, likely via stimulation of the PI3K pathway (Li, 2006).

Although there exists no consensus on the identity of pancreatic stem/progenitor cells, KIT-expressing cells exhibit many stem/progenitor cell features in the pancreas. In a study in which islet cell neogenesis was induced by pancreatic duct ligation in rats, KIT was found co-expressed with stem/progenitor cell markers such as nestin and NK2 homeobox 2 (NKX2.2) in the ligated portion of the pancreas. KIT^+ cells presented high proliferative activity and were upregulated in the compartments of the pancreas that are involved in islet cell neogenesis (Peters, 2005). In a model of rat pancreatitis, beta cell replenishment occurred after replication of a highly proliferative KIT^+ population (Gong, 2012).

In mice heterozygous for W^v ($W^v/+$) mutation, Krishnamurthy *et al.* observed severe loss of beta cells and reduced proliferative capacity accompanied by impaired glucose tolerance and decreased insulin secretion in 8 week-old males (Krishnamurphy, 2007). Interestingly, the same phenotype appeared in female mice at 40 weeks of age, probably due to differences in sex hormone function. The dysregulation of the PI3K-AKT-glycose synthase kinase 3β (GSK3β) pathway, downstream KIT, seems to be responsible for the onset of the diabetic phenotype in $W^v/+$ mice (Feng, 2012). The increase in beta cell death observed in $W^v/+$ mice, seemed to be associated to p53 upregulation and induction of Fas receptor activity in mouse islets, factors involved in cell cycle arrest and cell apoptosis, respectively (Feng, 2013). Furthermore, the overexpression of KIT in beta cells of $W^v/+$mice could partially reverse the diabetic phenotype. This overexpression improved insulin secretion in response to glucose challenge and insulin content in beta cells, in association with increased beta cell proliferation and consequently increased beta cell mass (Feng, 2012). In INS-1 cells, SCF was found to induce insulin receptor expression via KIT overexpression and to promote enhanced KIT and IR co-localisation (Feng, 2012). Substantial loss of islet vasculature was also observed in $W^v/+$ mice, which was again reversed by specific KIT overexpression in beta cells. Additionally, SCF induced VEGF-A production, a growth factor essential for islet vasculature formation, via KIT-PI3K-mTOR signaling pathway in INS-1 cells and mice primary islets (Feng, 2015).

6.7.4. Kidney

Embryologic nephrogenesis depends on the interaction of the ureteric bud and the metanephric mesenchyme via cellular and molecular signaling pathways. While SCF expression was found restricted to the ureteric bud, KIT expression was found in different locations in the murine developing kidney (Schmidt-Ott, 2005; Schmidt-Ott, 2006) (Fig. 3). In fact, a distinct KIT^+ population identified *in vivo* has been found to undergo apoptosis after imatinib treatment in organ cultures of metanephric kidneys, inducing reductions in ureteric bud branching and nephron number (Schmidt-Ott-2006). Conversely, exogenous SCF promoted the expansion of the KIT^+ population, thus accelerating kidney development *in vitro*. Similarly, in rats, a neonatal kidney derived KIT^+ cell population was found to fulfill all the criteria of stem cells: clonogenicity, self-renewal, and multipotentiality. This population expanded *in vitro* was able to integrate several compartments of the kidney, including tubules, vessels, and glomeruli following acute ischemia-reperfusion injury in rats, and contributed to functional and morphological improvement of the kidney (Rangel, 2013).

The role of the SCF-KIT system in kidney development or repair has been further demonstrated by using animal models such as the ACI rat model, which spontaneously exhibit unilateral renal agenesis (URA), or the renal ischemia-reperfusion injury (RIRI) murine model, which mimics human acute kidney injury (Bengatta, 2009; Bi, 2015; Samanas, 2015; Stokman, 2010). Previous studies that used the ACI rat model, demonstrated that the genetic locus known as Renag1, mapped to rat chromosome 14, was the sole genetic determinant of the URA phenotype found in reciprocal intercrosses between ACI and Brown Norway (BN) rats (Shull, 2006). Samanas *et al.* localized the locus Renag1 to a 379 kb region that contained a single protein coding gene, *KIT*, and proved that Renag1 was necessary and sufficient to elicit URA and associated urogenital anomalies in these animals (Samanas, 2015). A protective effect was associated with the SCF-KIT pathway in a RIRI murine model, since the inhibition of SCF by antisense oligonucleotides resulted in impaired renal function, increased tubular damage and increased tubular epithelium apoptosis (Strokman, 2010). In the same line, in a rat RIRI model, SCF together with G-CSF promoted kidney repair by mobilizing BMSCs and increasing HIF-1α, VEGF, and EPO expression, found to be involved in the resolution of various forms of renal injury (Tanaka, 2005; Bernhardt, 2006; Weidemann, 2008). Finally, in a

mouse model of folic acid-induced acute kidney injury, MMP9 was found to induce the secretion of SCF (sSCF) *in vivo* and *in vitro*, and sSCF inhibited the apoptosis of tubular epithelial cells *in vitro*, rescued the MMP9$^{-/-}$knock-out renal apoptotic phenotype *in vivo*, and improved renal function (Bengatta, 2009).

6.7.5. Liver

In humans, KIT expression was detected in hepatoblasts and biliary epithelial cells during early embryonic stages of liver development, and this expression progressively decreased with gestational age (Blakolmer, 1995) (Fig. 3). Moreover, KIT has been found increased in human acute and chronic liver injury as well as in murine models of liver injury (Fujio, 1994; Baumann, 1999), suggesting an implication of KIT in hepatic repair mechanisms. Recently, hepatic oval cells (HOC), which have been recognized as facultative liver progenitor cells (Faris, 2001; Fausto, 2003), have been found to be KIT positive (Li, 2013). KIT^{+} HOC cells transplanted into liver-injury-model rats significantly prolonged the survival time and improved liver function compared to their control littermates. Additionally, KIT^{+} HOC cells administered to rats also receiving liver transplantation reduced acute allograft rejection (Li, 2013).

7. Therapeutic use of KIT inhibition

7.1. Current inhibitors

Tyrosine kinase inhibitors are well established therapies for various types of malignancies (reviewed in Gimminger, 2010) in which uncontrolled signaling of tyrosine kinases leads to cancers, autoimmune or inflammatory disorders. TKI are small-molecular-weight molecules designed to block the ATP-binding site and prevent the autophosphorylation of tyrosine kinases, thereby inhibiting activation of intracellular signaling pathways (Krause, 2005). Imatinib was the first to be introduced into clinical oncology in 2001, as a potent BCR/ABL inhibitor (Capdeville, 2002), and it was then followed by the drugs sorafenib, dasatinib, sunitinib, nilotinib, gefitinib, erlotinib, bosutinib, lapatinib, pazopanib, and regorafenib (Mirshafiey, 2014). Although they share the same mechanism of action, they differ from each other in the spectrum of targeted kinases, pharmacokinetics, and substance specific adverse side effects (Hartmann, 2009). While some of them, including imatinib, were designed with a rather selective profile, later on they have proven to present a somewhat wider specificity (Karaman, 2008). The question of using selective or multitargeted inhibitors has been a matter of debate, particularly in the context of cancer. While selective kinase inhibitors might reduce unwanted side effects, very often tumors are dependent on more than one pathway, and thus a multitargeted therapy approach might provide higher efficacy and reduced treatment resistance. For diseases other than cancer in which the desired target might be only one specific pathway, we might speculate that selective inhibitors would provide better outcomes with better safety profiles.

Among the list of TKI already commercialized or being used in advanced phases of clinical trials, we find at least 16 that target KIT with a variable degree of specificity (Table 1) (Grimminger, 2010; Abbaspour Babaei, 2016). Most of them were designed to block pathways related to basic cellular processes such as proliferation, differentiation, and survival (BCR/ABL, FLT3, and KIT pathways), and/or angiogenesis (VEGF and PDGF pathways), in order to avoid tumor development. Some forms of KIT mutants were found to be resistant to imatinib, due to its inability to bind the active conformational form of KIT (Frost, 2002) and so, the second-generation of multitargeted KIT inhibitors were designed to target both active and inactive conformations (Von Bubnoff, 2005; Schittenhelm, 2006; Dubreuil, 2009). Masitinib, dasatinib, sunitinib, and pazopanib are potent KIT inhibitors (Galanis, 2015; Dubreuil, 2009), whereas VEGFR is the main target for sorafenib, semaxanib, axitinib, vatalanib, cabozantinib, tivozanib, and telatinib (Table 1).

7.2. Potential treatment for non-oncological diseases

Although all the TKI targeting KIT have been approved for the treatment of different types of cancer as a main indication, 7 of them have been and/or are being tested on clinical trials for the treatment of non-oncological diseases (Table 2). In this regard, autoimmune diseases such as rheumatoid arthritis or scleroderma, and respiratory diseases such as asthma, associated with a mast cell-inflammatory profile, are all on the KIT inhibitors' targeted list. In the same line, conditions presenting with neoangiogenesis and/or tissue remodeling including corneal neovascularization, psoriasis, pulmonary fibrosis, pulmonary arterial hypertension, and endometriosis are also good candidates. Finally, neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis might also beneficiate from these therapies.

7.2.1. Corneal neovascularization

Corneal neovascularization (CNV) of the normally avascular cornea is caused by a wide variety of common pathologic conditions such as infection, trauma, and loss of the limbal stem cell barrier (Chang, 2001). Moreover, most of the significant vision loss caused by age-related macular degeneration (AMD) is attributed to the aberrant neovascularisation of the coroid layer of the eye (Fine, 2000). VEGF is a major factor contributing to blood vessel development (Folkman, 1995; Matsuoka, 2004) together with PDGF, which is also an important mediator in neovascularisation (Song, 2005). Pazopanib (GlaxoSmithkline) is a multityrosine kinase inhibitor that targets VEGF and PDGF and inhibits angiogenesis (Kumar, 2007; Harris, 2008). In preclinical studies, inhibition and regression of laser-induced choroidal neovascularisation was observed following oral administration of pazopanibin mice, consistent

Table 1
Tyrosine kinase inhibitors that target KIT

Compound	Main targets	References
Axitinib *Inlyta (Pfizer)*	VEGFR, PDGFR, KIT	Hu-Lowe (2008)
Cabozantinib *Cabometix (Exelixis)*	VEGFR, MET, RET, KIT	Grullich (2014)
Dasatinib *Sprycel (Bristol Myers Squibb)*	BCR-ABL, SRC, KIT, Ephrins, PDGFR	Schittenhelm (2006); Kamath (2008)
Dovitinib	FLT3, KIT, FGFR, VEGFR, CSF-1R	Trudel (2005); Renhowe (2009)
Imatinib *Glivec (Novartis)*	BCR-ABL, KIT, PDGFR	Heinrich (2000), Waller (2014)
Masitinib	KIT, PDGFR	Dubreuil (2009)
Midostaurin *Rydapt (Novartis)*	PKC, VEGFR, KIT, PDGFR, FLT3	Fabbro (2000); Gleixner (2006)
Nilotinib *Tasigna (Novartis)*	BCR-ABL, KIT, PDGFR	Weisberg (2006); Vertovsek (2006); Liu (2011)
Pazopanib *Votrient (Novartis)*	VEGFR, FGFR, PDGFR, KIT	Sonpavde (2007)
Semaxanib	VEGFR, PDGFR, KIT, FLT3	Fong (1999); Smolich (2001)
Sorafenib *Nexavar (Bayer)*	RAF, VEGFR, KIT, PDGFR	Wilhelm (2004); Guida (2007)
Sunitinib *Sutent (Pfizer)*	VEGFR, PDGFR, FLT3, KIT, RET, CSF-1R	Sun (2003); Abrams (2003)
Tandutinib	FLT3, KIT, PDGFR	Pandey (2002); Corbin (2004)
Telatinib	VEGFR, KIT, PDGFR	Steeghs (2008); Eskens (2009)
Tivozanib *Fotivda (Aveo Oncology)*	VEGFR, PDGFR, KIT	Nakamura (2006)
Vatalanib	VEGFR, PDGFR, KIT	Wood (2000)

VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; KIT, cellular homolog for the feline sarcoma viral oncogene v-KIT; MET, mesenchymal-epithelial transition factor; RET, rearranged during transfection; FLT3, Fms-like tyrosine kinase 3; FGFR, fibroblast growth factor receptor; CSF-1R, colony stimulating factor 1 receptor; PKC, protein kinase C.

Table 2
Tyrosine kinase inhibitors in development for the treatment of non-oncological disorders.

Disease/condition	Tyrosine kinase inhibitor	Clinical trial ID[a]	Develomental status	Related publications
Corneal Neovascularization	Pazopanib	NCT01051700	Phase I	McLaughlin (2013)
		NCT01154062	Phase IIa	McLaughlin (2013)
		NCT01257750	Phase I/II	Amparo (2013)
Psoriasis	Pazopanib	NCT00358384	Phase I/II	None
	Masitinib	NCT01045577	Phase II	None
Systemic Sclerosis (Acute diffuse)	Dasatinib	NCT00764309	Phase I/II	Martyanov (2017)
	Nilotinib	NCT01166139	Phase II	Gordon (2015)
	Imatinib	NCT00512902	Phase I/II	Khanna (2011)
		NCT00573326	Phase II	Fraticelli (2014)
		NCT00555581	Phase II	Spiera (2011a)
		NCT01166139	Phase II	Haddon (2017)
		NCT01545427	Phase II	Pope (2011)
Rheumatoid Arthritis	Masitinib	NCT00913432	Phase II	Tebib (2009)
	Masitinib	NCT01410695	Phase II/III	None
	Imatinib	NCT00154336	Phase II	None
Severe Asthma	Masitinib	NCT00842270	Phase II	Humbert (2009)
		NCT01449162	Phase III	None
	Imatinib	NCT01097694	Phase II	Cahill (2017)
Idiopathic Pulmonary Fibrosis	Dasatinib	NCT02874989	Phase I	None
	Imatinib	NCT00131274	Phase II	Daniels (2010)
Pulmonary Arterial Hypertension	Nilotinib	NCT01179737	Phase II	b
	Sorafenib	NCT00452218	Phase I	None
	Imatinib	NCT00477269	Phase II	Ghofrani (2010)
		NCT00902174	Phase III	Hoeper (2013)
		NCT01392495	Phase III	Frost (2015)
Alzheimer's disease	Nilotinib	NCT02947893	Phase II	None
	Masitinib	NCT00976118	Phase II	Piette (2011)
		NCT01872598	Phase III	None
Multiple Sclerosis	Masitinib	NCT01450488	Phase II	Vermesch (2012)
		NCT01433497	Phase III	None
Amyotrophic Lateral Sclerosis	Masitinib	NCT02588677	Phase II/III	None
		NCT03127267	Phase III	None
Type I Diabetes	Imatinib	NCT01781975	Phase II	None
Endometriosis	Axitinib	NCT03481842	Phase I	None

[a] From clinicaltrials.gov
[b] Terminated due to severe adverse events.

with inhibition of VEGF and PDGF pathways (Takahashi, 2009). Under eye drop formulation, pazopanib was found to inhibit laser-induced choroidal neovascularization, as well as diabetic retinal vascular leukostasis and leakage in experimental models (Yafai, 2011; Thakur, 2011). Based on this preclinical data, several clinical trials have tested the safety and efficacy of oral or topical (eye drops) pazopanib for the treatment of corneal neovascularisation from different origins (Table 2). Both the oral and topical formulations were safe and well tolerated (Singh, 2014; NCT01134055; Amparo, 2013; McLaughlin, 2013), although only the oral form was able to show improvements in the best-corrected vision acuity (primary endpoint) and central retinal lesion thickness (McLaughlin, 2013).

Although all these clinical trials were performed on the basis of the VEGF and PDGF implication in neoangiogenesis, KIT also has a role in this process (Litz, 2006; Kim, 2011; Feng, 2015) and it is also a target of pazopanib, so the effects observed in these studies might be related in part to KIT inhibition. The SCF-KIT axis can mediate effects on neovascularisation through the increase of VEGF expression (Litz, 2006; Feng, 2015) or directly by recruiting and activating endothelial progenitor cells (Kim, 2011). In the specific context of corneal neovascularisation, by using a CNV mouse model, Liu and colleagues showed that SDF-1α neutralizing antibody was able to blunt CNV development by downregulating VEGF and KIT expression (Liu, 2012), highlighting the importance of KIT on this condition.

7.2.2. Psoriasis

Psoriasis is a common relapsing and remitting immune-mediated inflammatory disease that affects the skin and joints. This complex disease results from dysregulation in crosstalk between environmental factors, epithelial cells, and immune cells in genetically predisposed subjects (Perera, 2012). The involvement of innate immune cells, such as neutrophils, γδ T cells, mast cells and innate lymphoid cells, is increasingly appreciated in human psoriasis and psoriatic-like skin inflammation in mice (Lin, 2011; Cai, 2011; Teunissen, 2014). Moreover, mast cell numbers are increased in the upper dermis close to the epithelium in psoriatic plaques (Toruniowa, 1988), and the increased expression of both SCF and KIT in psoriasis seemed to be responsible for persistent mast cell growth and activation (Huttunen, 2002). Recently, mast cells were found to be major producers of IL-22 and IL-17 (Mashiko, 2015), crucial cytokines involved in the physiopathology of psoriasis (Wolk, 2004; Papp, 2012) and therefore, therapies targeting mast cells might be a good option for this chronic inflammatory skin disorder.

Although some publications described the appearance of psoriasis after imatinib treatment of patients suffering for different cancer conditions (Valeyrie, 2003; Paolino, 2016), a few others found opposite results. In two case report publications, patients receiving sorafenib for the treatment of different types of cancer presented a complete remission of resistant psoriasis (Fournier and Tisman, 2010; Antoniou, 2016), and similar results were found after imatinib treatment (Miyagawa-2002). Antoniou and colleagues argue that this effect might be achieved via VEGF inhibition, since this growth factor has been implicated in the angiogenesis process occurring in this pathology. However, one might speculate that the inhibition of mast cell activity by inhibiting KIT might be at least partly responsible for the beneficial effect of sorafenib. In this regard, masitinib, a pretty specific KIT inhibitor, was tested on a Phase II clinical trial for the treatment of patients with moderate to severe chronic plaque psoriasis (NCT01045577). Although the study was completed, no results have been published to date. A phase I study was performed with a topical form of pazopanib for the treatment of stable psoriatic plaques, and although the ointment was well tolerated and a small improvement was observed in the Psoriasis

Area Scoring Index (PASI) compared to placebo, the results were not statistically significant (GSK register Id:RES104031).

7.2.3. Scleroderma/systemic sclerosis

Systemic sclerosis (SS), also called scleroderma, is an autoimmune-mediated rheumatic disease characterized by widespread vasculopathy, inflammation and multi-organ fibrosis and dysfunction (Denton and Khanna, 2017). Although several medications are used to treat the skin disease associated with systemic sclerosis, global effective therapies do not exist (Khanna and Denton, 2010). TGFβ and PDGF are cytokines implicated in the pathological fibrosis of SS (Leask and Abraham, 2004; Trojanowska, 2008). In fact, autoantibodies against PDGF were found in the serum of SS patients and they were shown to stimulate the production of reactive oxygen species and the expression of collagen (Baroni, 2006). In the same line, postnatal induction of TGFβ signaling in mouse fibroblasts induced profound fibrosis of the dermis (Sonnylal, 2007). Nilotinib, dasatinib and imatinib have been shown to decrease fibrosis *in vitro* and in bleomycin models of SS (Akhmetshina-2008; Distler, 2007). The latter showed similar effects in animal models of other organ fibrosis such as pulmonary, renal, and liver fibrosis (Daniels, 2004; Abdollahi, 2005; Wang, 2005; Yoshiji, 2005). Additionally, several case reports stated a beneficial effect of imatinib in patients with treatment-refractory SS (Sfikakis, 2008; Sabnani, 2009; Chung, 2009). For this reason, all of these drugs have been tested in a myriad of clinical trials to determine their safety and efficacy in patients suffering from SS (Table 2).

Several pilot clinical trials in SS patients have been published with a focus on the safety and efficacy of imatinib in the treatment of both cutaneous and pulmonary disorders (Pope, 2011; Spiera, 2011a; Khanna, 2011; Guo, 2012; Prey, 2012). The results have been controversial with regard to efficacy due to open-label study designs and the small numbers of patients included, and all studies were characterized by a poor tolerability. However, in a subsequent study where lower doses of imatinib were used, an acceptable safety profile was demonstrated (Fraticelli, 2014). In general, imatinib-treated patients presented improved modified Rodnan skin thickness score (MRSS), as well as pulmonary % predicted forced vital capacity (FVC) (Khanna, 2011; Spiera, 2011b). Lower doses of imatinib showed improved or stabilized lung disease, but had no effects on skin thickness (Fraticelli, 2014). Nilotinib and dasatinib are second-generation TKI that are more potent than imatinib against non-mutated Abl and active against many imatinib-resistant BCR-ABL mutants (Shah, 2004; Weisberg, 2005; O'Hare, 2005). In a phase II pilot study (NCT01166139), nilotinib was well tolerated by the majority of SS patients and a subgroup of patients positively responded with a significant improvement in the MRSS. The responder patients were characterized by higher levels of gene expression associated with TGFβR and PDGFR signaling at baseline, and by a decrease in these same genes after treatment (Gordon, 2015). In a phase I/II clinical trial designed to evaluate the safety and efficacy of dasatinib for the treatment of scleroderma pulmonary interstitial fibrosis (NCT00764309), the drug presented an acceptable safety profile, but no significant clinical efficacy (Martyanov, 2017).

Mast cells have been implicated in the fibrotic process of systemic sclerosis. In fact, the density of dermal mast cells in the fingers has been associated with the severity of sclerosis, correlating with the patient's modified Rodnan skin score (Yukawa, 2013). In a murine model of scleroderma, increased levels of SCF and mast cell accumulation were found in the altered skin (Wang, 2005). Moreover, mast cells from SS patients were found to produce and secrete great amounts of active TGFβ (Hügle-2014), suggesting that they might contribute to the fibrosis observed in these patients. Considering this, the inhibition of KIT by the above mentioned TKI, and consequently the inhibition of mast cell proliferation, migration and degranulation, might be partially responsible for the effects observed in SS patients after TKI treatment. Further studies investigating the mechanisms of action of nilotinib, dasatinib, and imatinib in relation to SS disease, might shed light on the contribution of the SCF-KIT signaling pathway in the development of this disease.

7.2.4. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease associated with swelling and pain in multiple joints. Articular inflammation causes activation and proliferation of the synovial lining, expression of inflammatory cytokines, chemokine-mediated recruitment of additional inflammatory cells, as well as B cell activation with auto-antibody production (Firestein, 2003; Sweeney and Firestein-2004). Mast cells have been proposed as a putative target for RA therapies (Woolley, 2003). However, the role of mast cells in RA pathogenesis has been questioned based on results obtained from RA animal model studies. While the first studies using KIT-dependent MC-deficient mouse models proved to protect animals from developing RA after transfering them with K/BxN serum-inducing arthritis (Lee, 2002; Feyerabend, 2011), new studies using RA animal models independent of KIT mutations have found no differences in the development or severity of the disease (Feyerabend, 2011). For this reason, the role of mast cells in RA pathogenesis is still highly controversial and some authors considered it as redundant. More recently, two new publications support the idea that MC might be playing an essential role as immunomodulatory cells during the early phases of RA, while they might be dispensable in the late effector phases (Schubert, 2015; van der Velden, 2016).

Despite the controversy related to RA animal models, in humans, there is a major growing body of evidence implicating mast cells in the pathogenesis of RA, particularly by their ability to secrete proinflammatory cytokines and growth factors (Woolley, 2003). In fact, increased numbers of mast cells have been found in the synovium of patients suffering from RA, and their numbers correlated with the state of the disease. These mast cells stained positive for TNFα (Juurikivi, 2005), a cytokine being targeted by RA therapies (Bathon, 2000; Lipsky, 2000). Moreover, in cultures of human synovial tissue, the inhibition of KIT by imatinib mesylate was found to induce mast cell apoptosis accompanied by a decrease in TNFα production (Juurikivi, 2005).

Several case reports have been published in relation to the efficacy of imatinib on the treatment of RA (Miyachi, 2003; Eklund, 2003; Ames, 2008; Eklund, 2008; Vernon, 2009). While in some cases, imatinib was administered for the treatment of chronic myeloid leukaemia in patients who also suffered from RA (Miyachi, 2003; Ames, 2008; Vernon, 2009). In others, imatinib was purposely used to treat severe refractory RA. Two patients withdrew from the study of Ekklund *et al* (Eklund, 2008) due to adverse events, but in general, imatinib was well tolerated with mild to moderate adverse events. In the same line, a multicentre, uncontrolled, open-label, randomized, phase IIa clinical trial was launched in order to evaluate the efficacy and safety of masitinib for the treatment of RA (NCT00913432). Although at the beginning of the treatment, a high incidence of mild to moderate adverse events was observed, masitinib appeared to be generally well tolerated as well as effective for the treatment of refractory active RA (Tebib, 2009). These results encourage the development of new clinical trials to further evaluate the efficacy of this TKI for the treatment of RA.

7.2.5. Asthma

Asthma is a chronic inflammatory disease clinically characterized by variable airflow limitation partially reversible either spontaneously and/or after treatment. Clinical symptoms are associated with airway inflammation, airway hyperresponsiveness, and airway remodeling (Busse and Lemanske, 2001). Although most patients satisfactorily respond to current therapies, severe asthma patients remain difficult to control despite optimal management and an extensive re-evaluation of the diagnosis (Chanez, 2007). Therefore, novel drugs are still needed to treat severe refractory asthma.

The airways of asthmatic patients are commonly infiltrated by eosinophils, lymphocytes, macrophages and mast cells (Busse and Lemanske,

2001); these cells are likely to play a major role in asthma (Lambrecht and Hammad, 2015). Moreover, mast cell presence in the airways of asthmatic patients correlates with airway hyperresponsiveness and asthma disease severity (Bradding, 2006; Siddiqui, 2008). Inhibiting the SCF-KIT pathway, which regulates several biological processes for mast cells and eosinophils, may reduce their numbers and limit their effects in the pathophysiology of asthma. Studies carried out by using animal models of allergic/non-allergic asthma support the use of tyrosine kinase inhibitors as a potential therapy for this chronic disease. In this regard, imatinib, nilotinib, sunitinib, and masitinib proved to be effective in reducing airway hyperresponsiveness, inflammation, remodeling, and/or fibrosis in murine or feline asthma models (Berlin and Lukacs, 2005; Berlin, 2006, Huang, 2009; Lee-Fowler, 2012; Rhee, 2014). Moreover, some of these effects were demonstrated to be at least partly achieved by targeting the SCF-KIT signaling pathway (Huang, 2009; Rhee, 2014).

Based on these pre-clinical studies, masitinib and imatinib have been used in clinical trials to test their suitability for the treatment of severe asthma (Table 2). In a randomized, dose-ranging, placebo controlled, phase II clinical trial, masitinib showed improved asthma symptom scores despite a lack of significant effect on steroid weaning (Humbert, 2009). Currently, there's an ongoing phase III clinical trial to further test the efficacy of masitinib on patients with severe persistent asthma (NCT01449162). The efficacy of imatinib was also evaluated on a randomized, double-blind, placebo-controlledtrial in patients with poorly controlled severe asthma. Imatinib induced a significant decrease in airway hyperresponsiveness and tryptase release, and a trend but not significant decrease in mast-cell counts compared to the placebo arm (Cahill, 2017). This fact might point out a prominent role of imatinib in blocking the activation rather than the proliferation of mast cells in this specific context.

7.2.6. Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis is a progressive interstitial lung disease characterized by the accumulation of fibroblast/myofibroblasts with aberrant remodeling of the lung parenchyma. Clinically, it presents reduced lung volumes, impaired gas exchange, dyspnea, and death with a median survival from diagnosis of 3 to 5 years (ATS, 2000). Some studies carried out in multiple tissues, including the liver, kidney, heart and brain, showed the implication of the SCF-KIT axis in tissue remodeling and fibrosis (Sun, 2004; El Kossi, 2008; Tajima, 2010; Meloni, 2010). In the lung, alveolar fibroblasts from patients with diffuse interstitial fibrosis secreted more SCF than cells from sarcoidosis patients (Fireman, 1999).

Apart from the indirect role that SCF-KIT might have on eosinophils and mast cells inducing the production of fibrogenic factors, a direct role for SCF was found in a mouse model of bleomycin-induced pulmonary fibrosis. In this mouse model, SCF induced KIT^+ bone marrow-derived fibroblast-like cell migration to the lung causing fibrosis, and this effect was blocked either by a SCF neutralizing antibody or by using SCF-deficient mice (Ding, 2013). In two other murine models of pulmonary fibrosis, dasatinib proved to be effective by inhibiting myofibroblast activation and collagen deposition and/or reducing lung inflammation and fibrosis, finally leading to improved lung mechanics (Yilmaz, 2015; Cruz, 2016). Imatinib also proved to be effective in preventing bleomycin-mediated lung fibrosis (Aono, 2005; Azuma, 2007) and decreasing parenchymal fibrosis in asbestos-induced pulmonary fibrosis (Vuoriken, 2007) animal models. These promising results lead to the evaluation of imatinib effects on patients suffering from idiopatic pulmonary fibrosis (NCT00131274). However, this phase II, randomized, double-blind, placebo-controlled study failed to prove imatinib efficacy on survival rate or change in lung function among patients with idiopathic lung fibrosis despite its good tolerability (Daniels, 2010).

7.2.7. Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by vascular proliferation and remodeling of the pulmonary vascular bed, resulting in increased pulmonary vascular resistance, right heart failure, and death if not treated effectively (Farber and Loscalzo, 2004; Humbert, 2004). Current treatment options have been shown to improve exercise capacity, hemodynamic variables, and disease progression (Humbert, 2004), but the 3-year survival rate is <60% in patients with newly diagnosed PAH despite current therapies (Humbert, 2010), highlighting the need for improved therapeutic options.

PDGFR and KIT signaling are important in vascular smooth muscle cell proliferation and hyperplasia (Perros, 2008; Montani, 2011), one of the hallmarks of PAH (Morrell, 2009). In this regard, KIT^+ cells have been found to mobilize and accumulate in the pulmonary vasculature of patients with PAH (Toshner, 2009; Montani, 2011), and KIT-targeted therapy in murine models of chronic hypoxia has been shown to prevent pulmonary hypertension (Gambaryan, 2010; Gambaryan, 2011).

In humans, several case report studies showed encouraging results on the treatment of PAH patients by imatinib (Ghofrani, 2005; Patterson, 2006; Souza, 2006). Moreover, the first randomized, double-blind, placebo-controlled phase II clinical trial presented evidence of improvement in hemodynamics in PAH treated with imatinib, and suggested a greater efficacy of the drug in patients with more severe pulmonary hypertension (Ghofrani, 2010). Later on, the phase III Imatinib in Pulmonary arterial hypertension, Randomised, Efficay Study (IMPRES) showed that imatinib used as an add-on therapy improved exercise capacity and hemodynamics in patients with advanced PAH (Hoeper, 2013). However, serious adverse events were common in this trial and its extension (Frost, 2015), and the high discontinuation rate in the latter did not allow for conclusive results. An exploratory sub-study of the IMPRES clinical trial showed significant improvements in echocardiographic measures of right ventricular function as well as left ventricular size and early diastolic relaxation (Shah, 2015).

Two other TKI were tested in clinical trials for the treatment of PAH: sorafenib and nilotinib (Table 2). The former was a phase I clinical trial and there are no published results and the latter was terminated due to abundant serious adverse events. It should also be mentioned that dasatinib has been associated with increased PAH incidence in patients treated for CML, which can be totally or partially reversed after dasitinib withdrawal (Rasheed, 2009; Mattei, 2009; Dumitrescu, 2011).

7.2.8. Alzheimer's disease

Alzheimer's disease (AD) is a degenerative neurological disorder characterized by the accumulation of β-amyloid plaques and hyperphosphorylated tau protein tangles in the brain (Hardy and Selkoe, 2002). It is also the most common cause of dementia and disability in the older patient (Ferri, 2005). An important role in the pathogenesis of AD is also ascribed to immunological mechanisms in the brain in which participate astrocytes and microglia (Heneka, 2015). Current therapies are only able to temporarily ease symptoms, and so additional therapeutic options are needed.

Mast cells are found in both sides of the blood-brain barrier (Silverman, 2000; Nautiyal, 2008), and by releasing large amounts of proinflammatory mediators they are thought to play a crucial role in sustaining the inflammatory network of the central nervous system (Kinet, 2007). The SCF/KIT is known to regulate both mast cell and microglia activities (Galli, 1995; Kitamura, 2006, Zhang and Fedoroff, 1998). TKI targeting KIT may prove beneficial for the treatment of neurological disorders such as AD by blocking activated MC-microglia interactions (Skaper, 2014) and thus preventing neuroinflammation. In this line, Masitinib administered as add-on therapy to standard treatments in a phase II clinical trial slowed the rate of cognitive decline in Alzheimer's disease patients (Piette, 2011). Based on these positive results, a multicenter, double-blind, placebo-controlled, randomized

Phase III clinical trial to evaluate the safety and efficacy of masitinib in patients with alzheimer's disease was launched and still ongoing (NCT01872598).

Nilotinib was proved to be efficient in improving amyloid clearance and cognitive performance in animal models of AD (Lonskaya, 2013; Lonskaya, 2014). Although in these studies the mechanism of action was proven to implicate Abl signaling pathway, we cannot exclude the beneficial effects that might arise due to KIT signaling blockage, also targeted by this drug. A phase II clinical trial is ongoing for the evaluation of the impact of low doses of nilotinib on safety and clinical outcomes in patients suffering from AD (NCT02947893).

7.2.9. Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory condition that damages the myelin of the central nervous system leading to neurologic impairment and possibly severe disability (Steinman, 2001). Four different forms of MS are currently defined based on disease evolution and clinical characteristics: relapsing remiting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and progressive relapsing MS (PRMS) (Lublin, 2014). Despite the existence of several approved therapies for the treatment of RRMS and PRMS, no current therapies have proven to slow disease progression on the PPMS and SPMS subgroups.

In rats, imatinib proved to be effective in diminishing the development of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (Crespo, 2011), and Azizi and colleagues showed attenuated severity and delayed onset of EAE in mice (Azizi, 2014). In relation to these animal models, there is still an ongoing controversy regarding the role of MC in the EAE development, due to the variable results obtained depending on the mice strain and/or the immunization protocol used (Piconese, 2011; Costanza, 2012). In contrast, in humans, mast cells have been found in demyelinated lesions from MS patients (Ibrahim, 1996; Toms, 1990) and histamine and tryptase were present in the cerebrospinal fluid of MS patients (Russi and Brown, 2015; Kallweit, 2013), suggesting a potential role of MC in MS pathology. Hence, the blocking of mast cells via KIT inhibition might be behind the beneficial effects observed for TKI on MS. In this regard, a phase 2 clinical trial assessing the safety and clinical benefit of masitinib in the treatment of PPMS and SPMS patients, proved masitinib to be effective in improving the multiple sclerosis functional composite score, the primary endpoint of the study (Vermersch, 2012). Based on these positive results, a phase III clinical trial is currently ongoing (NCT01433497).

7.2.10. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is the most common degenerative disease that affects the motor neuron system. It primarily affects motor neurons in the brain, brainstem and the spinal cord, causing progressive degeneration and atrophy of skeletal muscles, ultimately leading to paralysis. Survival after diagnosis varies between 1 to 5 years on average (Zufiria, 2016) and the only approved treatment option, Riluzole, modestly improves this survival (Bensimon, 1994; Gurney, 1997).

It seems that glial cells, by proliferating and expressing inflammatory mediators in the degenerating spinal cord, play an important role in the paralysis progression in rodent models of ALS (Barbeito, 2004; Diaz-Amarilla, 2011). As mentioned in the alzheimer's disease section, the SCF/KIT axis is known to regulate microglia activation (Zhang and Fedoroff, 1998), and therefore, TKI inhibiting this pathway might prove beneficial for the treatment of ALS as well. After promising results in which masitinib was shown to significantly decrease the number of aberrant glial cells and prolong survival in a $SOD1^{G93A}$ mutant rat model of ALS (Trias, 2016), two clinical trials have been launched for assessing the safety and efficacy of masitinib in ALS patients (Table 2). A phase II/III clinical trial proved masitinib to be effective for the treatment of ALS as an add-on to riluzole therapy. In this regard, masitinib significantly improved the primary endpoint, the revised ALS functional rating scale (ALSFRS-R) compared to placebo (Petrov, 2017), although full analysis of the results is still not available. A phase III clinical trial is ongoing with a unique dose of masitinib for the evaluation of safety and efficacy of combined masitinib-riluzole versus placebo-riluzole therapy in the treatment of patients suffering from ALS (NCT03127267).

The positive results of masitinib for the treatment of ALS patients may stem from the achievement of the right balance between microglia proliferation and activation, suppressing the aberrant microgliosis but preserving some levels of this immune compartment. In fact, a recent publication highlights the important role of microglia in neuroprotection, which mediated the recovery of motor neuron degeneration in a mouse model of ALS (Spiller, 2018).

7.2.11. Type 1 diabetes

Type-1 diabetes (T1D) is an autoimmune disease in which dysfunctionand death of insulin-producing beta-cells is thought to arise from direct contact with immune cells and from exposure to cytotoxic pro-inflammatory cytokines and other toxic substances (Eizirik, 2001). Insulin is a lifesaving pharmacological therapy for people with type 1 diabetes but it requires constant auto-surveillance, the selection of the right insulin regimen and comprehensive diabetes education (McGibbon, 2018). Moreover, the correct management of glycemia does not prevent associated comorbidities such as cardiovascular disorders (Bjornstad, 2018).

A few case reports have shown that TKI used for the treatment of different types of cancer were able to render insulin independence to patients suffering from T1D (Templeton, 2008; Huda, 2014) and T2D (Veneri, 2005). In parallel, different animal models were used to better understand the mechanisms by which TKI can provide these effects. In this line, by using two different mouse models for diabetes, the streptozotocin-injected mouse and the non-obese diabetes (NOD) mouse, Hägerkvist and coworkers proved that imatinib protected these mice from diabetes at least partly by preserving β-cell mass (Hagerkvist, 2007). Also in NOD mice, another group was able to demonstrate that imatinib was preventing and reversing T1D, and that this effect was mainly due to a decrease in the inflammatory component of the disease via PDGFR inhibition (Louvet, 2008). More studies are needed to clarify the exact mechanism of action of these drugs but, in the meantime, imatinib is being assessed for the treatment of new-onset T1D patients in an ongoing phase II clinical trial (NCT01781975).

7.2.12. Endometriosis

Endometriosis is a chronic inflammatory disease of multifactorial etiology characterized by implantation and growth of endometrial glands and stroma outside the uterine cavity, commonly associated with infertility and pelvic pain (Giudice, 2010). The pathogenesis of endometriosis is complex and has not been fully elucidated, and therefore current treatments are limited and not as effective as desired (Vercellini, 2014).

Inflammation is another feature of endometriosis, associated with the excessive production of prostaglandins, cytokines and chemokines (Vercellini, 2014). In this line, mast cells were also found increased in the ovarian tissue, specifically in the stromal lesions of women suffering from endometriosis compared to normal ovarian tissues (Konno, 2003). Apart from KIT^{+} mast cells, KIT expression was also found to be increased in endometrial glandular cells from women with endometriosis compared to healthy women, and strong KIT protein expression was associated with the most invasive forms of endometriosis (Uzan, 2005). Moreover, SCF levels were significantly higher in the peritoneal fluid of women suffering from endometriosis (Osuga, 2000). Therefore, TKI targeting KIT and/or indirectly mast cell inflammation might represent a potential therapy for the treatment of endometriosis.

Several animal models have been used to prove the effect of TKI such as pazopanib, sunitinib, sorafenib, and imatinib in endometriosis. In this regard, imatinib, pazopanib, and sunitinib were shown to decrease the endometriosis score in a rat model of endometriosis and this was

associated with a decrease in KIT and VEGF scores in the endometriosis tissue (Yildiz, 2015; Yildiz, 2016). In another rat model, sunitinib was found to diminish endometriosis lesions and their severity, although no mechanisms were established (Pala, 2015). Based on these results, axitinib is being tested in an ongoing phase I/II clinical trial for the treatment of endometriosis (NCT03481842).

8. Conclusion

The involvement of KIT in several types of cancer has promoted great amounts of research in relation to its biological nature and its expression. The interest for deepening the knowledge about KIT functions has been extended to diseases of different natures and important roles in inflammatory diseases and immunological disorders have been conferred to the SCF/KIT axis. All this research has led to the development of multiple KIT-targeted tyrosine kinase inhibitors for the treatment of different types of cancer, that are currently being considered as feasible options for the treatment of other non-oncological pathologies. Although many of these non-oncological applications are still in a premature stage and awaiting more conclusive phase III testing, there is hope for improvement in therapeutic benefits, which can optimistically be envisioned for certain autoimmune and neurodegenerative diseases.

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Conflict of interest statement

A.B. has consulting and/or speaker arrangements with AstraZeneca-MedImmune, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Sanofi-Regeneron, Med-in-Cell, Actelion, Merck, Roche, and Chiesi; and receives grant money and/or research support from AstraZeneca-MedImmune, Boehringer-Ingelheim, Cephalon/Teva, GlaxoSmithKline, Novartis, Sanofi-Regeneron. P.D. is shareholder of AB Science. P.C. has consulting and/or speaker arrangements with Almirall, Boehringer Ingelheim, Johnson & Johnson, GlaxoSmithKline, Merck Sharp & Dohme, AstraZeneca, Novartis, Teva, Chiesi, Sanofi, and SNCF; he sits an advisory board for Almirall, Boehringer Ingelheim, Johnson & Johnson, GlaxoSmithKline, AstraZeneca, Novartis, Teva, Chiesi, Schering Plough, and Sanofi and receives grant money and/or research support from Almirall, Boston Scientific, Boehringer Ingelheim, Centocor, GlaxoSmithKline, AstraZeneca, Novartis, Teva, and Chiesi. The remaining authors declare no competing financial interest.

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