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REVIEW

The stem cell factor (SCF)/c-KIT signalling in testis and prostate cancer

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Abstract The stem cell factor (SCF) is a cytokine that specifically binds the tyrosine kinase receptor c-KIT. The SCF/c-KIT interaction leads to receptor dimerization, activation of kinase activity and initiation of several signal transduction pathways that control cell proliferation, apoptosis, differentiation and migration in several tissues. The activity of SCF/c-KIT system is linked with the phosphatidylinositol 3-kinase (PI3-K), the Src, the Janus kinase/signal transducers and activators of transcription (JAK/STAT), the phospholipase-C (PLC-γ) and the mitogen-activated protein kinase (MAPK) pathways. Moreover, it has been reported that cancer cases display an overactivation of c-KIT due to the presence of gain-of-function mutations or receptor overexpression, which renders c-KIT a tempting target for cancer treatment. In the case of male cancers the most documented activated pathways are the PI3-K and Src, both enhancing abnormal cell proliferation. It is also known that the Src activity in prostate cancer cases depends on the presence of tr-KIT, the cytoplasmic truncated variant of c-KIT that is specifically expressed in tumour tissues and, thus, a very interesting target for drug development. The present review provides an overview of the signalling pathways activated by SCF/c-KIT and discusses the potential application of c-KIT inhibitors for treatment of testicular and prostatic cancers.

Keywords C-KIT · KIT ligand · Prostate cancer · SCF · Signalling · Testicular cancer

Abbreviations

ERK	Extracellular-signal-regulated kinase
GNNK	Gly-Asn-Asn-Lys
Grb2	Growth factor receptor bound protein-2
JAK	Janus kinase
JNK	c-Jun N-terminal kinase
MAPK	Mitogen-activated protein kinase
mSCF	membrane-bound SCF
mTOR	mammalian target of rapamycin
p70S6K	p70 S6 kinase
PI3-K	Phosphatidylinositol 3-kinase
PLC-γ	phospholipase-C
Rb	Retinoblastoma
SCF	Stem cell factor
SH2	Src homology 2
sSCF	soluble SCF
STAT	Signal transducers and activators of transcription
tr-KIT	truncated c-KIT protein

Introduction

The c-KIT is a tyrosine kinase receptor belonging to the type III receptor tyrosine kinase (RTK) family, which has the stem cell factor (SCF) as its specific ligand. The SCF/c-KIT interaction triggers several signal transduction pathways that regulate fundamental biological processes, such as apoptosis, cell proliferation, differentiation and migration (Ronnstrand 2004).

Despite the important function of SCF and c-KIT in healthy tissues, namely in the control of gametogenesis,

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melanogenesis, and haematopoiesis (Cardoso et al. 2014; Figueira et al. 2014) it has been shown that the SCF/c-KIT system is associated with the development and progression of human cancers (Cardoso et al. 2014). Gain-of-function mutations in the c-KIT receptor and/or c-KIT overexpression have been related to the onset and progression of several types of tumours (Ali and Ali 2007; Ashman and Griffith 2013; Capelli et al. 2016; Di Lorenzo et al. 2004; Mitchell et al. 2017), which have placed c-KIT on the road of the anti-cancer therapy. Currently, c-KIT inhibitors interfering with c-KIT signal transduction pathways are being used for treatment of leukemias and gastrointestinal tumours (Ashman and Griffith 2013), and under evaluation for other oncological diseases.

The testicular and prostatic cancers are the emblematic representatives of male gender malignancies, for which increasing incidence has been reported worldwide in the recent decades (Ferlay et al. 2013). Prostate cancer is a common concern of aging male and age is its most recognized risk factor, whereas testicular cancer is a disease of young and middle-aged men (Damaschke et al. 2013; Filippou et al. 2016; Hayes-Lattin and Nichols 2009). Nevertheless, these urological cancers are commonly influenced by a variety of genetic, epigenetic, and environmental factors (Wu et al. 2016), and for both prostate and testicular cancers, the improvement of treatment strategies and better disease management are clearly warranted. For prostate cancer, the situation is even more urgent considering the progression of disease to advanced stages, with a great complexity of androgen-dependent and -independent signalling mechanisms and for which limited therapeutic options exist (Farooqi and Sarkar 2015). The present review summarizes the current knowledge concerning the expression of c-KIT and the SCF/c-KIT activated pathways in testicular and prostate cancer cases, and discusses the perspectives of treatment of these oncological diseases targeting the c-KIT receptor.

C-KIT receptor in the context of RTKs family

The RTKs are important regulators of intracellular signal-transduction pathways playing a crucial role in the control of cell fate decisions. The human RTK superfamily consists of 58 proteins grouped into 20 sub-families (Fig. 1) that share structural features and some functional roles (Blume-Jensen and Hunter 2001). The families are the ErbB / EGFR, epidermal growth factor receptor; InsR, insulin receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor; KLG/CCK, colon carcinoma kinase; NGFR, nerve growth factor receptor; HGFR, hepatocyte growth factor receptor; EphR, ephrin receptor; Axl, a Tyro3 PTK; Tie, tyrosine kinase receptor in endothelial cells; Ryk, receptor related to tyrosine kinases; DDR, discoidin domain receptor; Ret, rearranged during transfection; Ros, RPTK expressed in some epithelial cell types; LTK, leukocyte tyrosine kinase; Ror, receptor orphan; MuSK, muscle-specific kinase; LMR, Lemur and STYK1, serine, threonine, tyrosine kinase 1 (Blume-Jensen and Hunter 2001; Lemmon and Schlessinger 2010; Robinson et al. 2000). The EGFR, InsR and PDGFR families also are widely known as class I, class II and class III RTKs, respectively.

The general structure of RTKs (Fig. 1) encompasses the ligand binding domain in the glycosylated N-terminal extracellular region, a single transmembrane helix, and a cytoplasmic region that contains the tyrosine kinase domain, and C-terminal and juxtamembrane regulatory regions (Lemmon and Schlessinger 2010). The intracellular juxtamembrane region and the C-terminal tail differ in size and tyrosine content among family members, which creates differences in intracellular signalization. Nevertheless, RTKs differ mainly by the extracellular domains (Fig. 1) that display specific molecular features (immunoglobulin domains, cysteine, and leucine-rich domains, fibronectin type III domain, among others) in the distinct receptor families (Maruyama 2014; Segaliny et al. 2015).

The c-KIT belongs to the PDGFR family (Class III), that besides PDGFRα and PDGFRβ also includes the colony-stimulating factor 1 receptor (CSF1R) and the Fms-like tyrosine kinase 3 receptor (FLT3) (Verstraete and Savvides 2012).

Brief overview of the molecular biology of SCF/c-KIT system

C-KIT receptor

The c-KIT receptor was first described in 1986 as the transforming gene of the Hardy-Zuckerman 4 feline sarcoma virus and identified as the proto-oncogene *v-KIT* (Yarden et al. 1987). CD117, SCF receptor or KIT receptor are other common designations for c-KIT (Yarden et al. 1987). The main product of *c-KIT* gene is a single 5 kb transcript encoding a transmembrane glycoprotein with approximately 145–160 kDa that belongs to the type III RTK family (Yarden et al. 1987). This class of receptors is structurally characterized by the presence of three main functional regions (Mol et al. 2003) (Fig. 1): an intracellular domain, containing proximal and distal kinase domains separated by an interkinase domain, that is involved in signalling transduction; a transmembrane region constituted by a short hydrophobic chain of amino acids that anchors c-KIT at cell membrane; and an extracellular domain comprising five immunoglobulin-like domains, which participate in recognition of c-KIT ligand and receptor dimerization.

Distinct c-KIT protein variants have been identified over the years (Fig. 2). The use of an alternative 5′-donor splice site

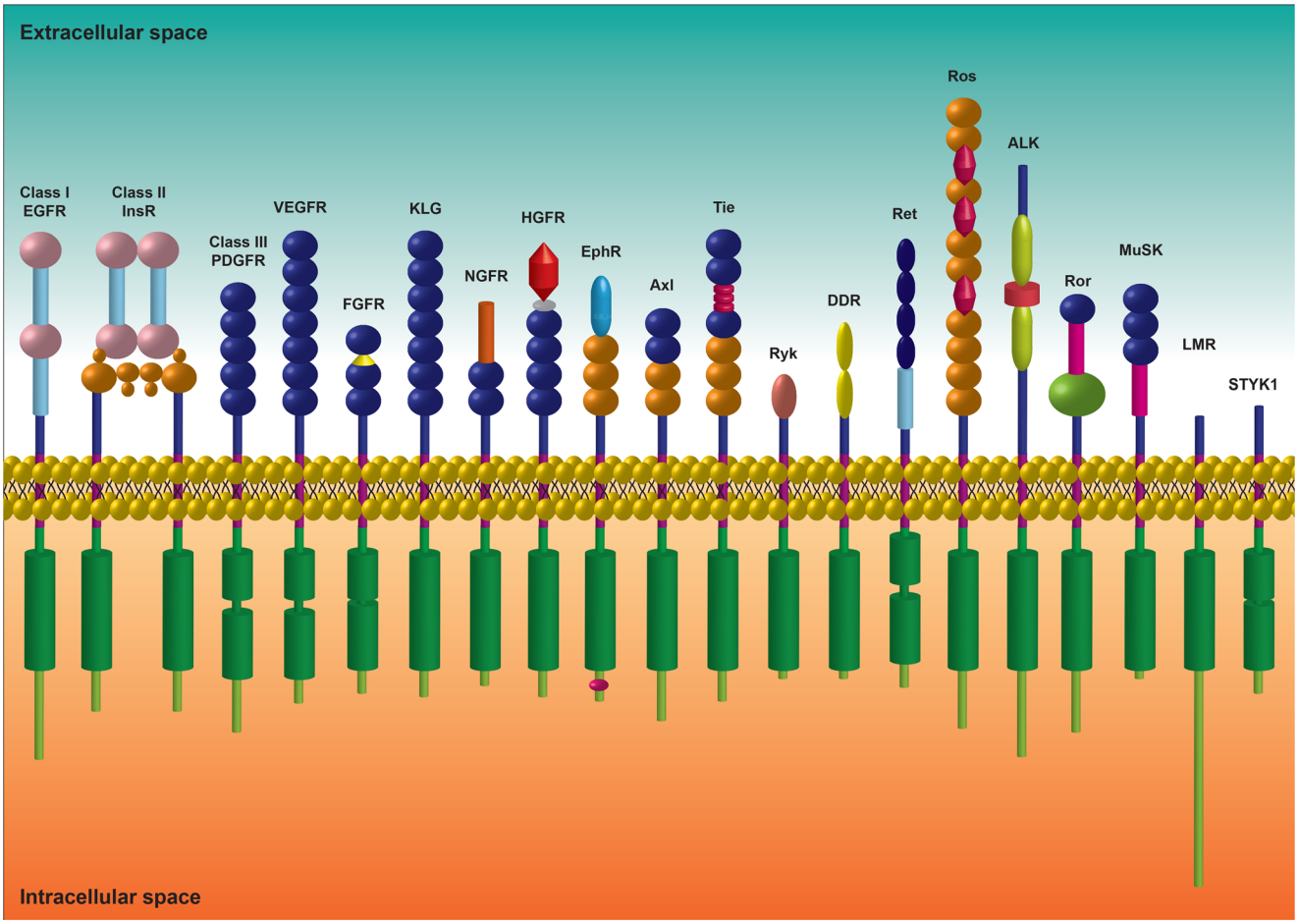

Fig. 1 General structure of RTKs families. The extracellular, transmembrane and intracellular structural domains of the 20 families of human RTKs are represented schematically. Green cylinders represent the intracellular regions containing the kinase domains and purple rectangles show the transmembrane region. The main structural differences between all RTKs classes are located in the extracellular domain and confer ligand specificity. The classical EGFR, InsR and PDGFR families are also known as class I, class II and class III RTKs, respectively. c-KIT belongs to the class III, PDGFR family. - L; - cysteine-rich; - fibronectin type III; - immunoglobulin domain; - acid box; - leucine-rich; - sema; - psi; - ephrin binding domain; - EGF; - WIF; - discoidin; - cadherin; - YWTD propeller; - mam domain; - Ldla; - fz; - kringle

produces c-KIT isoforms that differ by the presence or absence of the tetrapeptide Gly-Asn-Asn-Lys (GNNK) in the juxtamembrane region of the extracellular domain (Caruana et al. 1999). Recently, it was demonstrated that the GNNK peptide is an important regulatory element for fine tuning receptor activation and downstream signalling since GNNK-negative c-KIT variants displayed increased tyrosine phosphorylation and activity (Phung et al. 2013). In other words, the juxtamembrane region by the presence of GNNK peptide acts as a negative regulator of c-KIT activity.

A mechanism of alternative promoter usage originates a 30–50 kDa truncated c-KIT protein (tr-KIT, Fig. 2) that lacks the extracellular domain and the transmembrane region (Rossi et al. 1992). tr-KIT is also devoid of the first part of the kinase domain (Fig. 2) and, thus, do not display kinase activity (Rossi et al. 1992). However, tr-KIT seems to retain signalling transduction capability by interacting with other RTKs, or with other receptor types (Sette et al. 1998) as a scaffold protein at the cytoplasm.

Proteolytic cleavage of c-KIT releases the receptor from the cell membrane given rise to a soluble isoform (Fig. 2) that only contains the extracellular domain. This protein variant binds SCF with the same affinity as the full-length c-KIT, and it was suggested that it might play a role modulating the bioactivity of ligand (Dahlen et al. 2001).

SCF

The c-KIT ligand, the cytokine SCF also known as steel factor or mast cell growth factor, is a potent growth factor firstly

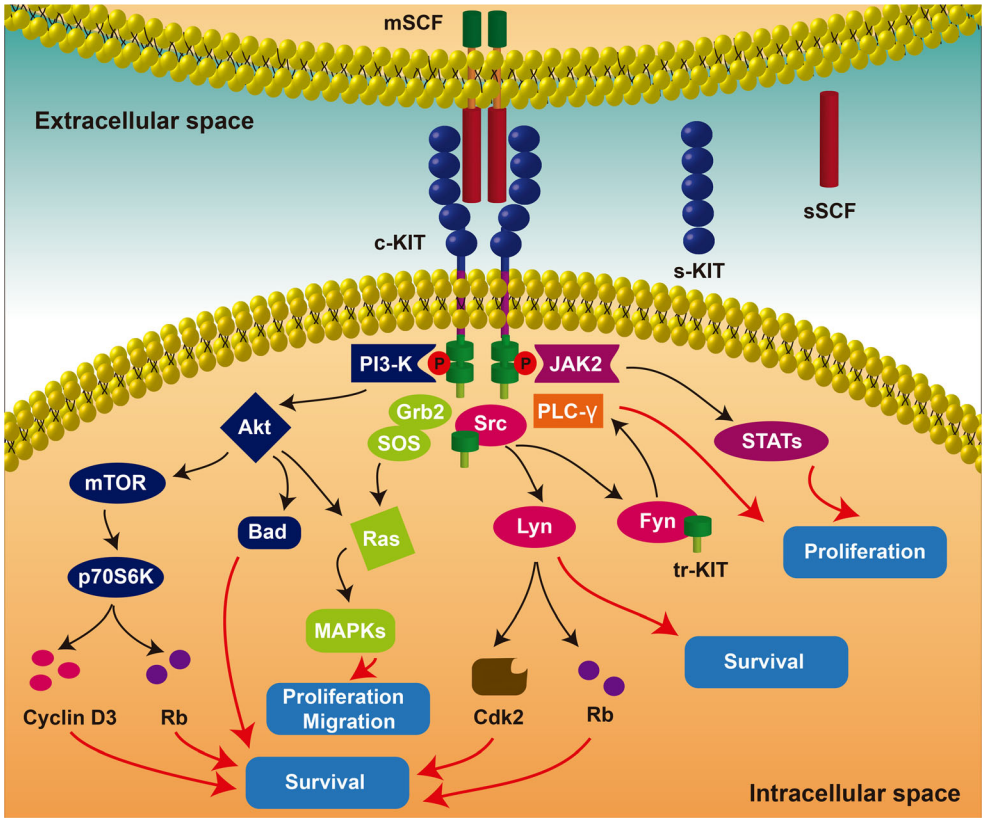

Fig. 2 Structure of SCF/c-KIT proteins and downstream signalling pathways. Membrane-bound SCF (mSCF) contains an extracellular domain (*red*) that is responsible for recognizing and binding to c-KIT, a transmembrane domain (*orange*), and an intracellular domain (*dark green*). SCF also exists as a soluble protein (sSCF) secreted to the extracellular space. The five immunoglobulin-like domains (*dark blue*) in the extracellular domain of c-KIT are involved in ligand-binding and receptor dimerization. The transmembrane domain (*violet*) anchors c-KIT at the cytoplasm membrane and the intracellular region (*green*) is responsible for signal transduction. The receptor can be proteolytically cleaved and released from cell membrane, giving rise to a soluble c-KIT (s-KIT) consisting only of the extracellular domain. A truncated form of c-KIT (tr-KIT) residing at cytoplasm lacks the extracellular and transmembrane domains but retains part of the kinase domain. Binding of SCF homodimer to c-KIT induces receptor dimerization and auto-phosphorylation, and consequent activation of downstream signalling cascades. The cell survival PI3K/Akt pathway (*dark blue*) depends on the phosphorylation of p70 S6 kinase (p70S6K) via mammalian target of rapamycin (mTOR), which leads to increased expression of cyclin D3 and phosphorylation of retinoblastoma protein (Rb). SCF/c-KIT/PI3K/Akt signalling also contributes to cell survival by inactivation of the pro-apoptotic factor Bad. The Src pathway (*pink*) controls proliferation, cell-cycle progression, and migration by distinct actions of Akt, Fyn, and Lyn kinases. c-KIT activates PLC-γ (*orange*), that can also be activated by tr-KIT through SRC member Fyn, which induces cell proliferation. SCF/c-KIT signalling has also been linked with the activity of JAK/STAT pathway (*purple*) through the activation of JAK2 and consequent phosphorylation of STAT transcriptional regulators, which enhance proliferative activity. Activation of the MAPK pathway (*light green*) occurs upon binding of adaptor proteins, such as growth-factor receptor-bound protein-2 (Grb2) and guanine nucleotide exchange factor, son of sevenless (SOS), which determines the activation of the small G-protein RAS and the propagation of kinases signalling cascade

identified in 1990 (Williams et al. 1990). The *SCF* gene encodes a 45 kDa glycoprotein predominantly located at plasma membrane (Mansuroglu et al. 2009).

The SCF protein contains three distinct regions (Fig. 2): the intracellular domain, the hydrophobic transmembrane domain, and the extracellular domain responsible for recognizing and binding c-KIT (Langley et al. 1994). Besides the full-length membrane-bound SCF (mSCF), soluble forms of SCF have also been identified (Fig. 2). The proteolytic cleavage of an alternative spliced variant originates a soluble SCF (sSCF) that also binds and activates c-KIT. However, sSCF promotes transient activation and faster degradation of c-KIT whereas mSCF induces persistent activity and prolongs the life span of receptor (Miyazawa et al. 1995).

Generalities of c-KIT activation by SCF

SCF is a noncovalent homodimer composed of two protomers; an hydrophobic crevice with a charged region on the tail of each protomer functions as the potential receptor-binding site (Zhang et al. 2000). Thus, SCF binds simultaneously two molecules of c-KIT, inducing a conformational change that exposes a key dimerization site located in the fourth immunoglobulin-like domain of c-KIT (Lemmon

et al. 1997). Receptor dimerization allows its autophosphorylation (Paulhe et al. 2009), and triggers the initiation of multiple signal transduction pathways (Ali and Ali 2007; Mol et al. 2003), namely, the phosphatidylinositol 3-kinase (PI3-K), the Src, the Janus kinase/signal transducers and activators of transcription (JAK/STAT), the phospholipase-C (PLC-γ) and the mitogen-activated protein kinase (MAPK). The physiological actions of c-KIT controlling cell survival, proliferation, differentiation, and migration depend on the activation of specific or overlapping pathways (Ronnstrand 2004) (Fig. 2), which endows the activity of SCF/c-KIT system of a great complexity. Disclosure of the c-KIT activated pathways in carcinogenesis will be a crucial step towards the development of c-KIT targeted therapies.

SCF/c-KIT signalling pathways

The PI3-K pathway

PI3-K heterodimer is one of the major pro-survival pathways influencing cell fate in a variety of tissues. The PI3-K regulatory subunit p85 contains two Src homology 2 (SH2) domains (Klippel et al. 1994) that are responsible for the interaction with c-KIT. Genetically modified mice lacking the p85 subunit of PI3-K displayed a dramatic reduction in the proliferative effects of SCF/c-KIT, which demonstrates the involvement of PI3-K downstream signal pathway (Fukao et al. 2002). The Tyr719 and Tyr821 residues in the interkinase domain of c-KIT are involved in PI3-K activation (Serve et al. 1994; Serve et al. 1995). PI3-K can also be indirectly activated by c-KIT through its binding to the tyrosine phosphorylated adaptor protein GAB2 (Nishida et al. 2002).

PI3-K activation in response to c-KIT is followed by the phosphorylation of downstream signalling molecules in the PI3-K cascade (Fig. 2), as is the case of cell survival regulator Akt (Nakai et al. 2005). Akt seems to mediate SCF/c-KIT/PI3-K signalling by phosphorylating the p70 S6 kinase (p70S6K) via mammalian target of rapamycin (mTOR) kinase (Feng et al. 2000). Phosphorylation of p70S6K leads to increased expression of cyclin D3 and phosphorylation of retinoblastoma (Rb) protein (Feng et al. 2000), allowing cell cycle progression and cell division. On the other hand, inhibition of mTOR by rapamycin prevented the SCF/c-KIT effects controlling cell survival and proliferation, cell adhesion, cytokine production and chemotaxis (Blume-Jensen et al. 1998; Feng et al. 2000).

The pro-apoptotic factor Bad is also a target of Akt upon SCF activation of the PI3-K pathway. Phosphorylation of Bad by Akt leads to its inactivation and, thus, contributes to cell survival (Blume-Jensen et al. 1998).

c-KIT mutations in the juxtamembrane and kinase domain (Table 1) have been described in human germ-cell tumours, the most common type of testicular cancer. All the mutations in the kinase domain constitutively activate the receptor (Table 1) and promote its association with PI3-K (Kemmer et al. 2004; Nakai et al. 2005; Tian et al. 1999). In addition, c-KIT activity in seminomas also phosphorylates Akt via PI3-K, thereby promoting the progression of germ-cell neoplasia (Nakai et al. 2005). Germ-cell tumours also appear to be enriched for expression of the GNNK-negative isoforms of c-KIT (Sakuma et al. 2003). These c-KIT variants lacking the GNNK tetrapeptide are strongly activated upon SCF binding and display pronounced signalling effects, namely, increased c-KIT phosphorylation and enhanced activation of MAP kinase protein ERK (Montero et al. 2008; Phung et al. 2013). Thus, blocking c-KIT activity would be a valuable strategy to treat testicular cancer, namely seminomas, since non-seminomas rarely express c-KIT (Izquierdo et al. 1995). At the present moment, the information concerning c-KIT inactivation in testicular cancer is very limited, but imatinib mesylate, the first tyrosine kinase inhibitor used as a

Table 1 c-KIT mutations identified in germ-cell tumours

Amino acid position	Amino acid change	Structural Region	Functional Effect*	References
557	W557R	Juxtamembrane domain	?	(Coffey et al. 2008; Sakuma et al. 2003)
814	D814Y	Kinase domain	Enhanced tyrosine kinase activity	(Piao and Bernstein 1996; Schnabel et al. 2005)
816	D816H, D816V or D816Y	Kinase domain	Enhanced tyrosine kinase activity	(Biermann et al. 2007; Rapley et al. 2004; Willmore-Payne et al. 2006)
820	D820G	Kinase domain	Enhanced tyrosine kinase activity	(Rapley et al. 2004; Willmore-Payne et al. 2006)
821	S821F	Kinase domain	Enhanced tyrosine kinase activity	(Biermann et al. 2007)
822	N822 K	Kinase domain	Enhanced tyrosine kinase activity	(Biermann et al. 2007)
823	Y823D	Kinase domain	Enhanced tyrosine kinase activity	(Biermann et al. 2007; Willmore-Payne et al. 2006)

*- all the identified mutations were reported to be insensitive to tyrosine kinase inhibitor imatinib;? – The exact consequence of c-KIT mutations in the juxtamembrane domain has not been demonstrated yet, but since this region is a negative regulator of c-KIT kinase activity (Phung et al. 2013) it is expected that they also could constitutively activate receptor

chemotherapeutic drug, has shown beneficial effects. A patient with disseminated testicular seminoma that was refractory to salvage chemotherapy had complete remission after administration of imatinib for 3 months (400 mg/day) (Pedersini et al. 2007). However, all the c-KIT mutations identified in germ-cell tumours (Table 1) have been indicated as resistant to imatinib, which is apparently explained by the capability of imatinib inhibiting kinase activity only in its inactive conformation (Lennartsson and Ronnstrand 2012; Todd et al. 2013). Therefore, it would be important to screen patients for the presence of imatinib-sensitive mutations before embracing for this therapy. On the other hand, since the described oncogenic mutations of c-KIT (Table 1) have shown to be insensitive to imatinib but sensitive to the second-generation tyrosine kinase inhibitor dasatinib, which binds to the kinase domains in its active conformation (Lennartsson and Ronnstrand 2012), it is warrantable to test dasatinib for treatment of germ-cell tumours.

The Src pathway

Studies in different types of cells have demonstrated that the SCF/c-KIT system activates several Src family members (Fig. 2), such as Src, Lyn and Fyn (Linnekin et al. 1997a; Samayawardhena et al. 2007). Src kinases interact with Tyr568 and Tyr570 in the juxtamembrane domain of c-KIT, but only phosphorylation of Tyr568 seems to be required for the activation of Src family members (Price et al. 1997). Moreover, c-KIT isoforms negative for the GNNK sequence in the juxtamembrane domain display stronger activation of Src members than GNNK-positive isoforms (Voytyuk et al. 2003).

The activation of Src pathway is associated with the SCF/c-KIT actions promoting cell proliferation. It was demonstrated that SCF activates Lyn before the G1 to S phase transition (Mou and Linnekin 1999). Lyn activation by SCF triggered cell cycle progression by increasing the activity of cyclin-dependent kinase 2 (Cdk2) and phosphorylation of Rb protein. Moreover, Src inhibitors caused a strong reduction in Akt phosphorylation in response to c-KIT signalling (De Miguel et al. 2002; Farini et al. 2007), which demonstrated that the activation of Akt survival pathway can also be mediated by the Src pathway. The alternative activation of Akt pathway via PI3-K or Src family members seems to be cell specific (De Miguel et al. 2002).

c-KIT signal transduction triggering the Src pathway is also important in the regulation of cell migration. Experiments in cells with deficient forms of Lyn or the use of Src family kinase inhibitors provided evidence for the involvement of the Src pathway in SCF-dependent migratory response (Farini et al. 2007; O'Laughlin-Bunner et al. 2001).

The activity of Src family members has been closely associated with the action of tr-KIT. The tr-KIT is a stronger activator of Src kinases, comparatively with the full-length protein (Paronetto et al. 2004; Paronetto et al. 2003). Higher levels of Src activity were found in prostate cancer cells and tissues expressing the tr-KIT (Paronetto et al. 2004). It is known that Src activity leads to the phosphorylation of the RNA-binding protein Sam68, and that this event is linked to the neoplastic transformation of prostate cells (Derry et al. 2003). Interestingly, Sam68 phosphorylation is only detected in prostate tumours expressing the tr-Kit (Paronetto et al. 2004). Moreover, the expression of tr-KIT seems to be tumour specific and markedly increases with the progression of prostate cancer (Paronetto et al. 2004), which renders tr-KIT a pharmacological target.

The tyrosine kinase inhibitor imatinib blocks the activity of the full-length c-KIT but has no effect on the tr-KIT, which may explain the little efficacy this drug has been showing in prostate cancer treatment, as well as, the inconsistency between results of in vitro experiments and clinical findings (Corcoran and Costello 2005; Tiffany et al. 2004). Several reports have shown the growth inhibitory actions of imatinib alone or in combination with other cytotoxic drugs in distinct cell line models of prostate cancer, namely, in androgen-sensitive (LNCaP) and castration-resistant models (DU145 and PC3) (Huang et al. 2012; Pinto et al. 2011). However, these findings failed to be translated into the clinical setting with imatinib treatment showing only modest efficacy (Corcoran and Costello 2005; Lipton et al. 2010; Mathew et al. 2004; Nabhan et al. 2012; Tiffany et al. 2004). Moreover, we recently showed that imatinib significantly decreased the viability of DU145 cells whereas augmented the survival of PC3 cells, which was accompanied by a distinct expression pattern of apoptosis regulators (Cardoso et al. 2015). Also, an angiogenic factor, the vascular endothelial growth factor (VEGF) displayed a distinct response to imatinib in DU145 and PC3 cells. Imatinib treatment diminished the expression levels of VEGF in DU145 cells whereas an opposite effect was seen in PC3 (Cardoso et al. 2015). These opposed effects of imatinib in distinct cell lines may contribute explaining the lack of efficacy of this anti-cancer drug controlling prostate tumour's growth and raise the concern about stimulation and progression of metastasis when applying imatinib treatment in prostate cancer patients. Ultimately, the expression levels of c-KIT and tr-KIT in DU145 and PC3 cells consubstantiate the distinct effects observed in response to imatinib, with PC3 cells displaying diminished expression of the full-length c-KIT and increased expression of tr-KIT (Cardoso et al. 2015). Overall, the current knowledge and the findings described above strongly stimulate future research aiming at discovering drugs that specifically block the tr-KIT.

The JAK/STAT pathway

The Janus kinases (JAKs) are cytoplasmic tyrosine kinases activated by ligand, which lead to phosphorylation and transcription of signal transducer and activation of transcription

(STAT) proteins (Kerr et al. 2003). After being phosphorylated, STATs dimerize and are translocated to the nucleus, where they regulate the transcription of target genes (Kerr et al. 2003). Signal transduction by SCF and its receptor was shown to be related to the JAK/STAT pathway (Fig. 2) by the activation of JAK2 (Deberry et al. 1997; Linnekin et al. 1997b). SCF induced the association of c-KIT with JAK2 and the consequent phosphorylation of JAK2 (Weiler et al. 1996). The transient activation of JAK2 in response to SCF was associated with the downstream activation of STAT1 and STAT5 (Deberry et al. 1997; Ryan et al. 1997). Moreover, SCF also increased the expression of JAK2 and STAT1 (Imura et al. 2012). It was also observed an increase in differentiation but not in the self-renewal of stem cells in the testis of the fruit fly, *Drosophila sp.*, in the absence of JAK/STAT signalling (Tulina and Matunis 2001). Thus, the activation of JAK2/STAT1 pathway seems to underpin the SCF/c-KIT actions regulating stem cell proliferation. Although the enhanced renewal of testicular stem cells has been linked with the development of germ-cell tumours (Chieffi 2014), the involvement of SCF/c-KIT and JAK/STAT signalling in testicular carcinogenesis remains to be clarified.

In the case of prostate cancer, the idea that a population of "cancer stem cells" implicated in the ontogeny of disease and therapeutic resistance also has been gaining consistency in the last years (Lin et al. 2016b; Yun et al. 2016). These cancer stem cells seem to be associated with the basal layer of prostate epithelium; a region reported to have high expression levels of c-KIT (Ceder et al. 2017; Leong et al. 2008). Moreover, it was demonstrated that tumorigenesis induced by prostate cancer stem cells is accompanied by the increased expression of c-KIT (Peng et al. 2015). Interestingly, several signalling pathways were shown to be deregulated in prostate cancer stem cells and accounting for its tumorigenic potential, which included the JAK-STAT pathway (Birnie et al. 2008; Lin et al. 2016a; Lin et al. 2016b).

The PLC-γ pathway

The phospholipase-Cγ (PLC-γ) pathway is one of the less characterized relatively to the activity of the SCF/c-KIT system. The activation of c-KIT by SCF leads to c-KIT autophosphorylation and its association with PLC-γ1 via the phosphorylated Tyr728 residue (Gommerman et al. 2000). Several reports demonstrated that the inhibition of PLC-γ disrupts the SCF effects in cells expressing c-KIT (Gommerman et al. 2000; Maddens et al. 2002). However, other study failed to detect PLC-γ activity induced by SCF/c-KIT, observing an activation of phospholipase D instead (Koike et al. 1993).

Interaction of tr-KIT with the PLC-γ pathway has also been described, though independently of SCF since this c-KIT variant is devoid of the extracellular domain (Rossi et al. 1992; Sette et al. 1998). It was demonstrated that tr-KIT in sperm is able to activate the PLC-γ1 in mouse oocytes (Schnabel et al. 2005; Sette et al. 1998). Moreover, it was proposed that the action of tr-KIT phosphorylating and activating PLC-γ1 is mediated by the interaction with the Src member Fyn. The physical association of tr-KIT with Fyn promotes the catalytic activity of Fyn and the consequent phosphorylation and activation of phospholipase (Sette et al. 2002).

Further studies are needed to establish a connection between the role of c-KIT activating PLC-γ and neoplastic conditions of male reproductive tract.

The MAPK pathway

Activation of the MAPK cascade occurs upon binding of SH2 adaptor proteins to the phosphorylated residues of RTKs, which determines the activation of small G-protein Ras. Phosphorylated Tyr703 and Tyr936 residues in the carboxyl-terminal tail of c-KIT were identified as binding sites for the adaptor proteins, growth factor receptor bound protein-2 (Grb2) and the guanine nucleotide exchange factor, son of sevenless (SOS) protein (Thommes et al. 1999). The Grb2/SOS complex has been shown to link RTKs to the Ras/MAPK pathway (Fig. 2). Cell signalling via c-KIT activates several MAPKs such as extracellular-signal-regulated kinase (ERK) 1/2, p38, c-Jun N-terminal kinase (JNK), and ERK5.

As expected, the MAPK pathway is linked with the proliferative activity of SCF upon activation of c-KIT. Inhibition of MEK/MAPK kinase effectively abolished the SCF-induced proliferation while the anti-apoptotic effect of SCF remained unchanged (Dolci et al. 2001). Moreover, membrane-bound and soluble isoforms of SCF seem to have specific MAPKs targets. The mSCF effectively induced cell proliferation through the ERK whereas the sSCF proliferative effects were achieved by the activity of p38 (Kapur et al. 2002).

SCF/c-KIT effects mediating cell migration also depend on the MAPK pathway via phosphorylation and activity of p38 (Kuang et al. 2008); MEK/MAPK inhibitors reduced the response to c-KIT by 30% (Farini et al. 2007).

Interestingly, it has been shown that the SCF/c-KIT activation of MAPK pathway is dependent on PI3-K signalling. The use of PI3-K inhibitors decreased the activation of RAF and ERK, but did not affect Ras activation (Wandzioch et al. 2004). The crosstalk between PI3-K/Akt and Ras/MAPK pathways has been described at multiple levels in distinct cell types endowing the cells with incredibly higher response patterns to the combinatorial variety of external stimuli (Aksamitiene et al. 2012). Moreover, it is known that abnormalities in MAPK signalling play a critical role in the development and progression of cancer (Dhillon et al. 2007). However, much is yet to be discovered about the relationship of SCF/c-KIT with MAPK pathway in male cancer, namely, in testicular and prostatic cancer.

Conclusion

The SCF/c-KIT system is involved in the control of basic biological processes, such as apoptosis, cell proliferation, differentiation, and migration. The deviation to the strict control of these cellular processes is closely related with the neoplastic transformation and tumours progression, thus, not surprisingly, deregulated actions of c-KIT have been associated with different types of human cancers.

Considerable research efforts have started to disclose the signalling pathways activated by c-KIT and how they, independently or in cross-talk, regulate cell fate and contribute to cell tissue homoeostasis. Moreover, it has been shown that due to the presence of gain-of-function mutations or overexpression of c-KIT, some of these pathways are overactivated in pathological conditions, as is the case of testicular and prostatic cancers. Therefore, the inhibition of c-KIT emerged as a promising strategy for treatment of testicular cancer, though being much less effective in the case of prostatic tumours. As discussed through the review, the differential response of human solid tumours to c-KIT inhibitors can be related with the existence of tissue-specific protein variants (e.g tr-KIT), and/or with c-KIT mutations. The characterization of c-KIT mutations sensitive to imatinib (or other second-generation tyrosine kinase inhibitors) in testicular and prostatic cancers deserves further investigation and should be a prerequisite before advancing in treatment. Moreover, a deeper understanding of c-KIT signalling mechanisms in cancer cells will be paramount to identify the crucial targets points for therapeutic intervention, which in the case of prostate cancer means the development of specific inhibitors for the tr-KIT.

Finally, human tumours are usually dependent on the activation of several survival and proliferation pathways. In this way, clarifying the interaction between the distinct signalling pathways driven by c-KIT (and its variants) in cancer cells might help to develop highly effective inhibitors acting simultaneously at different molecular targets. At this point, should also be included the microRNAs (miRNAs), a class of small endogenous RNAs with important actions in the regulation of gene expression and modulation of signalling pathways by its capability of enhancing or repressing the activity of downstream effectors. The role of miRNAs in prostate cancer was reviewed having been clear their oncogenic or tumour suppressor abilities, as well as the interaction with androgen receptor and other signalling pathways (Fayyaz and Farooqi 2013). This opens new avenues of research to ascertain the relationship between miRNAs and c-KIT signalling, which would be therapeutically relevant.

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