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Editorial

c-Kit expression in human normal and malignant stem cells prognostic and therapeutic implications

Abstract

The human stem cell factor/c-Kit signaling pathway is pivotal for the survival of embryonic, foetal and adult stem cells and for their fundamental role in generating healthy functioning cell and tissue types during embryonic, foetal and adult life. Common biological features between human stem cells and cancer cells include (A) self-renewal, (B) extensive capacity of proliferation, (C) migration to and homing at distant sites and (D) resistance to toxic agents. Given these shared attributes, cancer was proposed to originate from transforming mutation(s) in normal stem cells that dysregulate their physiological programs. This theory has been recently supported by the findings that among all malignant cells within a particular tumour, only cell fraction expressing stem cell markers such as c-Kit named 'cancer stem cells' has the exclusive potential to generate tumour cell population. The involvement of c-Kit and its mutation in various haematological malignancies and solid tumours are reviewed. The impacts of dysregulated c-Kit as oncogenic tyrosine kinase on autocrine stimulation and resistance to chemotherapy of cancer stem cells are evaluated. The significance and efficacy of molecular therapeutic targeting of c-Kit signaling pathway in the management of patients with c-Kit-positive malignancies are appraised.

Keywords: CD117; c-Kit; Embryonic; Drug resistance; Imatinib; Stem cells; Stem cell factor

More than a century ago, the forefather of modern pathology: Rudolf Virchow (1821–1902) has stated "*Omnis Cellula e Cellula*" [Every cell stems from another cell]. Adult human stem cells are responsible for substantial regeneration of body tissues throughout lifetime. They exist in significant numbers in human tissues with high regenerative capacity and high cellular turnover such as bone marrow, intestine and skin. Human bone marrow haematopoietic stem cell niche produces billions of mature blood cells each day. Also, half a ton of intestinal epithelium is regenerated during human lifetime through the intestinal stem cell niche. Moreover, about 1% of the whole human body skin is replaced each month through the basal epidermal stem cell niche.

In addition the human mesenchymal stem cells, prominent adult multi-potent stem cells, drive substantial regeneration in tissues with high regenerative capacity and low cellular turnover such as bone [1]. The continuous process of bone renewal throughout human lifetime results in a total turnover time of 3 years for the entire body skeleton.

Similarly human tissues with low regenerative capacity and low cellular turnover such as brain and heart contain small number of adult neural and cardiac stem cells for regeneration and repair. The neural stem cell niche resides in the subventricular zone and striato-thalamic groove of adult human brain [2].

1. Stem cell factor

Stem cell factor (SCF) is a major human cytokine for the self-renewal, proliferation and differentiation of numerous embryonic [3–6], foetal [7], umbilical cord [8] and adult haematopoietic [9], neural [10] and primordial [11] stem cells. SCF is also extensively expressed as a key survival and growth factor during several human developmental processes including germ cell development [12], haematopoiesis [13], melanocyte development [14], angiogenesis [15] and spermatogenesis [16].

SCF functions in two active isoforms: membrane-anchored for short-range signaling transmitted by cell–cell contacts and soluble for longer-range signaling transmitted by diffusion through the extra-cellular medium [17]. Stimulation with the soluble form results in rapid but transient auto-phosphorylation of Kit, whereas stimulation with the membrane-bound form results in more sustained phosphorylation [17]. The human physiological level of SCF in serum

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is between 1 and 3 ng/ml [18–20]. Interestingly, the same in vivo physiological concentrations have been shown to profoundly enhance in vitro the proliferation of several human colorectal, leukaemia, lung cancer and pancreatic cancer cell lines [21–23].

2. c-Kit (stem cell factor receptor/CD117)

Human c-Kit is a trans-membrane type III receptor protein-tyrosine kinase with an extra-cellular ligand-binding domain, single trans-membrane segment and a cytoplasmic kinase domain that functions as the stem cell factor receptor [24]. Human c-Kit has four isoforms for the binding of SCF that leads to receptor dimerisation and activation of protein kinase activity and its gene is located at chromosome [25]. The SCF forms a non-covalent dimer that binds to two c-Kit monomers and promotes c-Kit dimer formation [24,25].

3. c-Kit expression in normal stem cells

c-Kit expression was reported in both human and mouse undifferentiated embryonic stem cells with a role in maintaining their undifferentiated state and correlation with functional measures of their pluripotency [5,6,26–28]. The c-Kit transcript expression in human embryonic stem cells is greater than in differentiated cells proposing it as a marker for human embryonic stem cells owing to its correlation with pluripotency [5,6,29].

Similarly, c-Kit is expressed in adult bone marrow haematopoietic and mesenchymal stem cells [1,30] as well as foetal and umbilical cord haematopoietic stem cells [7,8] and its expression correlates with the self-renewal function of these foetal and adult stem cells.

The adult bone marrow stem cells expressing c-Kit are responsible for not only erythropoiesis and megakaryopoiesis [8,12] but also for the angiogenesis process driving cardiac repair after myocardial infarction following their migration to the heart [31]. Any c-Kit dysfunction impairs the ability of these adult bone marrow stem cells for efficient myocardial healing through deficient angiogenesis [32]. The interaction of c-Kit with membrane-bound SCF recruits microvascular endothelial progenitor cells to inflammed sites for driving angiogenesis [33].

Recently, human stem cells expressing c-Kit were also identified in adult liver and spleen that were shown to proliferate into hepatocyte/biliary and haematopoietic colonies, respectively [34,35].

4. c-Kit expression and mutations in malignant stem cells

Several haematological malignancies and solid tumours express c-Kit to various extents ranging from 2.3% to 100% in their clinical samples from patients as illustrated in Table 1 [36–73]. Six haematological malignancies and 16 solid tumours have been identified as c-Kit-positive malignancies so far (Table 1) and undoubtedly others could be identified in future studies. Over-expression and/or constitutive expression of c-Kit alone or concurrently with SCF leading to autocrine stimulation of several solid tumours including small cell lung carcinoma, neuroblastoma, pancreatic tumours, and colorectal carcinoma have been reported (Table 1). Also, c-Kit mutations involving exons 8 and 17 and to less extent in exons 9 and 11 have been identified in clinical samples from patients in about half of the malignant diseases studied so far (Table 1). Class I c-Kit mutations that triggers excessive proliferation in the malignant cell clone involves exon 8 that codes for the Kit extra-cellular domain and class II c-Kit mutations that trigger block in malignant cell differentiation involves exon 17, confirming their key involvement in malignant transformation.

In AML, class I c-Kit mutations are present in 20% of cases with inv (16) and only 6% of cases with t(8;21) whereas class II c-Kit mutations are present in 11–40% of cases with t(8;21) reflecting the heterogeneic nature of this malignant disease [41–45]. In AML, c-Kit is predominantly expressed in the CD34-positive stem cells capable of forming leukaemia colonies and maintaining the disease [74,75]. Also, c-Kit expression is significantly higher in AML blasts compared with normal bone marrow [76] and about one-third of AML blasts co-express c-Kit and SCF [77] suggesting autocrine and paracrine stimulation of c-Kit by SCF may play a primary role in the pathogenesis of AML.

Exon 11 of the cytosolic region of the juxtamembrane domain plays a critical role in the negative regulation of Kit dimerisation and its mutation common in about 70% of gastrointestinal stromal tumours (GISTs) [51,52] and sino-nasal T-cell lymphoma (polymorphic reticulocytosis) [46,47] may result in major amelioration of such inhibitory effect on c-Kit [78].

On the other hand, three large studies of c-Kit expression have confirmed Hodgkin's disease, B-cell lymphomas and uterine carcinomas as c-Kit-negative malignancies [79–81].

5. Drug resistance and poor prognosis in c-Kit-positive malignancies

Cancer patients with either over-expression and/or mutations of c-Kit in their clinical samples have significantly poor prognosis, lower survival rates and show resistance to chemotherapy in numerous clinical studies (Table 1). The c-Kit mutations involving exons 8 and 17 were shown to have an independent negative impact on overall and event-free survival by conferring higher relapse risk in AML patients with t(8;21) and to less extent with inv(16) [41–45]. Also, the increase in c-Kit mutations from low- to high-risk myelodysplastic syndromes and from de novo to relapsed AML confirms its role in malignant progression [40]. In col-