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Review

Regulatory role of Megakaryocytes on Hematopoietic Stem Cells Quiescence by CXCL4/PF4 in Bone Marrow Niche

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ABSTRACT

Platelet factor-4 (CXCL4/PF-4) is a member of CXC-chemokine family produced by megakaryocytic lineage and stored in platelet α-granules. Platelet stimulation by aggregating agents such as thrombin and ADP leads to CXCL4 secretion. CXCL4 plays several roles in coagulation, angiogenesis control, immune system modulation and spread of cancer. Megakaryocytes (Mks) are associated with the vascular niche in the bone marrow (BM) and are located in vicinity of BM sinusoids. Mk-derived CXCL4 is involved in several hematopoietic processes, including inhibition of megakaryopoiesis and maintenance of hematopoietic stem cell (HSC) quiescence. The major aim of this review article was to evaluate the role of CXCL4 in hematological malignancies, promotion of HSC quiescence as well as BM niche cells.

Contents

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1. Introduction

Megakaryocytes (Mks) are derived from hematopoietic stem cells (HSCs) and are recognized by their large size and specific morphological characteristics [1,2]. These cells are located in the vicinity of bone marrow (BM) sinusoids and are associated with the vascular niche [3–6]. Several studies indicate that MKs, which produce platelets, are involved in the regulation and protection of BM niches by production of cytokines and growth factors.

Platelet-derived factors play important roles in many biological processes such as hematopoiesis, inflammatory and immune responses, angiogenesis and hemostasis [7]. CXCL4 (platelet factor 4/PF4) and CXCL7 are the most frequently released platelet-derived chemokines, which have been recognized as important markers of the megakaryocytic lineage [8,9]. Furthermore, they have been demonstrated to downregulate normal and abnormal megakaryopoiesis *in vitro* [10]. Mks are also the major source of proangiogenic and antiangiogenic factors such as VEGF in the BM, which cause survival and proliferation of BM-derived sinusoidal endothelial cells in vitro [11]. *In vivo* studies in mouse models showed that angiogenic processes in BM are regulated by secreted factors from Mks and platelets, including thrombospondins 1 and 2 [12,13]. In addition to the aforementioned factors, other chemokines including C–C motif ligand 5 (CCL5), macrophage migration inhibitory factor (MIF), CXCL12 (stromal cell derived factor 1/SDF-1), and CXCL5 (epithelial neutrophil-activating peptide/ENA-78) are produced and released by platelets in high levels [8,14,15].

Specific cytokines, including GM-CSF, IL-3, IL-6, IL-11, IL-12 and erythropoietin (EPO), stimulate the proliferation of Mk progenitors [16]. IL-1α and leukemia inhibitory factor (LIF) play a role in Mk maturation and platelet release [16,17]. Moreover, thrombopoietin (TPO) is the most potent stimulator of hematopoietic progenitor cell (HPC) differentiation to the Mk lineage, which is involved in the maintenance of HSCs quiescence [18].

TPO has synergistic functions with other hematopoietic cytokines (including SCF, IL-11 and EPO) to enhance the proliferation of progenitor cells in vitro [19,20]. CXCL12 by itself and in combination with TPO increases the formation of megakaryocytes [21]. As a chemotactic factor, it also acts through endothelial cells of BM to increase the migration of Mks via CXCR4 [22].

The major aim of this review article was to evaluate the function of CXCL4 in hematological malignancies as well as its impact on BM niche cells and promotion of HSC quiescence.

2. Characteristics of CXCL4/PF-4

CXCL4 is a member of CXC chemokine family produced by Mks, which plays several roles in coagulation, angiogenesis control, immune system modulation and spread of cancer (Fig. 1) [23]. The genes encoding human CXCL4 and other members of the CXC chemokine family, including interleukin-8 (CXCL8/IL-8), granulocyte chemotactic protein-2 (CXCL6/GCP-2), growth-related oncogene (CXCL1/GRO-α), CXCL2/GRO-β, CXCL3/GRO-γ, neutrophil-activating peptide-2 (CXCL7/NAP-2) and epithelial cell-derived neutrophil-activating peptide (CXCL5/ENA-78) are localized to q13.1 locus in the global run-on (GRO) region of chromosome 4 [24,25]. Unlike the majority of CXC chemokine genes, which usually consist of four exons and three introns, CXCL4 gene includes three exons and two introns similar to CC chemokine genes [26].

CXCL4 is produced by Mks, is internalized in vesicles and is then packed in platelet α-granules [27,28]. CXCL4 is released from granules after platelet activation by platelet aggregating agents such as thrombin, adenosine 5-diphosphate (ADP) or arachidonic acid [29–31]. The ability to bind glycosaminoglycans (GAGs) is an important feature of CXCL4. Nearly all chemokines are able to bind heparin and heparin-sulfates (HS) but the ability of CXCL4 to bind GAGs is about 100-1000 times higher than other CXC family members. CXCL4 is the only chemokine directly related to other GAGs such as chondroitin sulfates [32,33]. Therefore, CXCL4 may take advantage of this characteristic to induce quiescence in HSCs by binding heparin or other HSC surface GAGs, enhancing HSC adhesion to stromal cells. This in turn could result in cell cycle arrest and entrance into the quiescence phase [34–36].

In addition to CXCL4, expression of the non-allelic gene variant known as PF4alt (CXCL4L1) by platelets has been indicated [23,37]. Unlike the CXCL4 stored in granules and released by platelet activation, CXCL4L1 seems to be continuously produced and released [23]. Both variants affect the same target cells with different biological efficacy, half-life and affinity for glycosaminoglycans [32,38]. During the innate immune response, CXCL4 and CXCL4L1 increase monocyte differentiation to macrophages or antigen-presenting cells (APC) in presence of IL-4 [39]. CXCL4 is also able to inhibit the development and maturation of Mk progenitor cells and colony-forming unit-Mks (CFU-Mks) [35,40]. Therefore, CXCL4 intervention to reduce the colony-forming units and percentage of colonies containing mature cells raises CXCL4 as a negative regulator of megakaryopoiesis [40,41]. The ability of CXCL4 (>2.5 μg/mL) to inhibit Mk progenitors, CFU-Mk (colony forming unit-megakaryocyte), mCFU-Mk (mixed CFU-Mk) and BFU-Mk (burst FU-Mk) has also been reported. CXCL4 (>5 μg/mL in vitro) inhibits colony formation by human BM multipotential CFU-GEMM (CFU-granulocyte, erythrocyte, monocyte and megakaryocyte), BFU-E (BFU-erythroid) and CFU-GM (CFU-granulocyte/macrophage). CXCL4 (1 μg/ml) plays an important role in hematopoiesis by binding to human $CD34^+$ hematopoietic progenitor cells via chondroitin sulfate [24,42]. Moreover, CXCL4 plays a key role in hematopoiesis through regulation of hematopoiesis by increasing progenitor cell adhesion. It is also involved in quiescence via interaction between HPCs and the chondroitin sulfate-containing moiety [36]. CXCL4 may indirectly bind and interfere with IL-8. Therefore, IL-8-dependent signaling is abrogated in hematopoietic progenitor cells [36]. Several other biological function of CXCL4 have also been recognized and the most important functions are summarized in Table 1. Understanding the precise mechanisms involved in each of these processes can reveal the influence of CXCL4 on HSCs as well as other BM cells.

3. Interaction of megakaryocytes and BM cells

The HSC niche is a specific anatomical location providing essential factors for survival, regulation and proliferation of hematopoietic stem cells. In addition to HSCs, mesenchymal stem cells (MSCs) are located in this site [43]. Overall, the BM consists of two supportive HSC niches: osteoblastic/endosteal and vascular/endothelial niches. Osteoblastic niche maintains HSCs in quiescence phase and provides a microenvironment for long-term HSCs involved in hematopoiesis [44,45]. In contrast, vascular niche, which is composed of sinusoidal endothelial cells, promotes the differentiation and proliferation of short-term HSCs [45–47].

The non-hematopoietic microenvironment surrounding HSCs plays an important role in regulating the function and fate of HSCs through the production of paracrine factors [34,48]. Most HSCs are in the G_0 phase of the cell cycle in the adult BM, a phenomenon known as quiescence. Several factors such as stem cell factor (SCF), transforming growth factor beta-1 (TGF-β1), angiopoietin (ANGPT1) and TPO are involved in HSC quiescence. Furthermore, CXCL12 and its receptor (CXCR4), adhesion molecules such as vascular cell adhesion protein 1 (VCAM-1), different selectins and extracellular matrix (ECM) proteins including fibronectin or

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