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Mini-review

Targeting SDF-1 in multiple myeloma tumor microenvironment

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ABSTRACT

Multiple myeloma (MM) is a type of B-cell malignancy that remains incurable to date. The bone marrow (BM) microenvironment plays a crucial role in MM progression. The chemokine SDF-1 (CXCL12) is an important actor of the BM microenvironment that has the ability to regulate numerous processes related to its malignant transformation during MM development. The activity of SDF-1 is mainly mediated by its specific receptor CXCR4, which is expressed at the surface of MM cells and various other BM cell types. Current treatments available for MM patients mainly target tumor cells but have limited effects on the BM microenvironment. In this context, SDF-1 and CXCR4 represent ideal targets for the normalization of the MM-supportive BM microenvironment. The present review focuses on the activity of SDF-1 in the MM BM microenvironment and the current efforts carried out to target the SDF-1/CXCR4 axis for treatment of MM.

Introduction

Chemokines are a superfamily of cytokines that act as chemoattractants and exert their action by binding to specific G-protein 7-span transmembrane receptors expressed on the plasma membrane of target cells [1]. Chemokines are responsible for the recruitment of immune cells in the body and are therefore essential for processes like inflammation and organ homeostasis [2]. SDF-1 (stromal cell-derived factor-1), also named CXCL12 or PBSF (pre-B cell-growth-stimulating factor), is a chemokine that is expressed by stromal cells and was initially characterized as a growth-stimulating factor for a B-cell progenitor [3,4]. In human, six isoforms of SDF-1 have been identified, with SDF-1 alpha being the major isoform of the protein [5,6].

SDF-1 plays a critical role in multiple processes during embryogenesis including hematopoiesis, cardiogenesis, vascular formation and neurogenesis, and knockout of SDF-1 in the embryo is lethal [4,7]. In adults, SDF-1 is responsible for the homing and retention of hematopoietic stem cells (HSCs) in the bone marrow (BM) and lymphocyte trafficking [8]. It is also involved in the recruitment of endothelial progenitor cells (EPCs) during the process of angiogenesis [9]. Knockout of SDF-1 in adult mice leads to disruption of HSC homeostasis [10]. SDF-1 has shown protumoral and prometastatic effects in a number of solid tumors as well as in hematologic malignancies such as leukemia, lymphoma and multiple myeloma (MM) [4,8,11,12]. CXCR4 is a specific receptor to SDF-1 which has a crucial importance in mediating its cellular effects. It is expressed not only on the surface of HSCs and lymphocytes but also on tumor cells such as MM cells, B-cell chronic lymphocytic leukemia (B-CLL) cells and breast cancer cells [13]. CXCR7 has recently been identified as another SDF-1-binding receptor and is highly expressed in malignant hematopoietic cells [14,15].

MM is an incurable B-cell malignancy characterized by abnormal proliferation of plasma cells in the BM. Patients with MM display multiple lytic lesions thus suggesting an active circulation throughout the body and homing to the BM of MM cells [16]. The BM milieu plays a crucial role in the pathogenesis of MM. During disease progression, BM niches transform to form an ideal environment for the homing and growth of MM cells [17,18]. These niches consist of several cell types such as stromal cells, endothelial cells, osteoclasts, macrophages, fibroblasts and immune cells [19–21]. As a major actor of the BM microenvironment, SDF-1 represents a target of interest for the normalization of MM-supportive BM niches and the inhibition of MM cell trafficking throughout the body. The present review reports on the multiple mechanisms of the MM-supportive influence of SDF-1 on the tumor microenvironment and describes the effects of targeting the SDF-1/CXCR4 axis for MM treatment.

SDF-1-dependent adhesion, migration and homing

The primary effect of SDF-1 and its receptor CXCR4 on MM cells is to promote migration, adhesion and homing to the BM. SDF-1 levels are higher in the BM of patients with MM compared to patients with monoclonal gammopathy of undetermined significance (MGUS) – a precursor condition of MM – or healthy individuals. Interestingly, SDF-1 is significantly enriched in specific areas of the BM colonized with MM cells [22]. Knockdown of SDF-1 in MM

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BM-mesenchymal stem cells (BM-MSCs) inhibits adhesion and migration of MM cells toward them [12,22]. Co-culture of these MM BM-MSCs with MM cells reduces activation of migration-related and pro-survival pathways in the latter [12,22].

SDF-1 acts on MM cells by inducing motility and cytoskeleton rearrangements which facilitate their colonization of distant BM niches [12]. Importantly, knockdown of CXCR4 in MM cells revealed the involvement of the P13K and ERK/MAPK pathways in SDF-1-dependent migration [12]. However, the modulation of adhesion, migration and homing of MM cells by SDF-1 involves complex mechanisms and various types of molecules have been uncovered as mediators of its activity.

Matrix metalloproteinases (MMPs) play a crucial role in tumor cell invasion, thanks to their ability to degrade the extracellular matrix. Evidence seems to indicate that SDF-1-dependent induction of MM cell invasiveness is partly mediated by MMPs. Indeed, it was demonstrated that the MMPs MT1-MMP and MMP-9 contribute to SDF-1-triggered MM cell invasion through matrigel [23]. A second study supports these findings by showing that SDF-1alpha exerts chemoattraction over the MM cell lines 5T2MM and 5T33MM and induces an increase of the MMP-9 levels in these cells which correlate with their invasive capacity [24].

The integrin alpha4beta1 or VLA-4 (Very Late Antigen-4) is another mediator of SDF-1 activity. It was shown that transendothelial migration of MM cells promoted by SDF-1 involves an upregulation of integrin alpha4beta1-dependent cell adhesion to the endothelium [25]. Another study demonstrated that upregulation of integrin alpha4beta1 by SDF-1 promotes MM cell adhesion to CS-1/fibronectin and VCAM-1 [26]. Sphingosine-1-phosphate cooperates with SDF-1 to promote this alpha4beta1-dependent mechanism of cell adhesion which also involves intracellular cAMP activity and activation of the GTPase RhoA [25,27]. Inversely, the growth factor TGFbeta1 can decrease MM cell adhesion to CS-1/fibronectin and VCAM-1 by downregulating SDF-1 [28].

While TGFbeta1 inhibits SDF-1, other growth factors such as HGF and IGF-1 synergize with SDF-1 to enhance migration of MM cells through activation of P21-activated kinase [29]. Members of another family of molecules, the GTPases RhoA, Rac1 and RaI, also play key roles in SDF-1-induced MM cell migration or adhesion to BM stromal cells. ROCK – an effector protein of RhoA- and RacI – mediates SDF1-induced polymerization of actin and activation of LIMK, SRC, FAK and cofilin [30,31].

SDF-1 in hypoxia and angiogenesis

It has been reported that the levels of SDF-1 in the peripheral blood of patients with MGUS and MM correlated with the degree of angiogenesis and plasma cell infiltration in their BM [32]. Additionally, conditioned medium containing SDF-1 obtained from a MM cell line promoted angiogenesis *in vitro* [32]. SDF-1 was found to be secreted at higher levels in the BM endothelial cells (ECs) from patients with MM compared to ECs from human umbilical cord (HUVEC), which are considered the normal counterpart to this cell type [33].

SDF-1 and its receptors are also involved in hypoxia-induced angiogenesis. A study demonstrated that following exposure to hypoxic conditions, the expression levels of SDF-1 in MM cells increased and hypoxia-inducible factor-2 (HIF-2) bound to the SDF-1 promoter. Interestingly, the induction of angiogenesis *in vivo* caused by overexpression of hypoxia-inducible factor in MM cells was inhibited when an antagonist of SDF-1 was administrated, indicating a mediating effect of SDF-1 in hypoxia-induced angiogenesis [34]. Hypoxic conditions also increased the expression of CXCR4 in MM primary cells and cell lines. Furthermore, higher levels of CXCR4 were induced in the MM cell line RPMI8226 by the angiogenic factor vascular endothelial growth factor (VEGF) [35]. The other receptor for SDF-1, CXCR7, is expressed at the surface of angiogenic mononuclear cells (AMCs) and plays a significant role in the trafficking and the homing of these cells to BM areas of MM growth and neoangiogenesis. Interestingly, the administration of an inhibitor of CXCR7 suppressed the trafficking of AMCs to these MM areas and delayed tumor progression. This study shows that MM tumor progression can be inhibited through the targeting of the microenvironment without having a direct effect on MM cells [15].

Recent reports indicate that targeting neo-angiogenesis may result in the inhibition of MM progression at very early stages of the disease [36,37]. In that regard, the effect of SDF-1 on angiogenesis makes it an interesting target for early treatment of MM.

SDF-1 and MM-related bone resorption

SDF-1-dependent modulation of the MM microenvironment is also exerted through modulation of osteoclastogenesis and bone resorption. It was shown that SDF-1 levels positively correlated with bone resorption in MM [38,39]. When recombinant SDF1 alpha was added to a culture of osteoclast precursors, an increase in osteoclast motility and activation was observed as well as a significant augmentation of the number and size of resorption lacunae [38]. Interestingly, stimulation of osteoclast formation by the MM cell line RPMI8226 was suppressed by a specific inhibitor of CXCR4. Another study performed in a mouse model of MM-mediated focal osteolysis confirmed the involvement of the SDF-1/CXCR4 axis in bone resorption. Indeed, bone loss was significantly inhibited in this model when an antagonist of SDF-1/CXCR4 was administrated. *In vivo* implantation of the MM cell line RPMI8226 modified to overexpress SDF-1 led to a significant decrease in bone volume and an increase in osteoclast recruitment in the tumor area [39].

The control of SDF-1 over osteoclast activity might be mediated by Bruton tyrosine kinase (BTK), a protein indispensable for B-lymphocyte development and involved in osteoclastogenesis. A study showed that BTK mediates migration toward SDF-1 and homing to the bone of MM cells and that its expression in MM cells correlates with cell-surface CXCR4. Furthermore, BTK is activated by SDF-1 in MM cells. In a MM xenograft mouse model, administration of an inhibitor of BTK inhibited osteoclast activity and bone resorption and moderately slowed down tumor progression [40].

SDF-1 and other actors of the BM environment

Tumor-associated macrophages (TAMs) are a type of tumor-infiltrating leukocytes that suppress anti-tumor immune response, induce angiogenesis and promote tumor progression. They have a similar phenotype to M2-polarized macrophages. Interestingly, secretion of SDF-1 by MM cells and BM stromal cells plays a key role in regulating recruitment of monocytes, which are precursors of macrophages. It was demonstrated that blockade of CXCR4 significantly decreased monocyte recruitment toward a culture medium conditioned by MM cells. Additionally, a higher number of CXCR4-expressing macrophages were found in the BM of patients with MM compared to patients with MGUS and healthy individuals [41].

Cancer-associated fibroblasts (CAFs) are a component of the stromal microenvironment with a supportive role in tumor progression and drug resistance. Interestingly, a study found that the number of CAFs in patients with active MM was higher than in patients in remission or with MGUS. These active MM CAFs promoted chemotaxis, adhesion, proliferation and resistance to apoptosis of MM cells and produced higher levels of oncogenic-related proteins including SDF-1 alpha, IL-6 and VEGF [42].

Targeting of the SDF-1/CXCR4 axis in MM

In 2008, the CXCR4 antagonist Plerixafor (AMD3100) was approved by the FDA for the mobilization of HSCs in the peripheral blood circulation before autologous transplant in patients with MM and non-Hodgkin lymphoma [43]. It was also shown that Plerixafor induced chemosensitization in MM cells [44]. More recently, as SDF-1 emerged as an interesting target for the normalization of MM-promoting BM niches, a number of molecules targeting the SDF-1/CXCR4 axis were studied.

Olaptesed pegol (ola-PEG) is a PEGylated high affinity L-RNA aptamer or Spiegelmer (Noxxon Pharma) that specifically binds SDF-1 to neutralize its activity. In the B-cell line Jurkat, Ola-PEG inhibited SDF-1-induced internalization of the CXCR4 receptor and inhibited chemotaxis in a dose-dependent manner. SDF1-mediated activation of CXCR7 was also suppressed by Ola-PEG [22].

In a xenograft model of MM, a significant reduction of tumor growth was observed in mice pretreated with Ola-PEG as compared to untreated mice and mice treated with Plerixafor. Ola-Peg-induced effects were also assessed in a mouse model of MM metastasis, showing a reduction of the colonization of distant BM niches by MM cells. Further *in vivo* work showed that Ola-PEG mobilizes MM cells in the blood circulation and acts synergistically with Bortezomib to reduce tumor burden, possibly by rendering the BM microenvironment less receptive to MM cells [22].

The ola-PEG compound is currently evaluated in two phase 2 clinical trials respectively in combination with Bortezomib and Dexamethasone in patients with relapsed MM and in combination with Bendamustine and Rituximab in patients with relapsed chronic lymphocytic leukemia (CLL) [45].

Several other compounds have been shown to have an effect on MM through targeting of the SDF-1/CXCR4 axis. Walterinnesia aegyptia venom (WEV), Thymoquinone and Sorafenib suppress SDF-1-mediated cytoskeleton rearrangements in MM cells, subsequently causing a reduction of chemotaxis and inducing apoptosis in these cells [46–49].

Studies evaluating an antibody directed against CXCR4 (BMS-936564/MDX-1338), as well as a CXCR4 antagonist (4F-benzoyl-TN14003), have shown antitumor activity in MM [50,51]. These molecules are under clinical investigation in patients with MM along with two other CXCR4-inhibiting molecules [52]. Gambogic acid inhibits SDF-1-mediated chemotaxis and MM-induced differentiation of macrophages to osteoclasts by preventing binding of p65 to the CXCR4 promoter [53].

Additionally, it has been shown that the expression levels of SDF-1 and CXCR4 were significantly reduced in MM patients treated with Thalidomide, a drug used for treatment of MM [54]. Anti-Notch treatment also reduced the SDF-1 and CXCR4 levels of MM cells and inhibited their infiltration of the BM in a MM xenograft mouse model [55]. Remarkably, Dexamethasone increases CXCR4 expression in MM cells while downregulating their expression and secretion of SDF-1 [35].

Conclusion

Successfully treating MM is challenging because of the high clonogenicity of MM cells and the important supportive role of the BM microenvironment that are responsible for disease progression. The current treatments mainly target MM cells and rarely target the BM environment, which can account for the high frequency of relapse and drug resistance phenomena in patients with MM that eventually result in fatality [18,56]. Therefore, transforming the MM tumor microenvironment to make it less receptive to MM cells and less supportive of their dissemination to distant BM niches appears a promising strategy for the treatment of MM.

SDF-1 is a pivotal regulator of the tumor microenvironment that has the ability to regulate multiple oncogenic processes such as angiogenesis, osteoclastogenesis or tumor cell migration and adhesion to stromal cells. These features make SDF-1 an ideal candidate for efficient targeting the MM BM microenvironment. As a matter of fact, compounds targeting SDF-1 and CXCR4 are currently assessed in clinical trials involving patients with MM [45,50,51].

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Conflict of interest

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