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SDF-1 (CXCL12) in haematopoiesis and leukaemia: impact of DPP IV/CD26

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1. ABSTRACT

DPP IV/CD26 contributes to cell signalling by various mechanisms: as a receptor or co-receptor, as a component of a membrane-associated signal transduction complex and by virtue of its exopeptidase activity. The presence of enzymatically active DPP IV in a variety of tissues and in plasma makes it challenging to review clinical consequences of chemokine turnover by DPP IV activity, even more so in times when the concept of DPP IV inhibition for therapeutic purposes has reached the stage of clinical application. Among the known substrates of DPP IV/CD26, Stromal cell-derived factor 1 (SDF-1, CXCL12) has gained attention in recent years as a critical mediator of chemotaxis and tissue invasion, especially in the context of malignant disease. SDF-1 and its receptor, CXCR4, differ from other chemokines and their respective receptors by a lack of redundancy and pleiotropism. Therapeutic intervention using CXCR4 antagonists has been proposed. It seems appropriate to review the role of SDF-1 in haematopoiesis and its malignant counterpart, leukaemia, and to assess the interference of DPP IV/CD26 with the SDF-1/CXCR4 axis as well as possible risks and benefits of DPP IV inhibition.

2. INTRODUCTION: SDF-1

Chemotaxis is defined as the directional migration of cells toward a gradient of a chemotactic cytokine (chemokine). Many different cell types have been shown to express receptors for chemokines which, in turn, show distinct patterns of expression in a tissue microenvironment. The interaction between such receptors and their respective ligands contributes to a coordinated trafficking and functional organization of cells within various tissue compartments (1). Accumulating evidence suggests that these physiologically important mechanisms of tissue-specific recruitment are functional in neoplastic cells (for review cf. 2).

In contrast to many chemokines and their respective receptors, SDF-1 and its receptor, CXCR4, lack the redundancy and pleiotropism commonly observed. Animals deficient for SDF-1 or CXCR4 show a similar, lethal phenotype, which includes a deficient B-lymphopoiesis and myelopoiesis, cardiovascular defects and abnormal neuronal development (3-5). SDF-1 is expressed constitutively in many organs, especially in the bone marrow, suggesting a critical role for SDF-1 and

CXCR4 in tissue homeostasis and haematopoiesis (6). SDF-1/CXCR4 shows a highly conserved amino acid sequence, acts across species barriers and has been shown to be of pivotal role for germ cell migration during zebrafish development (7, 8). The discovery that T-tropic HIV strains enter the cells using CXCR4 as a coreceptor (9, 10) ignited research on the clinical role of this monogamous chemokine-receptor pair.

3. SDF-1 AND HAEMATOPOIESIS

Haematopoietic stem cells critically depend on a stromal microenvironment that dynamically regulates their quiescence, expansion and differentiation (11). This functional and, as demonstrated recently (12, 13), anatomically identifiable site, the haematopoietic niche, is paradigmatic for the way in which chemokines secreted by stromal cells dictate stem cell behaviour and how a rapid response to external needs can be generated. Wright and colleagues have provided evidence for a uniquely restricted chemotactic responsiveness of haematopoietic stem cells to SDF-1/CXCL12 (14). The notion that CXCL12 is essential for HSC retention is corroborated by studies which showed that the interruption of SDF-1/CXCR4-signalling coincides with rapid release of stem cells from the bone marrow (15). In a similar fashion, SDF-1/CXCL-12 appears to be involved in chemotaxis (16) and retention of B-cell precursor cells in close proximity with a stromal environment (3, 17), and also allows mature, highly differentiated B cells, i.e. plasma cells, to cluster in distinct niches within the marrow (18).

Haematopoietic niches can be found scattered across the bone marrow in areas of regional hypoxia (19). Here, SDF-1 may be implied in haematopoiesis via Hypoxia-inducible factor-1 (HIF-1), a central mediator of tissue hypoxia (20). In hypoxic states, HIF-1 induces CXCL12 expression on endothelial cells and contributes to the emergence of a transient, conditional stem cell niche for CXCR4-mediated progenitor cell recruitment, thus allowing for tissue repair and cell expansion (21).

The role of SDF-1 in stem cell homing and recruitment has been shown to be inconsistent or, at least, differentially regulated with regard to the stage of development and the site of expression. Shortly after birth, murine haematopoietic stem cells show an engraftment defect when transiting distinct cell cycle phases, with a transient increase in SDF-1/CXCL12 expression. The defective engraftment can be overcome by *in vivo* administration of a CXCL12 antagonist (22).

4. SDF-1/CXCL12 IN ACUTE LEUKAEMIA

The contribution of SDF-1 and CXCR-4 to the mechanisms governing stem cell recruitment, protection and expansion is paradigmatic for the relationship between the stem cells and the stromal microenvironment. In the context discussed here, leukaemic blasts resemble their benign counterparts in that they cluster in distinct niches in the bone marrow and benefit from growth and survival signals provided by the surrounding stroma. In aggressive lymphomas, for example, the composition and gene expression pattern of the stromal environment can be of higher prognostic relevance than the malignant clone itself (23).

Controversial results make it difficult to appreciate the presence of CXCR4 on leukaemic blasts and the functionality of SDF-1-mediated signalling. In animal models, precursor-B-cell leukemic cells home to the bone marrow via an SDF-1 chemokine gradient and functional CXCR4 receptors (24-26). In acute myelogenous leukaemia, CXCR4 receptors also are functional and show different degrees of expression (27). Yet, in animal models, conflicting results have been published with regard to the pathophysiological importance of SDF-1 and CXCR4 in homing of myeloid blasts to the bone marrow (28, 29).

In many patients, minimal residual disease is a source for leukaemic relapse (30-32). The proximity of leukaemic blasts to stromal elements like fibronectin appears to be of critical importance, enabling the leukaemic cells to escape therapeutically intended elimination (33). In prostate cancer, SDF-1 enhances expression of fibronectin-binding alpha(v)beta(3) integrins, a hallmark of more aggressive tumor growth and metastatic spread to SDF-1-rich areas such as the bone marrow (34). High expression of CXCR4 by leukaemic blasts is an adverse prognostic indicator in AML and may at least in part contribute to the chemoresistance of residual blasts in the bone marrow (27).

5. TARGETING THE SDF-1-CXCR4 AXIS

The physiologic role of SDF-1 and CXCR4 has been disclosed only partly; however, their apparent involvement in leukaemia and minimal residual disease (35-37), cancer and metastasis (38, 39), rheumatoid arthritis (40) and many others ignited research on the therapeutic potential of CXCR4 antagonists. Among these, AMD3100 (41), a bicyclam derivative, was shown to effectively inhibit HIV entry and was initially developed as an antiviral agent (for review cf. 42). However, the focus of interest shifted towards haematopoiesis when AMD3100 was shown to mobilize CD34+ stem cells from the bone marrow into the bloodstream and to augment migration of bone marrow-derived endothelial progenitor cells into sites of neovascularization after myocardial infarction. AMD3100 is actively pursued as a stem cell mobilizing agent for autologous transplantation in patients with multiple myeloma and non-Hodgkin's lymphoma. In chronic lymphocytic leukemia (CLL), CXCR4 antagonists were shown to resensitize CLL cells to fludarabine-induced apoptosis, interfering with the SDF-1-mediated protective neighbourhood to surrounding stromal cells (40). Similarly, in B-cell precursor ALL, CXCR4 antagonists attenuated the migration of leukaemic blasts to the bone marrow and enhanced the cytotoxic effects of vincristine and dexamethasone (36). Taken together, CXCR4 antagonists have demonstrated therapeutic potential whenever the interaction of SDF-1/CXCL12 and CXCR4 was presumed to contribute to disease progression on leukaemia and other clinical conditions (40, 42).

6. SDF-1 AND DPP IV/CD26

The unique selectivity of the chemokine/receptor pair SDF-1/CXCR4, the lack of pleiotropism and redundancy together with their importance in germ cell migration during development are only conceivable in the presence of stringent endogenous control mechanisms. These include the modulation of SDF-1 expression as shown to be exerted by p53 (43), inhibition of CXCR4 expression (44), of CXCR4 homodimerization (45), or inactivation of functional SDF-1 via enzymatic degradation. Matrix metalloproteinases (MMP) truncate SDF-1 at the N-terminus at a specific cleavage site, i.e. position 4-5 (46). Unlike full-length SDF-1alpha, the MMP-cleaved chemokine was unable to block CXCR-4-dependent human immunodeficiency virus-1 infection of CD4(+) cells. Interestingly, SDF-1 (5-68) has been shown to possess neurotoxicity which leads to neuronal apoptosis in murine basal ganglia and may contribute to neurodegenerative processes observed in HIV-infected individuals (47).

DPP IV/CD26 truncates SDF-1 at the penultimate position, i.e. after a proline residue (48, 49). Chemokine degradation by DPP IV was shown to be determined by the presence of a freely accessible N terminus and the structure, with SDF-1, MDC, and I-TAC being converted with the highest efficiency (50, 51). The cleaved SDF-1_{3-68} was shown to be non-functional with regard to chemotaxis, anti-HIV-1-activity (52, 53) and homing of haematopoietic stem cells to the bone marrow (54). The *in vitro* ability of DPP IV/CD26 to cleave SDF-1, however, does not predict the occurrence and relevance of chemokine truncation by DPP IV/CD26 *in vivo* (55). Given the presence of enzymatically active DPP IV/CD26 on T lymphocytes, endothelial cells, fibroblasts and epithelial cells (55-57) as well as in plasma (58), there is a certain probability for SDF-1 peptides to encounter DPP IV during their bioavailability. Studies addressing the homing of haematopoietic stem cells to the marrow in the context of SDF-1 and DPP IV activity were performed using CD34-positive progenitor cells from cord blood (54). These haematopoietic stem cells were shown to co-express CXCR4 and CD26. Adult haematopoietic progenitor cells, however, lack CD26 expression and DPP IV activity (Hildebrandt, unpublished results).

Clues on a potential relevance of the impact exerted by DPP IV/CD26 on SDF-1 can be derived i) from the comparative assessment of full-length, i.e. functional SDF-1 and truncated SDF-$1_{3-68,}$ and ii) from the use of DPP IV inhibitors. Inhibition of DPP IV activity has emerged as a therapeutic concept for diseases such as diabetes, neurodegeneration, autoimmune diseases and cancer (59-61). In haematopoiesis, the application of DPP IV inhibitors was shown to increase homing and engraftment during cord blood transplantation, apparently due to a decrease in SDF-1 truncation (54). Similar results were observed in transplantation of adult haematopoietic progenitor cells (62). Conversely, the presence of functional DPP IV must be assumed to counteract SDF-1-mediated stem cell homing. The observation that haematopoietic stem cells from cord blood show an engraftment defect shortly after birth could at least partly be explained by the fact that, in contrast to adult stem cells, DPP IV is coexpressed on cord blood stem cells. Here, DPP IV would inactivate SDF-1 in close proximity to its receptor and thus negatively affect stem cell homing. In addition, DPP IV/CD26 could also contribute to the relatively high number of circulating haematopoietic progenitor cells in cord blood. In allogeneic stem cell transplantation, haematopoietic stem cells derived from cord blood usually require more time to engraft than adult blood stem cells, albeit counterbalanced by a lower incidence of severe graft-versus-host disease (63). In murine models of stem cell transplantation, the use of DPP IV inhibitors has been demonstrated to enhance engraftment (64). With regard to leukaemia, an enhanced homing of leukaemic blasts to the bone marrow as a way to enhanced chemoresistance and potential source of relapse is certainly not a desireable option. If, however, truncated SDF-1_{3-68} were able to interfere with functional SDF-1 as has been observed in engraftment of regular haematopoietic cells (54), a clearance of the bone marrow from residual leukemic disease would be feasible and ultimately depend on DPP IV activity. Interestingly enough, the comparative assessment of SDF-1 levels in the plasma of patients with acute myelogenous leukemia (65) revealed that the overall plasma concentration of SDF-1 was elevated when compared to healthy controls, yet consisted mostly of SDF-1_{3-68}. A difference in the availability of non-truncated SDF-1 could not be observed between patients with leukaemia and healthy controls. Therefore, DPP IV may exert a modulatory effect on the availability of functional SDF-1, reducing excessive amounts to concentrations within normal range. Albeit only hypothetical, the evidence presented here should give a note of caution to the use of DPP IV inhibitors in patients with malignant disease such as leukaemia, be it as part of an antineoplastic concept as suggested (60), be it for the treatment of diseases other than cancer or leukaemia. The unique selectivity of SDF-1, the lack of redundancy and its high degree of evolutionary conservation render therapeutic attempts to interfere with the SDF-1/CXCR4 axis attractive; however, the few endogenous regulatory elements known to date, including DPP IV/CD26, may be too important to form part of such a therapeutic approach.

7. SUMMARY

DPP IV/CD26 inactivates SDF-1 (CXCL 12) by N-terminal truncation. The remaining molecule, SDF-1_{3-68}, is devoid of SDF-1 chemokine activity and may compete with full-length SDF-1 for its cognate receptor, CXCR4. Given the selectivity of SDF-1 and CXCR4 in absence of the pleitropism commonly observed among chemokines and their receptors, the high degree of conservation and the activity of SDF-1 across species barriers, and the lethal phenotype of SDF-1- or CXCR4-deficient mice, both the biological activity of this chemokine as well as the mechanisms governing SDF-1 turnover must be attributed with critical biological relevance. In the manuscript presented here, evidence has been reviewed that corroborates a certain misuse of SDF-1 activity in

malignancy, especially leukaemia, to the propagation of the disease. Therapeutic approaches of interrupting the SDF-1-CXCR4 axis have been proposed. In the case of malignant disease, the few mechanisms known to date which exert a negative impact on SDF-1, matrix metalloproteinases and especially DPP IV, may be too important to become subject of therapeutically intended inhibition. The application of truncated SDF-1_{3-68} for therapeutic purposes, i.e. as a CXCR4 antagonist, has not been addressed to date.

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