Review

Functional diversity of SDF-1 splicing variants

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Abbreviations: AA, aminoacids; AMD3100, the company name of the substance; BM, bone marrow; CNS, central nervous system; CPN, carboxypeptidase-N; CT, computed tomography; CU, colitis ulcerosa; CXCL11, C-X-C ligand 11; CXCR4, C-X-C receptor 4; CXCR7, C-X-C receptor 7; EGL, external granular layer; GAGs, glycosaminoglycans; G-CSF, granulocyte-colony stimulating factor; HIV, human immunodeficiency virus; HMEC, human microvascular endothelial cells; IGL, internal granular layer; MMPs, metaloproteinas; MR, magnetic resonance; MS, multiple sclerosis; PGC, primordial germ cell; RA, rheumatoid arthritis; SDF-1, stromal-derived factor 1; SVZ, subventricular zone

Key words: SDF-1, CXCR4, CXCR7, splicing variant, isoform, cell based-therapy

SDF-1 is ubiquitously expressed in vertebrate tissues in a constitutive manner. It performs an essential role in cell migration and proliferation as well as participates in tissue-specific physiological processes such as neuromodulation. It is also involved in many pathological processes including: HIV infection, metastatic malignancy, chronic inflammatory disorders and benign proliferative diseases. SDF-1 is mostly regulated at the splicing, and not transcriptional level. Different splicing variants share agonist potency to their cognate receptor, CXCR4, but are characterized by distinct properties. SDF-1α is the predominant isoform found in all organs, but undergoes rapid proteolysis in blood. SDF-1β is more resistant to blood-dependent degradation, stimulates angiogenesis and is present in highly vascularized organs such as the liver, spleen and kidneys. In contrast, SDF-1γ is located in very active, less vascularized organs susceptible to infarction such as the heart and the brain. The understanding of the functional diversity of the different splicing variants will help in developing therapeutic strategies.

Introduction

Stromal-derived factor 1 (SDF-1) was defined in a murine bone marrow (BM) stromal cell line supporting hematopoietic cell culture. The development of a new signal sequence trapping method contributed to the identification of the SDF-1 gene. Then the two splicing variants of the SDF-1 gene product were described: SDF-1α and SDF-1β, consisting of 89 and 93 amino acids (AA) respectively. They were assigned to the intercrine cytokine family (chemokines) which is characterized by four conserved cysteines that form two disulfide bonds. Furthermore their expression was found in all organs except in blood cells. Independently, they were shown to be a sufficient factor capable of supporting rodent B-cell lymphopoiesis. Shortly thereafter human equivalents were reported and the SDF-1 gene was located on chromosome 10q, unlike the remaining chemokines. The striking similarity of the SDF-1 protein sequence between species and the gene’s unusual chromosomal location allowed its essential role in the functioning of vertebrates to be anticipated. This was confirmed by the perinatal death of animals lacking SDF-1. The identification of its cognate receptor (CXCR4) has brought us closer to understanding the functional complexity of SDF-1. CXCR4 has previously been known as a fusin due to its role in HIV entry into cells. Strong chemotactic activity in relation to monocytes/macrophages and lymphocytes but not neutrophils was found. What is more important is that SDF-1 was also shown to be capable of controlling the migration of cells in the early stages of development, such as progenitor and stem cells. Its effect on the biology of stem cells as well as HIV infection attracted many researchers to investigate in detail all aspects of SDF-1 function. Further data showed that the SDF-1/CXCR4 axis is also involved in the process of metastasis, chronic inflammatory disorders, benign proliferative diseases as well as the physiological function of bone marrow and the nervous system. Four more splicing variants were identified. The structure of SDF-1 is a key factor in the understanding of the biological role of particular splicing variants.

SDF-1 Structure

SDF-1 proteins are found in living organisms as monomers. SDF-1α consists of three exons, and the remaining splicing variants of SDF-1 share the same three exons and have a different fourth exon attached to a C-terminal residue. Between the disordered N- and C-terminal ends there is a well-ordered structure consisting of three parallel β-strands and an overlying α-helix. The N-terminus (residues 1–8) is responsible for SDF-1’s interaction with CXCR4. The first two AAs (amino acids) (Lys-1 and Pro-2)
take part in receptor activation while a further six AAs are involved in the binding of the chemokine to the receptor. The structured part together with the disordered C-terminus stabilizes receptor binding via its interaction with glycosaminoglycans (GAGs) on the cell surface. The positive charge of SDF-1 proteins, resulting from numerous basic AAs is worthy of note. In this way, negatively charged GAGs attract and hold SDF-1 down. Each fourth exon is disordered and carries an additional strong positive charge. Splicing variants differ in the length of the fourth exon and consequently in the strength of GAG binding.

**Splicing Variant-Based Regulatory Mechanisms of SDF-1 Activity**

**Degradation process.** SDF-1 is ubiquitously expressed in vertebrate tissues in a constitutive manner. Vertebrates have developed a method of maintaining the SDF-1 balance via the regulation of the degradation process. SDF-1 is proteolytically degraded at both ends. Proteolysis of the N-terminus takes place slowly, is splicing variant-independent and occurs in both: the blood and the tissues. It switches off chemokine activity and decreases SDF-1’s binding affinity to the receptor. Conversely, the degradation of the C-terminus is rapid, splicing variant-dependent and occurs only in the blood. It is mediated by carboxypeptidase-N (CPN), an enzyme also involved in the degradation of other proteins such as bradykinin and kallidin II. C-terminus proteolysis does not inactivate SDF-1, but decreases its activity by half, attenuating GAG-dependent stabilization of chemokines on the cell surface. However only SDF-1α, which is the predominant and also the smallest isoform, is susceptible to this process. It is likely that vertebrates have developed an additional, C-terminus-dependent regulation mechanism of the most prevalent isoform—SDF-1α. It may prevent homeostatic disequilibrium resulting from a sudden release of SDF-1α from the tissues into the blood. The attachment of the fourth exon during the splicing process prevents proteolytic degradation of chemokines at the C-terminus in the blood (Fig. 1). Thus SDF-1β which is virtually the same as SDF-1α, except in that the fourth exon consists of only four residues attached to a C-terminus, shows very similar activity in vitro and in tissues, but is twice as potent in the blood.

**Receptor binding.** Apart from susceptibility to C-terminus proteolysis, another regulatory mechanism of SDF-1 activity was observed. It was shown that GAG binding is necessary for leukocyte accumulation and prevents proteolytic attack, extending the lifespan of SDF-1 molecules. Therefore, GAG binding affinity, which varies among SDF-1 splicing variants, provides another regulatory mechanism specific to the SDF-1/CXCR4 axis. The fourth exon of the SDF-1γ isoform is long and strongly basic, giving it the highest affinity for GAGs ever observed for any chemokine. Thus, SDF-1γ binds to the cell surface immediately upon secretion and is almost never found in a disengaged state (Fig. 2). Although this splicing variant has less agonist potency, it is more efficient especially over a longer timeframe, thanks to the persistence of its interaction, which is mediated by the GAG-dependent stability of receptor binding. Intraperitoneal administration of SDF-1α and SDF-1γ produces virtually the same local inflammatory response after 3 hours, but after 16 hours, inflammatory reaction was present only in animals injected with SDF-1γ. SDF-1β, SDF-1ε and SDF-1β splicing variants have only been reported recently and no specific regulatory mechanism has been attributed to them to date.

**Tissue Distribution of SDF-1 Splicing Variants**

SDF-1α is the most widespread splicing variant. It participates in many local tissue-specific physiological processes such as the management of the HSC population in bone marrow, the guidance of primordial germ cells during development, neuro-modulation in the CNS, etc.

SDF-1β is expressed less abundantly and seems to be related to the vascular system. Its greater resistance to proteolysis within the blood predispose it to this role. Endothelial cells of cerebral microvessels in mice express SDF-1β selectively. Its upregulation was found following focal cerebral ischemia and was associated with the infiltration of CXCR4-expressing peripheral blood cells, such as macrophages. At the same time neuronal SDF-1α was transiently downregulated. SDF-1β also has a greater effect on angiogenesis in human microvascular endothelial cells (HMEC). In patients with systemic sclerosis, polymorphism within the C-terminal residues of SDF-1β predisposes to microvascular disease. An estimate of the distribution of SDF-1β transcripts in human organs revealed their presence mainly in highly vascularized organs such as the liver, spleen, bone marrow and kidneys, and their absence in the brain.

SDF-1γ is the predominant isoform in the adult rat brain, replacing SDF-1β which is abundant in embryonic life. In humans and mice, SDF-1γ was found mainly in the heart. However, following an experimental heart infarct in mice, no change in the quantity of SDF-1γ was found, but there was an increase in SDF-1α expression. The modest data on SDF-1γ
SDF-1 splicing variants

CXCR4 and the inhibition of HIV infection. It seems that SDF-1's binding affinity to CXCR4 plays a pivotal role. In fact, SDF-1γ revealed enormous binding affinity to the cell surface and proved to be the most potent blocker of HIV entry among all the SDF-1 splicing variants. Knowledge of SDF-1's antiviral effect was used for the synthesis of a small molecule (AMD3100) antagonizing the function of CXCR4. However, despite its potency in vitro, it failed to be efficient in vivo. The diversity of HIV phenotypes as well as a lack of GAG-dependent stabilization of AMD3100 on the cell surface could be the reason for its failure in clinical trials.

Metastatic malignancy. The mechanism of metastatic malignancy was elusive for long time. Recent research on the SDF-1/CXCR4 axis has shed some light on this process. The cells of many investigated tumors do not produce SDF-1 but do express CXCR4. Knowledge of SDF-1's antiviral effect was used for the synthesis of a small molecule (AMD3100) antagonizing the function of CXCR4. However, despite its potency in vitro, it failed to be efficient in vivo. The diversity of HIV phenotypes as well as a lack of GAG-dependent stabilization of AMD3100 on the cell surface could be the reason for its failure in clinical trials.

Pathology-Specific Role

HIV infection. The discovery of a natural ligand for the HIV co-receptor, CXCR4, opened new avenues in antiviral therapy. SDF-1 has been shown to interfere with HIV entry. Initial experiments suggested that SDF-1's antiviral activity is by way of downregulation and internalization of CXCR4. However, other studies have suggested distinct mechanisms for the activation of CXCR4 and the inhibition of HIV infection. It seems that SDF-1's binding affinity to CXCR4 plays a pivotal role. In fact, SDF-1γ revealed enormous binding affinity to the cell surface and proved to be the most potent blocker of HIV entry among all the SDF-1 splicing variants. Knowledge of SDF-1's antiviral effect was used for the synthesis of a small molecule (AMD3100) antagonizing the function of CXCR4. However, despite its potency in vitro, it failed to be efficient in vivo. The diversity of HIV phenotypes as well as a lack of GAG-dependent stabilization of AMD3100 on the cell surface could be the reason for its failure in clinical trials.

Figure 2. Splicing variant-dependent strength of SDF-1 binding to CXCR4 on the cell surface. The cell membrane is covered by negatively charged GAGs shown as blue spots. The active part of the SDF-1 molecule binding to the receptor is marked in green. Red shapes represent the positively charged part of the SDF-1 molecule stabilizing the process of receptor activation through their interaction with the negatively charged GAGs. (A) The red oval reflects the "standard" positive charge characteristic of all SDF-1 molecules. It is similar for SDF-1α and SDF-1β and is strong enough for short term receptor binding. Thus, only a limited number of SDF-1 molecules interact with the receptor at the same time, while most of them are in an unbound state. (B) In contrast, the addition of a long, strongly positively charged product of the fourth exon in the case of the SDF-1γ isoform, which is represented in the figure by a "tail" of red spots, facilitates a very strong and long-term stabilization of SDF-1 binding to CXCR4. It results in the persistency of SDF-1 activity which is shown by widespread binding of the SDF-1 molecule to its cognate receptor.

distribution indicates an association with less vascularized organs susceptible to infarction such as the brain and the heart. Thus the expression of SDF-1γ may not support vascularization, but due to the persistency of its activity, it may ensure a strong and long-term inflammatory response to an infarct necessary for the removal of large areas of necrotic tissue.

SDF-1δ, SDF-1ε and SDF-1ζ splicing variants have been described only recently in human tissues. They are all abundant in the pancreas. Additionally, SDF-1δ and SDF-1ε were found in the heart and liver, as well as in fetal and adult kidneys, but the expression of the former is more pronounced than that of the latter. SDF-1δ, on the other hand, was also detected in the spleen, fetal liver and lungs.

Thus different splicing variants display a similar effect in cells but are active in different tissues and physiological or pathological conditions.

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Metastatic malignancy. The mechanism of metastatic malignancy was elusive for long time. Recent research on the SDF-1/CXCR4 axis has shed some light on this process. The cells of many investigated tumors do not produce SDF-1 but do express CXCR4. In this way, a positive gradient develops between the tumor and the rest of the body. A high concentration of SDF-1 in lymph nodes and the resulting gradient inside lymphatic vessels strongly attracts tumor cells. This, in turn, may be responsible for the high frequency of metastases to the lymph nodes. SDF-1 activity in the blood seems to be less pronounced than in lymphatic vessels, but following entry into the blood, tumor cells progress further to the organs in accordance with the SDF-1 gradient. In this way, metastases are predominantly located in...
organs of higher SDF-1 concentration such as the lungs, bones, adrenal glands, and not in the heart or kidneys where SDF-1 expression is lower.27 The blood concentration of SDF-1 correlates positively with the presence of distant metastases in patients with gastric cancer.31 The elimination of CXCR4-bearing cells from pancreatic cancer selectively suppresses metastatic activity, without affecting tumorigenesis.32 The identification of the anti-metastatic substance, Zerumbone, whose activity is based on CXCR4 down-regulation has been reported recently.33 To conclude, a metastasis is not a passive and random occurrence, but is the result of an active migratory process.

**Chronic inflammatory disorders.** Chemokines also play a key role in the accumulation of inflammatory cells.34 Their aberrant expression may be responsible for the induction of chronic inflammatory processes such as rheumatoid arthritis (RA),35 multiple sclerosis (MS),36 colitis ulcerosa (CU)37 and allergic diseases.38 SDF-1 may be a common downstream executor of inflammatory cell accumulation regardless of circumstances upregulating its expression. This gives reason to hope that low molecular weight CXCR4 antagonists could be applied in chronic inflammatory disorders too.39,40 The functional role of particular SDF-1 splicing variants in the context of chronic inflammation has not yet been explored. However, one can hypothesize about the involvement of the splicing process and the disequilibrium of the proportions of particular variants.

**Organ-Specific Function**

**BM.** SDF-1 is critical for the maintenance of a proper BM micro-environment. It fetters progenitor and stem cells in the BM by creating a positive BM-blood gradient. The homing of hematopoietic stem cells (HSC) to BM following transplantation is also mediated by SDF-1.31 The mechanism of stem cell mobilization is not based on the release of SDF-1 to the blood but, quite to the contrary, on the disruption of SDF-1’s binding to CXCR4 in the BM. The traditional mobilizing factor—G-CSF increases the activity of N-terminus proteases (elastase, MMPs and cathepsin G) in the BM, which degrades both: SDF-1 and increases the activity of N-terminus proteases (elastase, MMPs to CXCR4 in the BM. The traditional mobilizing factor—G-CSF failure.43 Additionally, cells mobilized in this way are characterized by reduced chemotactic activity due to the partial destruction of CXCR4.15 The discovery of a mechanism of stem cell mobilization from the BM resulted in the introduction of novel mobilizing factors that interact with CXCR4 directly, CXCR4 blocking by the small molecule antagonist AMD3100 proved to be very effective even in cases of previous G-CSF failure.43 Additionally, cells mobilized in this way retain their hematopoietic properties in the blood.44

**Brain.** Like in other organs, SDF-1 also guides cells in the brain during the developmental period. Its role in the migration of embryonic cerebellar neurons from the external granular layer (EGL) to the internal granular layer (IGL) has been well defined.45 It is executed by the predominant isoform, SDF-1α, produced by nearby meningeal cells.46,47 Recently, the crucial role of SDF-1α in the development of the cerebral cortex and the dentate gyrus has also been reported.48,49 The regulation of the migration of dentate gyrus cells by SDF-1 continues throughout adulthood.50-52 It also participates in stroke-induced neuroblast migration from SVZ towards the lesioned area.53,54 Apart from its migratory function, SDF-1 has also been shown to be engaged in neuromodulation17,55 and axonal elongation from the entorhinal cortex towards the dentate gyrus.56 There is a species-specific predominance of particular splicing variants in the brain. In mice SDF-1β is the most abundant isoform, while in rats, it is SDF-1γ. In contrast, in the human brain both these isoforms are absent and only transcripts of SDF-1α have been found.57 One may speculate that the difference in tissue reaction to stroke could be attributed to species-specific isoform variability. Stroke in rodents elicits enormous attraction of blood leukocytes to the ischemic area followed by cavity formation. The inflammatory response of the human brain to infarction seems to be more limited, as very often preservation of tissue in the ischemic area is visible on control MR or CT scans. Such a difference could be ascribed to the splicing variance of SDF-1. The SDF-1β and SDF-1γ isoforms are more efficient in the blood, and so they are able to produce a strong chemotaxis of leukocytes in rodents. The human brain has only got SDF-1α at its disposal which is less effective in the blood due to C-terminus proteolysis and as a consequence leukocyte infiltration and cavity formation could be less prominent.

**CXCR7 - An Alternative Receptor for SDF-1**

Recently, an alternative receptor for SDF-1 has been described.57-58 It was initially reported as RDC1 in 1994,59 but only lately has the ligand for it been found. CXCR7 reveals high binding affinity to SDF-1 and CXCL11. It is a G-protein coupled receptor, but does not respond to Pertussis toxin application. Details of complementary60 and antagonistic61 interactions of both receptors: CXCR4 and CXCR7 were published. Its role in the development of the cardiovascular system was established in mice by inducing CXCR7 genetic deficiency.62 No developmental defects within the CNS were described.63 Focal brain ischemia upregulates CXCR7 expression in intact cortical regions but no migration of CXCR7-bearing cells was visible.64 CXCR7 is widely expressed in CXCR4-negative neuronal, vascular and glial cells but its function was not yet understood.65 A recent report about zebrafish primordial germ cell (PGC) migration revealed a scavenging role for CXCR7. It is expressed by somatic cells surrounding PGC chains, which through the uptake and sequestration of SDF-1 create a sharper directional gradient.66 A similar scavenging role for CXCR7 in the CNS cannot be ruled out. The influence of SDF-1 splicing variants on CXCR7 function has not yet been raised.

**Cell-Based Therapy**

Many critical cell functions such as: migration, proliferation and apoptosis inhibition are regulated by SDF-1. Thus there is value in employing this knowledge in the emerging field of cell transplantation.

SDF-1 can be employed for the appropriate trafficking of grafted cells. It guides intravenously administered CXCR4-bearing
cells to their destinations such as into an area of spinal cord injury, stroke or myocardial infarction. It also promotes the survival and stimulates the migration of intracerebrally injected cells towards the stroke area, and, intraventricularly administered, towards the area of traumatic injury. Intraparenchymal injection of SDF-1 into an intact brain additionally enhanced transplanted cell homing, whereas such an injection to an infarcted heart failed to recruit stem cells due to protease activity. The construction of a proteolysis resistant form of SDF-1 (S4V) has overcome this limitation.

SDF-1 can mediate a cell-dependent effect as well. The secretion of SDF-1 by transplanted cells enhanced neuroplasticity within the injured brain, preserved myocytes within the infarcted zone of the heart, and promoted the recruitment of stem and progenitor cells which resulted in enhanced angiogenesis and in an improvement in the contractile function of the heart. SDF-1 was also used for ex vivo priming of progenitors to promote conversion towards the desired phenotype. Such an approach was employed for angiogenesis and myocardial infarction.

The abovementioned mechanisms of SDF-1 involvement in cell-based therapies are associated with the presence of grafted cells at the diseased spots. However several papers revealed a clear positive effect of cell transplantation in animal models of stroke despite the absence of grafted cells within the brain. This phenomenon has not yet been explained. Thus the author of this review speculates on the pivotal role of SDF-1 in the achievement of these results. The production of SDF-1 by transplanted cells homed to peripheral organs increases the blood concentration of SDF-1 and consequently decreases the positive brain-blood gradient following stroke, thus preventing excessive leukocyte migration toward the infarcted tissue and limiting secondary brain injury.

Conclusions

Unlike other chemokines, SDF-1 is chiefly regulated at the splicing, and not transcriptional level. SDF-1α is the predominant and ubiquitously expressed splicing variant. It can play different roles (motogen, mitogen, neuromodulator) in various tissues. However it is rapidly degraded after entry into the blood. It is likely that in vertebrates this isoform is reserved for intra-organ signaling via local gradients. The production of the SDF-1β isoform is more limited, but due to its activity in the blood it seems to be designed for inter-organ communication via blood-mediated gradients as well as for supporting angiogenesis. Due to rapid and strong binding to GAGs, SDF-1γ reveals paracrine activity and is a potent inducer of local long-term inflammatory response. It was found in organs characterized by high activity, low vascularity and susceptibility to ischemia (brain and heart). It seems to function as a medium ensuring the efficient removal of large areas of necrotic tissue. A better understanding of the functional diversity of SDF-1 splicing variants should make usage of the SDF-1/CXCR4 axis more specific for therapeutic purposes.

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