HHS Public Access

Author manuscript

J Neuroimmunol. Author manuscript; available in PMC 2015 May 29.

Published in final edited form as:

J Neuroimmunol. 2008 July 31; 198(0): 31–38. doi:10.1016/j.jneuroim.2008.04.008.

CXCR4 signaling in the regulation of stem cell migration and development

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Abstract

The regulated migration of stem cells is a feature of the development of all tissues and also of a number of pathologies. In the former situation the migration of stem cells over large distances is required for the correct formation of the embryo. In addition, stem cells are deposited in niche like regions in adult tissues where they can be called upon for tissue regeneration and repair. The migration of cancer stem cells is a feature of the metastatic nature of this disease. In this article we discuss observations that have demonstrated the important role of chemokine signaling in the regulation of stem cell migration in both normal and pathological situations. It has been demonstrated that the chemokine receptor CXCR4 is expressed in numerous types of embryonic and adult stem cells and the chemokine SDF-1/CXCL12 has chemoattractant effects on these cells. Animals in which SDF-1/CXCR4 signaling has been interrupted exhibit numerous phenotypes that can be explained as resulting from inhibition of SDF-1 mediated chemoattraction of stem cells. Hence, CXCR4 signaling is a key element in understanding the functions of stem cells in normal development and in diverse pathological situations.

Keywords

stem cells; chemoattraction; chemokines; chemokine receptors

1. Introduction

The directed migration of cells is an important feature of the biology of all complex organisms. During development stem cells and fate restricted progenitors must migrate from the zones where they are generated to developing organs where they proliferate and differentiate in an organ specific manner. In adults, pluripotent stem cells and restricted progenitors are retained in many tissues in specific niche like regions where they can be expanded when required for purposes of tissue regeneration or repair. It is thought likely that many of the mechanisms that regulate the directed migration and development of stem cells

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in the adult recapitulate those occurring during the original development of the organism, and that adult stem cells have many properties in common with those found in the embryo. Indeed, it is possible that stem cells are deposited in niches during embryogenesis so that they can be called upon later when needed by the mature organism (Kucia et al., 2005b). Understanding the processes that regulate stem cell migration and development in adults is certainly important if such cells are to be used for therapeutic purposes. On the other hand, directed stem cell migration may also be a feature of pathology. An obvious example of this is the phenomenon of tumor metastasis, which is currently thought to depend on the directed migration of cancer stem cells. Clearly, therefore, it is essential to understand how such directed cell movements are produced and whether there are common features that underlie all of these mechanisms. In the last few years it has become clear that the process of directed cell migration is produced through the action of a family of small secreted proteins known as chemotactic cytokines or “chemokines”. These molecules probably orchestrate the movement of many stem/progenitor cells, including cancer stem cells, and so their actions are of key importance for understanding the mechanisms of both normal repair as well as stem cell related pathologies.

2. The Chemokine family

There are a large number of chemokines that have been identified to date, probably >50 in most mammals. As far as we know all the actions of chemokines are transduced through their stimulation of a family of related G protein coupled receptors (Tran and Miller, 2003). Consideration of the pattern of evolution of the chemokines and their receptors has revealed that a large expansion of the chemokine family occurred in parallel with the development of a sophisticated immune system in higher vertebrates (Huising et al., 2003). This makes sense as, apart from anything else, chemokines have been shown to be key regulators of leukocyte migration in higher organisms. Indeed, the chemokine system has been very widely studied in the context of inflammation, and drugs that block chemokine function may represent a novel class of anti-inflammatory agents. Furthermore, it has been demonstrated that the cellular receptors on leukocytes that mediate the infectivity of HIV-1 are chemokine receptors, primarily the CCR5 and CXCR4 receptors. Hence, drugs that block these receptors have also been developed for potential use in AIDS.

In this broader context however, one chemokine - CXCL12 (also called Stromal cell Derived Factor-1 or SDF-1) stands out as being evolutionarily very old (Huising et al., 2003). Indeed, homologues of SDF-1 and its receptor CXCR4 are present in animals that are so ancient that they do not possess an immune system (Huising et al., 2003). Hence, it is believed that there are primordial functions for chemokine signaling that do not concern the regulation of leukocyte migration. The idea that CXCR4 signaling is important in areas beyond immunology has now been widely documented. One of the first indications of this fundamental role for the SDF-1/CXCR4 signaling axis came from the analysis of the phenotypes observed for CXCR4 (Tachibana et al., 1998; Zou et al., 1998) or SDF-1 knockout mice (Ma et al., 1998; Nagasawa et al., 1996) or zebrafish (Knaut et al., 2005). In general, the phenotypes of these two types of mice appear very similar, consistent with the long held view that SDF-1 and CXCR4 constitute a unique signaling combination. However, it should be noted that recently another chemokine receptor, CXCR7, has also been shown

to bind SDF-1, and so it is possible that some of the effects of SDF-1 are not mediated by CXCR4. The full extent of the importance of CXCR7 signaling in development and adult function remains to be determined. (Miao et al., 2007; Sierro et al., 2007; Valentin et al., 2007).

There are a large and ever increasing number of phenotypes that have been observed to be associated with deletion of the SDF-1/CXCR4 genes. These include deficits in β-lymphopoiesis and myelopoiesis (Nagasawa, 2007; Nagasawa et al., 1996; Nie et al., 2004; Zou et al., 1998), cardiogenesis (Miao et al., 2007; Nagasawa et al., 1996; Zou et al., 1998), angiogenesis (Tachibana et al., 1998; Zou et al., 1998), neurogenesis (Lu et al., 2002; Stumm et al., 2003; Tran et al., 2007) and germ cell migration and development (Dumstrei et al., 2004). Basically, all of these phenotypes can be explained by the observation that CXCR4 signaling is important in regulating the migration of different types of stem/progenitor cells. This then appears to be the original role of chemokine signaling, and CXCR4 signaling in particular. Seen in this light the extensive role for chemokine signaling in the control of leukocyte trafficking can be thought of as an evolutionary development of this original function. Consistent with this idea, it has been demonstrated that of all chemokines and chemokine receptors, SDF-1 and CXCR4 are the most widely expressed during the development of the embryo (Knaut et al., 2005; Knaut et al., 2003; McGrath et al., 1999; Moepps et al., 2000; Rehimi et al., 2008; Tissir et al., 2004; Yusuf et al., 2005). Moreover, the expression patterns for both SDF-1 and CXCR4 are highly dynamic consistent with the possibility that they have shifting developmental roles in the formation of many different tissues. SDF-1 and CXCR4 expression has been observed in very early frog, chick, zebrafish and mouse embryos, as early as blastocyst formation. CXCR4 and SDF-1 are both expressed by embryonic stem cells derived from the inner cell mass of developing blastocyst and it was observed that SDF-1 enhanced the survival and migration of these cells (Guo et al., 2005). Thus, it is likely that CXCR4 signaling plays a central role in stem cell function from very early developmental times. In addition to its role in stem cell migration, development and organogenesis, CXCR4 signaling also seems to have tissue specific roles that are distinct and appropriate to each tissue. For example, in the development of the nervous system CXCR4 signaling also functions as an axon guidance cue (Chalasani et al., 2003; Chalasani et al., 2007; Lieberam et al., 2005). Hence, the role of CXCR4 signaling in development is complex and stage specific, ranging from an initial role in regulating the migration and functions of stem cells to tissue specific effects on differentiated cells.

3. Development of the nervous system

Examination of the phenotype of SDF-1 and CXCR4 knockout mice (Ma et al., 1998; Zou et al., 1998) demonstrated that among other phenotypes, a clear abnormality was observed in the development of the cerebellum. During the development of this part of the brain, cerebellar granule cell progenitors are localized in a subpial region known as the external granule cell layer (EGL), where they proliferate. Once the pool of progenitors has expanded sufficiently, postmitotic cells migrate inwardly to form the internal granule cell layer (IGL), which is the normal localization for mature granule cells. However, in CXCR4 and SDF-1 deficient mice it was observed that granule cell progenitors proceeded with their inward migration at an inappropriately early time resulting in ectopically localized progenitors

within the Purkinje cell layer. This phenotype can be explained by considering the normal distribution of CXCR4 and SDF-1 expression in the cerebellum during development. CXCR4 is expressed by proliferating progenitors in the EGL and SDF-1 is synthesized and secreted by the overlying meninges. Therefore, SDF-1 mediated chemoattraction serves as a signal for maintaining progenitors within the EGL (Klein and Rubin, 2004; Klein et al., 2001). This is a proliferative environment in which factors like Sonic hedgehog (SHH) stimulate progenitor division. Indeed SHH and SDF-1 have cooperative effects on progenitor proliferation. If CXCR4 signaling is interrupted progenitors are not retained in the EGL and respond to other chemoattractant factors resulting in their inappropriately early inward migration.

Following these initial reports, numerous other neuronal phenotypes have also been observed in SDF-1/CXCR4 deficient mice. In the hippocampal dentate gyrus (DG), for example, deletion of CXCR4 resulted in a significant phenotype in which granule cells were observed to be ectopically placed along the normal route of granule cell progenitor migration (Bagri et al., 2002; Lu et al., 2002). The development of the DG takes place in the period immediately after birth. Granule cells progenitors migrate from the wall of the lateral ventricle to form a “germinal matrix” in which they proliferate further and form the two blades of the DG. The expression patterns for SDF-1 and CXCR4 in the developing DG, as well as the phenotype of CXCR4 knockout mice, are consistent with a model in which SDF-1 is secreted by meningeal cells that line the route of migrating CXCR4 expressing progenitors, and that progenitors are stalled in their migration when CXCR4 signaling is interrupted. Other neuronal phenotypes observed in CXCR4 knockout mice include defects in the placement of developmentally important Cajal-Retzius cells (Berger et al., 2007; Paredes et al., 2006; Stumm et al., 2003), cortical GABAergic interneurons (Stumm et al., 2007; Stumm et al., 2003; Tiveron et al., 2006) and GnRH secreting forebrain neurons (Schwarting et al., 2006). In all of these situations it appears that the progenitors for these neurons utilize

SDF-1 mediated chemoattraction to attain their final positions, and that lack of CXCR4 signaling results in interrupted progenitor migration. Thus, these examples differ from the situation prevailing in the cerebellum where SDF-1 is used to maintain progenitors in a proliferative environment and where interruption of CXCR4 signaling results in abnormally enhanced early migration of progenitors. Nevertheless, the basis for each phenotype is the chemoattractive effect of SDF-1 on CXCR4 expressing neural progenitors. SDF-1 regulated stem cell migration is also a feature of the peripheral nervous system. Here CXCR4 is expressed by neural crest derived DRG progenitors migrating from the dorsal aspect of the neural tube and SDF-1 is expressed by mesenchymal cells that line their route of migration (Belmadani et al., 2005). Thus, the set up is similar to that in the developing DG. Disruption of CXCR4 signaling again results in a phenotype in which DRG neurons exhibit interrupted migration and this results in abnormally formed DRGs in mice, or trigeminal ganglia in zebrafish (Knaut et al., 2005). Zebrafish also exhibit a variety of other sensory cell phenotypes when CXCR4 signaling is disrupted (Li et al., 2004). The development of DRG neurons also highlights the fact that SDF-1 frequently has tissue specific effects during development in addition to those on stem cell migration. For example, SDF-1 has been observed to act as an axon guidance cue for developing axon growth throughout the nervous

system. This includes the axons of developing DRG neurons, where the action of SDF-1 reduces the repellant effects of the factor semaphorin 3A (Chalasani et al., 2007). Hence the growth pattern of sensory neuron axons is also abnormal in CXCR4 knockout mice. Subsequently embryonic DRG neurons express both CXCR4 receptors and SDF-1, suggesting some kind of autocrine effect of CXCR4 signaling on these cells (Belmadani et al., 2005; Odemis et al., 2005). Indeed, interference with CXCR4 signaling *in vivo* or in culture strongly reduces the survival of these neurons. Thus, depending on the stage of development, SDF-1 produces effects on progenitor migration, axon development and survival of DRG neurons. In adult animals SDF-1 assumes yet another role, acting as a neurotransmitter that can stimulate DRG neuron excitability and produce pain (Bhangoo et al., 2007; Oh et al., 2001). Furthermore, the expression of CXCR4 receptors by DRG neurons or glia may act as a binding site where T-tropic strains of HIV-1 can produce neuronal excitation and pain or possibly neuronal death (Melli et al., 2006; Oh et al., 2001). Therefore, it is clear that CXCR4 signaling has an important role during the entire lifetime of a DRG neuron. As in the example of DRG neurons, it has also been demonstrated that CXCR4 signaling has effects on the survival and proliferation of neural stem cells in other parts of the developing embryo and in the adult as well (see below).

4. Development of non neuronal tissues

The role of CXCR4 in the development of stem cells is not unique to the nervous system. CXCR4 expression by tissue specific stem cells has been reported for ES cells and germ cells as well as progenitors from skeletal muscle, heart, liver, endothelium, and renal and retinal epithelia (Ratajczak et al., 2006). Indeed, as is clear from the name “Stromal cell Derived Factor-1”, SDF-1 activated signaling also plays a key role in the development of hematopoietic stem cells which give rise to blood and related tissues. In mammals the first primitive hematopoietic stem cells (HSCs) are found in the yolk sac and the first definitive HSCs are localized a few days later in a structure termed the aorta-gonad-mesonephros (AGM). From the AGM, HSCs migrate to the fetal liver, which during the second trimester of gestation becomes the major mammalian organ for hematopoiesis. By the end of the second trimester of gestation, HSCs leave the fetal liver and colonize the bone marrow (BM). In mice deficient in SDF-1 or CXCR4, HSCs migrate appropriately from the AGM to the fetal liver, but not from the liver to the BM at later times (Nagasawa, 2007; Zou et al., 1998). This indicates that the latter migration is dependent on CXCR4 signaling, consistent with the observed extensive expression of SDF-1 by cells in the BM. In addition to the disposition of HSCs, CXCR4 signaling also has tissue specific roles in the development of leukocytes, β-lymphopoiesis being deficient in CXCR4 knockout mice (Nagasawa, 2007; Nie et al., 2004; Zou et al., 1998). Moreover, HSCs are still retained in the BM in adult mice through SDF-1 mediated chemoattraction, and disruption of this process allows efflux of HSCs into the blood (Chute, 2006; Lapidot et al., 2005; Nagasawa, 2007; Welner and Kincade, 2007). Indeed, this process is utilized clinically. Thus, CXCR4 antagonists such as the drug AMD3100 can be used to mobilize HSCs from the BM if this is required for therapeutic purposes such as collection of HSCs prior to transplantation (Cashen et al., 2007). Following transplantation, intravenously administered HSCs are observed to home to the BM in a CXCR4 dependent fashion and this phenomenon can be used to reconstitute a

depleted hematopoietic system in diseases such as chronic myelogenous leukemia and aplastic anemia (Chute, 2006; Dar et al., 2006; Lapidot et al., 2005).

A role for CXCR4 signaling during development has been recognized in numerous other instances. For example, primordial germ cells (PGCs) give rise to gametes in the gonads and are often the earliest cell lineage to be specified. Analysis of PGC migration in mice and zebrafish in which genes for SDF-1 or CXCR4 have been deleted, or in which expression of these molecules has been suppressed, shows aberrant colonization of the gonads by PGCs (Dumstrei et al., 2004; Raz, 2003). Cardiac development is also aberrant in CXCR4 or SDF-1 knockout mice. During development of the heart a subpopulation of cardiac neural crest cells migrate to colonize the outflow tract endocardial cushions prior to septation, the process through which a single outflow vessel, the trunctus arteriosus, becomes the ascending aorta and the pulmonary trunk (Snider et al., 2007). Migration occurs via the third, fourth and sixth pharyngeal arches (Jiang et al., 2000). However, in both CXCR4 and SDF-1 deficient mice the region of the ventricular septum is abnormal (Nagasawa et al., 1996; Zou et al., 1998). As SDF-1 is expressed in the developing heart tissue (McGrath et al., 1999) and CXCR4 is expressed in migrating cells of the neural crest (Belmadani et al., 2005), it is possible that interruption of this process is the basis for this phenotype. This would be consistent with other defects in neural crest development observed in CXCR4 knockout mice, including defects in formation of the DRG (see above, (Belmadani et al., 2005) and positioning of melanoblasts in hair follicles (Belmadani and Miller , unpublished observations). A further interesting phenotype identified in SDF-1/CXCR4 knockout mice is a deficiency in blood vessel development, initially observed in the gastrointestinal system (Tachibana et al., 1998). Consistent with such observations, CXCR4 receptors have been shown to be expressed by hemangioblasts, the earliest common precursor to hematopoietic and endothelial stem cells found in yolk sac blood islands (McLeod et al., 2006) and also by endothelial cells that can be derived from embryonic stem cells (ESCs) in culture (Chen et al., 2007). In the latter case these endothelial cells expressed CXCR4 and migrated towards an SDF-1 gradient. SDF-1 enhanced the formation of blood vessels in a Matrigel based assay. Hence, there is good reason to believe that CXCR4 signaling in endothelial progenitors is of considerable significance in the development of vascularization in the embryo. As we shall discuss these same properties are also important in vascular repair in the adult.

5. Adult stem cell development

It is clear from the above discussion that CXCR4 signaling is a widely used method for regulating the migration and development of stem cells occurring in many tissues during organogenesis. However, it is known that stem cells are retained in many adult tissues and can be expanded on demand to cope with stressful situations such as damage or infection, when they are required for tissue repair and to maintain tissue homeostasis (Kucia et al., 2005b; Ratajczak et al., 2006). A good example of this is the production of blood cells from HSCs that exist in the adult BM. The turnover rate of most blood cells is relatively fast compared to other tissues and so their numbers must be continuously restored. Thus, HSCs are constantly called upon to manufacture different types of blood cells in order to maintain the status quo for normal homeostasis or under conditions of stress such as infection or

injury when specific subsets of leukocytes must be rapidly expanded. As discussed above, the retention of HSCs in the adult BM is under the control of CXCR4 signaling and HSCs can be mobilized into the blood when this signaling is disrupted (Nagasawa, 2007). This is a basic model for many types of stem cell mediated repair programs in the adult. Thus, stem cells for repair of non-hematopoietic tissues may also be deposited in stem cell niches during development and are mobilized when required through the utilization of CXCR4 mediated signaling. Indeed, in addition to HSCs, the adult BM also contains other types of stem cells that can potentially be used for repair of different tissues (Fox et al., 2007; Kucia et al., 2005a). It is likely that these cells express CXCR4 receptors and can follow SDF-1 gradients to areas of damage where they are required for repair purposes. Consider, for example, the repair of endothelial tissue following damage to blood vessels. In this case SDF-1 can be released from platelets that become associated with the damaged region. CXCR4 expressing endothelial progenitors in the BM or elsewhere may then migrate to the damaged region (Hristov et al., 2007). Following myocardial infarction SDF-1 expression increases in the damaged portion of the heart and mesenchymal stem cells, also localized in the BM, can migrate to this region for cardiac repair purposes (Fox et al., 2007).

It has even been demonstrated that CXCR4 expressing mesenchymal stem cells can enter the brain following stroke (Hill et al., 2004) or under other circumstances (Sano et al., 2005). Indeed, a population of CXCR4 expressing cells that also express neuronal markers such as nestin, have been observed in the BM and are mobilized into the blood in response to stroke (Kucia et al., 2006). In this situation SDF-1 expression in the brain is upregulated primarily by perivascular astrocytes (Hill et al., 2004; Miller et al., 2005; Stumm et al., 2002). It is possible that the migrating BM cells may act as a potential source of new neurons under these or related circumstances. Normally speaking however, it would seem that the BM would not be a very convenient location for neural progenitors, particularly as the blood brain barrier would exclude their entry, except perhaps under conditions of injury when this barrier may become transiently permeable. As far as endogenous brain neural stem cells are concerned, it was thought for a long time that the nervous system was an exception and that new neurons were not produced from endogenous sources in the brains of higher mammals once they had attained maturity. However, it is now clear that this is not the case and that populations of neural progenitors that actively produce new neurons, oligodendrocytes and astrocytes exist primarily in the subventricular zone (SVZ) and the subgranular zone of the dentate gyrus (DG), but probably in other regions as well (Gould, 2007). As in the other examples, such as the BM discussed above, these cells are thought to exist in special stem cell niches where the various influences that are important for stem cell development can be coordinated (Palmer et al., 2000). In the brain both blood born and neuronal influences are thought to be important for the development of new neurons. It is thought that new neurons produced on an ongoing basis in the DG, for example, contribute to certain types of hippocampal plasticity, and that new neurons normally produced in the olfactory bulb appear to be of importance in maintaining odor detection in the context of constant neuronal turnover in this part of the brain (Conover and Notti, 2008; Gould, 2007). Therefore, this ongoing neurogenesis is envisaged as having a homeostatic role analogous to that of HSCs in replenishing leukocytes under normal circumstances. In addition, however, as with the BM, new neurons or glia derived from neural stem cells may contribute to the brain’s efforts

to repair itself in the face of injury. New neurons need to be produced to repair chronic neurodegeneration in conditions such as Amyotrophic Lateral Sclerosis (motor neurons) or Parkinson's Disease (dopaminergic neurons) or rapid neurodegeneration associated with stroke (Imitola, 2007; Steiner et al., 2006). On the other hand, new oligodendrocytes need to be produced in the context of demyelinating diseases such as Multiple Sclerosis. One may therefore ask whether there is a role for chemokine signaling in the development of adult neural stem cells under these various circumstances? It is certainly clear that neural stem cells located in the SVZ and DG express chemokine receptors including high levels of CXCR4 receptors (Berger et al., 2007; Tran et al., 2007). If we consider the DG as an example, CXCR4 is expressed by the most immature radial glia like stem cells as well as their progeny including rapidly amplifying cells, neuroblasts and immature granule neurons. Furthermore, SDF-1 is also expressed by neuronal cells in the DG (Banisadr et al., 2003; Stumm et al., 2002). The close juxtaposition of SDF-1 and CXCR4 in the adult DG suggests that CXCR4 may be an important regulator of adult neurogenesis in this part of the brain. Recent studies have demonstrated that SDF-1 is actually stored in neurotransmitter vesicles in DG neurons, including DG GABAergic interneurons such as Basket cells and granule cells (Tham et al., 2001). Both GABA and SDF-1 can be released in the DG and can regulate the functions of neural stem cells such as their proliferation (Bhattacharrya et al., unpublished observations). Thus, SDF-1 may normally help to integrate the level of neural activity in the DG with the ongoing level of neurogenesis.

It is also likely that chemokine signaling is important in neurogenesis that occurs in the context of brain pathology. For example, in response to neurodegeneration such as that occurring following a stroke, there are attempts by the brain to repair itself. This response involves the migration of endogenous neural progenitors from the SVZ and elsewhere to sites of brain repair, such as the area surrounding an infarct (Imitola, 2007; Ohab et al., 2006; Robin et al., 2006). It is likely that activated astrocytes localized in proximity to the brain lesion secrete chemokines such as SDF-1 that act upon chemokine receptors expressed by endogenous neural progenitors and stimulate their directed migration towards the site of the lesion (Belmadani et al., 2006). Moreover, one strategy for treating diseases like stroke is to introduce exogenous neural stem cells into the brain that might then participate in brain repair. Such a strategy is analogous to the use of HSCs to reconstitute damaged or irradiated BM. These neural progenitors, which can be expanded in cell culture, also express chemokine receptors and so can "home" to sites of chemokine production in the brain (Tran et al., 2004). In support of such possibilities it has been observed that both CCR2 (Liu et al., 2007) and CXCR4 (Ohab et al., 2006; Thored et al., 2006) expressing progenitors are found within stroke induced lesions in the brain and that interference with chemokine signaling blocks this recruitment (Belmadani et al., 2006; Ohab et al., 2006). The migration of neural progenitors is not only required for brain repair in the context of neurodegeneration but is also important in brain repair as the result of demyelination. Here again it is thought that the inflammatory response that is associated with demyelinating lesions can act as a source of chemokines that attract progenitors that then develop into oligodendrocytes for purposes of remyelination. In keeping with this possibility it has been demonstrated that oligodendrocyte progenitors (OPs) express chemokine receptors such as CXCR4 and that chemokines can produce (or sometimes inhibit) a chemotactic response of these cells (Dziembowska et al.,

2005; Kadi et al., 2006; Maysami et al., 2006). Injection of OPs into the lateral ventricle is associated with the migration of these cells to sites of demyelinating lesions and their clear development into oligodendrocytes (Banisadr et al., unpublished observations).

6. Chemokine signaling in disease

Although the above discussion highlights the important role of CXCR4 signaling in development and repair in many tissues, these same receptors may also play a role in several pathological processes in which stem cells migrate and develop improperly. A particularly important example of this process concerns the development of tumors. In this case it is currently thought that the growth of many tumors may depend to the properties of cancer "stem cells" which represent neoplastic versions of the stem cells that normally generate or repair most tissues. These cancer stem cells can give rise to tumor cells in primary tumors and can also metastasize to seed tumors in other areas of the body. Clearly it is important to identify the factors that help to enhance the growth and "health" of tumors and also contribute to their further distribution. Considerable evidence now suggests that chemokine signaling, and CXCR4 signaling in particular, can contribute to both of these phenomena (Kucia et al., 2005a; Orimo et al., 2005; Orimo and Weinberg, 2006). First SDF-1 is produced by many tumors where it can have autocrine growth promoting effects on the developing tumor and also enhance the growth of blood vessels that are important for further tumor growth and development indicating a key role for CXCR4 (or possibly CXCR7). Even more strikingly in the light of the above discussion is the possibility that expression of CXCR4 by cancer stem cells allows them to follow SDF-1 gradients and seed tumors at remote sites. It is clear that such sites are non random and commonly involve the lungs, liver, bone marrow or lymph nodes, areas of constitutively high SDF-1 expression. It is certainly also clear that the hypoxic environment prevailing in parts of a tumor allow HIF-1α induced upregulation of CXCR4 expression by different types of cancer stem cells and this process also helps them to "home" to sources of SDF-1 such as the bone marrow or other SDF1 producing tissues (Ceradini and Gurtner, 2005).

This aberrant role for SDF-1/CXCR4 signaling probably does not only involve the growth and metastasis of tumors, but almost certainly other types of diseases which involve the abnormal migration and subsequent growth of cells (Xu et al., 2007). For example, in pulmonary fibrosis (PF) aberrant development of fibroblast like cells in the lung produces fibroblastic foci and abnormal lung remodeling and eventually fatal lung dysfunction. It is likely that the source of this aberrant fibroblast production is a type of circulating fibroblast like progenitor cell called a fibrocyte-a type of circulating mesenchymal stem cell. These cells express CXCR4 receptors and can home to sources of SDF-1 (Agostini and Gurrieri, 2006; Scotton and Chambers, 2007; Snider et al., 2007). Although the reason is not clearly understood, it appears that in PF the lung produces increased amounts of SDF-1 leading to the attraction and development of fibrocytes. In animal models of the disease such as bleomycin administration to the lung, CXCR4 antagonists reduce fibrocyte influx and lung fibrosis. Thus, the potential role for CXCR4 signaling in diseases such as PF and cancer also suggest the possibility that CXCR4 antagonist drugs may constitute novel types of therapy in such disorders.

Thus, in these examples of stem cell related pathology, as well as in the normal development of the organism and the normal repair response of the adult, the effects of SDF-1/CXCR4 signaling appear to be of key regulatory importance.

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