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The Function Role of SDF-1/CXCR4 Signaling in Osteoarthritis

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Osteoarthritis (OA) is the most common cause of disability in the elderly [1]. Disability stems from the pain, stiffness, inflammation and limitations in mobility imparted by the degeneration of the articular cartilage that is trademarks of the disease. Unfortunately, current pharmacological therapy aimed at the mechanism of disease is relatively ineffective, largely because the etiology and pathogenesis of OA remain unknown.

Chemokines and their receptors are important in immune cell function, migration of stem cells, and regulation of cancer cell invasion. There are four groups of chemokine receptors: C, CC, CXC, and CX3C. Chemokine Receptor Four (CXCR4) is a seven-transmembrane G-protein-coupled receptor, whose activation leads to intracellular signaling cascades, downstream targets of which include MMP1 and VEGF [2,3]. The ligand for CXCR4 is the chemokine Stromal Cell Derived Factor One (SDF1) [4]. SDF-1 is an 8 KDa chemokine originally isolated from a bone marrow stromal cell line [5]. Although the mechanism of its release remains unknown, it appears to be related to the inflammatory cytokines IL-1β and TNF-α [6,7] . SDF-1 activates a wide variety of primary cells by binding to its specific receptor, CXCR4 to stimulate proliferation, differentiation, and apoptosis [8,9].

Recently, Kanbe and his colleagues found an interesting distribution pattern between SDF-1 and CXCR4 in human joint. Their studies show that SDF1 is primarily present in the articular chondrocytes in joints, and its receptor CXCR4 is present in the synovial membrane cells [10] which would allow these two molecules to participate in a paracrine regulatory mechanism allowing for induction of MMPs release. In chondrocytes, SDF-1 activates the calcium, Erk and p38 MAP kinase signaling pathways, thereby inducing the release of Matrix Metalloproteinase (MMPs) and other proteins [11-13]. In contrast, synovectomy, a surgical procedure that effectively relieves pain in OA patients, reduces circulating serum SDF-1 levels, thereby decreasing the release of MMPs from joint cartilage [14]. These studies suggest that SDF-1/CXCR4 singling is a key regulator of cartilage degradation during OA pathogenesis [10,11,14,15]. Studies have also demonstrated that SDF-1 and its receptor CXCR4 play an important role in growth plate development. CXCR4/SDF1 promotes chondrocyte hypertrophy in the chondro-osseous junction during endochondral bone formation by mediating type X and MMP-13, which are classic markers of hypertrophic chondrocyte differentiation [16]. Over-express chemokine SDF-1 results in rabbit growth plate closure [17]. All of these findings support the notion that elevated SDF-1/CXCR4 signaling in the joint may contribute significantly to cartilage matrix degeneration, and its inhibition could reduce this damage.

Development of agents that block CXCR4 has been propelled by the fact that it is a co-receptor for the human immunodeficiency virus. The drug AMD3100, a specific inhibitor of SDF-1 pathway, is a bicyclam with high specificity for CXCR4 and is the prototypical CXCR4 blocking drug [18]. It is already approved for human use. In chondrosarcoma cells, CXCR4 blockade with AMD3100 inhibits expression of MMP1 and invasion *in vitro* [19]. AMD3100 has been shown to inhibit collagen-induced joint inflammation [20]. Recently, Wei and his colleagues have demonstrated that attenuation of osteoarthritis via blockade of the SDF-1/CXCR4 signaling pathway in primary guinea pig OA model [21]. CXCR4, therefore, is an attractive target since it is over-expressed in OA cartilage chondrocytes. Blocking SDF1/CXCR4 signaling pathway is a novel therapeutic target for the prevention and treatment of osteoarthritis.

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