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Research Progress on the SDF-1/CXCR4 Axis in Cartilage Injury

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Abstract: The chemokine CXCL12, also known as stromal cell-derived factor 1 (SDF-1), is a small pro-inflammatory chemokine that primarily binds to CXC receptor 4 (CXCR4; CD184), serving as a major regulatory factor for cell transport and adhesion. When SDF-1 binds to CXCR4, it triggers intracellular signaling through several pathways that initiate processes such as chemotaxis, cell survival, proliferation, calcium influx, and gene transcription. The SDF-1/CXCR4 axis plays a crucial role in the development of bone marrow stem cells and the process of tissue regeneration. Repairing cartilage tissue necessitates a sufficient number of chondrocytes, making bone marrow mesenchymal stem cells particularly suitable for this purpose. This signaling pathway is essential for cartilage injury repair. It promotes stem cell migration and localization, regulates cell proliferation and differentiation, and inhibits inflammatory responses. This article reviews the current research advancements related to the SDF-1/CXCR4 axis in cartilage tissue repair.

Keywords: SDF-1/CXCR4 Axis; Cartilage Repair; Stem Cell Migration; Tissue Regeneration.

1. Introduction

Cartilage tissue damage is a significant health issue that affects patients' quality of life globally, primarily due to its prevalence and the challenges associated with treatment. Traditional treatment methods are often ineffective in repairing damaged cartilage, leading to the search for more effective therapies. The SDF-1/CXCR4 axis is a key molecular signaling pathway that regulates stem cell migration and tissue regeneration, garnering significant scientific interest. This axis is closely related to the localization and functional regulation of stem cells, playing a central role in promoting the self-repair of cartilage tissue and regenerative medicine. With the in-depth study of biomaterials and molecular signaling mechanisms, therapeutic strategies related to the SDF-1/CXCR4 axis provide new perspectives for repairing cartilage tissue damage. At the same time, the rapid development of personalized medicine has made it possible to create customized treatment plans tailored to individual patient characteristics, which not only improves treatment efficacy but also significantly increases safety. Despite these advances, practical applications face several challenges, including the complexity of signaling pathways, difficulties in spatiotemporal treatment control, patient response variability, and issues with clinical translation. This article reviews the research progress of the SDF-1/CXCR4 axis in repairing cartilage damage and discusses its potential and challenges in clinical applications.

2. Biological Characteristics of the SDF-1/CXCR4 Axis

Chemokines are small peptide molecules, typically between 8 and 12 kDa, that play a role in activating, migrating, and transporting cells. Chemokines bind to specific G protein-coupled seven-transmembrane receptors[1-3]. Most chemokines bind to multiple receptors, and the same receptor may bind to more than one chemokine. The chemokine CXCL12 (Stromal Cell-Derived Factor 1, SDF-1) binds to receptors CXC receptor 4 (CXCR4) and CXC receptor 7 (CXCR7). SDF-1 is found in various organs such as the lungs, liver, skeletal muscle, brain, kidneys, heart, synovial joints, and bone marrow. SDF-1 secretion is linked to tissue damage, including conditions like myocardial infarction, limb ischemia, toxic liver injury, excessive bleeding, total body irradiation, and damage from chemotherapy. CXCR4 is expressed by endothelial cells and pericytes in hypoxic, injured, or pathological tissues. CXCR4 is widely expressed in hematopoietic cells, including CD34+, HSC, T lymphocytes, B lymphocytes, monocytes and macrophages, neutrophils, and eosinophils, as well as in the brain, lungs, colon, heart, kidneys, liver, synovial joints, and bone marrow[4].

SDF-1 is also a homeostatic chemokine. The main function of homeostatic chemokines is to regulate the transport of hematopoietic cells and the structure of secondary lymphoid tissues. Studies on SDF-1 knockout indicate that the colonization of the bone marrow in late pregnancy is controlled by the SDF-1/CXCR4 pathway, which is crucial for the homing and transport of mesenchymal stem cells in the bone marrow microenvironment in adults[5].

Knocking out the CXCR4 or SDF-1 gene in mice results in impaired hematopoietic function. This is evident through defects in the transport of hematopoietic stem cells (HSC) from the fetal liver to the embryonic bone marrow, as well as abnormalities in heart and brain development and ossification[6, 7]. Functional CXCR4 is expressed in embryonic pluripotent stem cells and several types of tissue-specific stem cells, such as those in neural tissue, skeletal muscle, heart, liver, endothelium, renal tubules, and retinal pigment epithelium. These cells express functional CXCR4 and migrate or invade along the CXCL12 gradient. CXCR4+ pro-angiogenic cells consist of both immature and mature

hematopoietic cells, as well as endothelial and smooth muscle progenitor cells. These cells possess either direct or indirect pro-angiogenic properties. CXCL12 plays a role in mobilizing and recruiting these cells to the new angiogenic microenvironment, supporting revascularization and tissue growth in ischemic tissues[8, 9].

3. SDF-1/CXCR4 Axis Cell Biological Characteristics

The interaction between SDF-1 and its receptor CXCR4 facilitates cell migration, stem cell homing, and tissue repair. SDF-1, also known as CXCL12, binds to its receptor CXCR4 (a G protein-coupled receptor), initiating downstream signaling cascades that regulate cell behavior. By activating downstream pathways, it influences the migration, survival, and proliferation of different cell types[10]. The biology of the SDF-1/CXCR4 axis is illustrated in Figure 1.

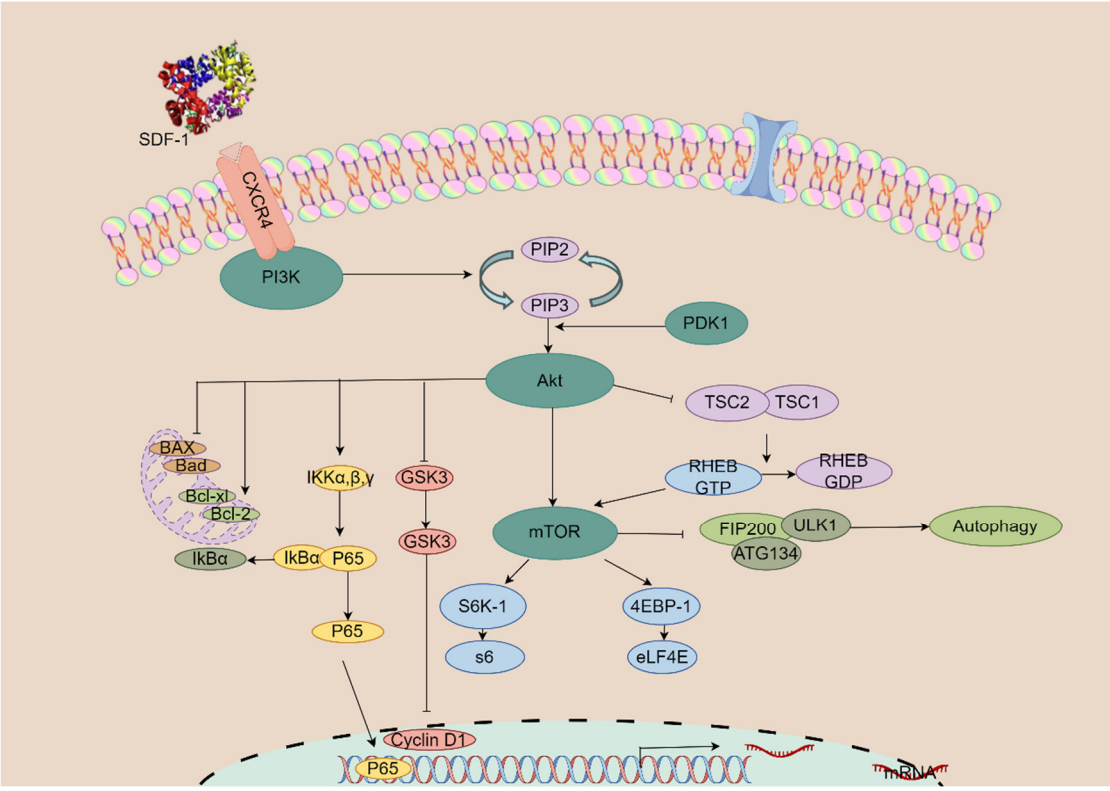


Figure 1. SDF-1/CXCR4 intracellular signaling pathway schematic (this figure is drawn by Figdraw)

The SDF-1/CXCR4 axis directs the movement of various cell types toward specific tissues or injury sites[11, 12]. The signaling pathway formed by SDF-1 and CXCR4 regulates multiple physiological activities, such as chemotaxis, cell survival, proliferation, intracellular calcium influx, and gene transcription. This axis is crucial for the migration and engraftment of stem cells under various pathological conditions, including acute pancreatitis and renal cell carcinoma[13, 14]. In the context of regenerative medicine, the role of the SDF-1/CXCR4 axis in promoting tissue repair and stem cell therapy has been studied. This axis promotes the migration of neural stem cells during neurodevelopment and plays a role in the pathophysiological processes of neurological diseases[15, 16]. Furthermore, SDF-1/CXCR4 signaling has been shown to accelerate fracture healing and promote endochondral bone repair under traumatic brain injury conditions[17]. The SDF-1/CXCR4 axis plays multifaceted roles in cell migration, stem cell homing, and tissue repair. Its intricate signaling pathways and interactions are significant for various biological processes, including cancer progression, regenerative medicine, and stem cell biology.

The SDF-1/CXCR4 axis triggers a series of signaling events that regulate cell behavior and responses. The SDF-1/CXCR4 axis promotes tumor growth, invasion, and metastasis by directly stimulating tumor cell proliferation, survival, and invasion[18, 19]. Targeting this axis has been proposed as a strategy to interfere with tumor cell migration and invasion[20]. In the context of stem cell biology, the SDF-1/CXCR4 axis plays a key role in stem cell migration and homing. Studies have shown that this axis regulates the migration of various types of stem cells, including mesenchymal stem cells, neural stem cells, and hematopoietic stem cells[13, 21, 22]. The SDF-1/CXCR4 axis guides stem cell migration and homing to specific tissues or injury sites, promoting tissue repair and regeneration[10]. Additionally, the SDF-1/CXCR4 axis impacts various diseases and conditions. In lung cancer, this axis has been shown to regulate cancer cell migration and invasion, thereby affecting the progression of non-small cell lung cancer[23]. In bladder cancer, inhibiting the SDF-1/CXCR4 axis suppresses cancer cell growth both in vitro and in vivo[24].

Furthermore, the SDF-1/CXCR4 axis regulates the apoptosis, migration, and cytokine secretion of bone marrow mesenchymal stem cells, underscoring its importance in stem cell behavior[22]. In regenerative medicine, researchers are exploring the potential of the SDF-1/CXCR4 axis to promote tissue repair and stem cell therapy. Research indicates that the SDF-1/CXCR4 axis enhances the migration and engraftment of stem cells under various pathophysiological conditions,

including acute pancreatitis and liver injury[25, 26]. Additionally, the SDF-1/CXCR4 axis induces neovascularization in ischemic, tumor, and injured tissues, thereby promoting angiogenesis and facilitating tissue repair[27]. In conclusion, the SDF-1/CXCR4 axis is crucial for cell migration and stem cell homing, affecting multiple biological processes and disease states.

4. The SDF-1/CXCR4 Axis Affects the Proliferation and Differentiation of Chondrocytes

The interaction between SDF-1 and CXCR4 initiates multiple signaling pathways that directly affect chondrocyte behavior and fate. Studies indicate that the SDF-1/CXCR4 axis regulates chondrocyte proliferation and differentiation. This regulation increases cell numbers and enhances cell viability[28]. Additionally, the SDF-1/CXCR4 axis is associated with the stimulation of chondrocyte hypertrophy, which is a key step in endochondral ossification[28]. The SDF-1/CXCR4 axis plays a role at the cartilage-bone interface during skeletal development, affecting the differentiation of chondrocytes into osteoblasts[28]. Furthermore, the SDF-1/CXCR4 axis induces the expression of matrix metalloproteinases in human endplate chondrocytes. This induction helps improve cartilage degradation in vitro and reduces nucleus pulposus degeneration in vivo[29]. The upregulation of CXCR4 expression in human endplate chondrocytes by SDF-1 suggests that this axis has a potential role in regulating cartilage homeostasis and degenerative processes. It has been reported that the SDF-1/CXCR4 axis induces apoptosis in human degenerative nucleus pulposus cells through the NF-κB pathway, highlighting its involvement in regulating cell survival and death in intervertebral disc degeneration[30].

In regenerative medicine, researchers have explored how the SDF-1/CXCR4 axis may promote chondrocyte autophagy and facilitate cartilage repair. Previous studies have indicated that SDF-1α promotes chondrocyte autophagy through the CXCR4/mTOR signaling axis, suggesting that this axis plays a role in regulating cellular processes that contribute to cartilage maintenance and repair[31]. Additionally, the stimulation of chondrocyte autophagy by the SDF-1/CXCR4 axis may help enhance cartilage regeneration and prevent cartilage degradation[31]. Moreover, the SDF-1/CXCR4 axis is related to the migration and differentiation of mesenchymal stem cells into cartilage tissue, regulating the migration of transplanted bone marrow mesenchymal stem cells to damaged cartilage sites, thereby promoting tissue repair and regeneration[25].

5. The Role of the SDF-1/CXCR4 Axis in Cartilage Tissue Engineering

The role of stem cells and the SDF-1/CXCR4 axis in cartilage regeneration is a well-explored area in regenerative medicine. This axis primarily helps recruit and migrate stem cells, which is essential for cartilage regeneration.

A key aspect of the SDF-1/CXCR4 axis in cartilage regeneration is its role in recruiting mesenchymal stem cells to the site of cartilage injury. Studies have shown that SDF-1 acts as a chemotactic molecule for mesenchymal stem cells by binding to the CXCR4 receptor, leading to their migration to the damaged cartilage tissue[32]. This recruitment of mesenchymal stem cells is crucial for initiating the repair process and promoting cartilage regeneration. Additionally, the SDF-1/CXCR4 axis promotes enhanced chondrogenic differentiation of mesenchymal stem cells. Research indicates that SDF-1 stimulation can promote the chondrogenic differentiation of mesenchymal stem cells, resulting in the formation of cartilage-like tissue[33]. This process involves signaling pathways that activate markers for chondrogenesis and stimulate the production of cartilage-specific extracellular matrix components.

In addition to promoting the recruitment and differentiation of stem cells, the SDF-1/CXCR4 axis also creates a favorable microenvironment for cartilage regeneration, participating in the regulation of inflammatory responses, promoting angiogenesis, and enhancing the tissue repair processes within the cartilage microenvironment[34]. By modulating the interactions between stem cells, immune cells, and other components of the microenvironment, the SDF-1/CXCR4 axis contributes to the overall success of cartilage regeneration.

Moreover, the SDF-1/CXCR4 axis has been shown to play a critical role in the homing and engraftment of stem cells in cartilage tissue. Studies indicate that this axis is essential for the successful integration of transplanted stem cells into the cartilage matrix, thereby improving tissue repair and regeneration[35]. This homing mechanism ensures that the transplanted stem cells can effectively promote the restoration of cartilage structure and function. Overall, the interaction between stem cells and the SDF-1/CXCR4 axis plays a key role in facilitating cartilage regeneration. By recruiting, differentiating, and creating a favorable microenvironment for stem cells, the SDF-1/CXCR4 axis enhances the regenerative capacity of cartilage tissue.

6. The Use of SDF-1/CXCR4 Axis Agonists and Antagonists Plays a Crucial Role in Cartilage Tissue Engineering

Agonists of the SDF-1/CXCR4 axis can stimulate the recruitment and migration of stem cells to the injury site, promoting tissue regeneration[33]. Modulating this axis with pharmacological agents can affect cell migration, differentiation, and tissue repair processes. By activating the CXCR4 receptor, the homing and engraftment of stem cells in damaged cartilage tissue can be enhanced, facilitating the repair process[36, 37]. The use of antagonists targeting the SDF-1/CXCR4 axis can also regulate the quality of cartilage injury repair; CXCR4 antagonists can block the interaction between SDF-1 and CXCR4, thereby inhibiting the migration and recruitment of stem cells to the damaged cartilage area[14]. This blockade can modulate the inflammatory response and prevent excessive tissue degradation, promoting a more controlled and regulated repair process[38]. Agonists and antagonists of the SDF-1/CXCR4 axis can activate downstream signaling cascades that promote cell proliferation, differentiation, and survival, enhancing the regenerative capacity of chondrocytes[39]. Conversely, antagonists can inhibit abnormal signaling pathways associated with cartilage degeneration and disease progression, providing targeted approaches for therapeutic intervention[40]. The targeted delivery of SDF-1/CXCR4 axis agonists or antagonists combined with stem cell transplantation can improve the homing and engraftment of

stem cells in damaged cartilage tissue, leading to more effective tissue repair. Additionally, incorporating SDF-1/CXCR4 axis modulators into tissue engineering scaffolds can further enhance the regenerative potential of these methods.

7. Conclusion

In summary, the research directions for the SDF-1/CXCR4 axis in cartilage repair are diverse and promising. Addressing current challenges and optimizing strategies will allow the SDF-1/CXCR4 axis to develop more effective cartilage repair methods. The SDF-1/CXCR4 axis offers a controllable approach for utilizing stem cells in cartilage tissue engineering. Future research in tissue engineering should further investigate the applications of the SDF-1/CXCR4 axis. This exploration could lead to more effective clinical strategies, ultimately improving the quality of cartilage injury repair.

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