

The Good, the Bad and the Ugly of Stromal Cell-Derived Factor 1a in Musculoskeletal Disorders

Dingqi Xie¹, Ximiao Yu¹, Yuhan Bao¹, Yiyao Ding¹, Miao Li², Quanming Wang³ and Lei Ding^{1*}

¹Jiangnan University Wuxi College of Medicine, Wuxi, Jiangsu, China

²Jiangnan University School of Humanities, Wuxi, Jiangsu, China

³Department of Orthopaedic Surgery, Jiangnan University Affiliated Hospital, Wuxi, Jiangsu, China

*Corresponding Author: Lei Ding, Associate Professor, Jiangnan University Wuxi College of Medicine, Wuxi, Jiangsu, China.

Received: May 08, 2020; Published: June 02, 2020

Abstract

Stromal cell-derived factor 1a (SDF-1a), alternatively named as CXCL12, is a chemokine playing multi-faceted roles in musculoskeletal disorders. It could attract chondrogenic progenitor cells to cartilage lesions, which would promote the repair of tissue injury resulted from mechanical insults. On the other hand, it acted as an inflammatory mediator that could exacerbate the pathological conditions of osteoarthritis and rheumatoid arthritis. Even worse, SDF-1a could act through its specific membrane receptor CXCR4 to facilitate the progression and bone metastasis of some malignant tumors. In this review, we focus on the research progress in the past decade examining the double-edged effect of this unique chemokine on common musculoskeletal disorders, including joint injury, arthritis, and tumor bone metastasis.

Keywords: SDF-1a; CXCR4; Cartilage Repair; Arthritis; Bone Metastasis

Introduction

Stromal cell-derived factor 1a (SDF-1a) is a small sized protein with a MW around 8 kDa. Since it contains a motif composed of two cysteines separated by one intervening amino acid (C-X-C) and functions as a chemokine ligand, SDF-1a is also named as CXCL12 (CXC motif chemokine ligand 12) and acts through its specific receptor C-X-C chemokine receptor type 4 (CXCR4) [1]. It can be synthesized and secreted by stromal cells in bone marrow as well as various other cell types such as immune cells, synoviocytes, and metastatic prostate cancer cells [2-4]. As a chemokine, SDF-1a mediates homing of progenitor cells to sites of tissue lesions where those progenitor cells can differentiate and proliferate to repair the damages (the good of SDF-1a). However, it can also attract lymphocytes and macrophages to the injury site to promote inflammatory responses, which has been implicated in the pathogenesis of rheumatoid arthritis (RA) and osteoarthritis (OA) (the bad of SDF-1a). Furthermore, recent research revealed that high-expression of SDF-1a was associated with metastasis of musculoskeletal tumors and promoted migration of cancer cells from other organs to the bone (the ugly of SDF-1a). In this review, we aim to summarize the recent research progress on the good, the bad, and the ugly of this unique chemokine SDF-1a in musculoskeletal disorders.

The good of SDF-1a: Biomaterials loaded with SDF-1a promoting articular cartilage repair

Cartilage degradation is a hallmark of OA and commonly occurs in RA. In addition, intraarticular fractures or tearing of ligaments frequently result in cartilage lesions. As a tissue lacking of vascular network, cartilage has very limited capacity of self-healing [5]. Biomaterials loaded with SDF-1a which can attract progenitor cells to the injury sites has become a promising strategy for tissue engineered cartilage repair.

Zhang, *et al.* fabricated type I collagen membrane scaffold using porcine Achille's tendon and then loaded it with recombinant human SDF-1a to repair partial-thickness cartilage defect on rabbit femoropatellar groove. This SDF-1a containing scaffold attracted mesenchymal cells and progenitor cells to form a reparative tissue inside the defect, which significantly improved self-healing of the cartilage defect

[6]. In addition to collagen-made scaffold, researchers also used Poly (D,L-lactic acid-co-glycolic acid) (PLGA) or fibrin/hyaluronic acid (HA) to deliver SDF-1a into articular defects and achieved significant improvement in cartilage repair. Their data showed that homing of bone marrow mesenchymal cells or chondrogenic progenitor cells harbored in the superficial zone of cartilage to the defect sites by SDF-1a was the key step in the repairing process [6-8].

The bad of SDF-1a: proinflammatory effect of SDF-1a propelling joint degeneration

In 2012, Xu and colleagues examined the levels of SDF-1a in synovial fluids (SF) of OA knees and discovered positive correlation between those levels and radiographic severity of the diseased knee evaluated by the Kellgren-Lawrence grading scale [9]. Furthermore, our study on the association between levels of SDF-1a in knee SF and characteristics of patients diagnosed with anterior cruciate ligament (ACL) injury revealed that SDF-1a levels were negatively correlated with time from injury or age of the patients and the negative correlation with time from injury was only observed in female patients. Since ACL injury can lead to post-traumatic OA and SDF-1a acts through CXCR4 to activate proinflammatory response resulting in the up-regulation of matrix metalloproteinases (MMPs) that degrade cartilage, the higher levels of SDF-1a in knee SF of female patients might partially explain why females tended to have more severe radiographic knee OA than males [10-12].

In addition to the participation in OA pathogenesis, SDF-1a played a crucial role in inflammatory bone destruction in RA affected joints. Kim., *et al.* showed that receptor activator of nuclear factor kappa-B ligand (RANKL), a major inducer of osteoclast differentiation and activation, could be up-regulated in RA synovial fibroblasts and CD4+ T cells by SDF-1a [13]. Grassi., *et al.* demonstrated that SDF-1a expression was elevated in synovial and bone tissues biopsied from patients with RA. More importantly, this chemokine could increase bone resorption capacity of osteoclasts by two-fold and this increased bone destruction was associated with the up-regulation of MMP-9 [14].

The ugly of SDF-1a: promoting bone metastasis

The bone is a major target organ for solid tumor metastasis, such as prostate cancer. Bone metastasis usually implies the progression of the primary tumor and is the common cause for cancer-related mortality. The red marrow of the bone consisting of the hematopoietic tissue gives permission to circulating tumor cells to enter the osteoblast niche from the vascular niche. Cells in the osteoblast niche highly express SDF-1a which exerts its chemotactic activity on tumor cells that express CXCR4. The binding of SDF-1a to CXCR4 elicits a series of biological responses that enable tumor cells to migrate from the primary site to the bone [15].

Sun and colleagues reported that SDF-1a could increase the adhesiveness and invasiveness of prostate cancer cells that is capable of metastasizing to bone while had no such effect on non-metastatic prostate cancer cells. This effect of SDF-1a was dependent on the activation of $\alpha v \beta 3$ integrin [16]. A study conducted by Akashi., *et al.* revealed that the expression of CXCR4, the major receptor for SDF-1a, was detected in 94.2% patients diagnosed with prostate cancer bone metastasis. Moreover, high expression level of CXCR4 in primary cancer tissue biopsied before any treatments was associated with poor cancer-specific survival of the patients [17]. By using RNA interference technique, Wang and colleagues demonstrated that SDF-1a binding to CXCR4 could up-regulate the expression of vascular endothelial growth factor (VEGF) and MMP-9 in prostate cancer cells, which led to tumor growth and bone metastasis [18].

Discussion

SDF-1a is a unique chemokine that displays its good, bad, and ugly sides in tissue-engineered cartilage repair, pathogenesis of OA and RA and bone metastasis of malignant tumors. However, the detailed molecular mechanisms employed by this chemokine to exert those dual actions still remain unclear. More investigations into SDF-1a signaling in musculoskeletal disorders are urged to better understand its role in cartilage regeneration and destruction and in bone metastasis. The more we know how this chemokine works, the better we utilize it to treat inflammation or tumors occurred in musculoskeletal system.

Conclusion

In summary, with proper drug-delivery system, SDF-1a can be used to repair defects in articular cartilage by attracting endogenous progenitor cells. However, its chemotactic effect should be considered when designing such system to avoid inflammatory damage to the tissue. Strategies targeting SDF-1a-CXCR4 axis in bone metastatic tumor cells are promising in terms of inhibiting tumor growth and reducing cancer-related mortality.

Conflict of Interest Statement

The authors have nothing to disclose.

Authors Contribution

Dingqi Xie, Ximiao Yu, Yuhan Bao, Yiyao Ding, Miao Li these authors have contributed equally to this work.

Acknowledgement

This study was funded by the National Innovation and Entrepreneurship Program for College Students of China (Grant#: 1282050205195418) and by the Jiangsu Provincial Natural Science Foundation of China grant awarded to Lei Ding (BK20171143).

Bibliography

1. Pozzobon T., *et al.* "CXCR4 signaling in health and disease". *Immunology Letters* 177 (2016): 6-15.
2. Guyon A. "CXCL12 chemokine and its receptors as major players in the interactions between immune and nervous systems". *Frontiers in Cellular Neuroscience* 8 (2014): 65.
3. Bragg R., *et al.* "Stromal cell-derived factor-1 as a potential therapeutic target for osteoarthritis and rheumatoid arthritis". *Therapeutic Advances in Chronic Disease* 10 (2019): 1753174307.
4. Gupta N and Duda DG. "Role of stromal cell-derived factor 1alpha pathway in bone metastatic prostate cancer". *Journal of Biomedical Research* 30.3 (2016): 181-185.
5. Carballo CB., *et al.* "Basic Science of Articular Cartilage". *Clinics in Sports Medicine* 36.3 (2017): 413-425.
6. Zhang W., *et al.* "The use of type 1 collagen scaffold containing stromal cell-derived factor-1 to create a matrix environment conducive to partial-thickness cartilage defects repair". *Biomaterials* 34.3 (2013): 713-723.
7. Wang Y., *et al.* "Stromal Cell-Derived Factor-1 Accelerates Cartilage Defect Repairing by Recruiting Bone Marrow Mesenchymal Stem Cells and Promoting Chondrogenic Differentiation and It; sup/and gt". *Tissue Engineering Part A* 23.19-20 (2017): 1160-1168.
8. Yu Y., *et al.* "Use of recombinant human stromal cell-derived factor 1alpha-loaded fibrin/hyaluronic acid hydrogel networks to achieve functional repair of full-thickness bovine articular cartilage via homing of chondrogenic progenitor cells". *Arthritis and Rheumatology* 67.5 (2015): 1274-1285.
9. Xu Q., *et al.* "Association of CXCL12 levels in synovial fluid with the radiographic severity of knee osteoarthritis". *The Journal of Investigative Medicine* 60.6 (2012): 898-901.
10. Ding L., *et al.* "Association of chemokine expression in anterior cruciate ligament deficient knee with patient characteristics: Implications for post-traumatic osteoarthritis". *Knee* 27.1 (2020): 36-44.

11. Kanbe K., *et al.* "Synovectomy reduces stromal-cell- derived factor-1 (SDF-1) which is involved in the destruction of cartilage in osteoarthritis and rheumatoid arthritis". *The Journal of Bone and Joint Surgery British* 86.2 (2004): 296-300.
12. Srikanth VK., *et al.* "A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis". *Osteoarthritis Cartilage* 13.9 (2005): 769-781.
13. Kim HR., *et al.* "Reciprocal activation of CD4+ T cells and synovial fibroblasts by stromal cell-derived factor 1 promotes RANKL expression and osteoclastogenesis in rheumatoid arthritis". *Arthritis and Rheumatology* 66.3 (2014): 538-548.
14. Grassi F., *et al.* "CXCL12 chemokine up-regulates bone resorption and MMP-9 release by human osteoclasts: CXCL12 levels are increased in synovial and bone tissue of rheumatoid arthritis patients". *Journal of Cellular Physiology* 199.2 (2004): 244-251.
15. Shi J., *et al.* "CXCL12-CXCR4 contributes to the implication of bone marrow in cancer metastasis". *Future Oncology* 10.5 (2014): 749-759.
16. Sun YX., *et al.* "Expression and activation of alpha v beta 3 integrins by SDF-1/CXC12 increases the aggressiveness of prostate cancer cells". *Prostate* 67.1 (2007): 61-73.
17. Akashi T., *et al.* "Chemokine receptor CXCR4 expression and prognosis in patients with metastatic prostate cancer". *Cancer Science* 99.3 (2008): 539-542.
18. Wang Q., *et al.* "Regulation of VEGF, MMP-9 and metastasis by CXCR4 in a prostate cancer cell line". *Cell Biology International* 35.9 (2011): 897-904.

Volume 11 Issue 7 July 2020

©All rights reserved by Lei Ding., *et al.*