Journal of Biosciences and Medicines, 2025, 13(9), 248-259
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

The Role of CXCL12 in Regulating Macrophage Polarization in the Pathogenesis of Osteoarthritis

Zeyu Hou[1], Jinyou Nie[1], Dinggui Lu[2*]

[1]Graduate School, Youjiang Medical University for Nationalities, Baise, China
[2]Department of Orthopedic Surgery, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China
Email: *ludinggui@163.com

How to cite this paper: Hou, Z.Y., Nie, J.Y. and Lu, D.G. (2025) The Role of CXCL12 in Regulating Macrophage Polarization in the Pathogenesis of Osteoarthritis. *Journal of Biosciences and Medicines*, **13**, 248-259.
https://doi.org/10.4236/jbm.2025.139021

Received: June 23, 2025
Accepted: September 6, 2025
Published: September 9, 2025

Abstract

Osteoarthritis (OA) is a degenerative joint disease that is common and significantly impacted in middle-aged and elderly people, and its accompanying inflammatory response plays a crucial role in the occurrence and progression of the disease. In recent years, studies have shown that the polarization state of macrophages plays a key role in the inflammatory response of OA. Macrophages are key players in OA pathology and their activation status has been extensively studied. Various studies have shown that macrophages may respond to stimuli in their microenvironment by changing their phenotype to a pro-inflammatory or anti-inflammatory phenotype, called macrophage polarization. Macrophages accumulate and polarize in many tissues (M1 or M2), such as synovial membrane, adipose tissue, bone marrow and joints, while resident macrophages, as well as other stromal cells (including fibroblasts, chondrocytes, and osteoblasts) form joints and function as a whole unit. We summarize findings related to macrophage polarization and osteoarthritis, including pathogenesis, molecular pathways, and treatments, to alleviate the progression of osteoarthritis disease.

Keywords

CXCL12, CXCL12/CXCR4, Macrophages, M1/M2 Polarization, Osteoarthritis, Signaling Pathways, Treatment Strategies

1. Introduction

Osteoarthritis (Osteoarthritis, referred to as OA) is a common joint disease world-

*Corresponding author.

wide, and is often found in middle-aged and elderly people. This disease is actually caused by a variety of factors, which causes degeneration of those joints, which in turn causes this degenerative change to occur from time to time. As human quality of life improves and our lifespans grows, the number of elderly people suffering from this disease is unfortunately increasing every year, as the WHO pointed out, it is called "immortal cancer" [1] [2]. As of now, according to the data we obtain, about 10% to 15% of adults worldwide are affected to various degrees by this disease. However, this situation is more common in the so-called middle-aged and elderly groups. If we look at our country, that is, in mainland China, the proportion of osteoarthritis is even a little higher among these middle-aged and elderly people, or perhaps as high as 30% to 50% [3]. This number does make people feel more popular. Generally speaking, patients often have some common symptoms, such as joint pain and stiffness, and the patient's late-stage quality of life is greatly reduced, which affects the patient's daily life and work. For now, the treatment methods of osteoarthritis are generally divided into several categories, non-pharmaceutical treatment, drug treatment and surgical treatment [4] [5].

Macrophages are multifunctional immune cells with excellent plasticity and are involved in the stages of inflammation, such as the occurrence, development and digestion. They are able to adapt to different organizational microenvironments and perform various functions. Traditionally divided into classical activation (M1) and selective activation (M2) phenotypes, recent advances reveal macrophage activation status profiles beyond this dichotomy. More and more studies have shown that the polarization imbalance of macrophages is a key pathological factor in various immune-related diseases such as autoimmune diseases and tumors [6]. Complex interactions of signaling pathways, transcriptional regulators, and epigenetic modifications coordinate macrophage polarization, allowing them to dynamically respond to various stimuli. The plasticity of macrophages plays a key role in tissue repair and regeneration, which coordinate inflammation, angiogenesis, and matrix remodeling to restore tissue homeostasis. By leveraging the potential of macrophage plasticity, novel therapeutic strategies for macrophage polarization can be developed for a variety of diseases, including chronic wounds, fibrotic diseases and inflammatory conditions. Ultimately, a deeper understanding of the molecular mechanisms that underpin macrophage plasticity will pave the way for innovative regenerative medicine and tissue engineering approaches [7].

2. Main Body

2.1. Macrophage Morphology of Osteoarthritis

Osteoarthritis is a disease that affects most joint tissues. In today's medical research field, a relatively abundant type of immune cell in inflammation and joint-related problems, like macrophages, is believed to have important associations with the emergence and progression of diseases. In the context of macrophage origin, macrophages come from two different lineages [8]. Macrophages are the

main component of the immune system and also play a regulatory role in the inflammatory environment of OA. Studies have shown that the polarization process of synovial M1 macrophages may be related to the increasing seriousness of osteoarthritis. However, more experimental evidence is needed to confirm the specific biological mechanism of this causal relationship. Previous studies have confirmed M1 macrophage-mediated cartilage destruction during OA progression [9]. Fahy *et al.* experimentally demonstrated that M1-related cytokines IL-6, IL-1b, TNF-α and tumorigenin M (OSM) can induce the destruction of chondrocytes, including downregulation of type II collagen and aggrecan synthesis. In addition, synovial M1 macrophages have also been shown to upregulate the production of proteolytic enzymes such as matrix metalloproteinase (MMP)-1, MMP3, MMP13, MMP9 agglomerase and cyclooxygenase-2, through which the effects of these enzymes can lead to joint degeneration [10]. From the above, macrophages play a relatively important role, and they participate in a series of important stages of the inflammatory response, which involve occurrence, development, and even digestion. However, the specific operating mechanisms of this have not been fully explained yet. To some extent, each critical stage is closely related to complex biological signaling pathways. Studies have shown that at different stages of the inflammatory response, macrophages exhibit different phenotypes, and the polarization states of macrophages (type M1 and type M2) will also affect the progress of OA. M1 macrophages are mainly proinflammatory and antibacterial effects, while M2 macrophages can be further subdivided into M2a, M2b and M2c. They exhibit anti-inflammatory properties and help tissue repair and remodeling, which mainly show anti-inflammatory and repair functions [11] [12].

2.2. Overview of Macrophage Polarization

In the study of biology, macrophages are an important part of the innate immune system. These cells show extremely high mutant adaptability and extremely high plasticity. The ability to present different functional states according to different stimuli received in different microenvironments, so this change is called Macrophage Polarization. It is crucial for tissue repair and maintenance of homeostasis in the body. Briefly, macrophages can present a unique, metastable functional phenotype in response to environmental cues—a process called macrophage polarization [13] [14]. During the process of macrophage polarization, a variety of different functional phenotypes can be presented, among which the two most classic phenotypes are: M1 type (classical activated type) macrophage M2 type (alternate activated type) macrophage [15]. The two have completely different functions in physiological and pathological environments, and are involved in inflammatory responses, immunosuppression, tissue repair and other processes respectively. In addition, M1/M2 is just two extremes of macrophage polarization. In actual cases, macrophage polarization is a continuous spectrum, not a dichotomy. Studies have shown that macrophage polarization is crucial for maintaining tissue repair and in vivo homeostasis [16]. Macrophage polarization usually refers to the

process in which macrophages generate unique functional phenotypes by responding to signals such as stimulation in tissues in specific microenvironments and transcription factors [13]. Udalova and colleagues have shown that the transcription factor IRF5 controls the plasticity of M1 macrophages in mice and humans. M1 macrophages, or classically activated macrophages, act as antibacterial and proinflammatory factors, which are activated in response to stimulation of type 1 helper T (Th1) cells [17]. Studies have shown that the polarization of synovial M1 macrophages may be closely related to the development process of osteoarthritis, that is, OA, and that changes in M1 cells may be one of the important factors that worsen the disease.

2.3. Application of Macrophage Polarization in the Treatment of Osteoarthritis

1) In recent years, the research on the polarization mechanism of macrophages has made great progress through technological advances, so it is a promising strategy for the treatment of osteoarthritis, a disease that affects most joint tissues and ultimately leads to degenerative joint lesions. In the current field of medical research, inflammation phenomena and one of the most abundant immune cells in various types of joints, macrophages, are widely believed to be important factors that may be involved in the entire occurrence and progress of the disease. Its treatments are diverse, including intra-articular (IA) injection, surgery, and cell therapy, but the need for more effective clinical therapies remains high. More effective ways to reduce inflammation progression is still needed. Methods for treating OA include roughly physical stimulation, chemical compounds and biological molecules. Studies have shown that most of these methods are related to macrophage polarization. Therefore, OA treatment with macrophage polarization as a potential target.

2) Under the continuous influence of specific microenvironmental conditions, macrophages with diverse morphologies have been demonstrated to have the ability to perform phenotypic switching based on external stimuli. Taking the pathogenesis of osteoarthritis as an example, the proinflammatory effect plays an important role. Many experimental data have confirmed this that M1 type macrophages occupy key positions in the immune system. An example that constitutes one of the important links in the early course of OA can be seen. The activation and polarization process of M1 type macrophages is mainly dominated by the regulation of inflammatory signals in tissues. M1 macrophages have the secretion behavior of various proinflammatory cytokines such as IL-1, IL-6 and TNF, and the intensity of inflammatory response has been significantly enhanced. Nowadays, relevant animal experiments have confirmed the conclusion that the occurrence of M1 polarization in synovial tissue will aggravate the OA-related symptoms in CIOA and DMM models. In contrast, when the Rheb gene is deletion, the mTORC1 pathway is enhanced, which promotes the development of the M2 polarization process, and ultimately results in a significant relief of CIOA symptoms in mice. The results show that mac-

rophage M1 polarization leads to the worsening progress of experimental OA [9]. Synovial macrophages function like an immune cell that plays an important role in the progression of osteoarthritis (OA). After reviewing some literature, we learned that activated macrophages are regulated by some signal pathways, such as NF-κB, MAPK, TGF-β, JAK/STAT, PI3K/Akt/mTOR and NLRP3 main pathways. These activated macrophages are polarized to M1 or M2 subtypes according to specific environments in the synovial tissue, synovial fluid, and peripheral blood of OA patients. Research conclusions show that the severity of OA is somewhat complex and vaguely related to a variety of factors. For example, in addition to some mutual influences between self-secretion, in fact, there is also a paracrine mechanism, which involves some immune cells, such as the difficult-to-describe relationship between macrophages and chondrocytes. This mutual influence through secretion, such as: inflammatory factors, growth factors, matrix metalloproteinase (MMP) and inhibitors (TIMP), all of which have an unnegligible effect in the beginning and development of OA, and cause the subsequent cartilage to be degraded and then further damaged. By treating those macrophages in the synovial membrane, the pain can be relieved and inflammation problems can be prevented when osteoarthritis continues to develop, thus avoiding damage to the cartilage tissue and reducing the formation of osteophytes. Transformation reprogramming of macrophages from M1 to M2 isoforms, exceeding the reduction in the number of activated macrophages, appears to be an effective therapeutic option for OA [18]. Therefore, we learned that M1 type related studies in synovial membranes of OA patients point out that there is a significant increase in the number of macrophages and a positive correlation with the severity of osteoarthritis (OA). In today's biomedical field, for M2 macrophages, they can produce some polarization manifestations due to various stimuli, although the specific mechanism of this polarization process still needs to be discussed in depth. Certain cytokines, such as IL-4, IL-10 and IL-13, can induce changes, and another type of glucocorticoid and immune complex with hormone effects is also involved in this process.

2.4. Basic Features of CXCL12

The CXCL12 molecule named SDF-1 is of great biological significance in the chemokine family. The main way of its function is to specifically bind to CXCR4 and CXCR7 receptors, thereby achieving regulatory effects on immune response processes and cell migration behavior. The regulatory efficacy that cannot be ignored has been proven to exist in the study of osteoarthritis pathological mechanisms. Examples show that the transition of macrophage polarization state and its recruitment behavior are significantly affected by this factor. CXCL12 signaling molecules released in the autocrine or paracrine pathways, experimental data show that they can lead to a decrease in the expression level of RUNX3 transcription factor. The sustained expression characteristics of CD4 and CD14 surface markers in the monocyte/macrophage population are also closely related to the biological activity of this factor [19]. There is a positive correlation between serum

levels of CXCL12 and the severity of osteoarthritis (OA), and has been observed by several researchers. After 60 patients with knee OA were included in the study, it was found that the significant increase in CXCL12 levels in their peripheral blood and joint cavity fluid, compared with the healthy control group. The evaluation results of the WOMAC scoring system also show that the concentration of this chemokine is positively correlated with it [20]. The operation mode of the above mechanism has not been fully explored. There are many links that need to be thoroughly examined, making it difficult for researchers to fully grasp its potential complexity. It shows that there are still significant limitations in the current stage of understanding of this problem.

2.5. The Role of PI3K/Akt/mTOR Signaling Pathway and OA

Targeting of key molecular and signaling pathways involved in OA pathogenesis has been extensively studied, where the PI3K/Akt pathway not only regulates the survival, migration and proliferation of macrophages, but also coordinates the response of macrophages to different metabolic and inflammatory signals [21] [22]. Its pathway is an important and very complex signaling pathway, in which more than 150 proteins have been identified to participate in this pathway [23]. Various molecules including insulin, glucose, a variety of growth factors and cytokines can also initiate PI3K/AKT/mTOR signaling [24]. Based on the available evidence, the PI3K/AKT/mTOR signaling pathway plays an indispensable role in the normal metabolism of joint tissues, and also participates in the development of OA [25]. Thus, through these effectors, PI3K/AKT/mTOR can function in many in vivo homeostasis processes, including cell cycle, cell survival, inflammation, metabolism, and apoptosis [26]. So understanding the role of PI3K/AKT/mTOR signaling pathways in osteoarthritis is beneficial for us to understand osteoarthritis. Including studies, downregulation of miR-34a promotes proliferation of chondrocytes in rat osteoarthritis and inhibits apoptosis through activation of the PI3K/Akt pathway [27]. Researchers have shown that Kongensin A, which targets PI3K, reduces inflammation-induced osteoarthritis by regulating macrophage polarization and alleviates inflammation signaling [28]. Benzophenone 3 (BP3) has also been shown to significantly alter the expression of toxicological targets and disrupt the PI3K/Akt signaling pathway, thereby promoting OA pathogenesis [29]. Some researchers have demonstrated that inhibiting the CXCL12a/CXCR4 signaling axis maintains the expression of metalloproteinase-3 tissue inhibitors through the PI3K/Akt pathway to solve the mechanism of AMD3100 to prevent OA [30].

In the current stage, in the study of intervention strategies for osteoarthritis (OA) pathological process, the discussion of the mechanism of PI3K/AKT/mTOR signaling pathway showed versatile characteristics. It is worth noting that the reconstruction of cartilage tissue homeostasis and the strengthening effect of the cellular autophagy process may be achieved through the inhibitory treatment of this signaling pathway; the mitigation effect of the degree of joint damage has also

been observed, which are usually caused by osteoarthritis. Examples show that the promotion of chondrocyte proliferation and the inhibition of apoptosis may be achieved through the activation of the PI3K/AKT/mTOR signaling pathway, which has potential value for the prevention and treatment of arthritis. It should be emphasized that the in-depth verification of the above research directions is still insufficient.

2.6. The Relationship between CXCL12 and Macrophages

1) Tumor-associated macrophages (TAM) in the tumor microenvironment is closely related to poor prognosis of gastric cancer (GC). The upregulation of HMGA1B/2 regulates macrophage polarization in a CXCL12/CXCR4-dependent manner through POU1F1, thereby promoting metastasis and metastasis of gastric cancer [31]. Studies have shown that malignant cells can secrete M2-like cytokines, such as IL-10, CCL2/3/4/5/7/8, CXCL12, VEGF and platelet-derived growth factor (PDGF), etc., so as to recruit more monocytes and M0 macrophages to a certain region and distinguish them into the M2 phenotype [32]. Fire needle acupuncture (FNA) reduces KOA by activating the SDF-1/CXCR4 pathway, regulating macrophage polarization and reducing cartilage damage and inflammation. Its experimental study showed that the ATI-2341 group showed a therapeutic effect similar to FNA, while the efficacy of the AMD3100 and AMD3100 + FNA groups was reduced. These findings highlight the therapeutic potential of FNA in KOA management [33].

Therefore, we can learn from these studies that activation of the CXCL12/CXCR4 pathway, modulate macrophage polarization and reduce cartilage damage and inflammation to alleviate KOA. These findings can be therapeutic potential in OA management.

2) Research progress of CXCL12 as a therapeutic target

Research has shown that miR-31 expression was detected by reverse transcription-quantitative polymerase chain reaction, and it was found that miR-31 was downregulated in cartilage tissues of OA patients. microRNA. org is used to predict the gene target of miR-31, and the dual luciferase reporter assay is used to verify that the CXC motif chemokine ligand 12 (CXCL12) is a direct target of miR-31. Experimental validation of data shows that miR-31 promotes chondrocyte viability and migration through direct targeting CXCL12, which provides evidence for CXCL12 as a potential target for OA treatment [34]. Knockdown of miR-107 In related research, scholars have discussed some molecular mechanisms a lot. It is worth noting that in a series of experiments, observations have shown that CXCL12 may serve as a target for miR-107, a specific microRNA. CXCL12 overexpression attenuates the role of miR-107 overexpression or HOTAIR knockdown in proliferation, apoptosis, and ECM degradation, so it can be concluded that CXCL12 is also considered to play a key role in regulating inflammatory responses and bone remodeling, and HOTAIR knockdown promotes chondrocyte proliferation, but inhibits OA chondrocyte apoptosis and ECM degradation by regulating

the miR-107/CXCL12 axis [35]. Therefore, it has important biological significance and clinical application value in the onset of osteoarthritis. Studying its functions and related signaling pathways will provide theoretical basis and practical guidance for the precise treatment of osteoarthritis.

3. Research Direction and Clinical Application Prospects

Among the regulatory pathways of macrophage polarization, the status of signaling pathways such as JAK/STAT, PI3K/AKT/mTOR is particularly critical. This pathway has a significant impact on the regulation of metabolic activity, intervention in proliferation behavior and maintenance of viability of these immune cells. The role it plays in the entire occurrence and development of inflammatory responses cannot be ignored. Examples support that in-depth exploration of this signaling pathway may open up a new research and development path for treatment strategies, and thus improve the prognosis of patients with osteoarthritis. It is worth noting that the CXCL12 molecule as a potential therapeutic target has shown encouraging application prospects. As an important chemokine, it plays a role by binding to CXCR4. A research team has begun to analyze and conclude that the correlation between serum CXCL12 levels and non-traumatic femoral head necrosis clinical periods exists. Experimental data show that the reduction in serum CXCL12/SDF-1 concentration is often accompanied by a tendency to worsen non-traumatic osteonecrosis [36]. Therefore, drugs targeting the CXCL12-CXCR4 axis show good prospects in the treatment of osteoarthritis (OA). For example, sodium hyaluronate-PDGF can interfere with the function of CXCL12, thereby showing protective effects on OA in preclinical models [37]. Astragalus IV, the main phytochemical in Astragalus, has been identified as a novel CXCR4 antagonist. Reduced ADAMTS5 overexpression in CXCL12-induced chondrocytes by blocking the Akt signaling pathway to achieve the effect of alleviating osteoarthritis, and in addition, its administration significantly repaired the damaged cartilage and subchondral bones of rats induced by MIA [38]. And it has been approved by the China National Medical Products Administration for human testing as an antiviral drug.

Therefore, the possibility that CXCL12 is considered a potential target for osteoarthritis treatment is emerging. However, the potential of CXCL12 as a therapeutic target, but at this stage, there is still no assessment of the long-term effects and safety related to CXCL12-based therapies, including its long-term efficacy and potential side effects.

4. Conclusion

In the practice of clinical treatment programs for osteoarthritis, hierarchical characteristics are most significantly reflected in the application of treatment measures. What needs to be paid full attention to are basic-level non-pharmaceutical interventions, among which the periodic development should be required to be modularized patient education. In terms of self-management skills, the programmatic training process must be emphasized, and the implementation of exercise pre-

scriptions must comply with standardized specifications. Differentiated designs should be applied to the formulation of weight loss plans for overweight people. The use of nonsteroidal anti-inflammatory drugs constitutes the core component of drug treatment. Conventional treatment methods include the injection of corticosteroids in the articular cavity. When the disease progresses to the end stage, the final choice often evolves into surgical interventions. Examples show that the effect of improving quality of life has been clinically confirmed, and the severity of symptoms has indeed been reduced through these standard therapies. It can be seen that there are still obvious shortcomings in improving cartilage tissue structure reconstruction. What needs to be carried out in depth is the research on signal path related mechanisms based on JAK/STAT, PI3K/AKT/mTOR and other signal pathways. The existing research data support that the special value of macrophage polarization phenomenon is reflected in the research field of M2 type activation process. It can be seen that the direction of screening out novel drug molecules is to promote the ability to transform M1 to M2.

Funding

Guangxi Natural Fund Project (2022JJA140041): Project name: Exploring the heterogeneity of meniscus endothelial cells and the molecular pathogenic mechanism in osteoarthritis based on single-cell transcriptome sequencing technology.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Neogi, T. and Zhang, Y. (2013) Epidemiology of Osteoarthritis. *Rheumatic Disease Clinics of North America*, **39**, 1-19. https://doi.org/10.1016/j.rdc.2012.10.004

[2] Heidari, B. (2011) Knee Osteoarthritis Prevalence, Risk Factors, Pathogenesis and Features: Part I. *Caspian Journal of Internal Medicine*, **2**, 205-212.

[3] Sun, X., Zhen, X., Hu, X., Li, Y., Gu, S., Gu, Y., *et al.* (2019) Osteoarthritis in the Middle-Aged and Elderly in China: Prevalence and Influencing Factors. *International Journal of Environmental Research and Public Health*, **16**, Article 4701. https://doi.org/10.3390/ijerph16234701

[4] Katz, J.N., Arant, K.R. and Loeser, R.F. (2021) Diagnosis and Treatment of Hip and Knee Osteoarthritis. *JAMA*, **325**, Article 568. https://doi.org/10.1001/jama.2020.22171

[5] Nowaczyk, A., Szwedowski, D., Dallo, I. and Nowaczyk, J. (2022) Overview of First-Line and Second-Line Pharmacotherapies for Osteoarthritis with Special Focus on Intra-Articular Treatment. *International Journal of Molecular Sciences*, **23**, Article 1566. https://doi.org/10.3390/ijms23031566

[6] Bashir, S., Sharma, Y., Elahi, A. and Khan, F. (2016) Macrophage Polarization: The Link between Inflammation and Related Diseases. *Inflammation Research*, **65**, 1-11. https://doi.org/10.1007/s00011-015-0874-1

[7] Yan, L., Wang, J., Cai, X., Liou, Y., Shen, H., Hao, J., *et al.* (2024) Macrophage Plasticity: Signaling Pathways, Tissue Repair, and Regeneration. *MedComm*, **5**, e658.

https://doi.org/10.1002/mco2.658

[8] Yuan, Z., Jiang, D., Yang, M., Tao, J., Hu, X., Yang, X., *et al.* (2024) Emerging Roles of Macrophage Polarization in Osteoarthritis: Mechanisms and Therapeutic Strategies. *Orthopaedic Surgery*, **16**, 532-550. https://doi.org/10.1111/os.13993

[9] Zhang, H., Lin, C., Zeng, C., Wang, Z., Wang, H., Lu, J., *et al.* (2018) Synovial Macrophage M1 Polarisation Exacerbates Experimental Osteoarthritis Partially through R-Spondin-2. *Annals of the Rheumatic Diseases*, **77**, 1524-1534. https://doi.org/10.1136/annrheumdis-2018-213450

[10] Fahy, N., de Vries-van Melle, M.L., Lehmann, J., Wei, W., Grotenhuis, N., Farrell, E., *et al.* (2014) Human Osteoarthritic Synovium Impacts Chondrogenic Differentiation of Mesenchymal Stem Cells via Macrophage Polarisation State. *Osteoarthritis and Cartilage*, **22**, 1167-1175. https://doi.org/10.1016/j.joca.2014.05.021

[11] Porta, C., Riboldi, E., Ippolito, A. and Sica, A. (2015) Molecular and Epigenetic Basis of Macrophage Polarized Activation. *Seminars in Immunology*, **27**, 237-248. https://doi.org/10.1016/j.smim.2015.10.003

[12] Weisser, S.B., McLarren, K.W., Kuroda, E. and Sly, L.M. (2013) Generation and Characterization of Murine Alternatively Activated Macrophages. In: Helgason, C. and Miller, C., Eds., *Methods in Molecular Biology*, Humana Press, 225-239. https://doi.org/10.1007/978-1-62703-128-8_14

[13] Canton, J. (2014) Phagosome Maturation in Polarized Macrophages. *Journal of Leukocyte Biology*, **96**, 729-738. https://doi.org/10.1189/jlb.1mr0114-021r

[14] Sica, A. and Mantovani, A. (2012) Macrophage Plasticity and Polarization: In Vivo Veritas. *Journal of Clinical Investigation*, **122**, 787-795. https://doi.org/10.1172/jci59643

[15] Van den Bossche, J., Neele, A.E., Hoeksema, M.A. and de Winther, M.P.J. (2014) Macrophage Polarization. *Current Opinion in Lipidology*, **25**, 367-373. https://doi.org/10.1097/mol.0000000000000109

[16] Patel, U., Rajasingh, S., Samanta, S., Cao, T., Dawn, B. and Rajasingh, J. (2017) Macrophage Polarization in Response to Epigenetic Modifiers during Infection and Inflammation. *Drug Discovery Today*, **22**, 186-193. https://doi.org/10.1016/j.drudis.2016.08.006

[17] Krausgruber, T., Blazek, K., Smallie, T., Alzabin, S., Lockstone, H., Sahgal, N., *et al.* (2011) IRF5 Promotes Inflammatory Macrophage Polarization and TH1-TH17 Responses. *Nature Immunology*, **12**, 231-238. https://doi.org/10.1038/ni.1990

[18] Zhang, H., Cai, D. and Bai, X. (2020) Macrophages Regulate the Progression of Osteoarthritis. *Osteoarthritis and Cartilage*, **28**, 555-561. https://doi.org/10.1016/j.joca.2020.01.007

[19] Sánchez-Martín, L., Estecha, A., Samaniego, R., Sánchez-Ramón, S., Vega, M.Á. and Sánchez-Mateos, P. (2011) The Chemokine CXCL12 Regulates Monocyte-Macrophage Differentiation and RUNX3 Expression. *Blood*, **117**, 88-97. https://doi.org/10.1182/blood-2009-12-258186

[20] LijiangTao, L., Minjuan, H., Yisheng, L., Jie, Z. and Yili, Y. (2025) Serum CXCL12 and S100A12 Levels in Peripheral Blood Fluid and Their Correlation with Severity in Patients with Knee Osteoarthritis. *Journal of Medical Biochemistry*, **44**, 11-16. https://doi.org/10.5937/jomb0-46310

[21] Song, G., Ouyang, G. and Bao, S. (2005) The Activation of AKT/PKB Signaling Pathway and Cell Survival. *Journal of Cellular and Molecular Medicine*, **9**, 59-71. https://doi.org/10.1111/j.1582-4934.2005.tb00337.x

[22] Vergadi, E., Ieronymaki, E., Lyroni, K., Vaporidi, K. and Tsatsanis, C. (2017) AKT Signaling Pathway in Macrophage Activation and M1/M2 Polarization. *The Journal of Immunology*, **198**, 1006-1014. https://doi.org/10.4049/jimmunol.1601515

[23] Jafari, M., Ghadami, E., Dadkhah, T. and Akhavan-Niaki, H. (2019) PI3K/AKT Signaling Pathway: Erythropoiesis and Beyond. *Journal of Cellular Physiology*, **234**, 2373-2385. https://doi.org/10.1002/jcp.27262

[24] Engelman, J.A., Luo, J. and Cantley, L.C. (2006) The Evolution of Phosphatidylinositol 3-Kinases as Regulators of Growth and Metabolism. *Nature Reviews Genetics*, **7**, 606-619. https://doi.org/10.1038/nrg1879

[25] Litherland, G.J., Dixon, C., Lakey, R.L., Robson, T., Jones, D., Young, D.A., *et al.* (2008) Synergistic Collagenase Expression and Cartilage Collagenolysis Are Phosphatidylinositol 3-Kinase/AKT Signaling-Dependent. *Journal of Biological Chemistry*, **283**, 14221-14229. https://doi.org/10.1074/jbc.m710136200

[26] Tang, F., Wang, Y., Hemmings, B.A., Rüegg, C. and Xue, G. (2018) PKB/AKT-Dependent Regulation of Inflammation in Cancer. *Seminars in Cancer Biology*, **48**, 62-69. https://doi.org/10.1016/j.semcancer.2017.04.018

[27] Tao, H., Cheng, L. and Yang, R. (2020) Downregulation of miR-34a Promotes Proliferation and Inhibits Apoptosis of Rat Osteoarthritic Cartilage Cells by Activating PI3K/AKT Pathway. *Clinical Interventions in Aging*, **15**, 373-385. https://doi.org/10.2147/cia.s241855

[28] Guo, Y., Wang, P., Hu, B., Wang, L., Zhang, Y. and Wang, J. (2024) Kongensin a Targeting PI3K Attenuates Inflammation-Induced Osteoarthritis by Modulating Macrophage Polarization and Alleviating Inflammatory Signaling. *International Immunopharmacology*, **142**, Article 112948. https://doi.org/10.1016/j.intimp.2024.112948

[29] Li, Y., Wang, G., Liu, P., Zhang, L., Hu, H., Yang, X., *et al.* (2024) The Impact of Benzophenone-3 on Osteoarthritis Pathogenesis: A Network Toxicology Approach. *Toxicology Research*, **13**, tfae199. https://doi.org/10.1093/toxres/tfae199

[30] Lu, W., He, Z., Shi, J., Wang, Z., Wu, W., Liu, J., *et al.* (2020) AMD3100 Attenuates Post-Traumatic Osteoarthritis by Maintaining Transforming Growth Factor-B1-Induced Expression of Tissue Inhibitor of Metalloproteinase-3 via the Phosphatidylinositol 3-Kinase/AKT Pathway. *Frontiers in Pharmacology*, **10**, Article ID: 1554. https://doi.org/10.3389/fphar.2019.01554

[31] Tang, C., Lei, X., Xiong, L., Hu, Z. and Tang, B. (2021) HMGA1B/2 Transcriptionally Activated-Pou1f1 Facilitates Gastric Carcinoma Metastasis via CXCL12/CXCR4 Axis-Mediated Macrophage Polarization. *Cell Death & Disease*, **12**, Article No. 422. https://doi.org/10.1038/s41419-021-03703-x

[32] Zhang, M., He, Y., Sun, X., Li, Q., Wang, W., Zhao, A., *et al.* (2014) A High M1/M2 Ratio of Tumor-Associated Macrophages Is Associated with Extended Survival in Ovarian Cancer Patients. *Journal of Ovarian Research*, **7**, Article No. 19. https://doi.org/10.1186/1757-2215-7-19

[33] Wei, J., Yang, X., Zhao, L., Liu, X., Ge, X., Zhang, J., *et al.* (2025) Fire Needling Acupuncture Attenuates Synovial Inflammation and Cartilage Degeneration in Knee Osteoarthritis via SDF-1/CXCR4-Mediated Macrophage Polarization. *Clinical Rheumatology*. https://doi.org/10.1007/s10067-025-07612-8

[34] Dai, Y., Liu, S., Xie, X., Ding, M., Zhou, Q. and Zhou, X. (2019) Microrna-31 Promotes Chondrocyte Proliferation by Targeting C-X-C Motif Chemokine Ligand 12. *Molecular Medicine Reports*, **19**, 2231-2237. https://doi.org/10.3892/mmr.2019.9859

[35] Lu, J., Wu, Z. and Xiong, Y. (2021) Knockdown of Long Noncoding RNA HOTAIR

Inhibits Osteoarthritis Chondrocyte Injury by miR-107/CXCL12 Axis. *Journal of Orthopaedic Surgery and Research*, **16**, Article No. 410. https://doi.org/10.1186/s13018-021-02547-7

[36] Zheng, S., Sun, C., Wen, Z., Liu, W., Li, X., Chen, T., *et al.* (2022) Decreased Serum CXCL12/SDF-1 Concentrations May Reflect Disease Severity of Non-Traumatic Osteonecrosis of Femoral Head. *Clinica Chimica Acta*, **529**, 87-95. https://doi.org/10.1016/j.cca.2022.02.009

[37] Wang, Z., Zhu, P., Li, H., Ye, B., Luo, Q., Cheng, J., *et al.* (2025) Sodium Hyaluronate-PDGF Repairs Cartilage and Subchondral Bone Microenvironment via HIF-1α-VEGF-Notch and SDF-1-CXCR4 Inhibition in Osteoarthritis. *Journal of Cellular and Molecular Medicine*, **29**, e70515. https://doi.org/10.1111/jcmm.70515

[38] Yang, K., Xie, Q., Tang, T., Zhao, N., Liang, J., Shen, Y., *et al.* (2023) Astragaloside IV as a Novel CXCR4 Antagonist Alleviates Osteoarthritis in the Knee of Monosodium Iodoacetate-Induced Rats. *Phytomedicine*, **108**, Article 154506. https://doi.org/10.1016/j.phymed.2022.154506