R E V I E W

Effects of Immune Cells and Cytokines on Different Cells in OA

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Abstract: The pathological manifestations of osteoarthritis (OA) involve the destruction of articular cartilage, synovial sac thickening, subchondral osteosclerosis and osteophyte formation. The types of cells involved in OA include chondrocytes, osteoblasts, osteoclasts, synovial fibroblasts, T cells, macrophages, and mesenchymal stem cells (MSCs). There are many effects of immune cells in OA, and innate immune cells such as dendritic cells and macrophages have significant roles in the pathogenesis of OA. On the other hand, the role of adaptive immune cells such as T-cell subsets, B-cell subsets, and NK cells is important in OA pathogenesis. MSCs not only play a key role in the dynamic balance and repair of OA tissue but also inhibit the immune system. Therefore, MSCs are a new potential therapeutic agent for OA. This review mainly summarizes the effects of various immune cells and cytokines on different cells in OA to find new effective therapeutic targets for OA therapy based on the immune system and cytokine activity sites to prevent the development of OA.

Keywords: osteoarthritis, immune cells, chondrocytes, mesenchymal stem cells, osteoblasts

Introduction

Osteoarthritis (OA) is a joint degenerative disease that can cause chronic pain and motor dysfunction and affects approximately 300 million people worldwide, which adds a serious economic burden to patients and society.[1] OA is caused by mechanical injury of joints and is also closely related to ageing.

Thus far, researchers have found that OA is much more complex than abrasive diseases and that metabolic and biochemical mechanisms are involved in development.[2] Ageing, obesity, and joint injury are the main risk factors for the progression of OA.[3] Although there have been many studies on the pathogenesis of OA, there is still no definite conclusion, and so there is no intervention to delay the progression of this disease.[4] Thus, there is a need for further examination of the pathogenesis of OA to meet future clinical demands for new treatments.

The pathogenesis of OA involves the destruction of articular cartilage, synovial bursa thickening, subchondral osteosclerosis and osteophyte formation.[5] The interaction between different tissues and cells is involved in these pathological manifestations. Understanding the complex interactions between different tissues and cells and their role in the initiation and progression of OA is important for clarifying the pathogenic mechanism of OA. The interaction and homeostasis between different tissues and cells in the joint system are prerequisites for the function of the joint system. Many factors affect the health of joints and bones, including the immune system, sex hormones, and the microbiota.[6,7] During the occurrence and development of OA, osteochondral factors closely interact with various molecules in the immune system to maintain the health of bones and joints.[8] Inflammatory mediators not only lead to abnormal tissue structure but also aggravate cartilage injury in OA.[9] Therefore, examining the effect of immune cells on different tissue cells in the pathogenesis of OA may provide new treatment strategies for OA. The purpose of this paper was to explore the effect of immune cells on different tissue cells in OA and provide new ideas for the treatment of OA.

Tissue and Cell Types Involved in the Pathogenesis of OA (Excluding the Immune System)

Cartilage and Chondrocytes

Articular cartilage plays a role in lubricating joints and bearing weight associated with joint activity.[10] Due to the limited supply of oxygen and nutrients, the regeneration ability of articular cartilage is low.[11] Chondrocytes can form an extracellular matrix (ECM) composed of proteoglycans and type II collagen.[12] In addition to chondrocytes, cartilage stem/progenitor cells (CSPCs), which account for approximately 10% of total cells, have recently been found in OA cartilage.[13,14] In recent years, single-cell RNA-seq analysis has shown various groups of chondrocytes in late OA, including steady-state chondrocytes, effector chondrocytes, prehypertrophic chondrocytes, and fibrochondrocytes.[15] When the metabolic state of chondrocytes changes, the synthesis and degradation of collagen become out of balance, which affects the function of joints and leads to osteoarthritis.

The development of subchondral osteosclerosis and osteophytes may gradually lead to dysfunction of the entire joint. In early-stage OA, the cartilage surface remains intact.[16] The first changes occur in the molecular composition of tissues and the ECM, which are characterized by a transient chondrocyte proliferative response and an increase in ECM protein synthesis, including collagen type II (Col II) and aggrecan.[16] With the development of OA, the synthesis of degrading proteases increases, leading to increased catabolic activity and decreased proteoglycan content. Subsequently, Col II is degraded, and its fragments stimulate several proteins associated with the catabolic state, such as MMPs and aggrecanases, which are members of the a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) family, and this change is accompanied by increased expression levels of inflammatory cytokines (IL-1), stress and apoptosis markers (caspases-3 and −9 and Bcl-2), and transcription factors [runt-related transcription factor 2 (Runx2) and Sox9].[17–19] Changes in articular cartilage composition and structure further stimulate chondrocytes to produce more catabolic factors involved in cartilage degradation. As the proteoglycan and collagen network breaks down, cartilage integrity is disrupted.[20] Subsequently, apoptosis occurs in articular chondrocytes, ultimately leading to the complete loss of articular cartilage.[21]

Cells in Subchondral Bone

Although subchondral bone destruction occurs during cartilage degeneration, subchondral bone is not abnormal in all patients with OA.[22] Moreover, in osteoarthritis in elderly individuals, the metabolic imbalance in chondrocytes occurs before abnormal subchondral bone remodelling.[23] In contrast, early microdamage of subchondral bone was first detected in trauma-induced OA phenotypes.[24] The microstructural changes in subchondral bone in OA include bone marrow oedema-like lesions and osteophytes caused by histopathological changes.[25] Osteoblasts differentiate from mesenchymal cells. During the pathogenesis of OA, the phenotype of osteoblasts changes, as indicated by increases in transforming growth factor (TGF)-β1,[26] vascular endothelial growth factor (VEGF)[27] and alkaline phosphatase activity. These changes can lead to osteoclast formation. Osteoclasts are mainly responsible for bone resorption.[28]

The Synovium and Synovial Cells

The changes in articular cartilage and bone on X-ray are one of the diagnostic criteria of OA, and little attention is given to synovial changes. In fact, the morphology and cellular composition of the synovium is also one of the manifestations of OA. Synovial changes in OA are classified as hyperplasia (chorionic hyperplasia), fibrosis (capsular fibrosis) and inflammation (diffuse inflammation and lymphatic plasma cell infiltration and accumulation), which usually coexist.[29] Synovitis has the features of fibroblast-like synoviocyte (FLS) proliferation and macrophage recruitment, leading to the proliferation of the inner layer of the synovium.[30] The subsynovial layer is also rich in macrophages, mast cells (MCs), B cells, and endothelial cells.[31] In addition, MCs are related to inflammation and cartilage destruction in OA.[32]

Adipose Cells and Adipose Cytokines

A possible source of adipocytokines in the knee joint is the subpatellar fat pad.[33] As an endocrine organ, adipose tissue can produce adipose cytokines that directly cause abnormalities in the structure and function of articular cartilage in

obese individuals.[34] In addition to cartilage injury, the role of adipose cytokines produced in the joint can further worsen the condition of the joint. Among the many adipose cytokines, the most typical are leptin, resistin, adiponectin, vaspin, omentin, visfatin and adipsin.[35]

Mesenchymal Stem Cells

Pluripotent stem cells exist in bone marrow and adipose tissue,[36] and bone marrow-derived mesenchymal stem cells (BMSCs) are the main pluripotent stem cells.[37] In vitro, synovial mesenchymal stem cells (SMSCs) showed high cartilage differentiation abilities.[38] Adipose tissue MSCs (AMSCs) can regulate inflammation. Current evidence suggests that AMSCs regulate the local microenvironment, which makes them conducive to repair, thereby delaying cartilage degeneration.[39]

Immune Cells

The main role of the immune system in organisms is to remove antigens, maintain environmental stability, and play an important role in safeguarding the health of the organism.[40] The innate immune system consists of cells and related mechanisms that can resist infection in a nonspecific way. Cells in the innate immune system recognize and act on pathogens nonspecifically. Unlike the acquired immune system, the innate immune system does not provide lasting protective immunity but exists in all animals and plants as a rapid response to infection. Innate immune cells include dendritic cells, macrophages and other cells. Adaptive immune cells are produced by individuals who are stimulated by antigenic foreign bodies in the external environment and include T-cell subsets, B-cell subsets and NK cells. T lymphocytes are a kind of haematopoietic cell. Studies have shown that there are changes in surface receptors of T lymphocytes, and the main factor affecting their functions is their differentiation status.[41] T helper (Th) cells can interact with other immune cells (such as B lymphocytes) based on cytokines and participate in immune regulation.[42] Th cells include multiple subpopulations. Th1 cells are polarized by interleukin (IL)-12 and secrete interferon-gamma (IFN γ)- and IL-2-related cytokines, providing support for the immune response.[43] Tumour necrosis factor-α (TNF-α) can mediate an increase in receptor activator of nuclear factor-kappa B ligand (RANKL) expression in macrophages, thus stimulating osteoclast formation.[44] B lymphocytes mature in bone marrow through C-X-C chemokine ligand 12 (CXCL12) signals, and their main function is to produce antibodies against pathogens.[45] However, B lymphocytes also provide antigens for T-cell activation, such as granulocyte colony-stimulating factor (G-CSF).[46] G-CSF can increase the proliferation of osteoclast progenitor cells.[47] MCs are immune cells that exist in tissue and are important in allergic reactions.[48] In addition, MCs can synthesize and release mediators scratched novo, including IL-6, TNF-α and VEGF. Previous research has shown that MCs are important in the regulation of bone turnover.[49] Inflammatory mediators expressed and secreted by neutrophils and osteoclasts can affect MSCs in different ways.[50] In addition, macrophages have two phenotypes: a proinflammatory state (called M1) and a pro-regenerative state (called M2).[51] Macrophages can also affect osteocytes through paracrine signal transduction or direct intercellular contact.[52]

Effect of Immune Cells on Chondrocytes

Chondrocytes are the basic components of cartilage tissue and can secrete ECM to maintain normal cartilage function. Many immune cells can affect the metabolism of chondrocytes by secreting cytokines. For example, macrophages, which are innate immune cells, can secrete IL-1β. IL-1β stimulates the production of a number of inflammatory mediators implicated in OA pathology. For instance, treatment of chondrocytes with these cytokines upregulates the expression of genes encoding inducible nitric oxide synthase (iNOS), soluble phospholipase A2, cyclooxygenase 2 (COX-2) and microsomal prostaglandin E synthase 1 and stimulates the release of nitric oxide (NO) and prostaglandin E2 (PGE2). NO and PGE2 contribute to articular inflammation and destruction by enhancing the activation and production of MMPs, inhibiting the synthesis of anabolic macromolecules such as collagen and proteoglycan, inhibiting the production of IL-1ra, and promoting chondrocyte apoptosis. IL-1β also induces the production of reactive oxygen species (ROS) such as NO and the superoxide anion, that generate hydrogen peroxide, peroxy nitrate and hydroxyl radicals,[53] which contribute to cartilage degradation. In addition, IL-1β downregulates the expression of antioxidant enzymes that scavenge ROS, including superoxide dismutase, catalase and glutathione peroxidase,[54] thereby accelerating the damaging effects of ROS

on cartilage. IL-1β affects the metabolism of chondrocytes through many signalling pathways. Most IL-1β is produced by macrophages, and some is produced by B and T cells and natural killer (NK) cells.[55] Activation of extracellular signal-regulated kinase (ERK) by IL-1β can reduce the production of ECM in cartilage.[56] In addition, IL-1β induces ECM degradation by inducing collagenase and aggrecanases,[57] which leads to chondrocyte hypertrophy and dedifferentiation and ultimately chondrocyte apoptosis.[58] Another dominant pathway in IL-1β-mediated OA progression is nuclear factor-kappa B (NF-κB), which, when activated, inhibits the expression of type II collagen and affects the metabolism of chondrocytes[59] (Figure 1). NF-κB regulates chondrocyte hypertrophy mainly through SRY-box transcription factor 9 (SOX9), bone morphogenetic protein 2 (BMP2), matrix metalloproteinases (MMPs) and HIF-2α.[60,61] For example, it has been reported that NF-κB is directly involved in the regulation of matrix metalloproteinase (MMP) expression, but a recent study showed that hypoxia-inducible factor-2α (HIF-2α) was mediated by NF-κB and involved in the development of OA.[62] More information about the role of the NF-κB signalling pathway in OA cartilage destruction can be found in other studies.[59,63,64]

TNF-α, which is mainly secreted by active macrophages and monocytes, is a pluripotent cytokine that is closely related to immune regulation. During the pathological changes of OA, these two receptors provide support for signal transduction.[65] TNF-α also induces the degradation of extracellular matrix (ECM) by inducing collagenase and aggregating enzymes, which is consistent with the effects of IL-1β.[66] In addition, Fujihara et al found that macrophages blocked the maturation of chondrocytes[67] (Figure 1).

Activated T cells can produce IL-6, including membrane binding (mbIL-6R) and soluble (sIL-6R). The exact role of IL-6 in OA is difficult to determine because IL-6 has beneficial and harmful effects. An in vitro study of chondrocytes showed that TIMP-1 could be induced by IL-6 alone, and the effect was more obvious when chondrocytes were also treated with sIL-6R.[68] Moreover, animal experiments showed that the prevalence and severity of OA in IL-6-knockout mice were higher than those in wild-type mice. Intra-articular injection of IL-6 can induce OA-like cartilage lesions.[69,70] IL-6 levels in the synovial fluid of end-stage OA patients was significantly higher than that of healthy controls, and IL-6 levels in synovial fluid are known to be associated with pain in OA patients.[71,72] In addition, the reduction in congenital formation of IL-6 is related to a lower risk of OA in the hand, as well as a lower risk of OA in the knee and hip joints.[73]
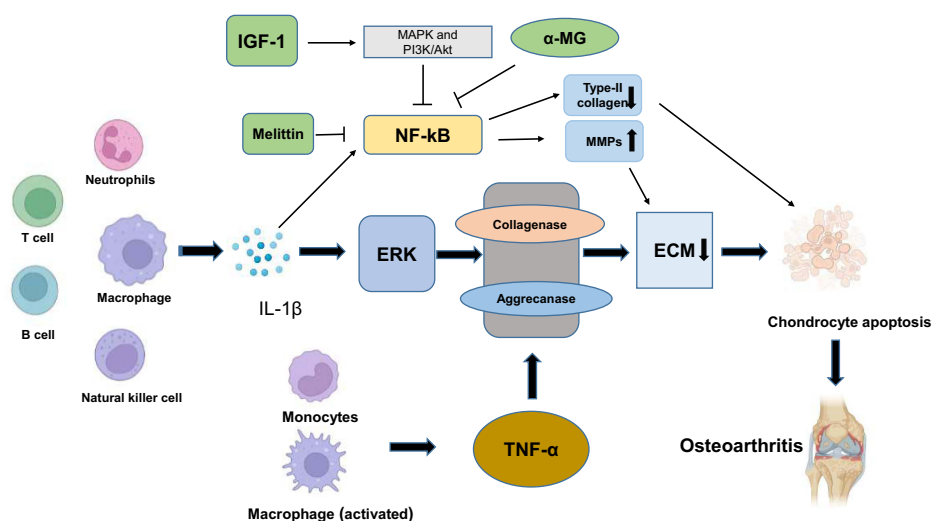

Figure 1 Effect of immune cells on chondrocyte apoptosis. Macrophages, T cells, B cells, NK cells and neutrophils can secrete IL-1β. IL-1β activates extracellular signal-regulated kinase (ERK) to reduce the production of cartilage ECM. TNF-α is secreted by monocytes and macrophages and results in the degradation of ECM by inducing collagenase and aggrecanase. In addition, IL-1β induces ECM degradation by inducing collagenase and aggrecanase, which leads to chondrocyte hypertrophy and dedifferentiation and eventually to chondrocyte apoptosis, resulting in osteoarthritis (OA). Another important signalling pathway by which IL-1β mediates the progression of OA is NF-κB. Activated IL-1β inhibits the expression of type II collagen and affects chondrocyte metabolism. In addition, MMPs degrade the ECM in a manner dependent on NF-κB, which leads to the degradation of chondrocytes. Insulin-like growth factor-1 (IGF-1) inhibits apoptosis in chondrocytes by regulating the MAPK and PI3K/Akt signalling pathways and inhibiting the NF-κB signalling pathway. Melittin inhibits the development of OA by inhibiting the decrease in type II collagen expression induced by NF-κB. In addition, alpha-mangostin (α-MG) inhibits the NF-κB pathway to limit the development of OA.

IL-17 produced by activated CD4+ lymphocytes can promote inflammation, which can activate T lymphocytes, especially in the early stage of inflammation, acting on a variety of cells and tissues.[74] IL-17 can upregulate catabolic factors and anabolic factors in isolated chondrocytes and induce cartilage degradation.[75] In addition, IL-1β, TNF-α and IL-6 promote the degradation of ECM and lead to the destruction of articular cartilage by stimulating the production of MMPs and aggregation proteases (ADAMTS), which are dominant in the progression of OA.[76]

Immune Cells Involved in Bone Remodelling in Subchondral Bone

Changes in subchondral bone caused by dynamic bone remodelling are an important link in the pathogenesis of OA. Osteoblasts and osteoclasts are important cells in bone remodelling. A recent study showed that reducing osteoclast formation and bone resorption could slow bone remodelling in subchondral bone and reverse the progression of osteoarthritis in mice.[77] For example, the administration of diarylbutyl phthalate (DP) blocked the formation of over-activated osteoclasts in subchondral bone and improved articular cartilage degeneration.[78]

Osteoclasts are a specific type of terminally differentiated cell.[79] Relevant experimental research showed that the system composed of osteoprotegerin (OPG) and RANKL plays an important role in regulating the formation of these cells and directly determines the differentiation of osteoclasts.[80] The combination of RANK and RANKL can promote the maturation of these cells, while OPG can inhibit the combination of the two, thereby inhibiting the maturation process of osteoclasts.[81] In OA, dysfunction of the OPG/RANK/RANKL regulatory system is closely related to histological changes in subchondral bone, and a proinflammatory osteoblast phenotype appears.[82]

B cells can regulate the maturation and differentiation of osteoclasts based on this system, which is also closely related to bone metabolism.[83,84] IL-7 is mainly derived from BM stromal cells.[85] Some experimental studies have shown that IL-7 has a significant effect on regulating bone homeostasis and is closely related to the integrity of bone structure.[86] Compared with that of normal mice, the bone mass of mice with IL-7 overexpression decreased, and osteoclasts increased, which confirmed its regulatory effect.[87] Toraldo's research shows that this cytokine could not promote bone absorption in T-cell-deficient nude mice. It has been found that G-CSF secreted by B cells can increase the proliferation of osteoclast progenitor cells. Activated B cells can also activate osteoclast formation by secreting RANKL.[88] Under physiological conditions, osteoprotegerin (OPG) produced by B cells can inhibit osteoclast differentiation.[89] In addition, coculturing M1 macrophages and MSCs could reduce the expression of OPG, which may have an indirect effect on osteoclast formation.[90] Proinflammatory cytokines secreted by macrophages may mediate direct effects on osteoclast formation, and these cytokines have been shown to increase osteoclast production[91] (Figure 2).

The effect of T lymphocytes on bone metabolism can be determined by the regulation of osteoclasts. A variety of cytokines secreted by T helper (Th) 17 cells, Treg cells, IL-17, and IL-22 can further induce the expression of M-CSF, RANKL and TNF-α, thereby promoting osteoclast maturation[92] (Figure 2). It has been reported that TH17 cells stimulate the recruitment of osteoclast progenitor cells by increasing chemokines that originate from bone marrow mesenchymal stromal cells.[93] Relevant experimental studies showed that IL-17 could promote the expression of RANK in progenitor cells and increase its sensitivity to RANKL stimulation, thus playing a role in regulating bone metabolism.[94] The mechanism of IL-17 in osteoclasts is still unclear, and no clear and consistent conclusion has been reached thus far. The existing experimental results are contradictory.[95] Cytokines released by Th1 and Th2 subtypes can promote the development of osteoclast precursors and reduce bone resorption. Precursors of osteoclasts secrete carbon monoxide, which blocks the proliferation of T lymphocytes.[96] Treg cells can also inhibit bone resorption, thereby promoting osteoclast apoptosis.[97]

Osteoblasts are dominant in bone synthesis and metabolism. Some scholars have found that abnormal expression of OPG and RANKL in osteoblasts may cause bone remodelling and reduced mineralization.[98] Structural and functional disorders of bone in OA are typically attributed to primary osteoblast dysfunction.[99] In addition, osteoblasts can produce many transcription factors, growth factors and other proteins involved in the pathogenesis of OA.[100] For example, osteoblasts can synthesize indispensable ECM proteins such as type I collagen, bone sialic acid protein, and osteopontin. Osteoblasts are also responsible for mineralizing the matrix through the deposition of phosphates, leading to bone remodelling and osteophyte formation.[100,101]
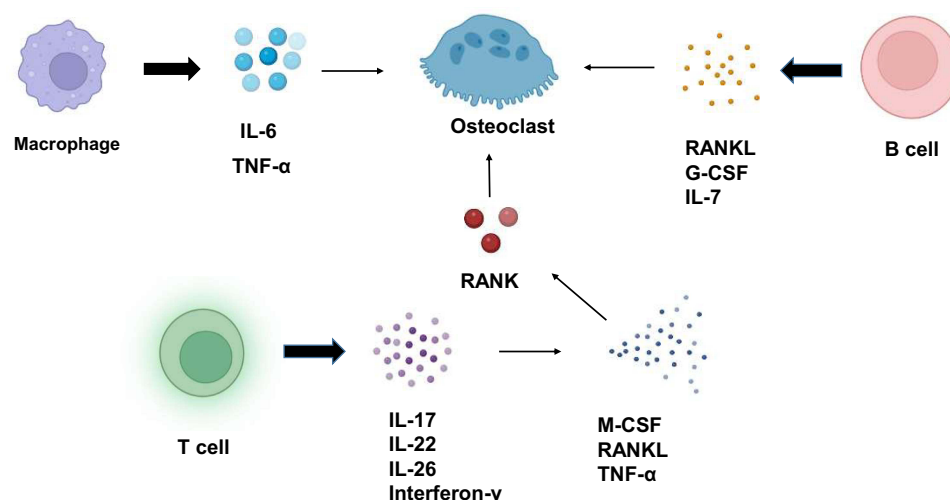
Figure 2 Effect of immune cells on osteoclasts. IL-7 secreted by B cells can increase osteoclasts. The G-CSF secreted by B cells can increase the proliferation of osteoclast progenitor cells and lead to an increase in osteoclasts. Activated B cells can also activate osteoclast formation by secreting RANKL. Proinflammatory cytokines secreted by macrophages can increase osteoclast production. A variety of cytokines secreted by a variety of T cells, such as IL-17 and IL-22, can further induce the expression of M-CSF, RANKL and TNF-α, thereby enhancing RANK levels in osteoclast precursors and promoting osteoclast maturation.

A variety of immune cells can regulate the maturation and activation of osteoblasts, and the corresponding mechanisms are complex. Interferon-γ is secreted by CD4+ T lymphocytes; this cytokine promotes the differentiation of bone marrow mesenchymal stem cells, while the activity of transforming growth factor-β (TGF- β) secreted by CD4+ T lymphocytes is negatively correlated with osteoblast differentiation.[102] IL-17F secreted by Treg cells can strongly promote osteoblastic differentiation in MSCs.[103] TNF-α can indirectly stimulate osteoclast production through RANKL produced by B cells.[104,105] IL-17 can induce the differentiation of MSCs into bone and promote the differentiation of osteoblasts.[106] M2 cells can release osteogenic growth factors such as bone morphogenetic protein 2 (which belongs to the TGF-β family subclass) under certain conditions to promote bone formation.[107] Neutrophils expanded by G-CSF in vitro can induce MSC and osteoblast apoptosis by producing reactive oxygen species (ROS).[108] Moreover, C-C motif chemokine ligand 2 (CCL2) plays an important regulatory role in immune regulation. Studies have shown that this factor binds to the receptor CC-chemokine receptor-2 (CCR2), thereby regulating the status of memory T cells and basophils, which can have a negative impact on immune function.[109] A large number of studies have shown that CCL2 is closely related to bone remodelling.[110] For example, IL-7 secreted by osteoblasts can promote the differentiation of B cells.[111]

Many MC-derived mediators can regulate bone metabolism by preventing osteoblast activity and/or promoting osteoclast production (TNF, IL-6). MCs are important in maintaining the stability of the intraosseous environment.[112] For example, TGF-β can stimulate osteoblast production, and IL-12 and IFN-γ can inhibit osteoclast formation[113] (Figure 3). Endothelial cells and osteoblasts showed that neutrophils induced osteogenic marker expression in osteoblasts in vitro, indicating that neutrophils affected osteoblasts.[114] In addition, an increase in the mineral deposition of osteoblasts was found in this model, indicating that neutrophils may undergo osteogenesis.[114]

Immune Regulation in Synovitis

Synovial fibroblasts (SFs) play an important role in synovitis. SFs secrete inflammatory cytokines and upregulate surface markers.[115,116] These cells act on T cells, dendritic cells, and B cells.[117,118] In addition, a study has shown that activated SFs restrict the proliferation and secretion of B cells.[119] Moreover, researchers have observed a negative feedback mechanism activated by SFs in macrophages.[120]

Compared with healthy synovium, OA synovium has an abundant T-cell population.[121,122] The proportion of T cells in OA synovium is second only to macrophages and may account for 20–25% of inflammatory cells.[123] IL-17 is mainly produced by Th17 subtype of helper T cells.[124] Previous studies have shown that IL-17 family cytokines induce the most effective changes in synovial transcriptional groups and chondrocytes in patients with OA.[125] IL-17RA and IL-17RC are
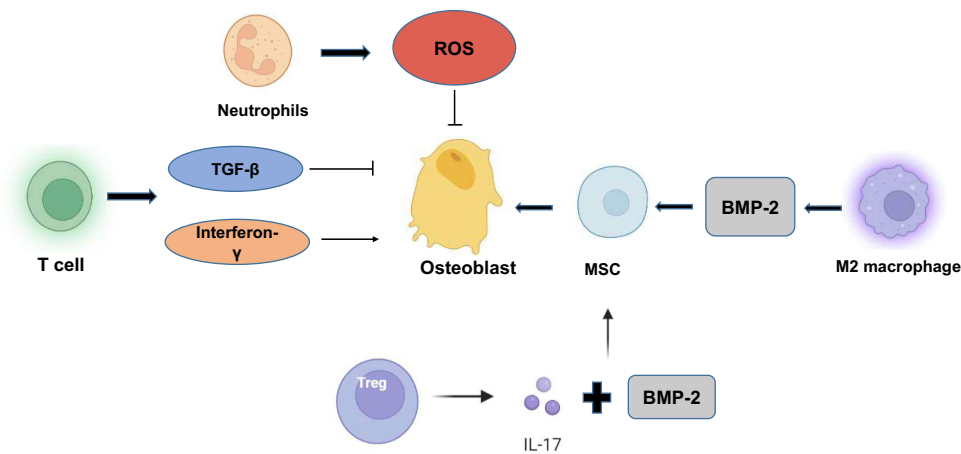
Figure 3 Effect of immune cells on osteoblasts. Interferon-γ can promote bone marrow mesenchymal stem cells to differentiate into osteoblasts, and the activity of TGF-β is negatively correlated with osteoblast differentiation. IL-17A and BMP-2 are secreted by Treg cells and can promote osteoblast differentiation by promoting MSC production. M2 macrophages can produce BMP-2 to promote bone formation. Neutrophils can induce apoptosis in osteoblasts by producing reactive oxygen species (ROS).

the main targets of IL-17, and IL-17RA is highly expressed in the inflamed synovial fibroblasts of patients.[126] IL-4, which is secreted by Th2 cells and MCs, is an effective regulator of the immune system and is often referred to as a prototype immunoregulatory cytokine.[127] The number of CD4 T cells in the subsynovial layer of OA patients was higher than that in the control group, which suggests that the production of IL-4 was mainly dependent on Th2 cells infiltrating the synovium.[128] IL-4 has a strong protective effect on cartilage. This factor inhibits the secretion of MMPs, so it can inhibit the degradation of proteoglycans.[129]

Synovitis is characterized by macrophage accumulation in the intimal lining[130] (Figure 4). As immune cells, synovial macrophages dominate the symptoms and structural progression of OA.[131] Macrophages are also associated with the severity of OA and joint symptoms.[132] In addition, macrophages can produce chemokines in inflamed joints.[133] These cells can be activated by a variety of stimuli, such as proinflammatory factors (IL-1β, TNF-α and IL-6) and immunoregulatory factors.[134,135] Moreover, IL-1β increases the levels of chemokines such as IL-8 and CCL2 and the expression of the cytokine IL-6, which causes synovitis and further produces more IL-1β.[136] Activated macrophages are regulated by the mTOR,[137] NF-κB A,[138] and JNK pathways. In OA synovial tissue and synovial fluid, macrophages are polarized into the M1 or M2 subtypes.[139] Relevant experimental studies showed that synovial macrophages can release large
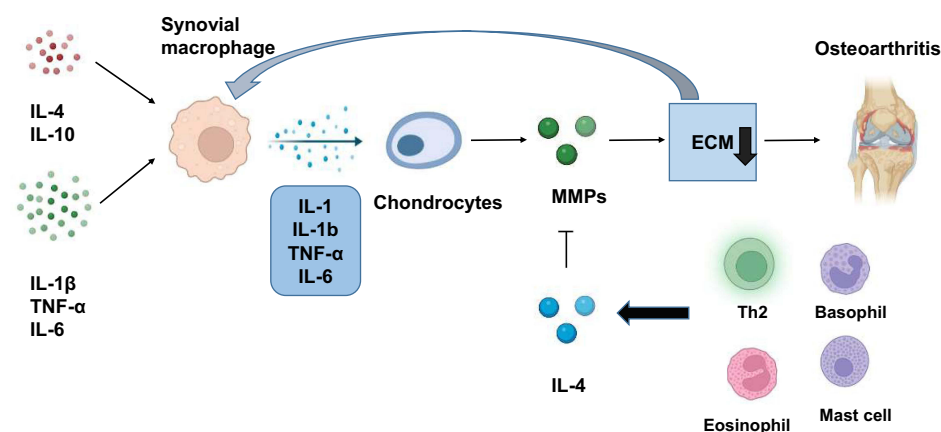

Figure 4 Effect of synovial macrophages on the pathogenesis of OA. Synovial macrophages can be activated by proinflammatory factors and immunoregulatory factors. Activated synovial macrophages can produce cytokines such as IL-1β, TNF-α, and IL-1, which promote chondrocytes to produce excessive matrix metalloproteinases (MMPs), leading to the degradation of ECM and the progression of OA. IL-4 is secreted by Th2 and MCs and can effectively inhibit the secretion of MMP to protect cartilage and prevent the progression of OA.

amounts of IL-1β-, TNF-α-, and IL-1-related factors after activation, and these factors can regulate the microenvironment of chondrocytes in many ways and promote the release of large amounts of MMPs, thereby degrading the ECM[140] (Figure 4). The components generated after degradation can activate macrophages, leading an increase in the level of inflammation, further promoting the degradation of cartilage and aggravating the disease.[141–143] The inflamed synovium promotes the release of intercellular adhesion molecule 1 (ICAM-1)- and VCAM-1-related factors. These factors have a certain adhesive effect, which leads to structural changes in the OA synovium.[144]

Adipose Cells and Adipose Cytokines Involved in the Pathological Development of OA

Recent studies have revealed that adipocytokines play an important role in the metabolism of cartilage, synovium and bone.[145,146] In the acute phase of inflammation, leptin has a proinflammatory effect through T-lymphocyte stimulation, resulting in the release of cytokines such as ILs and tumour necrosis factor-α (TNF-α) and increasing the activation levels of NK cells, macrophages and neutrophils.[147] Leptin can increase the anabolic activity of chondrocytes by inducing the expression of IGF-1 and TGF-β at the mRNA and protein levels.[148] Other studies, however, have shown a different view. Leptin upregulated the expression of ADAMTS-4 and ADAMTS-5, resulting in proteoglycan loss in the articular cartilage of rats.[149] The latest data show that leptin induces the gene expression of ADAMTS in human chondrocytes through mitogen-activated protein kinase and the NF-κB signalling pathway, which leads to a subsequent increase in the inflammatory process.[150] Adiponectin can protect articular cartilage by upregulating tissue inhibitor of metalloproteinase and reducing the expression of MMP-13 mediated by IL-1β.[151] Visceral adiponectin is catabolized to articular cartilage. This factor is produced by OA chondrocytes and can increase the activities of MMP-3, ADAMTS-4 and ADAMTS-5 in a rat model.[152] During osteophyte formation, Berry et al found that high leptin levels were related to an increase in bone formation markers.[153] In addition, visceral leptin has been shown to affect osteoblast proliferation and type II collagen production.[154] Adipocytokines can be partially detected in the synovium and synovial fluid of patients with OA. However, it is not clear whether adipocytokines can induce synovitis.[145]

Mesenchymal Stem Cells Treat OA by Regulating the Function of Immune Cells

MSCs are pluripotent cells with a high capacity for self-renewal. According to relevant research, bone marrow and adipose tissue are the most common sources of MSCs, and these stem cells can be found in skeletal muscle,[155] the periosteum[156] and the synovium.[157] MSCs have certain inhibitory effects on the immune system.[158]

MSCs can inhibit the activation of inflammatory M1 macrophages through cell-to-cell contact and paracrine signalling and promote their transformation into the anti-inflammatory M2 phenotype to alleviate arthritis. Moreover, MSCs can reduce the proliferation and cytotoxicity of NK cells, prevent autoreactive antibody generation, inhibit the activation of CD4+ Th1 cells and promote the production of Tregs.[159] In addition, MSCs can induce M1 macrophages to transform them into immunosuppressive cells by producing prostaglandin E2 (PGE2), thus alleviating arthritis and promoting cartilage regeneration.[160] MSC-derived TSC-6 interacts with CD44 on macrophages to reduce TLR2/NF-κB signal transduction, thereby alleviating the secretion of inflammatory mediators.[161,162] MSC-derived PGE2 is a cytokine that regulates effector CD4+ T cells. PGE2 inhibits the production of IFN-γ, thereby reducing inflammation driven by Th1 cells.[163] Spaggiari found that MSCs could prevent the maturation of dendritic cells (DCs).[164] MSC-derived interleukin-1 receptor antagonist (IL-1Ra) has anti-inflammatory effects on cartilage regeneration. When IL-1Ra binds to the corresponding IL-1R, the interaction of IL-1 and IL-1R is blocked. Therefore, chondrocyte apoptosis and the synthesis and chemokines were prevented.[165] In addition to the paracrine mechanism, MSCs can regulate the function of immune cells in a contact-associated manner. For example, MSCs can inhibit the proliferation of activated T cells through cell-to-cell contact.[166] At present, an increasing number of studies have shown that adipose-derived stem cells (ADSCs) can be used to treat articular cartilage injury because these cells are easy to harvest and show high cartilage production capacity. In addition, the exocrine factors derived from ADSCs have cartilage protective and anti-inflammatory properties.[167,168] Exosomes encapsulate various molecular components, mediate communication between

different cells and regulate a variety of biological processes, including the immune response and cell differentiation.[169,170] Therefore, an extracellular vesicle (EV)-mediated delivery system can effectively and efficiently treat OA because it can reactivate ageing MSCs and can be implemented using EVs from super donors. Therefore, the exocrine system may achieve cell-free therapy and provide the same clinical benefits without the potential risks associated with live cell infusions, such as immune rejection.[171] However, low production of exosomes is a great challenge in clinical practice.[172] Pang et al fabricated high-yield exosome-mimicking MSC-derived nanovesicles (MSC-NVs) with enhanced regenerative and anti-inflammatory capabilities.[173] The MSC-NVs were prepared using an extrusion approach and could increase chondrocyte and human bone marrow MSC differentiation, proliferation, and migration, in addition to inducing M2 macrophage polarization.[173]

Since the role of one cytokine in OA does not necessarily depend on the activation of another cytokine, inhibiting one cytokine may not be sufficient to prevent inflammation and the production of matrix-degrading enzymes. Therefore, the application of MSCs and other biotherapy methods that have a variety of anti-inflammatory effects and achieve significant clinical effects in many studies are worthy of future research attention to verify the effects of some anti-inflammatory factors.

Conclusion

The role of the immune system and immune cells in the pathogenesis of osteoarthritis cannot be ignored. However, little is known about the role of the immune system in osteoarthritis. Through the efforts of researchers around the world, the effects of immune cells on osteoarthritis tissue cells have gradually become clear. With the ageing of the world population, there are an increasing number of patients with osteoarthritis. Therefore, elucidating the role of immunity in the pathogenesis of osteoarthritis would be helpful to interfere with the occurrence of osteoarthritis in the context of immunology.

Author Contributions

All authors made significant contributions to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation or in all these areas. The authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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