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EDITORIAL

Osteoimmunology and osteonecrosis of the femoral head

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Osteonecrosis of the femoral head (ONFH) is a refractory disease, which often leads to collapse of the femoral head.[1,2] Each year, approximately 22,000 new cases occur in the USA and 75,000 to 150,000 in China.[3] There is no consensus on the pathogenesis of ONFH, despite many studies on the topic. Increasing evidence points to inflammatory osteoimmunology playing an indispensable role in the pathogenesis of ONFH.[4-8]

While immune cells such as macrophages are important for resolving inflammation and promote subsequent tissue repair, they also contribute to ONFH, suggesting that the disease arises as a result of immune system dysfunction.[5,8] Bone biology and immunology have recently been combined in the field of osteoimmunology to become an important focus of ONFH research.[9] We will summarize the current understanding of the osteoimmunology of ONFH, focusing on the important roles of macrophages, T and B cells, and neutrophils, as well as related signalling molecules.

Macrophages, a kind of "hyperplasticity" immune cell, play a pivotal role in the innate immune response.[10,11] Macrophages can "polarize" into different phenotypes depending on their microenvironment.[10,11] So-called "classically activated" M1 macrophages are pro-inflammatory, while "alternatively activated" M2 macrophages are anti-inflammatory.[10,11] After tissue injury, the body needs M1 macrophages to initiate an appropriate inflammatory response, but their continued activity leads to chronic inflammation, damaging the tissue.[11] Thus, at a suitable time, the body shifts macrophages to the M2 phenotype, and these cells promote tissue repair, remodelling, and angiogenesis.[10] In this way, a balance between M1 and M2 macrophages is critical, and disbalance in favour of the M1 phenotype can result in chronic inflammation.[12,13] Studies have demonstrated increased numbers of M1 macrophages in animal models of ONFH, and that necrotic bone can stimulate proinflammatory responses from macrophages through the activation of a specific pattern recognition receptor TLR4.[4] However, M2 macrophages play a key role in the resolution of inflammation and the regeneration of injured tissue,[14] especially in the late stage during the pathogenesis of ONFH.[15] The shift from M1 to M2 phenotype is effective for promoting survival of osteocytes, decreasing inflammatory cytokines, and alleviating the symptoms of ONFH.[5] These studies indicate that failure of M1 to repolarize to the M2 phenotype can cause chronic inflammation that includes secretion of various pro-inflammatory cytokines, which then contributes to ONFH.

T cells constitute a major part of cell-mediated adaptive immunity, which can be divided into T helper (Th) cells, regulatory T (Treg) cells, and cytotoxic T cells.[16] T cells produce the pro-inflammatory cytokines interleukin (IL)-23 and IL-33, and the levels of both interleukins may predict risk for ONFH.[6,17,18] Th17 cells are recruited to the inflamed synovium of ONFH, and their secretion of IL-17 can mediate chronic pain.[7] Elevated levels of Th17 and IL-17 are found in both inflamed synovium and peripheral blood in patients with ONFH, indicating a close correlation between inflammation and ONFH.[7] Th9 and Th17 cells secrete IL-9, which upregulates other inflammation-related cytokines as well as enzymes that degrade cartilage matrix.[19,20] ONFH patients show elevated levels of IL-9, but whether this cytokine promotes cartilage degeneration is unclear.[20] Treg cells secrete the anti-inflammatory cytokines IL-4, IL-10, and transforming growth factor beta (TGF-β), which inhibit osteoclast activity, thereby preventing bone damage.[8] Via cytotoxic T lymphocyte associated protein (CTLA-4), a kind of transmembrane receptor, inhibitory T cells can bind to

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osteoclast precursors to suppress the osteoclast activity. The reduction in the number of inhibitory T cells is shown to be associated with ONFH progression.[8] Physiologically, B cells induce humoral responses and inflammation, and their activation, together with elevated serum levels of TNF-α, IFN-γ, and IL-17A, has been associated with ONFH.[21] These studies suggest that T and B cells secrete many cytokines and interact with each other to regulate immune responses that play an important role in the pathogenesis of ONFH.

Neutrophils also contribute to the immune regulation in ONFH. After early infiltration during femoral head necrosis, neutrophils participate in bone remodelling, and the speed of necrosis may be related to the active immune defence and necrotic tissue-cleansing of neutrophils in the early stage of osteonecrosis.[22] Moreover, activated neutrophils release so-called "neutrophil extracellular traps" (NETs), which not only play a key role in innate immunity, but also regulate the function of immune cells by directly or indirectly altering levels of inflammatory cytokines.[23,24] One study revealed NET-forming neutrophils in the small blood vessels around the femoral head of ONFH patients, whereas such neutrophils were absent from the femoral heads of patients with osteoarthritis.[25] The NET-forming neutrophils appeared to disturb local blood flow, contributing to ischaemia of the femoral head. Since NETs stimulate thrombus formation and coagulation in animal models,[26] it is possible that NETs do the same in the small vessels surrounding the femoral head, contributing to ONFH. This NETs phenomenon is also one of the important indicators of pathogenesis of prothrombotic state of sickle cell anaemia (SCA), which may explain why SCA is an important risk factor for ONFH.[27]

The regulation of osteoimmunology in ONFH involves many signalling molecules. TLR4, which promotes M1 polarization of macrophages, can activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signalling pathway to induce the release of inflammatory mediators.[28,29] The TLR4/NF-κB pathway may connect the immune response with bone metabolism, and activation of this pathway may disrupt the balance between the two systems, decreasing bone regeneration and increasing bone resorption.[30] Several immune cells, such as B and T cells, participate in the immune response and bone remodelling by expressing receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG).[8,31] The OPG/RANK/RANKL axis controls the differentiation and activity of osteoblasts and osteoclasts, in order to maintain bone homeostasis and prevent bone loss.[8,32,33] This axis also influences vascular calcification and the immune system,[34] and it has been linked genetically to ONFH.[35] Indeed, proper mechanical stress acts via this axis to promote femoral head recovery, which may be a target to treat ONFH.[32] The Janus kinase (JAK)-signal transducer and activator of transcription (JAK/STAT) pathway plays an important role in bone metabolism and healing, and IL-9 acts via this pathway to induce cartilage degeneration.[20] Thus, blocking this pathway may reduce cartilage degeneration in ONFH.[20]

In summary, chronic inflammation is a distinctive feature of osteonecrosis, and persistent inflammation causes progressive collapse. The dysfunction of the immune system is key to the pathogenesis of ONFH. Our understanding of this dysfunction has advanced rapidly, with the combination of bone biology and immunology long considered separately from each other in the field of osteoimmunology; this field has become an important focus for ONFH research. Studies concerning the osteoimmunology of ONFH show promise for elucidating the pathogenesis of the disorder, as well as identifying potential new treatments. Nevertheless, there is still a long way to go before we can achieve thorough understanding of these new mechanisms in ONFH, and their further application in clinical therapy. Future research should clarify the inflammatory signalling mechanisms, as well as interactions between immune cells and other cell types that contribute to ONFH, and further relevant clinical studies are expected to be conducted with a view to bridging the theory-practice gap.

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