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REVIEW

Bone responses in health and infectious diseases: A focus on osteoblasts

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Summary Historically, bone was thought to be immunologically inactive with the sole function of supporting locomotion and ensuring stromaness functions as a major lymphoid organ. However, a myriad of pathogens (bacteria such as staphylococcus as well as viruses including alphaviruses, HIV or HCV) can invade the bone. These pathogens can cause apoptosis, autophagy and necrosis of osteoblasts and lead to lymphopenia and immune paralysis. There are now several detailed studies on how osteoblasts contribute to innate immune and inflammatory responses; indeed, osteoblasts in concert with resident macrophages can engage an armory of defense mechanisms capable of detecting and controlling pathogen evasion mechanisms. Osteoblasts can express the so-called pattern recognition receptors such as TOLL-like receptors involved in the detection for example of lipids and unique sugars (polysaccharides and polyriboses) expressed by bacteria or viruses (e.g. LPS and RNA respectively). Activated osteoblasts can produce interferon type I, cytokines, chemokines and interferon-stimulated proteins through autocrine and paracrine mechanisms to control for viral replication and to promote phagocytosis or lysis of bacteria for example by defensins. Uncontrolled and sustained innate immune activation of infected osteoblasts will also lead to an imbalance in the production of osteoclastogenic factors such as RANKL and osteoprotegerin involved in bone repair.

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Introduction

Many infectious agents can target the skeletal tissue. Bacteria can cause caries, periodontitis, periapical infection, osteomyelitis, septic arthritis and many more infectious diseases. Moreover, as the number of bone replacements performed annually increases, the risk of infection at the bone-implant interface is becoming an increasingly important issue. It is extremely difficult to treat these infections with antibiotics, and notably because of the increasing incidence of antibiotic resistance among the microorganisms affecting the skeleton. Osteomyelitis can lead to sequelae and, if uncontrolled, to patients death. The incidence of osteomyelitis varies greatly according to germ concentration, pathogenicity of the implicated pathogen or systemic factors such as nicotine, obesity or diabetes type 2. Osteomyelitis is typically of bacterial origin where *Staphylococcus (S.) aureus* is the most prevalent pathogen responsible for various community or hospital-acquired infections like the skin abscess, pneumonia or septic arthritis.[1] Infection of osteoblasts (OB) by *S. aureus* is a keystone determining element in the development of osteomyelitis in bone tissue. *S. aureus can* directly interact with OB. Each interaction specifically leads to the induction of various and distinct pathogenic responses of bone cells.[2] The bacteria can find a sanctuary inside bone cells and, hence, escaping from the innate immune defense mechanisms.

Bacterial infection-induced lymphopenia is also a matter of concern. Lymphopenia and therefore the subsequent immunosuppressed state may be due to alteration or the depletion of stromal bone cells with a loss of function in providing developmental cues to lymphocytes at the level of the bone marrow. Indeed, recent studies by Takayanagi and colleagues have shown that OB numbers were dramatically reduced in a mouse model of cecal ligation and puncture (CLP).[3] This model was used to mimic sepsis, a life-threatening organ dysfunction caused by the dysregulation of the host response to an infectious agent.[4] Sepsis has long been known to be associated with a late period of immunosuppression due to lymphopenia and which can lead, in severe cases, to secondary infections and death.[3,5,6] The loss of OB coincided with that of common lymphoid progenitors and provoking lymphopenia through IL-7 downregulation.[3] This observation further underpins the interaction between the immune and the bone systems in the context of an infectious disease.

Stromal cells of the bone such as osteoclasts (OC) are derived from macrophages and they could be directly stimulated by pathogen-associated molecular patterns (PAMPs) expressed by microbes.[7] PAMPs such as lipopolysaccharide (LPS) are known to interact selectively with a plethora of pattern recognition receptors (PRRs) strategically and abundantly expressed by OCs.[8] PRRs can be expressed at the cell membrane such as TOLL-like receptors (TLR) (e.g. TLR4) to detect extracellular bacteria or being localized in the cytosol (e.g. nucleotide-binding oligomerization domain-1, NOD 1) to detect intracellular infection.[9] Interestingly, it is also increasingly evident that the same PRRs are also expressed by OB arguing for possible direct effects of bacteria to OB's physiological and immune functions.[10] Viruses can also infect and affect OB as recently described for the chikungunya alphavirus (CHIKV).[11,12] It is now proposed that CHIKV-infected OB have an altered receptor activator of nuclear factor NF-κB ligand (RANKL) and osteoprotegerin (OPG) expression ratio and which may favor the activation of OC and bone destruction. This review will highlight the recent paradigm of a central role of OB in bone and immune functions during bacterial and viral infections.

Osteoblast functions in health

OB in many of the craniofacial bones in vertebrates are derived from the neural crest cells, a mesenchymal stem cell (MSC) type that is unique to vertebrates and is derived from the neural ectoderm. By contrast, OB in the rest of the axial skeleton and the appendicular skeleton are derived from the paraxial mesoderm and the lateral plate mesoderm, respectively.[13] New OBs are continuously generated after birth, both in the period of postnatal bone growth and during bone remodeling after peak bone mass has been reached. However, the origin of the OB progenitors in postnatal life is not well understood.

OB progenitors can be found at the level of the periosteum, a layered fibrous membrane covering the surface of bone tissues. A subset of OB can become osteocytes and are found within the bone matrix (Fig. 1). The rest of the OB is thought to either undergo apoptosis or become inactive bone-lining cells.[14] The mature bone tissue contains essentially osteocytes which form an extensive network with each other and with OB at the bone surface. Sclerostin, which is encoded by the gene SOST is produced by osteocytes, contributes to the regulation of bone remodeling in response to both mechanical and hormonal signals. OB are the chief bone-forming cells, with a capacity to produce several proteins such as osteocalcin (OCN), alkaline phosphatase (AP) and a large amount of type I collagen. The extracellular matrix (ECM) of the bone, which is rich in type I collagen, is known as the osteoid when is not yet mineralized. It is the accumulation of calcium phosphate in the form of hydroxyapatite that will ensure mineralization of the newly created bone. OB express many of the MSC markers such as vimentin but they can also be identified through the abundant expression of the transcription factor RUNX2 or, at a more advanced stage of differentiation, both RUNX2 and osterix (also known as SP7). Traditionally, OBs were thought to function in building the skeleton, which provides mechanical support, muscle attachment and a reservoir of phosphorus and calcium. However, it is now known that these cells have additional functions. Cells of the OB lineage contribute to the bone marrow microenvironment, which is essential for hematopoietic stem cell (HSC) homeostasis.[13]

The differentiation of OC from myeloid precursor cells requires the presence of the osteoclastogenic cytokine RANKL (member 11 of the TNF family) and its interaction with its receptor, RANK (receptor activator of NF-κB), which is expressed on the cell surface of OC precursors.[15] Enhanced production of RANKL by OB can stimulate osteoclastogenesis.[16] Osteoclastogenesis requires the proximity of OB and RANK-expressing OC precursors to one another. In adult