Review

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Tight relationships between B lymphocytes and the skeletal system

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Mounting evidence indicates that the immune system and the skeletal system share several regulatory nodes. B lymphocytes, which play key roles in immune homeostasis, are uniquely endowed with osteointeractive properties. From their early development to the plasma cell stage, they are in close proximity with the skeletal system and produce factors important for bone maintenance. Not surprisingly, perturbation of B lymphopoiesis affects bone mass. Reciprocally, inactivation of bone cell functions results in B cell development blocks. This new understanding is refining our insights into the pathogenesis of several diseases such as periodontitis and rheumatoid arthritis.

Osteoimmune crosstalk

The observations that abnormal activation of the immune system can lead to bone destruction and that mice rendered deficient in immunomodulatory molecules often develop an unexpected skeletal phenotype led to the view that multiple cross-interactions are required for the optimal functions of the immune system and the skeletal system. In addition to their spatial proximity within the bone marrow (BM) cavity, bone forming units (osteoblasts, OBs; see Glossary), bone resorbing cells (osteoclasts, OCs), and immune cells share a number of regulatory cytokines, chemokines, receptors, signaling molecules, and transcription factors. The network of cytokine interactions regulating bone loss is complex, involving synergistic effects, sequential and networked pathways, and redundant systems. Many of these cytokines not only regulate OBs and OCs directly but also modify the response of immune cells, including T lymphocytes, dendritic cells (DCs), and B lymphocytes.

B lymphocytes are key players in both innate and adaptive branches of immunity [1]. In addition, they are endowed with functions beyond the immune system, such as their involvement in tissue repair [2,3]. Here, we discuss the roles of B lymphocytes in the crosstalk with the skeletal system and some of the implications of B lymphocyte–skeletal interactions with regard to disease pathogenesis.

Codependency of bone homeostasis and B lymphocyte development

B cell development in the BM is initiated through a series of differentiation steps beginning from the hematopoietic

Glossary

Bone marrow stromal cells: non-hematopoietic cells in the bone marrow, some of which secrete growth factors that are important for the regulation of hematopoiesis and for immune system development.
Bone mineral density (BMD): a quantitative measure of the amount of mineral in the bone; low BMD is often correlated with diseases that weaken bone and leave patients more prone to bone fractures, such as osteoporosis and rheumatoid arthritis.
Cre-recombinase: an enzyme naturally produced by bacteriophage that has been adapted for genetic engineering to specifically excise DNA fragments flanked by 'loxP' sites. Expression of Cre under ubiquitous and cell specific promoters has facilitated the study of the role of genes in the biology of specific cell types.
Hematopoietic stem cell (HSC): the pluripotent cell in the mammalian bone marrow that gives rise to all blood lineages. HSCs can be categorized into long-term and short-term HSCs. HSCs self-renew into new HSCs, as well as differentiate into specific blood lineages, as directed by the local microenvironment and immune response needs.
Mesenchymal stem cell/multipotent stromal cells (MSCs): non-hematopoietic progenitor cells that can differentiate into osteolineage, adipocyte, and chondrocyte cell lineages in the bone marrow. MSCs have immunomodulatory effects, down-regulating inflammation. MSC populations support HSC and B cell development.
Niche: a broad term that refers to the cellular microenvironment that supports specific types of cells. For example, the 'stem cell niche' includes the cellular neighbors, secreted factors, and physical space that support self-renewal and maintenance of stem cells.
Osteoblast (OB): an osteolineage cellular intermediate between the MSC and the osteocyte. Overactivity of OBs can lead to abnormally high BMD levels. In addition to their role in bone development, OBs have been shown to be an important niche cell for HSCs and developing B lymphocytes.
Osteoclast (OC): a HSC-derived macrophage-like cell that functions to break down bone to remove old or dead osteocytes during the course of normal bone homeostasis. Overactivity of OCs can lead to osteoporosis.
Osteocyte (OCY): a terminally differentiated, highly mineralized bone cell that is embedded into the bone structure. OCYs are derived from immature OBs that have undergone the process of mineralization.
Osteopetrosis: a medical disorder that results in abnormally high bone mass. Despite their increased bone mass, osteopetrotic bones are of low quality and at risk of fracture.
Osteoporosis: a medical disorder that results in abnormally low bone mass. It can be caused by some medications used for cancer chemotherapy or by imbalanced levels of sex hormones, and is often seen in the aging population.
Periodontitis: a chronic inflammatory disease that leads to destruction of the gingiva and the underlying alveolar bone.
Rheumatoid arthritis (RA): a chronic inflammatory autoimmune disease that leads to disfigurement of the joints and is accompanied by bone loss due to erosion at the joints.

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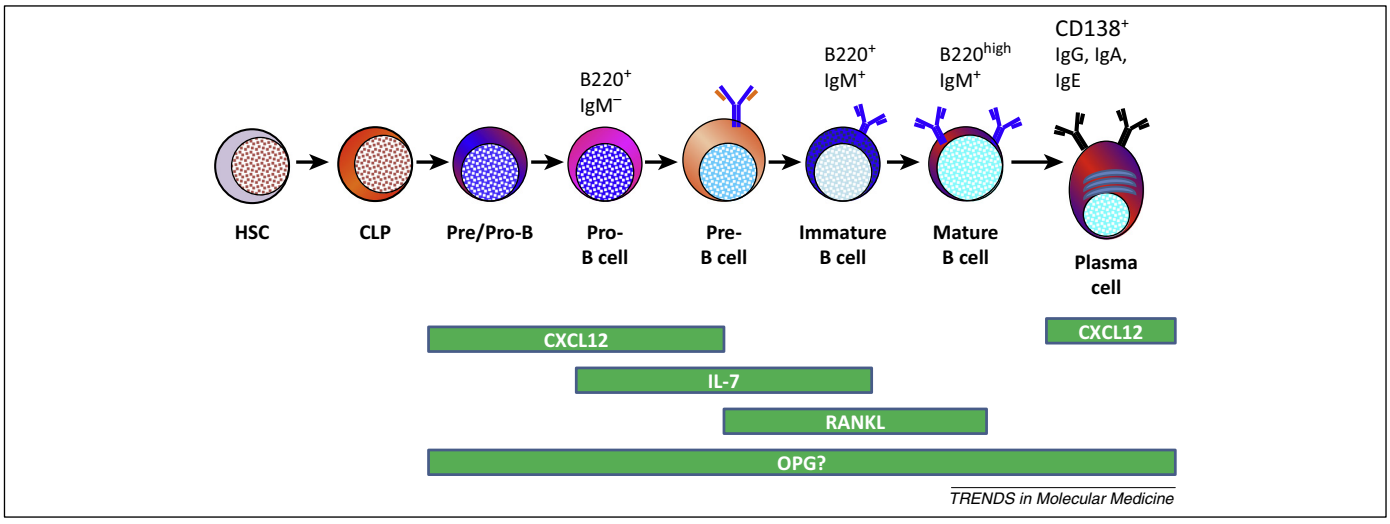

Figure 1. B cell developmental stages of maturation. Subsets of B cells allow interactions with the skeletal system. The green bars indicate stages of B cell development that depend on CXCL12, interleukin (IL)-7, stem cell factor (SCF), and osteoprotegerin (OPG) produced by bone marrow 'stromal cells', including mesenchymal stem cells/multipotent stromal cells (MSCs) and osteoblasts (OBs). The question mark next to OPG indicates that the dependence of the above B cell stages on OPG is unclear. Blue indicates Ig heavy chains, orange indicates surrogate light chains; entirely blue surface Ig is composed of Ig heavy chains with Ig light chains; black Ig indicates antibodies that are secreted by plasma cells. Abbreviations: HSC, hematopoietic stem cell; CLP, common lymphocyte progenitor; B220, CD45R, an isoform of the protein tyrosine phosphatase gene that is expressed on B lymphocytes; CXCL12, C-X-C motif chemokine 12; IgM, immunoglobulin M; CD138, syndecan 1, a cell surface marker of plasma cells; IgG, Immunoglobulin G; IgA, Immunoglobulin A; IgE, immunoglobulin E; RANKL, receptor activator of nuclear factor κB ligand.

stem cell (HSC). B cell maturation can be followed via the expression of specific combinations of cell surface markers, transcription factors, and differences in immunoglobulin (Ig) gene rearrangements and Ig surface expression at each developmental stage (Figure 1) [4–7]. B cell development occurs within the vascular microenvironment of the BM (Figure 2), and it is now well recognized that B cell precursors rely on growth factors that are produced by BM 'stromal cells' such as mesenchymal stem cells/multipotent stromal cells (MSCs) and OBs in that location within the bone. In particular, C-X-C motif chemokine 12 (CXCL12), stem cell factor (SCF), interleukin-7 (IL-7), receptor activator of nuclear factor κB ligand (RANKL), and osteoprotegerin (OPG) are critical for early B cell development (Figure 1) [5].

The relationship between abnormal bone phenotypes and the development and differentiation of hematopoietic

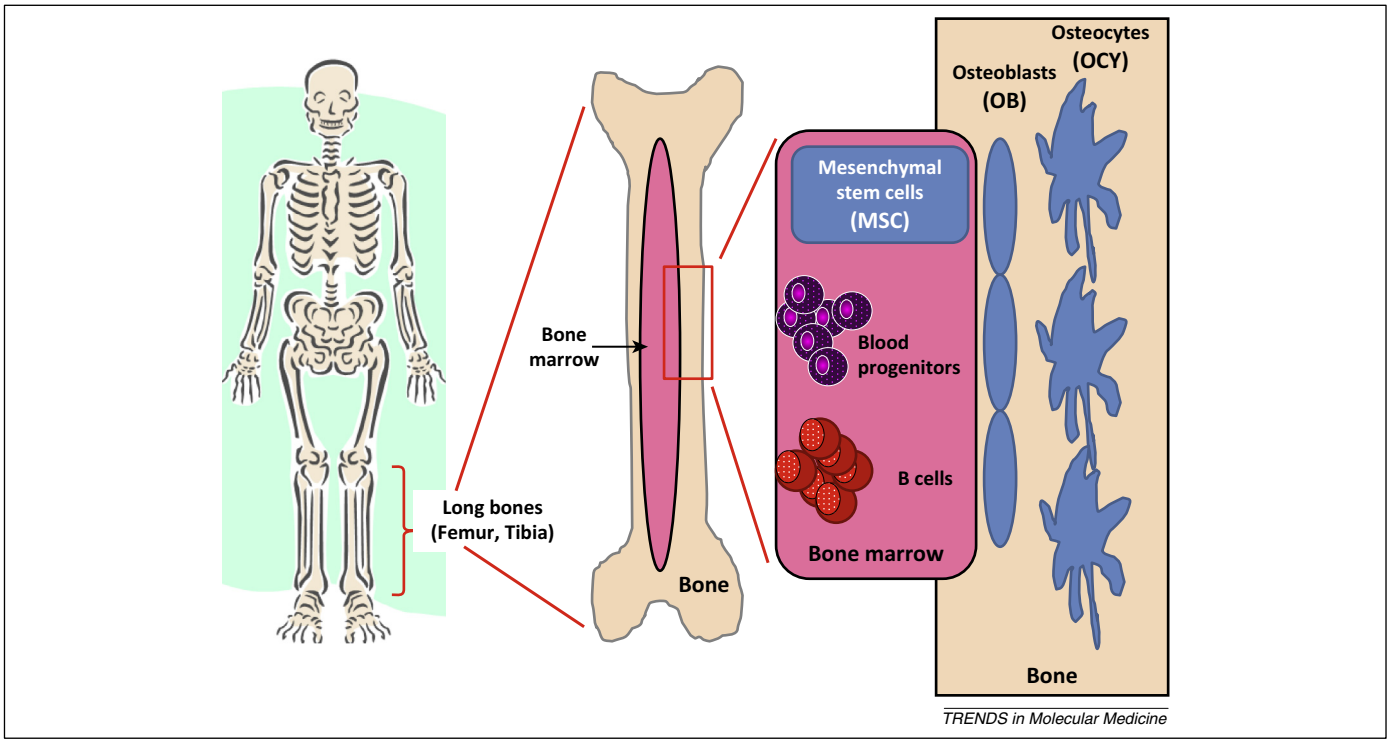

Figure 2. Spatial and functional relationships between cells within the bone. A scheme of the anatomy and cells in the long bones is shown. The femur and tibia bones of the leg contain mineralized bone (light pink) and a bone marrow (BM) cavity (pink center). Within the BM, normal blood and immune cell development (red) appear to depend on interactions between osteolineage cells such as MSC, OB, and OCY (blue). Abbreviations: MSC, mesenchymal stem cell; OB, osteoblast; OCY, osteocyte.