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Review

Extracellular matrix networks in bone remodeling

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ABSTRACT

Bones are constantly remodeled throughout life to maintain robust structure and function. Dysfunctional remodeling can result in pathological conditions such as osteoporosis (bone loss) or osteosclerosis (bone gain). Bone contains 100s of extracellular matrix (ECM) proteins and the ECM of the various bone tissue compartments plays essential roles directing the remodeling of bone through the coupled activity of osteoclasts (which resorb bone) and osteoblasts (which produce new bone). One important role for the ECM is to serve as a scaffold upon which mineral is deposited. This scaffold is primarily type I collagen, but other ECM components are involved in binding of mineral components. In addition to providing a mineral scaffolding role, the ECM components provide structural flexibility for a tissue that would otherwise be overly rigid. Although primarily secreted by osteoblast-lineage cells, the ECM regulates cells of both the osteoblast-lineage (such as progenitors, mature osteoblasts, and osteocytes) and osteoclast-lineage (including precursors and mature osteoclasts), and it also influences the cross-talk that occurs between these two oppositional cells. ECM influences the differentiation process of mesenchymal stem cells to become osteoblasts by both direct cell-ECM interactions as well as by modulating growth factor activity. Similarly, the ECM can influence the development of osteoclasts from undifferentiated macrophage precursor cells, and influence osteoclast function through direct osteoclast cell binding to matrix components. This comprehensive review will focus on how networks of ECM proteins function to regulate osteoclast- and osteoblast-mediated bone remodeling. The clinical significance of these networks on normal bone and as they relate to pathologies of bone mass and geometry will be considered. A better understanding of the dynamic role of ECM networks in regulating tissue function and cell behavior is essential for the development of new treatment approaches for bone loss.

Contents

Abbreviations: BMP, bone morphogenetic protein; DEXA, dual energy X-ray absorptiometry; DMP, dentin matrix protein; ECM, extracellular matrix; FGF, fibroblast growth factor; HSC, hematopoietic stem cell; MAGP, microfibril associated glycoproteins; MEPE, matrix extracellular phosphoglycoprotein; MSC, mesenchymal stem cell; MMP, matrix metaloproteinase; MP, matricellular protein; MT1-MMP, membrane type 1 matrix metaloproteinase; OI, osteogenesis imperfecta; PTH, parathyroid hormone; SLRP, small leucine rich proteoglycans; SIBLING, small integrin-binding ligand-linked glycoproteinproteins; TSP, thrombospondin; TGF, transforming growth factor.

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1. Introduction

To maintain a healthy skeleton with optimal mechanical integrity, bone is constantly remodeled throughout life through the coupled activities of bone resorbing osteoclasts and bone forming osteoblasts (Fig. 1). Pathological imbalance in these cellular processes can lead to disease conditions of bone loss, in particular osteoporosis. Osteoclasts arise from hematopoietic-origin progenitor cells, yet their development is regulated by cells of the osteoblast-lineage. Osteoblasts arise from mesenchymal progenitor cells, often referred to as mesenchymal stem cells (MSC). Osteoblasts form bone and then either undergo apoptosis, become bone-lining cells or can surround themselves with ECM that becomes mineralized to become osteocytes, which are embedded in the mineralized bone matrix.

Similar to other connective tissues, bone cells are not the primary constituents of bone by weight. Rather, the ECM produced by the osteoblasts makes up most of the dry weight of bone. This bone ECM determines the mechanical properties of the skeleton. The mineralized portion of bone tissue imparts rigidity and hardness to the material, while the organic components of the ECM provide flexibility. The mineralized portion of the ECM is composed largely of calcium-phosphate in the form of hydroxyapatite plus an extensive type I collagen-rich organic ECM. In addition to collagen, proteomic analysis of decalcified bone suggests that well-over 100 ECM proteins are present in bone (Jiang et al., 2007; Salmon et al., 2013). Similarly, analysis of osteoblasts show that ECM proteins represent 30% of the 315 proteins identified *via* secretome analysis (Kim et al., 2013).

While the ECM plays a significant role in structural tissue support and in serving as a site for cell adhesion, over the past 20 years it has become well-recognized that the ECM plays a far more dynamic role in regulating cell function and tissue morphogenesis. In the context of bone, select ECM components can play a role in modulating the assembly of the structural matrix, particularly in organizing the process of matrix mineralization. As well, the ECM can bind to extracellular growth factors, cell bound ligands and receptors, and proteases. In the context of these binding activities, the ECM can have either a positive or inhibitory effect on function. As an example, thrombospondin 1 binding to TGF-beta promotes TGF-beta activity (Bos et al., 2004), while the closely related family member, thrombospondin 2, is speculated to sequester and inhibit TGF-beta activity.

1.1. Overview of bone ECM compartments

In this review, we will discuss examples of ECM-dependent networks within the different tissue compartments of bone; thus, it is important to provide a brief overview of various ECM containing tissues of bone. Fig. 1 illustrates the simplified cellular anatomy of bone and illustrates that different tissue compartments are connected functionally and spatially. In addition to mineralized bone ECM other unique tissue types exist in association with bone, including, (1) marrow; (2) endosteum; (3) periosteum; and (4) the osteocyte perilucanar matrix. Marrow, endosteum, periosteum, and perilucanar matrix are all non-mineralized and contain ECM networks that can regulate the processes of osteoclast development and function, osteoblast progenitor proliferation and differentiation, and osteocyte function.

1.2. Marrow stroma

The marrow stroma is the loose connective tissue that supports hematopoiesis as well as MSC and osteoclast precursor cells. The ECM of marrow is loose and irregular, and histologically is not well-characterized. *In vitro* analysis of the ECM expressed and produced by marrow stromal cells suggest a ECM profile similar that of pre-osteoblasts (Bennett et al., 2007). The marrow stroma plays an important role in regulating hematopoietic stem cell differentiation as the stromal cells form the niche for hematopoiesis (Oritani and Kincade, 1996; Borojevic et al., 2004; Yin and Li, 2006).

1.3. Endosteum

The endosteum is composed of bone-lining cells, which are primarily osteoblast-lineage cells, with a specialized type of macrophage, termed OsteoMacs interspersed amongst them (Chang et al., 2008). While the ECM of the bone-lining cells is not well-described, these cells are proposed to serve a regulatory role and may be a significant source of mature osteoblasts in adults (Matic et al., 2014). These OsteoMac cells are reported to play a regulatory role in bone formation and resorption, and during these processes, can form a remodeling 'canopy'. The osteoblast-lineage derived bone-lining cells on the other hand can differentiate to become functional osteoblasts that form bone. The primary matrix component recognized at the endosteum is the osteoid, which is the unmineralized matrix secreted and assembled by osteoblasts. Osteoid will become mineralized bone matrix under conditions of normal bone maturation.

1.4. Periosteum

The periosteum has two primary histological layers, a fibrous layer that has denser, collagenous tissue and a cambium layer that is very cellular (Allen et al., 2004). These cells can be activated to produce bone during periods of periosteal expansion, and play a crucial role in bone regeneration and fracture repair (Colnot et al., 2012; Grcevic et al., 2012). With respect to key ECM proteins localized to the periosteum, the carboxylated matricellular protein (MP) periostin is a molecule found to be more