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Extended Abstract

A Review of Dysregulated Osteoblast and Osteoclast Coupling in Bone Disease and Failure

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Abstract

Human bones are formed through intramembranous and endochondral ossification followed by a period of appositional growth. Skeletal homeostasis of cancellous/trabecular and cortical bone tissue is sustained through a lifelong biological process known as bone remodeling. Bone remodeling is the balanced-integrated function of osteocyte signaling, osteoblast bone formation, and osteoclast bone resorption

In this review, the autocrine and paracrine factors that control the rate of bone synthesis and resorption as they attribute to osteogenic cell differentiation, localization, and function are reviewed. These factors direct the transition between each phase of the remodeling process: activation, resorption, reversal, formation, and mineralization.

The five primary intracellular signaling pathways that regulate osteogenic gene expression, cell function, localization, and survival include: Wnt/βcatenin, transforming growth factor-β, bone morphogenetic protein, arachidonic acid metabolism/prostaglandin synthesis, and receptor activator of nuclear factor κ B are also discussed. Several diseases are associated with dysregulated bone remodeling and aberrant signaling in osteogenic cells some hereditable and acquired genetic mutations result in skeletal diseases, like craniometaphyseal dysplasia, osteogenesis imperfecta, osteopetrosis, and myeloma bone disease. Other skeletal disorders are attributed to endogenous and exogenous induced hormonal imbalances, like postmenopausal osteoporosis or glucocorticoid steroid use, or cytokine imbalances that exacerbate inflammatory diseases, like rheumatoid arthritis.

The role of excessive resorption and inadequate bone formation have in these diseases that may result in overall decreased skeletal tissue integrity, chronic pain, pathological bone fractures, and mortality are also examined.

Normal bone remodeling is initiated through osteoclast activation by means of direct mechanical stress/structural impairment or hormonal signaling, estrogen or parathyroid hormone (PTH). Osteoclastogenesis begins when Bone Marrow Macrophages (BMM) exposed to granulocyte-macrophage colonystimulating factor (GM-CSF) form multinucleated osteoclasts that express receptor activator of nuclear factor κ B (RANK). Osteocytes may undergo apoptosis or secrete sclerostin, a Wingless/Integrated (Wnt) and bone morphogenetic protein (BMP) antagonist that suppresses osteoblastogenesis, and RANKL that binds RANK receptor on osteoclasts to promote differentiation and survival signals within the cells [4]. Osteoblasts also regulate osteoclastogenesis through secretion of osteoprotegerin, a soluble RANKL decoy receptor [5]. Bone metabolism is highly regulated by vitamin D, PTH, interleukin-1 (IL-1), and prostaglandins [6].

Bone remodeling is an integral part of counteracting ageassociated bone tissue decomposition and in healing aberrant bone fractures, but there are several heritable and acquired bone disorders that dysregulate and uncouple bone formation and resorption The pathophysiology of many diseases that affect bone health is attributed to the disruption of osteogenic molecular signaling pathways that ultimately control cellular differentiation, proliferation, survival, functionality, and localization. Inter and intracellular signaling events direct transcriptional regulation of osteometric genes and their concordant proteins and provide essential cues that control the transition through the different phases of the bone remodeling process.

The complex interconnectivity between receptor activation or inhibition, secretion or sequestration of molecular signaling moieties, and the cellular microenvironment that directs cell fate is not fully understood, but the roles of several well-defined pathways attributed to a number of bone disorders have been identified. This review explored the causal association between several well-recognized conditions and the mechanistic properties that alter the effectiveness of the bone remodeling process.