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Cells in Focus

The osteoblast-heparan sulfate axis: Control of the bone cell lineage

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Abstract

During osteogenesis, mesenchymal stem cells are recruited to the osteoblast lineage and progressively differentiate into osteoblasts that produce a mineralised extracellular matrix. Although most of the organic component of this matrix is comprised of collagen, growing evidence suggests the most bioactive element of a developing matrix is its heparan sulfate glycosaminoglycan complement. This species of linear, unbranched sugars contain protein-binding domains that regulate the flow of an astonishing number of mitogenic influences that coordinate mesenchymal stem cell commitment and growth, and ultimately, osteoblast phenotype. Among the heparan sulfate-binding factors known to be important to this process are sonic hedgehog, the fibroblast growth factors and their receptors, members of the transforming growth factor superfamily, as well as the collagens, laminins and fibronectins. How these sugars change during development to bring together the right combination of mitogenic/differentiative influences to trigger the successive phases of osteogenesis is currently the focus of intense research.
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Abbreviations: HS, heparan sulfate; HSPG, heparan sulfate proteoglycans; ECM, extracellular matrix; Wnt, wingless-int growth factor; FGF, fibroblast growth factor; FGFR, FGF receptor; BMP, bone morphogenic protein; BMPR, BMP receptor; TGF-β, transforming growth factor-beta; RANK, receptor activator of NF-κB; RANKL, RANK ligand; MSC, mesenchymal stem cell; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; CSPG, chondroitin sulfate proteoglycans; HBGF, heparin-binding growth factor; RUNX2, runt domain transcription factor 2; FAK, focal adhesion kinase; ERK, extracellular-signal-regulated kinase

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Cell-extracellular matrix nexus facts:

- Osteoblasts are responsible for bone formation and derive from mesenchymal stem cells.
- Osteoblasts are driven through their developmental program via the sequential presentation of extracellular matrix-residing signals.
- Osteoblasts secrete many crucial mitogens and adhesion factors that bind the extracellular sugar heparan sulfate, which in turn changes its binding properties for these factors during development.
- The orderly presentation of bioactive species via their heparan sulfate sugars can be used to control the progression of osteoblast precursors.

1. Introduction

The osteoblast is one of the two important cell lineages, the other being the osteoblast, that work together to maintain healthy bone tissue. Osteoblasts are often found in clusters at the bone surface, where they lay down new, specialised extracellular matrix (ECM) known as 'osteoid'. The formation of bone proceeds broadly through one of two ossification mechanisms: intramembranous, characteristic of the flat bones of ribs and skull, or endochondral, characteristic of appendicular skeleton and vertebral column (Fig. 1). As ECM is secreted and calcified around osteoblasts, osteoblasts become trapped and differentiate further into osteocytes. Osteocytes no longer secrete copious amounts of ECM; instead their role is one of homeostasis, exchanging wastes for nutrients from the blood, and regulating calcium release back into the blood stream (Horton, 1995). The activity of the osteoblasts and osteoblasts is tightly controlled, with communication between the cells via the RANK/RANKL system. As a result, in both normal developing and healing bone there is more osteoblastic activity, whereas in mature bone there is equal activity in both the osteoblastic and osteoblastic lineages. Such control is exerted through the ECM, which ultimately triggers a cascade of signals that regulate stem cell morphogenesis, including a plethora of cell survival and cell cycle progression events that shape development (see Fig. 2).

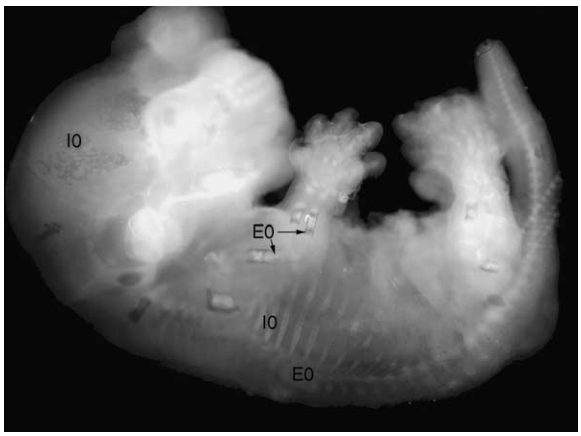

Fig. 1. Staining for the bone-commitment marker RUNX2 in an early mouse embryo reveals centres of early bone development. Bone formation during embryogenesis proceeds via two independent processes: intramembranous ossification (marked "IO" in flat bones such as the skull and ribs) that occurs through the differentiation of mesenchyma, and endochondral ossification ("EO" in the bones of the appendicular skeleton and vertebral column) which develops through a cartilaginous process. For both processes, the cells that are committing and growing within the bone lineage are now exchanging short range cell–cell, cell-growth factor and cell-matrix signals as tissue formation gets underway. The majority of these signals are being subtended by heparan sulfates.

2. Cell-ECM origin and plasticity

In contrast to osteoclasts, which are derived from haematopoietic stem cells, osteoblasts are derived from mesenchymal stem cells (MSCs). MSCs are the principal cells contributing to skeletogenesis, and their numbers expand appropriately to support the normal formation of distinct skeletal elements. These stem cells develop into the osteoprogenitors, which are transit amplifying cells that initially become competent and then commit to the bone lineage. These osteoprogenitors then differentiate in response to an evermore complex mixture of signals to become preosteoblasts. These strike a balance cell-growth and survival (Fig. 2). This balance is controlled by both circulating factors (growth factors, cytokines, and steroid hormones) and tissue architecture-related signals (cell–cell contact

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