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Mini review

Reprint of: Heparan sulfate as a regulator of endochondral ossification and osteochondroma development

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ABSTRACT

Most elements of the vertebrate skeleton are formed by endochondral ossification. This process is initiated with mesenchymal cells that condense and differentiate into chondrocytes. These undergo several steps of differentiation from proliferating into hypertrophic chondrocytes, which are subsequently replaced by bone. Chondrocyte proliferation and differentiation are tightly controlled by a complex network of signaling molecules. During recent years, it has become increasingly clear that heparan sulfate (HS) carrying proteoglycans play a critical role in controlling the distribution and activity of these secreted factors. In this review we summarize the current understanding of the role of HS in regulating bone formation. In human, mutations in the HS synthetizing enzymes Ext1 and Ext2 induce the Multiple Osteochondroma syndrome, a skeletal disorder characterized by short stature and the formation of benign cartilage-capped tumors. We review the current insight into the origin of the disease and discuss its possible molecular basis. In addition, we summarize the existing insight into the role of HS as a regulator of signal propagation and signaling strength in the developing skeleton.

Contents

1. Introduction

1.1. Endochondral ossification

The vertebrate skeleton develops by two mechanisms: intramembranous ossification, by which the flat bones of the skull, parts of the craniofacial skeleton and the clavicles are formed, and endochondral ossification, by which the rest of the craniofacial bones and the axial and appendicular skeleton are generated. The first step of both processes is

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the condensation of mesenchymal progenitor cells at the site of the future bones. During intramembranous ossification, the cells of the condensation directly differentiate into bone producing osteoblasts (Franz-Odendaal, 2011), whereas endochondral ossification is initiated with the formation of a cartilaginous template, which is subsequently replaced by bone. Cells of the cartilaginous condensations differentiate into two cell types: in the center they differentiate into chondrocytes, whereas the outer cells develop into a fibroblastic cell layer, the perichondrium, which surrounds the cartilage core (Fig. 1). The cartilage elements grow by proliferation of chondrocytes, which align in columns and secrete a collagen type II rich extracellular matrix (ECM). In the center of the cartilage anlagen cells exit the cell cycle and differentiate into prehypertrophic and Collagen X (Col X) expressing hypertrophic chondrocytes that finally undergo apoptosis. In parallel to the hypertrophic differentiation, cells in the flanking perichondrium differentiate into osteoblasts, forming the periosteum and the bone collar. The hypertrophic chondrocytes secrete blood vessel attracting factors leading to the vascularization of the periosteum and, subsequently, to the invasion of the hypertrophic cartilage with blood vessels. Accompanying osteoblasts and osteoclasts enter the hypertrophic region and replace the cartilage remnants with trabecular bone and bone marrow (Maes et al., 2010). Postnatally, secondary ossification centers develop at the distal ends of the bone. These remain separated from the primary region of ossification by descendants of the embryonic chondrocytes. These cells maintain their embryonic organization and form the growth plate, which enables the longitudinal growth of bones until growth plate closure at the end of puberty (Wuelling and Vortkamp, 2011).

Every step of endochondral ossification is tightly regulated by the concerted action of various growth factors, signaling molecules and cytokines. One of the key factors coordinating chondrocyte proliferation, the onset of hypertrophic differentiation and the ossification of the periosteum is the secreted growth factor Indian hedgehog (Ihh). Ihh acts together with Parathyroid Hormone related Peptide (PTHrP) in a negative feedback mechanism, which determines the length of the domain of proliferating chondrocytes (Lanske et al., 1996; Vortkamp et al., 1996). Ihh is expressed in prehypertrophic chondrocytes and signals to the proliferating chondrocytes and the flanking perichondrium, where it increases the proliferation rate and the differentiation of osteoblasts, respectively. Moreover, Ihh acts as a long-range morphogen inducing the expression of PTHrP in periarticular chondrocytes. PTHrP signals back to the proliferating chondrocytes, keeping them in a proliferating state. With increasing distance from the producing cells, PTHrP levels decrease. Once they decline below a certain threshold, hypertrophic differentiation is initiated and the differentiating chondrocytes start to express Ihh (Fig. 2).

Further signaling molecules controlling chondrocyte proliferation and differentiation include bone morphogenetic proteins (Bmp), fibroblast growth factors (Fgf), Wnt proteins and many others (for a review see Kronenberg, 2003). Bmp signaling is required to form the cartilage anlagen (Yoon et al., 2005). At later stages of chondrogenesis, Fgfs and Bmps act in part antagonistically, as Bmps induce chondrocyte proliferation and upregulate Ihh expression, while Fgfs inhibit these processes. In addition, Bmp signaling induces hypertrophic differentiation and Fgf signals accelerate the turnover of hypertrophic cells (Minina et al., 2002; Yoon et al., 2006). High Wnt signaling is required for the condensation of mesenchymal cells. A subsequent decrease in Wnt signaling allows the differentiation of chondrocytes, while osteoblast differentiation requires high levels of Wnt and Bmp signaling (Day et al., 2005; Hill et al., 2005). Although the genetic interactions of these and other signaling molecules in regulating endochondral bone

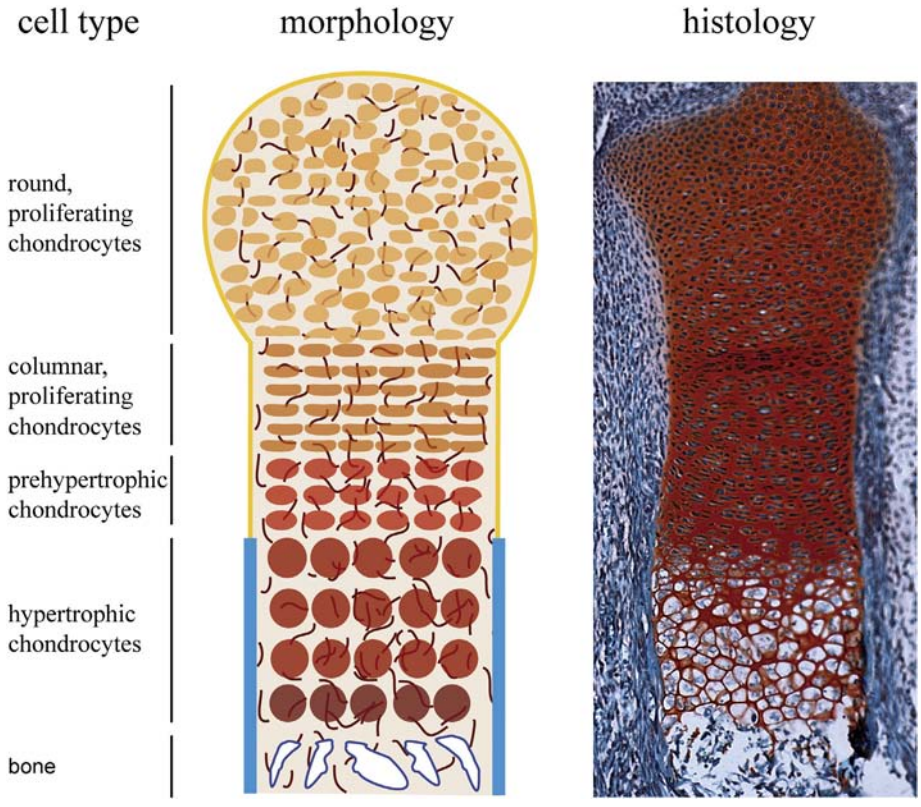

Fig. 1. Organization of the embryonic growth plate. In the embryonic growth plate, different chondrocyte subpopulations can be distinguished. The round, low-proliferating chondrocytes at the distal ends of the cartilage anlagen (light orange) differentiate into high-proliferating, columnar chondrocytes (orange). These cells exit cell cycle and differentiate into prehypertrophic (light red) and hypertrophic (dark red) chondrocytes that undergo apoptosis and are subsequently replaced by bone (blue) and bone marrow. In parallel, cells in the flanking perichondrium (yellow line) differentiate into bone forming osteoblasts (blue). HS (brown lines) is expressed in all chondrocyte subtypes and in bone. Safranin–Weigert staining labels chondrocytes in red and bone and the surrounding tissue in blue.

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