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MEETING REPORTS

Chondrocytes: Meeting Report from the 30th Annual Meeting of the American Society for Bone and Mineral Research

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The molecular mechanisms governing the progression of chondrocytes from immature to mature stages within the growth plate were a topic of intense interest at the 30th Annual Meeting of the American Society for Bone and Mineral Research. Previous publications have demonstrated that PTHrP maintains chondrocytes in a proliferative state whereas Runx2 and Runx3 promote chondrocyte hypertrophy (a postmitotic state) (1;2). Oral presentation 1044 (3) provided a biochemical mechanism through which PTHrP antagonizes Runx3. The authors showed that cyclin D1/Cdk4 (active in the G1 phase of the cell cycle) induced Runx3 ubiquitination and degradation through phosphorylation of Ser356, and argued that PTHrP likely represses Runx3 activity by this mechanism. Oral presentation 1045 (4) reported that Dmrt2 (doublesex and mab-3-related transcription factor 2) was highly expressed in prehypertrophic chondrocytes, consistent with the observation that Dmrt2 knockout mice exhibited growth retardation and malformation of ribs and sternum. Through *in vitro* studies by either overexpression or siRNA knockdown approaches, the authors showed that Dmrt2 activated Col10a1 but repressed Col2a1 expression. The authors concluded that Dmrt2 controls the growth plate by inhibiting the early-stage but promoting the late-stage chondrocyte phenotype. Oral presentation 1151 (5) dissected the mechanisms through which Akt/protein kinase B, a serine/threonine protein kinase, controls cartilage development. The authors studied the cartilage phenotypes of chondrocyte-specific transgenic mice expressing either a constitutively active (myristoylated Akt) or a dominant negative Akt. By using an organ culture system in the presence of pathway-selective chemical inhibitors, the authors concluded that the Akt-mTOR pathway played a dominant role in positively regulating chondrocyte proliferation, chondrocyte maturation, and cartilage matrix production. Akt-FoxO enhanced chondrocyte proliferation but inhibited maturation and matrix production, whereas Akt-Gsk3 negatively regulated all three aspects in the limb skeleton (although not in vertebrae where Gsk3 expression was low).

Intercellular signals that regulate cartilage development were also highlighted at the meeting. Notch signaling has recently been implicated in growth plate chondrocyte maturation and maintenance (6). Oral presentation 1268 (7) has advanced this line of research. By using both loss-of-function (deletion of RBPjk) and gain-of-function (overexpression of NICD) genetic approaches, the authors demonstrated that Notch-RBPjk signaling performs a dual function in cartilage development: it both inhibits chondrogenesis from limb mesenchyme and enhances chondrocyte maturation. The hypoxia-HIF-VEGF axis has been established as a critical regulator of cartilage biology (8;9). Oral presentation 1152 (10) reported the skeletal phenotype of mice with a mutated VEGF gene locus where the hypoxia-response-element (HRE) in the promoter was deleted. A portion of the mutant mice survived postnatally despite significantly less VEGF protein in bone, and they exhibited significant growth retardation both at birth and postnatally. The impaired growth was associated with a significantly thinner growth plate and a disproportionate

reduction of immature chondrocytes. In a related study, oral presentation 1153 (11) reported the chondrocyte-specific deletion of PHD2 (prolyl-hydroxylase-domain protein 2), which normally targets HIF1α for proteasomal degradation following hydroxylation under the conditions of normoxia. As expected, the PHD2-null chondrocytes contained greatly increased levels of HIF1α. The mutant mice were born normal but quickly became growth-retarded. The mutant growth plates showed a decrease in the proliferative zone length and in the BrdU labeling rate, but an increase in cartilage matrix mineralization likely related to the increased metaphyseal vascularization observed in these mice. Granulin/epithelin precursor (GEP) is a new cartilage growth factor reported at the meeting. Oral presentation 1048 (12) showed that GEP mRNA was highly expressed in growth plate and articular cartilage during both embryonic and postnatal development. GEP exhibited a potent chondrogenic property comparable to that of BMP2. *In vivo* genetic knockdown of GEP led to a sharp decrease in growth plate length, chondrocyte proliferation rate and in Col2a1 and Col10a1 expression.

Understanding the mechanisms maintaining the postnatal growth plate and articular cartilage is of both scientific and clinical significance. Oral presentation 1047 (13) reported that Cre-inducible expression of a dominant active form of β-catenin in adult mice by using the *Col2-CreER*^{T2} transgene in response to tamoxifen led to a loss of articular cartilage and the formation of osteophytes, phenotypes similar to those observed in osteoarthritis patients. Ihh is a critical regulator of both growth plate cartilage and bone formation, both in the embryo and after birth (14-16). In embryonic cartilage, Ihh maintains proliferative chondrocytes mostly through PTHrP, as forced activation of PTHrP signaling (Col2-promoter-driven expression of the Jansen-mutation PTHrP receptor transgene) in chondrocytes greatly restored growth plate organization in Ihh knockout mice (17). Similarly, oral presentation 1154 (18) showed that when Ihh was deleted at birth with *Col2-CreER* in response to tamoxifen, growth plate morphology was also largely normalized by the Jansen transgene during the first week of postnatal life. However, the transgene failed to preserve the postnatal growth plate without Ihh, as the growth plate was rapidly lost after two weeks.

In summary, the 30th Annual Meeting of the American Society for Bone and Mineral Research has witnessed considerable progress in understanding the molecular mechanisms that govern the diverse aspects of cartilage biology. Continued success in this research direction will provide a sound foundation for potential regenerative medicine of skeletal tissues.

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