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MEETING REPORT

Meeting Report from the 29th Annual Meeting of the American Society for Bone and Mineral Research

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CHONDROCYTES: A FEW PEARLS IN AN OCEAN OF BONES

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Though bone dominated the scene at this year's ASBMR meeting, cartilage made its presence felt in several interesting studies.

The “Sox trio”, a master regulator of chondrogenesis, is still in search of company. By screening chemical libraries, investigators have identified Runx1 as a transcription factor that works cooperatively with the “Sox trio” to induce chondrogenic differentiation *in vitro* (1). Intriguingly, however, mice lacking Runx1 in cartilage do not display an overt chondrocyte phenotype. All in all, Runx1 could be important for tissue repair and regeneration, but redundant in organogenesis.

In vivo and *in vitro* models meshed well when p63 was at center stage. p63 is a member of a gene family that includes the p53 tumor suppressor. It has been known for quite some time that mice lacking p63 exhibit severe limb deformities. Investigators have now reported that p63 plays an important role in cartilage development by regulating key genes for chondrogenesis such as *Sox6*, *Sox9* and *Col2a1* (2).

The list of transcription factors modulating chondrocyte terminal differentiation and hypertrophy is also growing. Investigators at last year's meeting reported that Hif-2α, one of the hypoxia responsive transcription factors, positively regulates collagen type X expression. Conversely, the transcriptional repressor TRPS1, which is associated with human tricho-rhino-phalangeal syndrome (TRPS), was shown to delay chondrocyte terminal differentiation. For both transcription factors, additional experimental evidence supporting their essential role in chondrocyte hypertrophy has now been presented (3;4).

Speaking of chondrocytes and hypertrophy, PTHrP, a key gatekeeper of terminal differentiation, at least in cartilage, comes to mind. While it is clear and well documented that this ligand delays hypertrophy, its main downstream targets are still uncertain. An elegant study provided evidence that the zinc finger protein Zfp521 antagonizes the transcriptional activity of Runx2, a positive modulator of hypertrophy, and lies downstream of PTHrP at the border between pre-hypertrophy and hypertrophy (5). Moreover, a novel extracellular matrix protein, ECM1 (extracellular matrix protein 1), a protein that has been linked previously to chronic inflammatory conditions, appears to be a direct downstream molecule of PTHrP in cartilage and, consistent with this finding, also a negative regulator of chondrocyte differentiation (6). Upstream of PTHrP is the morphogen Ihh; how is the expression of Ihh itself regulated? A nice piece of work suggested that the transcription factor ATF4 may be one of the physiological regulators of Ihh by directly targeting transcription of the Ihh gene (7).

Regarding established pathways in cartilage, in a real tour-de-force, researchers have discovered that, while a lack of Smad1, Smad5 or Smad8 does not generate any obvious phenotype when the genes encoding these proteins are individually deleted in cartilage, the conditional ablation of both Smad1 and Smad5 is bad news for chondrocytes that, on the contrary, tolerate

well the lack of both Smad1 and Smad8 (8). Moreover, the phenotype generated by the lack of both Smad1 and Smad5 is more severe than the one observed in growth plates in which co-Smad4 was conditionally deleted, thus challenging the dogma that co-Smad4 is required to mediate Smad signaling downstream of TGFβ and BMPs. The story gets even more complicated when inhibitory Smad6 and Smad7 enter the scene, as they appear to impair cartilage development through Smad-independent pathways (9).

Growth plate development has both a prenatal and a postnatal component, but whether chondrocytes follow similar rules before and after birth is something that still needs to be fully established. It has been known for a long time that the endocrine regulation of the postnatal growth plate is critically important. Particularly interesting is the role of thyroid hormones in chondrocytes. Researchers have reported that thyroid hormones promote chondrocyte hypertrophy, at least in part, through Igf1 modulation of canonical Wnt signaling (10); it is a complex but interesting loop. Notably, conditional deletion of the Igf1 receptor postnatally causes a severe chondrodysplasia by impairing both chondrocyte proliferation and differentiation (11). The calcium-sensing receptor is another important candidate for postnatal growth plate biology, as suggested by data that have been generated using an elegant tamoxifen-inducible system (12). All in all, the detailed molecular mechanisms that regulate the formation of the secondary ossification center and the closure of the epiphysis in the postnatal growth plate are still obscure, but progress continues to be made.

During its life, the goal of a chondrocyte is to make a specific matrix. Thus it is not surprising, though it remains extremely interesting, that matrix may feed back and somehow help the chondrocyte. In this regard, researchers have now provided clear evidence for a critical role of perlecan in FGF and VEGF signaling (13). Perlecan is a large, multidomain, heparan sulfate proteoglycan that interacts with extracellular matrix proteins, growth factors and receptors. Its knockout leads to a severe chondrodysplasia that resembles the growth plate phenotype caused by gain-of-function mutations of *FgfR3* in mice. Notably, expression of VEGF in hypertrophic chondrocytes is significantly upregulated in mice lacking perlecan, despite a delay in blood vessel invasion, suggesting that perlecan modulates VEGF activity. The data were confirmed in a transgenic model of perlecan overexpression (13). While perlecan seems to be important for VEGF and FGF signaling, matrilin-3, another matrix protein, could play a negative role in chondrocyte hypertrophy by modulating BMP signaling (14).

The ultimate events in the life of a chondrocyte are mineralization of the matrix and death, probably through apoptotic mechanisms. Experimental evidence supporting a critical role of annexin V (15) in mineralization of the matrix, through regulation of intracellular Ca^{2+} influx, and of phosphate uptake in the death of the chondrocyte has been presented. Chondrocytes may die not only because the activity of the pro-life protein Bcl2 is downregulated, but also because expression of the pro-apoptotic molecule Bnip3 is dramatically upregulated (16), and the two may be components of a loop that also involves phosphate.

Finally, a challenging question in chondrocyte biology is why the fetal growth plate is an avascular structure for most of its length. A molecule identified as “chondrostatin,” a naturally occurring collagen fragment, has some interesting anti-angiogenic properties (17); is chondrostatin a key factor for the avascularity of the fetal growth plate?

Conflict of Interest: None reported.

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