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MEETING REPORT

Chrondocytes: a few grains of softness in a hard bone world (ASBMR 2012)

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Meeting report from the 34th Annual Meeting of the American Society for Bone and Mineral Research, Minneapolis, MN, USA, 12–15 October 2012

This year at the annual ASBMR meeting, bone research had a preponderant presence, as it is often the case, but papers related to cartilage research garnered a lot of attention as well. Multiple aspects of cartilage development and homeostasis have been the subject of interesting presentations and discussions. Two topics, in particular, appeared to attract considerable interest, namely developmental regulation of the transition step from hypertrophic cartilage to bone, and identification of the signaling pathways involved in maintenance of healthy joints. In the next few paragraphs, we will briefly summarize the highlights of the meeting in the fields of cartilage development and homeostasis.

Chondrocyte Proliferation

Runx2 is a transcription factor well known for its essential role in both osteoblastogenesis and chondrocyte terminal differentiation. Data supporting an unsuspected role for Runx2 in chondrocyte proliferation have now been shown.[1]

Skt11 (also known as liver kinase b1) is a known tumor suppressor that acts upstream of the AMP activated kinase, which in turn inhibits the mTOR pathway. In this study,[2] the authors have reported that removal of Stk11 in chondrocytes delays chondrocyte hypertrophy and leads to the appearance of chondrosarcoma-like lesions in the mutant skeletal elements. Moreover, gene-expression profiling of the chondrosarcoma-like lesions has shown an increased expression of cell-cycle regulators in mutant cells. Taken together, these findings suggest that Stk11 could be a critical modulator of chondrocyte proliferation and chondrocyte hypertrophy during endochondral bone development.

SOD2 is mainly known for its role in protecting cells from mitochondrial oxidative stress. Data presented in poster[3] have indicated that SOD2 could have a role in regulating chondrocyte proliferation, highlighting once again the importance of metabolism in modulating basic processes of cell biology.

Chondrocyte Hypertrophy and Transition from Cartilage to Bone

New transcriptional regulators of chondrocyte hypertrophy and osteoblast differentiation have been identified, namely Foxp1/2/4. These transcriptional factors belong to the forkhead gene family, and are repressors of Runx2 via direct binding to the Runt domain.[4]

In addition, it has been shown that XBPS1 is a Runx2 cofactor and as such regulates chondrocyte hypertrophy.[5]

Last, Spry 2, which belongs to the Sprouty family of receptor tyrosine kinase inhibitors, has been identified as especially important in modulation of both chondrocyte hypertrophy and osteoblastogenesis.[6]

Surprisingly, despite the huge number of studies, it is largely unknown what exactly takes place at the transition between cartilage and bone. In particular, the fate of hypertrophic chondrocytes is still object of intense debate. Two models are currently highly debated in the field. The most popular model predicts that hypertrophic chondrocytes die by an apoptotic process, which immediately precedes blood vessel invasion and osteoblast recruitment. The critical involvement of phosphate and 1,25-dihidroxyvitamin D in modulating apoptosis of hypertrophic chondrocytes appears to further support this working hypothesis.[7] Conversely, according to the second, more controversial model, hypertrophic chondrocytes differentiate into osteoblasts. Experimental evidence has been presented at this meeting, suggesting that Col10a1-expressing chondrocytes can indeed undergo transdifferentiation into osteoblasts, and thus directly contribute to endochondral bone formation *in vivo*.[8]

It is commonly accepted that blood vessel invasion of cartilage is driven by chondrocytes. An interesting study presented at this meeting has provided convincing evidence that osteoblasts, upon parathyroid hormone (PTH) stimulation, can also contribute to modulate blood vessel invasion of the cartilaginous mold at the border between cartilage and primary spongiosa.[9]

Parathyroid Hormone-Related Peptide

In quest of transcription factors involved in the molecular mechanism of endochondral ossification, researchers have identified Forkhead Box C1 (FoxC1) as an important regulator of

PTH-related peptide (PTHrP) mRNA expression through interaction with Gli2 at specific promoter sites.[10]

The PTH/PTHrP receptor (PPR) is crucial for normal growth plate development. An interesting study discussed at this meeting[11] has provided evidence that G_sa is the major mediator of the anti-hypertrophic action of PPR also in the postnatal growth plate, and that G_sa and Gq/11 may act synergistically to maintain the quiescence of stem-like cells in round proliferative layer of the growth plate at postnatal stages.

Another elegant study has proven the existence of an important genetic interaction *in vivo* between PTHrP and HDAC4, both negative regulators of chondrocyte hypertrophy.[12] Along these lines, a role for HDAC3 in chondrocyte hypertrophy through regulation of Phlpp1 phosphatase has been suggested.[13]

The expression level of a new micro RNA, miR-im6, is increased after PTHrP exposure. This micro RNA has been identified as a positive regulator of chondrogenic differentiation, as well as a hypertrophic blocker within the bone marrow-derived stem cell population.[14]

Fibroblast Growth Factor-23

The role of fibroblast growth factor-23 (FGF23) in regulation of phosphate homeostasis is well established. It is largely unknown whether FGF23 can directly affect cartilage biology. Work presented in a poster[15] has indicated that FGF23, in presence of soluble alpha-klotho, suppresses both chondrocyte proliferation and chondrocyte differentiation, and these actions can be partially reversed by Indian Hedgehog administration *in vitro*.

Articular Surface Cartilage

A poster presentation[16] has provided unequivocal evidence that the duo Smad 2/3 is essential for terminal differentiation of postnatal growth plate chondrocytes.

Along these lines, it has been also shown that the transforming growth factor-β type II receptor[17] is needed to maintain postnatal joint integrity by both promoting chondrocyte proliferation and repressing hypertrophy.

Last, the Rbpj, transcriptional effector of Notch signaling, has been shown to have a critical and nonredundant role in postnatal homeostasis of articular cartilage homeostasis.[18,19]

Conflict of Interest

The authors declare no conflict of interest.

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