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MEETING REPORTS

Chondrocytes and Cartilage Biology: Meeting Report from the 31st Annual Meeting of the American Society for Bone and Mineral Research

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Tatsuya Kobayashi

Massachusetts General Hospital, Boston, Massachusetts, USA

A number of excellent papers on chondrocytes and cartilage biology were presented at the 2009 ASBMR Annual Meeting. It is difficult to summarize the overall research trend of this year's meeting because the research topics appear to be getting more and more diverse. In terms of methodology, studies using mouse genetics have increased substantially, which may be facilitating better communication between researchers sharing the same systems.

The major research topics in the area of chondrocytes and cartilage biology include signaling and transcription factors. In addition to well-studied signaling systems including BMPs and hedgehog/PTHrP, the roles of Wnt and Notch signaling in chondrocytes were explored. Two groups (1-3) reported that genetic ablation of RBPjK, a critical transcriptional mediator of Notch signaling, altered the differentiation of cells of the chondrocyte lineage at multiple stages, causing an expansion of hypertrophic chondrocytes. While the effect of over-activation of Notch signaling in cartilage development was reported in the chick/retroviral system 10 years ago, analysis of the precise mode of action of Notch signaling in chondrocytes became possible only after the system of conditional manipulation of Notch-related genes in mice was developed.

Chondrocytes in articular cartilage have different properties from those in the growth plate. The role of Wnt signaling in articular chondrocytes was investigated by genetically overexpressing or reducing β-catenin (4). Canonical Wnt signaling appears to be required for the self-renewal and proliferation of cells in the superficial layer of articular cartilage, suggesting that Wnt signaling can be a target in the treatment of joint diseases. The non-canonical Wnt, Wnt5a, was previously reported to antagonize canonical Wnt signaling and delay cartilage development in mice. At this year's meeting, in an *in vitro* system, Wnt5a was shown to regulate chondrocyte differentiation at multiple steps through distinct signaling pathways: the CaMK/NFAT pathway to promote early chondrocyte differentiation, and the NF-κB pathway to delay chondrocyte maturation (5). NF-κB is regulated by TAK1 kinase. TAK1 also mediates other signaling pathways including TGF/BMP signaling. The role of TAK1 in cartilage was investigated *in vivo* using conditional knockout mice (6). TAK1-deficient bones exhibited a delay in cartilage development and joint fusion, demonstrating the important role of this kinase in mediating BMP signaling. This result is consistent with a similar study reported by a different group earlier this year (7).

The role of non-Smad signaling of BMP in bone has been reported at previous meetings. This year, a new paradigm was proposed regarding the mechanism by which Smad-dependent and -independent pathways are differentially activated (8). Mice missing the immunoglobin family protein, neogenin, developed multiple skeletal defects. Neogenin appears to form a complex with BMP receptors at lipid rafts. This association between neogenin and BMP receptors is required for activating the

Smad-pathway but not the p38 pathway, suggesting that neogenin regulates Smad-dependent and -independent signaling upon ligand binding to BMP receptors. The MAP kinase pathways, including p38 and MEK/ERK, regulate the proliferation and differentiation of diverse types of cells including chondrocytes. MEK/ERK signaling is negatively regulated by neurofibromatosis 1 (NF1). Conditional deletion of the NF1 gene in chondrocytes, intervertebral discs and bone caused a reduction in chondrocyte mass in the growth plate, and deformities of discs and bone, recapitulating clinical features of patients with neurofibromatosis (9).

PTHrP signaling inhibits premature hypertrophic differentiation of growth plate chondrocytes. At this year's meeting, the role of PTHrP in articular chondrocytes was investigated. PTH administration in mouse models of osteoarthritis prevented cartilage degeneration (10). Conversely, deletion of PTHrP in articular chondrocytes caused osteoarthritic lesions (11). These findings suggest that PTHrP signaling protects articular chondrocytes against osteoarthritis.

With regard to studies about transcription factors, along with Runx2 (12;13) and Sox9, a few novel transcription factors were reported to be involved in chondrogenesis and cartilage maintenance. The transcription factor Dmrt2, predominantly expressed in prehypertrophic chondrocytes, appears to be regulated by Sox9/5/6, and potentiates the function of Runx2 through a physical interaction (14). Research investigating the novel transcription factor, zfp521, revealed that zfp521 negatively regulates chondrocyte differentiation and might mediate the action of PTHrP in the regulation of chondrocyte differentiation (15). The NFAT family transcription factor Nfat1 is highly expressed in adult articular chondrocytes. Loss of Nfat1 resulted in osteoarthritic changes, suggesting its role in the maintenance of adult articular cartilage (16).

A nice translational study identified a thienoindazole-derivative as a potent chondrogenic molecule by screening small compound libraries (17). This compound induces expression of Runx1, which appears to facilitate chondrogenic differentiation through its interaction with Sox5/6/9.

Epigenetics was also a hot topic. For instance, changes in DNA methylation upon chondrocyte differentiation were investigated (18). Methylation of CpG islands was examined in genes for which expression changes upon chondrocyte differentiation. Interestingly, CpG sites of the SDF1 gene are demethylated upon chondrocyte differentiation despite the downregulation of SDF1 expression, suggesting a novel role of CpG methylation. CpG methylation does not change in genes encoding transcription factors that are important for chondrocyte differentiation, including Sox5, 6 and 9, Runx2, Osterix, Snail or Nkx3.2. Wdr5, a subunit of histone H3 K4 methyltransferase complexes, was shown to be required for chondrocyte differentiation by positively regulating Runx2 expression (19).

One of the most impressive pieces of work presented at this year's meeting investigated the role of endoplasmic reticulum (ER) stress. Chondrocytes and osteoblasts produce large amounts of extracellular matrix proteins, and therefore receive constant ER stress. Maintaining proper ER stress responses is thought to be essential for chondrocyte functions. The novel ER stress transducer, BBF2H7, was found to play a critical role in regulating ER stress in chondrocytes (20;21). Mice missing BBF2H7 developed lethal chondrodysplasia with abnormal accumulation of matrix proteins in the ER. BBF2H7 acts as a transcription factor in a fashion similar to ATF6, and regulates Sec23a, a protein responsible for protein transport from the ER to the Golgi apparatus; this pathway appears to be unique to chondrocytes. This work presents a novel molecular mechanism by which chondrocytes respond to ER stress.

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