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Cartilage in osteoarthritic joints is not automatically osteoarthritic cartilage

In their study of a novel chordin-like BMP inhibitor, CHL2, Nakayama and colleagues (Nakayama et al., 2004) report on a newly identified BMP inhibitor that is specifically expressed in developing articular cartilages, as well as in connective tissues in reproductive organs. They also show the induction of CHL2 in mesenchymal progenitor cells during chondrogenic differentiation. After maturation, chondrocytes repress CHL2 expression. This, together with the functional properties of CHL2, is well shown in this overall very instructive paper. Interestingly, the authors also try to relate CHL2 expression and function to osteoarthritic cartilage degeneration of the joints. This is an important attempt to gain insights into the aetiology of this disorder from findings generated by basic research. Unfortunately, this aspect of the paper contains, in our opinion, a substantial mistake.

Nakayama and colleagues report on the re-initiation of CHL2 expression in osteoarthritic chondrocytes, a phenomenon that might obviously interrupt the potentially important activation of chondrocytes by BMPs: in particular, BMP2 and BMP7 are known to enhance the anabolic activity of adult articular chondrocytes (Chubinskaya et al., 2000; Fan et al., 2004). In fact, knockdown of BMP activity using antisense technology has recently been suggested to cause a significant imbalance in the anabolic-catabolic activity of articular chondrocytes in articular cartilage (Soeder et al., 2005).

Therefore, the misregulation of a BMP-antagonistic molecule such as CHL2 in osteoarthritic chondrocytes might cause the downregulation of chondrocyte anabolic activity and, thus, enhance the disease process. However, despite being an attractive concept, the proposed upregulation of BMP-inhibitory activity in osteoarthritic cartilage does not agree with some of the published data: first, many studies have shown that an overall upregulation of anabolic activity occurs in osteoarthritic chondrocytes (Aigner et al., 1992; Lippiello et al., 1977) and not a downregulation, as would be expected by the expression pattern reported by the authors. In particular, middle zone chondrocytes are anabolically hyperactive (Aigner et al., 1992; Aigner et al., 1997) and osteoarthritic chondrocytes appear to be rather hyper- than hyporeactive to BMPs (Fan et al., 2004).

Osteophytic cartilage is not osteoarthritic degenerated cartilage

It appears from figures 6B and 6C in Nakayama et al. (Nakayama et al., 2004) that the authors reported on osteophytic cartilage and not on degenerated osteoarthritic cartilage. These tissue types are found in many osteoarthritic joints, but are, however, biologically and developmentally very different (Aigner et al., 1995).

There are several features that distinguish osteoarthritic from osteophytic cartilage. Osteophytes are osteo-cartilaginous outgrowths that form mostly at the margins of osteoarthritic joints. Osteophytes derive from precursor cells within periosteal or synovial tissue and often merge with or overgrow the original articular cartilage. Osteophytic cartilage shows, depending on the stage of development (Gelse et al., 2003), many different features, and can closely resemble primary joint cartilage. In general, osteophytic cartilage is hypercellular (Fig. 6B), lacks a defined tidemark (Fig. 6B,C), and often a defined subchondral bone plate (Fig. 6C). It shows instead ingrowing vessels (Fig. 6C), and the extracellular matrix often shows a fibrocartilagenous appearance (Fig. 6B). We believe that these features identify the tissues shown in Fig. 6B and 6C as being osteophytic tissue despite their limited resolution. Clearly, distinguishing these two tissues types from each other is not easy, but histologists trained in joint morphology and pathology can usually do so.

Osteophytic tissue recapitulates chondroneogenesis in the adult

Osteophyte growth essentially re-capitulates chondroneogenesis in fetal development (Aigner et al., 1995; Gelse et al., 2003): thus, depending on the stage, more or less mature cartilage formation is observed, as well as processes like endochondral ossification. Osteophyte tissues derive from mesenchymal precursor cells. After being in a chondroprogenitor cell state, the cells become active matrix-producing chondrocytes. Finally, some of them become hypertrophic. In the lowest zones of osteophytes [well visible in Fig. 6C of Nakayama et al. (Nakayama et al., 2004)], vessels grow in and endochondral ossification takes place. Thus, overall osteophytic chondrocytes resemble, in many respects, fetal chondrocytes. This possibly explains why Nakayama and colleagues observed CHL2 being strongly expressed in these newly formed chondrocytes, as in the chondrocytes of the fetal growth plate investigated in their study. In fact, similar to fetal chondrogenesis, BMPs and TGFβs are thought to play an important role in osteophyte formation, and intra-articular application of these molecules has been shown to initiate osteophyte formation (Van Beuningen et al., 1998).

Conclusion

Clearly, CHL2 represents a new BMP-inhibitory molecule, which is a very interesting finding for cartilage and osteoarthritis research. If the expression of CHL2 is confirmed in normal adult chondrocytes, it could confirm CHL2 as an important player in the homeostasis of cartilage matrix maintenance. It will be even more interesting to investigate changes in the expression levels of CHL2 in primary degenerated osteoarthritic chondrocytes in vivo.

Note added in proof

The authors of the original article were invited to respond but did not take up the opportunity to do so.

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