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EDITORIAL

The interaction of canonical bone morphogenetic protein- and Wnt-signaling pathways may play an important role in regulating cartilage degradation in osteoarthritis

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See related research by Papathanasiou *et al.*, http://arthritis-research.com/content/14/2/R82

Abstract

Bone morphogenetic proteins (BMPs) and Wnts are important signaling protein families with key roles in embryologic, patterning, development, and tissue remodeling in growth. BMP and Wnt-β-catenin are highly evolutionarily conserved pathways that, though often regulating similar cellular events, are independent signaling mechanisms that can have complementary or antagonistic effects depending on various factors, including cell type and developmental stage. Although BMP and Wnt-β-catenin have the ability to act entirely independently, there is a developing body of evidence for specific extra- and intra-cellular molecular interactions and crosstalk that occur between BMP and Wnt-β-catenin signaling and that again this may be cell type-specific. In the previous issue of *Arthritis Research & Therapy*, Papathanasiou and colleagues provide novel insights into the role and direct interaction of BMP2 and canonical Wnt-β-catenin signaling in regulating chondrocyte hypertrophy and matrix metalloproteinase/a disintegrin like and metalloproteinase with thrombospondin type I motif (MMP/ADAMTS) synthesis in osteoarthritis.

In the previous issue of *Arthritis Research & Therapy*, Papathanasiou and colleagues [1] provide novel insights into the role and direct interaction of bone morphogenetic protein 2 (BMP2) and canonical Wnt-β-catenin signaling in regulating chondrocyte hypertrophy and matrix metalloproteinase (MMP)/aggrecanolytic ADAMTS (a disintegrin like and metalloproteinase with thrombospondin type I motif) synthesis in osteoarthritis (OA). OA is the most common cause of joint pain and disability, and with increasing age and obesity of the population, the already major socioeconomic importance will continue to increase. Currently, in most Western cultures, OA afflicts more than 10% of the entire population and over a third of those over 65; an estimated 25 to 30 million people in the US suffer from this disease. The central pathological feature of OA is often considered to be the progressive destruction of articular cartilage that normally provides the load-bearing surface in the joint. Much has been learned in recent years about the mechanisms that drive cartilage matrix breakdown and loss in OA, and chondrocyte-derived metalloproteinases, particularly the ADAMTS and collagenolytic MMPs, have a key role. It is evident that a phenotypic shift in the mature articular chondrocyte to a cell type that displays many characteristics typical of hypertrophic cells in the lower zones of the growth plate is a typical feature of OA and is associated with the progressive cartilage breakdown observed (reviewed in [2]). Less clearly understood are the specific signaling pathways involved in regulating the chondrocyte phenotype, how they interact, and whether this changes in health and in diseases such as OA.

BMPs and Wnts are important signaling protein families with key roles in embryologic, patterning, development, and tissue remodeling in growth. BMP and Wnt-β-catenin are highly evolutionarily conserved pathways that, though often regulating similar cellular events, are independent signaling mechanisms that can have complementary or antagonistic effects depending on various factors, including cell type and developmental stage (reviewed in [3]). Although BMP and Wnt-β-catenin have the ability to act entirely independently,

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there is a developing body of evidence for specific extra- and intra-cellular molecular interactions and crosstalk that occur between BMP and Wnt-β-catenin signaling and that again may be cell type-specific [3]. In addition to having a key role in development, BMPs and Wnts are emerging as critical regulators of bone and cartilage homeostasis in the adult and, importantly, in the onset and progression of musculoskeletal diseases.

BMPs are multi-functional growth factors that belong to the transforming growth factor-β super family. Evidence suggests that BMP signaling is mediated primarily through the canonical BMP-Smad pathway in chondrocytes. BMPs bind the type II receptor and phosphorylate type I serine or threonine receptors, which subsequently phosphorylate Smad1, Smad5, and Smad8. BMPs are known to induce human mesenchymal stem cells to differentiate into chondrocytes, and BMP2 is a crucial local factor for chondrocyte proliferation and maturation during endochondral ossification [4,5]. In their report, Papathanasiou and colleagues show not only that human end-stage OA chondrocytes produce BMP2 and BMP4 but also, importantly, that BMP2, but not BMP4, can drive expression of low-density lipoprotein receptor 5 (LRP5). LRP5 is one of the most important co-receptors in the canonical Wnt-β-catenin signaling pathway; binding of Wnt ligands to the frizzled/LRP co-receptor complex leads to β-catenin stabilization, nuclear translocation, and activation of target genes.

There is a large body of evidence demonstrating the central role for Wnt signaling in regulating adult bone turnover; increased β-catenin activity inducing bone production and inhibition of soluble antagonists is an emerging therapeutic approach for osteoporotic and inflammatory bone loss [6,7]. In cartilage, Wnt-β-catenin signaling plays a dual role; activity is essential for chondrocyte proliferation and maintenance of their phenotypic characteristics [8], but excessive activity increases chondrocyte hypertrophy and expression of cartilage degrades metalloproteinases [9]. The effect may be cell type-specific, and Wnt-β-catenin activation is essential for maintenance of the superficial zone chondrocyte phenotype and proteoglycan 4 (lubricin) expression [8]. Inhibition of β-catenin rapidly leads to downregulation of lubricin and increased collagen X expression in superficial zone chondrocytes. In chondrocytes from human end-stage OA cartilage, activation of canonical Wnt-β-catenin signaling by Wnt-2B and Wnt-16 can drive MMP and aggrecanase production [9]. Understanding the mechanisms that regulate Wnt signaling in chondrocytes in OA may provide keys to controlling cartilage degradation.

One of the most important findings by Papathanasiou and colleagues is the demonstration of a new and unique function of BMP2 in chondrocytes in acting as a regulator of canonical Wnt-β-catenin signaling. Treatment of both normal and OA primary human chondrocytes with BMP2 for 12 hours enhanced total β-catenin expression while diminishing the degradation of β-catenin (phospho-β-catenin). This was accompanied by significant increases in mRNA for key cartilage-degrading enzymes MMP-13 and ADAMTS-5 in concert with a shift toward a hypertrophic chondrocyte phenotype as measured by increased collagen X expression. This effect was absent in LRP5 small interfering RNA (siRNA) pretreated chondrocytes and did not occur with BMP4, suggesting the unique function of BMP2 in specifically upregulating LRP5 and augmenting Wnt-β-catenin signaling. The BMP2-driven increase in LRP5 mRNA was mediated through Smad1/5/8 binding to the LRP5 promoter.

The paper by Papathanasiou and colleagues adds to the accumulating evidence that increased or perhaps excessive activation of canonical Wnt-β-catenin signaling in chondrocytes is detrimental and contributes to OA cartilage degradation. Therapeutic approaches to block or suppress canonical Wnt-β-catenin signaling may protect cartilage damage in end-stage OA. There are many naturally occurring Wnt-β-catenin signaling antagonists, including dickkopf 1 (DKK1), secreted frizzled-related proteins (sFRPs), and sclerostin (SOST). Evidence suggests that circulating DKK1 levels negatively correlate with biomarkers of cartilage breakdown in patients with OA [10]; sFRP3 knockout mice have augmented cartilage proteoglycan loss in a collagenase-induced instability model of arthritis [11], and co-treatment of SOST with pro-inflammatory cytokines can attenuate cartilage matrix breakdown [12]. The role of SOST is interesting in light of the interaction between BMP2 and Wnt signaling pathways reported by Papathanasiou and colleagues. It appears that SOST can also function as a BMP antagonist in osteoblast and osteocytes by binding intra-cellularly to BMP7 and targeting the growth factor for proteosomal degradation [13]. This provides yet another mechanism by which BMP and Wnt signaling pathways may directly interact; it will be interesting to see whether this effect of SOST on BMP7 (and possibly other BMPs) also occurs in chondrocytes, particularly in OA, where chondrocyte SOST expression is increased [12].

The BMP and Wnt signaling pathways are critical in regulating chondrocytes and maintaining the health and integrity of cartilage matrix. In other cell types/organs such as those in bone, it is the combinatorial integration and complex crosstalk between these two pathways that are emerging as significant regulators of development and tissue homeostasis [3]. The findings by Papathanasiou and colleagues suggest that similar signaling pathway interactions may be important in chondrocytes and could play a role in the development and progression of OA.

A better appreciation of chondrocyte regulatory mechanisms may provide new avenues for development of therapeutic approaches for the treatment of OA.

Abbreviations

ADAMTS, a disintegrin like and metalloproteinase with thrombospondin type I motif; BMP, bone morphogenetic protein; DKK1, dickkopf 1; LRP, low-density lipoprotein receptor; MMP, matrix metalloproteinase; OA, osteoarthritis; sFRP, secreted frizzled-related protein; SOST, sclerostin.

Competing interests

The authors declare that they have no competing interests.

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