HHS Public Access

Author manuscript

Growth Factors. Author manuscript; available in PMC 2020 January 09.

Published in final edited form as:

Growth Factors. 2018 December ; 36(5-6): 187–195. doi:10.1080/08977194.2018.1548444.

Growth Factor Signalling in Osteoarthritis

Jian Huang, **Lan Zhao**, and **Di Chen**

Department of Orthopedic Surgery, Rush University Medical Center, Chicago, IL 60612, United States

Abstract

Osteoarthritis (OA) is one of the most common diseases, affecting more than 10% of populations and thus creating immense socioeconomic burden. The pathological changes of OA involve the entire joint, which is composed of multiple types of tissues and cells, exemplified by cartilage degradation, subchondral bone thickening, osteophyte formation, synovium inflammation and hypertrophy, and ligament degeneration. As joint homeostasis requires a complex network of growth factors to regulate anabolic and catabolic events, the dysregulation of growth factor signaling would have negative impacts on structure and function of multiple joint tissues and eventually lead to the onset and progression of OA. In this review, we will discuss TGF-β, NGF, Hedgehog and Wnt, the four growth factors which have received extensive attention in the field of OA and clinical/translational interrogation about their application in OA therapies.

Keywords

Osteoarthritis; TGF-β; NGF; Hedgehog; Wnt

Among synovial joint disorders, osteoarthritis (OA) is the most common form and causes pain and disability in 13.9% of adults aged 25 years and older in the United States (Lawrence et al., 2008). OA affects the entire joint and causes complex pathological changes, such as joint space narrowing, articular cartilage (AC) destruction, synovial inflammation and hyperplasia, osteophyte formation, and subchondral bone sclerosis. It is now recognized that OA is a highly heterogeneous joint disorder, therefore it is necessary to develop personalized therapeutics to treat OA (Tonge et al., 2014). As growth factors are essential regulators in the development, homeostasis and pathogenesis of the joint, the studies of growth factors in OA have accumulated and provided sophisticated understandings. In this review, we will focus on four growth factors, TGF-β, NGF, Hedgehog and Wnt, which have important functions in joint homeostasis and OA pathogenesis and could be used as potent medicine or promising drug targets for the treatment of OA. For quick reference, we also summarize in Table 1 in vivo findings for the roles of these growth factors in OA pathogenesis or treatment.

Corresponding authors: Jian Huang, [Jian_huang@rush.edu] Or Di Chen, [di_chen@rush.edu].

Disclosures: None

TGF-β superfamily

The TGF-β superfamily has attracted great attention regarding their pleiotropic roles in joint pathophysiology, including healthy joint homeostasis and OA pathogenesis. This family embodies 42 growth factors in humans (International Human Genome Sequencing 2001), which can be classified into two subfamilies: the TGF-β/Activin/Nodal subfamily, and the bone morphogenetic protein (BMP)/growth and differentiation factor (GDF)/Muellerian inhibiting substance (MIS) subfamily (Shi and Massague, 2003). For canonical activation of the TGF-β signaling pathway, a ligand of the TGF-β superfamily, e.g. TGF-β1, BMP-2, or other TGF-β family members, form dimers that bind to two type I and two type II receptors on cell membranes to constitute a heteromeric complexes, inside which the type II receptors phosphorylate the type I receptors, significantly enhancing the recruitment and phosphorylation of receptor-regulated Smads (R-Smads) transcription factors. Upon phosphorylation, two R-Smads and one Smad4 form heteromeric complexes and translocate into the nucleus, where they interact with additional transcription factors to control gene transcription. The differences of the two subfamilies of TGF-β ligands reside not only in their sequences, but also in the R-Smads that they activate, such as Smad2/3 activated by TGF-β/Activin/Nodal, or Smad1/5/8 activated by BMP/GDF/MIS. As Smad2/3 and Smad1/5/8 regulate different sets of gene expression, the two TGF-β subfamilies elicit contrasting cellular responses in joint homeostasis and OA pathogenesis. Thus, the two subfamilies will be separately discussed in terms of their roles in OA.

The TGF-β subfamily has been demonstrated to play instrumental functions in maintaining the integrity of articular cartilage. *In vitro* treatment of articular chondrocytes or articular cartilage organ culture with TGF-β stimulated the biosynthesis of both collagen and proteoglycan, two major cartilage matrix macromolecules contributing to the mechanical strength of articular cartilage (Redini et al., 1988; Morales and Roberts, 1988). In addition, TGF-β1 can block the catabolic effects of IL-1β on articular chondrocytes by dramatically inhibiting protease production (Chandrasekhar and Harvey, 1988) and also down-regulate IL-1 receptor expression (Réadini et al., 1993). Notably, TGF-β3 and phosphorylated Smad2 were evidently expressed in normal cartilage, whereas they were not detected in severe osteoarthritic cartilage (Blaney Davidson et al., 2006), suggesting that TGF-β signaling plays an important role in maintaining cartilage homeostasis that protects cartilage from destruction. Besides ample TGF-β production by chondrocytes, large amounts of TGF-β ligands are secreted in a latent form and stored in the extracellular matrix of cartilage (Morales et al., 1991). Thus, TGF-β in reservoir could serve as a device quickly responding to matrix perturbation due to cartilage wear and tear, as cartilage lesions induce protease production that acts on latent TGF-β activation, which provides protective effects to cartilage by antagonizing catabolic factors and stimulating matrix synthesis. Importantly, TGF-β represses terminal hypertrophic differentiation of chondrocytes (Ballock et al., 1993; Yang et al., 2001), which otherwise leads to higher expression of matrix metalloproteinase 13 (MMP13) and type X collagen, chondrocyte hypertrophy and apoptosis, and cartilage calcification. Together, TGF-β regulates a diverse array of joint pathophysiology, including cartilage metabolism and chondrocyte differentiation.

Studies using genetically modified mice with mutations within the TGF-β signaling pathway offer a great opportunity to study how TGF-β regulates OA pathogenesis *in vivo*. Homozygous Smad3 loss-of-function in mice caused comprehensive degenerative changes in joints resembling human osteoarthritis, including progressive degradation of articular cartilage, outgrowth of large osteophytes, reduced production of proteoglycans, and an aberrant increase of hypertrophic chondrocytes in synovial joints (Yang et al., 2001), suggesting that TGF-β/Smad3 signaling is vital for repressing chondrocyte differentiation and OA pathogenesis. Also, loss of responsiveness to TGF-β can be achieved by overexpression of a truncated type II TGF-β receptor, which retains the ability to bind to TGF-β but cannot phosphorylate Smad2/3 due to the deletion of its cytoplasmic domains, in order to generate a dominant-negative effect. Markedly, both OA-like phenotype and enhanced terminal differentiation of articular chondrocytes were observed in the mice expressing dominant-negative type II receptors (Serra et al., 1997). To further characterize if the loss of TGF-β signaling in chondrocytes contributes to OA pathogenesis, TGFβ receptor type II was deleted specifically in chondrocytes by *Col2-CreER* (Chen et al. 2007; Zhu, Chen, Lichtler, et al. 2008) and found that the decrease of TGF-β signaling in chondrocytes caused severe OA-like pathological changes in mice, concomitantly with a significant upregulation of genes encoding for cartilage degrading enzymes, including *Mmp13*, *Adamts5* and *Adamts4* (Shen et al., 2013).

Both *in vitro* data and mouse genetics studies indicated that TGF-β could be an effective agent to restore or prevent cartilage damage, a central histologic feature of OA. However, intra-articular injection or adenoviral overexpression of TGF-β appeared to have profound negative effects on the entire joint, including extensive osteophyte formation, synovial inflammation and hyperplasia (van Beuningen et al., 2000; Bakker et al., 2001). On the other hand, inhibition of TGF-β signaling in animal OA models reduced osteophyte formation and synovial thickening (Scharstuhl et al., 2003), and systemic administration of a TGF-β receptor I inhibitor or subchondral application of a TGF-β antibody alleviated subchondral sclerosis and cartilage degeneration (Zhen et al., 2013), substantiating the notion that TGF-β administration could cause deleterious effects in OA-inflicted joints, especially in terms of synovial hyperplasia and osteophyte formation. There are also studies describing that introduction of extra TGF-β may benefits OA treatment (Lee et al., 2001; Guo et al., 2006; Ivkovic et al., 2010), which administer fibroblasts, cultured mesenchymal stem cells or bone marrow aspirates with high level expression of TGF-β into the joints. Thus, the seemingly contradiction between different studies poses a significant difficulty on further developing TGF-β-based OA therapy, especially in terms of its safety and efficacy. Importantly, the heterogeneous nature of OA and the involvement of multiple tissue/cell types in a joint as a complex organ need to be thoroughly understood, in order to facilitate the evaluation and optimization of TGF-β-based therapeutic strategies.

In addition to the TGF-β subfamily, the BMP subfamily also represents potent regulators in osteogenesis and chondrogenesis. In addition, key factors in the BMP signaling, including BMP-2/4, pSmad1/5/8, and two BMP antagonists, Noggin and Gremlin1, are evidently expressed in articular cartilage (Yu et al., 2017). Thus, it is conceivable that BMPs are also critical modulators in OA pathogenesis. Similar to TGF-β, BMP-2 also promoted proteoglycan synthesis (Chubinskaya et al., 2008), which is positive for maintaining

cartilage integrity. Moreover, combination of BMP-2 and TGF-β1 under hypoxia has a synergistically strong effect in inducing chondrogenesis of human mesenchymal stem cells (Legendre et al., 2017). However, BMP-2 expression is increased in severely damaged cartilage whereas TGF-β is not detected, suggesting that BMP-2 has functions different from TGF-β (Blaney Davidson et al., 2006). Indeed, BMP-2 injection into osteoarthritic joints aggravated osteophyte formation (van Beuningen et al., 1998), although the sites of osteophyte growth were mostly close to the growth plate, different from the osteophyte formation site induced by TGF-β. Contrary to TGF-β that inhibits chondrocyte hypertrophy, BMP-2 induced chondrocytes into terminal differentiation through Smad1 and Smad5 (Kobayashi et al., 2005; Retting et al., 2009), which underlies the observation that BMP treatment increases MMP13 expression in sternal chondrocytes, since MMP13 is induced in hypertrophic chondrocytes (D'Angelo et al., 2000). However, inducible chondrocyte-specific BMP-2 overexpression does not induce structural alterations of articular cartilage in either healthy or osteoarthritic murine joints, while it causes severe osteophyte formation in the experimental OA models (Blaney Davidson et al., 2015), suggesting that elevated expression of BMP-2 at the postnatal stage may not have considerably deleterious effects in articular cartilage. Interestingly, a recent study demonstrated that BMP-2 deletion in joint tissues (as targeted by Gdf5-Cre) results in defective development and maturation of both the meniscus and articular cartilage, which could be an critical risk factor for the ageing-related OA pathogenesis in the BMP-2 deficient mice (Gamer et al., 2018). This confirms a previous study that mice with loss of BMP signaling, achieved by targeting BMP receptor type-1A with Gdf5-Cre, display a failure in maintaining postnatal articular cartilage (Rountree et al., 2004). Thus, BMP signaling is thought to be essential for proper development and maintenance of joint tissues including articular cartilage and meniscus, which is a key to prevention of OA pathogenesis. Together, detailed characterization of the TGF-β superfamily, including the TGF-β or BMP subfamily, would be helpful to design safe, effective therapies based on these potent growth factors to treat OA, a complex degenerative joint disease.

Nerve Growth Factor

Musculoskeletal pain is a primary symptom of OA and the major reason for the disability of OA patients. Thus, pain alleviation is a prime goal of OA treatment, which would greatly improve quality of life for OA patients. As radiographic features are poorly associated with pain symptoms in OA patients, the aetiology of pain may involve additional factors than structural deterioration of the joint (Hannan et al., 2000). Specifically, aberrant neuronal activities are believed to be essential to the generation and chronicity of pain. Particularly, nerve growth factor (NGF), a member of the neurotrophin family, is required by nociceptive neurons for their survival and function, and has been demonstrated to undergo significant upregulation in the joints of OA patients (Iannone et al., 2002). NGF binds to two transmembrane receptors, of which trkA is a tyrosine receptor kinase with a high affinity with NGF and $p75^{NTR}$ is a member of the tumour necrosis factor receptor superfamily with a low NGF-binding capacity (Shu and Mendell, 1999), resulting in the activation of a multitude of signalling pathways that sensitize neurons and stimulate growth of axons and dendrites. Specifically, the binding of NGF to its receptors promotes the formation of trkA

homodimers and trkA-$p75^{NTR}$ heterodimers and the autophosphorylation of the receptors, which then activate downstream signalling cascades such as mitogen-activated protein kinases (MAPK), also known as extracellular signal-regulated kinases (ERKs), and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-protein kinase B (PKB, also known as AKT), resulting in enhanced neuronal survival and growth (Kaplan et al., 1991; Verdi et al., 1994).

NGF is a major mediator of pain in mammals, as injection of NGF induced pain and hyperalgesia in animals (Lewin et al., 1993) and humans (Petty et al., 1994) in a dose-dependent manner. Moreover, it has been reported that articular chondrocytes isolated from OA patients have upregulated levels of NGF and trkA (Iannone et al., 2002) and NGF is present in the synovial fluid of some OA patients but not detectable in the synovial fluids from normal subjects (Aloe et al., 1992). Thus, antagonism of NGF has been proposed as a promising strategy to reduce OA pain. To date, clinical trials using monoclonal antibodies against NGF, tanezumab or fasinumab, have demonstrated that NGF inhibition significantly reduced musculoskeletal pain associated with OA, compared with placebo or non-steroidal anti-inflammatory drugs (NSAIDs) (Brown et al., 2013; Tiseo et al., 2014; Lane et al., 2010). However, an adverse event, i.e. rapidly progressive OA, was confirmed to occur frequently in the patients receiving anti-NGF therapy (Hochberg et al., 2016; Lane et al., 2010), prompting the US FDA to place a hold on all clinical trials of anti-NGF therapy. Thus, NGF antagonism displays both beneficial and adverse effects strikingly in treating OA. An explanation for this unexpected result could be that significant pain palliation may encourage the patients to use their joints more than they can endure. Nevertheless, it may also implicate that NGF signalling regulates a plethora of biological activities not confined to the nervous system, or that a proper interaction with NGF-directed neural activity is essential to the wellbeing of non-neural tissues inside a synovial joint. Thus, more extensive, in-depth studies about the function of NGF in OA pathophysiology and anti-NGF therapeutics to manage OA pain would help to stratify the patients and identify those who can receive significant pain mitigation with minimal adverse effects from NGF antagonism.

Hedgehog

Expression of dominant negative type II TGF-β receptor results in an OA-like phenotype and points to increased indian hedgehog (IHH) expression that could be responsible for hypertrophic differentiation of articular chondrocytes observed in OA (Serra et al., 1997). IHH, sonic hedgehog (SHH) and desert hedgehog (DHH), are three members of the mammalian Hedgehog family (Ingham and McMahon, 2001). As secreted peptide ligands, Hedgehog (Hh) proteins act both locally and remotely in a dose- and duration-dependent manner as important morphogens in development and key players in tissue homeostasis. For Hh ligands, the primary receptor is Patched 1 (PTCH1), a transmembrane protein that inhibits activities of the Hh pathway if unbound to the Hh ligands. The repression of Hh pathway by PTCH1 is mediated by its inhibition of Smoothened (SMO), a member of the G protein-coupled receptor (GPCR) superfamily. Thus, upon Hh binding, SMO is relieved from PTCH1 suppression and activates transcriptional factors named Gli (Gli1, Gli2, and Gli3 in vertebrates) to conduct specific sets of gene expression. Among three ligands, Ihh has been demonstrated to play multiple important functions in the development of bone and

cartilage, including its regulatory role in proliferation and hypertrophic differentiation of chondrocytes (Vortkamp et al., 1996; St-Jacques et al., 1999; Kobayashi et al., 2002; Long et al., 2001), as well as in osteoblast differentiation (St-Jacques et al., 1999; Chung et al., 2001). Predominantly produced by prehypertrophic chondrocytes, Ihh promotes the expression of parathyroid hormone-related protein (PTHrP) in periarticular chondrocytes, and keeps these chondrocyte proliferating without differentiating (Vortkamp et al., 1996; St-Jacques et al., 1999). Ihh also induces the differentiation of periarticular chondrocytes into columnar chondrocytes independently of PTHrP (Kobayashi et al., 2005). Moreover, Ihh is also required for the osteoblast differentiation of perichondrial cells that is essential to bone collar formation (Long et al., 2004). Because of its proliferation-stimulating effects on chondrocytes, Ihh was tested for its cartilage repairing potential, by delivering bone marrow coagulates with adenoviral expression of Ihh to osteochondral defects in the rabbit knees. The result was promising, suggesting the capability of Ihh in cartilage repair (Sieker et al., 2015).

The pathological features such as hypertrophy and apoptosis of articular chondrocytes and bony growth including osteophytes and subchondral sclerosis suggested that Ihh signalling, an important pathway in cartilage and bone development, may undergo aberrant changes during OA pathogenesis. An examination of gene expression in human cartilage samples with early focal OA-like lesions revealed that chondrocyte differentiation associated genes, such as *Col10a1*, *Mmp9*, *PTHrP* and *Ihh*, are upregulated in OA cartilage compared with normal healthy cartilage (Tchetina et al., 2005). Further investigations on human OA samples and a mouse model with surgically-induced OA demonstrated that the expression of the genes targeted by the Hh family, including GLI1, PTCH1 and HHIP, significantly increased in OA cartilage (Lin et al., 2009). Moreover, studies of multiple genetically modified mice showed that the levels of Hh signalling in chondrocytes are closely associated with the severity of OA, suggesting a causal effect of Hh signalling upregulation in the development of OA (Lin et al., 2009). Administration of a small molecule inhibitor for Smo, an indispensable factor for Hh activation, blocked Hh signalling in a mouse arthritis model and thus significantly reduced osteophyte formation (Ruiz-Heiland et al., 2012). Similarly, specific Ihh deletion in chondrocytes reduced the progression of surgically-induced OA in mice, as shown by a relatively intact cartilage surface and decreased expression of OA marker genes such as *Col10a1* and *Mmp13* (Zhou et al., 2014). In summary, aberrant activation of Hh signalling may underlie the pathogenesis of OA and inhibition of the Hh pathway could provide a therapeutic strategy for the OA treatment.

Wnt

Canonical Wnt signalling could be regarded as the most important pathway in bone biology if we focus on human genetic studies to identify the pivotal genes in bone diseases. A prominent example is that loss-of-function mutations in LRP5 cause reduced bone mass in patients with the autosomal recessive disorder osteoporosis-pseudoglioma syndrome (Gong et al., 2001). Mechanistic studies confirmed the role of LRP5 as a co-receptor in the canonical Wnt signalling, of which its crucial role in bone formation was substantiated by numerous additional human and mouse genetic studies. Like the TGF-β superfamily and Hh proteins, the members of the Wnt family are also secreted proteins playing fundamental

functions in a variety of processes in animal development. The central event in the Wnt signalling regarding its activation or deactivation is the stabilization or degradation of β-catenin, a transcriptional regulator. In the absence of Wnt, β-catenin would undergo phosphorylation by the destruction complex comprised of Axin, APC, and GSK3 and then degradation by the ubiquitin-proteasome system. Upon the physical interaction between Wnt and its receptors Frizzled and LRP5/6, the destruction complex is recruited by the receptors to the cell membrane and the ubiquitination of β-catenin is blocked, resulting in the stabilization and accumulation of β-catenin proteins, which translocate to the nucleus and activate transcription of its target genes (Nusse and Clevers, 2017). It is notable that Wnts also bind to some subfamilies of tyrosine kinase receptors, including those from the related to tyrosine kinase (RYK) and RTK-like orphan receptor (ROR) subfamilies, regulating canonical Wnt signalling and other pathways (Roy et al., 2018). However, their functional roles in OA pathogenesis remain to be identified.

As the Wnt signalling plays key roles in bone biology, it also receives great attention in the field of OA. It was reported that mechanical injury to cartilage explants induces expression of the canonical Wnt target genes *Axin2* and *c-Jun* (Dell'Accio et al., 2006). By inhibiting Dickkopf-1 (DKK-1), a Wnt signalling antagonist, in a mouse model of rheumatoid arthritis (RA), Diarra et al. observed osteophyte formation, which is frequently observed in OA, but not bone erosion, a histologic change associated with RA. This result suggested that the enhancement of Wnt signalling overrides bone-eroding pathways in RA to convert the bone-related phenotype and implicated that Wnt signalling had a dominant, positive regulatory function in osteophyte formation (Diarra et al., 2007). Moreover, elevated serum levels of DKK-1 and Frizzled-related protein (FRP), which is also a Wnt signalling inhibitor, are associated with the reduced risk of hip OA progression in elderly Caucasian women (Lane et al., 2007). Thus, these findings suggest that upregulation of Wnt signalling could be a causal factor in the development and progression of OA. Importantly, deletion of Exon 3 of the β-catenin gene in articular chondrocytes, which generates a mutant of β-catenin resistant to phosphorylation by GSK-3β and therefore causes persistent activation of the canonical Wnt signalling, leads to comprehensive OA-like changes including cartilage damage, osteophyte formation and new subchondral bone formation (Zhu et al., 2009). In addition, OA marker genes including *Mmp9*, *Mmp13*, and *Col10a1* are significantly upregulated in articular chondrocytes derived from the mice with β-catenin activation (Zhu et al., 2009). Thus, this study establishes a causal link between the activation of the Wnt/β-catenin signalling and the pathogenesis of OA, which has been corroborated by additional studies using alternative approaches to perturb the Wnt signalling. For examples, transgenic expression of Dkk-1 in chondrocytes inhibited the Wnt pathway alleviated cartilage destruction in surgically-induced OA knee joints (Oh et al., 2012), and intraarticular injection of a GSK-3 inhibitor GIN induces cartilage surface fibrillation, a decrease in glycosaminoglycan expression and chondrocyte hypocellularity (Miclea et al., 2011). In addition, aberrant increase of the Wnt signalling in non-cartilage joint tissues also has a negative impact on cartilage. Synovial overexpression of Wnt ligands through adenoviral transduction induces the Wnt signalling in the cartilage and leads to enhanced activity of cartilage-degrading enzymes and aggravated cartilage damage (van den Bosch et al., 2015; 2017), suggesting that Wnt signalling in synovium promotes catabolic effects in cartilage through increased production of matrix

metalloproteinases. Nevertheless, downregulation of Wnt signalling also had deleterious effects on articular cartilage as demonstrated by overexpression of ICAT, a small peptide inhibiting β-catenin-TCF binding, in chondrocytes (Zhu et al., 2008). Taken together, the perturbation of the Wnt/β-catenin cascade could be a key molecular mechanism underlying the pathogenesis of OA and therefore study of the Wnt signalling pathway would provide insights into the design of new therapeutics to treat OA.

In conclusion, we have accumulated considerable knowledge of the functions of TGF-β, NGF, Hedgehog, and Wnt proteins in joint homeostasis and degeneration, many of which holds promise for the invention of new therapies for OA treatment. Still, further investigations, particularly those on translational or clinical studies, would provide irreplaceable insights into the safety and efficacy of the therapies that are designed to boost or target these growth factors inside the joints.

Acknowledgements

We apologize to colleagues whose work was not cited in this introductory review due to space limitations. This work was supported by National Institutes of Health Grants R01 AR054465 and R01 AR070222 to DC.

References:

Aloe L, Tuveri MA, Carcassi U, and Levi-Montalcini R. 1992 “Nerve growth factor in the synovial fluid of patients with chronic arthritis.” Arthritis Rheum 35 (3):351–5. [PubMed: 1536673]

Bakker AC, van de Loo FAJ, van Beuningen HM, Sime P, van Lent PLEM, van der Kraan PM, Richards CD, and van den Berg WB. 2001 “Overexpression of active TGF-beta-1 in the murine knee joint: evidence for synovial-layer-dependent chondro-osteophyte formation.” Osteoarthritis and Cartilage 9 (2):128–36. doi: 10.1053/joca.2000.0368. [PubMed: 11237660]

Ballock R. Tracy, Heydemann Ahlke, Wakefield Lalage M., Flanders Kathleen C., Roberts Anita B., and Sporn Michael B.. 1993 “TGF-β1 Prevents Hypertrophy of Epiphyseal Chondrocytes: Regulation of Gene Expression for Cartilage Matrix Proteins and Metalloproteases.” Developmental Biology 158 (2):414–29. doi: 10.1006/dbio.1993.1200. [PubMed: 8344460]

Blaney Davidson EN, Vitters EL, van der Kraan PM, and van den Berg WB. 2006 “Expression of transforming growth factor-β (TGF-β) and the TGF-β signalling molecule Smad2P in spontaneous and instability-induced osteoarthritis: role in cartilage degradation, chondrogenesis and osteophyte formation.” Annals of the Rheumatic Diseases 65 (11):1414–21. doi: 10.1136/ard.2005.045971. [PubMed: 16439443]

Blaney Davidson EN, Vitters EL, Bennink MB, van Lent PL, van Caam AP, Blom AB, van den Berg WB, van de Loo FA, and van der Kraan PM. 2015 “Inducible chondrocyte-specific overexpression of BMP-2 in young mice results in severe aggravation of osteophyte formation in experimental OA without altering cartilage damage.” Ann Rheum Dis 74 (6):1257–64. doi: 10.1136/annrheumdis-2013-204528. [PubMed: 24448347]

Brown MT, Murphy FT, Radin DM, Davignon I, Smith MD, and West CR. 2013 “Tanezumab reduces osteoarthritic hip pain: results of a randomized, double-blind, placebo-controlled phase III trial.” Arthritis Rheum 65 (7):1795–803. doi: 10.1002/art.37950. [PubMed: 23553790]

Chandrasekhar Srinivasan, and Harvey Anita K.. 1988 “Transforming growth factor β is a potent inhibitor of IL-1 induced protease activity and cartilage proteoglycan degradation.” Biochemical and Biophysical Research Communications 157 (3):1352–9. doi: 10.1016/S0006-291X(88)81024-6. [PubMed: 3144973]

Chen M, Lichtler AC, Sheu TJ, Xie C, Zhang X, O’Keefe RJ, and Chen D. 2007 “Generation of a transgenic mouse model with chondrocyte-specific and tamoxifen-inducible expression of Cre recombinase.” Genesis 45 (1):44–50. doi: 10.1002/dvg.20261. [PubMed: 17211877]

Chubinskaya Susan, Segalite Diane, Pikovsky Dmitriy, Hakimiyan Arnavaz A., and Rueger David C.. 2008 “Effects induced by BMPS in cultures of human articular chondrocytes: Comparative studies.” Growth Factors 26 (5):275–83. doi: 10.1080/08977190802291733. [PubMed: 18651287]

Chung Ung-il, Schipani Ernestina, McMahon Andrew P., and Kronenberg Henry M.. 2001 “Indian hedgehog couples chondrogenesis to osteogenesis in endochondral bone development.” The Journal of Clinical Investigation 107 (3):295–304. doi: 10.1172/JCI11706. [PubMed: 11160153]

D’Angelo M, Yan Z, Nooreyazdan M, Pacifici M, Sarment DS, Billings PC, and Leboy PS. 2000 “MMP13 is induced during chondrocyte hypertrophy.” J Cell Biochem 77 (4):678–93. [PubMed: 10771523]

Dell’Accio F, De Bari C, El Tawil NM, Barone F, Mitsiadis TA, O’Dowd J, and Pitzalis C. 2006 “Activation of WNT and BMP signaling in adult human articular cartilage following mechanical injury.” Arthritis Res Ther 8 (5):R139. doi: 10.1186/ar2029. [PubMed: 16893455]

Diarra D, Stolina M, Polzer K, Zwerina J, Ominsky MS, Dwyer D, Korb A, et al. 2007 “Dickkopf-1 is a master regulator of joint remodeling.” Nat Med 13 (2):156–63. doi: 10.1038/nm1538. [PubMed: 17237793]

Gamer LW, Pregizer S, Gamer J, Feigenson M, Ionescu A, Li Q, Han L, and Rosen V. 2018 “The role of Bmp2 in the maturation and maintenance of the murine knee joint.” J Bone Miner Res. doi: 10.1002/jbmr.3441.

Gong Y, Slee RB, Fukai N, Rawadi G, Roman-Roman S, Reginato AM, Wang H, et al. 2001 “LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development.” Cell 107 (4):513–23. [PubMed: 11719191]

Hannan MT, Felson DT, and Pincus T. 2000 “Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee.” J Rheumatol 27 (6):1513–7. [PubMed: 10852280]

Hochberg MC, Tive LA, Abramson SB, Vignon E, Verburg KM, West CR, Smith MD, and Hungerford DS. 2016 “When is osteonecrosis not osteonecrosis?: Adjudication of reported serious adverse joint events in the Tanezumab clinical development program.” Arthritis Rheumatol 68 (2):382–91. doi: 10.1002/art.39492. [PubMed: 26554876]

Iannone F, De Bari C, Dell’Accio F, Covelli M, Patella V, Lo Bianco G, and Lapadula G. 2002 “Increased expression of nerve growth factor (NGF) and high affinity NGF receptor (p140 TrkA) in human osteoarthritic chondrocytes.” Rheumatology (Oxford) 41 (12):1413–8. [PubMed: 12468822]

Ingham Philip W., and McMahon Andrew P.. 2001 “Hedgehog signaling in animal development: paradigms and principles.” Genes & Development 15 (23):3059–87. doi: 10.1101/gad.938601. [PubMed: 11731473]

International Human Genome Sequencing, Consortium. 2001 “Initial sequencing and analysis of the human genome.” Nature 409:860. doi: 10.1038/3505706210.1038/35057062https://www.nature.com/articles/35057062#supplementary-informationhttps://www.nature.com/articles/35057062#supplementary-information . [PubMed: 11237011]

Ivkovic A, Pascher A, Hudetz D, Maticic D, Jelic M, Dickinson S, Loparic M, Haspl M, Windhager R, and Pecina M. 2010 “Articular cartilage repair by genetically modified bone marrow aspirate in sheep.” Gene Therapy 17:779. doi: 10.1038/gt.2010.16. [PubMed: 20220780]

Kaplan DR, Hempstead BL, Martin-Zanca D, Chao MV, and Parada LF. 1991 “The trk proto-oncogene product: a signal transducing receptor for nerve growth factor.” Science 252 (5005):554–8. [PubMed: 1850549]

Kobayashi T, Chung UI, Schipani E, Starbuck M, Karsenty G, Katagiri T, Goad DL, Lanske B, and Kronenberg HM. 2002 “PTHrP and Indian hedgehog control differentiation of growth plate chondrocytes at multiple steps.” Development 129 (12):2977–86. [PubMed: 12050144]

Kobayashi Tatsuya, Lyons Karen M., McMahon Andrew P., and Kronenberg Henry M.. 2005 “BMP signaling stimulates cellular differentiation at multiple steps during cartilage development.” Proceedings of the National Academy of Sciences of the United States of America 102 (50):18023–7. doi: 10.1073/pnas.0503617102. [PubMed: 16322106]

Kobayashi Tatsuya, Soegiarto Desi W., Yang Yingzi, Lanske Beate, Schipani Ernestina, McMahon Andrew P., and Kronenberg Henry M.. 2005 “Indian hedgehog stimulates periarticular

chondrocyte differentiation to regulate growth plate length independently of PTHrP." The Journal of Clinical Investigation 115 (7):1734–42. doi: 10.1172/JCI24397. [PubMed: 15951842]

Lane NE, Nevitt MC, Lui LY, de Leon P, and Corr M. 2007 "Wnt signaling antagonists are potential prognostic biomarkers for the progression of radiographic hip osteoarthritis in elderly Caucasian women." Arthritis Rheum 56 (10):3319–25. doi: 10.1002/art.22867. [PubMed: 17907185]

Lane NE, Schnitzer TJ, Birbara CA, Mokhtarani M, Shelton DL, Smith MD, and Brown MT. 2010 "Tanezumab for the treatment of pain from osteoarthritis of the knee." N Engl J Med 363 (16): 1521–31. doi: 10.1056/NEJMoa0901510. [PubMed: 20942668]

Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, Gabriel S, et al. 2008 "Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II." Arthritis Rheum 58 (1):26–35. doi: 10.1002/art.23176. [PubMed: 18163497]

Lee Kwan Hee, Song Sun U., Hwang Tae Sook, Yi Youngsuk, In Suk Oh, Lee Joung Yoon, Choi Kyoung Baek, Choi Mi Sook, and Kim Seong-Jin. 2001 "Regeneration of hyaline cartilage by cell-mediated gene therapy using transforming growth factor β1-producing fibroblasts." Human Gene Therapy 12 (14):1805–13. doi: 10.1089/104303401750476294. [PubMed: 11560773]

Legendre F, Ollitrault D, Gomez-Leduc T, Bouyoucef M, Hervieu M, Gruchy N, Mallein-Gerin F, Leclercq S, Demoor M, and Galera P. 2017 "Enhanced chondrogenesis of bone marrow-derived stem cells by using a combinatory cell therapy strategy with BMP-2/TGF-β1, hypoxia, and COL1A1/HtrA1 siRNAs." Sci Rep 7 (1):3406. doi: 10.1038/s41598-017-03579-y. [PubMed: 28611369]

Lewin GR, Ritter AM, and Mendell LM. 1993 "Nerve growth factor-induced hyperalgesia in the neonatal and adult rat." J Neurosci 13 (5):2136–48. [PubMed: 8478693]

Lin AC, Seeto BL, Bartoszko JM, Khoury MA, Whetstone H, Ho L, Hsu C, Ali SA, and Alman BA. 2009 "Modulating hedgehog signaling can attenuate the severity of osteoarthritis." Nat Med 15 (12):1421–5. doi: 10.1038/nm.2055 [pii]. [PubMed: 19915594]

Long F, Chung UI, Ohba S, McMahon J, Kronenberg HM, and McMahon AP. 2004 "Ihh signaling is directly required for the osteoblast lineage in the endochondral skeleton." Development 131 (6): 1309–18. doi: 10.1242/dev.01006. [PubMed: 14973297]

Long F, Zhang XM, Karp S, Yang Y, and McMahon AP. 2001 "Genetic manipulation of hedgehog signaling in the endochondral skeleton reveals a direct role in the regulation of chondrocyte proliferation." Development 128 (24):5099–108. [PubMed: 11748145]

Miclea RL, Siebelt M, Finos L, Goeman JJ, Lowik CW, Oostdijk W, Weinans H, Wit JM, Robanus-Maandag EC, and Karperien M. 2011 "Inhibition of Gsk3beta in cartilage induces osteoarthritic features through activation of the canonical Wnt signaling pathway." Osteoarthritis Cartilage 19 (11):1363–72. doi: 10.1016/j.joca.2011.07.014. [PubMed: 21911068]

Morales TI, Joyce ME, Sobel ME, Danielpour D, and Roberts AB. 1991 "Transforming growth factor β in calf articular cartilage organ cultures: Synthesis and distribution." Archives of Biochemistry and Biophysics 288 (2):397–405. doi: 10.1016/0003-9861(91)90212-2. [PubMed: 1716871]

Morales TI, and Roberts AB. 1988 "Transforming growth factor β regulates the metabolism of proteoglycans in bovine cartilage organ cultures." J Biol Chem 263 (26):12828–31. [PubMed: 3166454]

Nusse R, and Clevers H. 2017 "Wnt/β-Catenin Signaling, Disease, and Emerging Therapeutic Modalities." Cell 169 (6):985–99. doi: 10.1016/j.cell.2017.05.016. [PubMed: 28575679]

Oh H, Chun CH, and Chun JS. 2012 "Dkk-1 expression in chondrocytes inhibits experimental osteoarthritic cartilage destruction in mice." Arthritis Rheum 64 (8):2568–78. doi: 10.1002/art.34481. [PubMed: 22488261]

Petty BG, Cornblath DR, Adornato BT, Chaudhry V, Flexner C, Wachsman M, Sinicropi D, Burton LE, and Peroutka SJ. 1994 "The effect of systemically administered recombinant human nerve growth factor in healthy human subjects." Ann Neurol 36 (2):244–6. doi: 10.1002/ana.410360221. [PubMed: 8053664]

Réadini F, Mauviel A, Pronost S, Loyau G, and Pujol JP. 1993 "Transforming growth factor β exerts opposite effects from interleukin-1β on cultured rabbit articular chondrocytes through reduction of interleukin-1 receptor expression." Arthritis & Rheumatism 36 (1):44–50. doi: 10.1002/art.1780360108. [PubMed: 8424835]

Redini F, Galera P, Mauviel A, Loyau G, and Pujol JP. 1988 “Transforming growth factor β stimulates collagen and glycosaminoglycan biosynthesis in cultured rabbit articular chondrocytes.” FEBS Letters 234 (1):172–5. doi: 10.1016/0014-5793(88)81327-9. [PubMed: 3164687]

Retting Kelsey N., Song Buer, Yoon Byeong S., and Lyons Karen M.. 2009 “BMP canonical Smad signaling through Smad1 and Smad5 is required for endochondral bone formation.” Development 136 (7):1093–104. doi: 10.1242/dev.029926. [PubMed: 19224984]

Rountree RB, Schoor M, Chen H, Marks ME, Harley V, Mishina Y, and Kingsley DM. 2004 “BMP receptor signaling is required for postnatal maintenance of articular cartilage.” PLoS Biol 2 (11):e355. doi: 10.1371/journal.pbio.0020355. [PubMed: 15492776]

Roy JP, Halford MM, and Stacker SA. 2018 “The biochemistry, signalling and disease relevance of RYK and other Wnt-binding receptor tyrosine kinases.” Growth Factors 36 (1–2):15–40. doi: 10.1080/08977194.2018.1472089. [PubMed: 29806777]

Ruiz-Heiland G, Horn A, Zerr P, Hofstetter W, Baum W, Stock M, Distler JH, Nimmerjahn F, Schett G, and Zwerina J. 2012 “Blockade of the hedgehog pathway inhibits osteophyte formation in arthritis.” Ann Rheum Dis 71 (3):400–7. doi: 10.1136/ard.2010.148262. [PubMed: 22233602]

Scharstuhl Alwin, Vitters Elly L., van der Kraan Peter M., and van den Berg Wim B.. 2003 “Reduction of osteophyte formation and synovial thickening by adenoviral overexpression of transforming growth factor β/bone morphogenetic protein inhibitors during experimental osteoarthritis.” Arthritis & Rheumatism 48 (12):3442–51. doi: 10.1002/art.11328. [PubMed: 14673995]

Serra Rosa, Johnson Mahlon, Filvaroff Ellen H., LaBorde James, Sheehan Daniel M., Derynck Rik, and Moses Harold L.. 1997 “Expression of a truncated, kinase-defective TGF-β type II receptor in mouse skeletal tissue promotes terminal chondrocyte differentiation and osteoarthritis.” The Journal of Cell Biology 139 (2):541–52. doi: 10.1083/jcb.139.2.541. [PubMed: 9334355]

Shen J, Li J, Wang B, Jin H, Wang M, Zhang Y, Yang Y, Im H-J, O’Keefe RJ, and Chen D. 2013 “Deletion of the transforming growth factor β receptor type II gene in articular chondrocytes leads to a progressive osteoarthritis-like phenotype in mice.” Arthritis Rheum 65 (12):3107–19. doi: 10.1002/art.38122. [PubMed: 23982761]

Shi Y, and Massague J. 2003 “Mechanisms of TGF-β signaling from cell membrane to the nucleus.” Cell 113 (6):685–700. [PubMed: 12809600]

Shu XQ, and Mendell LM. 1999 “Neurotrophins and hyperalgesia.” Proc Natl Acad Sci U S A 96 (14): 7693–6. [PubMed: 10393882]

Sieker JT, Kunz M, Weissenberger M, Gilbert F, Frey S, Rudert M, and Steinert AF. 2015 “Direct bone morphogenetic protein 2 and Indian hedgehog gene transfer for articular cartilage repair using bone marrow coagulates.” Osteoarthritis Cartilage 23 (3):433–42. doi: 10.1016/j.joca.2014.11.008. [PubMed: 25463442]

St-Jacques Benoit, Hammerschmidt Matthias, and McMahon Andrew P.. 1999 “Indian hedgehog signaling regulates proliferation and differentiation of chondrocytes and is essential for bone formation.” Genes & Development 13 (16):2072–86. [PubMed: 10465785]

Tchetina EV, Squires G, and Poole AR. 2005 “Increased type II collagen degradation and very early focal cartilage degeneration is associated with upregulation of chondrocyte differentiation related genes in early human articular cartilage lesions.” J Rheumatol 32 (5):876–86. [PubMed: 15868625]

Tiseo PJ, Kivitz AJ, Ervin JE, Ren H, and Mellis SJ. 2014 “Fasinumab (REGN475), an antibody against nerve growth factor for the treatment of pain: results from a double-blind, placebo-controlled exploratory study in osteoarthritis of the knee.” Pain 155 (7):1245–52. doi: 10.1016/j.pain.2014.03.018. [PubMed: 24686255]

Tonge DP, Pearson MJ, and Jones SW. 2014 “The hallmarks of osteoarthritis and the potential to develop personalised disease-modifying pharmacological therapeutics.” Osteoarthritis Cartilage 22 (5):609–21. doi: 10.1016/j.joca.2014.03.004. [PubMed: 24632293]

van Beuningen HM, Glansbeek HL, van der Kraan PM, and van den Berg WB. 1998 “Differential effects of local application of BMP-2 or TGF-β1 on both articular cartilage composition and osteophyte formation.” Osteoarthritis Cartilage 6 (5):306–17. doi: 10.1053/joca.1998.0129. [PubMed: 10197165]

van Beuningen HM, Glansbeek HL, van der Kraan PM, and van den Berg WB. 2000 “Osteoarthritis-like changes in the murine knee joint resulting from intra-articular transforming growth factor β injections.” Osteoarthritis and Cartilage 8 (1):25–33. doi: 10.1053/joca.1999.0267. [PubMed: 10607496]

van den Bosch MH, Blom AB, Sloetjes AW, Koenders MI, van de Loo FA, van den Berg WB, van Lent PL, and van der Kraan PM. 2015 “Induction of canonical Wnt signaling by synovial overexpression of selected Wnts leads to protease activity and early osteoarthritis-like cartilage damage.” Am J Pathol 185 (7):1970–80. doi: 10.1016/j.ajpath.2015.03.013. [PubMed: 25976248]

van den Bosch MH, Blom AB, van de Loo FA, Koenders MI, Lafeber FP, van den Berg WB, van der Kraan PM, and van Lent PL. 2017 “Brief report: Induction of matrix metalloproteinase expression by synovial Wnt signaling and association with disease progression in early symptomatic osteoarthritis.” Arthritis Rheumatol 69 (10):1978–83. doi: 10.1002/art.40206. [PubMed: 28678406]

Verdi JM, Birren SJ, Ibanez CF, Persson H, Kaplan DR, Benedetti M, Chao MV, and Anderson DJ. 1994 “p75LNGFR regulates Trk signal transduction and NGF-induced neuronal differentiation in MAH cells.” Neuron 12 (4):733–45. [PubMed: 7512816]

Vortkamp A, Lee K, Lanske B, Segre GV, Kronenberg HM, and Tabin CJ. 1996 “Regulation of rate of cartilage differentiation by Indian hedgehog and PTH-related protein.” Science 273 (5275):613–22. [PubMed: 8662546]

Guo X, Zheng Q, Yang S, Shao Z, Yuan Q, Pan Z, Tang S, Liu K, and Quan D. 2006 “Repair of full-thickness articular cartilage defects by cultured mesenchymal stem cells transfected with the transforming growth factor β 1 gene.” Biomedical Materials 1 (4):206. [PubMed: 18458408]

Yang X, Chen L, Xu X, Li C, Huang C, and Deng C-X. 2001 “TGF-β/Smad3 signals repress chondrocyte hypertrophic differentiation and are required for maintaining articular cartilage.” The Journal of Cell Biology 153 (1):35–46. doi: 10.1083/jcb.153.1.35. [PubMed: 11285272]

Yu X, Kawakami H, Tahara N, Olmer M, Hayashi S, Akiyama R, Bagchi A, Lotz M, and Kawakami Y. 2017 “Expression of Noggin and Gremlin1 and its implications in fine-tuning BMP activities in mouse cartilage tissues.” J Orthop Res 35 (8):1671–82. doi: 10.1002/jor.23463. [PubMed: 27769098]

Zhen G, Wen C, Jia X, Li Y, Crane JL, Mears SC, Askin FB, et al. 2013 “Inhibition of TGF-β signaling in mesenchymal stem cells of subchondral bone attenuates osteoarthritis.” Nat Med 19 (6):704–12. doi: 10.1038/nm.3143 [pii]. [PubMed: 23685840]

Zhou J, Chen Q, Lanske B, Fleming BC, Terek R, Wei X, Zhang G, Wang S, Li K, and Wei L. 2014 “Disrupting the Indian hedgehog signaling pathway in vivo attenuates surgically induced osteoarthritis progression in Col2a1-CreER T2 ; Ihhfl/fl mice.” Arthritis Research & Therapy 16 (1):R11. doi: 10.1186/ar4437. [PubMed: 24428864]

Zhu M, Chen M, Lichtler AC, O’Keefe RJ, and Chen D. 2008 “Tamoxifen-inducible Cre-recombination in articular chondrocytes of adult Col2a1-CreER(T2) transgenic mice.” Osteoarthritis Cartilage 16 (1):129–30. doi: 10.1016/j.joca.2007.08.001. [PubMed: 17888690]

Zhu M, Chen M, Zuscik M, Wu Q, Wang YJ, Rosier RN, O’Keefe RJ, and Chen D 2008 “Inhibition of β-catenin signaling in articular chondrocytes results in articular cartilage destruction.” Arthritis Rheum 58 (7):2053–64. doi: 10.1002/art.23614. [PubMed: 18576323]

Zhu M, Tang D, Wu Q, Hao S, Chen M, Xie C, Rosier RN, O’Keefe RJ, Zuscik M, and Chen D. 2009 “Activation of β-catenin signaling in articular chondrocytes leads to osteoarthritis-like phenotype in adult β-catenin conditional activation mice.” J Bone Miner Res 24 (1):12–21. doi: 10.1359/jbmr.080901. [PubMed: 18767925]

Table 1.

A summary of *in vivo* evidence for the roles of the growth factors discussed in this review.

Growth factor	Evidence for anti-OA roles	Evidence for pro-OA
TGF-β	• Overexpression of dominant negative type II TGF-β receptor in mice causes articular cartilage (AC) degeneration, osteophyte growth, and hyperplastic synovium [1]. • Smad3$^{-/-}$ mice exhibit AC destruction, osteophytes, reduced production of proteoglycans (PG), and an increase of hypertrophic chondrocytes [2]. • Chondrocyte-specific deletion of type II TGF-β receptor in mice resulted in AC degradation, osteophytes, and increased subchondral bone [3]. • TGF-β1 injection stimulates PG synthesis in murine joints [4]. • Injection of TGF-β1-expressing fibroblasts or mesenchymal stem cells into rabbits shows cartilage regeneration [5, 6]. • Implantation of TGF-β1-transduced bone marrow aspirates repairs cartilage defects in sheep [7].	• Repeated TGF-β1 injection induces chondro-osteophyte formation [4]. • Injection of TGF-β in mice causes cartilage lesion at tide mark and osteophyte formation [8]. • Adenoviral expression of TGF-β1 in mice results in synovial hyperplasia and chondro-osteophyte formation [9]. • Overexpression of TGF-β antagonist, such as mLAP-1, Smad6, and Smad7 in mice decreases synovial thickening and/or osteophyte formation [10]. • Systemic injection of SB505124, an inhibitor of type I TGF-β receptor, or implantation of TGF-β antibody in the subchondral bone of rats attenuates subchondral sclerosis and AC degeneration [11].
BMP	• BMP-2 injection stimulates PG synthesis in murine joints [4]. • Loss of BMP-2 or BMP receptor type-1A in mice leads to a failure in maturation and maintenance of articular cartilage and meniscus, leading to spontaneous OA [12, 13].	• Repeated BMP-2 injection or inducible chondrocyte-specific overexpression of BMP-2 induces chondro-osteophyte formation [4, 14].
NGF	• Treatment of tanezumab, a monoclonal antibody against NGF, is associated with rapidly progression of OA in the clinical trials of knee and hip OA pain [15].	• Tanezumab and fasinumab, both monoclonal anti-NGF antibodies, have demonstrated efficacy in pain palliation [15, 16, 17].
Hedgehog	• Delivery of bone marrow coagulates with adenoviral expression of Ihh improves cartilage repair in the rabbit knees [18].	• Haploinsufficiency of Ptch1, overexpression of Gli2, or constitutive activation of Smo, which all upregulate Hedgehog signaling, cause OA in mice [19]. • Genetic or pharmacological inhibition of Hedgehog signaling by deactivating an allele of Smo, deleting Ihh, or administrating small molecule inhibitors, attenuated OA in mice [19, 20, 21].
Wnt	• Inhibition of Wnt signaling in articular chondrocytes by expressing ICAT causes articular cartilage destruction [22].	• Expression of degradation-resistant β-catenin in chondrocytes, or induction of Wnt signaling in synovium causes OA in mice [23, 24]. • Transgenic expression of Dkk-1, a Wnt antagonist, in chondrocytes alleviated cartilage

Growth factor	Evidence for anti-OA roles	Evidence for pro-OA
		degradation in knee joints with surgically-induced OA [25].

[1] Serra et al., 1997;

[2] Yang et al., 2001,

[3] Shen et al., 2013;

[4] van Beuningen et al., 1998;

[5] Lee et al., 2001;

[6] Guo et al., 2006;

[7] Ivkovic et al., 2010;

[8] van Beuningen et al., 2000;

[9] Bakker et al., 2001;

[10] Scharstuhl et al., 2003;

[11] Zhen et al., 2013;

[12] Gamer et al., 2018;

[13] Rountree et al., 2004;

[14] Blaney Davidson et al., 2015;

[15] Lane et al., 2010;

[16] Brown et al., 2013;

[17] Tiseo et al., 2014;

[18] Sieker et al., 2015;

[19] Lin et al., 2009;

[20] Ruiz-Heiland et al., 2012;

[21] Zhou et al., 2014;

[22] Zhu et al., 2008;

[23] Zhu et al., 2009;

[24] van den Bosch et al., 2015;

[25] Oh et al., 2012.