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Review
TGF-β and osteoarthritis

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Summary

Objective: Cartilage damage is a major problem in osteoarthritis (OA). Growth factors like transforming growth factor-β (TGF-β) have great potential in cartilage repair. In this review, we will focus on the potential therapeutic intervention in OA with TGF-β, application of the growth factor TGF-β in cartilage repair and on the side effects of TGF-β treatment that could occur.

Methods: This review summarizes peer-reviewed articles published in the PubMed database before November 2006. In addition, this review is supplemented with recent data of our own group on the use of TGF-β as a cartilage reparative factor in OA.

Results: TGF-β is crucial for cartilage maintenance and lack there of results in OA-like changes. Moreover, TGF-β supplementation can enhance cartilage repair and is therefore a potential therapeutic tool. However, application of TGF-β supplementation provides problems in other tissues of the joint and results in fibrosis and osteophyte formation. This can potentially be overcome by local inhibition of TGF-β at sites of unwanted side-effects or by blocking downstream mediators of TGF-β that are important for the induction of fibrosis or osteophyte formation.

Conclusion: Current understanding of TGF-β suggests that it essential for cartilage integrity and that it is a powerful tool to prevent or repair cartilage damage. The side-effects that occur with TGF-β supplementation can be overcome by local inhibition of TGF-β itself or downstream mediators.

Key words: TGF-β, Osteoarthritis, Cartilage, CTGF, BMP-2, Fibrosis, Osteophytes.

Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis, involving cartilage, synovium and bone. The main characteristics are cartilage damage, synovial fibrosis, sclerosis of the subchondral bone and osteophyte formation at the joint margins[1]. Clinically, OA is characterized by joint pain, tenderness, occasional effusions and eventually loss of joint function. The cause of OA is unknown in most cases. It is highly feasible that there is not one main initiating event of OA, but that several different events can lead to a common disease pathway eventually leading to the same disease. Regardless of the initiating trigger cartilage damage is the main event in OA. Cartilage has a very limited intrinsic reparative capacity. As a consequence, cartilage damage results in progressive disease. This makes it crucial to target cartilage damage at an early stage to prevent further progression.

Cartilage

Cartilage is non-vascular and nutrients are provided by the synovial fluid. On a weight base it is mainly composed of collagens and proteoglycans. Collagens provide tensile strength and proteoglycans retain water molecules in the matrix. In humans, cartilage is composed of three zones: superficial, middle and deep zone, each with a distinct composition. The superficial zone includes disc-shaped chondrocytes and the collagen fibers are aligned along the surface. The middle zone has a higher proteoglycan content than the superficial zone, cells are more spherical and the collagen fibers are orientated isotropically. The deep zone contains spherical cells and collagens have a peripendicular orientation[1].

Cartilage damage in OA has several hallmarks. Initially, in contrast to what is expected during damage, an increased synthesis of matrix molecules is observed. However, in time cartilage matrix degradation exceeds matrix deposition resulting in net matrix loss. In early OA the cartilage surface is still intact, but shows some focal edema or even minor fibrillations. The chondrocytes then start to proliferate and form cell clusters. In addition, chondrocyte hypertrophy can be observed. Subsequently, the superficial zone shows fibrillations and loss of chondrocytes. The fibrillations then progress into fissures that extend into the mid zone, followed by cartilage erosion, denudation of bone and finally deformation[2].

Chondrocytes can be stimulated by catabolic cytokines to release cartilage degradation products, ultimately leading to damage. In the 1980s catabolin, now termed interleukin-1 (IL-1), was discovered to play a role in OA. Several groups described its capacity to induce metalloproteinases in cartilage and its ability to stimulate chondrocytes to degrade both proteoglycan and collagen[3,4]. The exact nature of

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the major mediator of chondrocyte activation in OA is not identified yet, but IL-1β is considered to be a principle mediator of joint damage in OA[5]. It causes destruction of cartilage by increasing enzyme activity and inflammation while inhibiting synthesis of enzyme-inhibitors[6]. IL-1 and tumor necrosis factor-α (TNF-α) can stimulate chondrocytes to produce of nitric oxide (NO)[7], matrix metalloproteinases (MMPs)[8], aggrecanases (ADAMTS)[9] and suppress the synthesis of aggrecan and collagen[10–14].

In normal cartilage there is constant degradation as well as synthesis of cartilage matrix molecules, controlled by the chondrocytes. A high degradation rate does not necessarily implicate OA as long as there is enough compensation by synthesis. Besides catabolic factors OA chondrocytes also express anabolic factors, like insulin-like growth factor-1 and transforming growth factor (TGF)-β that stimulate extracellular matrix (ECM) production[15–18]. Increased synthetic activity in early OA has been found accompanied with an upregulation of TGF-β expression[19,20]. The initial increase in production of ECM that is found in OA shows that OA is more than just accelerated cartilage degradation. Unfortunately, the increased anabolic impulse is only a temporary state characteristic for early OA and therefore cannot compensate for the overall catabolic insult to cartilage.

Chondrocytes in OA cartilage are different from normal cartilage in their cytokine and growth factor expression patterns. For instance, chondrocytes from fibrillated OA cartilage display higher levels of intracellular IL-1α and β and upregulated plasmamembrane-bound IL-1RI, whereas the decoy receptor IL-1RII is downregulated in OA chondrocytes[21,22]. Thus, not only are there higher levels of IL-1 present in OA joints, but OA chondrocytes are also more sensitive to IL-1, thereby increasing susceptibility to IL-1 induced cartilage damage. Not only fibrillated areas show different expression patterns, also cartilage proximal to macroscopic OA lesions show a higher binding of TNF-α and IL-1β compared to chondrocytes from morphologically normal cartilage from the same joint[23].

In our studies, we found that the anabolic growth factor TGF-β was expressed in high levels in normal cartilage, but was almost absent in OA cartilage[24]. We also showed that blocking TGF-β made cartilage more susceptible to damage[25]. TGF-β is a potent inducer of cartilage ECM synthesis and a very potent counteracting agent of IL-1 actions[26,27]. Therefore, lack of TGF-β causes a reduction in ECM deposition and suppression of catabolic stimuli is drastically reduced. Thus, the balance between catabolic and anabolic factors that maintains cartilage integrity is shifted toward the catabolic side in OA. Not only through elevation of catabolic stimuli, but also through a dramatic decrease in anabolic stimuli, like TGF-β. Therefore, it seems that administration of TGF-β will provide a potentially good tool for therapeutic intervention.

TGF-β

The TGF-β family consists of over 35 members and includes, besides TGF-βs, activins and bone morphogenetic proteins (BMPs)[28]. They play vital roles in development and homeostasis of various tissues. They regulate cell proliferation, differentiation, apoptosis and migration, as well as control ECM synthesis and degradation. Moreover, these factors mediate cell and tissue responses to injury and modulate immune functions[29]. In mammals, there are three isotypes of TGF-β, called β1, β2 and β3. All isoforms show a high degree of homology of 84–92%. The expression of the three isoforms is differently regulated at the transcriptional level due to different promotor sequences[30–32]. TGF-β is secreted as an inactive complex comprised of a TGF-β dimer, its propeptide LAP (latency associated peptide) and LTBP (latent TGF-β binding proteins)[33,34]. Therefore, the secreted TGF-β requires activation before it can bind to its receptor. Activated TGF-β binds to the TGF-β type II receptor to form a complex that recruits the TGF-β type I receptor, which is activated by phosphorylating the serine/threonine residues. There is an additional third TGF-β receptor, also known as betaglycan, which allows high-affinity binding of mainly TGF-β2 to the TGF-β receptor type II[29].

Upon receptor phosphorylation, R-SMADs (mothers against decapentaplegic homolog 2 (SMAD2) or 3) are presented to the receptor by SARA (SMAD-anchored for receptor activation) and phosphorylated. Then the phosphorylated R-SMADs form a complex with the Co-SMAD (SMAD4), and translocate to the nucleus where they can act either as, or in orchestrate with, transcription factors[29,35,36]. I-SMADs (SMAD6 and 7) can inhibit TGF-β signaling by interfering with R-SMAD phosphorylation, thereby functioning as a negative feedback system.

TGF-β can also activate Erk, Jun N-terminal kinase (JNK) and p38 mithogen-activated protein kinase (MAPK) pathways[37]. Cross-talk between the SMAD-pathway and other TGF-β signaling pathways has also been reported[36,37]. They can interact by SMAD phosphorylation by ERK or JNK, by controlling SMAD7 expression and by nuclear interaction between SMAD complexes and MAPK-activated transcription factors. The latter depends on the structure of the target promotors[38]. MAPK activation is not TGF-β signaling specific and can be triggered by various extracellular stimuli, such as IL-1 and TNF-α. Therefore, the SMAD-MAPK interactions are not solely the result of multifaceted TGF-β signaling downstream of the receptors, but are a result of interacting cytokines that together modulate the SMAD/MAPK signals[38]. The mechanism of alternative TGF-β signaling pathways and their biological consequences is poorly understood since there are many factors that can activate the MAPK pathways at various levels, most of which are able to interact.

Genetic aspects of OA and TGF-β

Family studies can indicate a relation between genetically determined factors and the development of OA. In humans, a relationship between TGF-β and OA symptoms has been shown in Japanese women. A polymorphism of TGF-β1 on position 29 (T to C, amino acid 10) positioned in the signal sequence region of TGF-β1 is related to an elevated prevalence of spinal osteophytosis and ossification of the posterior longitudinal ligament[39,40]. This TGF-β polymorphism was also associated with bone mineral density (BMD) and fracture risk in postemenopausal Chinese women[41]. The same polymorphism appears to protect Japanese women from osteoporosis[42,43]. However, in a sample of post-menopausal German women a relationship between increased BMD and the C29 polymorphism was not found[44].

Other studies showing a relationship between TGF-β1 activity and bone mass are reports of the rare autosomal dominant disorder, Camurati–Engelmann disease. The long bones of patients with Camurati–Engelmann disease show osteosclerosis. The osteosclerosis is associated with a number of mutations in the TGF-β1 gene. All of these observed mutations result in an elevated activity of TGF-β1

in these patients[45,46]. Since an inverse relationship between osteoporosis and OA has been suggested in the literature[47,48] elevated bone mass due to increased TGF-β activity might be related to the development of OA.

Asporin, which is abundantly expressed in cartilage of OA patients, inhibits TGF-β mediated expression of cartilage matrix genes like collagen type II and aggrecan and reduces accumulation of proteoglycans[49]. Kizawa *et al.*[49] have found a asporin polymorphism that showed a significantly higher frequency in OA. They found that this particular (D-14) polymorphism has a stronger inhibitory effect on TGF-β than the common D-13 repeat. This indicates that in OA there is a higher frequency D-14, resulting in strong TGF-β inhibition, which can result in reduction of ECM of cartilage. This suggests that reduced TGF-β action might be correlated with increased susceptibility to OA. However, the study performed by Kizawa *et al.* included only Japanese patients. When repeated in a Spanish Caucasian population, by Rodriguez-Lopez *et al.*[50] the higher susceptibility to OA in patients with the D-14 polymorphism was no longer found. In UK Caucasians, a trend was seen toward a higher degree of D-14 polymorphism in OA patients, but this was only significant in a specific subset of patients[51]. However, in a different ethnic group, Han Chinese, the OA susceptibility was found again[52]. The susceptibility was not limited to OA, Torres *et al.* also found that patients with rheumatoid arthritis (RA) that carried the D-14 polymorphism more frequently produced rheumatoid factor and had an earlier onset of the disease. Although the repeat might not be the major influence in RA, it was concluded to influence the outcome of the disease[53]. The studies mentioned above show that TGF-β inhibition can aggravate OA and RA.

Mice deficient for TGF-β1 show 50% embryonic lethality and animals that are born alive develop severe inflammatory disorders and die within 1 month[54,55]. Mice with a knockout gene for TGF-β2 and TGF-β3 show numerous developmental defects and perinatal death. Mice lacking TGF-β2 have numerous structural defects in the skeletal elements and show joint laxity[56]. This indicates that TGF-β2 is involved in skeletal development. Animals with a nonfunctional gene for the type I receptors ALK1 or ALK5 or the SMAD proteins 2 and 4 are embryonic lethal[57–60].

Null mice for SMAD3 developed degenerative joint disease resembling human OA, as characterized by progressive loss of articular cartilage, formation of osteophytes and increased expression of type X collagen. These data indicate that SMAD3 signaling is essential for repressing chondrocyte terminal differentiation, a hallmark of human OA[61]. This observation is supported by studies in mice that overexpress a dominant negative TGF-β type II receptor in skeletal tissues[62]. These mice developed progressive skeletal degeneration that strongly resembles human OA. The articular surface shows hypertrophic cartilage as judged by the expression of type X collagen. Supportive of these findings, we found reduced TGF-β receptor in cartilage of aged mice which are prone to develop OA[25] and demonstrated reduced TGF-β signaling via Smad2 during experimental models of murine OA[24]. Our data support earlier findings by Boumediene *et al.*[63] in rabbits and by Verdier *et al.*[64] in humans that show a reduction in TGF-β receptor expression during OA. In addition, mice that lack the LTBP-3 also show altered chondrocyte differentiation and early OA development[65,66]. These observations show that interference with TGF-β signaling in chondrocytes results in abnormalities in chondrocyte differentiation and the development of OA.

TGF-β and cartilage

Lack of TGF-β or an abnormality in TGF-β signaling apparently results in cartilage phenotype that resemble cartilage pathology in OA. We recently showed a strong reduction of TGF-β receptor expression as well as a reduction in active TGF-β signaling in aged mice in a strain that is prone to develop OA[25]. Moreover, we showed a similar reduction in TGF-β signaling in murine models for OA[24]. Furthermore, we showed that inhibition of endogenous TGF-β led to increased damage to cartilage[25]. TGF-β has been shown to be very beneficial for cartilage as it stimulates chondrocytes *in vitro* to induce elevation of proteoglycan and collagen type II production[15–17,67]. Also *in vivo* TGF-β proved to have beneficial effects on cartilage such as stimulation of proteoglycan synthesis in cartilage[68].

Not only does TGF-β stimulate ECM production, it also counteracts the main catabolic players in OA. Our group has shown that TGF-β counteracts 38% of the genes that are regulated by IL-1. For example, TGF-β counteracts IL-1 up regulation of MMP-13 and -14, which have been found important mediators of cartilage damage. In addition, IL-1 downregulation of collagen and ECM-related genes are counteracted by TGF-β[9]. Hui *et al.* show that TNF-α promotes MMP dependent collagen breakdown, which can be prevented by TGF-β 1 in bovine cartilage explant cultures. In addition, TGF-β1 reduced expression and secretion of collagenases and induced tissue inhibitor of matrixmetalloproteinases (TIMP) production[69]. In addition, IL-1β has been shown to inhibit proteoglycan biosynthesis in a dose-dependent manner in porcine articular cartilage and increase the rate of degradation in proteoglycans. TGF-β was able to recover the IL-1 induced proteoglycan reduction[70,71]. TGF-β is not only able to counteract the effects of IL-1, but can also reduce IL-1 signaling by downregulation of its receptors and increasing the expression of the decoy receptor IL-1Ra, thereby counteracting at several levels[26,27,72–74].

Overall, IL-1 and TNF-α produce matrix proteases and suppress the synthesis of collagen and proteoglycan. TGF-β is able to counteract the net effect of catabolic cytokines by stimulating the synthesis of matrix components, of protease inhibitors and down regulating the expression of cytokine receptors and cartilage-degrading enzymes[75]. These studies show that TGF-β can potently counteract catabolic effects in cartilage and stimulate ECM production and can be used as a potential treatment for cartilage destruction in OA.

TGF-β supplementation

Lack of TGF-β signaling results in susceptibility to cartilage damage, therefore TGF-β supplementation should aid in cartilage maintenance or repair. For years many researchers have focused on this TGF-β quality. We have shown that multiple injections of TGF-β induce strong and long-lasting stimulation of proteoglycan synthesis and increase the glycosaminoglycan content in patellar cartilage in mice under arthritic conditions[68,70]. TGF-β stimulation of proteoglycans is a long-lasting effect. A single injection of 200 ng TGF-β into a murine knee joint stimulated proteoglycan synthesis for 3 weeks and elevated proteoglycan content for 2 weeks. Triple injections prolonged the increase in proteoglycan content for 3 weeks[76]. In a survey, Grimoud *et al.*[77] concluded that TGF-β expression and the use of gene transfer might provide an approach for treatment of OA lesions in cartilage.

Unfortunately, the effects of injecting TGF-β into a joint are not limited to cartilage. Chondrocytes are embedded in the cartilage without direct contact with other cells. The non-vascular properties make chondrocytes dependent on their direct environment for signals. This makes it very hard to target cartilage without involvement of other tissues. This implies that TGF-β supplementation in a joint also results in responses of other tissues that are in contact with the synovial fluid. TGF-β is implicated in fibrosis in many organs like eye, lung, heart, liver, kidney, pancreas and skin[78]. The synovial tissue in articular joints is susceptible to TGF-β induced fibroplasias and fibrosis. As a consequence, multiple injections of TGF-β induce synovial fibrosis in murine knee joints[68]. In contrast to the lack of sufficient TGF-β expression in cartilage in progressive OA, it is abundantly present in synovial tissue. Therefore, TGF-β might also be involved in the synovial hyperplasia that is observed in OA. Besides being a potent inducer of synovial fibrosis, TGF-β is also able to induce osteophytes similar to those found in OA[68,79]. TGF-β expression as well as active TGF-β signaling is found highly expressed in osteophytes in OA, suggesting a role for TGF-β in OA-induced osteophytes. This shows that TGF-β itself is abundantly present in OA joints, but not at the location where it is needed: in the cartilage. Because of the role of TGF-β in fibrosis and osteophyte formation, the use of TGF-β as a therapeutic agent for cartilage repair should be evaluated thoroughly as side effects will likely occur or aggravate already existing pathology if TGF-β exposure is not confined to the articular cartilage. Another fact that should be addressed more closely is the fact that several groups have demonstrated reduced TGF-β receptor expression during OA. So even if TGF-β supplementation could be confined to cartilage, the question remains whether these chondrocytes are at all sensitive to TGF-β and if so whether the sensitivity is high enough to overcome the cartilage damage.

TGF-β inhibition

The experiments discussed above are all circumstantial evidence of TGF-β involvement in the OA-changes like fibrosis and osteophyte formation. The only real proof of a protective role for TGF-β in OA and a role in induction of fibrosis and osteophytes can be obtained by blocking endogenous TGF-β during OA to see whether cartilage damage is aggravated by the lack of TGF-β and if fibrosis and osteophyte formation can be prevented.

Our group has shown that inhibition of TGF-β with a soluble receptor enhanced proteoglycan loss and reduced cartilage thickness[80]. Serra *et al.*[62] overexpressed a dominant negative TGF-β receptor resulting in terminal chondrocyte differentiation and OA. This proves that endogenous TGF-β is important for maintaining cartilage integrity.

Inhibition of TGF-β in a murine model for OA revealed that indeed TGF-β plays a role in OA-induced synovial fibrosis and osteophyte formation as both were reduced by blocking TGF-β by adenoviral overexpression of different TGF-β inhibitors: SMAD6, SMAD7 or LAP[81]. Moreover, we showed that it is possible to isolate the beneficial effect of TGF-β on cartilage from its fibrotic side effect on synovium by simultaneous transfection of the synovial lining with both a TGF-β and a SMAD7 adenovirus. This way the synovial lining was protected from TGF-β as the cells expressed SMAD7 and did not respond to TGF-β. The TGF-β that they produced was secreted into the synovial fluid and could reach the cartilage where it induced elevation of proteoglycan content, even in a murine OA-model[82]. This shows that there are ways to overcome the problem of TGF-β side effects in the joint.

Potential secondary pathways

We showed that simultaneous overexpression of SMAD7 with TGF-β blocks fibrosis while the cartilage protective effects of TGF-β remain. But this is not the only possibility to overcome the problem of having to compartmentalize TGF-β effects in a single tissue of the joint. Another potentially fruitful approach of abolishing TGF-β side effects, while preserving the beneficial effects of TGF-β, is to evaluate the secondary pathways that might be involved in the side effects. To enhance cartilage ECM formation with TGF-β while preventing synovial fibrosis, the putative TGF-β -induced secondary mediator that induces fibrosis should be identified. Connective tissue growth factor (CTGF/CCN2) is a good candidate as it is directly induced by TGF-β through a TGF-β response element in the CTGF-promotor. Moreover, CTGF is an established player in various fibrotic disorders including nephropathy, Crohn's disease, liver fibrosis, scleroderma, systemic sclerosis, lung fibrosis and heart fibrosis[83–90]. We demonstrated that CTGF is indeed able to induce synovial fibrosis on its own, but it did not compare to the magnitude of fibrosis induced by TGF-β. In addition, TGF-β induced fibrosis was persistent for months, whereas CTGF-fibrosis was only transient[91]. One must keep in mind that during TGF-β overexpression, there is always induction of CTGF. Therefore, one can imagine that CTGF and TGF-β work synergistically. Wahab *et al.*[92] established that CTGF augments TGF-β signaling by reducing the negative feedback through SMAD7 and enhancing SMAD2 phosphorylation. They showed that together, TGF-β and CTGF stimulated PAI-I and Col II expression more strongly than TGF-β alone, whereas CTGF itself had no effect. In skin-fibrosis, Mori *et al.*[93] suggested that TGF-β is needed for the initial impulse to induce fibrosis and that CTGF is important for maintenance. We have found that TGF-β is expressed in OA synovium mainly in early stages, whereas in later stages of OA CTGF was more abundantly expressed[24]. CTGF has been frequently suggested as a potential target for fibrosis therapy and this might also be the case in OA. More research is required to verify this.

Besides its role in fibrosis, CTGF has been found to have chondrogenic effects[94–99]. In spite of these findings, adenoviral expression of CTGF in murine knee joints resulted in reduction of proteoglycan content of the cartilage indicating deleterious effects[91]. Moreover, CTGF overexpression did not induce osteophyte formation[80]. Although it is still possible that CTGF can elicit chondrogenesis under explicit conditions, CTGF injection into murine knee joints had opposite effects. This might be due to CTGF-induced fibrosis, which can result in excretion of catabolic factors into the joint, ultimately leading to loss of proteoglycans in cartilage. If indeed CTGF mediates or aggravates TGF-β-induced fibrosis it would be very beneficial to block CTGF to get rid of the TGF-β induced fibrosis while maintaining TGF-β effects on cartilage.

In addition to fibrosis, TGF-β induces osteophytes. Secondary mediators might play essential roles in TGF-β induced osteophyte formation. A potent inducer of osteophytes is BMP-2. BMP belongs to the TGF-β superfamily and shares some of the TGF-β functions. BMP has been shown to compensate for TGF-β in SMAD3 deficiency. Chondrocytes that are SMAD3 deficient, therefore lacking TGF-β signaling, have a high up regulation of BMP-signaling indicating

a compensatory mechanism[100]. Therefore, it is possible that BMPs share some of the TGF-β functions in osteophyte formation, making it a potential candidate for mediating TGF-β induced osteophyte formation. We have shown that BMP-2 is able to induce osteophytes in murine knee joints[101]. It is still under investigation whether osteophytes as seen in OA are BMP-dependent and it remains to be investigated whether TGF-β induced osteophytes involve BMP-activity.

We found that expression of BMP-2 is low in normal cartilage, but elevated staining is seen around osteoarthritic lesions[24]. Whether its elevated expression in osteoarthritic lesions is a means of repair or a pathological feature remains to be investigated. BMP-2 appears not to be a factor that is present in cartilage under normal conditions. Thus, blocking of BMP-2 will not likely interfere with normal cartilage homeostasis although it might play a role as secondary mediator of TGF-β induced cartilage repair. If BMP-2 does not have this role in cartilage repair, it is a potential target for blocking osteophyte formation.

Although TGF-β repair of cartilage also implies inducing side effects, we show that there are ways to overcome this problem. They should be further investigated before application of TGF-β as a therapeutic agent for cartilage repair purposes.

Conclusions

Many researchers have demonstrated a role for TGF-β in cartilage homeostasis. A strong correlation between lack of TGF-β and predisposition to cartilage damage has been shown. Several studies suggest that lack of TGF-β might induce susceptibility to OA, while others show that TGF-β can counteract catabolic cytokines and in that way overcome many cartilage-degrading events. This suggests that TGF-β is a potential tool for repair of OA cartilage or prevention of further degradation. TGF-β application also implies fibrosis and osteophyte formation. A potential solution to this problem is either compartmentalized inhibition of TGF-β signaling, in non-articular tissues, or blocking of secondary mediators. The solution to cartilage damage might not be restricted to blocking a single cytokine or stimulating a single growth factor, but rather a selection of factors that together provide the anti-osteoarthritic properties that are required. The latter can provide a possibility for use of TGF-β as a tool to not only overcome OA damage in cartilage, but maybe also prevent cartilage destruction. Moreover, if selectively blocking TGF-β should prove to be effective, not only will we be able to prevent TGF-β side effects, but possibly also prevent OA-like side effects like synovial fibrosis and osteophyte formation, thereby providing an all-round therapeutic intervention.

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