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TGF-β Action in the Cartilage in Health and Disease

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1. Introduction

Transforming growth factor-β (TGF-β) is a pleiotropic cytokine that plays a critical role in the maintenance of healthy cartilage [1-4]. Aberrant TGF-β signaling has been implicated in a number of cartilage-related disorders including gout [5-6], lupus [7-8], rheumatoid arthritis [9] and osteoarthritis (OA) [1-3]. Although much progress has been made in understanding the molecular mechanism of TGF-β action in normal and OA cartilage, this knowledge has not translated into the development of a therapeutic strategy to slow or reverse the progression of the disease. In this chapter, we will highlight recent advances in understanding the role of TGF-β signaling in normal cartilage, the changes that occur in the TGF-β signaling pathway components in OA and the potential of targeting the TGF-β signaling pathway as a therapeutic strategy for the treatment of this disease.

2. TGF-β signaling

Members of the TGF-β superfamily, including TGF-βs, activins and bone morphogenetic proteins (BMPs), are critical for development and homeostasis [10-12]. They regulate diverse cellular processes including proliferation, differentiation and migration as well as extracellular matrix (ECM) production [11-14]. The three mammalian TGF-β isoforms (TGF-β1, -β2, -β3) share significant sequence (approximately 75% identity) and structural similarity [15-19]. However, the phenotypes of TGF-β isoform knockout mice do not overlap [20] and the isoforms exhibit distinct spatial and temporal expression in developing/regenerating tissues and in pathologic responses [21], suggesting distinct functions *in vivo*.

TGF-β is synthesized as a homo-dimeric pro-protein (pro-TGF-β) and is processed in the trans-Golgi network by furin-like enzymes. Cleavage by furin results in the formation of a mature TGF-β dimer along with its pro-peptide, known as latency associated peptide (LAP). TGF-β remains non-covalently associated with LAP and is in an inactive state. In most cases, this small latent complex associates with the latent TGF-β binding protein (LTBP) which forms a disulphide bond with LAP, giving rise to a large latent complex. Once secreted, the large latent complex becomes attached to the ECM by covalent cross-linking of LTBP with ECM proteins which is catalyzed by a transglutaminase [22-25].

TGF-β activation involves its dissociation from the latent complex which is necessary for TGF-β binding to its receptors and for mediating its biological effects [25]. Latent TGF-β can be activated by physical processes including acidification, alkalization and heat denaturation, and biological processes involving proteolysis or protein-protein interactions [22, 24-26]. Many serine proteases such as plasmin and thrombin, and several matrix metalloproteinases (MMPs) such as MMP-2, -9, -13 and -14 have been implicated in TGF-β activation [24]. In addition, thrombospondin-1 (TSP-1) has been shown to bind LAP directly and is thought to cause a conformational change in LAP that leads to activation of latent TGF-β [27]. Although the precise mechanisms of TGF-β activation *in vivo* in different tissues remain to be determined, it is likely to be a critical step for regulating TGF-β bioavailability [22, 24-26].

TGF-β signals through a pair of transmembrane serine/threonine kinases known as the type I (TβRI, also known as activin receptor-like kinase-5 or ALK5) and type II (TβRII) TGF-β receptors [10-12]. TGF-β binds TβRII, a constitutively active kinase, which then phosphorylates and activates TβRI/ALK5 [28-29]. Activated ALK5 phosphorylates intracellular Smad2 and Smad3 proteins, which then bind to Smad4 and accumulate in the nucleus where they interact with various co-activators, co-repressors and transcription factors to regulate gene expression [30-31]. TGF-β has also been shown to activate another TGF-β type I receptor known as ALK1 which phosphorylates Smad-1, -5 and -8 [32-34]. In addition, TGF-β activates several non-Smad pathways including mitogen-activated protein (MAP) kinase pathways (ERK, JNK and p38), Rho-like GTPase pathways and phosphatidylinositol-3-kinase (PI3K)/Akt pathways [35-36].

3. Regulation of TGF-β signaling

Intracellular regulation of TGF-β signaling involves the interplay of many cytoplasmic proteins including FKBP12, TRIP-1, STRAP, TRAP-1, SARA, HSP90 [37] and nuclear proteins such as TGIF, c-Ski, SnoN and Evi-1 [31]. The inhibitory Smads or I-Smads, which include Smad6 and Smad7, play critical roles in negative feedback regulation of TGF-β/BMP signaling by forming stable complexes with the activated type I receptors thereby blocking Smad phosphorylation [38-39]. Smad6 and Smad7 also act as adaptor proteins that recruit E3 ubiquitin ligases such as Smurf1 and Smurf2 to the TGF-β type I receptors and induce their ubiquitination and proteosomal degradation [40].

Extracellular control of TGF-β signaling is orchestrated by many factors including those that regulate activation of latent TGF-β as described in Section 2. In addition, several ECM components such as decorin and biglycan bind TGF-β and regulate its bioavailability [41]. Other extracellular molecules such as lipoproteins have been shown to sequester TGF-β ligand into an inactive pool [42]. TGF-β co-receptors such as endoglin, betaglycan and CD109 are emerging as important factors that regulate many aspects of TGF-β signaling in health and disease.

Endoglin (CD105) is a single-pass transmembrane homo-dimeric glycoprotein that is expressed mainly in endothelial cells. It binds TGF-β1 and TGF-β3 with high affinity in the presence of TβRII but does not bind the TGF-β2 isoform [43]. Endoglin has been shown to (i) alter TβRII and TβRI (ALK1 and ALK5) phosphorylation status, (ii) promote TGF-β/ALK1 signaling, (iii) suppress TGF-β/ALK5/Smad2/3 signaling and (iv) antagonize TGF-β-induced MAP kinase signaling through a β-arrestin-2-dependent mechanism [44-45].

Betaglycan, also known as TGF-β type III receptor, is a homologue of endoglin and is a more ubiquitously expressed transmembrane glycoprotein. It binds all three TGF-β isoforms (TGF-β1, -β2, -β3) with high affinity and enhances their binding to the signaling receptors, especially that of the TGF-β2 isoform [43, 46-47]. Betaglycan has been shown to direct clathrin-mediated endocytosis of TβRII and ALK5 [48], and enhance TGF-β signaling via Smad and MAP kinase pathways [49-51]. Conversely, betaglycan has also been reported to promote β-arrestin2-dependent TGF-β receptor internalization and down-regulation of TGF-β signaling [52].

CD109 is a glycosyl phosphatidylinostol (GPI)-anchored protein and a member of the α2-macroglobulin/complement family. It is found on activated T-cells and platelets, endothelial cells and many human cancer cell lines [53-56]. We have recently identified CD109 as a TGF-β co-receptor which binds TGF-β1 with high affinity, forms a heteromeric complex with the TGF-β signaling receptors and inhibits Smad2/3 signaling in different cell types [57-58]. Recent results indicate that CD109 inhibits TGF-β signaling by promoting TGF-β receptor internalization and degradation in a Smad7/Smurf2-dependent manner [57, 59]. Taken together, these studies demonstrate that the TGF-β co-receptors endoglin, betaglycan and CD109 play critical roles in regulating TGF-β signaling.

4. TGF-β and cartilage

Articular cartilage is an avascular tissue that receives its nutrients from synovial fluid, a thin layer of fluid surrounding the cartilage. The only cell type found in cartilage is the chondrocyte which are embedded in an extensive ECM made of mainly collagens and proteoglycans [60]. Type II collagen is the main collagen found in articular cartilage and is important for providing tensile strength [61-62]. Aggrecan is the main proteoglycan of articular cartilage and provides structural support by retaining water in the matrix [63]. Articular cartilage is commonly divided into four distinct zones, namely the superficial zone, middle zone, deep zone and calcified cartilage [60]. The zones differ in collagen organization, proteoglycan content and chondrocyte morphologies [60].

TGF-β plays a number of roles in the development, growth and maintenance of articular cartilage. During cartilage development, TGF-β stimulates chondrogenic condensation [64-65], chondroprogenitor cell proliferation and chondrocyte differentiation [66-67]. TGF-β also inhibits terminal differentiation or "hypertrophy" of chondrocytes thereby blocking endochondral bone formation [68-69] and allowing formation of articular cartilage at the end of the long bones [70]. The maintenance of mature articular cartilage is dependent on the action of TGF-β which not only stimulates production of ECM proteins such as type II collagen and aggrecan, but also blocks degradation of ECM proteins by increasing production of protease inhibitors such as tissue inhibitor of metalloproteases (TIMPs) [69, 71]. TGF-β also counteracts the catabolic effects of interleukin (IL)-1 and tumor necrosis factor (TNF)-α on cartilage[69, 71].

The potent anabolic effects of TGF-β on articular cartilage *in vivo* in animal models are well known. TGF-β injected into the periosteum of rat or mouse femur induces chondrocyte differentiation and cartilage formation [72-73]. Local administration of TGF-β into murine knee joints stimulated articular cartilage repair [74] and healing of full-thickness cartilage defects [75-76]. Conversely, blocking endogenous TGF-β using a soluble form of TβRII impaired articular cartilage repair in a murine model of experimental OA [77]. In addition,

expression of a dominant negative TβRII in cartilage resulted in an OA-like phenotype in the mouse [78]. Furthermore, Smad3 knockout mice develop degenerative joint disease resembling human OA [70]. In addition, decreased TGF-β expression and Smad2 phosphorylation are associated with a reduced protective effect during OA progression [79]. Evidence for a causal relationship between TGF-β and OA in the human is further supported by the identification of asporin (a proteoglycan that sequesters TGF-β in the ECM and inhibits TGF-β function) as an OA susceptibility gene [80-83]. However, TGF-β also has been shown to have undesirable effects on cartilage. A number of studies have reported that TGF-β treatment of normal murine joints is associated with osteophyte outgrowth, inflammation and synovial fibroplasia [84-86]. Thus, normal cartilage function may dependent on a narrow range of bioactive TGF-β levels, and concentrations above or below this level may lead to alterations in TGF-β signaling, resulting in abnormal cartilage function.

5. Altered expression and function of TGF-β pathway components in osteoarthritis

OA is a chronic degenerative joint disease characterized by articular cartilage degradation, subchondral bone alterations and synovial inflammation [87-88]. The cause of OA is unknown but risk factors include aging, obesity, abnormal mechanical loading and anatomical abnormalities [89]. Subchondral bone alterations contribute to the initiation and/or progression of OA by producing catabolic factors that degrade the overlying cartilage [90]. Synovial inflammation is thought to be induced by cartilage matrix degradation products that are phagocytosed by macrophages of the synovial lining. The macrophages, in turn, secrete pro-inflammatory mediators into the synovial fluid that diffuse into the cartilage, thereby creating a vicious circle of synovial inflammation and cartilage degradation [90]. The current chapter focuses on the role of TGF-β signaling in articular cartilage homeostasis and its deregulation in OA.

5.1 TGF-β ligands and their activation

Several studies suggest that TGF-β isoform (TGF-β1, -β2, -β3) levels are down-regulated in OA cartilage. For example, TGF-β1 protein levels were shown to be decreased in human OA cartilage [91-92] and TGF-β3 levels were shown to be reduced in both spontaneous (STR/Ort) and collagenase-induced mouse models of OA [79]. In addition, TGF-β1 and TGF-β2 levels were moderately decreased in rabbit OA cartilage [93]. In constrast, a number of studies have demonstrated that TGF-β isoform expression is up-regulated in OA cartilage. TGF-β1, -β2 and -β3 levels were found to be increased in human OA [94-96] and TGF-β1 and -β3 levels were elevated in a papain-induced mouse model of OA [77]. Furthermore, TGF-β2 was increased in a surgically-induced model of early OA in rats [97]. One possible explanation for these discrepancies is that TGF-β isoform expression may vary during the course of OA. For instance, TGF-β levels might increase in the early stages of OA to counteract the catabolic effects of inflammatory cytokines such as IL-1β or TNF-α [98-99]. However, with the progressive loss of TGF-β receptor expression (see Section 5.2), chondrocytes may eventually lose their responsiveness to TGF-β, leading to a decrease in TGF-β levels due to the loss of TGF-β auto-induction [100]. Future studies using age-, race- and gender- matched normal and OA human articular cartilage and a better characterization

of TGF-β isoform expression in the different animal models during OA progression will be needed to resolve this issue.

Although TGF-β isoform levels are altered in OA, it is not known whether these changes represent active TGF-β levels. Moreover, accumulating evidence suggests that components of the large latent complex may be disrupted in OA. For example, both LTBP-1 and LTBP-2 were shown to be increased in human OA cartilage [97, 101-102] and in experimental models of OA [97, 101]. Although LTBP-1 [103-104] and LTBP-2 [105] knockout mice do not display an OA phenotype suggesting that these proteins may not contribute to the OA process, LTBP-3 knockout mice develop an OA phenotype and display features resembling those of mice with impaired TGF-β signaling [106-107]. These results suggest that LTBP-3 might have a protective effect against OA progression. It is also possible that studies using LTBP-1 and LTBP-2 knockout mice in an experimental OA setting may reveal a role for these proteins in OA progression. Interestingly, the levels of TGF-β activators are also upregulated in human OA and in a variety of animal models of OA. Transglutaminase-2 (TG-2), the predominant transglutaminase subtype in hypertrophic chondrocytes, are higher in knee [108-109] and femoral [110] cartilage in human OA and in experimental OA models [97, 101, 111]. Whether the enhanced TG-2 expression in OA correlates with increased TGF-β activation or LTBP cross-linking to ECM remains to be determined. In addition, TSP-1 levels are increased in the cartilage in mild and moderate OA, but decreased in severe OA [112]. Intra-articular gene transfer of TSP-1 was shown to reduce disease progression in a collagen- or anterior cruciate ligament transection-induced OA in rats [113-114]. This is consistent with the notion that TSP-1 mediates latent TGF-β activation in OA cartilage and that the up-regulation of TSP-1 is an adaptive response in an attempt to increase cartilage repair.

5.2 TGF-β receptors

Increasing evidence indicates that TGF-β receptor expression levels are altered in OA. TβRII levels were shown to be decreased in human OA cartilage [92] and in a rabbit OA model [93]. In addition, TβRII mRNA expression was decreased in cultured human OA chondrocytes as compared to normal chondrocytes *in vitro* [115]. These results suggest that loss of TβRII during OA might represent an intrinsic defect of human OA chondrocytes. The notion that loss of TβRII might contribute to the initiation and/or progression of OA is supported by a study showing that a truncated, kinase-defective TβRII expressed in mouse skeletal tissue was associated terminal chondrocyte differentiation and the development of OA-like features [78]. A more recent study has shown that conditional expression of dominant negative TβRII inhibits cartilage formation in mice [116]. Thus, loss of TβRII expression and/or activity may not only promote an OA-like phenotype but may also contribute to OA progression by limiting the ability of cartilage to repair itself. Future studies using cartilage-specific knockout of TβRII may provide further insight into the role of this TGF-β receptor in OA pathogenesis.

Emerging evidence indicates that the expression of TGF-β type I receptors is also altered in OA. Our group has shown that in addition to the canonical TGF-β type I receptor ALK5, human chondrocytes also express ALK1 [34]. Both ALK5 and ALK1 are required for TGF-β-induced Smad1/5 phosphorylation whereas only ALK5 is essential for TGF-β-induced Smad3 phosphorylation in these cells [34]. We also demonstrated that ALK1 inhibits

whereas ALK5 potentiates the expression of type II collagen and PAI-1 in chondrocytes, indicating that ALK1 and ALK5 elicit opposite efffects in chondrocytes [34]. More recent data suggest that both ALK5 and ALK1 levels are decreased in mouse models of OA, but that ALK1 expression decreases to a lesser extent than that of ALK5, suggesting that the ratio of ALK1/ALK5 increases during OA [117]. Interestingly, ALK1 has been identified as one of the genes upregulated in a mensical tear rat model of OA [101] whereas ALK5 levels were dramatically reduced in partial meniscectomy and post-surgery training rat model of OA [118]. These two latter studies are consistent with the notion that the ALK1/ALK5 ratio increases during OA. In human OA cartilage, ALK1 mRNA expression highly correlates with MMP-13 levels whereas ALK5 mRNA levels correlate with aggrecan and collagen type II levels [117]. Collectively, these data suggest that alterations in the expression of TGF-β signaling receptors (TβRII and ALK5/ALK1) play an important role in OA pathogenesis and that an increase in the TGF-β/ALK1 pathway activation relative to that of the TGF-β/ALK5 pathway activation is likely to be a critical event in the OA disease progression.

5.3 Smads

Since TGF-β receptor levels are altered in OA, it can be anticipated that activities of downstream signaling mediators such as Smad2 and Smad3 are also altered. Indeed, Smad2 phosphorylation levels are reduced in cartilage during OA progression in both spontaneous- (STR/Ort) and collagenase-induced mouse models of OA [79] and in cartilage of old mice as compared to young mice [119]. Although Smad3 phosphorylation was not examined in these models, a recent study has reported decreased Smad3 phosphorylation levels in the Smurf-2 transgenic mice which spontaneously develop an OA-like phenotype [120]. Together, these studies suggest that OA is associated with reduced TGF-β/ALK5/Smad2/3 signaling.

The potential importance of Smad3 in OA is further underscored by the finding that Smad3 knockout mice develop a degenerative joint disease resembling human OA [70] and intervertebral disc degeneration [121]. Moreover, several genetic studies in humans suggest that mutations in the Smad3 gene may be an important factor in OA. A missense mutation in the Smad3 gene was found in a patient with knee OA and was associated with elevated serum MMP-2 and MMP-9 levels [122]. A single nucleotide polymorphism (SNP) mapping to the Smad3 intron 1 was shown to be involved in risk of both hip and knee OA in European populations [123]. Furthermore, several mutations in the Smad3 gene were found in individuals that presented early-onset OA [124]. Although the functional significance of these mutations in Smad3 remains to be determined, these studies suggest that alteration in Smad3 function may play a role in the pathogenesis of OA.

A shift in the balance of signaling from Smad2/3 towards Smad1/5 is thought to play an important role in OA pathogenesis. TGF-β signals through both of these pathways in human chondrocytes with the Smad1/5 pathway opposing the Smad2/3 pathway [34]. This is consistent with the findings in endothelial cells [32-33], skin fibroblasts [125] and in chondrocyte terminal differentiation [126]. Although Smad-1, -5 and -8 expression levels and subcellular localization in human OA cartilage did not differ significantly from that of normal cartilage, two Smad1 gene splice variants of unknown significance were reduced in OA cartilage [127]. When the reported decrease in ALK5 expression and Smad2/3 signaling (see above) in OA cartilage is taken into account, it is possible to envision that a shift in TGF-β signaling away from the ALK5/Smad2/3 pathway and towards the ALK1/Smad1/5/8

pathway may occur, contributing to OA progression. However, whether such a shift is an adaptive response without a causal relationship to OA progression cannot be ruled out at this time.

As mentioned above, Smad7/Smurf2-mediated TGF-β receptor degradation is an important mechanism for the termination of TGF-β signaling [38-39]. Although Smad7 expression levels in human OA cartilage did not significantly differ from that of normal cartilage [128] it did show an age-related increased expression in murine cartilage [119] suggesting that age might be an important factor to consider when comparing Smad7 expression levels in OA versus normal cartilage. In addition, Smurf2 is increased in human OA cartilage as compared to normal cartilage [129] and Smurf2-transgenic mice spontaneously develop an OA-like phenotype [129]. Because Smad7 and Smurf-2 work in concert to promote TGF-β receptor degradation, these data suggest that increased Smad7/Smurf2 action resulting in decreased TGF-β receptor levels might be involved in OA pathogenesis.

5.4 MAP kinases

In addition to the Smad pathway, TGF-β also activates several non-Smad pathways including MAPK kinase (ERK, p38, JNK) pathways, Rho-like GTPase signaling pathways and PI3K/Akt pathways [35-36]. TGF-β-activated kinase-1 (TAK1), a MAP3 kinase activated by TGF-β and other pathways, plays a critical role in cartilage development and function [130]. TGF-β signaling via TAK-1 stimulates type II collagen synthesis in chondrocytes in a Smad3-independent manner [131]. On the other hand, activation of MAPK kinase activity by cytokines such as IL-1β or TNF-α decreases Smad3/4 DNA binding and ECM production in chondrocytes [132]. In addition, activating transcription factor (ATF)-2 works synergistically with Smad3 to mediate TGF-βs inhibition of chondrocyte maturation [133]. These studies suggest extensive cross-talk between Smad and non-Smad pathways in chondrocytes which should be taken into account when considering the role of aberrant TGF-β signaling in OA.

5.5 TGF-β co-receptors

TGF-β co-receptors such as endoglin, betaglycan and CD109 have emerged as important regulators of TGF-β signaling and responses with critical roles in diseases such as cancer and organ fibrosis [43, 47, 54, 58, 134-136]. This section focuses on the available information on these TGF-β co-receptors in cartilage health and disease.

Endoglin (CD105): We have previously shown that endoglin is detected in human articular cartilage *in vivo* and in primary human articular chondrocytes *in vitro* [137]. We have also demonstrated that endoglin enhances TGF-β-induced Smad1/5 signaling and suppresses Smad2/3 signaling and ECM production in human chondrocytes [138]. Importantly, we found that endoglin protein levels are increased in human OA cartilage as compared to normal cartilage [138]. These results are in agreement with the microarray data showing that endoglin mRNA levels are increased in human OA cartilage [102] and in a rat model of OA [97]. Interestingly, elevated circulating and synovial fluid endoglin are associated with primary knee OA severity, suggesting that endoglin may be a useful biomarker for determining disease severity and/or play a causative role in OA pathogenesis [139].

Betaglycan: Our group has shown that betaglycan is expressed in human chondrocytes and that it forms a complex with the signaling receptors and endoglin in a ligand- and TβRII-

independent manner [137]. Betaglycan levels in damaged versus intact human OA cartilage were similar [140] although normal cartilage was not analyzed in this study. Furthermore, betaglycan levels did not change in a rat model of OA [97]. However, betaglycan expression was shown to be increased in adult human articular cartilage in response to mechanical injury [141]. These results suggest that elevated betaglycan expression might be important in secondary OA when joint trauma is involved. Interestingly, betaglycan expression was shown to be increased in mesenchymal stem cells from the femur channel [142] and in trabecular bone from the iliac crest [143] of OA patients. These studies suggest that altered betaglycan expression or function in bone might play a role in OA pathogenesis.

CD109: Information available on CD109 expression or function in cartilage is limited. CD109 was detected in conditioned media of human articular chondrocytes in monolayer culture [144-145] and in that of bovine cartilage explants treated with IL-1β or TNF-α [146]. These studies suggest that CD109 is released from the chondrocyte cell surface which is in agreement with our previous studies on skin cells [58, 147]. We have detected CD109 protein in conditioned media and cell lysates of human OA and normal human articular chondrocytes cultured in monolayer (Finnson and Philip, unpublished data). Recently, CD109 was detected in peripheral circulation and synovial fluid as a component of CD146-positive lymphocytes in patients with various musculoskeletal diseases [148]. The precise mechanisms by which TGF-β co-receptors may contribute to deregulation of TGF-β action in OA remain to be determined.

6. Targeting the TGF-β pathway for osteoarthritis therapy

Several components of the TGF-β signaling pathway display altered expression in human OA cartilage and in experimental models of OA. Genetic manipulation of some of the TGF-β pathway components in mice leads to OA-like phenotypes or to delayed OA progression in experimental OA models. These findings suggest that targeting specific components of the TGF-β pathway may represent a suitable therapeutic strategy for the treatment of OA. Many groups have studied the effect of exogenous TGF-β to promote cartilage repair and/or prevent cartilage degradation. Early studies showed that intra-articular injection of recombinant TGF-β1 into murine joints conferred protection against IL-induced articular cartilage destruction [149-150] although this effect was not observed in older mice [150-151]. Subsequently, exogenous delivery of TGF-β1 was shown to restore depleted proteoglycans in arthritic murine joints [74] and to stimulate proteoglycan synthesis and content in normal murine joints [152]. In addition, TGF-β injected into the osteoarthritic temporomandibular joint of rabbits was shown to have a protective effect on articular cartilage degradation [153]. Although these studies support the notion that TGF-β promotes cartilage repair, its use has been hampered by undesirable side effects including inflammation, synovial hyperplasia and osteophyte formation [84-86, 152, 154]. In this regard, several studies suggest that adjuvant therapies might be used to circumvent the undesirable effects TGF-βs on the osteoarthritic joint. For example, TGF-β was shown to stimulate cartilage repair and the resulting synovial fibrosis could be blocked by Smad7 overexpression in the synovial lining [155]. Such findings suggest that strategies designed to take advantage of the beneficial effects of TGF-β on cartilage repair and simultaneously block its unwanted side effects will be a fruitful avenue for the development of this molecule for OA therapy.

Another important factor to consider when developing a TGF-β-based strategy for OA therapy is that TGF-β may have differential effects on the chondrocyte itself, depending on the cellular context. We have shown that TGF-β signaling in chondrocytes occurs through two different TGF-β type I receptors, ALK5 and ALK1, with ALK1/Smad1/5 pathway opposing ALK5/Smad2/3 signaling and ECM production in human chondrocytes [34]. These data suggest that ALK1 signaling might interfere with the chondroprotective effects of TGF-β. Furthermore, others have shown that ALK1 expression is highly correlated with MMP-13 expression in human OA cartilage and that ALK1 stimulates MMP13 expression in chondrocytes [117]. Thus, a better approach for OA therapy might involve treatment with TGF-β while simultaneously blocking ALK1 activity in chondrocytes. Alternatively, targeting molecules that tip the balance of signaling away from ALK1 and towards ALK5 in OA chondrocytes might also prove to be beneficial. However, there are others who argue that the critical transition from a non-reparative to a reparative cell phenotype involves switching from ALK5-mediated fibrogenic signaling to ALK1-mediated chondrogenic signaling [156]. Therefore, further research on understanding the role of ALK5 and ALK1 signaling pathways in regulating chondrocyte phenotype is needed.

Targeting TGF-β co-receptors for the treatment of human diseases is an attractive concept. Endoglin, betaglycan and CD109 exist both as membrane-anchored and soluble forms due to enzymatic shedding of their ectodomains [134-135, 157-158] and soluble forms of these proteins have been shown to bind and neutralize TGF-β [58, 159, 160, 2001 #587]. One way that these soluble proteins might be used in combination with TGF-β for OA therapy would be to restrict TGF-β expression to the OA chondrocytes. For example, one can use an adenoviral vector containing a type II collagen-specific promoter to drive TGF-β expression in the cartilage while blocking the adverse side effects (synovial fibrosis) of exogenous TGF-β in the joint by co-administration of a soluble co-receptor protein into the synovial fluid. The soluble co-receptor because of its higher molecular weight would not readily diffuse into the cartilage from the synovial fluid [161-162] to block TGF-β action in chondrocytes but would sequester any TGF-β that diffuses from the cartilage into the synovial fluid. Alternatively, TGF-β co-receptor expression in chondrocytes might be targeted directly to promote cartilage repair. Our results indicate that endoglin inhibits TGF-β-induced ALK5-Smad2/3 signaling and ECM production and enhances TGF-β-induced ALK1-Smad1/5 signaling in human chondrocytes [138]. These findings suggest that reducing endoglin expression in OA chondrocytes might promote cartilage repair.

7. Concluding remarks

TGF-β is a critical regulator of articular cartilage development, maintenance and repair. Studies to date indicate that several extracellular, cell surface and intracellular components of the TGF-β pathway display altered expression or activity in OA suggesting that they might represent potential targets for therapeutic treatment of this disease. TGF-β has been shown to promote cartilage repair and its therapeutic use might be improved by "compartmentalized" inhibition of TGF-β activity in synovial tissues to halt or reverse synovial fibrosis and osteophyte formation. Targeting TGF-β co-receptors such as endoglin, betaglycan and CD109 represent new opportunities to explore aberrant TGF-β signaling in OA and to discover new strategies for manipulating the TGF-β pathway for OA therapy.

8. List of abbreviations

ALK, activin receptor-like kinase; ATF, activating transcription factor; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; Evi-1, ecotropic virus integration site 1 protein homologue; FKBP, FK506 binding protein; GPI, glycosyl phosphatidylinositol; HSP, heat shock protein; IL, interleukin; JNK, c-jun N-terminal kinase/stress-activated protein kinase; kDa, kilodalton; LAP, latency associated peptide; LTBP, latent TGF-β binding protein; MMP, matrix metalloproteinase; OA, osteoarthritis; PI3K, phosphatidylinositol 3-kinase; SARA, Smad anchor for receptor activation; Ski, Sloan Kettering Institute proto-oncogene; Sno, ski-related novel protein; SNP, single nucleotide polymorphism; Smurf, Smad ubiquitin regulatory factor; STRAP, serine-threonine kinase receptor-associated protein; TAK, TGF-β activated kinase; TG, transglutaminase; TGF-β, transforming growth factor-beta; TGIF, TGF-β-induced factor; TIMP, tissue inhibitor of metalloproteinase; TSP, thrombospondin; TNF, tumor necrosis factor; TRAP, TGF-β receptor-associated protein; TRIP, TGF-β receptor-interacting protein.

9. References

[1] van der Kraan PM, Goumans MJ, Blaney Davidson E, Ten Dijke P. Age-dependent alteration of TGF-β signalling in osteoarthritis. Cell Tissue Res 2011.

[2] van den Berg WB. Pathomechanisms of OA: 2010 in review. Osteoarthritis Cartilage 2011; 19: 338-341.

[3] Finnson K, Chi Y, Bou-Gharios G, Leask A, Philip A. TGF-β signaling in cartilage homeostasis and osteoarthritis. Front Biosci 2011; S4: 261-268.

[4] Song B, Estrada KD, Lyons KM. Smad signaling in skeletal development and regeneration. Cytokine Growth Factor Rev 2009; 20: 379-388.

[5] Chang SJ, Chen CJ, Tsai FC, Lai HM, Tsai PC, Tsai MH, et al. Associations between gout tophus and polymorphisms 869T/C and -509C/T in transforming growth factor β1 gene. Rheumatology (Oxford) 2008; 47: 617-621.

[6] Dalbeth N, Pool B, Gamble GD, Smith T, Callon KE, McQueen FM, et al. Cellular characterization of the gouty tophus: a quantitative analysis. Arthritis Rheum 2010; 62: 1549-1556.

[7] Kriegel MA, Li MO, Sanjabi S, Wan YY, Flavell RA. Transforming growth factor-β: recent advances on its role in immune tolerance. Curr Rheumatol Rep 2006; 8: 138-144.

[8] Kim EY, Moudgil KD. Regulation of autoimmune inflammation by pro-inflammatory cytokines. Immunol Lett 2008; 120: 1-5.

[9] Pohlers D, Brenmoehl J, Loffler I, Muller CK, Leipner C, Schultze-Mosgau S, et al. TGF-β and fibrosis in different organs - molecular pathway imprints. Biochim Biophys Acta 2009; 1792: 746-756.

[10] Heldin CH, Moustakas A. Role of Smads in TGFβ signaling. Cell Tissue Res 2011; DOI: 10.1007/s00441-011-1190-x.

[11] Wu MY, Hill CS. TGF-β superfamily signaling in embryonic development and homeostasis. Dev Cell 2009; 16: 329-343.

[12] Wharton K, Derynck R. TGF-β family signaling: novel insights in development and disease. Development 2009; 136: 3691-3697.

[13] Moustakas A, Heldin CH. The regulation of TGFβ signal transduction. Development 2009; 136: 3699-3714.

[14] Heldin C, Landstrom M, Moustakas A. Mechanism of TGF-β signaling to growth arrest, apoptosis, and epithelial-mesenchymal transition. Current Opinion in Cell Biology 2009; 21: 166-176.
[15] Schlunegger MP, Grutter MG. An unusual feature revealed by the crystal structure at 2.2 A resolution of human transforming growth factor-β2. Nature 1992; 358: 430-434.
[16] Mittl PR, Priestle JP, Cox DA, McMaster G, Cerletti N, Grutter MG. The crystal structure of TGF-β3 and comparison to TGF-β2: implications for receptor binding. Protein Sci 1996; 5: 1261-1271.
[17] Hinck AP, Archer SJ, Qian SW, Roberts AB, Sporn MB, Weatherbee JA, et al. Transforming growth factor β1: three-dimensional structure in solution and comparison with the X-ray structure of transforming growth factor β2. Biochemistry 1996; 35: 8517-8534.
[18] Daopin S, Piez KA, Ogawa Y, Davies DR. Crystal structure of transforming growth factor-β2: an unusual fold for the superfamily. Science 1992; 257: 369-373.
[19] Radaev S, Zou Z, Huang T, Lafer EM, Hinck AP, Sun PD. Ternary complex of TGF-β1 reveals isoform-specific ligand recognition and receptor recruitment in the superfamily. J Biol Chem 2010; 285: 14806-14814.
[20] Bottinger EP, Letterio JJ, Roberts AB. Biology of TGF-β in knockout and transgenic mouse models. Kidney Int 1997; 51: 1355-1360.
[21] Roberts AB, Sporn MB. Differential expression of the TGF-β isoforms in embryogenesis suggests specific roles in developing and adult tissues. Mol Reprod Dev 1992; 32: 91-98.
[22] Ramirez F, Rifkin DB. Extracellular microfibrils: contextual platforms for TGFβ and BMP signaling. Curr Opin Cell Biol 2009; 21: 612-622.
[23] Hynes RO. The extracellular matrix: not just pretty fibrils. Science 2009; 326: 1216-1219.
[24] Jenkins G. The role of proteases in transforming growth factor-β activation. Int J Biochem Cell Biol 2008; 40: 1068-1078.
[25] Annes JP, Munger JS, Rifkin DB. Making sense of latent TGF-β activation. Journal of Cell Science 2003; 116: 217-224.
[26] Wipff PJ, Hinz B. Integrins and the activation of latent transforming growth factor β1 - An intimate relationship. Eur J Cell Biol 2008; 87: 601-615.
[27] Murphy-Ullrich JE, Poczatek M. Activation of latent TGF-β by thrombospondin-1: mechanisms and physiology. Cytokine Growth Factor Rev 2000; 11: 59-69.
[28] Massague J, Gomis RR. The logic of TGF-β signaling. FEBS Lett 2006; 580: 2811-2820.
[29] Shi Y, Massague J. Mechanisms of TGF-β signaling from cell membrane to the nucleus. Cell 2003; 113: 685-700.
[30] Schmierer B, Hill CS. TGFβ-Smad signal transduction: molecular specificity and functional flexibility. Nat Rev Mol Cell Biol 2007; 8: 970-982.
[31] Ross S, Hill CS. How the Smads regulate transcription. Int J Biochem Cell Biol 2008; 40: 383-408.
[32] Goumans M, Valdimarsdottir G, Itoh S, Rosendahl A, Sideras P, ten Dijke P. Balancing the activation state of the endothelium via two distinct TGF-β type I receptors. Embo J 2002; 21: 1743-1753.

[33] Goumans MJ, Valdimarsdottir G, Itoh S, Lebrin F, Larsson J, Mummery C, et al. Activin receptor-like kinase (ALK)1 is an antagonistic mediator of lateral TGF-β/ALK5 signaling. Mol Cell 2003; 12: 817-828.
[34] Finnson KW, Parker WL, ten Dijke P, Thorikay M, Philip A. ALK1 opposes ALK5/Smad3 signaling and expression of extracellular matrix components in human chondrocytes. J Bone Miner Res 2008; 23: 896-906.
[35] Mu Y, Gudey SK, Landstrom M. Non-Smad signaling pathways. Cell Tissue Res 2011; DOI: 10.1007/s00441-011-1201-y.
[36] Zhang YE. Non-Smad pathways in TGF-β signaling. Cell Res 2008; 19: 128-139.
[37] Wrighton KH, Lin X, Feng XH. Phospho-control of TGF-β superfamily signaling. Cell Res 2009; 19: 8-20.
[38] Yan X, Chen YG. Smad7: not only a regulator, but also a cross-talk mediator of TGF-β signalling. Biochem J 2011; 434: 1-10.
[39] Briones-Orta MA, Tecalco-Cruz AC, Sosa-Garrocho M, Caligaris C, Macias-Silva M. Inhibitory Smad7: Emerging Roles in Health and Disease. Curr Mol Pharmacol 2011; 4: 141-153.
[40] Inoue Y, Imamura T. Regulation of TGF-β family signaling by E3 ubiquitin ligases. Cancer Sci 2008.
[41] Macri L, Silverstein D, Clark RA. Growth factor binding to the pericellular matrix and its importance in tissue engineering. Adv Drug Deliv Rev 2007; 59: 1366-1381.
[42] Grainger DJ, Byrne CD, Witchell CM, Metcalfe JC. Transforming growth factor β is sequestered into an inactive pool by lipoproteins. J Lipid Res 1997; 38: 2344-2352.
[43] Bernabeu C, Lopez-Novoa JM, Quintanilla M. The emerging role of TGF-β superfamily co-receptors in cancer. Biochim Biophys Acta 2009; 1792: 954-973.
[44] Pardali E, ten Dijke P. Transforming growth factor-β signaling and tumor angiogenesis. Front Biosci 2009; 14: 4848-4861.
[45] ten Dijke P, Goumans MJ, Pardali E. Endoglin in angiogenesis and vascular diseases. Angiogenesis 2008; 11: 79-89.
[46] Bilandzic M, Stenvers KL. Betaglycan: A multifunctional accessory. Mol Cell Endocrinol 2011; 339: 180-189.
[47] Gatza CE, Oh SY, Blobe GC. Roles for the type III TGF-β receptor in human cancer. Cell Signal 2010; 22: 1163-1174.
[48] McLean S, Di Guglielmo GM. TβRIII directs clathrin-mediated endocytosis of TGFβ type I and II receptors. Biochem J 2010; 429: 137-145
[49] Finger EC, Lee NY, You HJ, Blobe GC. Endocytosis of the type III TGF-β receptor through the clathrin-independent/lipid raft pathway regulates TGF-β signaling and receptor downregulation. J Biol Chem 2008; 283: 34808-34818.
[50] Santander C, Brandan E. Betaglycan induces TGF-β signaling in a ligand-independent manner, through activation of the p38 pathway. Cell Signal 2006; 18: 1482-1491.
[51] You HJ, Bruinsma MW, How T, Ostrander JH, Blobe GC. The type III TGF-β receptor signals through both Smad3 and the p38 MAP kinase pathways to contribute to inhibition of cell proliferation. Carcinogenesis 2007; 28: 2491-2500.
[52] Chen W, Kirkbride KC, How T, Nelson CD, Mo J, Frederick JP, et al. β-arrestin 2 mediates endocytosis of type III TGF-β receptor and down-regulation of its signaling. Science 2003; 301: 1394-1397.

[53] Solomon KR, Sharma P, Chan M, Morrison PT, Finberg RW. CD109 represents a novel branch of the α2-macroglobulin/complement gene family. Gene 2004; 327: 171-183.
[54] Hashimoto M, Ichihara M, Watanabe T, Kawai K, Koshikawa K, Yuasa N, et al. Expression of CD109 in human cancer. Oncogene 2004; 23: 3716-3720.
[55] Schuh AC, Watkins NA, Nguyen Q, Harmer NJ, Lin M, Prosper JYA, et al. A tyrosine703serine polymorphism of CD109 defines the Gov platelet alloantigens. Blood 2002; 99: 1692-1698.
[56] Lin M, Sutherland DR, Horsfall W, Totty N, Yeo E, Nayar R, et al. Cell surface antigen CD109 is a novel member of the alpha 2 macroglobulin/C3, C4, C5 family of thioester-containing proteins. Blood 2002; 99: 1683-1691.
[57] Bizet AA, Liu K, Tran-Khanh N, Saksena A, Vorstenbosch J, Finnson KW, Buschmann MD, Philip A. The TGF-β co-receptor, CD109, promotes internalization and degradation of TGF-β receptors. Biochim Biophys Acta 2011; 1813: 742-753.
[58] Finnson KW, Tam BY, Liu K, Marcoux A, Lepage P, Roy S, et al. Identification of CD109 as part of the TGF-β receptor system in human keratinocytes. FASEB J 2006; 20: 1525-1527.
[59] Bizet AA, Tran-Khanh N, Saksena A, Liu K, Buschmann MD, Philip A. CD109-mediated degradation of the TGF-β receptors and inhibition of TGF-β responses involve regulation of Smad7 and Smurf2 localization and function. Journal of Cellular Biochemistry 2011; doi: 10.1002/jcb.23349
[60] Bhosale AM, Richardson JB. Articular cartilage: structure, injuries and review of management. Br Med Bull 2008; 87: 77-95.
[61] Eyre DR. Collagens and cartilage matrix homeostasis. Clin Orthop Relat Res 2004: S118-122.
[62] Eyre DR, Weis MA, Wu JJ. Articular cartilage collagen: an irreplaceable framework? Eur Cell Mater 2006; 12: 57-63.
[63] Heinegard D. Proteoglycans and more--from molecules to biology. Int J Exp Pathol 2009; 90: 575-586.
[64] Goldring MB, Tsuchimochi K, Ijiri K. The control of chondrogenesis. J Cell Biochem 2006; 97: 33-44.
[65] Onyekwelu I, Goldring MB, Hidaka C. Chondrogenesis, joint formation, and articular cartilage regeneration. J Cell Biochem 2009; 107: 383-392.
[66] Kawakami Y, Rodriguez-Leon J, Izpisua Belmonte JC. The role of TGF-βs and Sox9 during limb chondrogenesis. Curr Opin Cell Biol 2006; 18: 723-729.
[67] Quintana L, zur Nieden NI, Semino CE. Morphogenetic and regulatory mechanisms during developmental chondrogenesis: new paradigms for cartilage tissue engineering. Tissue Eng Part B Rev 2009; 15: 29-41.
[68] van der Kraan PM, Blaney Davidson EN, van den Berg WB. A role for age-related changes in TGF-β signaling in aberrant chondrocyte differentiation and osteoarthritis. Arthritis Res Ther 2010; 12: 201.
[69] van der Kraan PM, Blaney Davidson EN, Blom A, van den Berg WB. TGF-β signaling in chondrocyte terminal differentiation and osteoarthritis: modulation and integration of signaling pathways through receptor-Smads. Osteoarthritis Cartilage 2009; 17: 1539-1545.

[70] Yang X, Chen L, Xu X, Li C, Huang C, Deng C-X. TGF-β/Smad3 signals repress chondrocyte hypertrophic differentiation and are required for maintaining articular cartilage. J. Cell Biol. 2001; 153: 35-46.

[71] Blaney Davidson E, van der Kraan P, van den Berg W. TGF-β and osteoarthritis. Osteoarthritis Cartilage 2007; 15: 597-604.

[72] Chimal-Monroy J, Diaz de Leon L. Differential effects of transforming growth factors β1, β2, β3 and β5 on chondrogenesis in mouse limb bud mesenchymal cells. Int J Dev Biol 1997; 41: 91-102.

[73] Joyce ME, Roberts AB, Sporn MB, Bolander ME. Transforming growth factor-β and the initiation of chondrogenesis and osteogenesis in the rat femur. J Cell Biol 1990; 110: 2195-2207.

[74] Glansbeek HL, van Beuningen HM, Vitters EL, van der Kraan PM, van den Berg WB. Stimulation of articular cartilage repair in established arthritis by local administration of transforming growth factor-β into murine knee joints. Lab Invest 1998; 78: 133-142.

[75] Hunziker EB. Growth-factor-induced healing of partial-thickness defects in adult articular cartilage. Osteoarthritis Cartilage 2001; 9: 22-32.

[76] Hunziker EB, Rosenberg LC. Repair of partial-thickness defects in articular cartilage: cell recruitment from the synovial membrane. J Bone Joint Surg Am 1996; 78: 721-733.

[77] Scharstuhl A, Glansbeek HL, van Beuningen HM, Vitters EL, van der Kraan PM, van den Berg WB. Inhibition of endogenous TGF-β during experimental osteoarthritis prevents osteophyte formation and impairs cartilage repair. J Immunol 2002; 169: 507-514.

[78] Serra R, Johnson M, Filvaroff EH, LaBorde J, Sheehan DM, Derynck R, et al. Expression of a truncated, kinase-defective TGF-β type II receptor in mouse skeletal tissue promotes terminal chondrocyte differentiation and osteoarthritis. J. Cell Biol. 1997; 139: 541-552.

[79] Blaney Davidson EN, Vitters EL, van der Kraan PM, van den Berg WB. Expression of transforming growth factor-β (TGFβ) and the TGFβ signalling molecule Smad-2P in spontaneous and instability-induced osteoarthritis: role in cartilage degradation, chondrogenesis and osteophyte formation. Ann Rheum Dis 2006; 65: 1414-1421.

[80] Loughlin J. The genetic epidemiology of human primary osteoarthritis: current status. Expert Rev Mol Med 2005; 7: 1-12.

[81] Ikegawa S. New gene associations in osteoarthritis: what do they provide, and where are we going? Curr Opin Rheumatol 2007; 19: 429-434.

[82] Ikegawa S. Expression, regulation and function of asporin, a susceptibility gene in common bone and joint diseases. Curr Med Chem 2008; 15: 724-728.

[83] Dai J, Ikegawa S. Recent advances in association studies of osteoarthritis susceptibility genes. J Hum Genet 2010; 55: 77-80.

[84] van Beuningen HM, van der Kraan PM, Arntz OJ, van den Berg WB. Transforming growth factor-β1 stimulates articular chondrocyte proteoglycan synthesis and induces osteophyte formation in the murine knee joint. Lab Invest 1994; 71: 279-290.

[85] van Beuningen HM, Glansbeek HL, van der Kraan PM, van den Berg WB. Osteoarthritis-like changes in the murine knee joint resulting from intra-articular transforming growth factor-β injections. Osteoarthritis Cartilage 2000; 8: 25-33.

[86] Bakker AC, van de Loo FA, van Beuningen HM, Sime P, van Lent PL, van der Kraan PM, et al. Overexpression of active TGF-β1 in the murine knee joint: evidence for synovial-layer-dependent chondro-osteophyte formation. Osteoarthritis Cartilage 2001; 9: 128-136.
[87] Alcaraz MJ, Megias J, Garcia-Arnandis I, Clerigues V, Guillen MI. New molecular targets for the treatment of osteoarthritis. Biochem Pharmacol 2010; 80: 13-21.
[88] Goldring MB, Goldring SR. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. Ann N Y Acad Sci 2010; 1192: 230-237.
[89] Zhang Y, Jordan JM. Epidemiology of Osteoarthritis. Clin Geriatr Med 2010; 26: 355-369.
[90] Martel-Pelletier J, Pelletier JP. Is osteoarthritis a disease involving only cartilage or other articular tissues? Eklem Hastalik Cerrahisi 2010; 21: 2-14.
[91] Wu J, Liu W, Bemis A, Wang E, Qiu Y, Morris EA, et al. Comparative proteomic characterization of articular cartilage tissue from normal donors and patients with osteoarthritis. Arthritis Rheum 2007; 56: 3675-3684.
[92] Verdier MP, Seite S, Guntzer K, Pujol JP, Boumediene K. Immunohistochemical analysis of transforming growth factor β isoforms and their receptors in human cartilage from normal and osteoarthritic femoral heads. Rheumatol Int 2005; 25: 118-124.
[93] Boumediene K, Conrozier T, Mathieu P, Richard M, Marcelli C, Vignon E, et al. Decrease of cartilage transforming growth factor-β receptor II expression in the rabbit experimental osteoarthritis-potential role in cartilage breakdown. Osteoarthritis Cartilage 1998; 6: 146-149.
[94] Xiao J, Li T, Wu Z, Shi Z, Chen J, Lam SK, et al. REST corepressor (CoREST) repression induces phenotypic gene regulation in advanced osteoarthritic chondrocytes. J Orthop Res 2010; 28: 1569-1575.
[95] Pombo-Suarez M, Castano-Oreja MT, Calaza M, Gomez-Reino JJ, Gonzalez A. Differential up-regulation of the three TGF-β isoforms in human osteoarthritic cartilage. Ann Rheum Dis 2009; 68: 568-571.
[96] Nakajima M, Kizawa H, Saitoh M, Kou I, Miyazono K, Ikegawa S. Mechanisms for asporin function and regulation in articular cartilage. J. Biol. Chem. 2007; 282: 32185-32192.
[97] Appleton CT, Pitelka V, Henry J, Beier F. Global analyses of gene expression in early experimental osteoarthritis. Arthritis Rheum 2007; 56: 1854-1868.
[98] Malemud CJ. Anticytokine therapy for osteoarthritis: evidence to date. Drugs Aging 2010; 27: 95-115.
[99] Pujol JP, Chadjichristos C, Legendre F, Bauge C, Beauchef G, Andriamanalijaona R, et al. Interleukin-1 and transforming growth factor-β1 as crucial factors in osteoarthritic cartilage metabolism. Connect Tissue Res 2008; 49: 293-297.
[100] Kim SJ, Angel P, Lafyatis R, Hattori K, Kim KY, Sporn MB, et al. Autoinduction of transforming growth factor β1 is mediated by the AP-1 complex. Mol Cell Biol 1990; 10: 1492-1497.
[101] Wei T, Kulkarni NH, Zeng QQ, Helvering LM, Lin X, Lawrence F, et al. Analysis of early changes in the articular cartilage transcriptisome in the rat meniscal tear model of osteoarthritis: pathway comparisons with the rat anterior cruciate transection model and with human osteoarthritic cartilage. Osteoarthritis Cartilage 2010; 18: 992-1000.

[102] Aigner T, Fundel K, Saas J, Gebhard PM, Haag J, Weiss T, et al. Large-scale gene expression profiling reveals major pathogenetic pathways of cartilage degeneration in osteoarthritis. Arthritis Rheum 2006; 54: 3533-3544.

[103] Todorovic V, Frendewey D, Gutstein DE, Chen Y, Freyer L, Finnegan E, et al. Long form of latent TGF-beta binding protein 1 (Ltbp1L) is essential for cardiac outflow tract septation and remodeling. Development 2007; 134: 3723-3732.

[104] Drews F, Knobel S, Moser M, Muhlack KG, Mohren S, Stoll C, et al. Disruption of the latent transforming growth factor-β binding protein-1 gene causes alteration in facial structure and influences TGF-β bioavailability. Biochim Biophys Acta 2008; 1783: 34-48.

[105] Shipley JM, Mecham RP, Maus E, Bonadio J, Rosenbloom J, McCarthy RT, et al. Developmental expression of latent transforming growth factor beta binding protein 2 and its requirement early in mouse development. Mol Cell Biol 2000; 20: 4879-4887.

[106] Dabovic B, Chen Y, Colarossi C, Obata H, Zambuto L, Perle MA, et al. Bone abnormalities in latent TGF-β binding protein (LTBP)-3-null mice indicate a role for LTBP-3 in modulating TGF-β bioavailability. J Cell Biol 2002; 156: 227-232.

[107] Dabovic B, Chen Y, Colarossi C, Zambuto L, Obata H, Rifkin DB. Bone defects in latent TGF-β binding protein (LTBP)-3 null mice; a role for LTBP in TGF-β presentation. J Endocrinol 2002; 175: 129-141.

[108] Johnson K, Hashimoto S, Lotz M, Pritzker K, Terkeltaub R. Interleukin-1 induces pro-mineralizing activity of cartilage tissue transglutaminase and factor XIIIa. Am J Pathol 2001; 159: 149-163.

[109] Heinkel D, Gohr CM, Uzuki M, Rosenthal AK. Transglutaminase contributes to CPPD crystal formation in osteoarthritis. Front Biosci 2004; 9: 3257-3261.

[110] Orlandi A, Oliva F, Taurisano G, Candi E, Di Lascio A, Melino G, et al. Transglutaminase-2 differently regulates cartilage destruction and osteophyte formation in a surgical model of osteoarthritis. Amino Acids 2009; 36: 755-763.

[111] Huebner JL, Johnson KA, Kraus VB, Terkeltaub RA. Transglutaminase 2 is a marker of chondrocyte hypertrophy and osteoarthritis severity in the Hartley guinea pig model of knee OA. Osteoarthritis Cartilage 2009; 17: 1056-1064.

[112] Pfander D, Cramer T, Deuerling D, Weseloh G, Swoboda B. Expression of thrombospondin-1 and its receptor CD36 in human osteoarthritic cartilage. Ann Rheum Dis 2000; 59: 448-454.

[113] Jou IM, Shiau AL, Chen SY, Wang CR, Shieh DB, Tsai CS, et al. Thrombospondin 1 as an effective gene therapeutic strategy in collagen-induced arthritis. Arthritis Rheum 2005; 52: 339-344.

[114] Hsieh JL, Shen PC, Shiau AL, Jou IM, Lee CH, Wang CR, et al. Intra-articular gene transfer of thrombospondin-1 suppresses the disease progression of experimental osteoarthritis. J Orthop Res 2010; 28: 1300-1306.

[115] Dehne T, Karlsson C, Ringe J, Sittinger M, Lindahl A. Chondrogenic differentiation potential of osteoarthritic chondrocytes and their possible use in matrix-associated autologous chondrocyte transplantation. Arthritis Res Ther 2009; 11: R133.

[116] Hiramatsu K, Iwai T, Yoshikawa H, Tsumaki N. Expression of dominant negative TGF-β receptors inhibits cartilage formation in conditional transgenic mice. J Bone Miner Metab 2011.

[117] Blaney Davidson EN, Remst DF, Vitters EL, van Beuningen HM, Blom AB, Goumans MJ, et al. Increase in ALK1/ALK5 ratio as a cause for elevated MMP-13 expression in osteoarthritis in humans and mice. J Immunol 2009; 182: 7937-7945.

[118] Gomez-Camarillo MA, Kouri JB. Ontogeny of rat chondrocyte proliferation: studies in embryo, adult and osteoarthritic (OA) cartilage. Cell Res 2005; 15: 99-104.

[119] Blaney Davidson EN, Scharstuhl A, Vitters EL, van der Kraan PM, van den Berg WB. Reduced transforming growth factor-β signaling in cartilage of old mice: role in impaired repair capacity. Arthritis Res Ther 2005; 7: R1338-1347.

[120] Wu Q, Huang JH, Sampson ER, Kim KO, Zuscik MJ, O'Keefe RJ, et al. Smurf2 induces degradation of GSK-3β and upregulates β-catenin in chondrocytes: a potential mechanism for Smurf2-induced degeneration of articular cartilage. Exp Cell Res 2009; 315: 2386-2398.

[121] Li CG, Liang QQ, Zhou Q, Menga E, Cui XJ, Shu B, et al. A continuous observation of the degenerative process in the intervertebral disc of Smad3 gene knock-out mice. Spine (Phila Pa 1976) 2009; 34: 1363-1369.

[122] Yao JY, Wang Y, An J, Mao CM, Hou N, Lv YX, et al. Mutation analysis of the Smad3 gene in human osteoarthritis. Eur J Hum Genet 2003; 11: 714-717.

[123] Valdes AM, Spector TD, Tamm A, Kisand K, Doherty SA, Dennison EM, et al. Genetic variation in the Smad3 gene is associated with hip and knee osteoarthritis. Arthritis Rheum 2010; 62: 2347-2352.

[124] van de Laar IM, Oldenburg RA, Pals G, Roos-Hesselink JW, de Graaf BM, Verhagen JM, et al. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. Nat Genet 2011; 43: 121-126.

[125] Pannu J, Nakerakanti S, Smith E, Dijke Pt, Trojanowska M. Transforming growth factor-β receptor type I dependent fibrogenic gene program is mediated via activation of Smad1 and ERK1/2 pathways. J. Biol. Chem. 2007; 282: 10405–10413.

[126] Valcourt U, Gouttenoire J, Moustakas A, Herbage D, Mallein-Gerin F. Functions of transforming growth factor-β family type I receptors and Smad proteins in the hypertrophic maturation and osteoblastic differentiation of chondrocytes. J Biol Chem 2002; 277: 33545-33558.

[127] Bau B, Haag J, Schmid E, Kaiser M, Gebhard PM, Aigner T. Bone morphogenetic protein-mediating receptor-associated Smads as well as common Smad are expressed in human articular chondrocytes but not up-regulated or down-regulated in osteoarthritic cartilage. J Bone Miner Res 2002; 17: 2141-2150.

[128] Kaiser M, Haag J, Soder S, Bau B, Aigner T. Bone morphogenetic protein and transforming growth factor beta inhibitory Smads 6 and 7 are expressed in human adult normal and osteoarthritic cartilage in vivo and are differentially regulated in vitro by interleukin-1β. Arthritis Rheum 2004; 50: 3535-3540.

[129] Wu Q, Kim KO, Sampson ER, Chen D, Awad H, O'Brien T, et al. Induction of an osteoarthritis-like phenotype and degradation of phosphorylated Smad3 by Smurf2 in transgenic mice. Arthritis Rheum 2008; 58: 3132-3144.

[130] Gunnell LM, Jonason JH, Loiselle AE, Kohn A, Schwarz EM, Hilton MJ, et al. TAK1 regulates cartilage and joint development via the MAPK and BMP signaling pathways. J Bone Miner Res 2010; 25: 1784-1797.

[131] Qiao B, Padilla SR, Benya PD. TGF-β activated kinase 1 (TAK1) mimics and mediates TGF-β-induced stimulation of type II collagen synthesis in chondrocytes

independent of Col2a1 transcription and Smad3 signaling. J. Biol. Chem. 2005; 280: 17562-17571.

[132] Roman-Blas JA, Stokes DG, Jimenez SA. Modulation of TGF-β signaling by proinflammatory cytokines in articular chondrocytes. Osteoarthritis Cartilage 2007; 15: 1367-1377.

[133] Ionescu AM, Schwarz EM, Zuscik MJ, Drissi H, Puzas JE, Rosier RN, et al. ATF-2 cooperates with Smad3 to mediate TGF-β effects on chondrocyte maturation. Exp Cell Res 2003; 288: 198-207.

[134] Hagiwara S, Murakumo Y, Mii S, Shigetomi T, Yamamoto N, Furue H, et al. Processing of CD109 by furin and its role in the regulation of TGF-β signaling. Oncogene 2010; 29: 2181-2191.

[135] Hockla A, Radisky DC, Radisky ES. Mesotrypsin promotes malignant growth of breast cancer cells through shedding of CD109. Breast Cancer Res Treat 2009; 124: 27-38.

[136] Leask A. Targeting the TGFβ, endothelin-1 and CCN2 axis to combat fibrosis in scleroderma. Cell Signal 2008; 20: 1409-1414.

[137] Parker WL, Goldring MB, Philip A. Endoglin is expressed on human chondrocytes and forms a heteromeric complex with betaglycan in a ligand and type II TGFβ receptor independent manner. J Bone Miner Res 2003; 18: 289-302.

[138] Finnson KW, Parker WL, Chi Y, Hoemann C, Goldring MB, Antoniou J, et al. Endoglin differentially regulates TGF-β-induced Smad2/3 and Smad1/5 signalling and its expression correlates with extracellular matrix production and cellular differentiation state in human chondrocytes. Osteoarthritis Cartilage 2010; 18: 1518-1527.

[139] Honsawek S, Tanavalee A, Yuktanandana P. Elevated circulating and synovial fluid endoglin are associated with primary knee osteoarthritis severity. Arch Med Res 2009; 40: 590-594.

[140] Tsuritani K, Takeda J, Sakagami J, Ishii A, Eriksson T, Hara T, et al. Cytokine receptor-like factor 1 is highly expressed in damaged human knee osteoarthritic cartilage and involved in osteoarthritis downstream of TGF-β. Calcif Tissue Int 2010; 86: 47-57.

[141] Dell'accio F, De Bari C, Eltawil NM, Vanhummelen P, Pitzalis C. Identification of the molecular response of articular cartilage to injury, by microarray screening: Wnt-16 expression and signaling after injury and in osteoarthritis. Arthritis Rheum 2008; 58: 1410-1421.

[142] Rollin R, Alvarez-Lafuente R, Marco F, Garcia-Asenjo JA, Jover JA, Rodriguez L, et al. Abnormal transforming growth factor-β expression in mesenchymal stem cells from patients with osteoarthritis. J Rheumatol 2008; 35: 904-906.

[143] Sanchez-Sabate E, Alvarez L, Gil-Garay E, Munuera L, Vilaboa N. Identification of differentially expressed genes in trabecular bone from the iliac crest of osteoarthritic patients. Osteoarthritis Cartilage 2009; 17: 1106-1114.

[144] Polacek M, Bruun JA, Elvenes J, Figenschau Y, Martinez I. The secretory profiles of cultured human articular chondrocytes and mesenchymal stem cells: implications for autologous cell transplantation strategies. Cell Transplant 2011; 20:1381-93.

[145] Polacek M, Bruun JA, Johansen O, Martinez I. Differences in the secretome of cartilage explants and cultured chondrocytes unveiled by SILAC technology. J Orthop Res 2010; 28: 1040-1049.

[146] Stevens AL, Wishnok JS, Chai DH, Grodzinsky AJ, Tannenbaum SR. A sodium dodecyl sulfate-polyacrylamide gel electrophoresis-liquid chromatography tandem mass spectrometry analysis of bovine cartilage tissue response to mechanical compression injury and the inflammatory cytokines tumor necrosis factor-α and interleukin-1β. Arthritis Rheum 2008; 58: 489-500.

[147] Tam B, Larouche D, Germain L, Hooper N, Philip A. Characterization of a 150 kDa accessory receptor for TGF-β1 on keratinocytes: direct evidence for a GPI anchor and ligand binding of the released form. Journal of Cellular Biochemistry 2001; 83: 494-507.

[148] Dagur PK, Tatlici G, Gourley M, Samsel L, Raghavachari N, Liu P, et al. CD146+ T lymphocytes are increased in both the peripheral circulation and in the synovial effusions of patients with various musculoskeletal diseases and display pro-inflammatory gene profiles. Cytometry B Clin Cytom 2010; 78B: 88-95.

[149] van Beuningen HM, van der Kraan PM, Arntz OJ, van den Berg WB. Protection from interleukin 1 induced destruction of articular cartilage by transforming growth factor β: studies in anatomically intact cartilage in vitro and in vivo. Ann Rheum Dis 1993; 52: 185-191.

[150] van Beuningen HM, van der Kraan PM, Arntz OJ, van den Berg WB. In vivo protection against interleukin-1-induced articular cartilage damage by transforming growth factor-β1: age-related differences. Ann Rheum Dis 1994; 53: 593-600.

[151] Scharstuhl A, van Beuningen HM, Vitters EL, van der Kraan PM, van den Berg WB. Loss of transforming growth factor counteraction on interleukin 1 mediated effects in cartilage of old mice. Ann Rheum Dis 2002; 61: 1095-1098.

[152] van Beuningen HM, Glansbeek HL, van der Kraan PM, van den Berg WB. Differential effects of local application of BMP-2 or TGF-β1 on both articular cartilage composition and osteophyte formation. Osteoarthritis Cartilage 1998; 6: 306-317.

[153] Man C, Zhu S, Zhang B, Hu J. Protection of articular cartilage from degeneration by injection of transforming growth factor-β in temporomandibular joint osteoarthritis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009; 108: 335-340.

[154] Blaney Davidson E, Vitters E, van Beuningen HM, van de Loo F, van den Berg W, van der Kraan P. Resemblance of osteophytes in experimental osteoarthritis to transforming growth factorβ-induced osteophytes: limited role of bone morphogenetic protein in early osteoarthritic osteophyte formation. Arthritis Rheum 2007; 56: 4065-4073.

[155] Blaney Davidson EN, Vitters EL, van den Berg WB, van der Kraan PM. TGFβ-induced cartilage repair is maintained but fibrosis is blocked in the presence of Smad7. Arthritis Res Ther 2006; 8: R65.

[156] Plaas A, Velasco J, Gorski DJ, Li J, Cole A, Christopherson K, et al. The relationship between fibrogenic TGFβ1 signaling in the joint and cartilage degradation in post-injury osteoarthritis. Osteoarthritis Cartilage 2011.

[157] Velasco-Loyden G, Arribas J, Lopez-Casillas F. The shedding of betaglycan is regulated by pervanadate and mediated by membrane type matrix metalloprotease-1. J Biol Chem 2004; 279: 7721-7733.

[158] Hawinkels LJ, Kuiper P, Wiercinska E, Verspaget HW, Liu Z, Pardali E, et al. Matrix metalloproteinase-14 (MT1-MMP)-mediated endoglin shedding inhibits tumor angiogenesis. Cancer Res 2010; 70: 4141-4150.

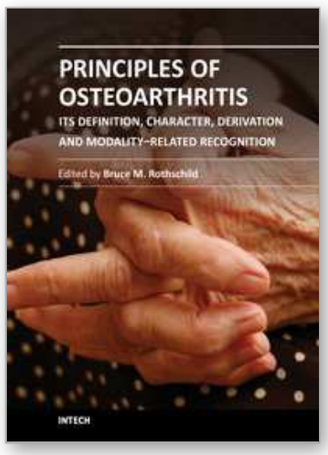
[159] Vilchis-Landeros MM, Montiel JL, Mendoza V, Mendoza-Hernandez G, Lopez-Casillas F. Recombinant soluble betaglycan is a potent and isoform-selective transforming growth factor-β neutralizing agent. Biochem J 2001; 355: 215-222.

[160] Venkatesha S, Toporsian M, Lam C, Hanai J, Mammoto T, Kim YM, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med 2006; 12: 642-649.

[161] Urech DM, Feige U, Ewert S, Schlosser V, Ottiger M, Polzer K, et al. Anti-inflammatory and cartilage-protecting effects of an intra-articularly injected anti-TNF{alpha} single-chain Fv antibody (ESBA105) designed for local therapeutic use. Ann Rheum Dis 2010; 69: 443-449.

[162] van Lent PL, van den Berg WB, Schalkwijk J, van de Putte LB, van den Bersselaar L. The impact of protein size and charge on its retention in articular cartilage. J Rheumatol 1987; 14: 798-805.

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Principles of Osteoarthritis- Its Definition, Character, Derivation and Modality-Related Recognition

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This volume addresses the nature of the most common form of arthritis in humans. If osteoarthritis is inevitable (only premature death prevents all of us from being afflicted), it seems essential to facilitate its recognition, prevention, options, and indications for treatment. Progress in understanding this disease has occurred with recognition that it is not simply a degenerative joint disease. Causative factors, such as joint malalignment, ligamentous abnormalities, overuse, and biomechanical and metabolic factors have been recognized as amenable to intervention; genetic factors, less so; with metabolic diseases, intermediate. Its diagnosis is based on recognition of overgrowth of bone at joint margins. This contrasts with overgrowth of bone at vertebral margins, which is not a symptomatic phenomenon and has been renamed spondylosis deformans. Osteoarthritis describes an abnormality of joints, but the severity does not necessarily produce pain. The patient and his/her symptoms need to be treated, not the x-ray.

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