REVIEW

Age-dependent alteration of TGF-β signalling in osteoarthritis

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Abstract Osteoarthritis (OA) is a disease of articular
cartilage, with aging as the main risk factor. In OA, changes
in chondrocytes lead to the autolytic destruction of
cartilage. Transforming growth factor-β has recently been
demonstrated to signal not only via activin receptor-like
kinase 5 (ALK5)-induced Smad2/3 phosphorylation, but
also via ALK1-induced Smad1/5/8 phosphorylation in
articular cartilage. In aging cartilage and experimental
OA, the ratio ALK1/ALK5 has been found to be increased,
and the expression of ALK1 is correlated with matrix
metalloproteinase-13 expression. The age-dependent shift
towards Smad1/5/8 signalling might trigger the differenti-
ation of articular chondrocytes with an autolytic phenotype.

Keywords Aging · Bone morphogenetic protein ·
Osteoarthritis · Osteophyte · Signalling · Smad ·
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Introduction

Osteoarthritis (OA) is the most universal joint disease with an
increasing prevalence in the Western world attributable to the

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aging population (Restrepo and Rozental 1994). The primary
characteristic of OA is the destruction of articular cartilage
but synovial inflammation, the formation of osteophytes and
sclerosis of the subchondral bone are features of this common
disease (Loeser 2010). Unfortunately, articular cartilage has a
limited repair capacity and therefore damaged cartilage will
not heal. As a result, loss of articular cartilage in OA is
progressive and will ultimately result in loss of joint function.
Pain, tenderness, joint stiffness, crepitus and synovial
effusions are the most common clinical symptoms. However,
early OA is usually not clinically noticed because of the
absence of innervation in articular cartilage. Pharmalogical
interventions are mainly focused at pain and no therapy that
interferes with the disease process has as yet been
developed. The ultimate "therapy" for OA is the replacement
of damaged joints by artificial ones but artificial joints
have only a limited time span and cannot be applied in all
affected joints.

The cause of OA is, in most cases, unknown (primary OA)
but a number of risk factors have been identified, such as
gender and obesity. However, the main risk factor for primary
OA is age (Zhang and Jordan 2010). In their study in the
USA, Murphy et al. (2008) have estimated that nearly half of
the adults will develop symptomatic knee OA by age
85 years. Many ideas have been put forward to explain the
association between OA and aging. The oldest theory linking
OA with aging is that the cartilage destruction observed in
OA joints is just a result of simple wear and tear processes.
Nevertheless, normal use has not been shown to increase the
risk for OA (Marmor 1969). An alternative explanation is
based on the clear changes that are observed in the
extracellular matrix of aging cartilage. The size of the
proteoglycan responsible for the pressure-resilient properties
of cartilage, namely aggrecan, becomes shorter with age
(Lark et al. 1995). Moreover, cross-linking between the
collagen fibrils and glycation end products significantly
increase in human aging cartilage, making the matrix more

brittle and more vulnerable to mechanically induced damage (Verzijl et al. 2001; DeGroot et al. 2004).

The homeostasis of articular cartilage is totally dependent on the embedded cartilage cells, the chondrocytes, and therefore, we can anticipate that age-related changes in chondrocytes are involved in the OA disease process. Chondrocytes in OA cartilage show markers of apoptosis and this has been suggested to be related to OA (Blanco et al. 1998). However, human OA is an extremely slow progressive disease, probably taking decades to become clinically overt, and this is not in agreement with the high numbers of apoptotic cells reported in OA cartilage. Loss of chondrocyte energy supply by degeneration of mitochondrial function has also been suggested as a causative factor in the loss of cartilage homeostasis (Martin and Buckwalter 2003). Another mechanism involving mitochondrial activity is oxidative stress by reactive oxygen species, since the loss of insulin-like growth factor (IGF)-I receptor signalling, the main anabolic factor of articular chondrocytes, is observed during aging (Fortier and Miller 2006). Oxidative stress has been suggested to induce chondrocyte senescence and to inhibit IGF-I receptor signalling (Studer et al. 2000). Alteration in responses to growth factors other than IGF-I can play a role in the OA process. We have found that chondrocytes in aged mice have an altered response to the cytokine transforming growth factor-β (TGF-β) compared with chondrocytes in young mice and that this might be causally related to OA (Scharstuhl et al. 2002b; Fortier and Miller 2006; Blaney Davidson et al. 2005, 2006b). Therefore, the focus of the present review is on this age-related change in TGF-β signalling in OA.

TGF-β signalling via serine/threonine kinase receptors and Smads

TGF-β signals via heteromeric complexes of transmembrane serine/threonine type I and type II receptors. The type I receptors, also termed activin receptor-like kinases (ALKs), act downstream of type II receptors and determine receptor specificity (Heldin et al. 1997). TGF-β belongs to a large family of structurally related cytokines that also includes bone morphogenetic proteins (BMPs). TGF-β mainly signals via the broadly expressed type I receptor ALK5. In endothelial cells, TGF-β has been shown to signal via ALK1, a feature that recently has been found to be shared with chondrocytes (Blaney Davidson et al. 2009; Goumans et al. 2002, 2003b). BMPs signal via ALK1, -2, -3 and −6. Upon type I receptor activation, intracellular signalling is initiated by the phosphorylation of receptor-regulated (R) Smad proteins. Whereas ALK5 stimulates Smad2/3 phosphorylation, ALK1, -2, -3 and −6 mediate the activation of Smad1/5/8 (Blaney Davidson et al. 2009;

Finnson et al. 2008). Phosphorylated R-Smads form heteromeric complexes with the common mediator (co)-Smad4. These heteromeric complexes accumulate in the nucleus where they, together with co-activators and repressors, control transcriptional responses (Heldin et al. 1997). Frequently, these two main intracellular Smad pathways are found to act opposing each other, even antagonizing each other, for example by forming so-called mixed Smad2/3-Smad1/5/8 complexes (Daly et al. 2008; Goumans et al. 2003a, 2003b, 2007). Both the Smad2/3 and Smad1/5/8 signalling cascade have been reported to control chondrocyte differentiation.

OA and chondrocyte differentiation

Cartilage can be divided into temporary and permanent cartilage. Articular cartilage is a permanent tissue, whereas cartilage in the growth plate is only present during childhood and early adolescence. Cartilage formation (chondrogenesis), as can be seen in the developing embryo, is a strictly regulated process (Lefebvre and Bhattaram 2010). Mesenchymal precursor cells condense and initiate chondrogenic differentiation. Differentiation of precursor cells into differentiated chondrocytes is characterized by cell proliferation and the deposition of cartilage-specific molecules, such as type II collagen and aggrecan. In the growth plate, the stage of differentiated chondrocytes is followed by chondrocyte terminal differentiation. This results in chondrocyte hypertrophy and the breakdown of cartilage and bone deposition. During terminal differentiation, chondrocytes enlarge, up to tenfold, and express type X collagen and matrix metalloproteinase 13 (MMP13). The latter enzyme is crucial during the degradation of the cartilage matrix in the growth plate, with loss of this enzyme in knockout mice resulting in a non-functional growth plate (Inada et al. 2004). Alternatively, in articular cartilage, chondrocyte terminal differentiation is inhibited, resulting in stable cartilage in the synovial joints. However, during OA development, chondrocytes in articular cartilage undergo phenotypic changes that bear a close resemblance to the alteration that occurs in terminally differentiating chondrocytes in the growth plates (Tchetina et al. 2005). Terminal differentiation of chondrocytes in the growth plate and changes in articular chondrocytes in OA cartilage cannot be considered as entirely identical processes, although alterations in these cells show a number of parallel characteristics (such as the high expression of MMP13), which are most likely controlled by similar mechanisms.

TGF-β is involved in all stages of chondrogenesis, from condensation to terminal differentiation. Data from in vitro studies of mesenchymal precursor cells indicate that TGF-β is the main initiator of chondrogenesis in these cells (Iwasaki et

al. 1993; Mackay et al. 1998). Mesenchymal condensation, proliferation of chondroblasts and the deposition of cartilage-specific extracellular matrix molecules is strongly stimulated by TGF-β.

In the initial stages of chondrocyte differentiation, TGF-β acts primarily as a stimulator in the progression of chondrocyte differentiation. However, this is different from the role of TGF-β in the late stages of differentiation. TGF-β clearly blocks chondrocyte terminal differentiation (Serra et al. 1997; Yang et al. 2001). Mice knocked out for Smad3 express elevated numbers of hypertrophic chondrocytes in articular cartilage (Yang et al. 2001). Furthermore, TGF-β blocks the expression of the terminal differentiation marker type X collagen in cultures of primary mouse limb bud mesenchymal cells (Zhang et al. 2004). Smad2 and 3 are essential signalling molecules in the inhibitory effect of TGF-β on chondrocyte terminal differentiation and Smad3 appears to play a more prominent role than Smad2 (Alvarez and Serra 2004). These findings clearly demonstrate that TGF-β stimulates the early stages of chondrocyte differentiation but blocks chondrocyte terminal differentiation.

Whereas terminal differentiation is blocked by signalling via Smad2/3, we and others have shown that terminal differentiation strictly requires Smad1/5/8 signalling (Hellingman et al. 2011). In knockout mice, the loss of both Smad 1 and 5 has been shown to result in the obstruction of chondrocyte terminal differentiation and severe cartilage defects. In addition, the inhibitory Smad6 and Smurf1 and 2 are known inhibitors of mainly Smad1/5/8 signalling interfering with Smad signalling and accelerating proteosomal breakdown of phospho-Smads. Mice overexpressing either Smad6 or Smurf1 demonstrate inhibition of chondrocyte terminal differentiation (Horiki et al. 2004). Overexpression of Smurf2 in differentiating chicken chondrocytes stimulates chondrocyte terminal differentiation and maturation as a result of reduced Smad2/3 signalling (Wu et al. 2008b).

The transcription factor Runx2 plays a major role in the control of chondrocyte terminal differentiation. Mice that lack functional Runx2 also completely lack bone formation, because chondrocyte terminal differentiation is absent (Hecht et al. 2007). Runx2 is a central switch that integrates the signals of both Smad pathways, thereby controlling chondrocyte terminal differentiation (Javed et al. 2008, 2009; Miyazono et al. 2004; Lian et al. 2003; Leboy et al. 2001). Smads have been reported to modulate chondrocyte differentiation by a physical interaction with Runx2. Complex formation of Runx2 with Smad1 is vital for the function of Runx2, whereas the interaction of Smad3 with Runx2 inhibits Runx2 functioning (Hjelmeland et al. 2005; Kang et al. 2005; Javed et al. 2008, 2009; Zheng et al. 2007). Apparently, Runx2 can be switched on or off by different Smads, thus controlling chondrocyte terminal differentiation.

Chondrocyte terminal differentiation is thought to play a major role in OA development and Smad signalling regulates this process. However, other factors in addition to the Smad signalling routes can affect chondrocyte differentiation and play a potential role in OA development. Chondrocytes can be activated by inflammatory cytokines, by the Wnt signalling cascade or by extracellular matrix-derived triggers (Blom et al. 2004, 2007, 2009; Goldring et al. 2008; Xu et al. 2007; Kawaguchi 2009; Zhu et al. 2009). Of note, most of these factors also influence TGF-β and Smad signalling, modulating the stability and activity of the various Smad routes and hence adapting the effect of TGF-β on chondrocyte differentiation and OA development.

Genetic aspects of TGF-β and OA

A relationship between the genetic variants of TGF-β itself, TGF-β signalling and binding molecules and OA is reported in humans. Elevated TGF-β1 activity has been suggested to be associated with elevated bone mass and OA. Elevated bone mass is thought to be related to OA development, since the opposite, osteoporosis, appears to protect against OA (Livshits et al. 2010). The long bones of patients with Camurati-Engelmann disease show osteosclerosis. Camurati-Engelmann disease is associated with a mutation in the TGF-β1 gene, resulting in elevated TGF-β activity attributable to an altered binding of lamina-associated polypeptide-1 to mature TGF-β1 (Saito et al. 2001; Wu et al. 2006). Spinal osteophyte formation, an indication of OA development, is associated with variants of the TGF-β1 gene in Japanese women (Yamada 2000; Yamada et al. 2000). This variant also protects this population from osteoporosis, stressing the inverse relationship between low bone mass and OA. However, in a population of German women, no such relationship could be confirmed between this TGF-β1 variant and bone mass (Hinke et al. 2001).

Another genetic variant, in this case proposed to result in decreased TGF-β activity, is reported for asporin, a small leucine-rich proteoglycan. Asporin is a TGF-β inhibitor that is highly expressed in articular cartilage. In Asian populations, the so-called D-14 variant is associated with OA (Kizawa et al. 2005; Song et al. 2008; Jiang et al. 2006). This D-14 variant is a stronger TGF-β inhibitor than the common D-13 variant. Reduced TGF-β activity is proposed to result in decreased synthesis of cartilage-specific extracellular matrix molecules and thus leads to OA (Kizawa et al. 2005). However, in Caucasians, an association between the asporin D-14 variant and OA is lacking in most of the investigated populations (Atif et al. 2008; Rodriguez-Lopez et al. 2006).

Mutations and genetic variation in the Smad3 gene are associated with OA (Yao et al. 2003; van de Laar et al.

2011; Valdes et al. 2010). Increased expression of Smad3 and several key elements of the TGF-β signalling pathway have been found by van de Laar et al. (2011). A relationship between increased Smad3 signalling and OA is unexpected, since studies in transgenic mice have shown that the loss of Smad3 results in accelerated chondrocyte terminal differentiation and OA (Wu et al. 2008a; Yang et al. 2001). Moreover, overexpression of Smurf2 in mice, leading to the inhibition of Smad3 signalling, elicits cartilage damage in vivo (Wu et al. 2008a). This discrepancy can be explained on the basis that either too much or too little Smad3 activity will lead to OA or that different mechanism are involved in the various patient groups. Changes in connective tissues related to altered Smad3 signalling in patients with an aortic phenotype can indirectly result in OA attributable to altered joint stability. On the other hand, genetic variants that will result in decreased Smad3 signalling will produce OA by another mechanism, most probably related to changes in chondrocyte differentiation.

The above-described studies indicate that changes in TGF-β or TGF-β signalling components are related to OA development. Since primary OA is a highly common disease, subtle genetic variations can be expected to contribute to this aging-related disease but not to play a critical role. Moreover, genome-wide association studies have been unsuccessful in detecting genes that have a major contribution to OA in the general population (Panoutsopoulou et al. 2011). This indicates that gene variations might not play a major role in primary OA but that general aging processes might be at the root of the development of this degenerative disease. We propose that an age-related alteration in TGF-β signalling plays a crucial role in the OA disease process.

Shift in ALK1/ALK5 balance in ageing and OA

In our initial studies, comparing the counteracting effect of TGF-β on interleukin-1-induced cartilage damage in young and old mice, we observed that TGF-β was able to counteract the deleterious effect of interleukin-1 in young mice but not in old ones (Scharstuhl et al. 2002b; van Beuningen et al. 1994a). This finding encouraged us to investigate the differences in TGF-β signalling in the cartilage of young and old animals. An age-related loss of the TGF-β type I receptor ALK5 and phosphorylation of Smad2/3 in murine articular cartilage was one of the most striking findings (Blaney Davidson et al. 2006b). The expression of non-phosporylated Smad2 or Smad3 was no different in young and old animals. Since OA development and aging are highly correlated, we also studied the relationship between OA and alterations in TGF-β signalling components in two experimental models of OA. In both models used, namely the meniscus destabilization model and

STR/ORT mice (spontaneous OA), OA development was associated with a striking loss of ALK5 expression (Blaney Davidson et al. 2006b).

In parallel in vitro studies, we have demonstrated that chondrocytes, like endothelial cells, also use ALK1 as a TGF-β type I receptor (Blaney Davidson et al. 2009; Finnson et al. 2008; Goumans et al. 2002). In chondrocytes, this results in the activation of the Smad1/5/8 route (Blaney Davidson et al. 2009; Finnson et al. 2008; Goumans et al. 2002). Interestingly, expression of this alternative TGF-β receptor does not diminish to a comparable extent as ALK5 during aging and experimental OA (Blaney Davidson et al. 2009). As a consequence of the sharp drop in ALK5 and only a small reduction in ALK1 expression, the ALK1/ALK5 ratio is strongly elevated in aged and OA articular chondrocytes. The increased ALK1/ALK5 ratio is reflected in an increased Id1/PAI1 expression ratio, indicating a shift from Smad2/3 to Smad1/5/8 signalling during aging and OA in murine cartilage (Blaney Davidson et al. 2009).

Keeping the regulation of chondrocyte differentiation in mind, we can anticipate that a shift in TGF-β signalling from ALK5 to ALK1 will affect chondrocyte differentiation.

A dominant expression of ALK5 will result in mainly Smad2/3 signalling, whereas ALK1 dominance will lead to the activation of the Smad1/5/8 pathway. The balance of these routes has been shown to control chondrocyte differentiation via Runx2 (see above).

We have further demonstrated that, in chondrocytes, the overexpression of constitutive active ALK5 (Smad2/3) results in increased aggrecan expression, whereas constitutive ALK1 (Smad1/5/8) expression leads to increased expression of MMP13 (Blaney Davidson et al. 2009). Moreover, inhibition of ALK5 expression by using short interfering RNA causes the elevated expression of MMP13, the major cartilage degrading enzyme in OA (Billinghurst et al. 1997). Thus, MMP13 expression is apparently determined by the balance in ALK1 (Smad1/5/8) and ALK5 (Smad2/3) signalling. Of note, the cartilage of human OA knee joints shows a significant correlation between ALK1 and MMP13 mRNA expression (Blaney Davidson et al. 2009). These observations indicate that ALK1 signalling stimulates changes in chondrocyte differentiation that are similar to the chondrocyte phenotype demonstrated in OA cartilage, a phenotype characterized by the highly elevated expression of MMP13 (Billinghurst et al. 1997; Reboul et al. 1996).

We postulate that, because of frequent sub-clinical micro-traumata to the cartilage matrix, TGF-β is released from the extracellular matrix. In articular chondrocytes of young articular cartilage, TGF-β acts as a repair factor, stimulates the synthesis of matrix molecules and keeps the cells in a quiescent state by the inhibitory effect of TGF-β, via Smad2/3, on the progression of chondrocyte differentiation. During the aging of chondrocytes and OA

development via an until now unknown mechanism, signalling through ALK1 and Smad1/5/8 is favoured compared with signalling via ALK5 and Smad2/3. The dominant Smad1/5/8 signalling triggers the articular chondrocytes to leave their quiescent state. This stimulates the progression to a chondrocyte phenotype with characteristics comparable with those of hypertrophic chondrocytes normally only found in the growth plates. These hypertrophic chondrocytes are essential for the removal of the cartilage matrix, mainly by MMP13, to make bone deposition possible (Stickens et al. 2004). These chondrocytes have an autolytic phenotype degrading their surrounding cartilage matrix, as observed in OA cartilage (Fig. 1).

TGF-β and osteophyte formation

We propose a role for TGF-β not only in the regulation of chondrocyte behaviour and cartilage destruction, but also in another feature of OA, namely osteophyte formation. Osteophytes are outgrowths at the margins of the joint that originate from activated mesenchymal stem-cell-like periosteal cells lining the articulating joint surface and can lead to clinical problems (van der Kraan and van den Berg 2007). We have shown, in murine models, that the injection of TGF-β or BMPs results in osteophyte formation in the knee joint (van Beuningen et al. 1994b, 1998, 2000). Cartilaginous osteophytes can be seen within 1 week after injection and, after 1 month, these structure have ossified and are true osteophytes.

The osteophytes induced by BMPs or TGF-β injection are not identical. Osteophytes induced by TGF-β originate from the periosteal cells lining the joint, whereas in the case of BMP-2-induced osteophytes, cells in the, not yet closed, murine growth plate contribute to the formation of the osteophytes (van Beuningen et al. 1994b, 1998). During experimental OA, the pattern of osteophyte formation closely resembles that of TGF-β-induced osteophytes but is quite different from the pattern induced by BMP-2 (Blaney Davidson et al. 2007). Moreover, the outer layer of osteophytes developing during experimental OA strongly express TGF-β1 and phospho-Smad2/3. The latter is not only confined to the surface cells, but also shows strong positive cells in the deeper layer of the osteophytes. Smad1/5/8 signalling is mainly observed in hypertrophic chondrocytes in the late stages of osteophyte formation (own data, not shown).

To explore further the role of TGF-β in the process of osteophyte formation, we performed blocking studies using specific TGF-β inhibitors. TGF-β activity was blocked by means of a scavenging soluble TGF-β type II receptor extracellular domain, by intra-articular overexpression of LAP-1 or by intra-articular overexpression of Smad7. All three treatments resulted in a significant reduction in osteophyte formation compared with controls. Overexpression of adenoviral Smad6, targeting mainly the Smad1/5/8 route, was far less effective than Smad7 overexpression (Scharstuhl et al. 2002a, 2003). In addition, adenoviral overexpression of gremlin, a BMP inhibitor, fully blocked BMP-2-induced osteophyte formation. However, the blocking of BMP activity by gremlin neither inhibited TGF-β-induced nor experimental OA-associated osteophyte formation (Blaney Davidson et al. 2007). These observations clearly demonstrate that TGF-β plays a dominant role in the induction of osteophytes, at least in murine OA models, and that the role of BMPs is limited in the early stages. The latter finding does not exclude a role for BMPs during cartilage maturation, as is seen in developing osteophytes (Lories et al. 2005).

TGF-β is released, and partly activated, from damaged joint tissues during OA development or by inflammation accompanying the OA process. Mesenchymal stem cells in the periosteum are triggered, by the released TGF-β, to initiate chondrogenic differentiation, as has been shown in vitro by using periosteum explants (O'Driscoll et al. 1994). The mesenchymal cells go through a developmental process similar to that seen in the growth plates. Cartilage deposition is followed by chondrocytes maturation leading to chondrocyte hypertrophy and finally to replacement by bone. This indicates that TGF-β most likely not only plays a role in cartilage destruction, but also in the concomitant formation of new cartilage and bone, namely the osteophytes.

TGF-β and synovial fibrosis

Synovial fibrosis can be often observed in OA-affected joints (Revell et al. 1988). We have shown that both the injection and the adenoviral overexpression of TGF-β results in substantial synovial fibrosis characterized by fibroblast proliferation and collagen accumulation (Bakker et al. 2001; van Beuningen et al. 1994b). Moreover, the blocking of TGF-β itself or of TGF-β signalling results in a significant decrease in synovial fibrosis in murine experimental OA models (Blaney Davidson et al. 2006a; Scharstuhl et al. 2003). These findings indicate that TGF-β is an important driving-force for synovial fibrosis in OA and contributes to the characteristic stiffness of affected joints.

Concluding remarks and targets for therapy

We postulate that TGF-β plays a central role in OA development, being a protective factor initially but later playing a role in OA pathogenesis characterized by cartilage destruction, osteophyte formation and synovial fibrosis. In our view, the OA process is driven by the loss of the Smad2/3 block and acquirement of the Smad1/5/8 push

Fig. 1 Transforming growth factor-β (TGF-β) plays a role in key characteristics of osteoarthritis (OA): cartilage damage, osteophyte formation and synovial fibrosis. TGF-β is required for the maintenance of healthy cartilage during which it signals primarily via Smad2/3. With age and OA, a shift in the activin receptor-like kinase 5 (ALK5):ALK1 ratio is established, favouring Smad1/5/8 signalling and leading to a loss of the cartilage protective role of Smad2/3. We suggest a role for this balance shift towards ALK1 in cartilage damage during OA development. In addition, TGF-β is a crucial factor in the onset of osteophyte development. In later stages of osteophyte development, bone morphogenetic proteins (BMP) might be equally important. TGF-β is a major player in fibrotic diseases and, during OA, it induces synovial fibrosis
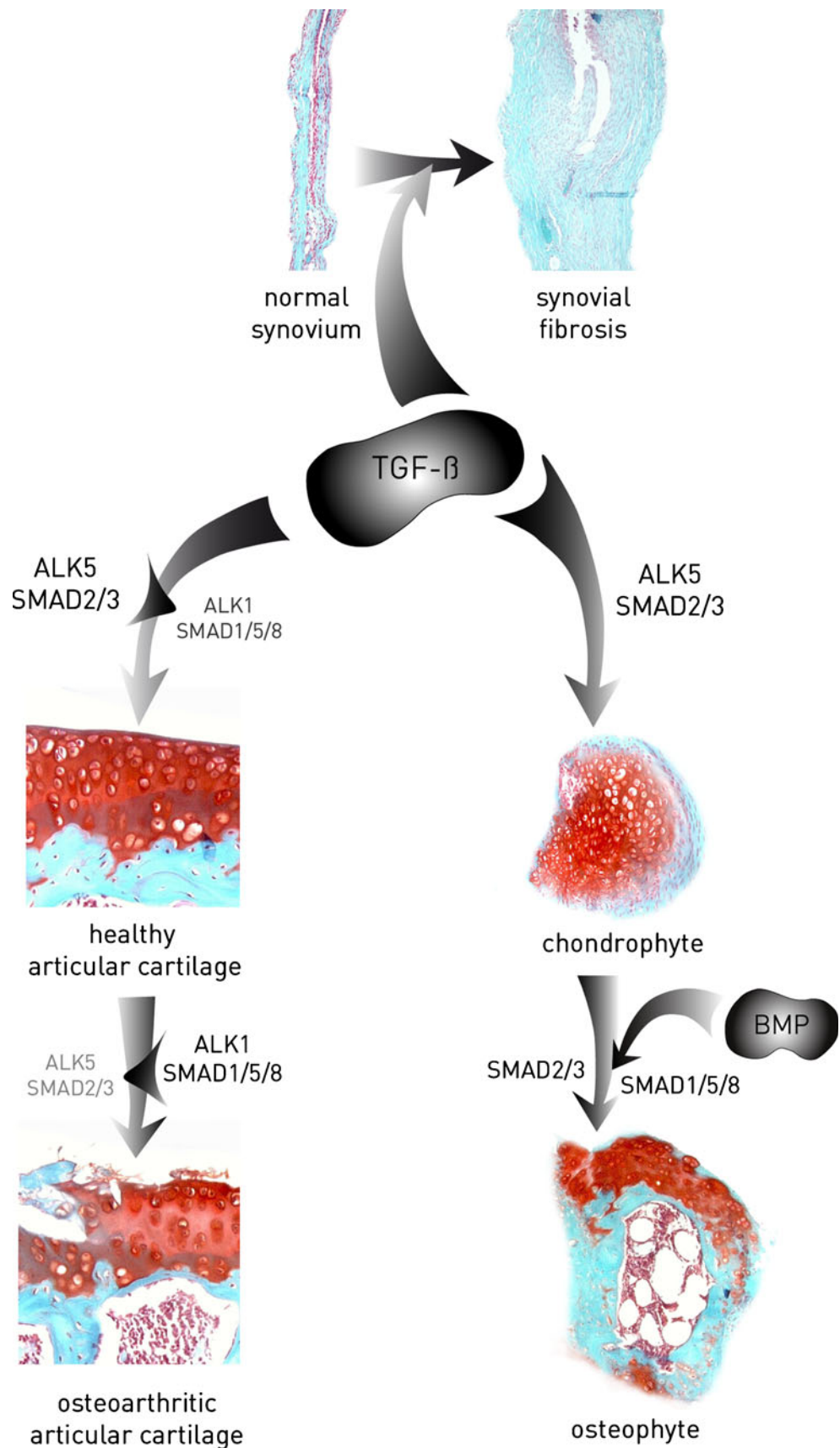
on chondrocyte differentiation in articular chondrocytes leading to an advancement of chondrocyte differentiation and finally an autolytic phenotype. In addition, TGF-β released by tissue damage and inflammation triggers periosteal cells to form osteophytes and to stimulate a fibrotic reaction of the synovial fibroblasts.

Since this view does not regard OA as a simple and unavoidable result of wear and tear, pharmalogical interventions should be an option. OA is initially a focal process and not all chondrocytes will show an OA-like phenotype. Some cells will have an autolytic phenotype, whereas other cells will still be in a quiescent healthy state of differentiation. These cells could be targeted for therapy to block further progression of the OA process.

A disbalance of ALK1/ALK5 and loss of dominant Smad2/3 signalling is at the basis of the OA process, in our view. Specific ALK1 inhibitors that can penetrate cartilage or compounds specifically stimulating the Smad2/3 route should be developed and tested in pre-clinical models of OA. To date, no effective therapy has been developed for OA that interferes with disease progression. Painkillers and joint replacements are the only therapeutic options at the moment. The blocking of the Smad1/5/8 pathway or stimulation of smad2/3 signalling, combined with the use of MMP13 inhibitors to block the autolytic phenotype of fully OA chondrocytes, should be pursued as potential remedies. The proposed treatments would hit the OA process at its foundation, inhibiting the generation of chondrocytes with an autolytic phenotype.

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