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Review

The relationship between fibrogenic TGFβ1 signaling in the joint and cartilage degradation in post-injury osteoarthritis

A. Plaas †‡, J. Velasco ‡, D.J. Gorski ‡, J. Li †, A. Cole ‡, K. Christopherson ‡§, J.D. Sandy ‡‖ *

† Department of Internal Medicine (Rheumatology), Rush University Medical Center, Chicago, IL, USA
‡ Department of Biochemistry, Rush University Medical Center, Chicago, IL, USA
§ Department of Internal Medicine (Hematology/Cell Therapy), Rush University Medical Center, Chicago, IL, USA
‖ Department of Orthopedic Surgery, Rush University Medical Center, Chicago, IL, USA

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SUMMARY

Objective: To review the literature on modulation of chondrocyte activities in the osteoarthritic joint, and to discuss these changes in relation to established hard and soft tissue repair paradigms, with an emphasis on transforming growth factor beta (TGFβ1)-mediated signaling which can promote either a chondrogenic or fibrogenic phenotype.

Methods: Papers addressing the close relationship between repair in general, and the specific post-injury response of joint tissues are summarized. Different interpretations of the role of TGFβ1 in the emergence of an "osteoarthritic" chondrocyte are compared and the phenotypic plasticity of "reparative" progenitor cells is examined. Lastly, emerging data on a central role for A-Disintegrin-And-Metalloproteinase-with-Thrombospondin-like-Sequences-5 (ADAMTS5) activity in modulating TGFβ1 signaling through activin receptor-like kinase 1 (ALK1) and activin receptor-like kinase 5 (ALK5) pathways is discussed.

Results: The review illustrates how a transition from ALK5-mediated fibrogenic signaling to ALK1-mediated chondrogenic signaling in joint cells represents the critical transition from a non-reparative to a reparative cell phenotype. Data from cell and *in vivo* studies illustrates the mechanism by which ablation of ADAMTS5 activity allows the transition to reparative chondrogenesis. Multiple large gene expression studies of normal and osteoarthritis (OA) human cartilages (CAs) also support an important role for TGFβ1-mediated pro-fibrogenic activities during disease progression.

Conclusions: We conclude that progressive articular CA damage in post-injury OA results primarily from biomechanical, cell biologic and mediator changes that promote a fibroblastic phenotype in joint cells. Since ADAMTS5 and TGFβ1 appear to control this process, agents which interfere with their activities may not only enhance endogenous CA repair *in vivo*, but also improve the properties of tissue-engineered CA for implantation.

Introduction

The primary goal of osteoarthritis (OA) therapy continues to be the protection of the articular cartilage (CA), since its progressive degradation commonly leads to partial or total loss of joint function. On the other hand, it is now well established that traumatic injury to the knee joint, frequently involves the ligaments, menisci, articular CA and subchondral bone. All these tissue types, in addition to synovium (SY), perichondrium, fat pad and joint capsule, co-operate to optimize function of the whole joint organ, and injury to any one or more can be expected to elicit a multi-tissue post-injury wound repair response. Injury to the joint can involve traumatic events, such as intra-articular fractures, ligament tears and/or meniscal damage; in a broader sense, it can also be non-traumatic and encompass aberrant biomechanics, due to varus or valgus malalignment, contralateral adaptations to joint replacement surgery or growth abnormalities. It is outside the scope of this article to review the extensive clinical literature on these topics, however it is now generally accepted that any such joint injury very often results in the initiation and/or progression of human and animal OA[1–5].

The post-injury joint responses have been documented by radiographic and magnetic resonance imaging (MRI)-based methods, and this has provided a comprehensive database of

* Address correspondence and reprint requests to: J.D. Sandy, Department of Biochemistry, RUMC, 1735 W Harrison Street, Cohn 520, Chicago, IL 60612, USA. Tel: 1-312-942-8249; Fax: 1-312-942-3053.
E-mail address: John_Sandy@rush.edu (J.D. Sandy).

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location-specific and tissue-specific changes[4,6–17]. For example, rupture of the anterior cruciate ligament (ACL) results in localized CA matrix changes, and because of the anatomy of the ACL, the damage is usually most extensive on the posterior aspect of the lateral tibial plateau and lateral femoral condyle[6]. Such damage can be long-lived, since even 1 year after ACL reconstruction, the CA overlying a bone bruise may still exhibit altered MRI signals[8]. Non-traumatic injury, such as chronic varus overloading, has also been shown to result in both subchondral bone attrition[17] and thinning of the articular CA in the overloaded sub-compartment[9].

Key mediators of soft tissue and fracture repair in OA joints

Placing a pathological process in the context of normal physiology often brings important insights which might otherwise remain hidden. In essence, all healing responses are aimed at restoring a functional tissue architecture through steps of inflammation, progenitor cell migration, proliferation, differentiation, and finally matrix restoration[18–21]. Despite this paradigm, joint tissue injury commonly results in degenerative, rather than regenerative changes in the articular CA.

A widely supported explanation for this is that joint injury activates pathways that result in transformation of the stable articular chondrocyte to a hypertrophic phenotype, and that this terminal differentiation results in CA matrix autolysis and tissue degeneration. On the other hand, the injury response within or above subchondral bone can also be viewed as a recapitulation of the process of bone fracture healing, in which chondrocytes produce a stabilizing cartilaginous fracture callus. Subsequently the cells hypertrophy, and the associated matrix is resorbed during replacement with bone. In addition, severe joint trauma, such as ACL rupture, is often accompanied by not only impact injury to the CA[8], but also subchondral microfractures and extensive bone bruising[22–24] which is further characterized by necrotic and fibrogenic regions, and microtrabecular fractures with sclerosis[8,22]. In addition, subchondral microfractures with active callus formation have been reported[22,25] and the sclerosis around such fractures also suggests an attempted fracture healing response. Indeed, in a study of the osteochondral junction in OA, both VEGF and PDGF proteins have been identified in chondrocytic cells associated with fibrovascular tissue[26]. Further, a role for these mediators in osteoblasts of the subchondral bone plate is consistent with the finding that the expression levels of VEGF, and the abundance of interleukin (IL)6, IL8, and transforming growth factor beta (TGFβ1) are significantly higher in osteoblasts from sclerotic bone than from normal[27,28]. Therefore microfracture, bone bruising and sclerosis may also alter mediator levels in the fluid–filled perforating channels of the subchondral bone[29] and thereby induce progenitor cell proliferation and migration into the deep zones of the CA[30].

However, injury to the soft tissues of the joint space (meniscus, ligaments, joint capsule) activates a soft-tissue wound-healing response, much as in dermal repair, and such an environment in the joint would lead to transition of chondrocytes (and progenitors) to a fibrogenic phenotype (see schematic, Fig. 1). The growth factors, cytokines and their cellular sources (blood cells, neutrophils, macrophages, vascular and pluripotent progenitor cells) in the post-injury joint space are likely the same as those implicated in dermal wound healing in general (summarized in Table I). These mediators have been assayed in fluids and tissues from human skin burns, wounds and grafts[31–33] and surgical repairs[34] and identified by the presence of transcripts and/or protein[18,35] in multiple wound repair models[19–21,36]. Notably, each have also been identified in

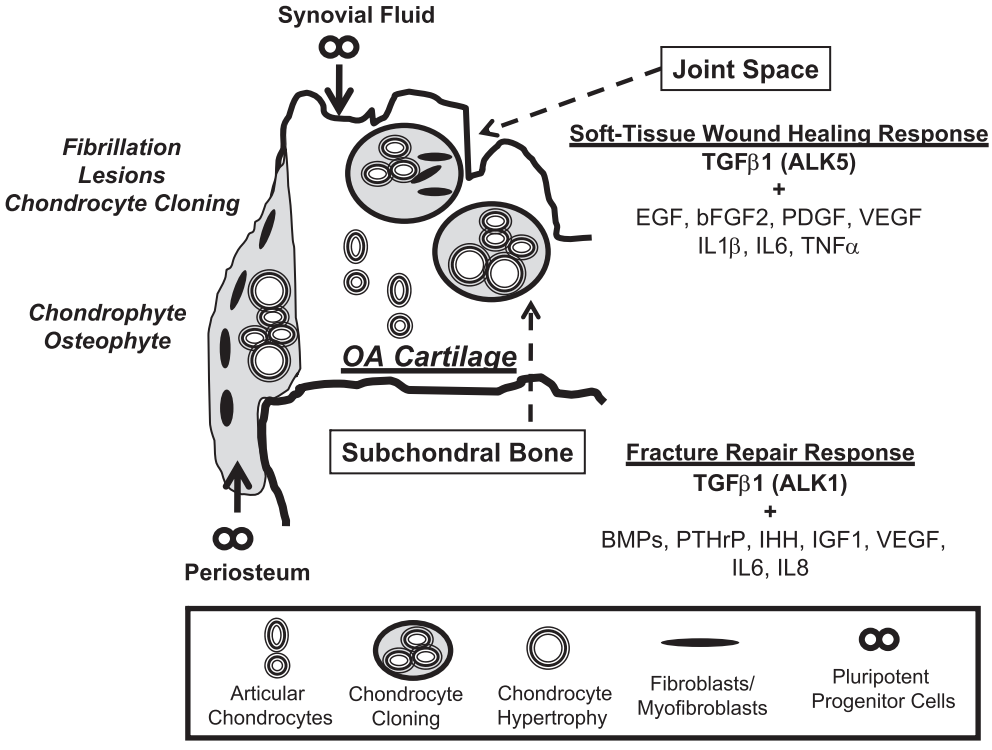

Fig. 1. Schematic of tissue and cell responses to TGFβ1 that result in remodeling and destruction of articular CA. OA CA is shown which contains clonal groups of chondrocytes, hypertropic chondrocytes and fibroblastic cells. Pluripotent progenitor cells in the superficial zone CA or released from the SY and periosteum post-injury can be incorporated into such clones. Mediators released as a result of soft-tissue wound-healing (Joint Space) or fracture repair (Subchondral Bone) response following acute or chronic joint injuries stimulate clonal formation and cellular differentiation. TGFβ1 signaling in the presence of ADAMTS5 can promote pro-fibrotic pathway. Inhibition of the enzyme is followed by activation of Smad1,5,8 occurs, resulting in chondrogenic responses and pro-anabolic activity in chondrocytes. The cell types involved are identified in the boxed area below the scheme.

Table I
Wound healing mediators in dermal and joint tissues showing their source and major effects on cellular responses

Factor	Joint tissue source	Joint tissue repair responses	Wound cell source [20–23]	Wound healing responses [20–23]
EGF	SY[133]; OA SF[134]	Chondrocyte proliferation; ion transport, decreased matrix production	P,M,F	Epithelialization
FGF-2	SY[135–137]; AT[138]; OP[137]; OA SF[139–142]	Anti-apoptotic; prochondrogenic	M,EP,END,F	Angiogenesis Granulation tissue ECM production
TGFβ1	CA[143]; SY[144]; OP[137, 145]; OA SF[47, 48]	Pro-catabolic (MMP-13); chondrocyte hypertrophy	P,M,EP,END,F	Epithelialization, Granulation Tissue Fibroplasia
BMPs	SY[152]; CA[146–148]; BO[149, 150]; OA SF[151]	Prochondrogenic; Osteophytes	SC	Hairfollicle formation
PDGF	CA[143]; SY[153, 154]; OA SF[47]	Stimulates reparative responses in fibrochondrocytes; anti-hypertrophic	P,M,F	Granulation tissue Fibroplasia Contraction
VEGF	CA[155–159,163]; SY[158–161], AT[138]; OA SF[47, 162]	Delays reparative responses in meniscus and CA	P,N,M,END,F	Angiogenesis
IL1β	CA[143]; SY[180]; post ACLT SF[164–167]; OA SF[48, 167–170]	CA and meniscal matrix degradation	N,M,EP	Inflammation Epithelialization
IL6	CA[171, 172]; AT[138, 173]; PC[174]; Post ACL SF[164, 175]; OA SF[48, 169]	CA matrix degradation	N,M,EP	Inflammation Epithelialization
TNFα	CA[143]; SY[176]; AT[138]; Post ACLT SF[167,170,175, 177,178]; OA SF[48,168,169].	CA matrix degradation	N,M,EP	Inflammation Epithelialization

Abbreviations: ACLT: Anterior cruciate ligament tear; AT: Adipose tissue; OP: Osteophyte; PC: Plasma Cells; END: endothelial cells; EP: epithelial cells; F: Fibroblasts; M: Macrophages; N: Neutrophils; P: Platelets.

joint tissues and synovial fluids (SFs) (see Table I) and the likely roles for each in joint tissue repair responses have also been described in both *in vivo* and *in vitro* model systems[37–42].

A pivotal role for TGFβ1 in the wound environment of the OA joint

In considering the likelihood that any of these mediators might affect cellular behavior within the injured joint environment, it is notable that the mean concentration of TGFβ1 in OA SFs ranges from 0.75 ng/ml[43] to 4.95 ng/ml[44], which is similar to that found in dermal wound fluids[32–34]. Perhaps more than any other mediator, TGFβ1 has been found to regulate a very wide range of cellular behaviors, which include cell proliferation and migration, inflammation, control of immune functions, carcinogenesis and extracellular matrix (ECM) synthesis and degradation. It is for these reasons that a pivotal role for TGFβ1 in responses to joint injury and OA development has been studied and discussed in such detail[45–50]. In relation to human OA, TGFβ1 has historically been considered as a central anabolic or reparative mediator, together with IGF-1[51], FGF-2[52] and bone morphogenetic protein (BMP)-7[53]. In addition, TGFβs are also regulators in the *in vitro* differentiation of mesenchymal progenitors to reparative chondrocytes, using 3D culture conditions[54–56].

A central role for TGFβ1-induced signaling in human OA is also supported by recent genetic linkage analyses. Firstly, a single nucleotide polymorphism (SNP) in human Smad3 has been linked to the incidence of hip and knee OA in a 527 patient cohort[57] and secondly, a polymorphism in the human asporin gene has been linked to hip OA[58,59], a finding which is relevant since asporin[60] interferes with TGFβ1 binding to TGFβRII. An important consideration in interpreting these associations is that at present, there is little information as to which joint tissue(s) are primarily affected by the mutations, and how the mutated molecule affects disease incidence or progression.

Mechanisms by which TGFβb1 signaling causes activation of 'anabolic' pathways vary with cell type and the ECM composition of a particular tissue[61]. These signaling pathways thereby drive critical repair events, but they are also responsible for epithelial mesenchymal transition (EMT) transformations[62,63] underlying fibrogenic disorders[64,65] and tumorogenesis[66,67]. The complex signal transduction events which follow TGFβ1 interaction with its kinase receptors and co-receptors has been extensively studied and is summarized in a number of recent reviews[68,69]. In brief, substrates for TGFβ1-induced phosphorylation include the Smad family of proteins, as well as ERK, JNK and p38, and the RhoGTPases (Cd42, Rac1, RhoA)[70,71] (Fig. 2). In addition, TGFβ1 signaling can be regulated by the presence of other soluble mediators such as EGF[72,73], bFGF-2[74], angiotensin[75], interferon (INF)γ[76], TNFα[75,77] and the activity of other receptors such as EGFR[78] and the estrogen receptor[79].

TGFβ1 signaling requires the participation of ECM and cell-surface components which regulate homo- and heterodimerization of TGFβRs[61,80]. For example, when TGFβ1 binds to endoglin in the presence of TGFβRII, Smad1/5 phosphorylation is enhanced and Smad2 phosphorylation inhibited[81]. Of particular interest with respect to CA matrix turnover, hyaluronan (HA)/CD44 complexes can regulate TGFβ1-dependent ECM production in both tissue regeneration and fibrosis[82–85] and this is likely mediated by cell membrane dynamics that create focal adhesions (FAs) and lipid rafts. Such membrane microdomains sequester adapter proteins which, in turn, regulate endocytotic trafficking of complexes[86–89], such as TGFβ1/TGFβRII/activin receptor-like kinase 1 (ALK1).

Within this complex framework, TGFβ1-mediated signaling has been widely implicated in the progression of OA, primarily through an apparent capacity to regulate the conversion of a normal articular chondrocytes to the "hypertrophic" phenotype. For example, IHC and mRNA studies in mouse and human OA CAs have shown an enrichment of ALK1-positive relative to activin receptor-like kinase 5 (ALK5)-positive cells. This change was associated in human samples with enhanced MMP-13 expression[90], which was interpreted as resulting from a phenotypic switch to a hypertrophic OA phenotype[46,91,92]. In separate studies on this question, it has been shown that the blockade of ALK5-mediated TGFβ1 signaling seen in Smad3−/− mice, accelerates chondrocyte hypertrophy and also that murine over-expression of Smurf-2, which inhibits TGFβ1/Smad-3 signaling, results in spontaneous CA loss *in vivo*[49,93]. In related studies with SV-immortalized murine chondrocytes, over-expression of transfected ALK1 or blocking ALK5 with siRNA also

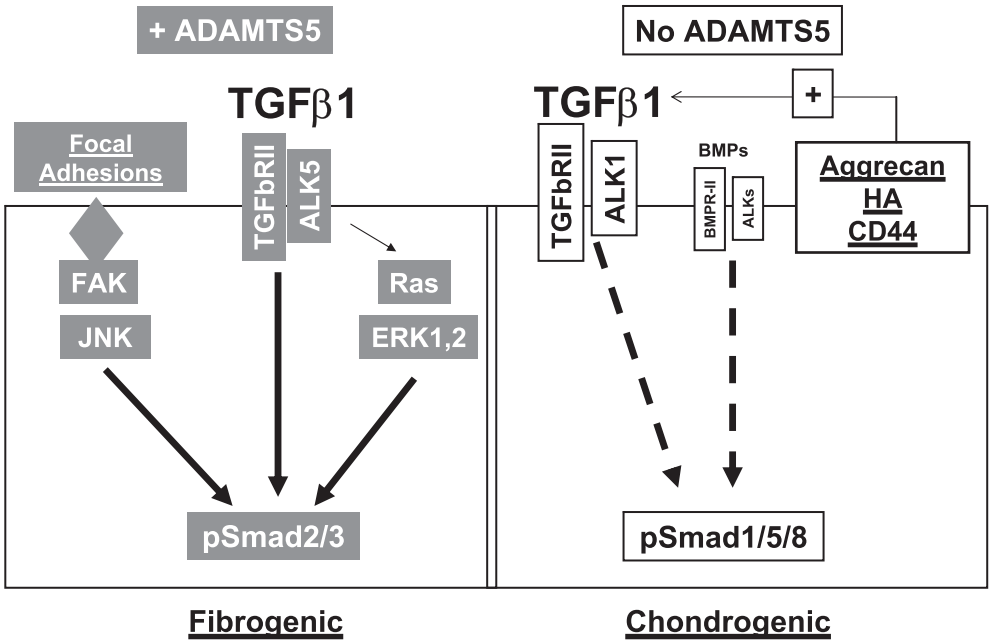

Fig. 2. Schematic of ADAMTS5-mediated control of pro-fibrotic/prochondrogenic TGFβ1 signaling in mesenchymal cells. The schematic describes the proposed modulation of TGFβ1 signal transduction through the ALK5-fibrogenic pathway and the ALK1-chondrogenic pathway. ALK5/Smad2,3 signaling is shown to require ADAMTS5 and can be further supported by pFAK at focal adhesion and pERK1,2 generated *via* the non-canonical TGFβ1 pathway. ALK1/Smad1,5,8 occurs in the absence of ADAMTS5 when it is enhanced by the presence of HA-aggrecan bound near the cell surface by CD44.

induced MMP-13 expression[93]. In summary, this series of papers[46,49,90–94] have linked a high level of TGFβ1/ALK1-mediated signaling, along with a high expression of col10 and MMP-13, to the emergence of hypertrophic chondrocytes. Since col10 and MMP-13 have been widely interpreted as markers of hypertrophic or "osteoarthritic" chondrocytes, this has engendered a general agreement that TGFβ1 signaling through the ALK1/Smad1/5/8 pathway in chondrocytes is a hallmark of OA development[81,92,93,95].

As stated above, we are proposing in this review that the alternative pathway of TGFβ1 signaling, through ALK5/Smad2/3, causes the transition of chondrocytes and chondroprogenitors to a fibrogenic phenotype, resulting in many of the destructive processes of OA, such as aggrecan depletion, which are initiated at the articular surface and progress throughout the tissue[96–98].

Several pivotal papers, also consistent with a central role for the TGFβ1-ALK5 axis in CA matrix destruction *in vivo* have been published recently. The first describes dosing growing rats with an antifibrogenic agent (GW788388) targeted specifically at ALK5-mediated TGFβ1 signaling[99]. It was found, that blocking ALK5 had profound effects on the chondrocyte and matrix dynamics of the epiphyseal growth plate. Specifically, inhibition of ALK5 signaling resulted in an elevated expression of prochondrogenic genes in the perichondrium, and in the resting, proliferative and pre-hypertrophic zones of the plate, along with an elevated proteoglycan abundance and a decrease in collagen-resorbing proteinases. These data fully support the model presented in Fig. 2, which predicts the activation of ALK1-mediated chondrogenesis as a result of inhibition of ALK5-mediated fibrogenesis. Two other papers[100,101] are also consistent with the model implicating A-Disintegrin-And-Metalloproteinase-with-Thrombospondin-like-Sequences-5 (ADAMTS5) in the control of TGFβ1 signaling. These workers showed that high ADAMTS5 activity, generated in a microRNA-140 knockout mouse, is accompanied by a reduction in aggrecan in the growth plate, mild-dwarfism and early-onset OA. Conversely, over-expression of microRNA-140 in CA, reduced ADAMTS5 levels and protected the mice against aggrecan loss in an inflammatory murine model. In a related paper[102] it was shown that in addition to ADAMTS5 inhibition, miRNA-140 directly suppresses Smad3 levels, further suggesting a mechanistic link between ADAMTS5 activity and control of TGFβ1 signaling.

Pro-fibrogenic ALK-5 mediated TGFβ1 signaling in OA CA

Recent studies from our own laboratory[103–107], and others[108–113], have indicated that the damaging effects of TGFβ1 signaling in OA results from a loss of prochondrogenic ALK1-signaling and up-regulation of the ALK5 pathway. For example, three independent gene expression analyses of normal and OA human CA[112–114] showed a significant up-regulation of col1 and/or col3 (~10-fold) in OA, but no enhancement of col10, consistent with the conclusion that many chondrocytes in human OA CAs have acquired a fibrogenic phenotype. Such a transition is also supported by immunohistochemistry of CAs removed from human and animal knees early after joint injury and at joint replacement[111,115,116]. Thus, a microscopic pannus-like tissue over the CA surface was seen in the majority of OA joints inspected in one study[116], and on IHC the cells stained positive for aggrecan and Col2 but also for Col1, MMP-1, MMP-3 and MMP-13. In addition, chondrocytes near lesions in OA CAs have been shown to stain strongly for alpha-smooth muscle actin (aSMA), a standard marker for TGFβ1-mediated conversion of fibroblasts to myofibroblasts in fibrous tissues[117]. Lastly, a pro-fibrogenic role for TGFβ1 in OA is also consistent with the common observation that in the human disease, the articular CA is gradually replaced by fibroCA[111,118,119].

The phenotypic plasticity of mesenchymal progenitors in OA

A large number of groups have now reported that OA progression is accompanied by the accumulation of mesenchymal progenitor cells in joint tissues and fluids (Fig. 1). Such cells have been found to populate sites of CA destruction[120] and may be concentrated in the superficial layer of the tissue in early OA[121].

Mesenchymal progenitors can also be isolated from the SY[122,123] and the infrapatellar fat pad[124] of OA joints. In addition, injurious microfracture of subchondral bone can activate and recruit marrow- or periosteum-derived progenitor cells to the deep and calcified CA zones in the immediate vicinity[125].

Of high significance in this field is the pioneering work of two groups who have studied progenitors isolated from human SFs and synovial membranes. Particularly interesting is the finding that the concentration of progenitors in OA SFs, particularly after injury, is about 20-fold higher than in RA, consistent with them being derived from injured joint structures rather than the bone marrow[126,127]. Indeed, single cell marker analysis supports the view that SF cells with multi-lineage potential are derived from the SY itself. Further characterization of these cells has suggested that they also have the capacity to repair fibrous tissues such as ligament and meniscus[128], as shown by cell tracking studies in animal models. *In vitro* studies with fluid-derived progenitors have also illustrated their adherence to and migration into damaged CA surfaces[129], consistent with studies on superficial layer progenitors which have been shown to engraft into fibrous structural tissues such as bone and tendon[130]. It therefore appears that the progenitors which accumulate in the joint after traumatic injury, and also in established OA, have the plasticity to transition into either chondrogenic cells for CA repair or fibrogenic cells for repair of joint structures such as ligament and meniscus.

With respect to the potential for CA repair with such cell populations, there has been a long history of attempts to optimize reparative conditions for both exogenous and endogenous cell sources. Recent reviews on the subject[131–133] continue to describe limitations related to the problems of cell source, phenotypic stability and poor repair tissue integration. Clinically, procedures which encourage endogenous progenitors to enter the joint, such as subchondral abrasion, have achieved some success, however in general the tissue formed is fibro-cartilaginous and has poor biomechanical properties.

ADAMTS5-regulation of TGFβ1 signaling – a new role for pericellular aggrecan turnover

Details of the mechanism by which fibrogenic cells can readily arise in OA joints, were obtained from our recent studies with ADAMTS5−/− mice[103,106,134]. Advanced knee joint OA was induced in mice using the DMM injury model or the newly developed TTR model[103]. The TTR model involves intra-articular injection of TGFβ1, to mimic acute injury[45,135], followed by 2 weeks of uphill treadmill to maintain aberrant and stressful loading on the knee. With wild-type mice in both OA models, CA erosion was found to be spatially associated with a fibrous overgrowth from the peri-articular soft tissues, such as SY, periosteum and meniscal attachments. Most significantly however, it was found that in ADAMTS5−/− mice, the overgrowth by fibrogenic cells and matrix did not occur and CA erosion was eliminated. Instead, in joint regions of maximal biomechanical stress, there was no aggrecan loss but higher than normal amounts of aggrecan were deposited in the CA. This illustrated, unexpectedly, that a transition from TGFβ1-induced fibrosis to chondrogenesis could be achieved *in vivo* simply by the elimination of ADAMTS5 activity (Fig. 2).

This conclusion was further validated by the remarkable finding that the post-injury chondrogenic response seen in the joint tissues of ADAMTS5−/− mice also occurs during dermal repair in these same mice[134]. However, in this case the accumulation of aggrecan leads to failure of the healing response, due to the absence of the appropriate dermal fibroblast population. Further, it was shown that successful dermal regeneration in wild-type mice is accompanied by an increased expression of ADAMTS5, the pro-fibrogenic genes col1, col3, TGFβ1 and TGFβRII, and also ALK5 in late-stage granulation tissue, prior to wound contraction and dermal regeneration. In contrast, in the dermis of ADAMTS5−/− mice the expression of these fibrogenic genes was not enhanced. Instead, prochondrogenic genes such as aggrecan, ALK1 and the activin receptors [activin A receptor 1 (ACVR1), activin A receptor 2a (ACVR2a) and activin A receptor-like 1 (ACVRL1)] were strongly upregulated throughout the wound healing period. Most significantly, these differences in the TGFβ1 signaling response were also seen in primary cultures of newborn skin fibroblasts from the two mouse strains. Thus, TGFβ1 treatment of wild-type cells resulted in the expected fibrogenic ALK5/Smad2/3-phophorylation, whereas ADAMTS5−/− cells, treated under the same conditions, lacked the Smad2/3 phosphorylation response, but had robust ALK1/Smad1/5/8 phosphorylation. In addition to this, and consistent with the need for cell–matrix interactions in TGFβ1 signaling, it was found that the ALK1-mediated phosphorylation response by ADAMTS5−/− fibroblasts was itself dependent on a pericellular CD44-HA-aggrecan matrix. Thus elimination of HA-aggrecan from the pericellular space, by CD44 knockout in ADAMTS5−/− mice or by treatment of ADAMTS5−/− cell layers with *Streptomyces hyaluronidase*, resulted in the restoration of fibrogenic TGFβ1-induced Smad2/3 phosphorylation (Fig. 2).

A similar modulation of TGFβ1 signaling by removal of pericellular HA-aggrecan has also now been demonstrated in primary cultures of murine chondrocytes (Gorzki D and Plaas A, unpublished). Treatment of matrix-rich wild-type chondrocytes with retinoic acid results in complete degradation of the pericellular aggrecan and transition from a cobblestone to a spindle-shaped morphology. This transition is accompanied by robust TGFβ1-induced Smad2/3 phosphorylation, and a much diminished Smad1/5/8 phosphorylation. In contrast, ADAMTS5−/− chondrocytes treated with RA showed incomplete aggrecan degradation and these cells exhibit Smad1/5/8 phosphorylation as the dominant response to TGFβ1. These experiments further underline a central role for ECM components, in particular HA-aggrecan, in determining the emphasis and downstream effects of TGFβ1 signaling in both fibrogenic and chondrocytic cells. It therefore seems reasonable to assume that such a control mechanism applies not only to resident chondrocytes, but also to uncommitted progenitors responding to the wound environment.

Conclusions and therapeutic implications

We conclude from these observations that therapeutic inhibition of TGFβ1 signaling through ALK5/Smad2/3 in the post-injury OA joint should markedly diminish fibrogenic activities and generate a robust chondrogenic repair response. Data from isolated cell studies, murine OA models with mutant mice, and human OA CA gene expression analysis, together indicate that CA repair *in vivo* should result from a TGFβ1-driven process, in which concurrent treatment is designed to prevent the emergence of the fibrogenic phenotype in reparative progenitors. At the same time, our novel data on the pivotal role of ADAMTS5 in controlling TGFβ1 signaling should motivate new strategies to improve cell-based regenerative therapies for adult articular CA repair. Put simply, since inhibition of ADAMTS5 appears to promote TGFβ1-driven differentiation of progenitor cells to chondrocytes (also see[136]), it seems likely that CA will form wherever ADAMTS5 activity is blocked and an appropriate HA-based construct for cell–matrix interactions and aggrecan accumulation is also provided. Refinement of these strategies for successful *in vivo* repair will require a more in-depth understanding of the central role played by ADAMTS5 in regulating TGFβ1-mediated chondrogenic and fibrogenic reactions to tissue injury.

Author contributions

AP: Literature Survey; Manuscript Preparation.

JV: Literature Survey on dermal wound healing; performed experiments cited from authors laboratory.

DG: Performed experiments cited from authors laboratory.

JL: Performed experiments cited from authors laboratory.

AC: Literature survey and manuscript preparation on aspects of human OA.

KC: Literature survey and manuscript preparation on aspects of progenitor cell biology.

JS: Literature Survey; Manuscript Preparation.

Conflict of interest

The authors have no competing interests with respect to the content of this review.

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