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REVIEW

Chondrodysplasias and TGFβ signaling

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Human chondrodysplasias are a group of conditions that affect the cartilage. This review is focused on the involvement of transforming growth factor-β signaling in a group of chondrodysplasias, entitled acromelic dysplasia, characterized by short stature, short hands and restricted joint mobility.

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Introduction

Human chondrodysplasias are a group of conditions that affect the cartilage. It involves the growth, organization and development of the skeleton. The majority of bones in the skeleton are generated through two different mechanisms: the intramembranous and the endochondral ossifications. In the intramembranous process, mesenchymal cells originating from the neural crest and the cephalic mesoderm differentiate into osteoblast cells to form flat bones like cranial vault, maxilla, mandible or clavicles. In the endochondral process, the condensed mesenchymal cells proliferate, and differentiate into chondrocytes. The hyaline chondrocytes are differentiated into hypertrophic chondrocytes, which finally undergo apoptosis following bone matrix deposition. Some cartilage tissues persist within the growth plate positioned between the ossified epiphyses ends and diaphysis of the long bone, allowing continuous postnatal longitudinal bone growth.

Transforming growth factor-β (TGFβ) is important in chondrogenesis and osteogenesis. TGFβ belongs to a superfamily of related signaling proteins, the cytokines, that regulate a wide variety of biological processes, including cell growth, apoptosis differentiation, migration, extracellular matrix production, angiogenesis, immunity and development. This family also includes activins and bone morphogenetic proteins (BMPs).[1] Those cytokines signal through a well-characterized pathway of transmembrane serine–threonine kinase receptors and intracellular signaling molecules of the SMAD (mothers against DPP) family. Upon activation of Smad proteins by phosphorylation, they accumulate in the nucleus and regulate transcription.[2] The bioavailability of TGFβ itself, and thus its activity, is tightly regulated through the extracellular matrix (ECM). Extracellular regulation of TGFβ signaling can be observed at levels of the co-receptor (which controls the access of ligands to signaling receptors) or of ECM molecules such as fibrillin (Fibrillin-1 (FBN1)), involved especially in TGFβ bioavaibility.[3] TGFβ works synergistically with BMPs, depending on the stage of differentiation. In this review, we will focus on the recent TGFβ signaling involvement in a specific group of chondrodysplasias, the acromelic dysplasia.

TGFβ Signaling

TGFβ exists in at least three isoforms (TGFβ1, TGFβ2 and TGFβ3), which are highly conserved through evolution. They are synthesized inside cells as protein precursors. The N-terminal peptide, the latency-associated peptide (LAP), is necessary to permit the secretion of the molecule. Furin convertase cleaves the pro dimer of TGFβ to produce the small latent TGFβ complex.[4] The mature TGFβ remains noncovalently bound to the LAP. The small latent TGFβ complex can covalently bind to the large latent TGFβ-binding proteins (LTBPs) to form the large latent complex (LLC).[5] LTBPs (LTBPs 1–4) are closely related to fibrillins. They have the same organization, including repeating cysteine-rich domains, epidermal growth factor-like repeats, eight cysteine domains and TGF protein-binding domain. The C-terminus of LTBP1 binds to the N-terminal region of fibrillin-1, leading to a link between LLC and elastic microfibrils.[6] LTBP also interacts with other ECM components such as fibronectin.

To allow the activation of TGFβ, the LLC must be released from microfibrils and the ECM. Various modes of activation have been described, including protease-mediated cleavage and integrin or metalloprotease-mediated release. The mechanisms seem to depend on the cell type, but all activating mechanisms directly target LAP. One example involves the integrins that bind to the LLC via the RGD (Arg/Gly/Asp) sequence of LAP. The mechanism remains unclear, but interaction with the RGD domain of LAP may induce a conformational change leading to release or exposure of TGFβ.[7]

Some fragments of fibrillins are formed after proteolysis by elastases, particularly an internal fragment that has affinity to

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the N-terminal region of fibrilllin1. This interaction between the fragment of fibrillin and fibrillin microfibrils leads to the displacement of LTBP and release of the LLC. This contributes to the activation of TGFβ.[8] BMP1 has been shown to also have a role in the release of LLC by cleaving LTBP1 at two specific sites in the hinge region to release LLC.

Once the active and mature TGFβ is free in the ECM, binding to cellular receptors may occur. TGFβ signals via TGFβ type II receptor (TGFBR2) and TGFBR1 (also known as ALK5) in the vast majority of cell types. TGFβ binds to its TGFBR2, which recruits and phosphorylates TGFBR1. TGFBR1 then recruits and phosphorylates a receptor-regulated SMAD protein (R-SMAD), SMAD2 and/or SMAD3.[9]

There are eight Smad proteins that can be divided in the receptor-regulated SMADs (R-SMADs, SMAD1, 2, 3, 5 and 8), the co-mediator SMAD (SMAD4) and the inhibitory SMADs (SMAD6 and SMAD7). SMAD2 and SMAD3 respond to TGFβ and activin, whereas SMAD1, 5 and 8 function in BMP signaling pathways. Upon TGFβ binding, the type I receptor directly phosphorylates R-SMADs. Phosphorylated R-SMADs dissociate from the receptor and form heterodimers with SMAD4 and then translocate into the nucleus to induce or repress the expression of TGFβ/BMP target genes such as connective tisuue growth factor, plasminogen activator inhibitor-1 and other collagens.[10]

TGFβ and Chondrogenesis

TGFβ has a role in different stages of chondrogenesis, namely mesenchymal condensation, chondrocyte proliferation, ECM deposition and terminal differentiation. In the first step of chondrogenesis, TGFβ seems to have an important stimulatory role. The mesenchymal condensation is stimulated by TGFβ-induced increase of N-cadherin expression.[11] Smad3 but not Smad2 forms a complex with Sox9 and CEBP/p300 to activate genes for chondrogenesis.[12] Moreover, organotypic culture studies showed that Smad3 is necessary for TGFβ1-induced chondrocyte proliferation in mice. Key ECM proteins of cartilage, such as aggrecan and type II collagen, are deposited under stimulation of TGFβ.[13] It has been proven that the complex Smad3/4 and Sox9 bound to the enhancer region of type II collagen gene and then stimulated its synthesis via TGFβ.[14] In contrast, in later stages, TGFβ inhibits chondrocyte terminal differentiation and also the expression of terminal differentiation marker type X collagen.[15] Smad3 with Runx2 forms a complex leading to the inhibition of Runx2 function.[16] TGFβ then blocks cartilage matrix calcification and vascularization to maintain ECM integrity. Smad2 and Smad3 share redundant functions in terms of inhibiting hypertrophic differentiation. Indeed, the withdrawal of TGFβ in the culture medium is necessary to lead the differentiation of human mesenchymal cells in hypertrophic chondrocytes.[17] Yang *et al.*[18] have shown that Smad3 has a key role in maintaining the articular cartilage by preventing articular chondrocytes from undergoing terminal hypertrophic differentiation. Altogether, Smad2 seems to be more essential in early stages of development. Smad3 is more implicated in cartilage homeostasis as it mediates the TGFβ signaling to inhibit the chondrocyte terminal differentiation. This may be due to a difference in expression between Smad3 and 2 in the cartilage growth plate.

TGFβ Signaling and Mouse Models

In the past decade, the generation of mouse models with gene deletions and targeted gene modifications of the TGFβ signaling pathway component has revealed key roles of TGFβs in skeletal development *in vivo*. TGFβ1 knockout mice show reduced bone growth and mineralization.[19] TGFβ2 and TGFβ3 double-deficient mice display a malformation of ribcage and early embryonic lethality. Mouse models with inactivation of genes encoding the receptors TGFBR1 and R2 have also been generated. On using Dermo1-Cre, which permits the inactivation of TGFBR1 in all mesoderm-derived tissues, conditional knockout TGFBR1 mice have short and wide long bones and reduced trabecular bones.[20] Tgfbr2 has a role in developing the axial skeleton. Conditional Col2a1-Cre Tgfbr2 $-/-$ mice exhibit multiple defects in the base of the skull and in the vertebrae.[21] Conditional Prx1-Cre Tgfbr2 $-/-$ mouse models show impaired endochondral and intramembranous ossification. Indeed, the mice show malformation in long bones, joint and skull vault.[22]

Abnormally increased numbers of hypertrophic chondrocytes in the growth plate leading to dwarfism is observed in Smad3 knockout mice.[23] Smad3-deficient mice have a similar phenotype to that of mice expressing a transgenic dominant-negative Tgfbr2, suggesting that Smad3 has a key role in TGFβ signaling. The mice harboring a deletion of Tgfbr2 in tissues expressing Col2a1 and Prx1 exhibit axial skeleton defects, alteration in hypertrophic differentiation in growth plates and joint fusions in phalanges.[21,22] Homozygous *Smad4*-deficient mice died before day 7.5, but mutant embryos have reduced size. Specific deletion of *Smad4* in chondrocytes (chondrocyte-specific Cre, Col2a1-Cre, $^{co/co}$ transgenic mice) led in dwarf mice because of disorganized growth plate.[23] This growth plate is characterized by an expanded resting zone of chondrocytes, reduced chondrocyte proliferation, accelerated hypertrophic differentiation and increased apoptosis. Smad4-mediated TGFβ signals inhibit the chondrocyte hypertrophic differentiation and are required to ensure the normal organization of chondrocytes in the growth plate.[24] The cartilage-specific loss of Smad4 resembles in many aspects the phenotype of Smad3-deficient mice. These data suggest that, in contrast to BMP signaling, TGFβ signaling may be more dependent on Smad4. Finally, the targeted ablation of Smad4 in osteoblasts revealed that Smad4 is also required for maintaining normal postnatal bone homeostasis in mice. Indeed, bone mineral density, bone volume, bone formation rate and osteoblast numbers are reduced in *Smad4* mutant mice.[25]

TGFβ Signaling and Chondrodysplasias: Acromelic Dysplasia

The acromelic dysplasia group includes four disorders, namely the Weill–Marchesani syndrome (WMS), geleophysic dysplasia (GD), acromicric dyplasia (AD) and the Myhre syndrome (MS) (**Table 1**). They are all characterized by short stature, short hands and feet, stiff joints and 'muscular' build. These disorders are closely similar but distinct by additional clinical features.

Weill–Marchesani syndrome

WMS is characterized by (1) a microspherophakia, which corresponds to a smaller eye lens with a rounded shape, and (2) a dislocation of the lens. This may cause severe myopia

Table 1 Chondro-osseous features in acromelic dysplasia and marfanoid conditions

	Short stature short hands	*Tall stature arachnodactyly*	*Restricted joint mobility*	*Hyperlaxity*	*Osteoporosis*	*Increased bone density*	*Genes*
Weill–Marchesani syndrome	x		x				*FBN1* (AD) *ADAMTS10* (AR) *ADAMTS17* (AR)
Geleophysic dysplasia	x		x				*FBN1* (AD) *ADAMTSL2* (AR)
Acromicric dysplasia	x		x				*FBN1* (AD)
Myhre syndrome	x		x				*SMAD4* (AD)
Marfan syndrome		x		x	x		*FBN1* (AD)
Loeys–Dietz syndrome		x		x	x		*TGFBR1* (AD) *TGFBR2* (AD)
Camurati–Engelmann disease		x		x		x	*TGFB1* (AD)
Shprintzen–Goldberg syndrome		x					*SKI* (AD)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.

(because of the spherical form), as well as glaucoma and/or cataract.[26,27] Two modes of inheritance have been reported: autosomal dominant and autosomal recessive. We first showed that *FBN1* is responsible for the dominant form of WMS.[28] Subsequently, we identified mutations in *ADAMTS10* (*A Disintegrin-like And Metalloproteinase domain (reprolysin type) with ThromboSpondin type 1 repeats*) in the autosomal recessive form of WMS.[29] *ADAMTS17* mutations have also been identified in patients presenting with a 'Weill–Marchesani like' syndrome.[30] Patients present with short stature and lens dislocation with no brachydactyly, decreased joint mobility or thick skin; *LTPB2* mutations, which have been first identified in isolated ectopia lentis, are also associated with the autosomal recessive form of WMS or WMS-like phenotype.[31]

The review of 128 WMS patients reported in the literature does not allow the finding of any significant distinctive feature, supporting the clinical homogeneity of the disorder.[32] WMS appears to be a clinically homogeneous but genetically heterogeneous condition.

The function of ADAMTS10 is unknown. ADAMTS10 belongs to the ADAMTS family. The ADAMTS are secreted metalloproteinases composed of catalytic and ancillary domains.[33] The involvement of ADAMTS10 and FBN1 in the same disorder is highly suggestive of a functional relationship between ADAMTS10 and fibrillin-1. Very recently, a direct interaction between ADAMTS10 and fibrillin-1 has been demonstrated, with ADAMTS10 promoting FBN1 deposition in the ECM of cultured fibroblasts. These novel findings support a role of ADAMTS10 in microfibril biogenesis.[34] Microfibril ultrastructure analyses of WMS patient fibroblasts and mice have shown that modulation of the fibrillin microfibril scaffold can influence local tissue microenvironments. Interestingly, pathogenetic mechanisms caused by dysregulated WMS microenvironments do not lead to activation of TGFβ signaling in tissues.[35]

To date, the ADAMTS17 function is unknown. However, clinical and genetic findings support that ADAMTS10 and ADAMTS17 have a critical role in crystalline lens and connective tissue formations.

Geleophysic (GD, MIM231050) and Acromicric (AD, MIM 102370) dysplasias

GD is the most severe form of the acromelic dysplasia group. In 1971, the first report suggested an autosomal recessive mode of inheritance.[36] Additional features include a characteristic facial appearance (a 'happy' face with full cheeks, shortened nose, hypertelorism, long flat philtrum, thin upper lip), progressive cardiac valvular thickening often leading to early death, contractions of the gastrocnemius muscle and achilles tendon leading to tiptoe walking, tracheal stenosis and bronchopulmonary insufficiency. Lysomal-like storage vacuoles have been observed in various tissues. Radiological manifestations include delayed bone age, cone-shaped epiphyses, shortened long tubular bones and ovoid vertebral bodies (**Figure 1**).

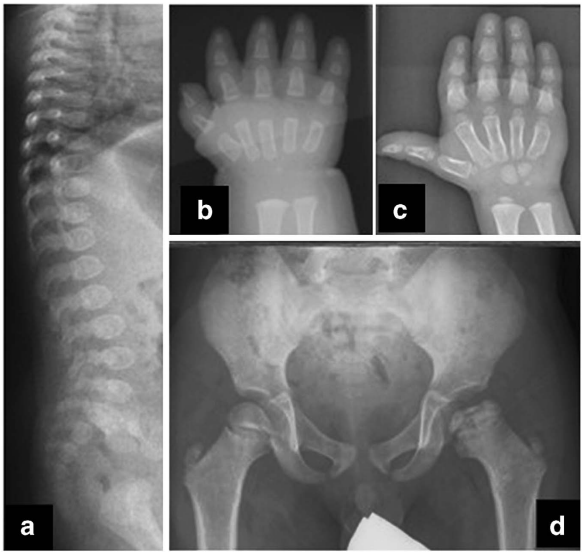

Figure 1 Radiological manifestations of geleophysic dysplasia. (**a**) AP view of the vertebrae (at 1 year of age), (**b**, **c**) hand X-ray (at 1 and 5 years of age) and (**d**) pelvic X-ray (at 5 years of age) of a GD patient. Note the ovoid vertebrae, the delayed bone age and cone-shaped epiphysis of the phalanges and the femoral epiphyseal dysplasia.

We first identified *A Disintegrin And Metalloproteinase with Thrombospondin repeats-like 2* gene (*ADAMTSL2)* as the disease gene of GD.[37] The ADAMTSL2 gene encodes a secreted glycoprotein of unknown function, sharing the ancillary domain of ADAMTS proteins but distinct by the absence of any catatytic domain, lacking therefore any enzyme activity. The exact function of ADAMTSL2 remains unknown. Using a yeast two-hybrid screen, we identified LTBP1 as one of

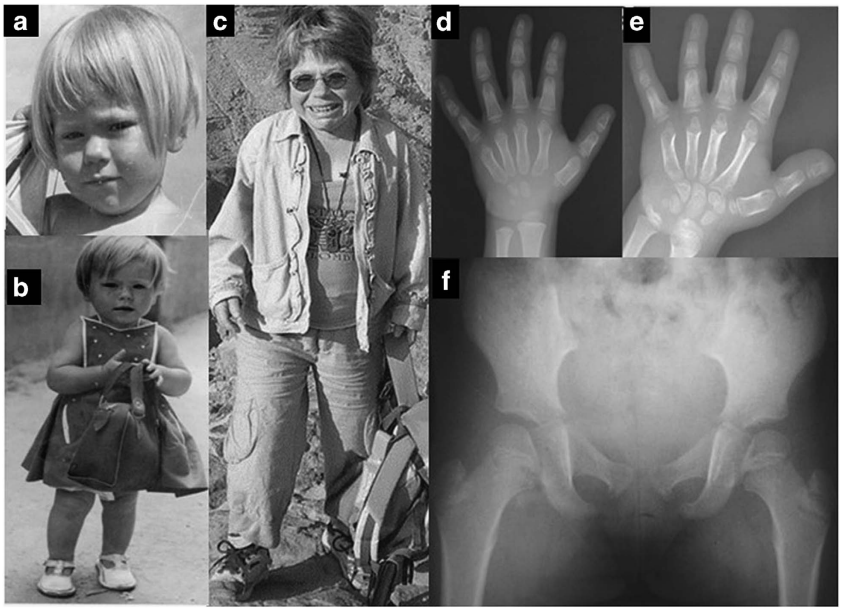

Figure 2 Clinical and radiological manifestations of acromelic dysplasia. AD patient at 6 (**a**), 3 (**b**) and 62 years old (**c**), respectively. (**d**, **e**) Hand and (**f**) pelvic X-rays of an AD patient at 10 years of age. Note the delayed bone age, internal notch of metaphysis of the fifth, fourth and third metacarpals and cone-shaped epiphysis of the phalanges. Note the internal notch of the femoral epiphysis, coxa valga and acetabular dysplasia.

its partners. We then hypothesized that ADAMTSL2 may be involved in the microfibrillar network. We indeed observed a significant increase in total and active TGFβ in the culture medium, as well as an enhanced nuclear localization of phosphorylated Smad2 in GD fibroblasts. All together, these data suggest that a dysregulation of TGFβ signaling is the underlying mechanism of GD and that ADAMTSL2 is directly involved in TGFβ bioavailability.[37] Microfibrillar network disorganization and enhanced TGFβ signaling were also consistently observed in GD/AD fibroblasts.[38] However, the absence of *ADAMTSL2* mutations in 19/33 GD patients supported genetic heterogeneity.[39]

AD is transmitted with an autosomal dominant mode of inheritance and is characterized by facial features—round face, well-defined eyebrows, long eyelashes, a bulbous nose with anteverted nostrils, a long and prominent philtrum, thick lips with a small mouth, a hoarse voice, pseudo-muscular build and skeleton features (internal notch of the femoral head, internal notch of the second metacarpal and the external notch of the fifth metacarpal)[40,41] (**Figure 2**).

To identify another disease gene for GD and the disease gene for AD, we performed exome sequencing and identified heterozygous *FBN1* mutations (15 missense and one insertion), all located in exon 41–42, encoding TGFβ-binding protein-like domain 5 of FBN1 in 19 GD and 10 AD cases.[38]

Although GD has been initially described as an autosomal recessive disorder, the identification of heterozygous *FBN1* mutations demonstrates a dominant form of GD, strictly fulfilling the diagnostic criteria for GD (including progressive cardiac valvular thickening, and early death in 3/19). Similarly, all AD cases fulfilled the diagnostic criteria of AD and had no cardiac involvement or early death.

Importantly, a direct interaction between ADAMTSL2 and FBN1 was also demonstrated, suggesting a dysregulation of FBN1/ADAMTSL2/TGFβ interrelationship as the underlying mechanism of the short-stature phenotypes.

Myhre syndrome

MS is characterized by prenatal and postnatal short stature, brachydactyly, facial dysmorphism (short palpebral fissures, maxillary hypoplasia, prognathism, short philtrum, thick skin, generalized muscle hypertrophy and restricted joint mobility). Older patients present consistently with deafness of the mixed conductive and sensory type. Other features include developmental delay with mental retardation or/and behavioral disturbance, cardiac defects, cryptorchidism and bone anomalies. Skeletal manifestations include thickened calvarium, cone-shaped epiphyses, shortened tubular bones, hypoplastic iliac wings, broad ribs and large vertebrae with short and large pedicles[42,43] (**Figure 3**). All reported MS cases are sporadic, and advanced paternal age at birth has been reported, supporting *de novo* dominant mutations.[42,43]

To identify the disease gene, we performed exome sequencing in 2 MS probands. Considering our previous findings of enhanced TGFβ signaling in GD/AD, we selected *SMAD4* as the best candidate gene based on its involvement in TGFβ/BMP pathways. Exome analysis detected the same heterozygous missense *SMAD4* mutation in the two MS patients tested (c.1498A>G; p. I500T). Direct sequence analysis of the coding regions in 9 additional MS cases led to the identification of three missense mutations in the MH2 domain of SMAD4 involved in transcriptional activation, all in an Isoleucine residue at position 500 (p.I500T; p.I500V; p.I500M). The mutations were not observed in MS parents, confirming that they occurred *de novo*.[44] Caputo *et al.*[45] confirmed these results by reporting eight other MS cases with *SMAD4* mutations also altering the Ile500 residue.

Following this initial study, we collected the DNA of 21 additional MS cases. We identified *SMAD4* mutations in a total of 29/32 cases. In 27 cases, the mutation affected Ile500 and in 2 cases it affected Arg496. The two different mutations led to the same phenotype.[43]

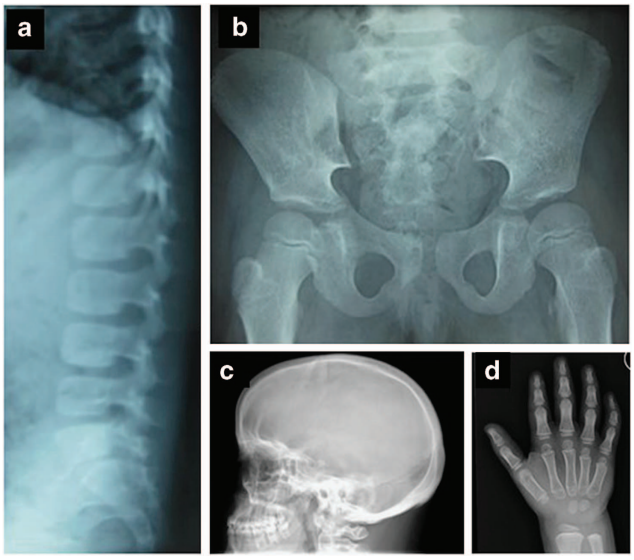

Figure 3 Radiological manifestations of Myhre syndrome. (**a**) AP view of the vertebrae (at 3 years of age), (**b**) pelvic and (**c**) skull X-ray (at 12 years of age) and (**d**) hand X-ray (at 2 years of age) of an MS patient. Note the thick pedicles of the vertebrae, short femoral neck, thick calvaria, delayed bone age and generalized brachydactyly.

SMAD4 has been considered a tumor suppressor. Loss-of-function mutations of *SMAD4* have been reported in the juvenile polyposis syndrome characterized by the presence of juvenile polyps in the gastrointestinal tract and increased colorectal cancer risk[46] (**Figure 4**). It is known that disruption of TGFβ signaling contributes to the formation of human malignancies,[47] and the protein instability of SMAD4 may contribute to the loss in cellular responsiveness to TGFβ signaling in tumors.[48] By contrast, in the Myhre syndrome, decreased ubiquitination level of SMAD4 and increased level of SMAD4 support a stabilization of SMAD4 protein. Functional SMAD4 is required for canonical signal transduction through oligomerization with phosphorylated SMAD2/3 and SMAD1/5/8. The nuclear localization of complexes combined with mutant SMAD4 stabilization observed in MS fibroblasts may support the ability of mutant SMAD4 to oligomerize with pSMAD1/3 and SMAD1/5/8 and translocate in the nucleus.[44]

Considering the involvement of the MH2 domain in transcriptional activation, our findings of impaired expression of TGFβ-driven target genes further support a loss of the transcriptional control function of the mutant complexes.

TGFβ Signaling and Overgrowth Conditions

The components of TGFβ signaling have also been involved in other conditions with skeletal features (**Table 1**). Indeed, the Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue caused by mutations in the FBN1 gene encoding fibrillin.[49] MFS is characterized by long bone overgrowth and arachnodactyly, as well as by connective tissue manifestations, including dislocation of the ocular lens and dilatation of the aortic root. Aortic root dilatation is the main cause of morbidity and mortality in MFS. Mutations in *FBN1* lead to increased TGFβ signaling. Interestingly, recent therapeutic advances demonstrated that the aortic-root diameter was reduced following losartan (an angiotensin II type 1 receptor blocker) therapy in a pediatric cohort of MFS patients.[50,51]

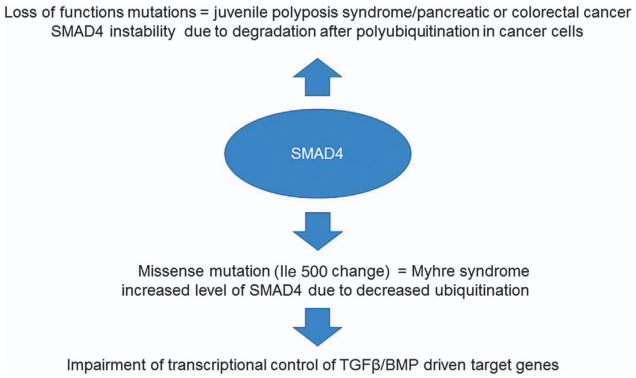

Figure 4 Spectrum of human diseases associated with SMAD4 mutations.

Mutations in either receptor TGFBR1 or TGFBR2 lead to Loeys–Dietz syndrome type 1a or 1b, respectively.[52,53] This syndrome is characterized by thin habitus, arachnodactyly, widely spaced eyes, bifid uvula and/or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and dissection.

The Shprintzen–Goldberg syndrome (SGS) is characterized by craniosynostosis, marfanoid habitus and skeletal, neurologic, cardiovascular and connective tissue anomalies. Doyle *et al.*[54] and Carmignac *et al.*[55] identified *de novo* heterozygous mutations in the SKI (v-ski avian sarcoma viral oncogene homolog) gene in 10 SGS patients. Cultured dermal fibroblasts from SGS patients with SKI mutations showed enhanced activation of TGF-beta signaling cascades compared with control cells.

Finally, Camurati–Engelman Disease (CED) is a rare autosomal dominant bone dysplasia, characterized by increased bone formation, cortical thickening of the diaphyses of the long bones and a tall and thin habitus. Activating mutations in the ligand, TGFB1, cause CED.[56,57] Using the CED transgenic mouse model, TGFβ has been shown to be essential for the proper coupling of osteoblastic and osteoclastic activity. The increased bone density only observed in CED (due to mutations in the latency-associated domain of TGFβ) supports bone-specific consequences of enhanced TGFβ signaling in this disorder.[58]

TGFβ in Another Cartilage Disease, Osteoarthritis (OA)

The important role of TGFβ in the maintenance of articular cartilage homeostasis has been established. Blocking TGFβ signaling in the articular cartilage leads to loss of proteoglycans and to cartilage degeneration, the main manifestations of osteoarthritis. SMAD3 gain-of-function mutations have been associated with incidence of hip and knee OA.[59] Inhibition of TGFβ signaling by deleting the TGFβ type II receptor in mesenchymal stem cells attenuates the OA.[60] Components involved in activation of latent TGFβ are often found to be dysregulated in OA. Ltbp3-null mice display OA phenotypes. During degeneration of the articular cartilage, the expression of TGFβ receptors is changed in the chondrocytes. The mRNA level for TGFBR2 has been found to be drastically reduced in early-stage OA in a rabbit model. The OA development is

accelerated with increased TGFBR2 degradation and down-regulation of TGFBR1 expression.

Potential Therapeutic Approach

The TGFβ signaling pathway can be considered as a potential therapeutic target in chondrodysplasias. In order to inhibit the excess of TGFβ, different tools have been developed: antisense TGFβ oligonucleotides inhibiting translation of TGFβ mRNA, soluble receptors acting on ligand–receptor interaction or antibodies against TGFβ. Clinical studies using TGFβ inhibition have been carried out at least in cancer, fibrosis and MFS.[50,61] In a small cohort of MFS cases, the use of angiotensin II type 1 receptor blocker therapy significantly slowed down the rate of progressive aortic-root dilation but did not impact the overgrowth.[50,51] These findings require confirmation in a randomized trial. In the geleophysic and acromicric dysplasias, the excess of TGFβ may be decreased by angiotensin II type 1 receptor blocker or antibodies against TGFβ. To date, we have no clue on the effect of this therapy on chondrogenesis. In contrast, recently exogenous TGFβ3 cultured with ovine mesenchymal stem cells in a biomaterial providing a scaffold stimulated the growth of the hyaline cartilage. Next, this new cartilage was integrated in a living tissue.[62] This demonstrated the potential for this treatment to regenerate the articular cartilage defects.[62]

Conclusion

Mutations in components of the TGFβ signaling pathway cause developmental abnormalities in the human skeleton. One of our challenges will be to understand how enhanced TGFβ signaling can be associated either with short stature or with overgrowth, supporting yet unknown mechanisms regulating TGFβ action, possibly including tissue-specific modulations of TGFβ signaling. TGFβ is also at the crossroads of several other pathways, including hedhehog, parathyroid hormone-related protein, and wingless signaling, which is also involved in skeletogenesis, leading to a picture of a complicated network. The study of human genetic disorders such as acromelic dysplasia improved the understanding of the role of TGFβ in cartilage formation. Mouse and human genetic phenotypes highlight the main role of specific components of these pathways. Better knowledge of TGFβ signaling may give us the opportunity to use TGFβ as a biological therapy for enhancing chondrogenesis—for example, in the case of OA.

Conflict of Interest

The authors declare no conflict of interest.

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