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Role of SMAD/TGF-β signalling pathway in connective tissue diseases

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Abstract

Several members of the TGF-β super family play important roles in connective tissue growth. The bone morphogenetic proteins (BMPs) induce early cartilage formation and MMP13 is a major enzyme targeting cartilage for the degradation of types II, IV, and IX collagen, proteoglycan, osteonectin and perlecan. In this review, we discuss the crosstalk between SMAD/TGF-β signalling pathway and therapeutic applications in connective tissue diseases.

Keywords: SATF3; Endotoxemia; Proinflammatory cytokine; HMGB1

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Introduction

Today, more than 400 different diseases are considered "connective tissue diseases," a complex branch of rheumatology that may involve many organs and tissues and present a very heterogeneous clinical manifestation. Genetic and environmental factors interplay in the pathogenesis of these disorders. For a long period, something was eventually forgotten within the disease spectrum. Connective tissue diseases have seen a rising interest from the scientific community over the last period as they present as an ever-enriching series, including diseases mainly affecting subjects in the first 2 decades of life down to subjects in later stages of life. The advent of biological therapies, often introduced in the clinical setting, renewed the interest in connective tissue diseases. Lately, the proposal of single disease definitions, with consequences on the planning of therapeutic options, posed the interest of basic science to uncover the pathophysiological pathways behind the onset and progression of different kinds of problems that can eventually affect patients with these conditions.

Connective tissue diseases have a striking impact on public health because they are chronic conditions that can eventually engage multiple organs. Almost 5% of the general population will suffer from a "classic" CTD (like Systemic Lupus Erythematosus, Systemic Sclerosis, Systemic Vasculitis, etc.) during their lifetime. However, the prospect of subjects suffering from some kind of CTD manifestation, especially looking at the pediatric patient group, is something occurring in more than 16% of the usual child diseases. Functional ability and quality of life are often reduced in these patients, and a multi-pronged strategy, taking into account pharmacological and non-pharmacological points of view, is often necessary to improve the clinical picture of patients with these conditions. Finally, one should not forget that the vast majority of patients with CTD experience damage and therefore more or less severe disabilities.

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1.1. Definition and Classification

Connective tissue diseases (CTDs) include a variety of entities characterized by modifications of the components of the extracellular matrix, including collagens. They are usually classified based on their genetic features, clinical presentation, auto-antibody positivity, extracutaneous involvement, and prognosis. Generally, in CTDs, a wound healing response is activated after tissue injuries by different noxious stimuli, leading to the development of non-healing ulcers associated with infiltration of inflammatory cells, fibroblast activation, and excessive synthesis or disorganization of extracellular matrix components.

SMADs are intracellular proteins activated by transforming growth factors (TGF-β) that are involved in maintaining connective tissue homeostasis. It is well known that the TGF-β/SMAD signaling cascade is involved in the wound healing process and that alterations in the expression or in the function of the molecules of this pathway can change the rate of appearance of different pathologies characterized by an altered turnover of extracellular matrix and by wound healing inductive dysfunctions (e.g., hereditary hemorrhagic telangiectasia, scleroderma, systemic and cutaneous lupus erythematosus, nephropathies, and other autoimmune systemic diseases). Indeed, by regulating one side of the activation and physiological functioning of fibroblasts (and stellate cells of the liver) and one side of the formation and remodeling of the extracellular matrix, the SMAD/TGF-β signaling pathway (SP) directly and indirectly participates in the pathogenesis and prognosis of these systemic or local disorders.

Epidemiology and Impact

Connective tissue diseases (CTD) are a heterogeneous group of disorders affecting multiple tissues and organs, including the immune system. They are very rare, with a mean prevalence in the population of 52.4 (min 24; max 80) per 100,000 inhabitants and an incidence of 28.1 (min 9.1; max 47.3) per 100,000 inhabitants per year. The European prevalence of systemic sclerosis (SSc) was reported to be 26.3 (5.6–40.7) per 100,000 inhabitants in a study by Vig and Wau's group. The highest prevalence of cutaneous systemic sclerosis was in the USA, with 132.9 (74.9–186.5) diagnosed cases per million. The highest annual incidence of systemic sclerosis was reported in Turkey, with 13.3 (IQR: 11.1–15.6) per million. The prevalence of systemic sclerosis ranged from 8.5 per 100,000 in Iran to 416.7 per 100,000 in the USA. and fibrosis, lung disease, and renal impairment, with a high burden on society's quality of life (QoL) [18,19]. Dystrophic calcifications can also develop on the skin, adding suffering for the patients and the burden of accommodations that occur.

CTDs are multifactorial diseases, and their therapy is often unsatisfactory with response insurance or partial response after the treatment or with numerous adverse events related to corticosteroid therapies and immunosuppressants. Retinal peripheral microvascular impairment (RPMI) has to be considered if a patient is affected by CTD-Syndrome, often complicated by delay in diagnosis and multiorgan involvement. The screening and early diagnosis could be contributory to manage the clinical spectrum of CTDs and relieve the global

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burden, adding an on-eye and systemic prophylaxis protocol for the active aged population. Further, osteoporosis occurs in up to 2/3 of polymyositis/dermatitis and up to 40% of systemic sclerosis patients. Why is the prevalence of this rare disease so high? A greater effort must be made, especially on the territorial level, and establish: do the active search and the prevalence demonstrate an improvement in survival? A better control of the disease?

Overview of SMAD/TGF-β Signalling Pathway

TGF-β is a multi-functional cytokine. It is necessary and has important biological effects regulating growth, cell differentiation, immune response, erythropoiesis, wound healing, fertilization, and apoptosis. As key signaling pathways of TGF-β, the SMAD/TGF-β signaling pathway has important significance in regulating growth and development, maintaining immune homeostasis, and ensuring ATP synthesis. Upon ligand binding, two TGF-β type I and type II serine/threonine kinase receptors, which possess distinct enzymatic domains, form a heteromeric complex and facilitate phosphorylation of the cytoplasmic domain of the type I receptor by the constitutively active type II receptor, initiating TGF-β signaling cascade. R-SMADs, which have been recruited and phosphorylated, dissociate from the receptor complex and form a heteromeric complex with SMAD4 (Co-SMAD).

These activated SMAD complexes then translocate to the nucleus where they support transcriptional activation. T is the docking protein. It mediates the cross-talk between the receptors. When the T molecule interacts with SMAD protein, SMAD protein increases its activity in cells. SMAD proteins are reported to participate in signaling cascade transduced by transforming growth factor β (TGF-β) molecule, which is a type of multifunctional regulator. TGF-β activates SMAD proteins in the signal cascade transduction, and then SMAD proteins increase their activity in cells. As this process happens inside of cells, it is called "intracellular signaling transduction in TGF-β superfamily." SMAD proteins play important roles in rebuilding all sorts of tissues. Besides, SMAD proteins always participate in cells' pathophysiological process, such as reactive sclerosis after injury, repairing liver fibrosis, and systemic sclerosis.

Structure and Function of TGF-β

Transforming growth factor-β (TGF-β) is a multifunctional peptide involved in cell growth, differentiation, apoptosis, and extracellular matrix production. It is a pleiotropic protein with antiproliferative effect and the ability to stimulate collagen formation in different tissues. It is a chemoattractant for various cells, including neutrophils, monocyte-macrophage cells, and fibroblasts. In monocytes and macrophages, TGF-β induces upregulation of adhesion molecules and potentiates phagocytic functions. There are three isoforms of TGF-β in humans, TGF-β1, TGF-β2, and TGF-β3. TGF-β1 and TGF-β3 are 70 to 80 percent homologous, especially in the carboxyl terminal, which is responsible for the biocompatible activity of TGF-β and the middle terminal part, which is responsible for the binding to TGF-β, like TβR II and activation of the TGF-β signaling cascade. The TGF-β extracellular part can bind to the propeptide area and be stored in the extracellular matrix. TGF-β acts by binding to serine/threonine kinase receptors (TβR), consisting of two types of receptors such as TGF-β

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type 1 (TβR I) and TGF-β type 2 (TβR II). The binding of TGF-β ligand to TβR II leads to two catalytic activities of TβR II, with the activation of TβR II promoting the activation of TβR I activity. TGF-β and TGF-β activated receptors interact with a molecule called SMAD, that is, a homolog peptide of the Sma protein, which is TGF-β-related in the roundworm, or called the mothers against decapentaplegic protein, a gene from Drosophila (MAD).

SMAD Proteins and Their Role

A further milestone in the study of the TGF-β pathway was the identification of the proteins that participate in this signaling. After the ligand binds to the TGF-β receptor, it leads to the activation of SMAD proteins. These are divided into at least three different groups depending on their specific function and role in the TGF-β signaling. A group of the inhibitory SMADs includes SMAD6 and SMAD7. They act through a negative feedback mechanism on the TGF-β signal termination. An exception is only the SMAD6, which is not usually involved in the inhibition of the canonical pathway. The receptor-regulated SMADs include SMAD2 and SMAD3, which are activated as a consequence of the binding of TGF-β signaling on the cell surface. In turn, the common mediator in the TGF-β pathway is the SMAD4 protein. SMAD4 forms a complex with C-terminus phosphorylated other SMADs. This new complex then translocates to the cell nucleus and acts as a transcription regulator. SMAD proteins are involved in a variety of cellular effects of TGF-β signaling. They participate in the up-regulation or down-regulation of the expression of the genes. However, we will review the work of SMAD proteins in the canonical signaling pathway in connection with human CD diseases. SMAD proteins are considered as the central part of the TGF-β pathway. Part of the other members of identified TGF-β signaling components (small GTPases, apoptosis proteins, HIPK 2, ParP-1, NF-κB, JNK) are related to the SMAD pathway, and their sum up effect is expanded to over 1600 potential related genes. The SMAD proteins also transmit messages about the availability of nutrients to the cell nucleus. That is why the SMAD proteins are involved in the regulation of, among other things, homeostasis and inflammation in the human body, which is also important in the pathomechanism of connective tissue diseases. Summing up, the analysis of the connection between connective tissue diseases and the SMAD proteins seems necessary from the perspective of science but also the clinical side. It will let us get closer to understanding the pathomechanism of autoimmune diseases and adjust therapeutic recommendations. In the contribution of Discovery Medicine, where 100 clinical advancements of 2020 were reported, two were based on the TGF-β pathway modulation. This shows the importance of the TGF-β pathway in the treatment opportunities for human diseases.

Connective Tissue Diseases Associated with SMAD/TGF-β Pathway

Connective tissue diseases are chronic inflammatory diseases with the potential to evolve into severe conditions. The pathogenesis of these conditions is not clearly understood, although there is evidence pointing to inflammation perpetuation, dysregulation of the immune system, autoimmunity, as well as the fibrogenesis process, which can lead to excess collagen production and connective tissue degradation. The involvement of Smad (mothers against

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decapentaplegic homolog) proteins in transducing the effects of TGF-β drew researchers' attention to investigate their role in connective tissue diseases, especially in fibrogenesis processes.

In fact, the involvement of the Smad family in several connective tissue diseases, particularly in systemic sclerosis (SSc) and rheumatoid arthritis (RA), raised the question of whether this signaling pathway could be a target for therapy. In this review, the pathophysiological mechanisms involving members of the Smad/TGF-β, MAPK (mitogen-activated protein kinases), and JAK/STAT (Janus kinase/signal transducers and activators of transcription) pathways in some CTDs will be analyzed. Systemic sclerosis (SSc) is a chronic connective tissue disease characterized by extensive vascular changes, autoimmune disturbances, and the accumulation of extracellular matrix (ECM) proteins in the affected organs. Furthermore, the morphological features suggest similarity between activated myofibroblasts in SSc and those in solid tumors, which produce massive amounts of ECM proteins. Moreover, accumulating evidence suggests that the pro-fibrotic effects of the TGF-β/Smad signaling pathway are orchestrated by key cytokines released from damaged endothelial and epithelial cells.

Systemic Sclerosis

Systemic sclerosis (SSc) is a rare complex connective tissue disease that involves the skin and various internal organs such as the lungs, intestinal tract, heart, and kidneys. The triggering and pathogenesis of SSc are not well understood. Nevertheless, the potential role of the SMAD/TGF-β pathway has recently led to the growing interest of researchers worldwide. Early endothelial cell injury leads to the release of endothelin-1 (ET-1) into the vasculature. There, it acts on the transforming growth factor-β (TGF-β) released at the same time. At the same time, TGF-β favors the gene expression of endothelin-converting enzyme, resulting in increased levels of endothelin-1, thereby establishing a vicious circle. In detail, the list of the crucial and most important points of action as well as an explanation of the assumed importance of the SMAD/TGF-β signaling pathway in the pathogenesis of SSc (endothelial injury, vasospasm, increased collagen synthesis, decreased degradation of collagen, tumor-specific alpha-like chain of type I procollagen; primitive expression, vascular manifestation, interstitial pulmonary changes, inhibited muscle repair, proliferation, and differentiation) and the relevance of this to a possible therapy is presented. This can be demonstrated by monotherapy with an ET-A/B-receptor antagonist.

Systemic sclerosis involves the skin and various internal organs such as the lung, intestinal tract, heart, and kidneys. The disease is characterized by the initial stage of a (sub)acute inflammation that is then followed by fibrosis, which is the hallmark of this disease. The elevated level of the active form of TGF-β in lesional and non-lesional skin of SSc patients and in sclerodermatous graft-versus-host disease suggests that this cytokine plays a central role in the pathogenesis of this disease. Increased expression of TGF-β in combination with enhanced SMAD2 phosphorylation has frequently been described in skin biopsies of patients with

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systemic sclerosis. Elevated TGF-β1 in the serum and scleroderma biopsies, increased serum and lesional and alveolar macrophages, and fibroblasts SMAD phosphorylation had previously been thought to be contributors in the disorder. A significant role of the SMAD/TGF-β signaling pathway has been proposed in SSc and renal fibrosis. Further work is required to investigate the involvement of the SMAD6 or SMAD7 in these processes and whether these inhibitory SMADs may also be involved in disc degeneration. To date, research and other interventions have been developed and are ongoing to study the role of the SMAD/TGF-β signaling pathway in SSc. If one targets an Smad/TGF-beta signaling, the next intriguing issue is whether various interactions or effect on other signal transduction pathways, dermatan sulfate, interleukin-2, and interferons alpha and beta or matrix proteins will emerge, thereby heralding in a new and practicable deduction. The most advantageous signal transduction pathway to intervene in might be the ERK1/ERK2 signal transduction pathway. The inhibition of SMAD/TGF-β signaling not only decreases the fibrotic reaction but is also very likely to enhance conventional therapeutic measures such as angiotensin convertase inhibitors.

Rheumatoid Arthritis

While RA is an immune-mediated chronic inflammatory disease with a progressive course, the pathological basis underlying this progressive course has a broad spectrum, including not only inflammation but also synovial hyperplasia and joint destruction. Furthermore, systemic complications damage the function of multiple tissues and organs, referred to as connective tissues, complicating the course of the disease. When discussing the pathogenetic pathway underlying the involvement of connective tissues in RA, it is reasonable to focus on the TGF-β/SMAD signaling pathways. The following section discusses the impact of the TGF-β/SMAD signaling pathway in connective tissues and the involvement of this pathway in relevant diseases in the connective tissues.

TGF-β ligands signal through the TGF-β/SMAD pathway in the connective tissue. It has been revealed that TGF-β signaling contributes to the pathophysiological mechanisms of inflammatory, metabolic, degenerative, and neoplastic diseases in the connective tissues. The TGF-β/SMAD pathway is bidirectionally related to the TGF-β-induced pathogenesis and resolution of these diseases, and SMAD is involved in the pathological TGF-interactions with the target cells in the connective tissues. A concept can be proposed for the treatment strategy of the diseases in the connective tissues that is associated with the SMAD regulation of the pathological functions of the Thy cell and Treg cell lineages. In conclusion, the findings in TGF-overexpression (transgenic) and knock-in/knock-out mice and patients are reviewed, showing that the SMAD/TGF-β signaling pathway plays a basic role in the connective tissue disease (CTD).

Experimental Models and Studies

The experimental approach techniques vary. The models of study of fibrotic diseases based on experimental techniques on animals use various explicit applications of information available in animal anatomy. It is connected to human pathology. In in vitro studies, the cellular responses

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can be investigated through the analysis of protein and gene expression, electrophysiology, intracellular signalling, cell viability (cytotoxicity), cell proliferation, apoptosis, differentiation, confocal microscopy, immunofluorescence, immunohistochemistry, immunocytochemistry, etc. The interaction of cytokines, growth factors will be an analysis of the receptor. Especially by using the anti-receptor binding of down-/upstream signalling as a blocking effect, the transceptor signal is a potential discussion. Therefore, the results of the animal models and in vitro studies have much to contribute in full handling of the pathway SMAD/TGF-β in CTD patients.

In in vivo studies, a genetically induced excess of ligands seems plausible, so in vitro studies in fibrotic diseases are primarily based on excess ligands applied to various effector cells. Simulating the SMAD/TGF-β degradation is basically an immunosuppressive value of TGF-β, in which various proteins have played a physiological role. In in vitro studies, appropriate treatments will help read the way of SMAD/TGF-β signal transduction to oxidative stress, inflammation, fibrogenesis, microvascular activity, system effects and, of course, cardiovascular effects. Every effort will be based on explaining the biochemical, cellular, pathophysiological interactions that are all mixed with the SMAD/TGF-β signal in general and specifically. The wide range of attracting biologically active substances is an actual analytical approach to symptomatic and causal treatment of these interstitial conditions. The in vitro study that resembles direct effects of a combination of collagen and TGF will be closed to the cellular short-term signal SMAD/TGF-β.

Animal Models

The involvement of the SMAD/TGF-β pathway in various connective tissue diseases has been extensively studied in animal models. Osteogenic signals for differentiation of synovium to cartilage can be led by BMP7 in an in vivo study using a SCID mouse model. After three weeks, corresponding to maturity, the newly formed tissue expressed genes of hypertrophic cartilage, which forms the very subchondral bone plate, and of regular cartilage. Intra-articular injection of TGF-β is able to protect from inflammation and cartilage loss in experimental OA in the rat. PTH, which is protective in an unstable rat meniscectomy model, is thought to promote articular cartilage repair via the activation of TGF-β-SMAD signaling. In a hypoxic microenvironment, inducing PTH and fineran acid, in this model, chondrocytic cells display inhomogeneous populations of hypertrophy-like and natural hypertrophic cells. This metabolic insufficiency may be the pathogenic background for chondrodysplastic diseases. In conclusion, animal models have been useful for the initiation of understanding the involvement of SMAD and TGF-β in joint-destructive diseases.

In a jaw ODDD mouse model, systemic TGF-β inhibition led to no phenotypic changes, whereas selective inhibition of TGF-β when using noggin overexpressing driven Tgfb1 induced joint regeneration. The latter model is of significance because it offers the possibility to study joint repair in adult mice, whereas the regeneration of calvarial sutures takes place under conditions of continuing growth in contrast to human adults. Even so, mice are widely used for testing

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whether new drug therapy will reduce mortality and morbidity of joint-destructive diseases. The chondrodysplasia of lectlys (mfr) mice are used for testing whether disruption of TGF-β function by systemic injections of anti-TGF-β mAbs accelerates fibrtarthopathies, or if a trigger is needed such as the transfer of gD-positive B-cells to gD-negative animals. The doses of anti-TGF-β mAb are important because there is an 8-1000-fold difference in lethal dose (LD). Most recently, it is tested whether inhibition of TGF-β (periarticularly) impacts restoration of the tensile functionality of enthesis. Even though the causal relation between SMAD/TGF-β and disease in animal models is not always clear, SMADs may offer new possibilities, e.g., SMAD-level examining inhibitors.

In Vitro Studies

Smad/TGF-β pathway has been extensively explored using in vitro studies, where experiments have been conducted within a controlled laboratory environment. In vitro studies have contributed to the current understanding of the Smad/TGF-β signaling pathway since the first publication from this field. These studies used specific stimuli such as pro-fibrotic cytokines or growth factors, as well as collagen synthesis inhibitors, to confirm the molecular processes essential in fibrosis. One of the initial insights from these in vitro studies was that the onset of fibrosis and scarring are prominently linked to the actions of TGF-β, which is expressed at increased levels in damaged interstitial spaces. Upon binding with its receptor, the cellular responses associated with TGF-β are then further modulated by activation of the consequential signaling.

Smad/TGF-β involvement with connective tissue diseases has been confirmed by various in vitro studies such as human scleroderma fibroblasts experiments, which demonstrated these fibroblasts' hyperresponsiveness to TGF-β as well as to connective tissue growth factor, histamine, leukotrienes, remodeling collagen, and oxidative stress while collagens VI/V and proteoglycans production were decreased. This, in turn, implicated human scleroderma fibroblasts as potentially defective in their ability to deactivate Transforming Growth Factor – beta type I receptor. Understanding Smad/TGF-β involvement in detail can also contribute to the development of a treatment that targets this particular issue. Furthermore, Smad/TGF-β is associated with various targets which reveal other possible pathways corrupted in connective tissue diseases. Smad/TGF-β surpasses in the central complexity of CDGS, which in turn can provide plenitude for the development of a wider range of targeted therapies to fight against CDGS.

Therapeutic Implications

The translational advantage of therapies targeting the SMAD/TGF-β pathway in CTDs remains unclear. Several drugs able to interrupt the TGF-β pathway at different levels are currently in place for pre-clinical or clinical testing; however, only a few molecules have been approved for the treatment of other conditions in humans. Clinical applications of molecules interfering with the TGF-β pathway should take into account the redundancy of this network and aim to restore the normal connective tissue pathway, rather than suppress or eliminate its activity. Finally, it

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is important to consider the difference in redundancy of extracellular elements disconnected from the SMA/TGF-β pathway. In this regard, targeting TGF-β in SSc is more deleterious, as other cytokines constitutively activated share the same pathological pathways.

The most common problem in selective antagonists of TGF-β ligand or TGF-β receptor is the compensative activation of other isoforms or of related molecules, leading to more severe or different side effects. Notably, as seen with synthesized targets of mTOR, there's (thrombospondin-1 activating elements to reduce fibrosis), specific siRNA, endostatin/cilengitide, resveratrol, and omega-3 derivatives, among others, the best interest would be shifted to products showing both anti-inflammatory and anti-fibrotic activity concomitantly. Due to the old age of the major large cohorts of patients and progressive fibrosis, dim-interventional trials with older drugs are needed, focusing on cancer risk prevention, establishing heart failure therapy in diastolic dysfunction, management of reduced flexibility organs in terms of infections, coordination, rehabilitation, physical prevention, and supportive psychotherapy. Importantly, repeated and/or prolonged salivary or plasma miR106b and/or anti-CCP dosing may be helpful for this fibrotic cardio-inflammatory phase dim-phase evaluation.

Current Treatments

Rheumatologists, pulmonologists, and dermatologists frequently use current treatments to modulate the SMAD/TGF-β pathway in daily practice to improve the outcomes of connective tissue disease patients. It is essential for rheumatologists to understand the principles of these treatments in order to improve their daily clinical work and to initiate and follow future studies with specific antagonists for this pathway. Modulators of the SMAD/TGF-β pathway used in clinical practice include ACE inhibitors, Losartan, and Imatinib.

ACE inhibitors: This class of drugs modestly reduces serum TGF-β concentrations by 11–20% at high doses in studies in patients with chronic kidney disease. The authors of the study showed that the 40 mg dose of Captopril was better than the 10 mg dose in improving joint mobility. Pulmonary and skin involvement was not significantly different between the groups, although the number of digital ulcers was not evaluated.

Losartan: Losartan is an AT1R antagonist from angiotensin. TGF-β upregulation following injury was significantly prevented with Losartan in two different animal models. In the clinical setting, data on the efficacy of AT1R blockers for renal fibrosis was provided. Treated patients showed significantly decreased levels of renal TGF-β1 mRNA expression, the number of myofibroblasts, infiltrating interstitial T cells, and expression of monocyte chemoattractant protein-1. Losartan also reverses the phenotypic changes up to one year, demonstrated recently in a 30-year-old woman with Loeys-Dietz syndrome previously under ACE inhibitor therapy with increasing skin manifestation under Quinapril. Following Losartan intake, the woman improved regarding Loeys-Dietz-specific manifestations, reduction of pain, and improved walking.

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Future Directions

Given the data provided by a web-based pathway analysis of connective tissue diseases, therapeutic strategies moving closer to the SMAD/TGF-β pathway and elegantly combining growth factor targeted therapies demonstrating significant muscle and skin improvements are currently under development. The role of the SMAD/TGF-β pathway in tissue fibrosis per se is well established, and there are multiple viral vectors that can be engineered to mediate the production of DNA or RNA complementary to kinase or receptor domains of targets including TGF-β and interleukin 6 signaling components. Re-engineering human HSC to knock out the TGF-β receptor I was an effective strategy to enhance HSC engraftment in vivo in an adult mouse.

In a recent ex vivo novel complex side population bioinformatics analysis on single patients with scleroderma myopathy that mimic both lesions of systemic sclerosis, it is suggested that evaluating genetic profiles may stratify perfect myosteatosis from inter- and intramuscular adipocyte's fibrogenic and vas popular cursors. From a future direction point of view, it is reasonable to hypothesize a further armamentarium against compacted myosteatosis in systemic sclerosis, especially targeting the monocyte chemoattractant protein 1/LOXL4 pathway, are promising targets for myosteatosis treatment in systemic sclerosis. Interstitial resistance seems to be driven by purinergic-p53 signaling axis and autophagic failure, since bone morphogenetic protein 4 enzyme-linked immunosorbent confirms a molecular link between compromised mitochondria and extreme fibrogenic reshaping of myoblasts.

Conclusion

Alterations of the TGF-β receptor I and II due to point mutations inside the kinase domain, which then lead to persistent activation of the SMAD proteins, are known to cause Marfan syndrome, Loeys-Dietz syndrome, and Vascular Ehlers-Danlos syndrome. Related to MMP-2 activation, TIMP-2 and its levels are a logical starting point and further studies should concentrate on these levels in patients with MFS and EDS. Information and data on expression levels of the regulators and participants in the pathway in CTD are still sparse and need to be addressed. It will also be interesting to investigate if certain exons or mutations/variants can serve as predictive markers for developing CTD in MFS and EDS populations.

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