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REVIEW

Candidate rejuvenating factor GDF11 and tissue fibrosis: friend or foe?

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Abstract Growth differentiation factor 11 (GDF11 or bone morphogenetic protein 11, BMP11) belongs to the transforming growth factor-β superfamily and is closely related to other family member—myostatin (also known as GDF8). GDF11 was firstly identified in 2004 due to its ability to rejuvenate the function of multiple organs in old mice. However, in the past few years, the heralded rejuvenating effects of GDF11 have been seriously questioned by many studies that do not support the idea that restoring levels of GDF11 in aging improves overall organ structure and function. Moreover, with increasing controversies, several other studies described the involvement of GDF11 in fibrotic processes in various organ setups. This review paper focuses on the GDF11 and its pro- or anti-fibrotic actions in major organs and tissues, with the goal to summarize our knowledge on its emerging role in regulating the progression of fibrosis in different pathological conditions, and to guide upcoming research efforts.

Keywords Fibrosis · Growth differentiation factor 11 · GDF11 · BMP11

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Introduction

Tissue damage repair is a fundamental process, critical for survival, allowing ordered replacement of dead or damaged cells. Even if this healing process is initially beneficial, it can become pathogenic under certain circumstances [1–3]. If unchecked, it can progress to considerable tissue remodeling and pathologic exchange of normal organ tissue architecture with formation of permanent scar tissue: fibrosis. Fibrosis is a characteristic feature of many chronic diseases that can end up in later stages with total organ failure of liver, lung, kidney, and heart [1, 4]. In the developed world, these fibrosis-driven diseases are a major cause of morbidity and mortality, accounting for 45% of all deaths [3].

The primary pathways associated with tissue injury and the development of fibrotic diseases are relatively well-studied in individual organs and are reviewed elsewhere [5–8]. Regardless of the fact that the causes of fibrotic diseases can be organ-specific and dissimilar, they all have common molecular mechanisms that is resulting in the uncontrolled and exacerbated production of extracellular matrix (ECM) components, and in the replacement of normal healthy tissue with nonfunctional fibrotic tissue [2, 9–12]. Deposited ECM components are mostly structural proteins (e.g., fibrous collagens I and III and elastin), adhesive proteins (e.g., laminin and fibronectin), and ground substance (e.g., glycosaminoglycans, such as hyaluronan and glycoproteins) [13].

The wound healing process in any organ generally proceeds through three phases that are partially overlapping but are functionally different [14, 15]. The first

phase is in most cases associated with damage and inflammation of the affected tissue. While some fibrotic changes/activation are the reflection of specific immune responses to an underlying infection (i.e., fibrosis due to infectious pathogens/microbes), the prototypical fibrosis is associated with a sterile inflammation that is caused by elevation of cell death in tissue [16–18]. Dying or damaged cells produce and release endogenous factors and signals known as alarmins or damage-associated molecular patterns (DAMPs) [16, 19–21]. These signals are detected by tissue infiltrating macrophages and specialized tissue-resident macrophages, like alveolar macrophages (lung), Kupffer cells (liver), and histiocytes (interstitial connective tissue). These activated macrophages produce various cytokines/mediators, including TGF-β, PDGF, CTGF, and insulin-like growth factor 1, which directly activate fibroblasts that are in turn involved in the first phases of wound healing. These secreted peptidic growth factors directly regulate the proliferation, survival, and activation of fibroblasts, leading to ECM deposition [22–24]. Activated fibroblasts refer to the fibroblasts that mediate fibrosis by producing ECM components and are also synonymously called "myofibroblasts" because of the production of actin stress fibers [25].

TGF-β plays a particularly prominent role in the induction and progression of fibrotic diseases. At the cellular level, there is a consensus that activated fibroblasts/myofibroblasts are the cell types responsible for the pathologic fibrotic process in many disorders [26–29]. Myofibroblasts are a very diverse and distinctive population of cells (mostly of mesenchymal origin), but a large body of evidence supports that a proportion of them arise through epithelial to mesenchymal transition (EMT) during fibrosis from epithelial cells [30–34]. Upon activation, myofibroblasts begin to express α-smooth muscle actin (αSMA) and display a marked increase in the production of fibrillary collagens (types I, III, V, and VI), vimentin, and other ECM macromolecules, coupled with an increase in tissue inhibitors of metalloproteinases (TIMPs). TIMPs in turn inhibit ECM-degrading enzymes [13, 35, 36] and pro-fibrotic macrophages also produce matrix metalloproteinases (MMPs) and TIMPs, which regulate inflammatory cell recruitment and ECM turnover [1, 3, 15]. In the third and final phase, the so-called maturation phase, the provisionally synthetized ECM is degraded and remodeled to rebuild original organ tissue architecture. Repeated chronic injury or deregulation of one of these key processes allows myofibroblasts to relentlessly produce ECM components, thus hampering over time organ functional structure and functionality [1, 15].

Organ-specific fibrotic features

Lung fibrosis

Compared with fibrotic lesions in other organs, progressive pulmonary fibrosis is particularly devastating and even relatively mild fibrotic lesions tend to be fatal [37, 38]. Pulmonary fibrosis scars and thickens the tissue around and between the alveoli in the lungs, rendering it more difficult for oxygen to pass into the bloodstream. Lung fibrosis can be induced by a variety of causes, including occupational and environmental factors, medications, and medical conditions. Resolution of lung fibrosis and restoration of organ/tissue function are rather limited in comparison with other organs, such as the liver [8]. In pulmonary fibrosis, pro-fibrotic cytokines are produced by resident epithelial, mesenchymal cells, and immune cells, including T and B lymphocytes, neutrophils, and predominantly resident alveolar macrophages [39–41]. These cytokines (TNFα, IL1α and 1β, PDGF, and TGF-β) activate ECM-producing mesenchymal cells of various origins, which include resident lung fibroblasts and fibroblastic bone marrow–derived cells such as circulating fibrocytes or monocytes [42–45]. Some lineage tracing studies have shown that up to 30–40% of cells expressing mesenchymal markers like vimentin and fibroblast-specific protein 1 (FSP1) might transdifferentiate from alveolar cells [46, 47]. Nonetheless, employment of EMT in lung fibrosis remains highly controversial and warrants additional research [48–50].

Kidney fibrosis

Early reports demonstrated that, during the process of renal fibrosis, epithelial cells can undergo EMT as a response to chronic injury and change their phenotype to mesenchymal [51, 52] with up to 35% of all activated fibroblasts originating from EMT [53, 54]. Subsequent studies did not support these findings [31, 55, 56], and the current consensus suggests that EMT derived cells compose a very small portion of the myofibroblast pool, while the predominant source of myofibroblasts consists of resident renal fibroblasts [57] and stromal cells

(kidney pericytes, perivascular fibroblasts, or mesenchymal stem cell–like cells) [58]. Nonetheless, tubular epithelial cells and endothelial cells may undergo a partial EMT or *in situ* EMT or "epithelial plasticity" after injury in vivo, which contributes to the development of renal fibrosis [59–61]. Moreover, a subset of kidney interstitial fibroblasts produce a consistent fraction of systemic erythropoietin (EPO), whose production is lost after fibroblast activation, thus linking renal fibrosis with anemia [62, 63]. Interestingly, supplementation with recombinant EPO substantially decreased myofibroblast-dependent ECM synthesis and ameliorated kidney fibrosis [64].

Cardiac fibrosis

The cardiac parenchyma is composed of muscle cells (cardiomyocytes) and non-epithelial cells, displaying a very limited regenerative capacity. Concerning fibrotic lesions, the heart stands out from other organs with its anatomically distinguishable "perivascular" and "interstitial/endomyocardial" fibrosis [8, 65]. Interstitial fibrosis could be subdivided into "reactive" and "replacement" fibrosis. The definition of reactive interstitial fibrosis is used to describe the expansion of the cardiac interstitial space as an adaptive response aimed to preserve the pressure generating capacity of the heart due to pressure overload. Although, chronic pressure overload could promote over time progression into a state of reparative/replacement fibrosis accompanied by myocardial cell death and formation of fibrotic scar tissue [66–69]. ECM production during heart fibrotic process is mainly mediated by the activation of resident cardiac fibroblasts, a unique and highly heterogeneous population of electrically non-excitable cells of diverse origin (although they are capable of electric coupling among each other and to neighboring cardiomyocytes). Cardiac fibroblasts represent the most important source of myofibroblasts in the fibrotic heart, accounting up to 15% of the total mouse heart cells [70–72]. Additionally, pericytes (epithelial-like cells in non-muscular microvessels and capillaries) and cardiac mesenchymal stromal cells could contribute with up to 10% of the activated fibroblasts pool [73, 74]. Taking into the account the shared expression of surface markers, transcription factors, and functional properties, it could be argued that fibroblasts, cardiac mesenchymal stromal cells (MSCs), and pericytes could represent the same cell type that have adapted due to the requirement of specialized functions by their surrounding microenvironment [70, 75]. Moreover, the contribution of endothelial-mesenchymal transition (EndMT) to cardiac fibrosis is matter of a lively debate and need to be further clarified [70, 76–79]. Small subsets of epicardial cells have been shown to activate and transition into cardiac fibroblasts after acute cardiac injury by EMT [68, 71, 80, 81].

Muscle fibrosis

The skeletal muscle is a dynamic tissue that is capable of restoring the tissue architecture with a well-orchestrated regeneration as response to physiological stimuli or severe injuries [82, 83]. Muscle fibrosis commonly appears as part of the natural repair mechanism following muscle injury due to sports injury/physical trauma, thermal and ionizing radiation, during aging or as the consequence of muscular dystrophies and metabolic disorders [84–87]. When not properly regulated, presence and persistence of fibrotic tissue negatively affects both functional and structural properties of skeletal muscle, hampers muscle fiber regeneration and increases susceptibility of the muscle tissue to re-injury [88–91].

Similarly to other organs, muscle fibrosis is closely associated and overlapping with inflammation state as a response to injury. Successful muscle regeneration begins with recruitment of white blood cells (neutrophils, macrophages) to the injury site to phagocytose damaged cells and initiate regeneration by producing cytokines, such as TNFα, IL6, and most importantly TGF-β [82, 92–94]. These secreted factors helps differentiate resident fibroblasts and mesenchymal profibrotic cells into myofibroblast cells that produce ECM components (type I, III, and VI collagens) [82, 95–97]. Moreover, these cytokines concurrently activate tissue resident myogenic satellite cells, which upon activation proliferate, fuse and form new myofibers that can be identified by centrally located nuclei. Over time, in normal physiological conditions, transiently deposited ECM is gradually remodeled, resorbed and replaced with viable and functional muscle tissue [98]. Nonetheless, regenerative capacity based on satellite cells is not unlimited, and exhaustion of the satellite cell population is an important factor of disease worsening in elderly or patients affected by severe muscular dystrophies, such as DMD (Duchenne muscular dystrophy) [82, 99].

Skin fibrosis

The skin represents a vital protective barrier between our body and surrounding environment and the formation of a scar after dermal injury is a crucial part of normal physiological mammalian skin tissue repair [100, 101]. Adult skin wounds heal by scarring, whereas fetal skin wounds have the ability to heal without scar formation until 24th week after gestation [102]. However, even some adult tissues heal with minimal scar formation like in the case of oral mucosa tissue [103, 104].

Upon injury, damaged cells produce DAMPs and PAMPs that are sensed by tissue-resident macrophages and patrolling monocytes [105] that in turn secrete cytokines and chemokines [106, 107]. These secreted factors like TGF-β , IL1, TNFα, PDGF, EGF, and FGF2 activate many different cell types, such as fibroblasts, adipocytes, resident and bone marrow–derived mesenchymal progenitor cells and pericytes, to form a heterogenic population of activated myofibroblasts that proliferate and produce ECM proteins (collagens I and III and fibronectin [108–110]). Moreover, differentiation of fibroblasts into myofibroblasts, which is regulated mainly by TGF-β, mediates wound contraction/closure due to high expression of αSMA and non-muscle type IIA and B myosin [111, 112].

A normal scar tissue is composed of loose fibrous connective tissue and is remodeled during the healing process. However, excessive ECM accumulation and cross-linking due to chronic inflammation and/or uncontrolled function of activated myofibroblasts lead to abnormal overgrowth of the scar and formation of a hypertrophic scar or a keloid [110, 113]. Hypertrophic scars grow after surgery, trauma, or burns and contractures across the joints, but always stay in injured zone. On the other hand, keloids develop as profuse scarring that extends beyond the limits of the original injury causing deformity, pruritus, and hyperesthesia [100, 114, 115].

Therapeutic possibilities for preventing pathological skin scarring are still limited and have been focused mainly on reducing inflammation and contraction of the wound [116–118]. TGF-β, as an inducer of myofibroblast differentiation, is considered a potential therapeutic target for the prevention of pathological scars [117, 119–121]. However, short temporal exogenous supplementation of TGF-β and other growth factors could be used for the stimulation and the formation of granulation tissue, which increases the speed of wound closure in diabetic wounds and foot ulcer healing [122, 123].

Liver fibrosis

The liver stands out from all other organs with regards to its regenerative capacity and the ability to resolve fibrotic lesions as based on evidence from animal models and observations from human livers [8, 124–126]. Regeneration and fibrosis share a common cascade of injury-induced events that diverge as a result of the chronicity of the damage/injury. In healthy individuals, a single injury of the liver tissue initiates a regenerative response with goal to reestablish tissue function and homeostasis. Repetitive injury hampers regeneration and diverts the homeostasis to a diseased state known as fibrosis. The tissue may still recover and resolve the fibrotic state as time progresses if no further damage is present. Alternatively, chronic injury and damage will consequently deteriorate the tissue further until it progresses to cirrhosis [127].

As a result to injury and cell damage, special liver-resident macrophages, known as Kupffer cells (up to 15% of the total liver cell population), immediately respond to injury by secretion of pro-fibrotic cytokines (TGF-β, PDGF and TNFα) [7, 128, 129]. Kupffer cells drop in numbers as inflammation/injury progresses, and monocyte-derived macrophages from the bloodstream in turn overtake control of injury signaling and repair by secreting high levels of TGF-β [130, 131]. Pro-fibrotic and inflammatory cytokines directly activates quiescent hepatic stellate cells (HSCs), an exclusive cell type present in liver tissue. They represent up to 8% of liver cells and are a major source of ECM producing myofibroblasts, originated through a process of transdifferentiation [128, 132], as opposed to the activation of parenchymal fibroblasts present periportally in the liver [8, 133].

If the regenerative capacity of the liver (governed by hepatocytes and/or cholangiocytes) is compromised as a consequence to chronic injury, the expansion of putative liver progenitor cells (LPCs, or oval cells) in the periportal area occurs in order to support or take over the regenerative processes [134, 135]. Such persistent damage can be caused by alcohol overconsumption, hepatoviruses or excessive lipid accumulation, and liver lipotoxicity associated with metabolism-associated non-alcoholic fatty disease (MAFLD), as the most

significant causes of liver fibrosis in developed countries [8, 128, 136, 137].

TGF-β superfamily

The TGF-β superfamily is a large group of proteins comprising of 33 structurally related members, including TGF-βs, activins, inhibins, growth differentiation factors (GDFs), glial-derived neurotrophic factors (GDNFs), nodal, lefty, and anti-Müllerian hormone [138–140]. The whole group was named after its first discovered prototypical member TGF-β1 [141, 142]. In general, all TGF-β ligands stabilize and activate specific tetrameric type II/type I receptor complexes, which in turn transduce the signal by phosphorylation of carboxy-terminal serine residues of cytoplasmatic SMAD complexes. The SMAD family has eight members, i.e., five receptor-SMADs (R-SMAD1, 2, 3, 5 and 8), one co-receptor SMAD (co-SMAD4) and two inhibitory-SMADs (I-SMAD6 and 7) [143]. In most cell types, TGF-βs and activins induce phosphorylation of R-SMADs 2 and 3 heteroduplexes, whereas BMPs induce phosphorylation of SMAD1, 5, and 8 receptor heterocomplexes. Both phosphorylated R-SMAD heterocomplexes bind with SMAD4 to form SMAD2/3/4 or SMAD1/5/8/4 heterocomplexes that are translocated to cell nucleus and induce appropriate gene transcription including the production of inhibitory-SMAD 6 and 7 that block and thus regulate activation of R-SMADs [139, 140, 144].

Over the years, TGF-β associated signaling pathways have been demonstrated to have pivotal roles in wound healing processes [145], EMT [30, 33, 146, 147] and fibrogenesis. TGF-β is one of the major players and most potent effectors of fibrosis in many organs and tissues [24, 66, 88, 142, 148–159], whereas its neutralization by inhibitors/antagonists led to significant amelioration of liver, heart and lung fibrotic lesions [148, 160–164]. In short, TGF-β fibrotic signaling progresses via two distinct pathways: SMAD2/3 dependent/canonical signaling [66, 150, 165] and non-canonical ERK1/2 MAPK, PI3K/AKT and JNK pathway [166–168].

In contrast to the classic TGF-β signaling inducing EMT and fibrosis, the TGF subfamily of BMPs/|GDFs was originally identified for its ability to induce bone and cartilage formation and to regulate growth and differentiation of chondroblast and osteoblast cells in vitro [169, 170]. These factors play an important role in early embryonic development, including dorsal-ventral patterning, organogenesis and cell differentiation, with expression tightly controlled in space and time [171, 172]. While TGF-β induces activation of the profibrotic SMAD2/3 pathway through ALK4/5 receptors, BMP/GDF signaling depends on ALK1/2/3 and 6 receptors, and SMAD1/5/8 pathway activation. Activation of SMAD1/5/8 pathway has the ability to counterbalance TGF-β induced intracellular signaling, though the involvement of BMPs/GDFs in tissue fibrotic processes is variable and less delineated than in the case of TGF-β [121, 173, 174].

BMPs/GDFs in tissue fibrosis

Bone Morphogenetic Proteins (BMPs) and Growth Differentiation Factors (GDFs) are multifunctional cytokines constituting the largest TGF-β subfamily, comprising of more than 20 ligands in mammals [139, 144, 173]. Because BMP/GDF family members were identified using multiple approaches, some are now known under many different names such as cartilage-derived morphogenetic proteins (CDMPs), GDFs, osteogenic proteins (OPs), osteogenin, and Vg-related (Vgr) [144]. To avoid any confusion, this review will use terms “BMP” and “GDF”. According to their sequence and structural homology BMP/GDF ligands can be classified into several different subgroups: BMP2 and 4; BMP5, 6, 7, 8 and 8B; BMP9/growth differentiation factor 2 (GDF2) and BMP10; BMP11/GDF11 and GDF8; BMP12/GDF7, BMP13/GDF6 and BMP14/GDF5; BMP15/GDF9b and GDF9; GDF1 and 3; BMP3 and BMP3b/GDF-10 [173, 175]. The following sections describe the role of BMPs/GDFs in fibrotic processes in various tissues.

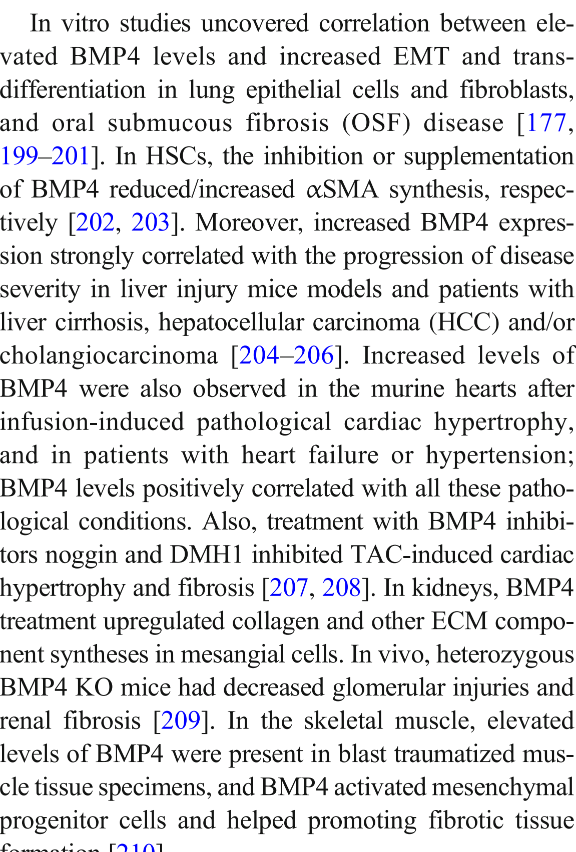
BMP2

BMP2 plays an important role in the development of bone and cartilage by inducing osteoblast differentiation [176], and helps to induce endocardial EMT and to instruct cardiac progenitor cells to form the heart-valve region and the myocardium chamber patterning [177, 178]. BMP2 knockout mice are embryonically lethal, triggering defects in amnion/chorion formation and in cardiac development [179]. Moreover, BMP2 seems to be involved in white and brown fat adipogenesis, and may have metabolic role manifested as the control of blood insulin and glucose levels [180, 181].

In mice models of liver injury, by either injections of carbon tetrachloride (CCL4) or alcohol consumption, increased synthesis of BMP2 in liver was observed as a consequence of hepatocyte injury [182, 183]. In vitro BMP2 treated HSCs have increased αSMA expression, to a greater extent compared with the ones induced by TGF-β treatment, accompanied by decreased proliferation [184]. In mice with pressure-overload induced collagen deposition by transverse aorta constriction (TAC), supplementation with recombinant BMP2 antagonized/inhibited TGF-β1/ROCK cardiac fibrotic signaling by the induction of SMAD6/Smurf1 complexes [185]. Conversely in renal fibrosis, administration of BMP2 into rats with unilateral ureteral kidney obstruction injury dramatically reduced interstitial collagen depositions in kidneys with concomitant reduction of TGF-β signaling; moreover, in vitro BMP2 treated renal fibroblasts produced less fibrotic markers, displaying reduced cell migration and promotion of EMT [186, 187]. In lung, BMP2 was showed to attenuate function of lung fibroblast and its signaling ablated bleomycin induced pulmonary fibrosis [188–190]. Other studies showed that BMP2 significantly increases as a consequence of cerulein-induced pancreatic injury, and heterozygous deletion of BMP type II receptor (BMPR2) promotes formation of pancreatic fibrotic lesions; in vitro, BMP2 treatment of pancreatic stellate cells inhibits TGF-β signaling, EMT, and ECM synthesis [191, 192]. In skin, it was observed that BMP2 expression was significantly increased in the epidermis and dermis of hypertrophic scar (HS) tissue, especially in the fibroblasts and mesenchyme of dermis, as compared with that in normal skin tissue. Moreover, the proliferation of HS fibroblasts and their production of type I collagen was significantly decreased by knocking down BMP2 [193].

BMP4

BMP4 is involved in development of bone, cartilage, tooth and limb (digit patterning) [194–196]. Loss of BMP4 is embryonically lethal due to defective embryonic mesoderm formation [197]. Moreover, BMP4 is required for the generation of primordial germ cells in the mouse embryo [198]. Considering that BMP4 and BMP2 share more than 92% sequence and structural homology and belong to the same BMP subgroup, one could expect similar courses of action [170, 173].



In vitro studies uncovered correlation between elevated BMP4 levels and increased EMT and transdifferentiation in lung epithelial cells and fibroblasts, and oral submucous fibrosis (OSF) disease [177, 199–201]. In HSCs, the inhibition or supplementation of BMP4 reduced/increased αSMA synthesis, respectively [202, 203]. Moreover, increased BMP4 expression strongly correlated with the progression of disease severity in liver injury mice models and patients with liver cirrhosis, hepatocellular carcinoma (HCC) and/or cholangiocarcinoma [204–206]. Increased levels of BMP4 were also observed in the murine hearts after infusion-induced pathological cardiac hypertrophy, and in patients with heart failure or hypertension; BMP4 levels positively correlated with all these pathological conditions. Also, treatment with BMP4 inhibitors noggin and DMH1 inhibited TAC-induced cardiac hypertrophy and fibrosis [207, 208]. In kidneys, BMP4 treatment upregulated collagen and other ECM component syntheses in mesangial cells. In vivo, heterozygous BMP4 KO mice had decreased glomerular injuries and renal fibrosis [209]. In the skeletal muscle, elevated levels of BMP4 were present in blast traumatized muscle tissue specimens, and BMP4 activated mesenchymal progenitor cells and helped promoting fibrotic tissue formation [210].

BMP6

BMP6 (or *VGR-1*, vegetal related 1) is expressed during embryo development and regulates early stages of osteoblast differentiation and cartilaginous tissue formation by stimulation of mesenchymal cell differentiation into chondrocytes [211–213]. Also, it was observed that BMP6 is produced by mammalian oocytes and its downregulation decreased fertility rates in mice [214].

In an in vitro model of renal interstitial fibrosis (TIF), treatment with recombinant BMP6 showed strong attenuation of TGF-β induced EMT and ECM synthesis. Moreover, BMP6 null mice with induced kidney obstruction injury had aggravated renal injury and fibrosis [215, 216]. On the contrary, a study employing a rat model of cisplatin induced renal fibrosis (CDDP) showed positively correlated levels of BMP6 with disease progression, and in vitro treatment with recombinant BMP6 increased αSMA expression levels in pericytes and in renal interstitial fibroblasts [217]. Similarly, elevated levels of BMP6 were observed in patients with metabolism associated fatty liver disease

(MAFLD) [218]. However, BMP6 null mice fed with high-fat and choline-deficient diets displayed more hepatic inflammation and fibrosis, and treatment of HSC with BMP6 attenuated their activity and profibrogenic gene expression [218]. In chronic obstructive pulmonary disease (COPD), BMP6 levels in patients with COPD were significantly decreased and negatively correlated with severity of COPD. BMP6 KO mice showed decreased total lung capacity and aggravated cigarette smoke induced inflammatory response. The deposition of collagen, fibronectin, and αSMA in the airway wall was similar between BMP6 KO and WT mice [219]. BMP6 is also well known to be crucial for regulating embryonic skin development. In dermal fibrosis, significantly elevated levels of BMP6 were observed in skin-derived fibroblasts of patients with localized scleroderma. Moreover, loss of BMP6 in skin derived fibroblasts induced profibrogenic hallmarks, such as elevated migration, proliferation, and collagen contraction. In in vivo murine model of bleomycin-induced dermal fibrosis, the BMP6-deficient mice showed significantly enhanced fibrosis compared with their wild-type littermates. Conversely, exogenous application of recombinant BMP6 significantly ameliorated dermal fibrosis in this murine bleomycin-induced dermal sclerosis model [220]. On the contrary, original paper from 1998 by Kaiser et al. describe high levels of BMP-6-specific RNA and protein in chronic human wounds of different etiology and in transgenic mice overexpressing BMP6 they observed significantly delayed re-epitheliazation of induced skin wounds with more prominent scar formation [221].

BMP7

BMP7 (or osteogenic protein-1; *OP-1*) plays a key role in the transformation of mesenchymal cells into bone/cartilage [176], and in the induction of mesenchymal-ephithelial transition (MET) of the metanephrogenic blastema in mammalian kidney development [222]. In adult kidney, BMP7 protein is important to maintain the homeostasis by inhibiting EMT [223].

BMP7 is one of the most studied bone morphogenic factors in the context of tissue anti-fibrotic reactions in various organ setups (Fig. 1) [222, 224–226]. BMP7 antifibrotic signaling occurs by activating/phosphorylating SMADs 1, 5, and 8 complexes, which in the nucleus induce upregulation of inhibitory SMADs 6 and 7; this, in turn, is most likely the cause for BMPs antifibrotic properties by blocking the TGF-β induced SMAD2/3 signaling pathway [225, 227–230]. BMP7 signaling is also able to block the activation of SMAD2/3 independent/noncanonical pathways like MAPKs, p38, ERK1/2, and JNK [231, 232].

Regarding liver fibrosis, BMP7 treated HSCs exhibited decreased activation and production of profibrotic markers, cytokines and ECM components [233, 234]. In rat and mouse models of induced liver fibrosis and injury BMP7 overexpression/supplementation significantly attenuated liver fibrosis, decreased expression of profibrotic markers and blocked EMT [233–238]. Likewise, in renal fibrosis, it has been shown that BMP7 exerted antifibrotic effects by inhibiting ECM deposition and EMT in tubular epithelial cells [227, 239, 240]. In vivo treatment with recombinant BMP7 significantly improved renal function, histology, and survival in mice models of chronic renal injury and fibrosis [222]. In lungs, BMP7 significantly reduced the progression of silica-induced fibrosis in rats via upregulation of the SMAD1/5/8 axis and downregulation of SMAD2/3 signaling [225]. In mouse heart, treatment with BMP7 had ameliorating effect on cardiac functions and formation of fibrotic lesions, and in vitro decreased activation of myocardial fibroblasts [241]. In skin fibrosis, BMP-7 treatment reduced excessive collagen I and III deposition in the scar tissues induced by thermal injury in mice; moreover, BMP-7 treatment inhibited excessive contraction of the scar by decreasing levels of αSMA at the site of injury [236]. On the other hand, Murray and colleagues in their study did not observed any amelioration of bleomycin-induced fibrosis in either the lung or skin in vivo. Supplementation with recombinant BMP7 had no effect on expression of pro-fibrotic genes and exerted no therapeutic benefit on collagen deposition in the skin fibrosis induced by subcutaneous administration of bleomycin [242]

BMP9/GDF2

BMP9 (also known as GDF2) is one of the most potent BMPs to induce orthotropic bone formation in vivo by differentiation of mesenchymal stem cells (MSCs) to osteoblast lineage [243]. BMP9 also plays a role in the induction and maintenance of embryonic basal forebrain cholinergic neurons (BFCN) to respond to the neurotransmitter acetylcholine [244]. Moreover, BMP9/GDF2 can regulate iron metabolism in hepatocytes [245].

Organ		Factors	References
Lung	Antifibrotic	BMP2, BMP6, BMP7	189–191,216,237,314
	Profibrotic	TGF-β, BMP4, BMP9, GDF11	152,155,178,200,202,253
Kidney	Antifibrotic	BMP2, BMP6, BMP7	187,216,228,233,241,265
	Profibrotic	TGF-β, BMP4, BMP6, BMP14, GDF11	[153,156,211,218,314,317
Heart	Antifibrotic	BMP2, BMP6, BMP7, BMP9, BMP14, GDF11	186,242,256,264,312,318,324
	Profibrotic	TGF-β, BMP4, BMP9, GDF11	158,208,209,255,267,275,277,310
Muscle	Antifibrotic		
	Profibrotic	TGF-β, BMP4, GDF11	88,160,211,326,329,330
Skin	Antifibrotic	BMP6, BMP7, GDF11	221,226,331,332
	Profibrotic	BMP2, BMP6	194,222
Liver	Antifibrotic	BMP2, BMP6, BMP7, GDF11	183–185,219,334
	Profibrotic	TGF-β, BMP4, BMP9, GDF11	158,159,203–205,207,211,247–249,279,280

Antifibrotic Profibrotic

Fig. 1 Summary of evidence for TGF-β and BMP/GDF family members in fibrotic processes in different organ setups

Concerning liver fibrosis, BMP9 was showed to activate HSC [246, 247], and in mice models of liver fibrosis it accelerated the progression of liver fibrotic lesions [246, 248–250] and positively correlated with advanced stages of liver fibrosis in human liver samples [249]. Thus, BMP9 was proposed to be a valuable serum diagnostic indicator that may be used for the clinical diagnosis of liver fibrosis, and its blocking/inactivation may serve as a part of anti-fibrotic treatment strategy [249, 251]. Conversely in lung tissue, BMP9 loss or inhibition partially prevented and protected against experimentally induced pulmonary hypertension [252]. Whereas treatment of rat pups with hyperoxia-induced experimental BPD (bronchopulmonary dysplasia) by BMP9 reduced/ameliorated alveolar enlargement, lung septal thickness and fibrosis [253]. Also, studies focusing on the hearts of individuals with hypertension and coronary heart disease suggested that BMP9 plays organ/tissue specific role in the pathophysiology of heart disease and fibrosis with significant ameliorating effects [254, 255].

BMP14/GDF5

BMP14 (also known as GDF5) is a secreted morphogen, which is expressed during embryonal development in several tissues including heart and limb bud [256–258] and has significant effect on angiogenesis, apoptosis, cell survival, differentiation, and migration [259–262].

Hearts of BMP14/GDF5-KO mice after 28 days post myocardium infarction (MI) had increased infarct scar expwww.ncbi.nlm.nih.gov/pm ansion and heart fibrotic tissue, decreased arteriolar density, ventricular dilation and contractility compared with WT littermates [263]. In patients with hydronephrosis accompanied by extensive fibrotic renal tissue, expression profiling of the TGF-β/BMP signaling related genes revealed GDF5 expression to be three times lower in patients with renal fibrosis than in healthy human controls [264].

Myostatin/GDF8

Myostatin (MSTN), or GDF8, is a blood-circulating factor that is mainly produced by the skeletal muscle, but basal expression is also detectable in heart and adipose tissue. MSTN serves as a negative modulator of muscle growth and tropism, and its mutations or targeted deletion in mammalian species cause muscle hypertrophy and hyperplasia [265, 266].

It has been reported that MSTN directly promoted muscle fibroblasts activation and fibrosis [267], and inhibition of MSTN ameliorated fibrosis after musculoskeletal injury or in dystrophic (mdx) mice [268–273]. Cardiac MSTN production inhibited cardiomyocyte

growth as well as induced ECM synthesis, cardiac fibrosis and alterations in ventricular function, thus compromising heart function [274, 275]. Conversely, mice deficient for MSTN displayed less myocardial fibrosis, less ventricular dilation, and improved cardiac function compared with their wild-type age matched counterparts [276]. In vitro exposure of HSC to MSTN induces increase in cell migration, reduces cell proliferation and elevates levels of TGF-β and procollagen expression [277, 278]. The work by Nishikawa et al. pointed out that higher serum levels of MSTN were independently linked with worsening and severity of liver disease in both male and female patients with liver cirrhosis [279].

GDF11

Growth differentiation factor 11 (GDF11), also known as bone morphogenetic protein 11 (BMP11) is a blood circulating factor belonging to the TGF-β superfamily [280]. GDF11 shares more than 90% amino acid sequence homology in its active form with the related MSTN [281]. Both GDF11 and MSTN are atypical members of BMP/GDF subfamily, because their signaling is carried out similarly to TGF-β, via activin II receptors (ACTRIIB) with the subsequent recruitment of the activin receptor-like kinases (ALKs) ALK4, ALK5 and ALK7 and not by ALK1, 2, 3 or 6 as in the case of other BMPs/GDFs [282]. In particular, ALK5 heterodimers are identified as the predominant receptor for GDF11 mediated signaling [283]. Intracellular signaling is carried out by receptor SMAD2/3 complexes, which associate with co-SMADs (SMAD4) and after translocation into the cell nucleus they promote and regulate gene expression [282, 284, 285]. GDF11 can also transduce signals concurrently by non-canonical pathways as other TGF-β family members do. Mitogen activated protein kinase (MAPK) is perhaps the main non-SMAD pathway subsequently activating routes such as p38, AKT, and JNK [286, 287].

Expression of GDF11 is very variable in the wide range of tissues, and it plays an important role throughout the mammalian embryonic development. GDF11 embryonic signaling helps formation of spinal cord anterior/posterior patterning, development of urogenital system, pancreas, spleen, stomach and olfactory neurogenesis [282, 288–291]. GDF11 also plays a notable role in various types of cancer diseases (breast, colorectal, liver and pancreatic cancers) with both tumor suppressive and tumor promoting properties, which is dependent on cell progeny, grade, differentiation and/or transformation [292–296].

During the past decade, several high profile studies showed that systemic supplementation of GDF11 levels reverses age-related phenotypes and had rejuvenating effect on heart and skeletal muscle in aged mice [297, 298], improved insulin sensitivity via restoring pancreatic β-cell function in diabetic mice [299], and improved the vascular and neurogenic rejuvenation in the brain of aged mice [299–303]. Since then, other studies seriously questioned the possible rejuvenation effects of GDF11 and doubted the age-associated decrease of circulating plasma GDF11 levels and related phenotypes in the muscle, heart and brain [304–307]. Furthermore, studies showed that restoration of GDF11 levels in old mice had no positive effect on heart structure or function [308] and significantly elevated levels of GDF11 had deleterious effects on aging skeletal muscle regeneration [304]. Importantly, supraphysiological levels of GDF11 were found to promote muscle loss and cachexia with premature death in mice [309–311].

These numerous controversial data highlight that the true local and systemic effects of GDF11 in health and disease are not fully delineated, and further extensive research needs to be done to fully elucidate and uncover the functions of GDF11. In this review we will focus specifically on the current evidence about GDF11/BMP11 and the process of organ fibrosis, which is less explored and established, when compared with the closely related MSTN.

GDF11 and organ-specific fibrosis

GDF11 in pulmonary fibrosis

In two independent cohorts of patients with chronic obstructive pulmonary disease (COPD), the plasma levels of GDF11 were decreased compared with healthy control subjects and they significantly positively correlated with pulmonary function data [312]. Production of GDF11 mRNA was traced to mesenchymal cells residing in the airway walls and its levels were significantly lower than in subjects with COPD. In vitro GDF11 treatment of lung resident cells and lung fibroblast exposed to the cigarette smoke extract (CSE) significantly inhibited cellular senescence and inflammation and significantly improved fibroblast-mediated tissue repair.

They also demonstrated that the administration of GDF11 ameliorated elastase-induced enlargement of alveolar spaces in vivo, suggesting that GDF11 might be involved in the pathogenesis of COPD.

In 2019, Kwapiszewska et al. used unbiased transcriptomic approach on patients with idiopathic pulmonary fibrosis (IPF) who underwent treatment with pirfenidone. Treatment with pirfenidone significantly ameliorated disease severity, inflammation and ECM production in lung tissue homogenates and lung fibroblast isolated from patients with IPF. Unbiased transcriptomic analysis revealed significantly downregulated levels of GDF11 (FC 1.73 ± 0.79) in patients with IPF after pirfenidone treatment, thus implying its role in lung IPF pathology [313].

GDF11 in kidney fibrosis

In mice model of kidney ischemia-reperfusion injury (IRI), elevated levels of GDF11/8 expression were observed shortly after injury. Systemic restoration of GDF11 in old mice, by injections of recombinant GDF11 (0.3 mg/kg/), 48 h before and after IRI significantly improved tubular injury and increased mice survival (50% GDF11 vs 30% CTL). However, GDF11 treatment increased proliferation and dedifferentiation (EMT) of proximal tubular cells accompanied by increased expression of Pax2 and vimentin [314]. In vitro treated human primary renal proximal tubule cells (hPTCs) with recombinant GDF11 had increased dedifferentiation (EMT), which was evidenced by elongated or stellate shape, with increased Pax2 and vimentin expression and decreased E-cadherin. The ERK1/2 signaling pathway was activated after GDF11 treatment in both in vitro and in vivo, and in vitro inhibition of ERK1/2 signaling by U0126 compound attenuated all GDF11-induced morphological and expression changes in hPTCs, suggesting that the observed effect of GDF11 was ERK1/2 dependent.

Pons et al. (2018) marked GDF11 as an inducer of kidney fibrosis, renal cell EMT, kidney dysfunction and failure [315]. They observed in vitro GDF11-mediated EMT transition of renal tubular epithelial cells (HK-2), accompanied by elevation of *collagen I*, *αSMA*, and *vimentin expression*, and reduced expression of E-cadherin. GDF11 mediated activation of renal fibroblast cells (NRK49f), as evidenced by induction of collagen and αSMA and spindle-shaped morphology with formation of actin stress fibers. In mice, these authors observed elevated expression of GDF11 (up to 3–6 fold higher) after acute kidney injury (AKI) or unilateral ureteric obstruction (UUO). Supplementation of GDF11 by either injection of recombinant GDF11 or CHO cells producing GDF11 induced gradual loss of weight and severe acute kidney injury with elevated BUN score (Blood Urea Nitrogen), creatinine, phosphate and reduced creatinine clearance. At necropsy, prolonged GDF11 treatment led to progressive decline of kidney mass, atrophy of the tubular epithelial cells and increased fibrosis and EMT evidenced by Sirius red/ Masson's trichrome staining and collagen immunohistochemistry. In heterozygous *Gdf11*$^{+/-}$ mouse the decreased systemic levels of GDF11 positively correlated with decreased degree of fibrosis and amelioration of fibrosis induced as a consequence to UUO.

GDF11 in heart fibrosis

Smith et al. described that GDF11 was not able to rescue aging-related pathological hypertrophy or improve cardiac function upon daily injection of rGDF11 (0.1 mg/kg) for 28 days in 2-year-old C57BL/6 mice [308]. They did not observe significant changes in cardiac fibrosis by histological assessment between GDF11 and vehicle treated animals. Nonetheless, they showed that in vitro treatment of normal human fibroblast with GDF11, MSTN or TGF-β significantly increased fibroblast activation in dose dependent manner, measured as fibronectin expression. Even low doses of GDF11 activated fibroblast to express fibronectin with an EC50 of 176pM, which was similar to the effects of MSTN with EC50 of 83pM.

On the contrary, in ischemia/reperfusion and myocardial infarction mice model, targeted delivery of GDF11 by non-invasive ultrasound-targeted microbubble destruction (UTMD) and cationic microbubble (CMB) method led in aged mice (23 months old) to significant improvement of cardiac function and reduced infarct scar size formation measured by Masson's trichrome staining. Additionally, GDF11 stimulated the proliferation of cardiac stem cells (CSCs) and increased homing of endothelial progenitor cells in old mouse hearts, thus helping in regeneration process [316].

Recently, Harper et al. (2018) tried to clarify some of the discrepancies in GDF11 mediated heart rejuvenation experiments published earlier [297, 298, 307, 317, 318]. In fact, initial rejuvenating studies reported age-related

changes in circulating GDF11 levels based on ELISA assays that could not distinguish between myostatin and GDF11, whereas levels of the latter one are inconsequentially lower (500 times lower) and likely to have lesser physiological relevance [307]. There was also a dispute about the idea that there is age-related pathological hypertrophy in old C57bl6 mice and that GDF11 therapy can reverse cardiac pathologies. These circumstances raised the possibility that the previously observed rejuvenation of the heart and muscle tissues mediated by GDF11 was built on an artifact and has not been adequately addressed. Thus Harper et al. performed a (blinded) dose ranging study, in which they treated with GDF11 for 14 days 12–13 week old C57BL6 mice with transverse aortic constriction (TAC) or sham surgery, a procedure that induces pathological cardiac hypertrophy and associated cardiac fibrosis [319–321]. Their results showed that daily injections of GDF11 caused a dose dependent reduction in body weight and heart mass in both normal and TAC mice, with disproportionately decreased heart weight in TAC mice [310]. Treatment with rGDF11 caused significant decrease in interstitial fibrosis only in TAC mice treated with 1.0 mg/kg dose but had no significant effect on perivascular fibrosis among all tested groups. Conversely, expression of collagen I mRNA was reduced in TAC mice treated with the doses of 1.0 and 5.0 mg/kg. Alleged antifibrotic effects of GDF11 were further tested on mouse embryonic fibroblasts (MEFs) by treatment with either rGDF11 or TGF-β. Obtained results were consistent with data from Smith et al. (2015), where GDF11 activated MEFs (defined by higher expression of collagen, αSMA vimentin), but to lesser extent as observed in TGF-β treated samples. The profibrotic results in MEFs did not explained observed in vivo differences in interstitial fibrosis deposition in GDF11 treated TAC mice, suggesting that GDF11 antifibrotic effect was not caused by direct action of GDF11 on cardiac fibroblasts.

In a recent study, Garbern et al. introduced loxP-flanked ("floxed") allele of Gdf11 and Myh6-driven expression Cre-recombinase to mice with goal to induce targeted deletion of GDF11 in mice cardiomyocytes. Deletion of GDF11 did not caused cardiac hypertrophy but rather caused left ventricular dilation in comparison with control mice carrying only the Myh6-cre or Gdf11-floxed alleles. No significant difference in fibrotic deposition was observed, regardless of the sex of the mice. Nonetheless, significant increase of fibrosis was observed between female and male mice upon introduction of a Cre-recombinase cassette, suggesting Cre-associated toxicity, as it was previously demonstrated by Pugach et al. (2015) thus making the results obtained in this study challenging to interpret, due to multiple confounding effects associated with the chosen experimental model [322, 323].

GDF11 and muscle fibrosis

In a recent paper, Jin et al. described the effect of blocking GDF11/MSTN function by GDF11PRO-Fc propeptide transduced using a AAV9 vector, injected through the vein in the mdx mice [324]. The *mdx mouse* is a popular model for studying Duchenne muscular dystrophy (DMD) and muscle fibrosis, because during aging and disease progression diaphragm and intramuscular fibrosis will develop, which is the hallmark of common dystrophic diseases [325, 326]. In mdx mice, systemic overexpression of GDF11PRO-Fc resulted in skeletal muscle hypertrophy without any significant change in cardiac mass after 12 weeks of treatment. Muscle performance was significantly improved measured as grip strength and rotarod latency time. Most importantly, propeptide blocking of GDF11/MSTN function significantly reduced intramuscular fibrosis evaluated in the *gastrocnemius* muscle and diaphragm of treated mdx mice. However, GDF11PRO-Fc treatment did changed other markers of the dystrophic pathology (proportion of centrally nucleated myofibers, serum CK or membrane permeability to IgG), suggesting that GDF11PRO-Fc gene delivery is not able to halt the progression of myofiber degeneration. Although, the decrease of fibrosis caused by blocking GDF11 may be challenged by the fact that used GDF11PRO-Fc has capability to neutralize both GDF11 and MSTN.

Nonetheless, those findings were consistent with the data by Rinaldi et al., who also employed mdx mice model, but with the daily i.p. injections of recombinant GDF11 (rGDF11) [327]. rGDF11 (0.1 mg/kg) treatment for 1 month did not ameliorated dystrophic disease progression and no beneficial effects were observed in the histology or strength of the muscles in GDF11 treated dystrophic animals. In contrast, GDF11 injections led to significant increase of collagen content detected in the *tibialis anterior* (TA) muscle when compared with control vehicle treated mice. Degree of fibrosis in the diaphragm and TA after cardiotoxin injury

was not significantly different between GDF11 and vehicle treated groups.

Conversely, in a rat model of compression-induced muscle injury, systemic treatment with recombinant GDF11 significantly attenuated muscle functional recovery and tissue regeneration after injury [328]. Furthermore, in all tested injured muscles treated with GDF11 were observed significantly enlarged areas of fibrotic lesions as opposed to muscle of vehicle treated mice.

Evidence based on rodent in vivo models suggests that systemic supplementation with GDF11 exacerbates muscle tissue fibrotic lesions, whereas blocking/neutralization of GDF11 signaling ameliorates muscle fibrosis.

GDF11 in skin wound healing

Upon injury, skin integrity must be promptly restored in order to maintain its functions. Peripheral blood mononuclear cells, resident skin cells, extracellular matrix, cytokines, chemokines, growth factors, and regulatory molecules participate in the wound healing process. A recent study investigated the role of a truncated more stable form of GDF11 in skin wound healing in diabetic mice (both type 1 and 2). The regenerative process occurred via stimulating dermal fibrosis via the YAP—Smad2/3—CTGF pathway [329]. GDF11 appears to be the key to progenitor proliferation and/or differentiation. It appears that GDF11 inhibits negative inflammatory responses in the skin and thus functions as an anti-aging factor; the protective role of GDF11 relies on a multi-factorial process involving several types of skin cells such as keratinocytes, fibroblasts and inflammatory cells [330]. In this paper, they discovered that GDF11 stimulates growth and secretion of ECM proteins including Collagen types I and II, elastin and fibronectin in HDFs. These findings suggest that rejuvenating effect of GDF11 could be expended to human skin in addition to the specific organs previously reported [331]. The main effect of GDF11 was the induction of collagen I and III, in both neonatal and adult fibroblasts, by triggering SMAD2/3 signaling in a TGF-β-like fashion. Moreover, by analyzing a number of plant extracts having GDF11 inducing activity, they discovered that a peptide/sugar preparation, obtained from *Lotus japonicus* somatic embryo cultures, were capable of restoring GDF11 expression in older fibroblasts and to activate the synthesis of collagen I, collagen III and periostin, an important protein involved in collagen assembly.

GDF11 in liver fibrosis

In the 2019 study by Dai et al., it was observed in human fibrotic liver samples and mice liver samples that after CCL4 or diethoxycarbonyl dihydrocollidine (DCC) injury the expression levels of GDF11 were increased, when compared with healthy controls [332]. The in vivo administration of GDF11 by adenoassociated virus (AAV-GDF11) in CCl4 or DDC-treated mice significantly reduced fibrosis in both mice models, as it was evidenced by lower hydroxyproline content, decreased Sirius Red and desmin staining and decreased expression of fibrogenic genes such as αSMA and collagen I and II. The authors showed that GDF11 administration expanded hepatic LGR5+ progenitor cells both in vitro and in vivo, and transplantation or ablation of LGR5+ cells in the CCL4 or DDC cirrhotic mice livers ameliorated or exacerbated liver fibrosis, respectively. Furthermore, the authors showed that activated myofibroblasts were the main producer of GDF11 in the fibrotic liver, which in turn activated LGR5+ progenitor cells and helped to ameliorate fibrosis. Both in vitro and in vivo targeted silencing of GDF11 in myofibroblasts by shRNA construct decreased the number of LGR5+ progenitor cells and led to exacerbated liver fibrosis. Finally, administration of GDF11 in mice fed with high-fat diet (HFD) led to significant decrease in total body weight, non-alcoholic fatty liver disease activity score (NAS score) and blood insulin and glucose levels. On the contrary, in patients with metabolic associated fatty liver disease (MAFLD) elevated expression levels of GDF11 were detected, which were not present in a high fat diet-induced MAFLD mouse model.

We have recently shown that GDF11 activated a pro-fibrogenic program in HSCs, evidenced by increased synthesis of αSMA, collagen I and vimentin. In obese (*ob/ob*) or lean wild type mice GDF11 mildly exacerbated hepatic collagen deposition and increased perivenular αSMA staining, without changes in liver steatosis, damage or inflammation. Ingenuity Pathway Analysis (IPA) of *ob*/*ob* liver samples uncovered significant negative association between GDF11 treatment and the activation of signaling pathways of aryl hydrocarbon receptor (AHR), BRCA1-dependent DNA

damage response and HGF signaling [333] (Frohlich et al. 2020). Inhibition of these pathways has been consistently associated to the development of liver fibrosis and disease [334, 335]. In morbidly obese patients, GDF11 mRNA levels tended to increase with NAFLD to NASH progression and correlated positively with increased Kleiner score. Levels of GDF11 also positively correlated with genes involved in MAFLD progression (PPARγ, CPT1, SREBP1, and Col1A1) [333].

Concluding remarks

It has been suggested that circulating levels of GDF11 decrease with age, and the restoration of youthful levels of systemic GDF11 can rejuvenate the function of multiple organs in old mice [297, 298]. However, the rejuvenating effects of GDF11 have been seriously questioned in recent years with more and more controversies piling up [304–308]. Taking into the account more than 90% sequence homology and similar intracellular signaling of GDF11 and MSTN, one would expect significant employment of GDF11 in various fibrotic process as showed in the case of MSTN [269, 273–275, 277].

Based on published observations, the role of GDF11 in the process of fibrosis in different organ and pathological setups seems currently undisputable (Fig. 1). Evidence suggested that GDF11 expression tend to be increased as a consequence to various types of insults in different organs and GDF11 had the ability to stimulate/activate fibroblast and promote EMT. However, the exact course of GDF11 action in the matter of pro/anti-fibrotic properties is complex, probably organ dependent, not fully delineated and to some extent controversial. These controversies and dissimilarities could arise from employing different in vitro and in vivo models with varying experimental setups/procedures, and various GDF11 delivery methods and dosages. Therefore, it is of utmost importance to further extend our knowledge about the real relevance of GDF11 in fibrotic processes. There is a critical need for epidemiological research which can address and validate observed in vivo and in vitro studies, especially given the current pharmaceutical investments to develop GDF11–based anti-aging strategies. Therefore, it is of utmost importance to identify potential adverse effects of the GDF11 supplementation at the population level. We are just making first steps in a long and challenging path to elucidate the real effects of "youth" GDF11 in this process.

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