Insulin-Like Growth Factor Binding Proteins-3 and -5: Central Mediators of Fibrosis and Promising New Therapeutic Targets

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Abstract: Fibrosis involves an orchestrated cascade of events including activation of fibroblasts, increased production and deposition of extracellular matrix components, and differentiation of fibroblasts into myofibroblasts. Epithelial-mesenchymal cross-talk plays an important role in this process, and current hypotheses of organ fibrosis liken it to an aberrant wound healing response in which epithelial-mesenchymal transition (EMT) and cellular senescence may also contribute to disease pathogenesis. The fibrotic response is associated with altered expression of growth factors and cytokines, including increased levels of transforming growth factor-β (TGF-β) and the more recent observation that increased levels of several insulin-like growth factor binding proteins (IGFBPs) are associated with a number of fibrotic conditions. IGFBPs have been implicated in virtually every cell type and process associated with the fibrotic response, making the IGFBPs attractive targets for the development of novel anti-fibrotic therapies. In this review, the current state of knowledge regarding the classical IGFBP family in organ fibrosis will be summarized and the clinical implications considered.

Keywords: Extracellular matrix, fibrosis, IGFBP, senescence, systemic sclerosis, idiopathic pulmonary fibrosis.

INTRODUCTION

Human Insulin-like Growth Factor Binding Proteins (IGFBPs) are a family of circulating proteins which bind Insulin-like Growth Factors-I and II (IGF-I and IGF-II) with high affinity, thereby prolonging the half-life of IGFs as well as modulating their availability and activity. In addition to their IGF-dependent actions, the IGFBPs also exert IGF-independent biological effects that involve neither binding of IGFs nor modulation of the IGF receptor (reviewed in [1-6]).

There are six “classical” IGFBPs, designated IGFBP-1 through IGFBP-6, with highly conserved N-terminal and C-terminal regions flanking non-conserved central domains. Despite structural similarities and binding of IGFs, the human IGFBPs have diverse functional properties including variable binding to the extracellular matrix and differing posttranslational modifications including glycosylation and phosphorylation. These properties contribute to IGFBP bioavailability through mechanisms such as altered IGF binding affinity or protection of IGFBPs from proteolytic digestion by IGFBP-specific proteases (reviewed in [1, 2, 4-6]). The IGFBP superfamily also includes several IGFBP-related proteins (IGFBP-rP) that share homology with the IGFBPs within the N-terminal domains, but lack the highly conserved C-terminal region and bind IGFs with lower affinity (reviewed in [2, 5]).

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EXPRESSION PATTERNS AND BIOLOGICAL FUNCTIONS OF IGFBPS

Most cell types produce one or more members of the IGFBP family, and cell-specific IGFBP expression profiles result in distinct patterns of IGFBPs in biological fluids, tissues and organs (reviewed in [7, 8]). The liver is the major source of circulating IGFs and IGFBPs (reviewed in [3]). Hepatocytes synthesize IGFBP-1, -2 and -4 and hepatic Kupffer cells synthesize IGFBP-2 and -3 [9].

IGFBP-3 is the major circulating carrier protein for IGFs and is also a potent anti-proliferative factor at the cellular level, functioning both through cell cycle blockade and induction of apoptosis (reviewed in [10]). IGFBP-5 is the most conserved of the IGFBPs. Only IGFBP-3, -5 and -6 have been demonstrated to possess nuclear localization signals (NLS) and are able to translocate to and localize in the nucleus through an importin-mediated mechanism [11-13]. IGFBP-3 NLS interacts most strongly with importin-β, IGFBP-6 NLS with importin-α, and IGFBP-5 NLS binds both importins with roughly equivalent affinity [11, 12].

IGFBPs exert cell- and tissue-specific effects and their expression patterns and concentrations are known to vary in a number of pathological states, including fibroproliferative conditions (reviewed in [14, 15]). While the majority of what is known about the IGFBP family has been described in cancer and immortalized cell lines, these effects do not necessarily reflect IGFBP functions in primary non-malignant cells.

IGF BINDING PROTEINS AS MEDIATORS OF ORGAN FIBROSIS

In contrast to normal tissue repair and maintenance, organ fibrosis results when excessive fibroblast activation
leads to deposition of extracellular matrix components and fibroblasts differentiate into contractile myofibroblasts. Despite the fact that fibrosis is a significant cause of morbidity and mortality that can affect any tissue and organ system, there currently are no FDA-approved anti-fibrotic therapies. Identification of druggable targets through a better understanding of the complex biology of fibrosis is of paramount importance.

The fibrotic response is also associated with increased expression of various growth factors and cytokines, including transforming growth factor-β1 (TGF-β1) and connective tissue growth factor (CTGF) (reviewed in [16]). More recently, altered IGFBP expression has also been described in a variety of fibroproliferative conditions. Thus, a better understanding of extracellular matrix regulation by the IGFBPs holds promise for the development of novel anti-fibrotic therapies. While this goal has yet to be realized, significant progress has been made using animal models of organ fibrosis, ex vivo organ culture, and in vitro cell culture systems.

**Skin Fibrosis**

Fibroproliferative disorders of the skin include hypertrophic and keloid scar formation and the classic skin thickening associated with localized and systemic sclerosis (SSc). Keloids are benign but disfiguring dermal tumors that result from aberrant wound-healing and are unique to humans. In contrast to hypertrophic scars, which develop within the boundaries of the original wound and eventually stabilize or regress, keloids grow continuously and invade beyond the original wound margins [17]. Multiple microarray studies have demonstrated upregulation of several of the IGFBP genes in keloid versus normal scar fibroblasts [18-21], including upregulation of IGFBP-3 when cells were cultured in the presence of hydrocortisone [18]. At the protein level, IGFBP-5 is increased in fibroblasts cultured from keloid nodules and in vivo in proliferative keloid tissue [22]. Using a fibroblast-keratinocyte co-culture system, Phan and colleagues demonstrated complex regulation of several IGFBPs in normal versus keloid-derived fibroblasts [23]. They noted increased IGFBP-3 mRNA and secreted protein when normal skin fibroblasts were cultured with keloid-derived keratinocytes, but interestingly observed reduced IGFBP-3 levels from keloid-derived fibroblasts cultured under identical conditions. Addition of recombinant human IGFBP-3 to the culture media inhibited proliferation of keloid-derived fibroblasts, although the authors do not comment on whether extracellular matrix production was affected. These observations led Phan and colleagues to propose modulation of IGFBP-3 as a potential therapy for keloids.

We have described increased expression of IGFBP-3 and -5 in primary cultures of fibroblasts from the affected skin of patients with SSc [24, 25]. In support of a mechanistic link between the IGFBPs and the development of fibrosis, we have demonstrated that IGFBP-3 and IGFBP-5 induce a fibrotic phenotype in fibroblasts in vitro [26] and that IGFBP-5 triggers dermal fibrosis in mice in vivo [27]. Using a novel ex vivo human skin organ culture model optimized in our laboratory, we have demonstrated that both IGFBP-3 and IGFBP-5 cause sustained increases in dermal and collagen bundle thickness in human skin explant culture [25]. The pro-fibrotic effects of IGFBP-3 and IGFBP-5 on normal skin do not generalize to all IGFBP family members, as IGFBP-4 does not result in dermal fibrosis and thickening in the same model [25].

**Allergic Airway Remodeling and Pulmonary Fibrosis**

Increased levels of IGFBP-3 and -5 have been demonstrated in several fibrotic pulmonary diseases [26, 28]. In a subset of patients with asthma, irreversible fibrotic lung remodeling may result from airway remodeling that includes characteristic subepithelial fibrosis and myofibroblast hyperplasia. Cohen and colleagues have demonstrated that the growth-stimulatory effect of TGF-β1 on human airway smooth muscle cells in vitro requires IGFBP-3 [29]. We have demonstrated that IGFBP-3 is increased in vivo in the airway epithelium of patients with asthma and that the concentration of IGFBP-3 in bronchoalveolar lavage fluid is increased after allergen challenge [28]. These observations suggest that IGFBP-3 secreted by the epithelium may act locally on airway fibroblasts and contribute to allergic airway remodeling in susceptible individuals.

Pulmonary sarcoidosis is a granulomatous disorder of unknown etiology that in a minority of affected individuals progresses to irreversible fibrotic lung remodeling [30]. Immunoblot analysis of bronchoalveolar lavage fluid from individuals with stage III sarcoidosis versus normal controls demonstrated increased IGFBP-3 [31]. It remains to be determined whether IGFBP expression profiles in stages I, II or III sarcoidosis may predict which individuals will go on to develop stage IV fibrotic disease. It is also unknown whether increased IGFBP-3 contributes directly to the development of sarcoid-associated pulmonary fibrosis, which would make this an attractive target for future therapies.

Idiopathic Pulmonary Fibrosis (IPF) is a progressive fibrotic disease of unknown etiology. Increased IGFBP-3 has been demonstrated in the bronchoalveolar lavage fluid of individuals with IPF [32]. Both IGFBP-3 and IGFBP-5 are increased in IPF lung tissue as well as in primary fibroblasts cultured from these tissues [26]. In support of a mechanistic link between the IGFBPs and pulmonary fibrosis, we have demonstrated that IGFBP-5 causes pulmonary fibrosis in mice [27] and interestingly also induces migration of primary human lung fibroblasts in vitro [33].

In addition to the hallmark skin thickening, systemic sclerosis is also associated with internal organ fibrosis. Based upon observations in SSc skin fibrosis and in IPF, it is reasonable to postulate that altered IGFBP expression also contributes to the development of SSc-associated pulmonary fibrosis. We have recently reported increased expression of several members of the IGF/IGFBP family in lung disease associated with SSc [34]. We have also observed that there is increased expression of the extracellular matrix glycoprotein Tenascin-C (TN-C) in vivo in lung tissue from individuals with SSc-associated pulmonary fibrosis versus normal human lung tissue [35]. Furthermore, IGFBP-3 induces TN-C production in primary human lung fibroblasts. Although TN-C and IGFBP-3 do not co-localize in individual cells, TN-C expression is detected in a subepithelial distribution around distal airways of SSc in regions underlying IGFBP-3-expressing epithelial cells [35]. This suggests that IGFBP-3...
secreted from distal airway epithelial cells may act locally on resident fibroblasts to increase extracellular matrix deposition and contribute to the development of fibrosis.

Gastrointestinal and Hepatic Fibrosis

The gastrointestinal tract is involved in a significant majority of patients with systemic sclerosis [36]. Based upon the association between IGFBP-3 and -5 and SSc-associated skin and pulmonary fibrosis, it is reasonable to hypothesize that the IGFBPs may be aberrantly expressed in the GI tract. This remains an unanswered question in the literature.

In Crohn disease, intestinal stricture formation affects approximately 30% of individuals and is a significant cause of morbidity [37]. IGFBP-5 is highly expressed in inflamed and fibrotic versus normal-appearing intestine in an experimental model of inflammatory bowel disease [38, 39] and in patients with Crohn Disease [40]. More recently it was reported that expression of IGFBP-3 mRNA and protein are significantly increased in smooth muscle cells isolated from intestinal strictures versus non-strictured, histologically normal resection margins from Crohn disease patients [41].

In the injured liver, activated hepatic stellate cells can differentiate into myofibroblasts that are responsible for fibrosis and ultimately cirrhosis. Comparison of the transcriptionsomes of quiescent, activated and transdifferentiated human hepatic stellate cells in vitro revealed that the expression of only a minority (less than 5%) of genes changed significantly, including induction of IGFBPs-3, -4, -5 and -6 with IGFBP-5 demonstrating the most dramatic increase [42]. The authors validated this observation in vivo in a mouse model of liver fibrosis, in which RT-qPCR analysis demonstrated a 10-fold up-regulation of collagen Iα1 and a 9-fold induction of IGFBP-5. In subsequent in vitro work using LX2 cells (a model for partially activated hepatic stellate cells) and human primary liver myofibroblasts, IGFBP-5 enhanced survival of both cell types via suppression of apoptosis through an IGF-independent mechanism and increased the expression of markers of fibrosis, including collagen Iα1 [43].

INTERACTIONS WITH A CLASSICAL MEDIATOR OF FIBROSIS, TGF-β, AND SIGNALING PATHWAYS

IGF binding proteins, particularly IGFBP-3 and IGFBP-5, have emerged in the literature with increasing frequency over the past two decades as important markers and mediators of organ fibrosis. Some of their actions are intertwined with classical mediators of fibrosis, such as TGF-β, whereas others are separate and distinct.

Fibroblasts and myofibroblasts are central cell types in normal wound healing as well as in the aberrant program leading to pathologic fibrosis. Myofibroblasts are mesenchymal cells that display characteristics of both fibroblasts and smooth muscle cells [44]. TGF-β1 can induce differentiation of fibroblasts into myofibroblasts through a Smad3-dependent mechanism [45]. We have demonstrated that expression of IGFBP-5 in dermal and pulmonary fibroblasts induces α-SMA and vimentin [27], suggesting that IGFBP-5 is also capable of inducing differentiation of fibroblasts into myofibroblasts. IGFBP-5 induces production of extracellular matrix by fibroblasts independently of IGF-I and via activation of MAPK signaling [46]. Additionally, we have demonstrated that early growth response (Egr)-1 is up-regulated by IGFBP-5 in a MAPK-dependent manner and is required for IGFBP-5-dependent induction of extracellular matrix production [46]. In further support of the hypothesis that IGFBP-5 promotes fibrosis through an Egr-1-mediated pathway, we have demonstrated increased Egr-1 levels in vivo in lung tissues and in vitro in primary fibroblasts of patients with IPF [46].

Treatment of primary lung fibroblasts with recombinant TGF-β1 results in a time-dependent increase in secreted IGFBP-3 protein, but not of secreted IGFBP-5 protein [26]. Direct stimulation of primary lung fibroblasts with recombinant IGFBP-3 induces production of the extracellular matrix components Tenascin-C (TN-C) and collagen Iα1, whereas silencing of IGFBP-3 inhibits TGF-β1-induced production of TN-C but has no effect on TGF-β1 induction of collagen Iα1 [35]. These observations suggest that IGFBP-3 and TGF-β regulate extracellular matrix composition through both related and independent mechanisms. In fact, we have demonstrated that increased production of TN-C by both TGF-β1 and IGFBP-3 requires the p38 mitogen-activated protein kinase (p38MAPK) pathway, although the c-Jun NH2-terminal kinase (JNK) pathway is required only by TGF-β1 [35].

The epithelial compartment is also implicated in the pathogenesis of fibrosis, and it is in the epithelium that IGFBP-5 and TGF-β have been demonstrated to have distinct effects (reviewed in [47]). It is well-recognized that TGF-β is pro-apoptotic and capable of inducing epithelial-mesenchymal transition in a subset of epithelial cells (reviewed in [14, 48]). In contrast, IGFBP-5 has been demonstrated to promote increased cell spreading, migration, and laminin production [47, 49]. Cross-talk between injured epithelium and adjacent mesenchymal cells is likely central to the pathogenesis of fibrosis, and IGFBP-5 is upstream of and may activate TGF-β [50], therefore IGFBP-5 may represent a more viable therapeutic target than TGF-β. For thoughtful and comprehensive discussions of TGF-β and IGFBP-5 in fibrosis, the reader is directed to two recent reviews by Allan et al. [50] and Sureshbabu et al. [14].

IGFBPs AS THE LINK BETWEEN SENESCENCE AND FIBROSIS

A revised vision of fibrogenesis has been prompted by the failure of immunosuppressive therapies to modify the progression of fibroproliferative disorders such as IPF and some forms of autoimmune interstitial lung disease (reviewed in [50]). One current hypothesis is that of an unregulated wound healing response [51], in which recurrent cycles of epithelial injury and repair lead to the activation, migration and transdifferentiation of mesenchymal fibroblasts and over-stimulation of this pathway results in excess deposition of extracellular matrix and fibrosis. Another related hypothesis extends this concept by linking fibrosis to senescence, proposing that repeated cycles of epithelial injury exhaust the ability of the affected epithelial cells to proliferate and they enter a state of replicative senescence. Fibroblasts then “fill in” where the epithelial cells have failed as a compensatory injury repair mechanism.

Cell senescence is somewhat broadly defined as an irreversible arrest of growth or proliferation and can be
triggered by telomere shortening or different forms of stress. Cellular senescence is associated with the aging process, and fibrosis is a well-recognized hallmark of aging in various organs. Additionally, for many fibroproliferative disorders increasing age is correlated with an acceleration of fibrosis. This is the case in IPF, which has been recognized for decades to increase in prevalence with age [52, 53] and more recently has been associated with short telomeres and with telomerase mutations in the familial form [54-58]. Interestingly, IPF is also more common in smokers [53, 59] and cigarette smoke extract has been reported to induce senescence in cultured lung fibroblasts and epithelial cells via down-regulation of Werner syndrome protein [60, 61].

Although senescent cells no longer proliferate, they do remain metabolically active and produce secreted growth factors and extracellular matrix components (reviewed in [62, 63]). IGFBP-3, -4, -5 and -6 have been reported to increase in different models of senescence. IGFBP-5 is significantly increased in human dermal fibroblasts and endothelial cells during replicative senescence [64-68]. IGFBP-3 is also increased in senescent human fibroblasts [69] and in the conditioned medium of human fibroblasts derived from older donors and from individuals with Werner syndrome of premature aging [70].

Rather than merely serving as markers of senescence, IGFBPs may play a direct role in the regulation of the senescence program. Using a human umbilical vein endothelial cell (HUVEC) model, Kim and colleagues have demonstrated that knockdown of IGFBP-5 or IGFBP-3 partially reverses senescence phenotypes in old HUVECs and that over-expression of or treatment with exogenous IGFBP-5 or IGFBP-3 induces senescence in young HUVECs [71, 72].

The relationship between IGFBPs, fibrosis, and senescence likely applies to subsets of fibrotic disorders and cannot be generalized at this point as IGFBP levels have not been evaluated in a comprehensive manner in all fibrotic disorders and affected organs.

**CLINICAL IMPLICATIONS: IGFBPs AS TARGETS FOR ANTI-FIBROTIC THERAPY**

Significant attention has been turned to targeting the major pro-fibrotic cytokine, TGF-β1, in an attempt to develop novel anti-fibrotic therapies. Indeed, TGF-β1 contributes to many fibrotic processes including fibroblast differentiation into myofibroblasts, increased deposition of extracellular matrix, and epithelial-mesenchymal transition (reviewed in [73]). Unfortunately, this approach has not yet met with significant success, and it is likely that multi-target combinatorial approaches will be required. Furthermore, the biology of the TGF-β family is complex and plays an important role in maintenance of homeostasis in multiple cellular compartments, including the immune system. In certain contexts TGF-β acts as a tumor suppressor. For example, loss of TGF-β signaling in fibroblasts has been implicated in the development of adjacent epithelial neoplasms in an animal model [74]. Thus, there is a need to explore alternative targets for anti-fibrotic therapy.

Altered IGFBP expression has also been described in virtually every cell type and biologic process implicated in the pathogenesis of fibrotic disease. IGFBP-5 has been implicated in epithelial apoptosis, epithelial-mesenchymal transition, fibroblast activation and transdifferentiation to the myofibroblast phenotype, and cellular senescence (reviewed in [50]). IGFBP-5 is upstream of and may activate TGF-β [50]. TGF-β1 growth inhibition and apoptosis can be mediated through IGFBP-3, and IGFBP-3 mRNA and protein expression is stimulated by TGF-β1 in several cell types [75-77]. IGFBP-3 has also been reported to activate TGF-β receptors and in some cases to directly inhibit cell growth independently of TGF-β1 [78]. The IGFBPs serve these and likely additional functions that are both complementary to and independent of TGF-β, and therefore represent attractive targets for the development of novel anti-fibrotic therapies. These therapies could conceivably involve silencing these IGFBPs, interrupting their cellular uptake and/or translocation, blocking their interaction with downstream effectors such as Egr-1, introducing a decoy receptor for the secreted forms of the proteins, or identifying components of potential negative regulatory loops that can be used for blocking the pro-fibrotic effects of IGFBP-3 and -5. Development of small molecule inhibitors of IGFBP action is another potential therapeutic modality that is currently under investigation. These approaches in combination with TGF-β targeting therapies, such as the inhibition of TGF-β activation and the neutralization of interacting integrins, hold much promise for the treatment of organ fibrosis.

**CONCLUSIONS**

Fibrotic diseases have been described in virtually every tissue and organ system and cause significant morbidity and mortality. There currently are no FDA-approved anti-fibrotic therapies, highlighting the need for a better understanding of the molecular mechanisms of fibrosis and the development of novel classes of therapeutic agents. The IGFBPs regulate multiple steps of the fibrotic cascade and thus hold great promise as drug targets in the continuing quest to cure fibrosis.

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**CONFLICT OF INTEREST**

The authors have no conflicts of interest to disclose.

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