Fibrosis is a nonphysiological scarring process, which is associated with excessive deposition of extracellular matrix (ECM) and which leads to impairment of organ function. Progression of chronic diseases in parenchymal organs such as liver, kidney, heart, and lung is associated with fibrosis, and the fibrotic process plays a principal role in the organs’ detriment. Fibrosis also plays an important role in the skin (from hypertrophic scars to sclerodermia), inflammatory bowel disease (causing strictures), in joints (rheumatoid arthritis but also joint replacement), and bone marrow (myelodysplastic syndromes). Additionally, the stroma of solid tumors can be considered fibrotic tissue (25, 26, 55). In short, fibrosis plays a role in the progression of many chronic diseases. Specific therapies to halt, or even to reverse, existing tissue fibrosis are not yet available in any organ. Because of the histomorphological similarities shared by fibrosis in all organs, the concept of common tissue fibrosis pathways that could be potential therapeutic targets in all organs is an attractive one (Fig. 1). There is ample hope that mechanistic understanding of the common fibrosis pathways will lead to development of drugs that are effective in all of these tissues in the future. Here we review common and organ-specific pathways of tissue fibrosis.

Activated Fibroblasts

Excessive deposition of ECM fibers is the eponymous lesion of fibrosis, and since Virchow’s work in the 19th century it is known that fibroblasts are the principal source of ECM in fibrosis (115). For this reason, fibroblasts are a focus of attention in fibrosis research and the inhibition of fibroblast-mediated ECM synthesis is a principal goal of antifibrotic therapeutic approaches. Nevertheless, fibroblasts have remained relatively elusive in molecular terms and, as a consequence, therapies to specifically target fibroblasts in fibrosis are not yet available (55). While fibroblasts are easy to culture as spindle-shaped cells and are widely utilized in biomedical sciences, their identification in vivo is challenging (55). Traditionally, fibroblasts in vivo were identified in the light microscope based on their location (within connective tissue) and their spindle-shaped cytoplasm and in electron microscopy based on their leaflet-like cytoplasm, prominent endoplasmatic reticulum, and prominent cytoskeleton (55, 131). In fibrosis, the principal source of collagen is “activated fibroblasts” (reflecting their increased biosynthetic and proliferative activities). Phenotypically, activated fibroblasts are characterized by a pronounced rough endoplasmatic reticulum, stress fibers, and a large nucleus. Since the observation that the majority of collagen-producing fibroblasts are labeled with antibodies to the filament α-smooth muscle actin (αSMA; 55), the terms “activated fibroblasts” and “myofibroblasts” are used synonymously to refer to the fibroblasts that mediate fibrosis. However, fibroblasts are a heterogeneous, specialized cell type and it has become evident that a more distinctive view on specialized fibroblast populations, requiring specific markers, is required (55).

Fibroblasts not only differ among organs, they also display heterogeneous phenotypes within single organs (i.e., in the kidney, lipid-laden fibroblasts from medulla differ from those in the cortex; 37), they fulfill specialized functions [a subpopulation of kidney fibroblasts is the principal source of erythropoietin (74, 88), and select atrial fibroblasts are constituents of the cardiac conduction system (16, 113)], and dermal fibroblasts can be traced to their original position from the body axis based on their Hox gene code (17). Molecular analysis of fibroblasts is particularly challenging, because a common marker that is specific to all fibroblasts does not exist (55). Markers that are commonly used to identify fibroblasts in vivo [i.e., αSMA, vimentin, fibroblast-specific protein 1 (FSP1), Desmin] only detect subpopulations of fibroblasts and none of them is specific for fibroblasts (for review, see Refs. 55 and 108). Distinct contributions of these fibroblast populations to fibrosis are not yet known (55). In this regard, it is entirely unknown whether fibroblasts switch expression of their marker profile of whether detected fibroblasts are truly distinct populations. While myofibroblasts (particularly αSMA-expressing) are considered principal mediators of fibrogenesis (in the liver, ~60% of myofibroblasts actively express collagen; 42, 75), the only fibroblast population that has been mechanistically proven

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Zeisberg M, Kalluri R. Cellular Mechanisms of Tissue Fibrosis. 1. Common and organ-specific mechanisms associated with tissue fibrosis. Am J Physiol Cell Physiol 304: C216–C225, 2013. First published December 19, 2012; doi:10.1152/ajpcell.00328.2012.—Fibrosis is a pathological scarring process that leads to destruction of organ architecture and impairment of organ function. Chronic loss of organ function in most organs, including bone marrow, heart, intestine, kidney, liver, lung, and skin, is associated with fibrosis, contributing to an estimated one third of natural deaths worldwide. Effective therapies to prevent or to even reverse existing fibrotic lesions are not yet available in any organ. There is hope that an understanding of common fibrosis pathways will lead to development of antifibrotic therapies that are effective in all of these tissues in the future. Here we review common and organ-specific pathways of tissue fibrosis.

epigenetics; fibroblasts; fibrosis; TGF-β

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to contribute to fibrogenesis is FSP1$^+$ fibroblasts (ablation of FSP1$^+$ fibroblasts in FSP1-tk transgenic mice ameliorates kidney fibrosis; 53). The field is further complicated by the fact that fibroblasts display different phenotypes and proliferative capacities with age, and it has been proposed that fibroblasts can differentiate along phenotypic stages similar to myeloid cells (9). Overall, analysis of fibroblasts is hindered by the lack of sufficient markers (particularly surface markers), and the evolving fibroblast heterogeneity has possibly contributed to the failure to develop fibroblast-specific therapeutic targets.

While there is a consensus that (activated) fibroblasts are the principal source of collagen and prominent mediators of fibrogenesis, it is not yet clear where these activated fibroblasts originate from (the fibroblast morphology does not offer known clues about their origin). In the traditional view, activated fibroblasts in healing wounds and fibrotic lesions derive from the resident fibroblasts through activation and proliferation. Exclusive contribution of this was first challenged by the observation that bone marrow-derived fibrocytes are recruited and contribute to fibrogenesis (15). Furthermore, epithelial cells are considered to contribute to fibroblast accumulation through epithelial-mesenchymal transition (107), vascular smooth muscle cells and pericytes have been reported to shed off vessels to become connective tissue fibroblasts (72, 100), and endothelial cells contribute to fibroblast accumulation through endothelial-mesenchymal transition (EndMT; 128). Overall, assessment of the contributions of these mechanisms differs widely among studies (which utilized different fibrosis models, fate mapping strategies, and marker analysis). While it is likely that all mechanisms contribute to fibroblast accumu-
lation under experimental conditions, their contribution to fibroblast accumulation (percentage-wise) and fibrogenesis may differ substantially among organs, and disease models and further studies will be required (12, 14, 50, 54, 59, 62, 70, 87, 92, 97, 101, 127, 136, 140; Fig. 2). It is difficult to translate findings that were generated in transgenic reporter mice to human pathologies, because, in the absence of reporter genes, fate mapping studies are not yet feasible. For example, in the kidney, there is a strong correlation of expression of epithelial-mesenchymal transition (EMT) markers within epithelial cells and progression of fibrogenesis (39, 43), but the ultimate fate of the cells cannot be assessed.

Microvasculature and Hypoxia

Fibrotic tissues in general appear macroscopically pale, reflecting microvascular rarefaction and diminished perfusion. As a result of decreased microvasculature, fibrotic tissues are often chronically hypoxic, which directly contributes to fibrogenesis through HIF1α-mediated signaling (23, 44, 77). Mechanistically, fibrogenesis is characterized by an impaired capacity to regenerate (or form new) vessels. Fibrosis is often associated with decreased VEGF levels, and upregulation of endogenous molecules with antiangiogenic activity and VEGF administration has been shown to be beneficial in experimental models of organ fibrosis (18, 51, 73, 125). How the endothelial cells are lost in the first place, however, is not clear yet, as low incidence of endothelial-cell apoptosis does not add up with the severity of microvascular rarefication (118, 125). EndMT is an additional mechanism that contributes to depletion of microvessels (94, 127–129). EndMT was originally observed in cardiac development, where mesenchymal cells (which form the atrioventricular cushion, the primordia of the valves and septa of the adult heart) are derived from the endocardium by an EndMT (27, 71, 83). We demonstrated that in the context of fibrosis of the adult heart, endothelial cells acquire a mesenchymal phenotype [in response to transforming growth factor-β1 (TGF-β1), contributing to rarefaction of the microvasculature and fibroblast accumulation (128). Inhibition of EndMT ameliorated experimental fibrosis in heart and kidney (70, 128, 129). In summary, microvascular injury is an important common constituent of organ fibrosis and a promising therapeutic target.

Sterile inflammation. Fibrosis in most cases is associated with inflammation. While the accompanying infiltrate can be reflective of a specific immune response to an underlying infection (i.e., fibrosis due to viral hepatitis or schistosomiasis in the liver or due to bacterial pyelonephritis in kidney), the prototypical fibrosis is associated with a sterile inflammation, likely in response to occurring cell death (5, 104). If inflammation is a facultative constituent of fibrogenesis or if the fibroproliferative response and inflammatory response are separate entities is a matter of debate and reviewed elsewhere (82, 121). Of note, antiinflammatory regimens are remarkably ineffective to halt fibrogenesis in clinical application, arguing that the fibroproliferative response is (at least in advanced stages) an independent process from the inflammatory reaction.

Parenchymal Injury

Per definition a scar substitutes for lost parenchymal cells, and fibrosis is invariably associated with progressive loss of the affected organ’s parenchyma (i.e., hepatocytes in the liver, nephrons in kidney, cardiomyocytes in heart). While parenchymal cells possess the capacity to regenerate per se, such regenerative ability is lost during fibrosis, triggering formation of the fibrotic scar (3, 6, 102, 124). In this regard, cross talk of the injured epithelium with fibroblasts and inflammatory cells is of foremost relevance for triggering the fibrotic process. In addition to release of profibrotic metabolites (i.e., reactive

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Fig. 2. Origins of activated fibroblasts. Fibrosis is associated with accumulation of collagen-producing (activated) fibroblasts (center, multicolored). Activated fibroblasts can derive via activation and subsequent proliferation from resident fibroblasts (blue). Bone marrow-derived fibrocytes are recruited to fibrotic lesions and contribute to accumulation of collagen-producing fibroblasts (red, top left). Endothelial cells can undergo an endothelial-to-mesenchymal transition to contribute to fibroblast accumulation (green, top right). α-Smooth muscle actin (αSMA)-positive vascular smooth muscle cells and pericytes have been proposed to shed off existing vessels and to contribute to accumulation of myofibroblasts (pink, bottom right). Epithelial cells can undergo an epithelial-to-mesenchymal transition and contribute to fibroblast accumulation (yellow, bottom left).
oxygen species), injured parenchymal cells govern fibrogenesis through secretion of chemokines and growth factors. The prototypical profibrotic growth factor, which plays a role in fibrogenesis in all organs, is TGF-β.

Transforming Growth Factor-β

TGF-β was originally identified as a factor that induces the capacity of anchorage-independent growth, a hallmark of malignant transformation, in embryonic kidney fibroblasts (95). The prominent role of TGF-β in fibrogenesis was first observed when subcutaneous injection of purified TGF-β induced fibrotic lesions at the injection site and was further corroborated by the observation that neutralization of TGF-β with antiserum ameliorated experimental fibrosis in the kidney, and in heart and liver as well (11, 20, 64, 96). TGF-β is overexpressed in all fibrotic tissues, and it induces collagen production in cultured fibroblasts irrespective of their origin (1, 45, 60, 99). To our knowledge, the pivotal relevance of TGF-β for tissue fibrosis has not yet been disputed in any organ, making TGF-β a principal target for potential antifibrotic therapies (66). However, fibrosis (i.e., in the liver) can occur independent of TGF-β, for example mediated through an IL-13-mediated pathway (56).

Genetics and epigenetics. During the past three decades considerable progress was made in identifying pathways that orchestrate tissue fibrosis. This knowledge, however, still offers little insight to explain the vastly different progression rates of fibrosis in individual patients with common underlying diseases and comorbidities. The root of the problem, i.e., why profibrotic pathways are more active in one patient than another, can be conceptually explained by their distinct genetic and epigenetic backgrounds (120). As it is well established that the genetic background of mice and rats (or other model organisms) affects the progression of fibrosis, it is highly likely that genetic polymorphisms equally impact fibrogenesis in human patients. However, it is proving to be difficult to link genetic polymorphisms to distinct disease progression rates. Numerous studies have been undertaken to explore the link between TGF-β—the prototypical fibrotic growth factor—and fibrosis susceptibility in a biased manner. Overall, several studies demonstrated association between TGF-β polymorphisms in kidney, lung, liver, and skin keloids, whereas multiple other studies failed to document such association (40, 57, 58, 76, 86, 91, 93, 110, 123). Most studies focused on single-nucleotide polymorphism (SNP) rs1982073, a T-to-C transition of the 29th nucleotide in the coding sequence, which encodes for a suppressor of the Ras oncoprotein to be selectively hypermethylated in fibrotic kidney fibroblasts (10). Since Rasall is also hypermethylated in activated hepatic stellate cells, the speculation that Rasall epigenetic silencing is part of a common fibrotic program is an attractive concept (112). In addition to impacting fibrotic fibroblast activation, epigenetics plays a role in the progressive loss of the parenchymal regenerative capacity (i.e., through histone modifications in tubular epithelial cells which cause cell-cycle arrest) or modulation of inflammatory cells. While epigenetic modifications in general are acquired in response to environmental stimuli, evidence is increasing that epigenetics also plays a role in determining the inherited susceptibility to develop fibrosis. For example, multigenerational transmittance of histone modifications at TGF-β1 and PPARγ loci can lower the susceptibility to develop liver fibrosis (138).

Organ-Specific Aspects of Fibrosis

While fibrosis follows similar pathways across different organs, justifying the term “tissue fibrosis,” each organ has unique features of fibrosis as well. Unique, organ-specific features of fibrosis are discussed from our personal experience below (Table 1).

Skin fibrosis. Fibrosis of the skin is the integral component of a variety of heterogeneous disorders including hypertrophic scars, keloids, and scleroderma (85). Hypertrophic scar formation is the best established (earliest known documentation of excessive scarring dates back to 1700 BC in The Smith papyrus), most common (an estimated 50 million patients suffer from excessive scar formation following surgery or trauma annually in developed countries) prototypical fibrotic lesion (35). As opposed to physiological scars, hypertrophic scars are raised above skin level (but are confined to the original wound) and they are often associated with pain and itching and cause disfigurement (35). In contrast, keloids are thick scar tissues, which “have escaped the boundaries of the original wound” (35). Keloids occur in all races, but black Africans are partic-

<table>
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<th>Table 1. Fibrogenesis in kidney, liver, heart, and lung</th>
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<td>Tennessee and many other states</td>
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<td>Spontaneous repair of acute injury</td>
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<td>Spontaneous repair of fibrotic lesions</td>
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<tr>
<td>Association of fibrosis with infection</td>
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<td>Fibrosis leading to cancer</td>
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Albeit similar appearance of fibrotic lesions, tissue fate differs substantially among organs. Liver displays by far the best regenerative capacity. Liver cirrhosis is considered a precancerous stage, and an association between pulmonary fibrosis and cancer exists but not in kidney and heart. Liver fibrosis is mostly due to viral infection; in kidney, heart, and lung, infections are not a common cause of fibrosis.
ularly susceptible. Unlike these trauma-associated localized fibrotic lesions, skin fibrosis (then referred as scleroderma) is the leading manifestation of systemic sclerosis, a rare connective tissue disease, which manifests with widespread fibrosis of the skin, but also lungs and other internal organs such as heart and kidney and widespread vasculopathy (38). Furthermore, scleroderma can manifest locally (then referred to as localized scleroderma), often in context with drug or toxin exposure, radiation, or metabolic disorders. The scleroderma, which is associated with systemic sclerosis, is particularly intriguing, as it is the leading manifestation of a systemic fibrotic syndrome, possibly highlighting the common pathways of tissue fibrosis (67, 78, 114). For example, analysis of systemic sclerosis reiterated the common impact of TGF-β1 on fibrogenesis.

Liver fibrosis. The liver stands out from all other tissues with regard to its capacity to regenerate fibrotic lesions, and based on our experience with animal models it is not surprising that reports of reversibility of fibrotic lesions in humans originated from observations of liver patients (Table 2). Because of the high prevalence of hepatitis virus infections, liver cirrhosis may well be the clinically most relevant form of tissue fibrosis worldwide. However, the strong association of infections and liver fibrosis suggests that other pathways (as opposed to the mostly noninfectious causes in other organs) may be at play in the liver. Furthermore, the liver has a unique capacity to regenerate per se as is known since the myth of Prometheus. As a result of the unique dynamics of liver fibrosis, use of Picro Sirius Red Staining or transmission electron microscopy to identify more cross-linked (and thus more stable) collagen fibers is especially useful for fibrosis assessment in the liver. The liver is also unique in the regard that stellate cells (neurocrest-derived, lipid-laden cells) are a major source of myofibroblasts (through a process often referred to as transdifferentiation) as opposed to the “activation” of “common” fibroblasts (which are also present as “perivascular fibroblasts”) in the liver.

Cardiac fibrosis. The heart stands out with regard to its distinct types of fibrotic lesions. Anatomically, “perivascular fibrosis” can be distinguished from interstitial (“endomyocardial”) and subendocardial fibrosis. So-called endocardial fibroelastosis (EFE) is a unique form of fibrosis found in newborns with congenital heart defects, which is characterized by subendocardial deposition of elastic fibers (29, 34, 63). Unlike in other organs discussed here, the cardiac parenchymal cells are muscle cells (cardiomyocytes) and not epithelial cells, displaying a very limited regenerative capacity. As a consequence of the absent regenerative ability of cardiomyocytes, extensive scarring (“physiological fibrosis”) is necessary to seal the heart following myocardial infarction, and the distinction between “physiological fibrosis” and “pathological fibrosis” is more evident in the heart than in any other tissue (19, 130). Cardiac fibroblasts are unique, as they also function as mechanoelectrical transducers (16, 113). Hence, the physiological role of fibroblasts (the most abundant cell type in the heart) is more obvious than in any other organ discussed here. Among all organs, assessment of fibrosis in live animals (or patients for that matter) is most challenging, because only functional measurement of diastolic dysfunction (disturbed relaxation of the heart due to increased stiffness) correlates with fibrosis, whereas biochemical blood tests that correspond with heart fibrosis are not available. As a result, cardiac fibrosis is still less appreciated in the clinical setting compared with fibrosis in liver and kidney, for example.

Kidney fibrosis. In the kidney we found the disparity between the renal capacity to regenerate severe acute injury and the irreversibility of fibrotic lesions to be most striking: while denuded tubular basement membranes can be repopulated without scar formation, kidney fibrosis without treatment is really irreversible. One reason may be the complexity of kidney architecture. With regard to kidney fibrosis, glomeruli and tubulointerstitium are viewed as separate entities: fibrosis of glomeruli (referred to as “glomerulosclerosis”) typically precedes the classic fibrosis involving the connective tissue between the tubules. Compared with the heart, fibroblasts in the normal kidney are relatively scarce. A subset of kidney fibroblasts is the principal source of erythropoietin in the body, possibly explaining the link between fibrosis and anemia in chronic kidney disease (erythropoietin expression is lost when fibroblasts become activated myofibroblasts; 7, 74, 88).

Lung fibrosis. Fibrosis of the lung causes primarily restrictive ventilator defects. While the fibrosis that is associated with most chronic lung pathologies (i.e., obstructive pulmonary diseases, emphysema) is not the primary determinant of a patient’s prognosis, generalized progressive pulmonary fibrosis is particularly devastating (84, 119). The two most intriguing forms are idiopathic pulmonary fibrosis and the pulmonary fibrosis as part of the systemic sclerosis (scleroderma) manifestation, leading to death of affected patients within two to six years (81). Compared with fibrotic lesions in other organs, relatively mild fibrotic lesions are fatal. While both idiopathic pulmonary fibrosis and systemic sclerosis-associated interstitial lung disease (SSc-ILD) are considered to follow similar pathways, antiinflammatory treatment is the standard for SSc-ILD, whereas antiinflammatory therapy rather worsens the prognosis of idiopathic pulmonary fibrosis (81, 121).

Implications of Antifibrotic Therapies for Common Pathways of Fibrogenesis

While the concept of common druggable organ fibrosis pathways is highly attractive, it is proving difficult to single out such relevant common pathways. As discussed above, “organ fibrosis” is not a monocausal disease, but rather an umbrella for a collection of chronic pathologies in multiple organs that are dependent on diverse and complex interactions of various cell types. Owing to the complexity and variability of organ fibrosis, it is difficult to establish a hierarchy according to relevance of involved mechanisms, possibly contributing to the failure to establish antifibrotic therapies for clinical application as yet. Nevertheless, numerous strategies have been proven to be successful in multiple models of organ fibrosis and there is additional information that can be gathered from failed clinical trials, to determine which pathway is truly relevant, and which is not. Among the most promising strategies to inhibit progression of fibrogenesis are modulation of the accompanying inflammation, pharmacological prevention of ECM deposition, correction of the altered epigenome, and the most obvious—inhbition of profibrotic growth factors (for review see Ref. 122). In this regard, inhibition of TGF-β1 ameliorated fibrogenesis in fibrosis models involving skin, liver, kidney, lung, and heart and clinical trials with neutralizing antibodies are underway involving systemic sclerosis, myelofibrosis and diabetic nephropathy (122). However,
Table 2. Specific aspects of organ fibrosis

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<tr>
<th>Kidney</th>
<th>Liver</th>
<th>Heart</th>
<th>Lung</th>
<th>Skin</th>
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<tr>
<td><strong>Top 3 etiologies</strong></td>
<td>Diabetes mellitus</td>
<td>Viral hepatitis</td>
<td>Hypertension</td>
<td>Idiopathic pulmonary fibrosis (IPF)</td>
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<td></td>
<td>Hypertension</td>
<td>Alcohol-induced</td>
<td>Coronary artery disease</td>
<td>Occupational diseases</td>
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<td>Glomerulonephritis</td>
<td>Nonalcoholic-steatohepatitis (NASH)</td>
<td>Aortic stenosis</td>
<td>Sarcoïdosis</td>
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<td><strong>Epidemiology</strong></td>
<td>Prevalence of chronic kidney disease ~5% of general population (US)</td>
<td>Prevalence of liver cirrhosis: ~5–10% of general population</td>
<td>Prevalence of diastolic heart failure ~1% of the general population</td>
<td>Prevalence 0.03% of general population</td>
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<td>Prevalence of end-stage renal disease ~0.2% of general population</td>
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<td><strong>Diagnosis</strong></td>
<td>Blood tests to assess excretory kidney function (serum creatinine, BUN, GFR)</td>
<td>Blood tests to assess global liver function</td>
<td>Functional assessment of diastolic dysfunction through Doppler echocardiography or invasive measurements (i.e., LVEDP)</td>
<td>Imaging (HRCT scan, chest X-ray)</td>
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<td></td>
<td>Kidney biopsy</td>
<td>Imaging (FibroScan, ARFI, MRI)</td>
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<td>Lung biopsy</td>
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<td>Liver biopsy</td>
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<td>Spirometry (restriction and impaired gas exchange)</td>
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<td><strong>Relevant classifications of fibrosis</strong></td>
<td>Area of kidney cortex occupied by fibrotic tissue (rel. %), glomeruli viewed as separate entity (glomerulosclerosis)</td>
<td>Distinction between fibrosis (early) and cirrhosis</td>
<td>Distinction between endomyocardial and perivascular fibrosis</td>
<td>Radiographic location and appearance (central vs. peripheral; upper lobes vs. lower lobes)</td>
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<td></td>
<td>Grading for inflammatory activity</td>
<td>Imaging (FibroScan, ARFI, MRI)</td>
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<td>Lung biopsy</td>
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<td><strong>Clinical reports of regression of established fibrosis</strong></td>
<td>Regression of fibrosis in patients with diabetic nephropathy 10 yr after pancreas transplantation (31, 32)</td>
<td>Liver fibrosis regresses upon removal of the pathogen (21, 30, 49, 105, 106)</td>
<td>Sporadic reports of improved diastolic dysfunction and regression of cardiac fibrosis in patients with hypertensive heart disease upon blood pressure normalization (13)</td>
<td>Case reports of pulmonary fibrosis regression upon treatment or removal of underlying pathogens</td>
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<td>Sporadic reports of improved kidney function upon intensified ACE inhibitor therapy (103)</td>
<td>Reports of regression of cirrhosis are debated (28, 52, 90)</td>
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<td><strong>Unique features</strong></td>
<td>Kidney fibrosis causes anemia due to cessation of erythropoietin production when renal fibroblasts become activated</td>
<td>Stellate cells contribute to liver fibrosis</td>
<td>Because cardiac fibroblasts are required for electromechanic coupling, fibrosis can cause atrial fibrillation</td>
<td>Mean time of survival of patients with IPF is &lt;6 yr</td>
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ACE, angiotensin-converting enzyme; ARFI, acoustic radiation force impulse imaging; BUN, blood urea nitrogen; GFR, glomerular filtration rate; HRCT, high-resolution computed tomography; LVEDP, left ventricular end diastolic pressure.
direct inhibition of TGF-β1 is not without risk, as it possesses strong anti-inflammatory activity (TGF-β1-knockout mice display generalized inflammation) and mutations of genes encoding for constituents of the TGF-β1 signaling pathway can be directly linked to gastrointestinal cancers.

In our experience, analysis of the antifibrotic potential of bone morphogenetic protein-7 (BMP7), a morphogen with TGF-β1-neutralizing activity, provided valuable insights into the common, functionally relevant pathways of organ fibrosis. BMP7 (synonym osteogenic protein-1, OP1) is the prototypical member of the family of bone morphogenetic proteins, which, as members of the TGF-β superfamily, signal through activation of activin-like kinase receptors and Smad transcription factors (135, 137). Our own interest in BMP7 stems from screening experiments in which we identified BMP7 as a potent inhibitor of TGF-β1-induced epithelial-mesenchymal transition (EMT). In subsequent studies, our group and others found administration of recombinant BMP7 to inhibit fibrosis in rodent fibrosis involving kidney (24, 47, 79, 109, 116, 132, 133), liver (61, 136), heart (48, 128), and colon (33), allowing for identification of mechanisms that are relevant for fibrogenesis across all organs. BMP7 inhibits ECM production by fibroblasts (132), decreases chemokine release by injured kidney epithelial cells (36), and inhibits EMT and EndMT programs (128, 133), reaffirming that these TGF-β1 signaling-controlled events are relevant common fibrosis pathways.

Future Directions - Reversal of Fibrosis

Deemed unthinkable a decade ago, several preclinical and clinical studies suggested that fibrosis cannot only be stopped, but that regeneration of fibrotic organs is possible. The most obvious evidence for regression of fibrotic lesions is the remodeling that occurs during maturation of hypertrophic scars. The strongest evidence for reversal of fibrosis involving parenchymal internal organs was provided in the liver, where several clinical studies reported resolution of fibrosis upon successful treatment of underlying hepatitis infections (30, 49). Regression of kidney fibrosis was reported in patients with underlying diabetic nephropathy upon successful pancreas transplantation (31, 32). Numerous studies reported possible regression of established fibrosis in animal models of fibrogenesis. Common to all reports of reversed fibrosis is that supplementation of matrix-degrading compounds was not necessary, suggesting that fibrotic ECM is turned over and that endogenous mechanisms for removal of deposited ECM exist (i.e., through macrophages). Furthermore, it is becoming evident that regeneration of the chronically injured parenchyma needs to be a cornerstone of potential fibrosis-reversing strategies. Currently, there are three principal strategies emerging to regenerate lost parenchyma: the best established strategies are cell-based approaches in which pluripotent progenitor cells are provided to repair injured organs (4, 8, 22, 68, 111). Other strategies are to stimulate the endogenous regenerative capacity. In this regard, supplementation of morphogens such as BMPs or Wnt proteins, which are believed to recreate the embryonic microenvironment, have been proven to be promising in preclinical studies (41, 133, 134). A third strategy involves correction of the aberrant epigenetics of chronically injured cells, to possibly rescue their physiological regenerative capacity (10, 124).

In summary, organ fibrosis is a rapidly evolving field and there is reason for optimism, that vast improvements that were made in deciphering underlying molecular mechanisms will finally translate to effective antifibrotic therapies. Tissue-specific aspects of fibrogenesis, which are needed for understanding the common features of organ fibrosis, are discussed in further detail in this THEME series.

REFERENCES


Tissue Fibrosis


