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NADPH Oxidase Inhibition in Fibrotic Pathologies

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Abstract

Significance: Fibrosis is a stereotypic, multicellular tissue response to diverse types of injuries that fundamentally result from a failure of cell/tissue regeneration. This complex tissue remodeling response disrupts cellular/matrix composition and homeostatic cell–cell interactions, leading to loss of normal tissue architecture and progressive loss of organ structure/function. Fibrosis is a common feature of chronic diseases that may affect the lung, kidney, liver, and heart.

Recent Advances: There is emerging evidence to support a combination of genetic, environmental, and age-related risk factors contributing to susceptibility and/or progression of fibrosis in different organ systems. A core pathway in fibrogenesis involving these organs is the induction and activation of nicotinamide adenine dinucleotide phosphate oxidase (NOX) family enzymes.

Critical Issues: We explore current pharmaceutical approaches to targeting NOX enzymes, including repurposing of currently U.S. Food and Drug Administration (FDA)-approved drugs. Specific inhibitors of various NOX homologs will aid establishing roles of NOXs in the various organ fibroses and potential efficacy to impede/halt disease progression.

Future Directions: The discovery of novel and highly specific NOX inhibitors will provide opportunities to develop NOX inhibitors for treatment of fibrotic pathologies. *Antioxid. Redox Signal*. 33, 455–479.

Keywords: NADPH oxidases, pharmacology, tissue repair and remodeling, myofibroblasts, aging, clinical

Introduction

TISSUE FIBROSIS IS invariably associated with a failure to maintain a normal epithelial/endothelial barrier in affected organs. This failure in efficient/effective cellular regeneration at the vascular interface (endothelium) or the luminal surfaces of the lung (airway epithelium), kidney (tubular epithelium), or liver (hepatic/biliary epithelium) can result in the activation of the subtending mesenchyme. This localized mesenchymal activation typically involves the expansion of tissue-resident mesenchymal progenitor cells, which differentiate into contractile cells known as myofibroblasts. Although both fibroblasts and myofibroblasts secrete/remodel the extracellular matrix (ECM), it is the myofibroblasts that contribute to tissue contracture and architectural distortion. The sustained and relentless activation of the mesenchyme may be further fueled by immune dysregulation, including the profibrotic polarization of tissue-resident/recruited macrophages. Thus, damage to epithelium/endothelium, fibroblast/myofibroblast activation, ECM remodeling, and immune dysregulation are salient and essential features of fibrosis involving all organs.

Over the past decade, accumulating evidence supports a role of nicotinamide adenine dinucleotide phosphate oxidases (NOXs) in tissue inflammation and fibrosis. The NOX family of enzymes comprises seven family members: NOX1, NOX2, NOX3, NOX4, NOX5; and dual oxidase (DUOX) homologs, Duox1 and Duox2. All NOX enzymes generate reactive oxygen species (ROS), either as superoxide anion ($O_2 \cdot^-$) or as hydrogen peroxide (H_2O_2), as the primary product of enzymatic catalysis and reduction of molecular oxygen (O_2). While the preponderance of data supports a critical role for NOX4 in fibrosis across all organ systems, in this review, we will explore reported functions of other NOX enzymes in the tissue injury, inflammation, and/or repair process. The homeostatic roles of NOX enzymes in some tissues/organs are also discussed.

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Finally, we highlight emerging strategies to target NOX enzymes in fibrotic pathologies involving different organ systems.

Lung Fibrosis

Causes and pathogenic mechanisms

Fibrosis involving the lung may be due to known causes such as occupational exposures, drugs, or an associated systemic connective tissue disease, or represent an ''idiopathic'' form referred to as idiopathic pulmonary fibrosis (IPF), the most common and lethal of all the fibrotic lung diseases. Although a specific ''cause'' of IPF has not been identified, there are known risk factors that include genetic and environmental factors, as well as aging. Based on this increased understanding of IPF pathogenesis, there is a growing impetus to eliminate the term ''idiopathic'' and introduce alternative classification schemes (246, 256–258, 264).

Genetic variants have been identified in both sporadic and familial cases of IPF. Familial cases have been estimated to account for between 2% and 20% (81, 124, 200); this variability is likely related to the populations studied as well as disease definitions. In general, rare variants are highly penetrant and have a large effect size. These variants include ''mutations'' in genes related to alveolar stability, including the surfactant proteins (SFTPs): SFTPC, SFTPA1, and SFTPA2; and another protein involved in surfactant metabolism, ATP-binding cassette-type 3 (ABCA3); and genes associated with telomere biology: TERT, TERC, DKC1, TINF2, RTEL1, PARN, and nuclear assembly factor 1 ribonucleoprotein (NAF1) (124). Sporadic cases of IPF have also been linked to a number of gene variants, which are more common, but typically with smaller effect sizes; these include genes linked to telomere maintenance (TERT, TERC), host defense functions (MUC5B, TOLLIP), and epithelial integrity (DSP, DPP9) (124). Among these, a MUC5B risk variant has a relatively high effect size and, due to its higher prevalence in the general population, may account for up to 30% of the genetic risk of developing IPF (66).

Environmental factors almost certainly contribute to risk of developing IPF. Although it is difficult to conduct and interpret such studies, most evidence supports the concept that IPF is a heterogeneous disorder caused by a number of environmental and occupational exposures; such exposures may include smoking, agriculture/farming, livestock, wood dust, metal dust, and stone/sand (241).

The pathogenesis of IPF involves the interactions between different cell types and the emergence of profibrotic phenotypes (Fig. 1). Alveolar epithelial cell apoptosis (50, 193, 251), senescence (215, 247), and epithelial-to-mesenchymal

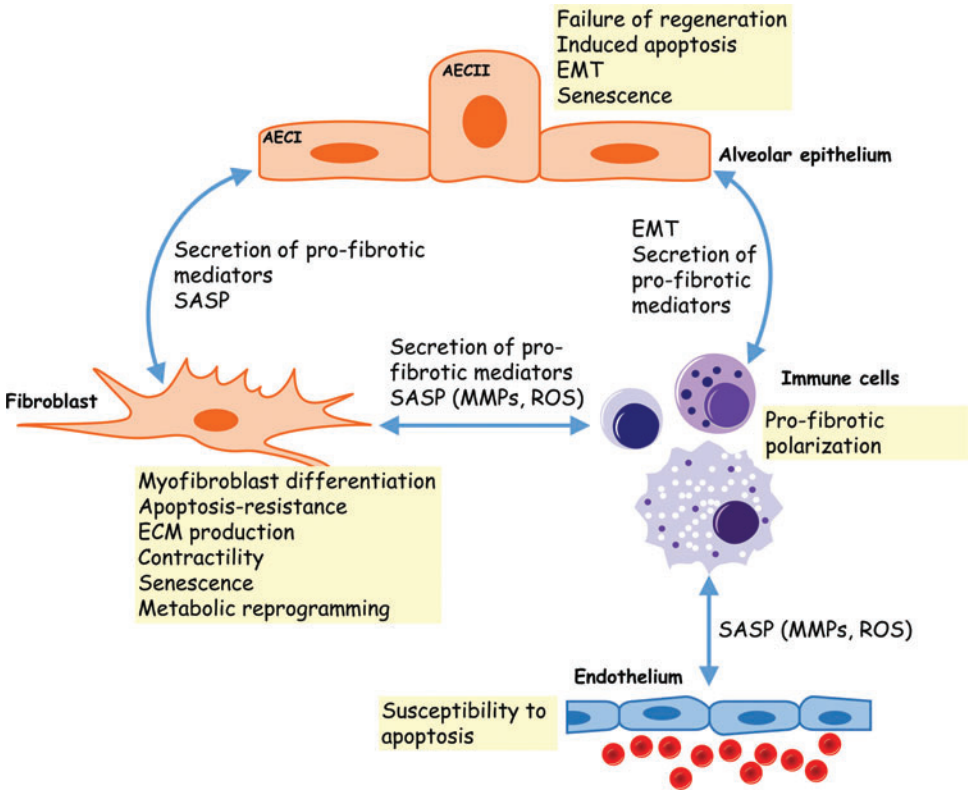

FIG. 1. Cellular interactions in pulmonary fibrosis. Communication between the different cellular effectors of pulmonary fibrosis involves secreted/paracrine mediators. Injured alveolar epithelial cells secrete proinflammatory factors that may sustain the recruitment/activation of immune cells to the site of injury. Immune cells amplify the inflammatory response and may polarize to a more profibrotic response that promotes myofibroblast differentiation and ECM remodeling. The SASP of epithelial cells and myofibroblasts has also been proposed to alter the phenotype of neighboring cells. AECI, alveolar epithelial cell type I; AECII, alveolar epithelial cell type II; ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition; MMPs, matrix metalloproteinases; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype. Color images are available online.

transition (EMT; 225, 277, 285) are thought to contribute to the early development of lung fibrosis. Impaired re-epithelialization, due to exhaustion of epithelial cell progenitors in response to chronic exposure to injury and/or aging, is likely to be a key driver of the pathogenesis of the disease (44). A pathological hallmark of lung fibrosis is the differentiation of lung fibroblasts into myofibroblasts and their accumulation within fibroblastic foci. The profibrotic cytokine transforming growth factor beta-1 (TGF-β1) stimulates myofibroblast differentiation (245). Myofibroblast differentiation is accompanied by enhanced secretion of ECM components and resistance to apoptosis (102–104). Pulmonary fibrosis has also been associated with the recruitment of macrophages and neutrophils at site of tissue remodeling (78, 89, 94, 172). In addition to profibrotic mediators, recruited macrophages and neutrophils release ROS that may perpetrate the fibrogenesis *via* the modulation of ECM synthesis and the polarization of macrophages toward a profibrotic phenotype (8, 84, 95, 96). In addition to the pathogenic mechanisms described above, cellular senescence has been the focus of numerous studies following the observation that senescent cells accumulate in the fibrotic lung (98, 215). Epithelial cells and fibroblasts have been shown to undergo senescence in IPF lungs (98, 215). One of the mechanisms by which senescent cells may influence phenotypes of neighboring cells is through secreted mediators referred to as the senescence-associated secretory phenotype (SASP) (242). Among SASP components are inflammatory cytokines (interleukin [IL]-6, IL-8, IL-1α), plasminogen activator inhibitor-1 (PAI-1), matrix metalloproteinases (MMPs), tissue inhibitors of matrix metalloproteinases (TIMPs), IGF-binding proteins, monocyte chemoattractant protein 1 (MCP-1), prostaglandin E2 (PGE2), and nitric oxide (NO) (52). These SASP-associated factors promote inflammation, tissue remodeling, and cell growth (188). The targeting of senescent cells with senolytics has been shown to ameliorate the severity of lung fibrosis in a murine experimental model of the disease (215).

Role of NOX enzymes in lung fibrosis

The rationale for targeting NOX4 as a therapeutic target to ameliorate lung fibrosis is based on the finding of high expression of this homolog in human IPF and from *in vivo* genetic/pharmacological targeting in murine experimental models of the disease (98, 99) (Fig. 2). NOX4 expression and activity increase after the stimulation of lung fibroblasts, *in vitro*, with TGF-β1 (99). NOX4 expression and activity are constitutively increased in lung fibroblasts isolated from IPF patients. NOX4, through the production of H_2O_2, mediates tissue-repair functions of myofibroblasts, which are effectors of ECM production and contraction (99). In addition to its role in sustaining myofibroblast activation, NOX4 supports lung fibroblast migration *via* a ROS-mediated RhoA/Rho kinase pathway (168).

More recently, we reported that metabolic reprogramming is required for myofibroblast activation (20, 267). This reprogramming relies on enhanced mitochondrial bioenergetics and biogenesis (20). These studies demonstrated that NOX4 regulates mitochondrial bioenergetics and biogenesis

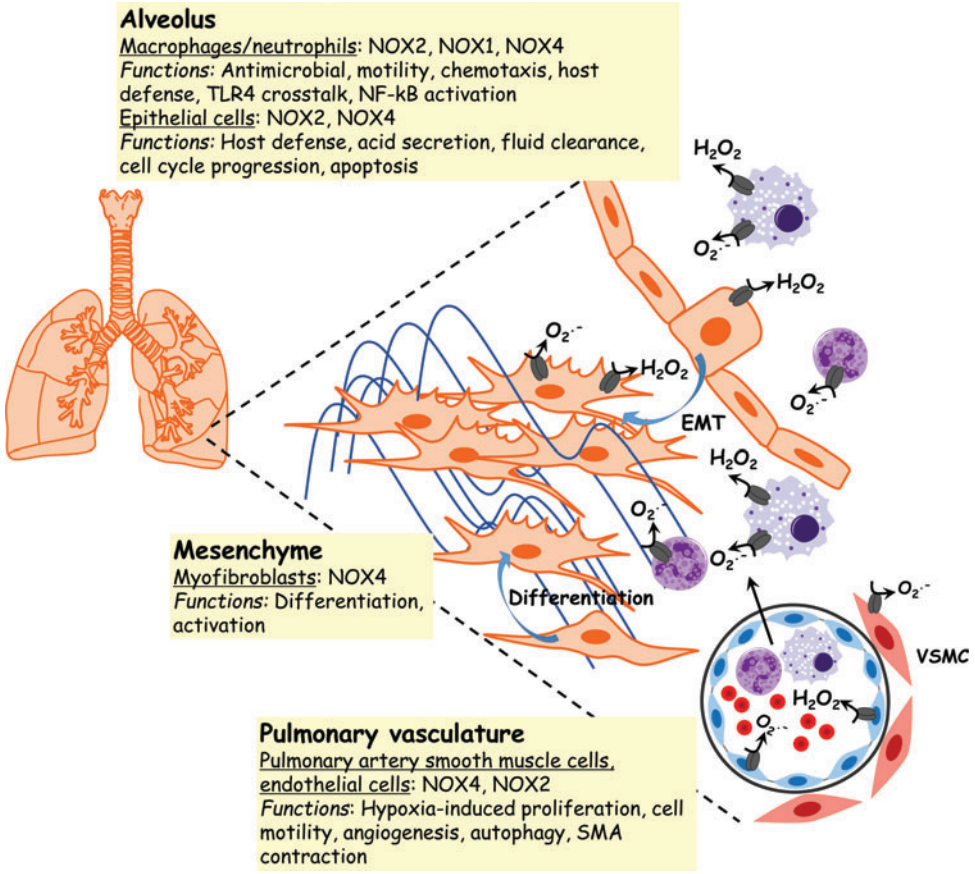

FIG. 2. NOX enzyme inhibition and antifibrotic therapies. Compounds that have proven beneficial in ameliorating fibrosis in animal models of organ fibrosis and/or in cellular models of myofibroblast differentiation. The discovery of these compounds resulted from three different drug discovery strategies: the development of small molecule inhibitors through high-throughput screening, application of herbal medicines, and the repurposing of prescription drugs. H_2O_2, hydrogen peroxide; NF-κB, nuclear factor-kappa B; NOX, nicotinamide adenine dinucleotide phosphate oxidase; VSMCs, vascular smooth muscle cells. Color images are available online.

in lung fibroblasts by modulating levels of nuclear factor erythroid-derived 2-like 2 (Nrf2) (19). The balance between NOX4 and Nrf2 also influences the fate of myofibroblasts to a senescent and apoptotic-resistant phenotype (98, 212).

Epithelial cell death and/or epithelial-to-mesenchymal cell transition are two mechanisms that have been proposed to contribute to the establishment of lung fibrosis along with myofibroblast differentiation (126, 127, 138, 165, 259). NOX4-deficient mice show decrease in epithelial cell apoptosis in response to airway injury with bleomycin (33). Differential expression analysis of pro-oxidant and antioxidant transcripts after EMT of lung epithelial cells also showed that downregulation of antioxidant transcripts correlated with an upregulation of NOX4 expression (196).

Macrophage recruitment and activation respiratory burst have been associated with the early inflammatory phase of lung fibrosis (72). Activation of the inflammasome and production of IL-1β in response to NOX-dependent release of ROS have been suggested to link macrophage respiratory burst and inflammation in lung fibrosis (234).

The progression of lung fibrosis depends on the development of comorbidities such as pulmonary hypertension (PAH) (70). Hypoxia, which may lead to PAH, stimulates the release of superoxide by endothelial cells *via* a NOX2-dependent pathway. NOX2-mediated ROS serve to mobilize endothelial cell progenitors that are necessary for vascular repair (219). Enhanced NOX activity also contributes to endothelial apoptosis and the remodeling of pulmonary arteries. In particular, NOX4 promotes the proliferation of smooth muscle cells involved in vascular remodeling (58, 63).

Mesenchymal stem cells (MSCs) participate in the repair process after tissue injury by ''homing'' to site of injury. MSCs can differentiate into another cell type to regenerate the epithelial barrier and/or mediate paracrine actions on resident cells to promote repair responses. Some evidence suggests that the self-renewal and recruitment of MSCs depend on a crosstalk between gp91^{phox} and matrix metalloproteinase-12 (MMP-12) (16). The crosstalk between vascular factors and perivascular NOX4 has also been implicated in establishing a favorable environment for engraftment of MSCs in fibrotic tissues (31). In particular, ectopic upregulation of hepatocyte growth factor (HGF) in endothelial cells inhibits perivascular NOX4 and facilitates engraftment of MSCs in fibrotic tissues of the lung and liver (31). On the contrary, targeted deletion of HGF in mice endothelial cells induces perivascular NOX4, and recapitulates the lung and liver fibrotic phenotypes (31).

Therapeutic strategies

Two U.S. Food and Drug Administration (FDA)-approved drugs, pirfenidone and nintedanib, are currently available to treat IPF patients (128, 204). These two drugs, however, have a limited efficacy and are not curative. They merely slow down the progression of IPF without increasing survival and ameliorating symptoms of the disease (202). Therefore, the development of alternative treatments remains a priority. Numerous studies have been undertaken to identify novel inhibitors of NOXs through drug library screening of small molecule inhibitors, traditional herbal medicines, and repurposing of prescription drugs (Fig. 3).

Small molecule inhibitors of NOX enzymes. The development of specific inhibitors of NOX enzymes has proved challenging due to the structure of NOX enzymes, their regulatory interactions, and the lack of a crystal structure, although partial structural information is obtained from modeling in cyanobacteria (163). The following gives an overview of the progresses made in the development of small molecule inhibitors of NOX enzymes.

VAS2870 and VAS3947 are triazolopyrimidine derivatives that have been reported to completely block NOX-associated activity in a variety of cellular models without specificity toward any NOX homologs (244, 261).

GKT137831 is the first small molecule inhibitor targeting NOX1/NOX4 (133). GKT137831 belongs to the pyrazolopyridine chemical series (133, 243). Preclinical studies using GKT137831 have demonstrated promising effects of this compound in ameliorating fibrosis in a murine experimental model of the disease (98). Notably, GKT137831 reverses age-associated persistent fibrosis in a murine experimental model of lung fibrosis in aged mice. In these studies, *in vivo* targeting of NOX4 decreased accumulation of myofibroblasts and collagen deposition at sites of remodeling. It also downregulated the expression of the senescent markers p16 and p21 (98). These data suggest that GKT137831 modulates the senescent and apoptosis-resistant phenotype of myofibroblasts.

Peptidic inhibitors of NOX enzymes have been designed to block the assembly of the functional NOX enzyme, promote autoinhibition of the NOX enzyme, or disrupt regulatory interaction of the NOXs with p22^{phox}, p47^{phox}, or p67^{phox} (49). Among peptides inhibitory of NOX2, NOX2ds-tat has been described as isoform specific (49). NOXA1ds targets the interaction of NOX1 and the activation domain of p67^{phox} (49). Pep1 and Pep3 target the interaction between NOX5 N-terminal tail containing the EF domain, responsible for NOX5 stimulation by Ca^{2+}, and its C-terminal catalytic dehydrogenase domain (49).

JQ1 is an inhibitor of the epigenetic readers, bromodomain-containing protein 3 and 4 (Brd3 and Brd4) (3). Pretreatment with JQ1 prevents TGF-β1-induced activation and differentiation of lung fibroblasts (232). These studies show that JQ1 treatment reduces NOX4 and SOD2 messenger RNA (mRNA) expression, thus shifting the imbalance between NOX4 and SOD2 that results from TGF-β1 stimulation of fibroblasts.

Herbal medicines. Magnesium isoglycyrrhizinate (MgIG) is a magnesium salt of 18α-glycyrrhizic acid stereoisomer. Glycyrrhizic acid is the main active ingredient in licorice, and has antioxidant and anti-inflammatory properties (145). MgIG treatment improves radiation-induced pulmonary fibrosis by attenuating lung collagen deposition and reducing levels of TGF-β1. MgIG mediates its effect on radiation-induced pulmonary fibrosis through a decrease in NOX4 expression, ROS production, and p38 mitogen-activated protein kinase (MAPK) phosphorylation (276).

Three compounds derived from herbal Chinese medicine have been reported to attenuate bleomycin or TGF-β1-induced lung fibrosis *in vivo*. These compounds restore the redox balance in myofibroblasts by reducing NOX4 and upregulating Nrf2 (98). These compounds are as follows: (i) costunolide, a natural occurring sesquiterpene lactone isolated from *Saussurea*

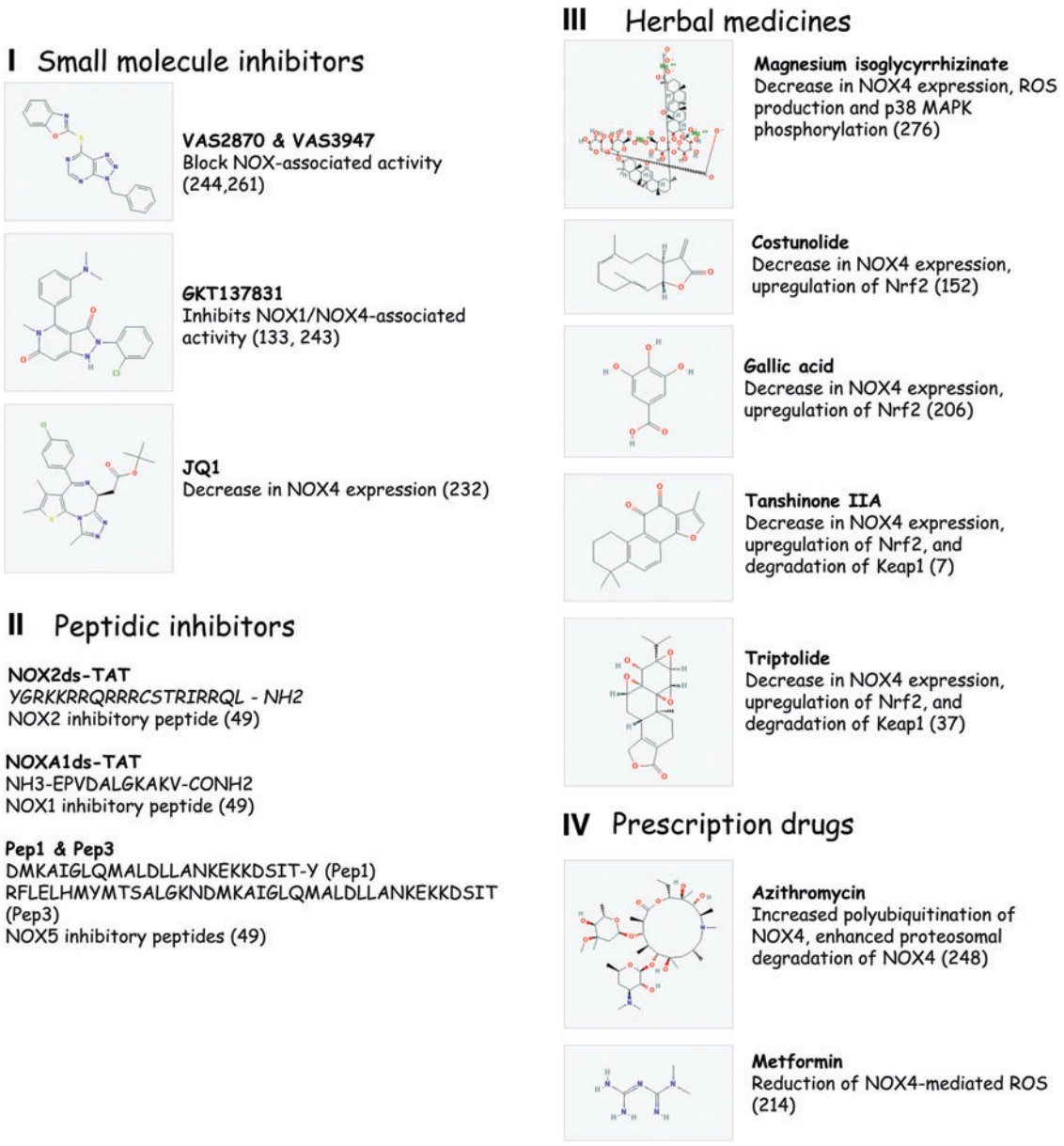

FIG. 3. NOX expression and function in lung fibrosis. NOXs are a source of ROS in alveolar epithelial cells, macrophages, neutrophils, myofibroblasts, endothelial cells, and VSMCs. H_2O_2 and $O_2\cdot^-$ participate in determination of cell phenotype and fate by regulating immune cell recruitment/activation, EMT, myofibroblast differentiation, and ECM remodeling, which may all contribute to the pathogenesis of lung fibrosis. H_2O_2, hydrogen peroxide; Keap1, Kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinase; Nrf2, nuclear factor erythroid-derived 2-like 2. Color images are available online.

lappa root (152); (ii) a novel gallic acid derivative derived from *Quercus infectoria* (206); and (iii) tanshinone IIA (Tan-IIA), isolated from the root of *Salvia miltiorrhiza Bunge* (7). Tan-IIa augments Nrf2 through promoting the degradation of Kelch-like ECH-associated protein 1 (Keap1). Of note, Tan-IIA-induced Nrf2 has been reported to increase intracellular glutathione (GSH) by shifting glutamate utilization by the tricarboxylic acid cycle toward GSH production (7).

Triptolide (TPL) is a diterpenoid epoxide isolated from *Tripterygium wilfordii*. It has been used in Eastern Asia to treat inflammatory and autoimmune disorders such as systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and asthma (39). TPL has been reported to reduce the recruitment of alveolar macrophages in a model of irradiation-induced lung fibrosis in mice. TPL has also been shown to inhibit NOX2- and NOX4-mediated ROS in alveolar macrophages, thus attenuating effects of paracrine actions of ROS on myofibroblast activation induced by irradiation (37).

Prescription drugs. Azithromycin is a macrolide-type antibiotic prescribed for respiratory, dermal, and urogenital bacterial infections. Because of its immunomodulatory property, it is also used to treat chronic inflammatory disorders (190). Azithromycin ameliorates bleomycin-induced

lung fibrosis in mice and prevents TGF-β1-induced myofibroblast differentiation *in vitro*. These effects of azithromycin have been associated with the stimulation of NOX4 degradation by the proteasome. In these studies, enhanced proteosomal degradation of NOX4 was shown to result from increased polyubiquitination of NOX4 after reduction of autophagy and activation of the unfolded protein response by azithromycin (248).

Metformin is a FDA-approved drug for treatment of type 2 diabetes. Metformin or 3-(diaminomethylidene)-1,1-dimethylguanidine is an AMP-activated kinase (AMPK) activator. AMPK is a bioenergetics sensor and metabolic regulator of cell adaptation to low energy conditions. In the bleomycin-injury model of lung fibrosis, AMPK activity is lower in fibrotic regions associated with metabolically active and apoptosis-resistant myofibroblasts (201). Treatment with metformin attenuates the fibrotic response to injury (201, 214). Sato *et al.* demonstrated that metformin prevents myofibroblasts differentiation by reducing NOX4-mediated ROS, which support TGF-β1-induced Smad2/3 phosphorylation. These studies show that inhibition of NOX4 expression by metformin leads to reduction in NOX4-mediated ROS (214).

Kidney Fibrosis

Causes and pathogenic mechanisms

Diabetes and hypertension are the most prominent causes of progressive kidney diseases characterized by renal fibrosis. Pathological renal fibrosis can affect the glomeruli (glomerulosclerosis), the tubulointerstitium (interstitial fibrosis), and the vasculature (vascular sclerosis). As described for the lung, myofibroblasts are responsible for the accumulation and the contractility of the scar tissue observed in renal fibrosis. EMT has been reported to give rise to myofibroblasts along with the differentiation of mesenchymal fibroblasts, pericytes, and perivascular fibroblasts into myofibroblasts upon exposure to profibrotic factors (151, 156, 169). EMT of podocytes is involved in glomerulosclerosis (253), while EMT of tubular epithelial cells has been reported in conjunction with interstitial renal fibrosis (286). Many profibrotic factors have been described as mediators of renal fibrosis in response to injury. However, angiotensin II (Ang II) drives the fibrogenic process *via* stimulating the release of other profibrotic factors such as TGF-β1 (22, 235), platelet-derived growth factor (PDGF) (107), connective-tissue-derived growth factor (CTGF) (274), NOX (199), PAI-1 (170), tumor necrosis factor-alpha (TNF-α) (198), osteopontin (263), and vascular cell adhesion molecule-1 (VCAM-1) (130). Mesangial cell-, macrophage-, and ECM-derived TGF-β1 sustains ECM deposition through stimulation of ECM synthesis and inhibition of its degradation (24, 91). TGF-β1 also promotes EMT of tubular epithelial cells (156). CTGF contributes to the pathogenesis of renal fibrosis through the modulation of matrix-degrading metalloproteinases (275). PAI-1 has been suggested to promote fibrogenesis *via* upregulation of fibronectin and type III collagen in the kidney (183). In addition to the release of profibrotic mediators, Ang II induces nuclear translocation of the transcription factor nuclear factor-kappa B (NF-κB), which induces gene expression of a number of proinflammatory and profibrotic mediators (129, 158, 268, 272). Ang II-mediated activation of NF-κB has been described to support the expression of tissue transglutaminase (153). Ang II-mediated expression of tissue transglutaminase in the fibrotic kidney may participate in the activation of ECM-bound latent TGF-β1 (217). TGF-β1-induced oxidative stress responses in mesangial and endothelial cells have been implicated in the pathogenesis of renal fibrosis (34). One proposed mechanism may be oxidative-stress-mediated neutralization of the protective role of mesangial NO against renal fibrosis (155). In the unilateral ureteral obstruction (UUO) model of renal fibrosis, alteration of renal hemodynamics is an early event triggered by increased activity of vasoconstrictor systems such as the renin–angiotensin system (73). Mesangial cells have been implicated in the regulation of the kidney tubuloglomerular feedback (203). Notably, mesangial cells have been suggested as a source of ROS that enhance tubuloglomerular feedback by quenching NO, thus counteracting NO-mediated vasodilation of glomerular afferent arterioles (155). TGF-β1 treatment of primary mouse mesangial cells has been shown to upregulate the production of ROS *via* augmenting the activity of NOX2, NOX4, and Duox2 (34). Of note, as opposed to the antifibrotic role of NO suggested above, some studies have reported an association between high levels of inducible nitric oxide synthase (iNOS) and the progression of kidney remodeling in UUO mice (230).

Role of NOX enzymes in kidney fibrosis

NOX enzymes have been implicated in the regulation of the kidney function through their role in gluconeogenesis (262), glucose transport (93), tubuloglomerular feedback (260), renal hemodynamics (218, 222), and electrolyte transport (112, 226) (Fig. 4). NOX4 is the NOX isoform that is most abundantly expressed in the renal cortex. NOX4 localizes to mesangial cells, podocytes, tubular epithelial cells, and endothelial cells. $p47^{phox}$ and $p22^{phox}$ are expressed in tubular epithelial cells along with NOX4 (85). NOX2, $p67^{phox}$, $p47^{phox}$, and $p22^{phox}$ mRNA are also expressed in podocytes (90). NOX1 is localized with NOX2 and NOX4 in different regions of the nephron (thick ascending limb, macula densa, apical area of distal convoluted tubules) as well as in the vasculature and glomeruli (35, 36). NOX5 has been localized to the tubular and glomerular regions in biopsies of human kidney tissue (113), and NOX3 has been reported to be expressed in the fetal kidney (42).

NOX4 has been shown to play a role in diabetes-induced renal fibrosis in mice and rats. In these experimental models, hyperglycemia increases the expression and activity of NOX4. This increase in NOX4 expression has been linked to the upregulation of TGF-β1 levels, phosphorylation of p38 MAPK, and fibronectin deposition in the kidney (220). Transient receptor potential cation channel 6 (TRPC6), a member of the family of transmembrane Ca^{2+} channels, is an important modulator of glomerular dynamics, alterations of which have been associated with the development of renal fibrosis (106). NOX4-generated ROS have been implicated in the downregulation of TRPC6 expression in mesangial cells (88). Cannabinoid receptor type 1 (CB_1) is G_i/G_0 protein-coupled receptor that is activated upon binding of endocannabinoids such as anandamide and 2-arachidonyl glycerol (160). While identified as one of the most abundant G-protein-coupled receptors in the brain (101), CB_1 is also expressed in adipocytes (207), liver (55), skeletal muscle

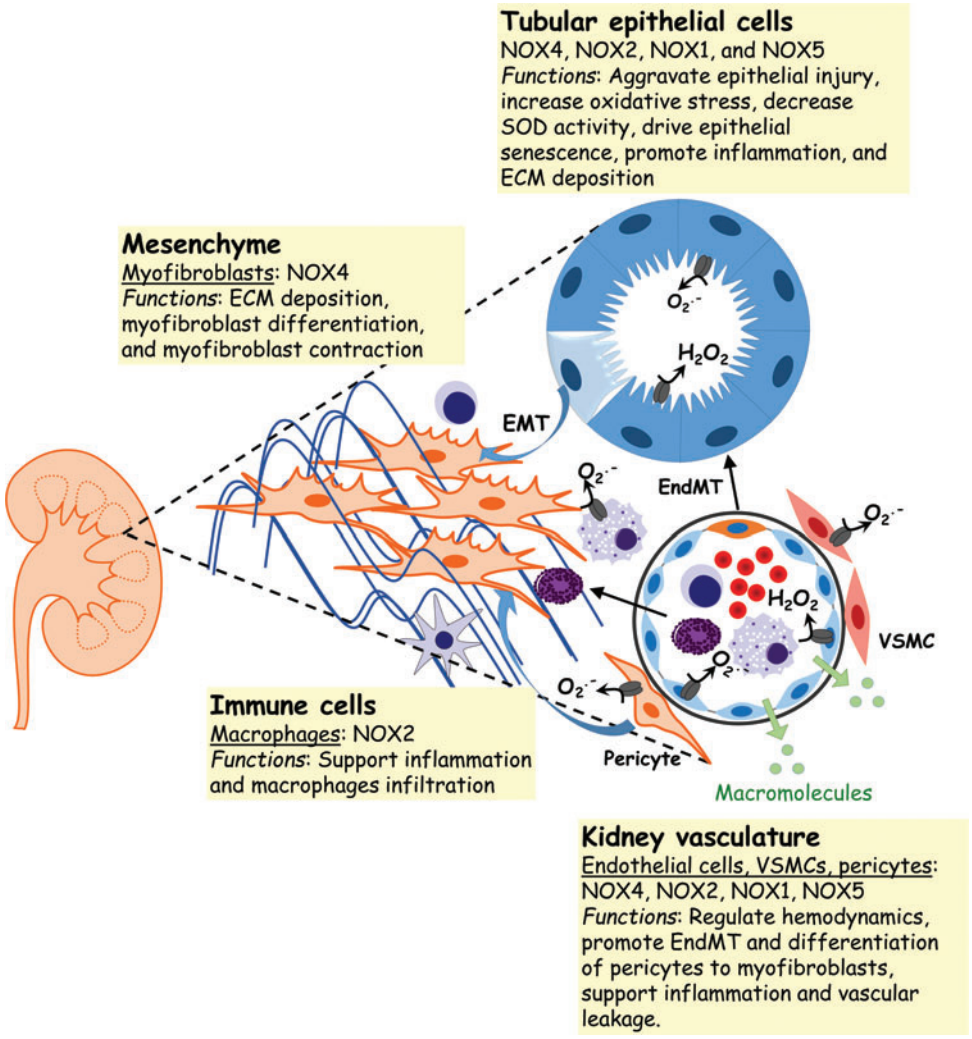

FIG. 4. NOX expression and function in kidney fibrosis. NOXs constitute a major source of ROS in the kidney. Renal NOXs modulate a variety of cell functions that are involved in kidney fibrosis such as inflammation, ECM deposition, myofibroblast differentiation/contraction, and EndMT. Renal NOXs have also been shown to regulate vascular tone, hemodynamics, inflammation, and remodeling. EndMT, endothelial to mesenchymal; SOD, superoxide dismutase. Color images are available online.

(105), and kidney (137). In the kidney, CB_1 has been localized in podocytes (118), mesangial cells (149), proximal tubule cells (136, 250), distal tubule cells (136), and intercalated cells (136). In the murine model of cisplatin-induced renal fibrosis, upregulation of NOX4 gene expression has been linked to the activation of the CB_1 (175). In this experimental model, CB_1 antagonists or genetic deletion of CB_1 receptors have been shown to reduce the expression of NOX2 and NOX4, thus reducing oxidative stress induced by cisplatin (175). Evidence of NOX2 involvement in renal fibrosis comes from the use of experimental models of diabetes-induced renal fibrosis. NOX2 expression is upregulated in the renal cortex of diabetic mice, and its inhibition has been linked to lower oxidative stress, enhanced superoxide dismutase (SOD) activity, and amelioration of renal fibrosis (77). However, contrary to these studies, NOX2 expression has been reported to remain unchanged in the renal cortex of db/db mice, a widely used experimental model of type 2 diabetes (220). NOX1 upregulation in the glomeruli and cortical tubules of diabetic mice has been associated with larger glomerular volume, increased mesangial matrix, and upregulated levels of the DNA double-strand break markers p27 and γH2AX; these effects on glomerular structure, ECM deposition, and senescence were attenuated in NOX1 KO mice (288). Data related to the role of NOX5 in renal fibrosis *in vivo* come from studies using a humanized murine model of NOX5 overexpression (113). In these studies, overexpression of NOX5 in mesangial cells and vascular smooth muscle cells (VSMCs) was associated with enhanced ROS production, deposition of collagen IV and fibronectin, immune infiltration, mesangial cells expansion, and glomerulosclerosis (113).

Therapeutic strategies

In the following sections, we discuss pharmacological approaches that have proven beneficial in the amelioration of experimental renal fibrosis through the inhibition of NOX-mediated oxidative stress and/or expression.

Small molecule inhibitors. Lysophosphatidic acid (LPA) is a proinflammatory mediator that is elevated in the serum of diabetes patients and in the kidney of a murine model of type 2 diabetes mellitus (281). LPA acts through binding/activation of its G protein-coupled receptors (LPAR1–6) (233). AM095 is a specific inhibitor of LPAR1 (237). Studies using the streptozotocin (STZ)-induced murine model of diabetic nephropathy showed that treatment with AM095, a specific antagonist of LPAR1, reduces inflammation through the modulation of the TLR4/NF-κB pathway; this is associated with a reduction in ROS levels, in part by decreasing NOX2 expression (139).

NOX1, NOX2, and NOX4 expression is augmented in diabetic end-stage kidney disease (132). Oral administration of APX-115, a pan-inhibitor of NOX enzymes, attenuates fibrosis associated with diabetic end-stage kidney disease in a murine model of STZ-induced kidney disease. Treatment with APX-115 decreases the expression of profibrotic markers such as TGF-β1, α-smooth muscle actin (SMA), fibronectin, and collagen IV (132). Restoration of peroxisomal function and mitochondrial biogenesis are among the mechanisms suggested to mediate effects of APX-115 on kidney fibrosis downstream of NADPH inhibition (132). APX-115 also reduces kidney remodeling in a rat model of diabetic kidney disease by reducing inflammation, evidenced by decreases in the expression of the proinflammatory marker CD68, and reduced levels of IL-6 and MCP-1 (61).

Fluorofenidone or [1-(3-fluorophenyl)-5-methyl-2-(1H)-pyridone] (FD) is a derivative of the antifibrotic drug, pirfenidone (157). FD treatment reduces NOX2 and NOX4-mediated oxidative stress as well as $p47^{phox}$ expression in rat proximal tubular epithelial (NRK-52E) cells *in vitro* and in the kidney of a rat model of UUO-induced renal fibrosis *in vivo* (199). In this model, hampered oxidative stress upon FD treatment is associated with a reduction in the expression of collagen Ia1 and fibronectin as well as lower levels of the oxidative stress marker, malondialdehyde, and MAPK signaling. FD has also been shown to decrease the expression of the profibrotic markers, collagen I and TGF-β1, *via* inhibition of NOX4 in NRK-52E cells (192). Of note, most studies used high concentrations of FD (2 m*M* for *in vitro* studies and 500 mg/kg/day for *in vivo* studies), thus raising concerns related to the specificity of this compound toward NOXs.

Tissue expression of NOX4, $p22^{phox}$, and $p47^{phox}$ is upregulated in the renal cortex of db/db mice. Treatment of db/db mice with GKT136901, a NOX1/NOX4 inhibitor, blocks NOX4-dependent fibrotic signaling in the kidney after exposure to high glucose. Notably, GKT136901 inhibits high-glucose-mediated ROS, prevents phosphorylation of p38 MAPK, and decreases the expression of TGF-β1/2 and fibronectin (220).

Herbal medicines. Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a phytoestrogen that has been identified in >70 species of plants and their products such as grapes, wine, and berries (209). Resveratrol is an activator of sirtuins (23) that mediates antisenescence (144), antioxidant (141), and anti-inflammatory properties (51, 143). Studies using dietary resveratrol showed that resveratrol ameliorates renal function and tubulointerstitial fibrosis in the kidney of aged mice (111). These beneficial effects of resveratrol appear to be through the modulation of the renin–angiotensin system. Resveratrol downregulates the angiotensin-converting enzyme/Ang II/angiotensin II type 1 receptor (ACE/Ang II/AT1R) signaling axis and upregulates the ACE2/Ang 1–7/Mas axis that is protective against kidney remodeling. Resveratrol also reduces the expression of the oxidative stress markers NOX4, 8-hydroxy 2′-deoxyguanosine (8-OHdG), 3-nitrotyrosine in the aged murine kidney. Of note, in these studies, resveratrol had no significant effect on the expression of NOX2 (111). In diabetic nephropathy, interstitial fibrosis results, in part, from the proliferation of interstitial fibroblasts and their activation to myofibroblasts. The proliferation of interstitial fibroblasts depends on the activation of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) by NOX4-mediated ROS. Studies using the rat kidney fibroblast cell line (NRK-49F) and db/db mice demonstrate that resveratrol attenuates interstitial fibrosis by inhibiting fibroblast proliferation through activation of AMPK and subsequent downregulation of NOX4 expression (97).

Rosmarinic acid is an ester of caffeic acid and 3, 4-dihydroxyphenyllactic acid. Rosmarinic acid is a component of plants of the *Lamiaceae* family, including *Rosmarinus officinalis* (rosemary), *Perilla frutescens* (perilla), *Salvia officinialis* (sage), *Mentha arvense* (mint), and *Ocimum basilicum* (basil) (142). It has antioxidant and anti-inflammatory properties, and is used to treat reactive airway diseases, in particular asthma (210). Rosmarinic acid attenuates $CdCl_2$-induced renal inflammation and fibrosis through reduction of the TGF-β1/SMAD3 signaling pathway and associated NOX activity. Overall decreases in H_2O_2 and NO production have been observed in response to rosmarinic acid treatment *in vitro* (studies using renal mesangial cells) and *in vivo* (studies in a murine experimental model of cadmium-induced nephrotoxicity) (116). *P. frutescens* has also been reported to reduce high-glucose-induced kidney remodeling *via* the suppression of NOX4 and NOX2 activity in association with the activation of the metabolic regulator AMPK (125).

Icariin is a bioactive constituent isolated from the Chinese medicine, Ying Yang Huo. It is a prenylated flavonol glycoside with reported potent cardiovascular protective functions (265). Icariin treatment reduces inflammation and fibrosis in the UUO model of renal fibrosis in mice. Icariin mediates its effect by decreasing the proinflammatory mediators, NF-κB, cyclooxygenase-2, and IL-1-β. Icariin also restores the renal oxidant/antioxidant balance through inhibition of TGF-β1-induced NOX4 activity and increases in the expression of the antioxidant enzymes, catalase and SOD (38).

Punica granatum (pomegranate) is rich in phenolic compounds, such as tannins (gallotannins and ellagitannins) and anthocyanins (rutinosides, pentosides, and glucosides of cyanidin, pelargonidin, and delphinidin) (6, 74). Pomegranate peels contain higher amounts of bioactive compounds than those found in the juice (135, 185); these peels are recognized as dietary antioxidants with antimicrobial, anticancer, antiobesity, antidiabetic, antiulcerogenic and antihypertensive, and antimutagenic properties (15, 17, 62, 65, 92, 185, 231). *In vivo* studies using pomegranate peel extract-stabilized gold nanoparticles (PPE-AuNP) have been shown to attenuate nephropathy and associated kidney fibrosis in the murine model of STZ-induced diabetic nephropathy. In this model, STZ-induced hyperglycemia sustains the production of NOX4-mediated ROS *via* the formation of advanced glycation end products (AGE). The binding of AGE to the receptor for advanced glycation end products (RAGE) increases NOX4 expression and leads to phosphorylation of $p47^{phox}$. Beneficial effects of PPE-AuNP on diabetic nephropathy are mediated, in part, by a decrease in AGE-RAGE stimulation of NOX4 expression and $p47^{phox}$ phosphorylation. In addition, PPE-AuNP reduces inflammation through modulation of the MAPK/NF-κB/STAT3 axis and promotes antioxidant defenses *via* activation of the PI3K/AKT/Nrf2 signaling (164).

Peptides/amino acids. Chronic activation of the renin–angiotensin system *via* stimulation of the ACE/Ang II/type 1 angiotensin receptor (AT1) signaling pathway leads to

hypertensive kidney disease (HKD), characterized by glomerular sclerosis and interstitial fibrosis (289). The heptapeptide Ang1–7 is derived from the hydrolysis of Ang II by the angiotensin-converting enzyme ACE2 (29). Ang1–7 mediates vasodilation through its binding to the G protein-coupled receptor, Mas, and this ACE2/Ang1–7/Mas axis counteracts profibrotic effects of ACE/Ang II/AT1 activation (290). Aldosterone-induced HKD in rats recapitulates the glomerular damage/fibrosis associated with the disease; in this HKD model, infusion of Ang1–7 decreases levels of the profibrotic factors, TGF-β1, TIMP-1/TIMP-2, FGF-1 and downregulates NOX2 mRNA expression in the kidney (40). The protective effect of Ang1–7 against kidney remodeling has also been demonstrated in Akita mice, a murine model of type 1 diabetes. Ang1–7 administered to Akita mice reduces kidney oxidative stress and NOX4 expression, in association with decreased expression of the profibrotic markers, TGF-β1 and collagen IV (223).

Glycine is a nonessential amino acid that is a precursor of reduced GSH, the most abundant intracellular antioxidant (167). Glycine is also used for the synthesis of creatine, purines, and heme (26, 68, 82). Glycine treatment has been shown to attenuate tubular interstitial fibrosis in the murine model of STZ-induced diabetes. In this model, amelioration of kidney remodeling in response to glycine treatment was associated with a decrease in renal oxidative stress and NOX4 mRNA expression (255).

Prescription drugs. Sitagliptin is a dipeptidyl peptidase 4 inhibitor that is approved for the treatment of type 2 diabetes mellitus (79). Sitagliptin ameliorates tubulointerstitial fibrosis associated with doxorubicin (DOX)-induced nephropathy in rats. This effect of sitagliptin results from a decrease in the expression of the NLRP3 inflammasome, and a decrease in the mRNA expression of NOX2, $p47^{phox}$, and $p67^{phox}$ (115).

Aliskiren is a renin inhibitor that causes vasodilatation and is prescribed to treat hypertension (221). Paricalcitol is a synthetic vitamin D analog that is prescribed to treat hyperparathyroidism (179). Administration of aliskiren (*via* a miniosmotic pump) or paricalcitol (intraperitoneal injection) decreases the expression of the profibrotic markers, α-SMA and collagen IV, in a murine experimental model of UUO-induced kidney fibrosis (47); antifibrotic effects of these drugs are associated with a decrease in NOX1 and NOX2 expression and a decrease in levels of p-Erk, p-p38 MAPK, and NF-κB activation. Administration of aliskiren alone decreases the expression of NOX1 and NOX2 in the kidneys of UUO mice without having a significant effect on NOX4 expression; in contrast, paricalcitol alone significantly reduces NOX4 expression in the obstructed kidney. Monotherapy with either drug reduces the number of apoptotic cells detected by TUNEL in the fibrotic kidney (47).

Candesartan, approved for the treatment of hypertension, blocks Ang II receptors (87). Pioglitazone is a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist (56) that restores insulin sensitivity and is a prescribed drug for treatment of type 2 diabetes (59). The administration of candesartan and pioglitazone to db/db mice decreases glomerulosclerosis and glomerular oxidative stress. This effect of candesartan and pioglitazone on renal fibrosis is associated with a decrease in the expression of NOX2 and $p22^{phox}$ and enhanced expression of Cu/Zn-SOD and extracellular SOD (77).

Liver Fibrosis

Causes and pathogenic mechanisms

Liver fibrosis results from chronic exposure to injuries of diverse etiology (249). Sources of such injury may include viral infections, alcoholism, xenobiotic intoxication, and systemic metabolic diseases such as diabetes, obesity, nonalcoholic fatty liver disease, and nonalcoholic steatohepatitis (NASH) (25). As described for other organs, liver fibrosis is thought to result from common fibrogenic pathways linked to a dysregulated tissue-repair response (191). Epithelial injury may initiate this dysregulated repair process (53), often associated with release of danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) (5, 171). The recognition of DAMPs and PAMPs by Kupffer cells (hepatic-resident macrophages), hepatocytes, and immune cells triggers hepatic inflammation (12, 57). Hepatic inflammation involves the mobilization of macrophages, lymphocytes, eosinophils, and dendritic cells. Inflammatory mediators responsible for the mobilization and activation of these immune cells in the liver include TNF-α, IL-1, IL-6, C-X-C motif chemokines, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage-CSF, and the NLRP3 inflammasome (57). Injured epithelial cells, endothelial cells, and activated immune cells secrete profibrotic mediators that set the stage for the fibrogenic phase of liver injury. These profibrotic mediators include PDGF, Ang II, CTGF, and TGF-β1 (67, 187, 254, 278). Fibrogenesis leads to progressive accumulation of ECM, destruction of the liver tissue architecture, decline in liver function, and portal hypertension (194). The putative cell-of-origin of liver myofibroblasts that deposit and remodel the ECM in the liver have been intensely studied. EMT and activation of resident mesenchymal progenitors, bone-marrow-derived fibrocytes, or hepatic stellate cells (HSCs) have all been implicated in contributing to the myofibroblast population in the fibrotic liver (1, 60, 122, 131, 182, 205). However, *in vivo* lineage tracing studies carried out in a murine model of liver fibrosis have shown that >95% of liver myofibroblasts come from the transdifferentiation of HSCs and the activation of portal fibroblasts (108).

Role of NOX enzymes in liver fibrosis

The role of increased oxidative stress in the pathogenesis of liver fibrosis is based on studies using clinical samples and experimental animal models of liver fibrosis (11, 211, 273) (Fig. 5). NOX4 expression has been shown to be elevated in a murine model of steatosis-induced fibrosis (21). In this model, hepatocyte-specific deletion of NOX4 results in lower oxidative stress, reduced lipid peroxidation, and attenuation of liver fibrosis (21). NOX4-derived ROS have also been implicated in the transdifferentiation and proliferation of HSCs (211). $NOX2^{-/-}$ mice are protected against CCl_4-induced liver fibrosis (11). These studies support a role of NOX2 in the regulation of both the expression of matrix metalloproteinase-2 and -9 (MMP-2 and MMP-9) and the expression of the MMPs tissue inhibitors, TIMP-1 and TIMP-2. NOX2 has also been shown, *in vitro*, to be the source of ROS in HSCs and Kupffer cells (186). NOX2 has been shown to mediate the activation of HSCs into myofibroblasts after phagocytosis of dying hepatocytes (114). NOX1 KO

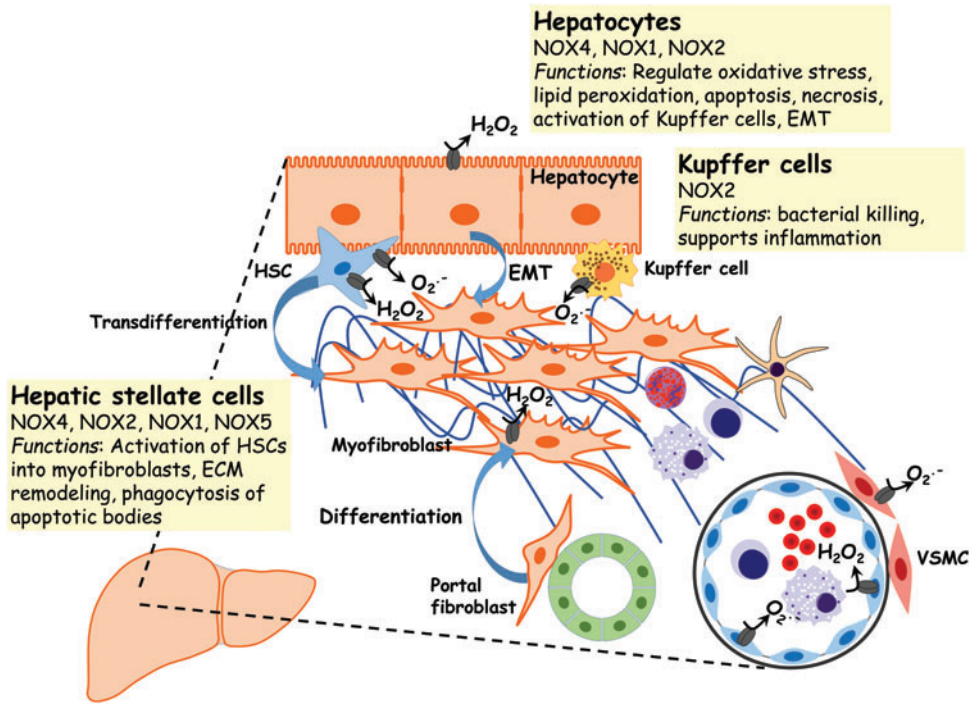

FIG. 5. NOX expression and function in liver fibrosis. The expression/activity of NOXs supports the increase in oxidative stress and altered redox signaling in the pathogenesis of liver fibrosis. NOX-generated ROS contribute to apoptosis and/or necrosis of hepatocytes after injury. Hepatocyte NOX-dependent ROS may activate hepatic Kupffer cells, resident macrophages of the liver. H_2O_2 and $O_2\cdot^-$ from activated NOXs mediate the activation and transdifferentiation of HSCs into myofibroblasts, as well as in the phagocytosis of apoptotic bodies by HSCs. HSCs, hepatic stellate cells. Color images are available online.

mice are also protected against CCl_4-induced liver fibrosis (134). NOX1 is also expressed and activated in HSCs. NOX1, similar to NOX2 and NOX4, has also been implicated in the transdifferentiation and proliferation of HSCs (134). *In vitro* studies using a genetic approach to delete NOX5 in HSCs have also suggested that NOX5 may be involved in the activation of HSCs through the modulation of p38 MAPK (9).

Therapeutic strategies

Small molecule inhibitors. The NOX1/NOX4 inhibitor, GKT137831, ameliorates liver inflammation and fibrosis in a murine model of CCl_4-induced liver fibrosis (10). These studies applied the CCl_4-induced liver fibrosis model to WT mice and to mice harboring the SOD1 G37R mutation (SOD1mu), which increases the catalytic activity of NOX1; however, the drug protected both WT and SOD1mu mice. GKT137831 impedes hepatic lipid peroxidation, as evidenced by lower levels of 4-HNE, in liver tissue, along with a downregulation in the gene expression of profibrotic markers and NOX4 in HSCs isolated from WT or SOD1mu mice (10).

Herbal medicines. 2,3,5,4′-Tetrahydroxystilbene-2-O-β-D-glucoside (TSG) is a bioactive polyphenolic component of *Polygonum multiflorum* (266). TSG has been reported to protect against end-stage hepatic fibrosis associated with NASH (269). TSG treatment of low-density lipoprotein receptor knockout mice fed a high fat diet to induce NASH resulted in lowering of collagen accumulation in the liver with reduced expression of TGF-β1 and α-SMA. In addition, TSG decreased NOX2 and NOX4 expression, and enhanced the hepatic antioxidant activity *via* the upregulation of SOD, catalase, and GSH (269). Of note, TSG administration has been reported to aggravate acetaminophen-induced hepatotoxicity in mice due to enhanced expression of cytochrome P450 (271).

Ferulic acid is a dietary antioxidant found in many plants and vegetables. It is a phenolic compound particularly abundant in bamboo sprouts, beetroot, cabbage, broccoli, and spinach (284). *In vitro* treatment of human HSCs (LX-2 cells) with methyl ferulic acid (MFA) inhibited TGF-β1-induced expression of α-SMA, collagen I, TGF-β receptor I, NOX4, and $p22^{phox}$ (43). This reduction in the expression of profibrotic markers was associated with a decrease in the phosphorylation levels of Smad2/3 (43). Furthermore, MFA reduced fibrosis markers such as hydroxyproline, hyaluronic acid, procollagen III, and collagen IV in the serum of a rat model of hepatic fibrosis (43). Modulation of the TGF-β1/NOX4-mediated ROS signaling pathway has been suggested as the mechanism of MFA's protective effect on liver fibrosis (43).

Ursolic acid is a lipophilic pentacyclic triterpenoid found in the peel of fruits and herbs such as apples, bearberry, lavender, and coffee leaves (110). Pretreatment of HSCs with ursolic acid prevents TGF-β1-induced differentiation of HSCs into myofibroblasts (279). This effect of ursolic acid *in vitro* on HSC activation has been linked to both a reduction in the expression of the NOX2 and its subunits, $p67^{phox}$, $p22^{phox}$, and Rac1 and inhibition of the hedgehog signaling pathway (279). More recent studies have shown that ursolic acid also protects against CCl_4-induced liver fibrosis in rats (80). These studies showed that administration of ursolic acid ameliorates fibrosis *via* downregulation of TGF-β1, collagen I, and TIMP-1 gene expression (80); this decrease in profibrotic marker expression is accompanied by a reduction in CCl_4-induced expression of NOX4, $p67^{phox}$, NOX2, $p47^{phox}$, NOX1, $p22^{phox}$, and Rac1 proteins in the liver tissue (80).

Polydatin is a glucoside of resveratrol that has been shown to attenuate CCl_4-induced liver fibrosis in mice (283). Polydatin treatment reduces CCl_4-induced liver fibrosis in mice *via* the attenuation of oxidative stress and inflammation.

Lower hepatic levels of the oxidative stress markers, 4-hydroxy-2-nonenal (4-HNE) and NOX4, have been shown in response to polydatin treatment (283). The reduction of the inflammatory response upon polydatin administration is characterized by decreased macrophage recruitment and reduced gene expression of TNF-α and MCP-1 (283).

Quercetin or 3, 3′, 4′, 5, 7-pentahydroxyflavone is a plant pigment that is abundant in many fruits, vegetables, and grains (147). Quercetin has been reported to improve bile duct ligation (BDL)-induced liver fibrosis in rats through downregulation of NOX1 expression (120). Quercetin also decreases the expression of Rac1, a small GTPase protein that enhances NOX1 activity, and upregulates the activity of SOD and catalase in the liver tissue of rats in the BDL liver fibrosis model (120).

Antioxidants. Apocynin is a natural organic compound that has been described as a NOX inhibitor (14). α-Lipoic acid (ALA) is an antioxidant produced by plants, animals, and humans. In cells, ALA serves as a cofactor for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase in mitochondria (208). Administration of both apocynin and ALA attenuated concanavalin A-induced liver fibrosis in rats (71). These studies showed that apocynin and ALA treatment reduces hepatic levels of hydroxyproline, α-SMA, and TGF-β1 as well as diminish levels of the proinflammatory markers, IL-6 and TNF-α. This treatment also restores the antioxidant capacity of the liver through augmentation of SOD and GSH while decreasing mRNA expression of NOX4 and NOX1 (71).

Prescription drugs. Fluvastatin (Flu) is a prescription drug that limits the production of cholesterol and prevents its accumulation in blood vessel walls (189). Flu treatment ameliorates steatohepatitis-induced liver fibrosis in rats *via* lowering collagen accumulation and decreasing the expression of α-SMA (45). Flu treatment also downregulates mRNA expression of collagen 1, TIMP-1, IL-6, iNOS, and intercellular adhesion molecule 1 (ICAM-1). *In vitro* treatment with Flu prevents palmitate-induced injury of hepatocytes by reducing intracellular ROS and the secretion of proinflammatory factors such as TNF-α and IL-6 (45). These studies also show that Flu treatment downregulates NOX2 mRNA.

Peptides. Similarly to kidney fibrosis, delivery of Ang1–7 attenuates liver fibrosis induced by BDL in rats (30). In these studies, the authors demonstrate that fibrogenesis depends on the activation of the NLRP3 inflammasome/IL-1β signaling axis by NOX4. Protective effects of Ang1–7 were proposed to be mediated by restoration of the altered redox balance in HSCs by lowering NOX4-driven oxidative stress and augmenting the Nrf2/ARE antioxidant defenses (30).

Cardiac Fibrosis

Causes and pathogenic mechanisms

The term cardiac fibrosis encompasses two subtypes of fibrosis affecting the heart, namely replacement fibrosis and reactive fibrosis. Replacement fibrosis is a reparative process initiated upon cardiomyocyte injury. Replacement fibrosis deposits scar tissue to replace the loss of cardiomyocytes due to necrosis, and is associated with systolic ventricular dysfunction. Reactive fibrosis is triggered by stimuli such as mechanical stress, myocardial inflammation, and metabolic dysregulation. These stimuli activate fibrogenic responses in absence of cardiomyocyte death. Reactive fibrosis leads to the accumulation of fibrous tissue around cardiomyocytes and the heart vasculature; in contrast to replacement fibrosis, reactive fibrosis is associated with diastolic dysfunction (216).

Activated myofibroblasts deposit fibrils of collagen I and III that constitute scar tissue in cardiac fibrosis (216). Lineage tracing studies have shown that resident cardiac fibroblasts are the main source of activated myofibroblasts in the heart (4, 174). Profibrotic mediators support the activation and differentiation of cardiac myofibroblasts. Macrophage-derived IL-10, TGF-β1, and PDGF are prominent profibrotic factors that mediate myofibroblast differentiation and activation (69, 195). Degranulation of mast cells after cardiomyocyte injury also releases proinflammatory and profibrotic mediators such as TNF-α, TGF-β1, IL-4, PDGF, chymase, and tryptase (76, 121, 162, 178, 224, 228). Recruited T cells have been suggested to participate in the reprogramming of macrophage toward a profibrotic phenotype, and to support the activation and differentiation of myofibroblasts. Direct interactions between Th1 lymphocytes and cardiac fibroblasts have been suggested to enhance the production of fibroblast-derived TGF-β1 (180). Th2 lymphocyte-derived IL-4 and IL-13 (48) have been implicated in the stimulation of collagen synthesis by myofibroblasts (83). Neutrophils have been proposed to play a role in the development of fibrosis in the aging heart through the establishment of a peptidylarginine deiminase 4-dependent neutrophil extracellular trap formation (166). In addition to the release of profibrotic mediators by recruited immune cells, the renin–angiotensin–aldosterone system promotes the differentiation of cardiac fibroblasts into myofibroblasts through the engagement of AT1 and mineralocorticoid receptor-driven signaling (119, 252). Furthermore, crosstalk between injured cardiomyocytes, endothelial cells, and resident cardiac fibroblasts has been reported to stimulate and sustain the differentiation of fibroblasts into myofibroblasts (213).

Role of NOX enzymes in cardiac fibrosis

Many of the profibrotic mediators described above, in particular Ang II and TGF-β1, mediate their effects on cardiac myofibroblast activation and differentiation *via* stimulating ROS production (159, 197). Cardiac fibroblast-derived ROS participates in matrix accumulation and remodeling (148). The ROS-generating enzymes, NOX4 and NOX2, are the predominant NOX isoforms expressed in the heart (2, 18). Both NOX4 and NOX2 are expressed in cardiomyocytes, endothelial cells, and fibroblasts (280). NOX4 is also found in smooth muscle cells (270). *In vivo* studies using NOX4- or NOX2-deficient mice have confirmed a role for both these homologs in the pathogenesis of cardiac fibrosis (2, 54, 117). NOX4-produced H_2O_2 mediates the differentiation of cardiac fibroblasts (54), and may contribute to cardiomyocyte apoptosis (2). NOX2 has been reported to mediate Ang II-induced cardiac fibrosis (117). More recently, studies have shown increased cardiac NOX1 mRNA expression in a murine model of DOX-induced cardiac fibrosis; in addition,

conditioned medium from NOX1-depleted H9c2 cardiomyocytes loses its ability to upregulate collagen3a1 mRNA expression in cardiac fibroblasts (109). NOX2 has been suggested to mediate endothelial-to-mesenchymal transition in cardiac fibrosis (176). Selective expression of NOX5 in VSMCs of humanized transgenic mice increases cardiac oxidative stress and fibrosis (173) (Fig. 6).

Therapeutic strategies

Small molecule inhibitors. Mitoquinone (MitoQ) is a mitochondria-targeted antioxidant that accumulates within the mitochondrial matrix due to the positive charge of its triphenylphosphonium moiety (227). MitoQ treatment attenuates left ventricular pressure overload-induced cardiac remodeling (86). These studies showed that MitoQ treatment, *in vivo*, restores the cardiac oxidant/antioxidant balance. The protective effect of MitoQ appears to result from both a reduction in NOX4-mediated oxidative stress and an increase in Nrf2-driven antioxidant defenses (86). Furthermore, MitoQ administration lowers levels of the profibrotic cytokine, TGF-β1 (86).

As with fibrosis involving the lung, kidney, and liver, the NOX1/4 inhibitor GKT137831 has been shown to attenuate cardiac fibrosis in a murine model overexpressing human NOX4 in cardiac myocytes (282). These studies showed that GKT137831 treatment reduces oxidative-stress-mediated activation of the AKT/mTOR and NFκB signaling pathways.

Herbal medicines. Protocatechuic acid or 3,4-dihydroxybenzoic acid is a metabolite that is derived from poylphenols found in green tea (140). Protocatechuic acid has antioxidant properties and has been shown to prevent differentiation of cardiac fibroblasts into myofibroblasts (229). Protocatechuic acid blocks myofibroblast differentiation by inhibiting NOX4-mediated ROS production and phosphorylation of p38 MAPK. Inhibition of the NOX4/ROS/p38 signaling pathway leads to reduced expression of the profibrotic markers, α-SMA, collagen I, and CTGF (229).

Astragaloside IV is a traditional Chinese medicinal herb derived from *Astragalus membranaceus* that is proposed to mediate antioxidant, anti-inflammatory, immunoregulatory, anticancer, hypolipidemic, and antihyperglycemic properties (154). *A. membranaceus* extracts contain polysaccharides, flavonoids, and saponins (154). Astragaloside IV ameliorates cardiac fibrosis and cardiac function in a murine model of DOX-induced cardiomyopathy (150). Astragaloside IV mediates its protective effects against DOX-induced cardiac fibrosis *via* the inhibition of NOX2- and NOX4-mediated oxidative stress (150). This reduction in NOX-mediated ROS is associated with a decrease in cardiomyocyte apoptosis triggered by DOX injury (150). Astragaloside IV treatment has also been reported to ameliorate cardiac fibrosis in ApoE$^{-/-}$ mice, a murine experimental model of hyperlipidemia that develops cardiac hypertrophy and fibrosis (146). In this model, astragaloside IV restored the expression of the proliferative marker Ki67 and decreased that of NOX4 and p16^{INK4a}, a biomarker of cellular senescence (146).

Carthamus tinctorius L. or safflower belongs to the family of Asteraceae. Safflower extracts contain bioactive components such as flavonoids, quinochalcones, alkaloids, and polyacetylenes (287). Treatment with safflower extracts

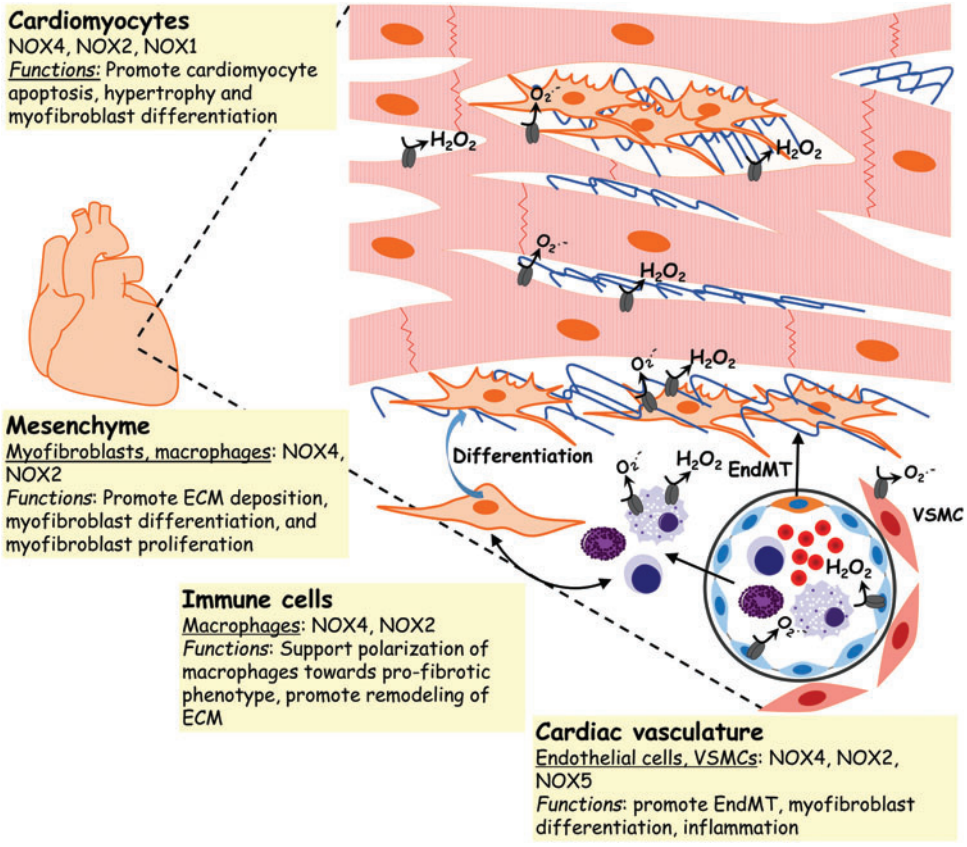

FIG. 6. NOX expression and function in cardiac fibrosis. In the fibrotic heart, NOXs have been implicated in cardiomyocyte apoptosis and hypertrophy. NOXs are also involved in the differentiation of mesenchymal fibroblasts into myofibroblasts that deposit exuberant ECM. NOXs also contribute to the polarization of macrophages to a profibrotic phenotype. Color images are available online.

reduces NOX2-mediated oxidative stress in the heart of NO-deficient hypertensive rats (28). In this experimental model, lower levels of the profibrotic mediators TGF-β1 and MMP-9 were linked to a decrease in NOX2 expression (27).

Luteolin-7-diglucuronide (L7DG) is a bioactive compound extracted from the leaves of *Verbena officinalis* (32). L7DG pretreatment prevents the development of cardiac fibrosis in response to isoproterenol-induced myocardial injury in mice (181). These studies showed that L7DG pretreatment decreases the accumulation of interstitial collagen and α-SMA levels in heart tissues of isoproterenol-injured mice. Moreover, L7DG treatment reduced the expression of genes encoding NOX subunits (181), namely *CYBA* ($p22^{phox}$), *CYBB* ($gp91^{phox}$), *NCF1* ($p47^{phox}$), *NCF2* ($p67^{phox}$), *NCF4* ($p40^{phox}$), and *RAC2* (240). L7DG also downregulated mRNA expression of the profibrotic markers, Col1a1, Col1a2, Col3a1, Col2a1, fibronectin, elastin, CTGF, and collagen triple helix repeat containing-1 (181).

Prescription drugs. Trimetazinide (TMZ) is a piperazine compound that prevents ischemia and is a prescribed drug for treatment of angina (46). TMZ was first described as a modulator of metabolism that shifts mitochondrial substrate utilization (75). TMZ ameliorates cardiac fibrosis associated with diabetes-mellitus-induced cardiomyopathy in rats (239). In this experimental model of cardiomyopathy, TMZ reduced the occurrence of oxidative DNA damage, and decreased the expression of NOX2 and $p47^{phox}$ mRNA. Of note, these studies also showed that TMZ does not reverse the increase in $p22^{phox}$ mRNA expression observed in the myocardium of diabetic rats. Furthermore, reduction of myocardial oxidative stress in diabetic rats upon TMZ treatment attenuates the cardiac inflammatory response (239).

Febuxostat is a xanthine oxidase inhibitor (XO) that is approved for the treatment of gout (64). High salt intake leads to increased cardiac mass in rats due to cardiomyocyte hypertrophy and interstitial fibrosis (123). Febuxostat administration reversed the increase in XO and NOX activity associated with high-salt-induced hypertension in rats (177). Febuxostat treatment also reduced the expression of collagen I, TGF-β1, phospho-ERK, ACE, and ATR1 (177).

Similar to protective effects of metformin on lung fibrosis, administration of metformin after myocardial infarction ameliorated cardiac fibrosis and decreased levels of cardiac galectin-3 (13). Galectin-3 is a β-galactoside binding lectin that mediates myofibroblast proliferation and activation (100, 161, 238). A reduction in galectin-3 release by myofibroblasts, through the modulation of the mitochondrial NOX4/PKCα signaling pathway by AMPK, has been proposed as a mechanism for the salutary effects of metformin on cardiac fibrosis after myocardial infarction (13).

Peptide. As described for kidney fibrosis, Ang1–7 has been reported to ameliorate cardiac fibrosis, although by apparently different mechanisms (41). Activation of cardiac fibroblasts observed in cardiac fibrosis is mediated by enhanced extracellular calcium influx *via* TRPC3 channels (184), as well as by augmented NOX4 expression (54). Administration of Ang1–7 reduces collagen accumulation and mitigates the activation of cardiac fibroblasts by AngII (41). These studies suggest that Ang1–7 exerts its effect on cardiac remodeling through the reduction of either (or both) extracellular calcium influx and oxidative stress. The mechanism proposed to support the protective effects of Ang1-7 is by a reduction in NOX4-mediated oxidation of CaMKIIδ and GSSG, and thus lower levels of CTGF and ERK1/2 MAPK activation (41).

Conclusion

Fibrosis involving diverse organ systems such as the lung, kidney, liver, and heart may involve common pathophysiologic mechanisms. Accumulating evidence indicates that an upregulation in the expression and activation of ROS-generating NOX enzymes represents a conserved fibrogenic mechanism across these organs. As such, NOX enzymes constitute a promising therapeutic target to ameliorate fibrosis, either through a preventative strategy or by arresting progression of established fibrosis. A large number of preclinical studies in experimental animal models have reinforced the legitimacy of NOXs as attractive targets for organ fibrosis. Notably, these studies have demonstrated *in vivo* attenuation of the severity of fibrosis, acceleration of its resolution, and/or arrest of its progression. Some of the NOX-targeted therapies appear to have redox-modulatory effects rather than a specific effect on NOX enzymes (14). The currently available preclinical models of organ fibrosis do not recapitulate the progressive nature of the disease in humans; using aging models may be more representative of the pathology (98), and the emerging use of human organoid models may be more predictive of therapeutic responses (236). Finally, a more thorough understanding of signaling targets/intermediates of the NOXs, their cell-specific expression and targeting, and the development of more specific, potent, and safe strategies to inhibit specific NOX homologs will advance drug discovery/development for fibrotic pathologies that currently carry high morbidity and mortality.

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Abbreviations Used

4-HNE = 4-hydroxy-2-nonenal
8-OHdG = 8-hydroxy 2′-deoxyguanosine
ABCA3 = ATP-binding cassette-type 3
ACE = angiotensin-converting enzyme
AECI = alveolar epithelial cell type I
AECII = alveolar epithelial cell type II
AGE = advanced glycation end products
ALA = α-lipoic acid
AMPK = AMP-activated kinase
Ang II = angiotensin II
AT1 = type 1 angiotensin receptor
AT1R = angiotensin II type 1 receptor
BDL = bile duct ligation
CaMKII = Ca^{2+}/calmodulin-dependent protein kinase II
CB_1 = cannabinoid receptor type 1
CTGF = connective tissue-derived growth factor
DAMPs = danger-associated molecular patterns
DOX = doxorubicin
Duox = dual oxidase
ECM = extracellular matrix

Abbreviations Used (Cont.)

EMT = epithelial-to-mesenchymal transition
EndMT = endothelial-to-mesenchymal
ERK1/2 = extracellular signal-regulated protein kinase 1 and 2
FD = fluorofenidone or [1-(3-fluorophenyl)-5-methyl-2-(1H)-pyridone]
FDA = U.S. Food and Drug Administration
Flu = fluvastatin
G-CSF = granulocyte-colony stimulating factor
GSH = glutathione
H_2O_2 = hydrogen peroxide
HGF = hepatocyte growth factor
HKD = hypertensive kidney disease
HSCs = hepatic stellate cells
ICAM-1 = intercellular adhesion molecule 1
IL = interleukin
iNOS = inducible nitric oxide synthase
IPF = idiopathic pulmonary fibrosis
Keap1 = Kelch-like ECH-associated protein 1
L7DG = luteolin-7-diglucuronide
LPA = lysophosphatidic acid
MAPK = mitogen-activated protein kinase
MCP-1 = monocyte chemoattractant protein 1
MFA = methyl ferulic acid
MgIG = magnesium isoglycyrrhizinate
MitoQ = Mitoquinone
MMPs = matrix metalloproteinases
mRNA = messenger RNA
MSCs = mesenchymal stem cells
NAF1 = nuclear assembly factor 1 ribonucleoprotein
NASH = nonalcoholic steatohepatitis
NF-κB = nuclear factor-kappa B
NO = nitric oxide
NOX = nicotinamide adenine dinucleotide phosphate oxidase
Nrf2 = nuclear factor erythroid-derived 2-like 2
PAH = pulmonary hypertension
PAI-1 = plasminogen activator inhibitor-1
PAMPs = pathogen-associated molecular patterns
PDGF = platelet-derived growth factor
PGE2 = prostaglandin E2
PPAR-γ = peroxisome proliferator-activated receptor-gamma
PPE-AuNP = pomegranate peel extract-stabilized gold nanoparticles
RAGE = receptor for advanced glycation end products
ROS = reactive oxygen species
SASP = senescence-associated secretory phenotype
SFTPs = surfactant proteins
SMA = smooth muscle actin
SMAD = mothers against decapentaplegic homolog
SOD = superoxide dismutase
STZ = streptozotocin
Tan-IIA = tanshinone IIA
TGF-β1 = transforming growth factor-beta 1
TIMPs = tissue inhibitors of matrix metalloproteinases
TMZ = trimetazinide
TNF-α = tumor necrosis factor-alpha
TPL = triptolide
TRPC6 = transient receptor potential cation channel 6
TSG = 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside
UUO = unilateral ureteral obstruction
VCAM-1 = vascular cell adhesion molecule-1
VSMCs = vascular smooth muscle cells
XO = xanthine oxidase inhibitor