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TRANSLATIONAL REVIEWS

You Say You Want a Resolution (of Fibrosis)

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Abstract

In pathological fibrosis, aberrant tissue remodeling with excess extracellular matrix leads to organ dysfunction and eventual morbidity. Diseases of fibrosis create significant global health and economic burdens and are often deadly. Although fibrosis has traditionally been thought of as an irreversible process, a growing body of evidence demonstrates that organ fibrosis can reverse in certain circumstances, especially if an underlying cause of injury can be removed. This body of evidence has uncovered more and more contributors to persistent and nonresolving tissue fibrosis. Here, we review the present knowledge on resolution of organ fibrosis and restoration of near-normal tissue architecture. We emphasize three critical areas of tissue homeostasis that are necessary for fibrosis resolution, namely, the elimination of matrix-producing cells, the clearance of excess matrix, and the regeneration of normal tissue constituents. In so doing, we also highlight how profibrotic pathways interact with one another and where there may be therapeutic opportunities to intervene and remediate pathological persistent fibrosis.

Keywords: fibrosis; resolution of fibrosis; fibroblasts; extracellular matrix turnover; pulmonary fibrosis

Clinical Relevance

This review provides an update on an important and rapidly evolving area of fibrosis biology, namely resolution of fibrosis. We believe this represents a valuable holistic view of this field and integration of its various subfields.

What is the problem with fibrosis? It is not that fibrosis occurs. On the contrary, exuberant matrix accumulation, the defining hallmark of fibrosis, is a critical aspect of a wound-healing response to tissue injury. This "excess" matrix serves several functions but most importantly provides structural integrity during wound healing. The problem with fibrosis is when it persists. A normal wound response in the very late stages of healing should exhibit the degradation and resolution of that excess matrix so that all that is left is normal tissue. Here, we review the data on that resolution phase. In our opinion, resolution of fibrosis requires the following three essential components: *1*) the cessation of excess matrix production, *2*) the clearance of the excess matrix, and *3*) the regeneration of normal tissue architecture. Several recent reviews have addressed some of the biology underlying the resolution of fibrosis (1–3), but it has been several years since this area has been last reviewed and we believe recent advances in the field mandate a reevaluation. Furthermore, we believe this third area of regeneration has been less well studied in the context of fibrosis and have included studies from outside the field that inform our understanding. Placing these three elements side by side in a review can also give us a holistic view of the different areas of pathobiology that lead to persistent fibrosis and how they may interact with one another.

Persistence of Matrix-Producing Cells

Fibroblasts are the primary cell type responsible for producing matrix and maintaining tissue integrity during the normal wound-healing response (4). In physiologic conditions, activated fibroblasts promote wound contraction, epithelial cell migration, and matrix degradation, all

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critical contributions to wound healing. The persistence of activated fibroblasts that continue to exuberantly produce matrix beyond these controlled phases of scar tissue resolution is likely a key mechanism necessary for the development of pathological, persistent, and nonresolving fibrosis. An ample body of evidence demonstrates that activated collagen-producing cells do not appropriately respond to apoptotic signals in nonresolving fibrosis (5–7). Matrix-producing cells exhibit resistance to normal programmed cell death in several fibrotic diseases, including scleroderma and liver and lung fibrosis (8–11). In some cases, this is linked to changes in cellular metabolism (12–16), redox balance (17, 18), innate immune or inflammatory pathways (19–21), environmental cues from extracellular matrix (ECM) or other cells (22), or imbalances between proapoptotic and antiapoptotic factors (23–25). In other cases, the underlying cellular mechanisms leading to apoptosis resistance are not well understood.

TGF-β1 as a Central Player

Of the many pathways involved in this process, TGF-β1 (transforming growth factor β1) is known to activate fibroblasts, attenuate myofibroblast apoptosis, and mediate the intrinsic pathway of apoptosis, suggesting that the persistence of profibrotic fibroblasts may be chiefly controlled by sustained TGF-β1 signaling (26, 27). Furthermore, the biomechanical properties of the fibrotic ECM activate latent TGF-β1 (28) and modulate apoptosis resistance in myofibroblasts through TGF-β1–dependent and independent mechanisms (29, 30), implicating a role of the ECM itself in resisting apoptosis in fibrotic myofibroblasts; this is discussed in more detail below. It is important to note that in contrast to fibroblasts, in lung epithelial cells, TGF-β1 activity induces a proapoptotic cascade (31), highlighting the idea that this pathway has pleiotropic effects that are context and cell-type specific.

Several groups have contributed to a body of literature suggesting that aberrations in cellular metabolism are central to fibroblast persistence and that this may be mediated by TGF-β1. Decreased activation of AMPK (5′ AMP–activated protein kinase) is an integral step in resistance to apoptosis in both human and mouse models of fibrosis (32–34). The prevailing evidence indicates that AMPK plays a critical role in promoting TGF-β1–differentiated myofibroblast deactivation and apoptosis by exerting control over cellular autophagy and mitochondrial biogenesis pathways (32). Metformin-induced activation of AMPK is capable of reversing the phenotypic effects of fibrosis by stimulating autophagy and ECM turnover in mouse and human models of lung (32) and kidney (34) fibrosis. Other established roles of AMPK, such as clearance of apoptotic cells (35), may be relevant in the context of the resolution of fibrosis. Studies in mice have shown that metformin inhibits the canonical fibrotic TGF-β1–signaling pathway by dampening NOX4-induced generation of reactive oxygen species (33), thus restoring fibroblast sensitivity to apoptosis and promoting the resolution of fibrosis.

Oxidative Stress and Mitochondria

Other studies of the nonresolving fibrosis that appears to be characteristic of aged animals have identified changes in redox metabolism and subsequent impairment of the *Nrf2* (nuclear factor erythroid 2–related factor 2)-induced antioxidant response as a common shared pathway in both mouse and human models of persistent fibrosis (36–39). It is known that oxidative stress plays a role in the pathogenesis of fibrosis (40–42) and that TGF-β1 enhances reactive oxygen species formation and diminishes the antioxidant response in several cell types (43–47). These findings, combined with the fact that TGF-β1 is well characterized as a canonical activator of myofibroblasts in wound healing and fibroproliferative diseases (48), seem to implicate mitochondrial function (49–51) as a central arbiter of apoptosis resistance in the context of fibrosis. Oxidant-induced mitochondrial DNA damage contributes to the senescent phenotype of idiopathic pulmonary fibrosis (IPF) fibroblasts (50), and the exogenous administration of thyroid hormone that improves mitochondrial bioenergetics has been shown to ultimately lead to the resolution of disease in mouse models of experimental lung fibrosis (51). We speculate that the resistance to apoptosis of collagen-producing cells under conditions of fibrosis is closely linked to aberrant cellular redox dynamics and antioxidant responses governed by the mitochondrion. This dovetails with the idea that aberration of proapoptotic and antiapoptotic effectors chiefly regulated by the mitochondrion also leads to the same phenotype (52). Thus, the mitochondrion in matrix-producing fibroblasts likely is a key node in cellular behavior governing the nonresolution of fibrosis.

Priming for Apoptosis

Recent evidence has shown that in the fibrotic milieu, myofibroblasts are actually primed to undergo apoptosis rather than resist apoptosis altogether (52). Cellular bases for this phenomenon revolve around relative increases in mitochondrial priming, which allows for tight control over myofibroblast apoptosis via the BCL-2 family of proteins known to regulate cell death (52–55). This paradigm is reinforced in the greater degree of mitochondrial priming observed in fibrotic myofibroblasts that persist despite being primed for apoptosis (54). Pharmaceutical manipulation of the BCL-2 pathway that mediates resistance to apoptosis induces cell death and reverses dermal fibrosis in mouse models of scleroderma (52). Because fibrotic cells are dependent on such antiapoptotic pathways for survival, future studies should investigate them as therapeutic targets for the resolution of persistent fibrotic disease.

Dedifferentiation

Activated fibroblasts are also programmed to dedifferentiate after normal wound healing resolves. Although once considered irreversible, the activation of fibroblasts has been shown to spontaneously reverse in animal models of liver (56) and lung (57) fibrosis. *MyoD* (myoblast determination protein 1), a master regulator of myogenesis (58), acts as a critical switch for fibroblast activation (57); elevated *MyoD* expression induces myofibroblast differentiation (59); and genetic silencing of *MyoD* restores myofibroblast susceptibility to dedifferentiation and apoptosis (60), and this is lost with aging. Agonist activation of peroxisome proliferator-activated receptor γ potently reverses myofibroblast differentiation and collagen deposition *in vivo* (61). Both *in vitro* and *in vivo* studies of carbon tetrachloride– and alcohol-induced liver fibrosis have demonstrated that activated fibroblasts revert to an inactive state that is primed to

reactivate during the resolution of fibrosis (56, 62). These studies provide promising arguments that targeting dedifferentiation may be an effective way to resolve established fibrosis.

Matrix Stiffness

The pathological response of fibroblasts to the stiff mechanical environment of nonresolving fibrosis also contributes to resistance to resolution in several ways. There are changes in tissue mechanics in all cases of tissue injury. The matrix stiffness characteristic of fibrosis appears to generate a feed-forward loop that augments pathogenic fibroblast activation and matrix production in a circular fashion (63, 64). In addition, stiff matrix can lead to apoptosis resistance in fibroblasts through TGF-β1–mediated and non-TGF-β1–mediated means, as discussed above. A recent mechanistic study on myofibroblast-generated contractile forces demonstrates that activated fibroblasts populating stiff matrix can activate quiescent fibroblasts and propagate fibrotic expansion solely via long-range tissue-level mechanical cues without any soluble or paracrine interactions (65).

Studies of explanted fibroblasts from fibrotic human lungs have identified diseased ECM as a predominant driver of pathological fibrotic gene expression (22), although this may be due to other cues in addition to stiffness. Several of these genes are targets of microRNA 29 (miR-29), an established mediator of TGF-β1–induced fibrosis (66, 67), and encode ECM proteins that are upregulated in human IPF, such as collagens and thrombospondins (22). There is a suggestion that fibrosis-induced changes in gene expression regulated by ECM may primarily occur at the level of translational control; work published by Parker and colleagues (22) suggested a model for fibrotic progression in which diseased ECM initiates and/or maintains a positive feedback loop to propagate the expression of fibrotic proteins. Of note, this model aligns with the pattern of contiguous fibrotic spread seen in human IPF (22). This hypothesis is corroborated by mouse studies that highlight the roles stiff matrix plays in selectively shortening the 3′ untranslated region and promoting the expression of fibrosis-related transcripts, such as type I collagen (68). Stiffness likely also influences the behavior of other cell types in the fibrotic milieu, for example by modulating the effects of TGF-β1 signaling (69); this deserves future study in fibrosis.

A potential mechanism by which fibroblasts respond to stiffness is through sensing extracellular cues that are then transduced via a change in the metabolism of the internal cellular state. For example, the cell-surface glycoprotein Thy1 (thymocyte differentiation antigen 1) binds inactive α(v) integrin (70), a positive mediator of fibrosis in multiple organs (71), and alters its baseline avidity to

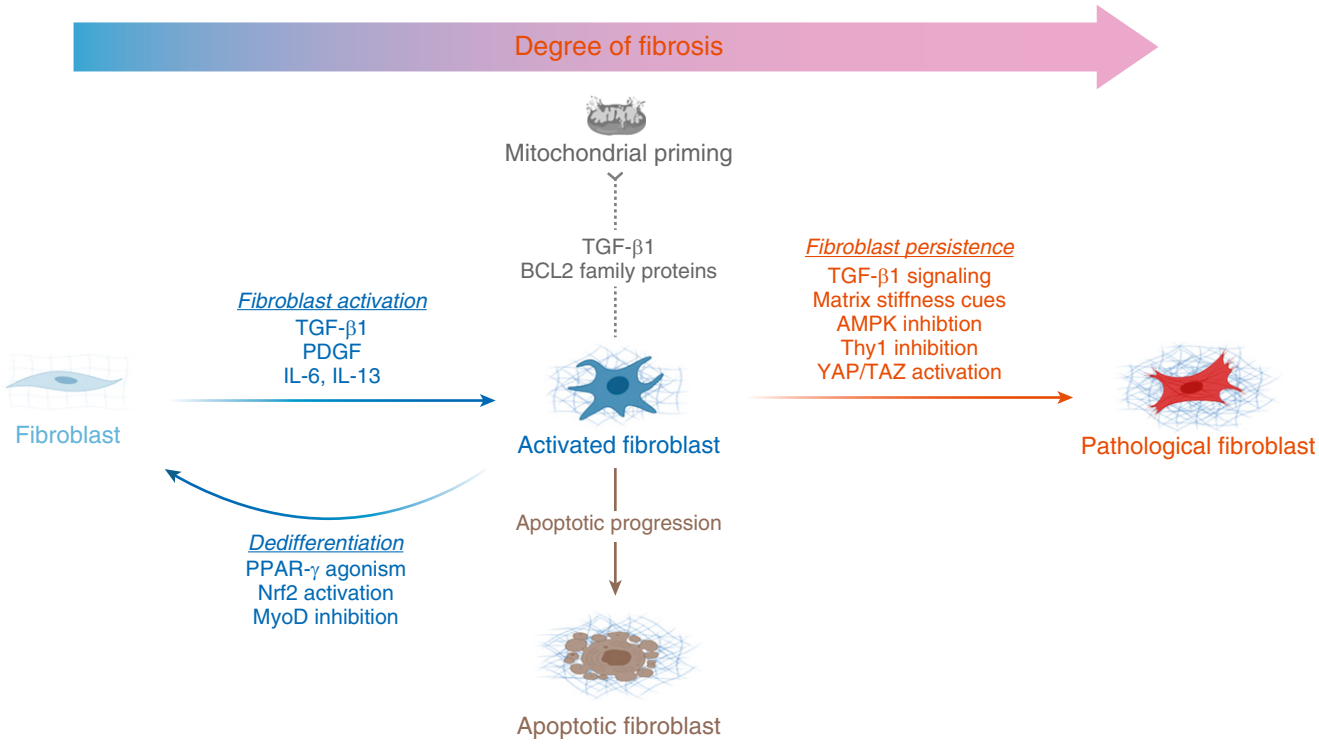

Figure 1. Schematic representation of the cellular events leading to pathological persistence of fibroblasts. This overview of the activation and persistence of fibroblasts in pathological fibrosis highlights the distinct mechanisms that drive tissue fibrosis. In normal physiological conditions, the secretion of profibrotic cytokines drives fibroblast activation and matrix production. Activated fibroblasts are primed for cell death and either dedifferentiate via transcriptional control of profibrotic genes or undergo apoptosis. In pathological fibrosis, the fibrotic milieu persists as activated fibroblasts bypass inactivation pathways by way of aberrant activation of profibrotic signaling, inhibition of antifibrotic molecules, and stiff matrix–induced feed-forward loops. AMPK = 5′ AMP-activated protein kinase; BCL2 = B cell lymphoma-2; PPAR-γ = peroxisome proliferator–activated receptor γ; MyoD = myoblast determination protein 1; Nrf2 = nuclear factor erythroid 2–related factor 2; PDGF = platelet-derived growth factor; TAZ = transcriptional coactivator with PDZ binding motif; TGF-β1 = transforming growth factor-β1; Thy1 = thymocyte differentiation antigen 1; YAP = yes-associated protein 1.

ECM ligands, thereby negatively regulating fibroblast activation and mechanotransduction. Surface expression of Thy1 is decreased in activated fibroblasts in *in vivo* models of persistent lung fibrosis, and exogenous administration of soluble Thy1 reverses fibrosis in a dose-dependent manner (72, 73), exemplifying a relevant avenue through which diseases of persistent fibrosis may be therapeutically resolved. Several groups have identified pronounced activation of YAP (yes-associated protein) and TAZ (transcriptional coactivator with PDZ-binding motif), homologous profibrotic transcription cofactors of the Hippo pathway, as a key step in stiffness-induced fibroblast activation and induction of the fibrotic niche (74–76). The precise mechanisms that govern this process remain unknown, but recent evidence indicates that the activation of dopamine receptor D1 in fibrotic mesenchymal cells inhibits YAP/TAZ function and induces the resolution of fibrosis *in vivo* (77). Knockdown of TBK1, a candidate regulator of stiffness-induced fibroblast activation identified via an RNA interference screen, also seems to ameliorate YAP/TAZ-induced fibrogenesis (78, 79). Notably, however, a paper from Herrera and colleagues showed that stiffness-induced signaling did not, in fact, control miR-29 expression via YAP/TAZ or other pathways, underscoring a knowledge gap in our current understanding of the interplay between matrix stiffness, YAP/TAZ-mediated lung fibrosis, and miR-29 signaling and of what might be the nonmechanical cues that control miR-29 (80). Regardless, that stiff matrix seems to exert its influence through TGF-β1 and that TGF-β1 tightly controls the YAP/TAZ system makes the YAP/TAZ pathway an attractive therapeutic target for resolving diseases of fibrosis. The established pathways that contribute to persistence of matrix-producing cells in pathological fibrosis are summarized in Figure 1.

ECM Turnover

Even if all matrix-producing cells are eliminated from fibrotic tissue, the

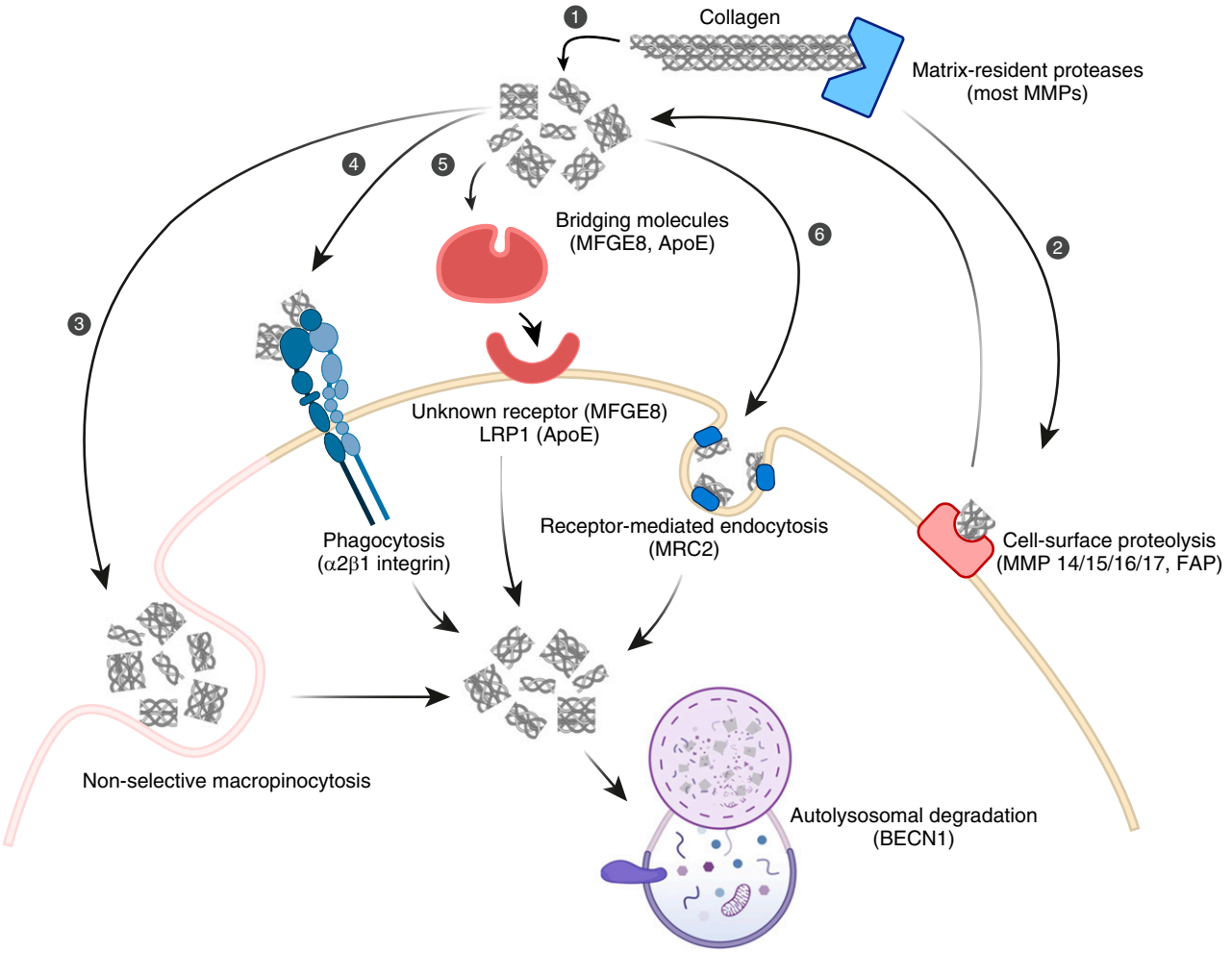

Figure 2. Collagen degradation and internalization are mediated by several pathways. Collagen fibrils are cleaved *1*) in the extracellular space and *2*) at the cell surface. The resulting fragments are internalized through *3*) macropinocytotic, *4*) phagocytic, and *5*) endocytic pathways and are ultimately degraded by the lysosome. *1*) Extracellular proteolysis of collagen fibrils. *2*) Cell-surface degradation of collagen fibrils. *3*) Nonselective actin-dependent micropinocytosis. *4*) Integrin α2β1–mediated phagocytosis. *5*) Opsonization and cellular uptake of collagen fragments. *6*) Cell-mediated endocytosis of collagen fragments. ApoE = apolipoprotein E; BECN1 = beclin 1; FAP = fibroblast activation protein; LRP1 = LDL receptor related protein 1; MFGE8 = milk fat globule-epidermal growth factor 8 protein; MMP = matrix metalloproteinase; MRC2 = mannose receptor C type 2.

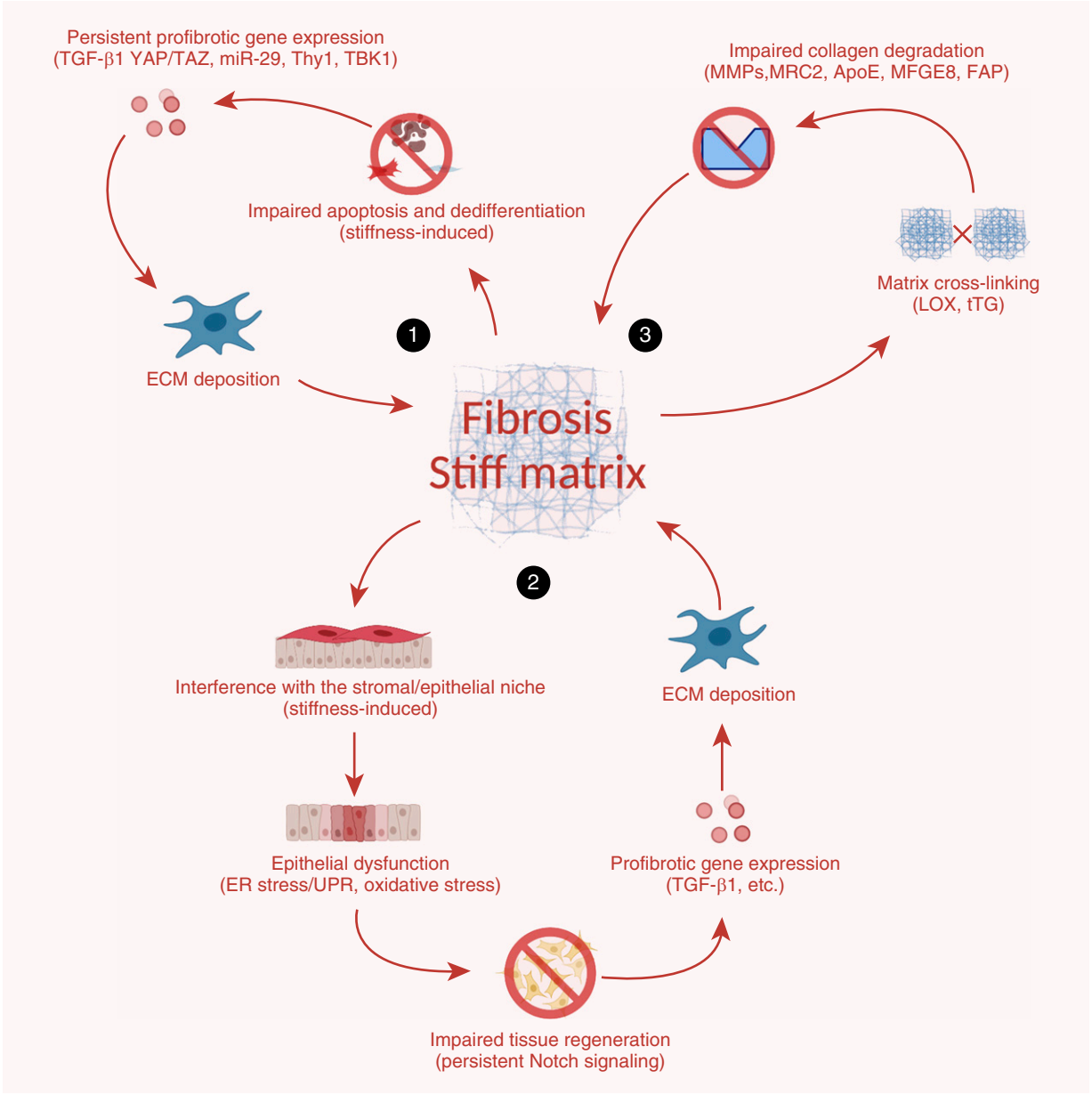

Figure 3. Profibrotic feed-forward mechanisms of nonresolving fibrosis. Positive feed-forward loops are associated with the fibrotic matrix that sustain and amplify the fibrotic phenotype. *1*) Stiff and fibrotic extracellular matrix signals impair normal fibroblast apoptosis and differentiation and lead to persistent expression of profibrotic genes that contribute to increased matrix stiffness. *2*) These cues also compromise normal epithelial function and tissue regeneration, leading to dysfunctional TGF-β1 activity and amplified extracellular matrix deposition. *3*) Enzymatic cross-linking of persistent fibrotic matrix further exacerbates the aberrant mechanical milieu by physically impeding the collagen degradative machinery. ECM = extracellular matrix; ER = endoplasmic reticulum; LOX = lysyl oxidase; miR-29 = microRNA 29; TBK1 = tank-binding kinase 1; tTG = tissue transglutaminase; UPR = unfolded protein response.

restoration of normal tissue architecture requires the clearance of excess ECM. A growing body of literature has demonstrated that the clearance of matrix components is essential for the resolution of organ fibrosis (81–83). Collagen is the most abundant constituent of both normal ECM and fibrotic ECM. Systematic reviews of the mechanisms underlying collagen degradation and clearance have been published elsewhere (84); we will not focus on these. It is important to note that the resolution of fibrosis would also require the degradation of other ECM molecules, such as proteoglycans (85) and elastins (86, 87), but collagen catabolism is the most thoroughly understood area of ECM degradation in the field. The currently established collagen degradation pathways are depicted in Figure 2 and detailed below.

Matrix and collagen degradation take place by both an extracellular proteolytic route (88–90) and a process of cell-mediated uptake and degradation

(82, 91–93). Both processes are important in the resolution of fibrosis. Several lines of inquiry indicate that extracellular proteolysis and cell-mediated uptake of collagen work both sequentially and in parallel to clear fibrotic tissue in normal wound healing (94, 95). Diseases of persistent fibrosis are marked by impaired collagenolytic activity of tissue (81). A concomitant imbalance between proteolytic enzymes and their inhibitors has been well described. In general, this area has been difficult to study *in vivo* because enzymes that participate in matrix degradation (e.g., MMPs [matrix metalloproteinases]) have complex regulation and cleave multiple substrates with pleiotropic-signaling effects (96–99). Thus, interference with their activity or genetic deletion models in mice can produce phenotypes that are unexpected based solely on their matrix-cleaving activity (100–102). Excessive covalent cross-linking of collagen fibers by the LOX (lysyl oxidase) family of enzymes (103) and tissue transglutaminase (104) may further impair collagen turnover in the fibrotic milieu. Therapeutic strategies targeting LOX enzymes have shown impressive reductions in tissue fibrosis in preclinical mouse studies (105), but clinical trials have produced disappointing results (106), possibly because of the inherent difficulties of targeting proteins widely expressed in connective tissue. This may also speak to the difficulty in targeting the nonenzymatic cross-linking of matrix that occurs over time and that would not be expected to be directly affected by targeting cross-linking enzymes (107, 108).

Genetic deletion or normal age-related decrement of expression of key proteins involved in cell-mediated collagen degradation leads to exaggerated or persistent fibrosis in several mouse models. Examples include *Mfge8* (milk fat globule-epidermal growth factor 8), an opsonin for collagen (92); *Beclin1*, an autophagy protein (109–110); and *Mrc2*, an endocytic receptor for collagen (111–116). *Fap*, a cell-surface endopeptidase that is upregulated in fibrosis (117, 118) also appears to regulate collagen degradation via cellular uptake pathways. Studies of global *Mrc2* deletion in mice (119, 120) do not answer the question of which cell type is most responsible for contributing to exaggerated fibrosis, but expression data show that *Mrc2* is primarily expressed on stromal cells and fibroblasts in particular (116, 121–125). Of note, *Mrc2* is differentially expressed during the early and late stages of wound healing (126), underscoring a need to functionally elucidate when one collagen degradation pathway may be spatiotemporally favored over another. The activation of urokinase plasminogen activator, an *Mrc2*-associated protease whose activity is inversely related to the severity of fibrosis, reduces parenchymal stiffness and enhances activated fibroblast apoptosis, ultimately resolving established lung fibrosis in mice (127). These findings suggest that *Mrc2* may be a key mediator of resolution of fibrosis by activating several associated pathways of collagen degradation.

A recent paper demonstrated a novel pathway of cell-mediated uptake and degradation of collagen via *ApoE* (apolipoprotein E) and its receptor LRP1 (128). *ApoE* deletion in mice decreases collagen clearance by macrophages chiefly during the resolution phase of experimental fibrosis, and exogenous administration of APOE promotes resolution without any noticeable effects on the progression of disease or peak fibrosis; this effect is due to opsonization of collagen. Such data reinforce the idea that myeloid cells, especially macrophages, participate in cell-mediated collagen degradation in parallel with stromal cells or fibroblasts among other cell types. A prior study of hepatic fibrosis in mice shows that macrophage deletion at an early time point mitigates fibrosis, whereas macrophage deletion at a late time point, at which time fibrosis is well established, leads to the persistence of fibrosis (129). Although the mechanism surrounding this phenomenon is not fully delineated, MMP13 colocalizes with scar-associated macrophages in the liver, and the deletion of MMP13 in the same hepatic fibrosis model inhibits the resolution of disease (130), suggesting a critical role of macrophage-derived metalloproteinases in resolving fibrosis. These findings support the idea that macrophages contribute to the resolution of fibrosis, at least via clearance of matrix.

These pathways are some of the most robustly studied in the resolution of fibrosis. However, other mechanisms of cell-based matrix degradation have been shown to occur in other contexts, including phagocytosis and micropinocytosis (131–134). Open questions in the field include the following: Which of these different modes of matrix degradation dominate depending on specific cell types, tissue contexts, or tissue injuries? How might these different modes be constrained spatiotemporally? How are all of these different modes of matrix degradation regulated? How are these all linked?

Regeneration of the Niche and Normal Tissue

Transitioning from fibrotic tissue to normal parenchyma necessarily involves the clearance of excessive matrix, but this is insufficient for the total resolution of fibrosis. Regeneration of normal tissue to occupy the formerly fibrotic niche must also take place. This is an area that is relatively understudied in the field of fibrosis, but there is much to learn from studies of acute organ injury such as influenza infection (135–137), embryonic development (138, 139), and cancer (140, 141). Recent studies in the field have established different epithelial progenitors of normal parenchyma based on origin (142–144), cell-surface markers (145–148), and anatomic location (149). Understanding which cells can proliferate and regenerate normal tissue is critically important. Of course, resolving fibrosis is not only a matter of regenerating normal epithelium (150, 151) but also, in the case of the lung, the entire alveolus, the complicated epithelial–endothelial gas-exchanging unit, such that it appropriately integrates into the airway and vascular network. How this may occur remains poorly understood despite published work on the regeneration of the epithelial layer (152–154). Studies have demonstrated that the supportive stroma itself (155) can provide growth factors and establish a niche for lung regeneration, perhaps through paracrine signaling.

Although it is clear that physiological tissue regeneration is necessary for the complete resolution of fibrosis, there are fewer data proving that failed regeneration actively prohibits this process. When certain epithelial progenitors are dysfunctional in the mouse lung, failed tissue regeneration generates cystic structures that appear similar to the parenchymal honeycombing

patterns seen in IPF (142), suggesting that impaired tissue regeneration is causally related to the persistence of matrix in diseases of continued and nonresolving fibrosis. This hypothesis is supported by the observation that alveolar epithelial stem cells (156) isolated from IPF tissue have impaired regenerative ability compared with healthy tissue (157), highlighting the lung stem-cell population as an important mediator of functional tissue regeneration. Injured epithelium can recruit profibrotic macrophages via CCL2/12 (158), corroborating earlier studies (159) that establish epithelial injury as a driver of pulmonary fibrosis and providing a direct link between abnormal epithelial signaling and both the initiation and the maintenance of the fibrotic cascade. Another line of evidence supporting this concept arises from the observation that genetic disorders of telomere maintenance lead to some of the most penetrant forms of familial fibrosis (160–163). The precise mechanistic link between short telomeres and fibrosis is not yet known, but several studies in humans and mice suggest that an abnormal capacity for epithelial regeneration is a hallmark feature of telomeropathy (164, 165). In conditional mouse knockout models of the telomere shelterin protein TRF1 in alveolar epithelial cells, telomere dysfunction leads to spontaneous fibrosis (164). The deletion of TRF2 in the same cell type leads to a similar pathological fibrosis-like response (165), providing convincing evidence that normal telomere function is critical in preventing or resolving fibrosis.

Short telomeres are seen in alveolar epithelial cells of patients with IPF and telomeres grow short with age in *Trf1*-knockout mice (164), recapitulating the clinical observation that age is the greatest risk factor for IPF (166). In mice, normal aging exhausts the lung stem-cell population, thereby blunting the lung's ability to regenerate damaged tissue (167). This aging-related decrement of a crucial regenerative cell type may also help to explain why age is the strongest risk factor for IPF. Restoring epithelial stem-cell function or regenerating such cells in patients will remain a significant therapeutic challenge. Of note, markers of endoplasmic reticulum (ER) stress have been detected in alveolar epithelial cells in mouse models of persistent lung fibrosis (168) and in human disease (169) models of persistent lung fibrosis. This finding, combined with the fact that lung epithelial cells commonly exhibit short telomeres in fibrosis (161–164), suggests that dysfunctional epithelium may play a more significant role in impeding the resolution of fibrosis than once believed. A recent study showing that abnormal surfactant protein expression in alveolar epithelium leads to ER stress and the spontaneous development of lung fibrosis lends credence to this idea (170). We believe these data bolster the need to systematically investigate the mechanisms by which dysfunctional epithelium contributes to nonresolving fibrosis, potentially through ER stress and protein misfolding, among other pathways.

Senescent cells (including fibroblasts and epithelial cells among other cell types) may play a role in limiting normal tissue regeneration because the retention of senescent cells is associated with persistence of fibrosis in the lung (171, 172), heart (173), skin (174), liver (175), and kidney (176). However, the role of senescent cells in lung fibrosis is controversial; paradoxically, they can contribute to both fibrotic progression (177) and fibrotic resolution (178). This seeming bidirectional control over the physiological tissue repair program also deserves greater study, especially in the context of developing "senotherapeutics," drugs that specifically induce apoptosis in senescent cells and present an interesting therapeutic avenue for normal tissue regeneration and the subsequent resolution of fibrosis.

Interplay and Future Directions

A vexing aspect of fibrosis is that although many key features, cell types, pathways, and molecules have been identified, it has been difficult to pinpoint the etiopathological origin of disease. For example, it is unclear whether dysfunctional epithelium, through telomeropathy, ER stress, or another cause, marks the starting point of fibrosis (179, 180) or whether excess matrix functionally destroys the niche for epithelial regeneration and initiates a pathological response (181, 182). Ample data supporting the hypothesis that dysfunctional epithelium is primarily responsible for instigating fibrosis exist. The efferocytosis of injured lung epithelium (179) and secretion of connective tissue growth factor (180) by alveolar epithelial cells can both independently initiate fibrosis in addition to the pathways we have described above. Likewise, excess matrix could be considered a key initiator of fibrosis. Fibrotic tissue provides a physical platform for novel intercellular and cell–ECM interactions that control cellular specification and differentiation (181, 182) and potentially preclude normal wound-healing responses.

Answers to such questions are difficult to tease out and, among other questions of causality and dependency, are matters of great debate. However, they would speak to the interdependence of the different aspects of biology we have heretofore discussed that contribute to the impaired resolution of fibrosis. As discussed previously, a feed-forward mechanism that promotes fibroblast resistance to apoptosis as a consequence of tissue stiffness can lead to more matrix production and, hence, more tissue stiffness, resulting in an aberrant positive feedback loop of collagen synthesis (22, 183, 184). Increased collagen cross-linking is also associated with upregulated activity of cross-linking enzymes that arises from fibroblast activation, and increasingly cross-linked collagen is more difficult to degrade by cellular or noncellular means (185–187), providing another feed-forward mechanism for nonresolving fibrosis in the context of matrix turnover. Some areas of interplay between the areas we have described are not well characterized. Replacement of the regenerative niche by fibrotic tissue seems to inhibit normal tissue regeneration, but we do not know to what extent an abnormal niche influences fibroblast behavior in terms of matrix production and turnover or to what extent it influences epithelium in terms of signaling to profibrotic macrophages. Cellular cross-talk is undoubtedly an exciting and important area of active study in the field of fibrotic resolution (188, 189).

It is difficult to theorize why so many endogenous feed-forward loops exist (Figure 3), but we speculate that these pathways serve a function in the normal physiology of wound healing or tissue regeneration. For example, is durotaxis

crucial to the recruitment of fibroblasts to a fresh thrombus? The existence of these feedback loops, however, may provide a potential explanation as to why fibrosis is ubiquitous in organ injury and is a feature of so many chronic diseases (190) and to why we actually may never find a unifying shared etiology among different fibrotic diseases. One can imagine that with the existence of multiple feed-forward loops, the pathological cycle of fibrotic disrepair could arise via many disparate etiologies (i.e., entry into these loops may occur at any point). At the same time, feed-forward loops act as promising therapeutic targets for diseases of fibrosis because interventions in such cycles would pay exponential dividends in the resolution of disease and restoration of normal tissue function. Thus, understanding these three critical areas of fibrosis biology and their interplay provides numerous opportunities for therapeutic intervention that may alleviate human suffering caused by diseases of nonresolving fibrosis. ■

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