Fibrosis — A Common Pathway to Organ Injury and Failure

Don C. Rockey, M.D., P. Darwin Bell, Ph.D., and Joseph A. Hill, M.D., Ph.D.

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Anna Rath

Background

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- Authors:
    - Don C. Rockey, M.D.,
    - P. Darwin Bell, Ph.D.
    - Joseph A. Hill, M.D., Ph.D.

Fibrosis I

- One third of deaths worldwide
- High morbidity and mortality
- Almost all organ systems:
    - Eyes
    - Skin
    - Lung
    - Heart
    - Pancreas
    - Liver
    - Kidney
- Causes physical organ deformation, which impairs organ function

Fibrosis II

- Not irreversible “scar”
- Highly plastic nature and dynamic process
- Degree of plasticity appears to vary
- Injury-> Complex cellular and molecular response
  - Short term: adaptive features
  - Long term: -> parenchymal scarring -> cellular dysfunction -> organ failure

Pathogenesis

Pathogenesis I

- Diverse diseases in different organ systems associated with fibrosis -> Common pathogenic pathways
- Interplay between factors that promote the biosynthesis, deposition and degradation of extracellular matrix proteins
- Triggered by acute and chronic inflammation
  - Injury stops: Resorption of extracellular matrix proteins-> promoting organ repair
  - Injury persists: Unremitting activation of effector cells -> continuous deposition of extracellular matrix -> progressive scarring & organ damage

Pathogenesis II

- The matrix proteins that compose the fibrotic scar, consists of:
  - Interstitial collagen (types I and III)
  - Cellular fibronectin
  - Basement-membrane proteins (e.g. Laminin)
- Fibroblasts and myofibroblasts:
  - Key fibrosis effectors
  - Responsible for synthesis of extracellular matrix proteins

Pathogenesis III

- Four phases:
  - Phase 1: Initiation of response
  - Phase 2: Activation of effector cells
  - Phase 3: Growth of extracellular matrix
  - Phase 4: Dynamic deposition of extracellular matrix

    -> Progression to fibrosis & organ failure

Cellular level I

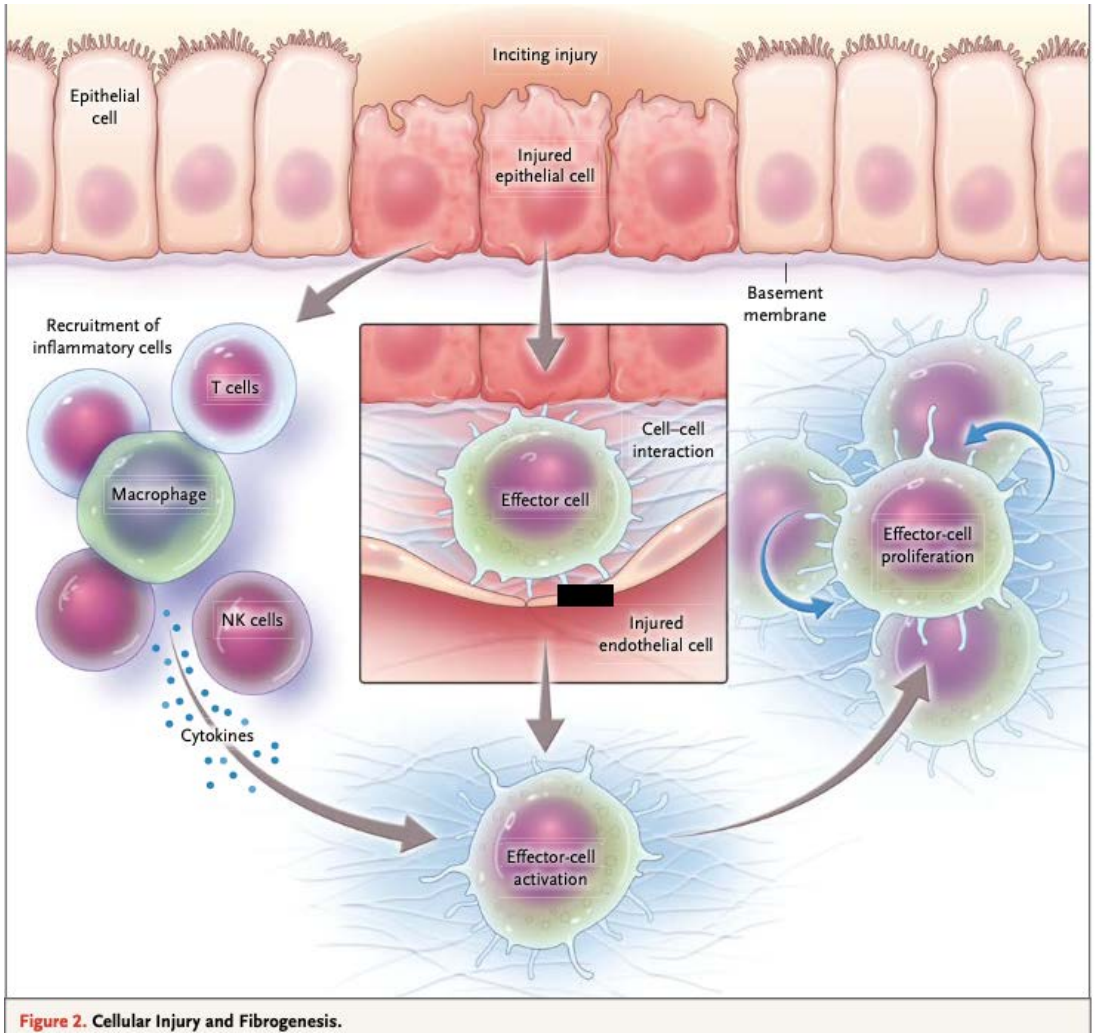

Figure 2. Cellular Injury and Fibrogenesis.

Cellular level II

- Inflammation -> Injury of resident epithelial cells and endothelial cells -> enhanced release of inflammatory mediators
- -> Recruitment of a wide range of inflammatory cells
- -> Inflammatory cells elicit the activation and proliferation of effector cells
- -> Fibrosis progresses

Fibrogenic effector cells

- Fibroblasts, fibrocytes, tissue-specific pericytes, myofibroblasts
- Mesenchymal origin
- Derived through epithelial-to-mesenchymal transition
- Autocrine loops
- Cell–cell interactions lead to further activation of effector cells
- Produce:
  - Extracellular matrix proteins
  - Peptides
  - Cytokines
  - Growth factors

Myofibroblasts

- Produce large amounts of extracellular matrix
- Derived from fibroblasts or from other mesenchymal cells
- Express smooth-muscle proteins
- Contractable
- -> Contractile mediators trigger pathological tissue contraction
- -> Distortion of parenchymal architecture -> promotes disease pathogenesis and tissue failure

Macrophages

- Prominent role in interstitial fibrosis
- Often driven by the TGF-β pathway
- Can be protective
- Certain populations phagocytose apoptotic cells that promote the fibrogenic process and activate matrix-degrading metalloproteases

Extracellular matrix

- Cascades triggered by exposure of effector cells to molecules that stimulate the biosynthesis and secretion of extracellular matrix proteins
- Modify the wound milieu
- Stimulates fibrogenic effector cells in an autocrine fashion
- Stimulates fibrogenesis through activation of integrins
- Matrix synthesis counterbalanced by matrix-degrading metalloproteases

Molecular pathway I

- Wide-ranging and complex:
  - Platelet-derived growth factor (PDGF)
  - Connective-tissue growth factor (CTGF)
  - Vasoactive peptide systems (angiotensin II, endothelin-1)
  - Angiogenic pathways
  - Integrins
  - Endothelin
  - Transforming growth factor beta (TGF-β)

Molecular pathway II

- TGF-β cascade
  - Major role
  - Involves multiple signaling cascades
  - Potent stimulator of the synthesis of extracellular matrix proteins
  - Synthesized and secreted by inflammatory cells and effector cells
  - Autocrine and paracrine function

Molecular pathway

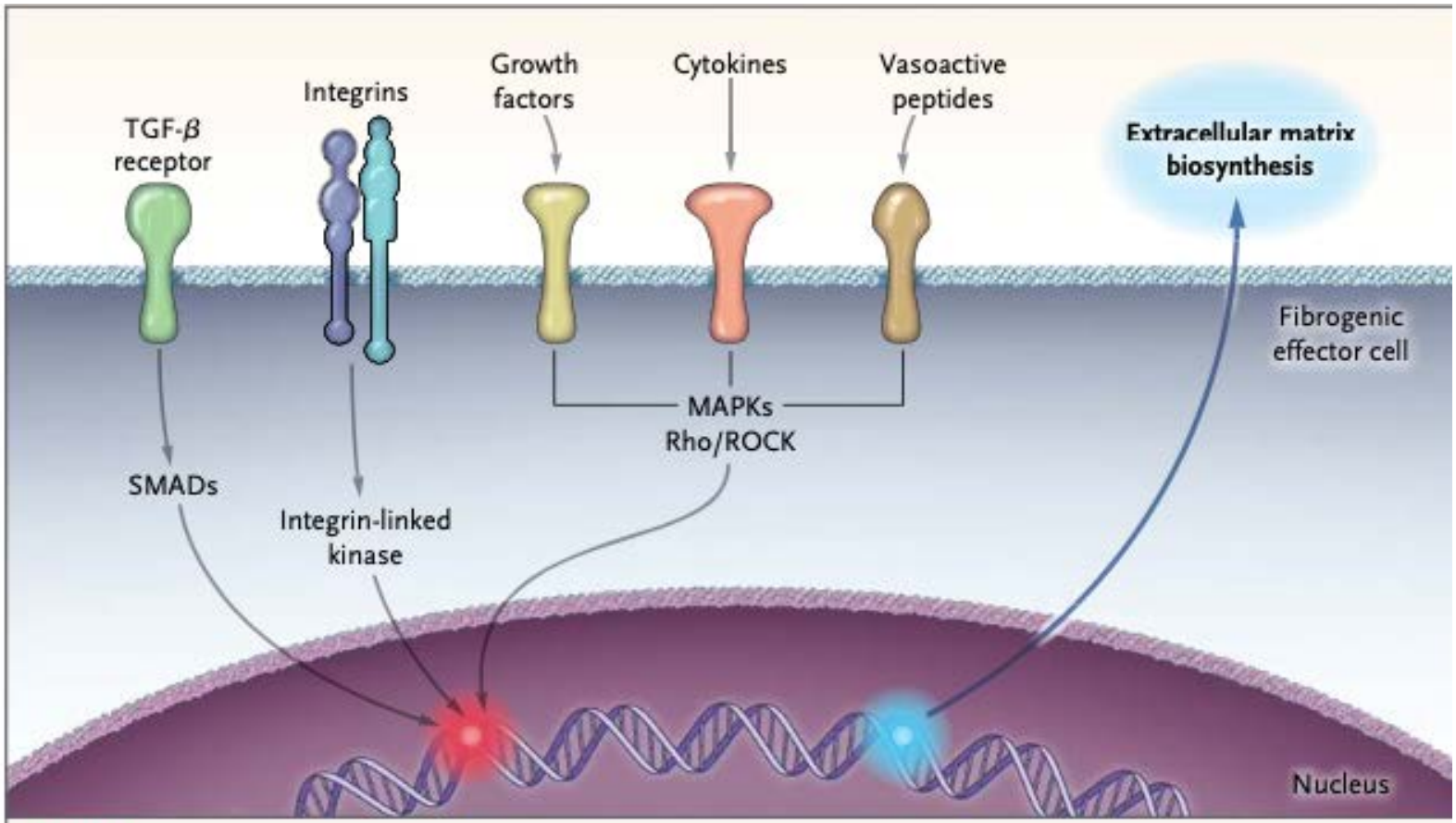

Figure 3. Molecular Pathways in Fibrosis.

Genetics

- Kidney: Mutations in *FAN1* -> Karyomegalic interstitial nephritis
- Liver: Mutation in *PNLAP3* -> Fibrosis mediated by ethanol / associated with fatty liver disease
- Lung: Mutations in *TERT* and *MUC5B*
- Number of genes are important for fibrosis mediated by HCV infection
- Epigenetic regulation:
  - Fibroblasts from patients with IPF have changes in DNA methylation
  - Regulatory noncoding RNAs also involved

Mechanisms and Adverse Clinical Effects

Cardiac fibrosis I

- Extensive structural and functional remodeling after injury
- Hypertrophy of cardiac myocytes, with excessive deposition of extracellular matrix
- Myocardial fibrosis
  - Reactive fibrosis : in perivascular spaces and corresponds to similar fibrogenic responses in other tissues
  - Replacement fibrosis: occurs at the site of myocyte loss
- Attributed to cardiac fibroblasts
  - Proliferate and differentiate into myofibroblasts after injury
  - Driven by classic factors such as TGF-β, endothelin-1, and angiotensin II

Cardiac fibrosis II

- -> Proarrhythmic effects
- -> Systolic and diastolic dysfunction
- Collagenous septa in heart -> discontinuous slowing of conduction
- Increased incidence of sudden cardiac death
- 3% increase in the extracellular volume fraction of fibrous tissue, associated with a 50% increase in the risk of adverse cardiac events

Hepatic fibrosis

- Variety of effectors synthesize extracellular matrix especially hepatic stellate cells
- Hepatic stellate cells
  - Pericyte like
  - Undergo transformation into myofibroblasts after injury
- Pathway unique to the liver: Toll-like receptor 4 (TLR4)
  - Activated on the surface of stellate cells by intestinal bacterial lipopolysaccharides from the gut
  - -> Triggering cell activation and fibrogenesis
  - -> Linking fibrosis to the microbiome
  - TLR4 expression associated with portal inflammation and fibrosis
- End result: cirrhosis
  - -> Portal hypertension
  - -> Wide range of devastating complications with adverse effects on survival

Renal fibrosis

- Hypertension and diabetes are leading causes of renal fibrosis
  - High glomerular capillary pressure -> proteinuria -> activation of cytokines and complement -> infiltration of immune cells -> **fibrosis** -> diminishes renal blood flow -> hypoxia & activation of hypoxia-inducible factor 1 -> triggers nephron collapse and fibrotic replacement
- Renin–angiotensin–aldosterone axis important
- Location of initial injury decisive of clinical consequences
  - ->Loss of function and organ failure
  - -> Anemia
  - -> Regulation of electrolyte balance and pH is disrupted

Pulmonary fibrosis I

- Less dynamic than other fibrosis
- Wide range of diseases: idiopathic, scleroderma, sarcoidosis, infection, result of environmental exposures
- Injury to alveolar epithelial cells activates pulmonary fibroblasts, provoking their transformation to matrix-producing myofibroblasts
- Activated lung fibroblasts may cause apoptosis of alveolar cells -> further fibroblast activation
- Research focused on TGF-β signaling and interstitial pericytes

Pulmonary fibrosis II

- Parenchymal honeycombing
- Reduced lung compliance
- Restrictive lung function
- Hindered gas exchange -> abnormal oxygenation and clinical dyspnea
- Progressive pulmonary fibrosis -> pulmonary hypertension, right-sided heart failure, respiratory failure
- Idiopathic pulmonary fibrosis (IPF): progressive fibrosis without substantial inflammation, unlike other fibrosing diseases, poorly understood

Other fibrosis

- Retroperitoneum:
  - Rare
  - Inflammation and fibrosis of retroperitoneum
  - Mostly idiopathic, or drugs, infections, autoimmune and inflammatory stimuli, and radiation
- Skin: scleroderma
  - Skin fibroblasts and myofibroblasts are activated through the TGF-β–SMAD signaling pathway
- Nephrogenic systemic fibrosis:
  - Widespread organ fibrosis
  - In patients with renal insufficiency with exposure to gadolinium-based contrast material
  - Prevention

Therapy

Therapies I

- Elimination of the stimulus is the first and most efficacious approach
- Promising preclinical studies BUT not confirmed in clinical trails
- Specific therapies are limited
- Not clear what pathogenic or clinical factors promote reversibility
- Regression leads to improved clinical outcomes
- Progression slowly, therapy may be required for extended periods
- Slowing the progression more realistic therapeutic goal than eliminating it

Therapies II

- The best indication for reversibility: in HBV positive patients with cirrhosis with antiviral therapy
  - Reduction of fibrosis
  - Reversion of cirrhosis
  - Reduction of incidence of clinical complications
- Reversion by elimination of effector cells and shifts in the balance of matrix synthesis and degradation
- Specific targets for hepatic and pulmonary fibrosis

Therapies for cardiac fibrosis I

- Therapies with secondary effects on fibrosis
  - ACE inhibitors
  - Statins
  - Aldosterone antagonists
  - Histone deacetylase inhibitors

- -> Reduction of ventricular arrhythmia
- Slow rate of ventricular tachycardias
- Reduce incidence of sudden cardiac death

Therapies for cardiac fibrosis II

- Promising ideas is based on premise that cardiac fibroblasts can be reprogrammed into cardiomyocyte-like cells
  - -> Would promote normal tissue regeneration
  - Shown in murine model:
  - -> Improvements in contractile function

Therapies for renal fibrosis

- Therapies typically target underlying disease processes
- ACE inhibitors and angiotensin-receptor blockers:
  - Ameliorate renal damage and fibrosis
  - Through multiple pathways (also TGF-β)
- Aldosterone antagonists:
  - Inhibitation or slowing the progression of fibrosis
- New therapies target:
  - Bone morphogenetic protein-7
  - NADPH oxidase (NOX1 and NOX4)
  - SMAD3 and SMAD4 pathways

Therapies for hepatic fibrosis I

- Hepatocytes capable of regeneration
- Especially amenable to therapeutic intervention
- Even cirrhosis can be reversed
  - Eradication of HCV infection
  - Antiviral therapy for HBV infection
  - Glucocorticoid therapy for autoimmune hepatitis
  - Phlebotomy for hemochromatosis
  - Relief of biliary obstruction
  - Stopping of alcohol consumption in alcoholic hepatitis
- -> Clearly reverses fibrotic change
- -> Improve clinical outcome

Therapies for hepatic fibrosis II

- Colchicine:
  - Suppresses collagen secretion
  - Theoretically prevents fibrosis
- Interferon γ-1b and Farglitazar:
  - Inhibit stellate cell-mediated fibrogenesis
  - Studied in HCV patients unresponsive to primary antiviral therapy
  - No beneficial effects on fibrosis
- Polyenephosphatidylcholine, Silymarin, Ursodeoxycholic acid:
  - no benefit
- Vitamin E:
  - modest effects on histologic fibrosis in patients with nonalcoholic steatohepatitis

Therapies for pulmonary fibrosis

- Interferon γ-1b:
  - Efficacy in preclinical studies
  - No benefit in human clinical trials
- Endothelin-receptor antagonists:
  - No benefit
- Pirfenidone:
  - Presumably has effects on TGF-β production
  - Reduced disease progression
  - Increased survival in patients with idiopathic pulmonary fibrosis
  - Reduction in forced vital capacity
  - Reduction in mortality
  - Raising the possibility of a reversal in fibrosis
- Nintedanib:
  - Slowed disease progression
- Outcomes based on clinical results

Table 1. Pathways and Processes in Fibrogenesis and Current Treatments.*

Organ	Pathways and Processes	Diseases	Drugs	Summary of Effectiveness	Source of Data†
Heart	Aldosterone antagonism, TGF-β antagonism, RAS inhibition, cGMP inhibition, inhibition of cholesterol synthesis, inhibition of Na-K-Cl cotransporter	Heart failure, cardiomyopathy, hypertrophic cardiomyopathy, cardiomyopathy induced by type 2 diabetes, heart failure or cardiomyopathy induced by hypertension	Spironolactone, eplerenone, canrenone, pirfenidone, sildenafil, statins, ACE inhibitors, ARBs, torsemide, MRAs	ACE inhibitors, ARBs, and MRAs are associated with decreased fibrosis on MRI and decreased arrhythmogenesis (the latter suggests effects of drugs on fibrosis)	Kosmala et al.,[67] Giannetta et al.,[68] Antonopoulos et al.,[69] Roubille et al.,[70] TORAFIC Investigators Group[71]
Liver	RAS inhibition, inhibition of collagen synthesis, inhibition of effector-cell fibrogenesis, inhibition of oxidative stress, signaling of PPAR γ-agonists	Many diseases of the liver	ACE inhibitors, ARBs, colchicine, interferon γ-1b, vitamin E, pioglitazone, farglitazar	Specific antifibrotic agents listed have generally been ineffective in halting or reversing fibrosis	Sanyal et al.,[72] Kim et al.,[73] Kershenobich et al.,[74] Morgan et al.,[75] Muir et al.,[76] Pockros et al.,[77] McHutchison et al.[78]
Kidney	RAS inhibition, aldosterone antagonism, TGF-β antagonism, Nrf2 pathway	Primarily renal diseases related to hypertension or diabetes	ACE inhibitors, ARBs, spironolactone, pirfenidone, bardoxolone	ACE inhibitors and ARBs are moderately effective in slowing progression of diabetic nephropathy (indirectly suggesting effects on fibrosis)	Lambers Heerspink et al.,[79] Ruggenenti et al.,[80] Bonventre,[81] Guney et al.,[82] Sharma et al.,[83] de Zeeuw et al.[84]
Lung	TGF-β antagonism, direct inhibition of effector-cell fibrogenesis, multikinase inhibition, inhibition of oxidative stress	Primarily idiopathic pulmonary fibrosis	Pirfenidone, interferon γ-1b, bosentan, ambrisentan, macitentan, nintedanib, acetylcysteine	Pirfenidone and nintedanib led to improvements in clinical outcomes	Raghu et al.,[85-87] King et al.,[88] Richeldi et al.,[89] Martinez et al.[90]
Skin	Endothelin-receptor antagonism, multikinase inhibition	Scleroderma, nephrogenic systemic fibrosis	Bosentan, imatinib mesylate	Small studies show modest effects	Kuhn et al.,[91] Kay and High[92]

* ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, cGMP cyclic guanosine monophosphate, MRA mineralocorticoid-receptor antagonist, MRI magnetic resonance imaging, Nrf2 nuclear factor erythroid 2–related factor, PPAR peroxisome proliferator-activated receptor, RAS renin–angiotensin system, and TGF-β transforming growth factor beta.

† Detailed information about specific trials is provided in Table S1 in the Supplementary Appendix.

Conclusion

Conclusion

- Great interest in slowing, arresting, or reversing the progression of fibrogenesis
- Need for a deeper comprehension of the pathogenesis
- Therapies targeting fibrogenesis specifically are missing

Thank you for your attention!