

Fibrosis: When the Repair Process Becomes the Disease

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Abstract. Fibrosis exemplifies a protective repair mechanism that can become pathological when matrix accumulation and mechanical signaling persist. This paper examines a feedback model of fibroblast activation, tissue stiffening and organ dysfunction while distinguishing it from the many causes of fibrotic disease.

A rational response with harmful long-term costs

When tissue is injured, fibroblasts and other stromal cells build extracellular matrix to preserve structural continuity. This is often indispensable. Persistent or excessive deposition, however, can obstruct gas exchange in lung, disturb hepatic architecture, compromise renal filtration or impair movement. An organ can consequently lose function even after the initiating insult has been reduced. The clinical expression depends on which structures were damaged and how much functional reserve remains.

The matrix is an active participant

In fibrotic tissue, collagen density, crosslinking and stiffness change the signals encountered by fibroblasts and resident cells. Mechanotransduction pathways including YAP/TAZ can translate stiffness into gene expression that favors contractility and further matrix production. Experimental work in lung fibrosis documents this reciprocal relationship. One can therefore formulate a precise positive-feedback loop: injury produces matrix; matrix stiffness favors a profibrotic phenotype; that phenotype adds more matrix.

Not every fibrosis has one switch

Progressive fibrosis may involve transforming growth factor beta, inflammation, epithelial damage, toxic exposure, autoimmune disease, ischemia and numerous organ-specific factors. A mechanistic essay should not imply that YAP/TAZ is the solitary driver or that blocking it would be sufficient. Some fibrotic processes continue because the original disease remains active; others carry residual irreversible architectural change after disease control.

What makes a treatment truly antifibrotic?

Reducing an inflammatory biomarker, easing dyspnea or improving laboratory chemistry can be valuable without reversing established scar. A convincing antifibrotic benefit should specify whether an intervention slows new collagen production,

promotes remodeling, preserves organ function or improves survival and quality of life. These effects are not interchangeable. Even a genuine molecular antifibrotic action in cell culture does not establish whole-patient efficacy.

Hypotheses that can be contrasted

The driver hypothesis holds that matrix mechanics actively maintain fibrosis; the marker hypothesis holds that stiff matrix mainly records cumulative injury while ongoing damage drives the disease. The mechanisms may coexist. Disease-specific studies linking stiffness manipulation to downstream fibroblast behavior and organ performance would help separate them.

The Institute's position

Fibrosis is an unusually strong example of the principle that disease can persist through the consequences of its own attempted repair. The thesis adds conceptual coherence, not a new universally curative approach. Established management of organ-specific fibrotic disease remains essential while experimental mechanisms are evaluated.

Fibrosis in several organs does not make it one disease

In the lung, fibrosis may restrict gas transfer and tissue compliance; in the liver, it changes hepatic architecture and portal resistance; in kidney, it contributes to progressive loss of filtration units. Each organ also has disease-specific triggers, cell populations and trajectories. Shared mediators justify comparative research, but they do not establish an interchangeable intervention. A treatment that affects cultured lung fibroblasts may not be safe or effective for kidney fibrosis.

Why stiffness feedback is an appealing maintaining mechanism

The fibrotic matrix changes its own signaling environment. Mechanical stress can activate pathways promoting further matrix synthesis, creating a plausible source of persistence after the initial inflammatory drive decreases. Experimental perturbation of YAP/TAZ in fibroblast models supports the existence of such loops. Translating that finding demands attention to compensating pathways and the indispensable functions of mechanotransduction in normal tissue repair.

The endpoints must be ordered

A candidate antifibrotic treatment might slow progression without removing existing matrix. It might improve exercise capacity through unrelated mechanisms. It might normalize a biomarker while leaving organ performance unchanged. Each result answers a different question. The Institute should reserve the word 'regeneration' for demonstrated restoration of structure or specialized cell function, rather than using it as a synonym for stabilization or symptomatic improvement.

Selected scientific reading

1. Liu F et al. [Mechanosignaling through YAP and TAZ drives fibroblast activation and fibrosis. Am J Physiol Lung Cell Mol Physiol. 2015.](#)

2. [Campisi J et al. Cellular senescence: a link between cancer and age-related degenerative disease? Semin Cancer Biol. 2011;21:354–359.](#)
3. [Kataru RP et al. Fibrosis and secondary lymphedema: chicken or egg? Transl Res. 2019;209:68–76.](#)

Editorial status: Conceptual scientific essay, not peer reviewed. Not original clinical data, a treatment protocol or medical advice. Selected readings are not a systematic review. Evidence and interpretation should be assessed independently.