

17. Fibrosis: When the Repair Process Becomes the Disease

Absurd Health Institute | Medical Concept Papers, Volume Four | IV. The tissue remembers

Publication type: Revised medical concept and hypothesis essay — not peer reviewed **Corrective edition:** 17 October 2026 **Substantive text:** 1,260 words

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.

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.

The difference between closing a wound and reconstructing an organ

Fibrosis is often described as excessive collagen, but the deeper problem is that repair can restore continuity without restoring the original arrangement of specialized cells, vessels and extracellular material. Dense matrix in an injured organ may stabilize the region and protect it from immediate failure. Yet replacement of functioning parenchyma with scar can reduce the organ's reserve. A liver that becomes increasingly fibrotic can retain many active cells while its vascular architecture and portal resistance deteriorate; the clinical consequences are therefore partly mechanical and partly metabolic.

A systemic therapy directed at inflammation may have less impact when fibrosis has become an autonomous structural constraint. This does not mean all fibrosis is irreversible. Regression has been documented in selected circumstances, including after successful treatment of some chronic liver diseases. The extent and clinical significance of reversal depend on stage, underlying cause and the capacity to reconstruct microarchitecture. Terms such as 'regenerate' and 'detoxify' should not be substitutes for measurements of functional tissue.

Fibroblasts respond to force and chemistry

Transforming growth factor-beta is a central profibrotic signaling node in many experimental contexts, but mechanical feedback can maintain activity through pathways such as YAP/TAZ. Contractile myofibroblasts change tissue tension while producing matrix. Cross-linked matrix then changes the forces experienced by surrounding cells. The loop provides a candidate mechanism for fibrosis persisting after the initiating injury lessens. It remains important to distinguish cell culture findings from clinical proof that manipulating one pathway will reverse advanced human fibrosis.

Organ-specific conditions matter. Idiopathic pulmonary fibrosis, renal interstitial fibrosis, cirrhosis and post-surgical scarring have different initiating events and different opportunities for restoration. Even within one organ, inflammation, vascular remodeling and epithelial failure may interact differently across disease stages. A universal antifibrotic proposal is therefore intrinsically less informative than a specific model with defined cell populations and endpoints.

Reversal must be defined in patient terms

Clinical trials should track organ performance, symptoms, progression, hospitalization and safety, alongside structural measures such as imaging or tissue sampling when appropriate. An intervention that slows decline can be valuable without literally dissolving scar tissue. Conversely, less collagen in an experimental sample may fail to improve function if blood vessels and parenchymal architecture are not restored. Researchers must ask whether the therapy changes matrix amount, matrix organization, cell survival, vascular transport or all of them.

Fibrosis illustrates a central theme in terrain medicine: a biological response can be adaptive at one time and maladaptive at another. That fact is not enough to choose a treatment. The precise therapeutic question is whether a particular wound-healing program is still necessary for integrity, whether it has become excessive, and whether its modification can improve function without weakening the tissue it was protecting.

Why organ-specific antifibrotic success matters

Some diseases already have clinical treatments that slow fibrotic progression, demonstrating that changing aspects of a profibrotic program can matter to patients. But even a treatment that slows loss of lung function does not necessarily restore normal alveolar architecture. The distinction between slowing progression and reversing fibrosis is essential for evaluating experimental therapies. A drug could yield substantial clinical benefit while failing to decrease the tissue's total scar burden on short-term imaging.

Research should also pay attention to when a feedback loop becomes self-maintaining. Early injury may require ongoing inflammation or toxic exposure to drive matrix production, whereas established myofibroblast-matrix interactions might help maintain the state later. A time-course experiment could ask whether eliminating the original trigger at successive stages changes the rate of matrix accumulation and function. If the late tissue recovers after trigger removal, the strong autonomy hypothesis is weakened. Such experiments make the concept of 'repair becoming disease' more precise and more useful.

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 and evidentiary note

This is an expanded conceptual synthesis, not original clinical research or a clinical treatment protocol. It preserves selected references from the original edition, whose bibliographic metadata have not all been independently reverified. Claims about specific diagnoses and treatments require appropriate primary evidence and professional assessment. Mechanistic plausibility does not establish therapeutic efficacy.