



‘Even when the wound is healed, the scar remains’

In medical school, we all learned the cardinal signs of inflammation—*rubor*, *tumor*, *calor*, and *dolor*—as described in the writings of the Roman physician Aulus Cornelius Celsus approximately 2,000 years ago. A fifth sign, *functio laesa* (loss of function), was added by Rudolf Virchow in the 19th century. But all inflammation is not the same, and the ultimate effect of inflammation depends as much on how it is resolved as on why it occurred.

The outcome is influenced by the nature of the inflammatory trigger, the regenerative potential of the involved tissue, and the systemic and regional metabolic and immune milieu, as well as by how the initial trigger is suppressed and the inflammatory process shut down. As dramatic and disabling as an initial flare of gout can be, there is no expected tissue damage or residual loss of function following its resolution. Acute infection with *Histoplasma capsulatum* results in localized calcified nodules in the lungs and spleen, usually without compromise of organ function. But a return to baseline function is less certain when even a low level of inflammation cannot be shut down or when the resolution of inflammation and repair of acute tissue injury results in an overly vigorous localized fibrotic tissue response. An even more dramatic outcome occurs when there is a generalized response to inflammatory cytokines, environmental triggers, and activated cells in (presumably) genetically predisposed individuals, as in patients who develop pulmonary fibrosis or systemic sclerosis.

Pathogenic fibrosis represents a dysregulated pathologic response to chronic tissue inflammation or injury that may occur in any organ. Instead of restoration of the normal tissue biology, there is excessive accumulation of extracellular matrix that is not readily degraded. A fibrotic scar is not always disadvantageous. It can be an adaptive wound-healing response to injury; stopping the bleeding and closing off a wound to external infectious organisms is more likely to improve survival than a slower initial restoration of totally normal tissue. A cutaneous scar of focal fibrosis in the calf from a dog bite does not have the same clinical impact as a focal fibrotic scar from a small myocardial infarction that results in an arrhythmogenic nidus for ventricular tachycardia, or as an intestinal stricture that results from the inflammation of Crohn disease.

Persistent or repetitive inflammatory or ischemic insults to internal organs may lead to progressive scarring that culminates in organ failure, as discussed in this issue of the *Journal* by Sierra and colleagues¹ in their article on cirrhosis resulting from steatohepatitis. While successful treatment of metabolic dysfunction–associated steatohepatitis is currently directed at the factors driving metabolic liver injury, understanding the cellular and molecular mechanisms underlying fibrogenesis in general is critical for developing targeted antifibrotic therapies that may be relatively agnostic to the nature of the initial trigger.

The fibrogenic response seems to follow a somewhat shared sequence in different organs involving overlapping phases: initiation following primary tissue injury, activation of reparative effector cells, and elaboration of extracellular matrix resistant to resorption. This process is orchestrated by complex interactions among multiple cell types, including inflammatory cells (macrophages, T cells), epithelial cells, and endothelial cells.² The final participant in this cellular ballet generating the collagen-heavy sclerotic matrix is the myofibroblast. The origin of this actin-enriched fibroblast-like cell has been debated for years. A recent paper suggests that, at least in the kidney,

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the origin is primarily the transdifferentiated fibroblast, and not resident or bone marrow–derived macrophages or epithelial cells.³ This may not be the same in all organs.

Central to fibrogenesis is the transforming growth factor beta (TGF beta) signaling pathway. TGF beta seemingly functions as a master regulator across many normal and pathogenic fibrotic conditions. Over 30 years ago, it was shown that TGF beta can drive the conversion of fibroblasts to myofibroblasts.⁴ TGF beta derived from M2 (anti-inflammatory) macrophages binds to serine-threonine kinase type II receptors on many cell types, including fibroblasts, where it activates SMAD proteins, which translocate to the nucleus to drive profibrotic gene expression.^{5,6} TGF beta potently stimulates extracellular matrix protein synthesis, particularly types I and III collagen, while simultaneously inhibiting matrix degradation by suppressing protease activity and inducing protease inhibitors.

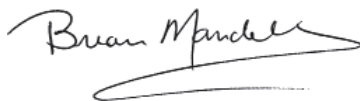
Agents targeting TGF beta, including neutralizing antibodies, receptor antagonists, and antisense RNA inhibitors, have demonstrated efficacy in preclinical models, though translation into clinical practice has remained challenging,⁵ in part due to TGF beta's pleiotropic effects and complicated, chameleon-like behavior. Almost all cells can elaborate TGF beta, and many cells have receptors that bind TGF beta. Fibroblasts can both elaborate and bind TGF beta, thus enabling a positive autocrine feedback loop. In an inflammatory space, the major sources of TGF beta likely include M2 macrophages and platelets.

The functional behavior of TGF beta is extremely context dependent. Factors impacting its biological effect include absolute concentration, the balance between its 3 different isoforms (which are all secreted in a latent form and bind differently to the same receptors), the type and physiologic state of the cells in the local environment, and, importantly, the composition of the local cytokines. TGF beta in the presence of significant interleukin 2 exerts an anti-inflammatory effect, while in the presence of interleukin 6, an interleukin 17–mediated proinflammatory effect is observed.

Dampening the enthusiasm to develop anti-TGF beta therapies is the observation that TGF beta knockout mice rapidly develop extreme systemic inflammatory reactions, with massive lymphocyte and macrophage infiltration in the heart and lungs, autoantibodies, immune complex deposition, and a wasting syndrome resulting in death.⁷ In preclinical studies, adverse events from inhibiting TGF beta have included bleeding, cardiac valvulopathies, abnormal wound healing, and inflammatory reactions. Titrating the degree, and perhaps the organ location, of inhibition remains a challenge.

In steatohepatitis, the progression from simple steatosis to fibrosis involves lipotoxic hepatocyte injury, inflammatory activation, and generation of matrix-producing myofibroblasts from hepatic stellate cells. The recognition that hepatic fibrosis is reversible has catalyzed the development of numerous targeted therapies, with several agents now approved or in late-stage clinical trials. Whether these will be uniquely effective in treating fibrosis in organs with less regenerative potential than the liver remains to be seen.

Note: The aphorism comprising the title of this article is attributed to the Latin writer Publilius Syrus.⁸



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