

Tissues are composed of cells surrounded by extracellular matrix. If an event injures the cells or matrix, resident and inflammatory cells release cytokines that stimulate cell division and the production and deposition of new matrix. Normally, when tissue integrity and physiological function have been restored, the repair process is terminated. However, failure to halt repair results in fibrotic disease because continued accumulation of extracellular matrix impairs tissue function, ultimately causing organ failure.

The cytokine transforming growth factor- β (TGF- β) plays a central role in tissue repair. Among TGF- β 's multiple actions is strong induction of extracellular matrix deposition by simultaneously stimulating the production of matrix proteins, inhibiting proteases that degrade matrix, and modulating the expression of matrix receptors on the cell surface. TGF- β 's potency in stimulating matrix deposition has offered hope that it might be used clinically to enhance healing of problem wounds (1). At the same time overproduction of TGF- β has now been linked to the pathogenesis of numerous experimental and human fibrotic disorders (2). Thus TGF- β is a double-edged sword with both therapeutic and pathological potential.

In this issue of *The Journal*, Bernasconi and colleagues (3) report fascinating results illuminating the delicate balance between TGF- β 's beneficial actions in normal tissue repair and its fibrogenic potential. Duchenne muscular dystrophy (DMD) is caused by a genetic absence of the protein dystrophin. For unclear reasons dystrophin-deficient cells die, causing myofiber destruction and eventually muscle degeneration. An inflammatory cell infiltrate appears in areas of myofiber degeneration followed by increased deposition of matrix proteins that leads to muscle fibrosis. To these investigators the sequence of cell death followed by inflammation and fibrogenesis suggested the process of tissue repair and the involvement of TGF- β .

They found elevated levels of TGF- β 1 mRNA and TGF- β 1 protein in areas of fibrotic muscle. Elevated TGF- β 1 also correlated with the degree of fibrosis in the dystrophic muscle and production of TGF- β 1 was higher in patients with DMD compared with those with another type of dystrophy or with spinal muscular atrophy. These results suggest that muscle cell death leads to increased TGF- β 1 as part of tissue repair, but the continued production of TGF- β 1 causes tissue fibrosis. This is another example of TGF- β as a double-edged sword. The clinical importance of this work is that it emphasizes the role of fibrosis in the pathogenesis of DMD and suggests that early use of an antifibrotic agent might be beneficial.

In another study, TGF- β has been implicated in the pathogenesis of adult respiratory distress syndrome (ARDS). The lungs of mice with ARDS induced by hemorrhage show severe inflammatory cell infiltrates, intraalveolar hemorrhage, and interstitial edema. Pulmonary mononuclear cells and alveolar

macrophages contain increased levels of TGF- β mRNA. Treatment of mice with an anti-TGF- β mAb completely prevented the histological changes of ARDS (4). In humans with ARDS, levels of type III collagen, a matrix protein whose production is stimulated by TGF- β , are elevated in bronchoalveolar lavage fluid and these increases are strongly associated with an increased risk of death (5). Based on these reports it is reasonable to assume that TGF- β -induced fibrogenesis is an important contributor to the mortality of ARDS.

The ability of TGF- β to stimulate pathological accumulation of extracellular matrix has been demonstrated repeatedly in animals (2). Mice injected with TGF- β to suppress tumor growth rapidly developed cachexia and multiorgan fibrosis and died. Rats injected with high doses of TGF- β in toxicology studies developed widespread fibrotic changes including glomerulosclerosis. Perhaps because of its large blood supply or its filtration function, the kidney seems to be particularly sensitive to TGF- β -induced fibrogenesis. TGF- β has now been implicated as a cause of fibrosis in most forms of experimental and human kidney disease (2).

The kidney's vulnerability to the effects of TGF- β was unexpectedly highlighted when the TGF- β 1 gene was coupled to the albumin promoter to achieve liver expression in transgenic mice (6). While TGF- β 1 was elevated in liver and plasma and fibrotic changes were seen in several tissues including the liver, the mice with the highest plasma TGF- β 1 levels rapidly developed renal failure and died. At autopsy the kidneys showed glomerular and tubulointerstitial fibrosis and an overall histological picture resembling rapidly progressive glomerulonephritis.

In addition to its fibrogenic properties, TGF- β is a powerful immunoregulatory molecule. Elevated plasma TGF- β levels recently found in the lupus mouse were implicated in defective host defense mechanisms and decreased survival in response to bacterial infection (7). These findings raised the possibility that TGF- β might play a role in the increased risk of bacterial infection in patients with autoimmune diseases. Again we see the double-edged sword of TGF- β (8).

The new study by Bernasconi and colleagues (3) along with the others mentioned above suggest that antagonizing the actions of TGF- β might be beneficial in a number of human diseases. Therapeutic efficacy of TGF- β antibodies has already been shown in disease models involving kidney, lung, skin, joint, arterial wall, and brain (2). It is hoped that testing of TGF- β antagonists moves toward clinical trials before TGF- β is linked to fibrogenesis in yet another disease.

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