Fibrosis, Regeneration, and Aging: Playing Chess with Evolution

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In this issue of JASN, Lyoda et al. report that administration of nilotinib, a second-generation inhibitor of cellular Abelson (c-ABL) kinase, starting at 2 weeks after subtotal nephrectomy decreases glomerular hypertrophy, glomerular sclerosis, tubulointerstitial inflammation, and fibrosis in remnant kidneys and improves renal function and survival. These results are consistent with those obtained with Imatinib, the c-ABL inhibitor prototype, in models of glomerular disease and unilateral ureteral obstruction (UUO). Nilotinib is also effective in animal models of pulmonary and hepatic fibrosis. Iyoda et al. suggest that nilotinib may prove useful in limiting the progression of chronic kidney disease (CKD) to ESRD.

Imatinib was approved by the Food and Drug Administration to treat Philadelphia chromosome–positive chronic myeloid leukemia (CML) in 2001 and has been remarkably successful. The Philadelphia chromosome contains a constitutively active oncogenic tyrosine kinase (BCR-ABL) created through translocation of a section of human chromosome 9 containing PDGF receptor α (PDGFRα), c-KIT, and CSF1R. Dasatinib is also active against DDR1 and 2 and as potent against PDGFRα/H11022 (SCF) receptor c-KIT as Imatinib over the first year. Nilotinib and dasatinib were approved in 2006 for patients who have CML and are experiencing relapse or are intolerant to Imatinib. Recent clinical trials comparing nilotinib and dasatinib with Imatinib showed superiority of nilotinib and dasatinib compared with Imatinib over the first year.

Imatinib, nilotinib, and dasatinib are competitive inhibitors of various tyrosine kinases with different pharmacologic profiles. Imatinib inhibits discoidin domain receptor 1 (DDR) > PDGF receptor α/β (PDGFRα/β) > stem cell factor (SCF) receptor c-KIT > DDR2 > BCR-ABL1. Dasatinib is more potent against DDR1 and 2 and as potent against PDGFRα/β, c-KIT, and CSF1R. Dasatinib is also active against DDR1 and 2 and as potent against PDGFRα/β, c-KIT, and CSF1R. Dasatinib is more potent against DDR1 and 2 and as potent against PDGFRα/β, c-KIT, and CSF1R.

See related article, “Calcium Mediates Glomerular Filtration through Calcineurin and mTORC2/Akt Signaling,” on pages 1453–1461.
against PDGFRβ, c-KIT, other kinases such as lymphocyte-specific kinase, and SRC family tyrosine kinases YES and FYN.

The cytokines and tyrosine kinase receptors inhibited by imatinib, nilotinib, and dasatinib are important regulators of the two main mechanisms of tissue injury repair, regeneration and fibrosis. These cytokines and receptors are differentially used during evolution and development but can coexist in mature mammals within the same tissue. Similar cytokines in a cell- and context-specific manner regulate regeneration and fibrosis, but one of the two mechanisms is preferentially used depending on the intensity and persistence of the initial inflammatory response.

Fish, salamanders, and larval frogs regenerate lost appendages, but amputation of a limb in a frog after metamorphosis results in formation of a distal pad of scar tissue. Skin wounds in mammalian fetuses during early stages of gestation heal without scars. This capacity is markedly blunted but not completely lost at more advanced stages of gestation and in mature animals. For example, small skin wounds can heal without scarring, and gingival papillae can regenerate completely if excised. Reduced platelet degranulation and immaturity of the immune system in salamanders, larval frogs, and mammalian embryos limit the accumulation of inflammatory cytokines and allow for expression of genes involved in tissue patterning. In contrast, release of cytokines such as PDGF and TGF-β in the context of a competent immune system results in the infiltration of neutrophils and macrophages and accumulation of proinflammatory cytokines, activating powerful and redundant fibroproliferative pathways.

Iyoda et al. contend that the beneficial effect of nilotinib on interstitial fibrosis and renal progression is due to inhibition of PDGFR, c-ABL, CSF1R, and T and B cell proliferation. Inhibition of DDR-1 and c-KIT might also play a role. We briefly reviewed how the aforementioned nilotinib targets affect tissue response to injury.

The PDGF family consists of homo- or heterodimeric polypeptides (PDGF-AA, AB, BB, CC, and DD) and two receptors, α and β. PDGF-C binds to the PDGFRα, activates fibroblast proliferation, and promotes interstitial fibrosis, whereas PDGF-B and D bind to PDGFRβ and promote glomerulosclerosis and, secondarily, interstitial scarring. PDGF-C and PDGFRα are upregulated in interstitial myofibroblasts. Inhibition of PDGFR by an anti-PDGFR-α or a tyrosine kinase inhibitor reduces UUO-induced interstitial fibrosis in rats and mice.

c-ABL is an important downstream effector of noncanonical TGF-β signaling. TGF-β isoforms (TGF-β1, TGF-β2, TGF-β3) bind to heterotetrameric type I and type II serine/threonine kinase receptors. Upon formation of the receptor complexes, the constitutively active type II receptor phosphorylates the type I receptor, activating canonical and noncanonical signaling. Canonical signaling involves phosphorylation of Smad2 and Smad3 proteins, which after complexation with Smad4 translocate to the nucleus and modulate gene expression. Noncanonical signaling involves multiple pathways, including phosphatidylinositol-3-kinase (PI3K). Activation of PI3K with focal adhesion kinase 2 acting as an essential scaffold is a branch point for the activation of p21-activated kinase-2–c-ABL and Akt-TORC1 signaling. Noncanonical signaling through c-ABL and TORC1 induces fibroblast proliferation, increasing the number of myofibroblast precursors. Of note is that whereas TORC1 inhibition inhibits fibrosis in multiple animal models of renal progression, it delays recovery from ischemia reperfusion injury. Canonical Smad2/3 signaling induces transition of fibroblasts into myofibroblasts and accumulation of extracellular matrix proteins. Interestingly, TGF-β1 and TGF-β2 stimulate whereas TGF-β3 inhibits fibrosis.

CSF-1 is an important regulator of macrophage function and innate immunity. It is produced by tubular epithelial cells in response to injury and binds to CSF-1R on macrophages, causing intrarenal recruitment, proliferation, and activation. When the offending influence is transient, macrophages mediate tissue repair, which is also fostered by CSF-1 and CSF-1R in tubular epithelial cells stimulating proliferation and reducing apoptosis. On the contrary, when the offending injury persists, regeneration is prevented and macrophages promote inflammation and fibrosis.

DDRs interact and become phosphorylated in response to collagen. After UUO, interstitial macrophages strongly express and require DDR1 activation for normal migration. DDR1 null mice are protected from interstitial fibrosis after UUO and from bleomycin-induced pulmonary fibrosis. Loss of DDR1 expression in the kidney delays renal fibrosis and inflammation in hereditary type IV collagen disease.

SCF binds to c-KIT and induces differentiation, proliferation, and survival in various cell types. Both c-KIT and its ligand SCF are expressed in tubules damaged by ischemia/reperfusion, enhance survival, and inhibit apoptosis. Renal expression of SCF is increased after subtotal nephrectomy, but it is not known whether it has a role in disease progression.

Fibrotic response to injury is a major cause of organ failure. In the kidney, interstitial fibrosis is the final common pathway to ESRD. Interstitial fibrosis is also a feature of the aging kidney. It is characterized by proliferation and transformation of fibroblasts into myofibroblasts, deposition of fibronectin and collagens I and III into the interstitium, and microvascular rarefaction. The origin of the interstitial myofibroblasts is controversial. Recent studies point to renal pericytes as the main source. They detach from endothelial cells in response to injury, migrate into the interstitial space, and transform into myofibroblasts, whereas the peritubular capillaries regress and disappear. There is also evidence that pericytes serve as local, quiescent progenitor cells. Thus, the biology of renal pericytes provides a link among fibrosis, microvascular rarefaction, aging, and CKD progression.

It is not immediately obvious how fibrosis and aging serve a useful purpose. The concept of antagonistic pleiotropy postulates that genetic traits beneficial up to the age of reproduction might exert detrimental effects later in life. Thus, fibrosis likely...
developed to provide a survival advantage to early vertebrates in response to various forms of tissue injury, whereas age-related and fibrotic diseases are the price one pays to protect the survival of the genetic pool.10,11

Iyoda et al.1 suggest that c-ABL inhibitors might prove clinically useful in limiting the progression of CKD. A number of issues need to be considered regarding the feasibility of translating their observations into clinical trials.

Effects seen in the preclinical animal models are often stronger than those seen in the human disease because intervention usually occurs at the time of disease development.10 The importance of the timing of intervention has been best studied in wound healing in the skin. Agents such as TGF-β3 and neutralizing antibodies against TGF-β1 and TGF-β2 produce the best results when applied within 48 hours after wounding and are much less effective when applied later.10,32

This may be because the initial release of TGF-β and PDGF from platelets and infiltrating macrophages triggers powerful and redundant cytokine and cellular cascades that have been evolutionarily optimized to ensure the success of the fibrotic response.

There are situations in clinical practice in which development of interstitial fibrosis can be anticipated—for example, the development of chronic allograft nephropathy after an episode of acute rejection. Here, treatment with imatinib for a short period might be sufficient to prevent chronic allograft nephropathy, as shown in an experimental rat model.33 In many cases, however, interventions would be initiated after the fibrotic process is well established and response to therapy is less certain.

An optimal response to intervention at an advanced stage of disease would need not only to interrupt fibrogenesis but also to cause regression.34 Regression of bone marrow fibrosis has been observed in clinical trials for CML, and regression of dermal fibrosis has also been reported in scleroderma, graft-versus-host disease, and nephrogenic systemic fibrosis.35–38 In contrast, whereas regression of pulmonary fibrosis has been shown in bleomycin-induced experimental models, the only randomized, placebo-controlled, double-blind trial of imatinib in mild to moderate idiopathic pulmonary fibrosis did not show any effect on survival or clinical outcome.39

Another consideration is safety and tolerability. Imatinib, nilotinib, and dasatinib have a reasonable safety profile.5–7,32,34–40 Common adverse effects, including fluid retention, muscle cramps, creatine kinase elevation, nausea, diarrhea, and bone marrow suppression, can be managed with dosage reduction. Although more serious complications are relatively rare, prolongation of the QT interval, acute renal failure, and development of Fanconi syndrome have been reported.41–44 Some signaling pathways inhibited by these drugs are renoprotective in models of ischemia-reperfusion injury18,20,24; therefore, if clinical trials of cABL inhibitors were to be implemented, renal function would need to be monitored closely. One study suggested a greater decline in renal function in patients who have CML and are treated long term with imatinib than that expected from aging alone.45

In summary, c-ABL tyrosine kinase inhibitors block many pathways that play a major role in the development of interstitial fibrosis and may prove useful in limiting the progression of CKD, but some of these pathways are also renoprotective and contribute to tissue repair. Progression from preclinical to clinical trials will need to take into consideration the timing of intervention, the nature of the underlying renal disease, the likelihood that fibrosis will regress, and the regenerative capacity of the kidney, as well as safety and tolerability including the possibility of unanticipated adverse effects on renal function.

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