Negatively Regulating the Cell Cycle Can Be Positive

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Our understanding of the mechanisms underlying renal disease has increased significantly in the past decade with the application of molecular and cellular biological approaches. In this issue of JASN, Gherardi et al. (1) have taken these basic mechanisms to the next level, i.e., new therapeutic approaches. The authors focused on inhibiting specific cell cycle proteins (cyclin/cyclin–dependent kinase complexes) in glomerular disease on the basis of the rationale that podocytes, normally fully differentiated and nonproliferating cells, undergo proliferation, dedifferentiation, and possibly apoptosis in collapsing glomerulopathy. These fundamental biological processes are controlled by cell cycle regulatory proteins, which were originally described as essential orchestrators of cell cycle progression and cell proliferation (2,3).

Progression through each phase of the cell cycle requires the formation of a specific complex, comprising a cyclin and a partner cyclin-dependent kinase (CDK). Proliferation requires the sequential activation of cyclin D-CDK4/6 (in early G1), cyclin E-CDK2 (in late G1), cyclin A-CDK2 (in S phase), and cyclin B-CDC2 (in M phase). In addition, the cell cycle is also coordinated by endogenous negative cell cycle regulatory proteins called CDK inhibitors, such as p15 INK4b, p16 INK4a, p21Waf1/Cip1, and p27Kip1. These bind to and inhibit the activity of cyclin/CDK complexes (2–4).

There is a growing body of literature to show that, in addition to their control of proliferation, specific cell cycle regulatory proteins also regulate other biologic processes, including hypertrophy, differentiation and, apoptosis during the initiation and resolution phases of the renal diseases (2,3,5). Therefore, controlling these molecules, which are involved in many of the renal responses to injury, might be expected to be an effective approach to treat kidney diseases.

Recently, considerable excitement has surrounded the discovery or design of several small molecules that specifically inhibit the kinase activity of certain cyclin/CDK complexes. These are now potentially useful for clinical practice. Originally, the potential use of pharmacological CDK-inhibitors was limited to cancer biology (6). Currently, at least three compounds with CDK inhibitory activity (flavopiridol, UCN-01, roscovitine) have entered clinical trials (7). In addition to cancer, possible clinical applications are being investigated in nonmalignant disorders, including cardiovascular and neuronal diseases, and in viral infections (6,8–11).

Is there a role for small molecule cell cycle inhibitors in renal disease? In this issue of JASN, Gherardi et al. (1) show that the pharmacological CDK inhibitor, Roscovitine (CYC202) reduced proteinuria and tissue injury in experimental HIV-1 collapsing (or cellular) glomerulopathy (12). Collapsing glomerulopathy, a variant of focal segmental glomerulosclerosis, is characterized by segmental and global collapse of the glomerular capillaries, which is accompanied by proliferation of podocytes and severe tubulo-interstitial changes (13). Collapsing glomerulopathy is not restricted to patients with HIV-associated nephropathy (13). Clinically, collapsing glomerulopathy is characterized by nephrotic syndrome, and the development of rapidly progressive renal failure. In their elegant study design, Gherardi et al. (1) showed that inhibiting CDKs significantly reduced the development of collapsing glomerulopathy in mice, as well as proteinuria and the decline in renal function. This study extends prior work by this group, which previously demonstrated that the CDK-inhibitor, flavopiridol, also prevented the development of murine collapsing glomerulopathy (14).

The CDK inhibitor, roscovitine, has also been successfully used to inhibit mesangial cell proliferation in vitro by suppressing CDK2 kinase activity to decrease mesangial cell proliferation in the Thy-1 model of immune-mediated glomerulonephritis (15). This was accompanied by a decrease in extracellular matrix accumulation and an improvement in renal function. Finally, a protective effect of roscovitine was also reported in an animal model of ischemia-reperfusion injury of the kidney (16), and more recently in experimental membranous nephropathy (17).

A low incidence of adverse effects of small molecule inhibitors is crucial for success. In this regard, Gherardi et al. (1) reported that there were no significant adverse effects. Serious adverse effects have also not been apparent in clinical phase I and phase II trials. Thus, pharmacological small molecule CDK inhibitors may be a potential tool for future therapeutic intervention in certain renal diseases characterized by proliferation, including collapsing glomerulopathy. One can speculate that small molecule cell cycle inhibitors may have other potential therapeutic roles in nephrology as well; for example, in hemodialysis graft and fistula restenosis, where the hallmark of these lesions is myointimal proliferation.

Can other components of the cell cycle be future targets for therapy in inflammatory renal diseases? As stated earlier, endog-
enous CDK inhibitors such as p15, p16, p21, and p27 limit proliferation by inhibiting specific cyclin/CDK complexes. Intra-articular adenosvirial gene therapy with p16 has been shown to improve experimental rheumatoid arthritis (18), and the intravenous delivery of an adenosviral p27-p16 vector inhibited balloon injured neointimal hyperplasia in rabbit carotid arteries and peritoneal coronary arteries (19). There is also evidence that the overexpression of “endogenous” CDK inhibitors has an impact in renal disease. Phosphorothiorated antisense oligodeoxynucleotides to p21 attenuate hyperglycemia-induced mesangial cell hypertrophy (20), and the use of adenovirus transfection of p21 protects cultured renal proximal tubular cells from cisplatin-induced apoptosis, as do pharmacological CDK inhibitors (21). Although gene therapy of endogenous CDK inhibitors has been successful only to renal cells in vitro, its application to human renal diseases is the next challenge. However the rapidly advancing technology in this field gives us hope for the future (22).

In summary, there is a large body of literature supporting a critical role for cell cycle regulatory proteins in renal diseases (2,3). These initial discoveries are now being successfully applied to therapeutics, as the paper on successful treatment of collapsing glomerulopathy elegantly demonstrates. This new and novel approach to therapy of glomerular diseases with a proliferative component joins a number of other less toxic and more specific approaches to treating kidney diseases that encourage optimism that we are nearing the end of a long and frustrating era of having little to offer these patients except toxic combinations of corticosteroids and nonselective immunosuppressive drugs.

References


See related article, “Reversal of Collapsing Glomerulopathy in Mice with the Cyclin-Dependent Kinase Inhibitor CYC202,” on pages 1212–1222.