Mesangial cell (MC) proliferation characterizes immune-mediated glomerular injury. Proliferation is regulated at the level of the cell cycle by positive (cyclins and cyclin dependent kinases, CDK) and negative (CDK-inhibitors) cell cycle regulatory proteins. Inhibiting CDK2 activity reduces MC proliferation and matrix accumulation in experimental glomerulonephritis. We recently showed that CDK2 activity was also increased in apoptotic MC in the absence of proliferation, suggesting that CDK2 regulates both growth and death pathways. In contrast to MC, podocytes (Podo) typically do not proliferate, and studies have shown that the apparent lack of proliferation underlies the development of glomerulosclerosis. Our studies showed that immune-mediated Podo injury is associated with an increase in the CDK-inhibitors p21 and p27. Moreover, inducing Podo injury in p21-/- and p27-/- mice is associated with an increase in Podo proliferation. In contrast to immune-mediated MC injury, diabetic nephropathy (DN) is characterized by MC hypertrophy, and not proliferation. Our studies showed that the CDK-inhibitors p21 and p27 increased in MC exposed to hyperglycemia and in experimental DN. A role for these CDK-inhibitors in mediating hypertrophy was confirmed by the lack of hyperglycemia-induced hypertrophy in p21-/- and p27-/- MC in vitro. Taken together, these studies show that specific cell cycle regulatory proteins are critical regulators of glomerular proliferation, hypertrophy and apoptosis, and should be considered as potential targets in the design of future therapeutic interventions.