

## PODOCYTES

### Regulators of podocyte quiescence and inability to proliferate:

It had been known for some time that in contrast to all other kidney epithelial cells, adult podocytes are unable to proliferate adequately. The mechanisms were not known. Our lab focused on cell cycle proteins in order to explain the inability of adult podocytes to proliferate, and we identified the following mechanisms.

1. podocytes have a high constitutive expression of the cell cycle inhibitors p27 and p57, and following injury, readily increase the levels of the cell cycle inhibitor p21 (a).
2. although podocytes can be stimulated to enter the cell cycle, all these cell cycle inhibitors bind to, and inhibit G1, S and M phase cyclin-CDK complexes (b, c). This effectively shuts down proliferation.
3. to prove a biological role for cell cycle inhibitors, we deleted p21 and p27, and showed that when podocytes were injured, they readily engaged the cell cycle, and proliferated. However, podocyte proliferation under these conditions was not reparative, because uncontrolled cell cycle regulation lead to exuberant cell excess, and scarring.
4. we showed that DNA damage occurs following injury, and that the upregulation of p53 and other DNA damage proteins leads to cell cycle arrest (d).

- (a) **Shankland SJ**, Floege J, Thomas SE, Nangaku M, Hugo C, Pippin J, Henne K, Hockenberry DM, Johnson RJ, Couser WG. Cyclin kinase inhibitors are increased during experimental membranous nephropathy: potential role in limiting glomerular epithelial cell proliferation in vivo. *Kidney Int.* 1997 52(2):404-13. *PMID: 9263996*
- (b) Petermann A, Hiromura K, Pippin J, Blonski M, Couser WG, Kopp J, Mundel P, **Shankland SJ**. Differential expression of D-type cyclins in podocytes in vitro and in vivo. *Am J Pathol.* 2004 164(4):1417-24. *PMID: 15039229*
- (c) Kim YG, Alpers CE, Brugarolas J, Johnson RJ, Couser WG, **Shankland SJ**. The cyclin kinase inhibitor p21CIP1/WAF1 limits glomerular epithelial cell proliferation in experimental glomerulonephritis. *Kidney Int.* 1999 Jun;55(6):2349-61. *PMID: 10354282*
- (d) Pippin JW, Durvasula R, Petermann A, Hiromura K, Couser WG, **Shankland SJ**. DNA damage is a novel response to sublytic complement C5b-9-induced injury in podocytes. *J Clin Invest.* 2003 Mar;111(6):877-85. *PMID: 12639994*