Nature Reviews Nephrology **9**, 554 (2013); published online 3 September 2013; doi:10.1038/nrneph.2013.159

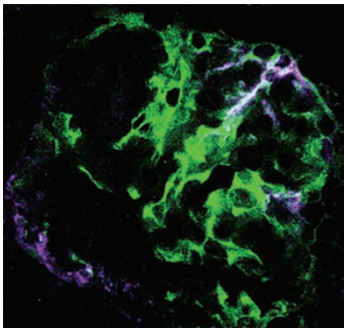
GLOMERULAR DISEASE

Albuminuria inhibits podocyte regeneration

New data from Paola Romagnani and colleagues suggest that albuminuria contributes to progressive glomerulosclerosis by inhibiting the differentiation of renal progenitor cells (RPCs) into podocytes. "Our findings provide a biological rationale for the clinical use of drugs to promote podocyte regeneration and induce regression of glomerular diseases," says Romagnani.

Previous studies by Romagnani and colleagues, and by other groups, have shown that RPCs in the Bowman capsule can differentiate into podocytes and could potentially replace them after injury. In the current study, Romagnani and colleagues used primary cultures of human RPCs and various strains of transgenic mice treated with adriamycin (as a model of human focal segmental glomerulosclerosis [FSGS]) to investigate their hypothesis that proteinuria might contribute to the progression of glomerulosclerosis by suppressing this regeneration.

The researchers found that exposure of human RPCs to transferrin and IgG reduced their viability, whereas exposure to human serum albumin inhibited their differentiation into podocytes by sequestering retinoic acid and preventing the retinoic-acid-response element (RARE)-mediated transcription of podocyte-specific genes. In transgenic mice with adriamycin-induced nephropathy, blockade of retinoic acid synthesis increased proteinuria, inhibited RARE activation in RPCs and their differentiation into podocytes, and reduced podocyte number, resulting in worsening of glomerulosclerosis. In contrast, treatment with retinoic acid reversed albuminuria-induced inhibition of RARE in RPCs, resulting in an increase in their differentiation into podocytes, an increase in podocyte number, and a decrease in proteinuria.



Glomerulus of a transgenic mouse with adriamycin-induced nephropathy and mild proteinuria. Image shows podocytes (green) and renal progenitor cells (purple) that have migrated over the glomerular tuft and acquired podocin. Image courtesy of P. Romagnani, Department of Biomedical, Experimental and Clinical Sciences, Nephrology Section, University of Florence, Italy.

"These results provide a novel explanation of why albuminuria is a predictive factor for progression to glomerulosclerosis, and also explain why RPCs induce the generation of hyperplastic glomerular lesions in FSGS instead of promoting regeneration," concludes Romagnani. She explains that in the presence of severe albuminuria, RPCs proliferate to replace injured podocytes but are unable to fully differentiate into these cells. This proliferation leads to the amplification of a population of immature podocytes and generation of the glomerular hyperplastic cellular lesions that are observed in FSGS.

Romagnani suggests that restoring the capacity of RPCs to differentiate into podocytes—for example by exogenous administration of retinoic acid—could promote the regeneration of podocytes and potentially result in the regression of glomerular disease.

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Original article Peired, A. *et al*. Proteinuria impairs podocyte regeneration by sequestering retinoic acid. *J. Am. Soc. Nephrol.* doi:10.1681/ASN.2012090950