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GLOMERULAR DISEASE

Innate immunity—*APOL1* interaction

Genetic variants of *apolipoprotein L1* (*APOL1*) are associated with an increased risk of kidney disease in African Americans. Now, researchers have found that interferons and Toll-like receptor (TLR) agonists significantly increase *APOL1* expression and stimulate the appearance of new *APOL1* transcript variants. They say their study shows that antiviral pathways might trigger the onset of kidney disease in susceptible individuals who express the high-risk *APOL1* variants, and identifies potential therapeutic targets for the treatment of *APOL1*-associated kidney disease.

To investigate the potential contribution of interferons to *APOL1*-associated kidney disease, Brendan Nichols and colleagues first assessed *APOL1* genotype in biopsy samples from a cohort of patients who had developed collapsing glomerulopathy following interferon treatment; all were found to carry the *APOL1* high-risk genotype. Transfection of HEK293 cells with wild-type *APOL1* and the *APOL1* risk alleles, demonstrated that the risk variants were toxic to cells when expressed at high levels.

The researchers then assessed the ability of interferons to upregulate *APOL1* in cultured endothelial cells and podocytes. In both cell types, IFN-α, IFN-β and IFN-γ stimulated *APOL1* expression. Interferon exposure also resulted in the appearance of two *APOL1* transcript variants. Administration of a double-stranded RNA mimic and TLR3 agonist to cultured cells also increased *APOL1* expression. Further experiments identified two distinct pathways regulating *APOL1* expression: one involving classical interferon signalling, and an interferon-independent TLR3 pathway involving TBK1, NFκB and Jak kinases.

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Original article Nichols, B. *et al.* Innate immunity pathways regulate the nephropathy gene *apolipoprotein L1*. *Kidney Int.* doi:10.1038/ki.2014.270