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CHRONIC KIDNEY DISEASE

Potassium efflux in APOL1 nephropathy

The increased risk of chronic kidney disease in people of recent African descent compared to European–Americans is almost entirely attributed to the presence of two *APOL1* genetic variants (G1 and G2) in this population. Now, findings by Martin Pollak and colleagues show that *APOL1* risk variants induce cytotoxicity by promoting intracellular K^+ losses and through the dysregulation of signalling pathways required for cell survival.

The researchers used a tetracycline-mediated *in vitro* system to study the effects of wild-type (G0), G1, and G2 *APOL1* allelic expression in human embryonic kidney cells. Cytotoxicity was markedly increased 12 h after induction of G1 or G2 variant expression compared to G0, and the cells appeared swollen. This phenotype had striking similarities to that of K^+ depletion in mammalian cells, and the researchers confirmed that both the G1 and G2 alleles could promote a decline in intracellular K^+ content by acting as a K^+ pore in the cell membrane. This effect was prevented by culturing the cells in medium in which Na^+ was replaced with K^+.

The phosphorylation status of regulatory proteins of cell survival signalling pathways was analysed prior to the onset of cell death in G1 or G2 variant-expressing cells. The level of phosphorylated STAT3 was reduced by 75% in these cells compared to G0-expressing cells, and the p38–MAPK pathway was markedly upregulated. Of note, STAT3 phosphorylation is dependent on the transmembrane protein GP130, which is degraded as a result of activated p38–MAPK signalling.

The researchers propose that cytotoxicity in APOL1 nephropathy might be mediated by increased K^+ efflux via a G1 or G2 APOL1 cation pore, which promotes p38–MAPK signalling and inhibits STAT3 activity. They note that a deeper understanding of APOL1-mediated kidney injury is necessary to translate such findings into treatment strategies for affected patients.

Jessica K. Edwards

ORIGINAL ARTICLE Olabisi, O. A. APOL1 kidney disease risk variants cause cytotoxicity by depleting cellular potassium and inducing stress-activated protein kinases. *Proc. Natl Acad. Sci. USA* http://dx.doi.org/10.1073/pnas.1522913113