INNATE IMMUNITY

APOL1 variants contribute to racial disparity in sepsis

> “mitochondrial defects in *G2APOL1* cells are linked to the inflammatory endothelial phenotype as a result of leakage of mtDNA into the cytosol”

Individuals of African ancestry are more likely to die from sepsis than individuals of European ancestry and are also disproportionately affected by COVID-19, with both higher infection rates and more severe disease. A study published in *Immunity* suggests that genetic variants in apolipoprotein L1 (*APOL1*) contribute to this susceptibility, by affecting mitophagy in endothelial cells and allowing the release of mitochondrial DNA (mtDNA) that activates inflammasome and nucleotide sensing pathways.

APOL1 risk variants are present only in individuals of African ancestry and have arisen as a result of positive genetic selection, as they confer protection against *Trypanosome brucei* infection, which causes African sleeping sickness. Analysis of 57,000 participants of African ancestry indicated a statistically significant association between *APOL1* risk variants and sepsis. Plasma samples from individuals with sepsis showed higher plasma APOL1 levels in patients who developed more severe disease, including acute kidney injury. In patients with COVID-19, plasma APOL1 levels were higher in those experiencing kidney injury than those without and in those who ultimately succumbed to the disease. In patients with sepsis or with COVID-19, high APOL1 levels also correlated with increased plasma levels of pro-inflammatory cytokines and chemokines, as well as with markers of endothelial dysfunction and vascular damage. The authors suggest that both the *APOL1* risk genotype and the increase in APOL1 expression are critical for disease development.

To explore the role of APOL1 in endothelial dysfunction, the authors generated mice in which expression of a human *APOL1* risk allele (*G2APOL1*) or wild-type allele is induced specifically in endothelial cells. Endothelial expression of *G2APOL1* was associated with loss of glomerular capillary fenestrations and delamination of alveolar capillaries, and led to increased vascular permeability. Moreover, transcripts for endothelial glycocalyx remodelling (an indicator of endotheliopathy), vascular inflammation and adhesion were upregulated in mice expressing *G2APOL1*.

Consistent with a role in sepsis, mice with endothelial *G2APOL1* showed higher mortality following lipopolysaccharide (LPS)-induced endotoxaemia or caecal ligation and puncture, suffering more severe end-organ damage, kidney disease and lung damage compared with control mice. The more severe disease in *G2APOL1*-expressing mice was associated with higher expression of pro-inflammatory proteins and markers of endothelial damage. Indeed, single-cell sequencing revealed 534 differentially expressed genes in endothelial cells of *G2APOL1* versus wild-type mice; notably, interferon-signature genes were upregulated and cell junction genes were downregulated in cells expressing the *G2APOL1* allele.

So, what links endothelial *G2APOL1* to the inflammatory phenotype? Microscopic examination showed potential defects in mitochondria and mitophagy in *G2APOL1* endothelial cells. Indeed, a mitophagy reporter gene indicated lower basal mitophagy and starvation-stimulated mitophagy, leading to an accumulation of mitochondria in *G2APOL1* endothelial cells. Other defects associated with G2APOL1 expression included reduced mitochondrial function, loss of mitochondrial negative membrane potential and attenuated autophagy.

So, the authors hypothesized that the mitochondrial defects in *G2APOL1* cells are linked to the inflammatory endothelial phenotype as a result of leakage of mtDNA into the cytosol. Consistent with this, analysis of the cytosolic fraction indicated higher mtDNA content in *G2APOL1* endothelial cells than wild-type cells. Moreover, *G2APOL1* cells showed activation of the cytosolic DNA sensing NLRP3 inflammasome and cGAS–STING pathways. Depletion of mtDNA using ethidium bromide treatment reduced this activation, and knockdown of *Cgas* and *Sting* mRNAs prevented induction of the downstream inflammatory genes.

Finally, the authors tested the role of this pathway in sepsis. Genetic deletion of *Nlrp3*, *Gsdmd*, *Casp1* and *Sting* rescued the endothelial barrier defect of *G2APOL1* endothelial cells in vitro and in vivo. And treatment of G2APOL1^{+} mice with small-molecule inhibitors of caspase 1, gasdermin D and STING reduced the weight loss, inflammatory response, end-organ damage and mortality following LPS-induced sepsis.

These data show that the *APOL1* risk genotype is a key determinant of sepsis — through mitochondrial dysfunction and pro-inflammatory endothelial changes — and could explain an important racial disparity observed in sepsis incidence and severity amongst individuals of African ancestry.

Lucy Bird

Credit: Roc Canals/Getty

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