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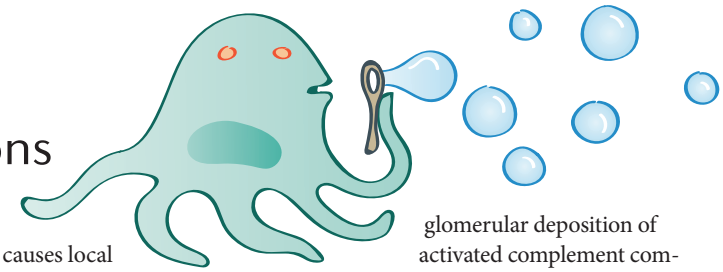
THROMBOTIC MICROANGIOPATHIES

VEGF–complement interactions



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Dysregulation of epithelial-cell-derived VEGF in the eye and kidney is associated with wet age-related macular degeneration (ARMD) and glomerular thrombotic microangiopathy (TMA), respectively. ARMD and TMA are also associated with complement dysregulation and genetic variants in the complement inhibitor, factor H (FH). New research demonstrates a link between local VEGF availability and complement inhibition in the retina and glomerulus that is mediated by changes in FH expression. "This study links VEGF to complement regulation for the first time, and also provides the first demonstration that complement proteins can be produced in the glomerulus," explain researchers Moin Saleem and Lindsay Keir. "Locally produced VEGF by podocytes or retinal pigment epithelium (RPE) cells increases key complement regulators such as FH in a paracrine manner on endothelial cells in the microcirculation. Importantly loss of VEGF, either by damage to the VEGF-producing cells or by anti-VEGF therapy leads to reduced regulation of complement and causes local vascular damage and disease."

Saleem says that their study started as an investigation into the cause of TMA in Shiga-toxin-induced haemolytic uraemic syndrome — a condition linked to complement dysregulation. "Following the seminal paper from Susan Quaggin's group showing that podocyte-specific deletion of VEGF causes renal TMA, we hypothesized that podocyte-derived VEGF regulates complement on glomerular endothelial cells," he explains. "Martin Friedlander's work on VEGF and RPE cells suggested there could be a similar mechanism in the eye, leading to this collaboration."

The researchers used a range of genetic models as well as *in vitro* studies of glomerular endothelial cells and conditionally immortalized podocytes, to show that VEGF induced FH synthesis by glomerular endothelial cells, whereas VEGF inhibition led to reduced FH expression and increased glomerular deposition of activated complement components C3d and C4d. Similar observations were made in primary human RPE cells. Further investigation showed that the effect of VEGF on FH is mediated via PKCα–CREB signalling in endothelial cells. Assessment of RPE cells and podocytes from patients with mutations in FH associated with ARMD and atypical haemolytic uraemic syndrome, respectively, revealed increased complement deposits, and a heightened response to VEGF antagonism.

Saleem and Friedlander say that their work provides insight into the pathogenesis of ARMD and TMA as well as a possible explanation for the vascular damage that sometimes occurs with anti-VEGF therapy for neovascularization, tumours and ARMD.

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