Complement regulation at necrotic cell lesions is impaired by the age-related macular degeneration-associated factor-H His402 risk variant.

Lauer N, Mihlan M, Hartmann A, Schlötzer-Schrehardt U, Keilhauer C, Scholl HP, Charbel Issa P, Holz F, Weber BH, Skerka C, Zipfel PF (2011) Complement regulation at necrotic cell lesions is impaired by the age-related macular degeneration-associated factor-H His402 risk variant. *J Immunol* 187(8), 4374-4383.

Abstract

Age-related macular degeneration is a leading form of blindness in Western countries and is associated with a common SNP (rs 1061170/Y402H) in the Factor H gene, which encodes the two complement inhibitors Factor H and FHL1. However, the functional consequences of this Tyr(402) His exchange in domain 7 are not precisely defined. In this study, we show that the Tyr(402) His sequence variation affects Factor H surface recruitment by monomeric C-reactive protein (mCRP) to specific patches on the surface of necrotic retinal pigment epithelial cells. Enhanced attachment of the protective Tyr(402) variants of both Factor H and FHL1 by mCRP results in more efficient complement control and further provides an anti-inflammatory environment. In addition, we demonstrate that mCRP is generated on the surface of necrotic retinal pigment epithelial cells and that this newly formed mCRP colocalizes with the cell damage marker annexin V. Bound to the cell surface, Factor H-mCRP complexes allow complement inactivation and reduce the release of the

proinflammatory cytokine TNF-α. This mCRP-mediated complement inhibitory and anti-inflammatory activity at necrotic membrane lesions is affected by residue 402 of Factor H and defines a new role for mCRP, for Factor H, and also for the mCRP-Factor H complex. The increased protective capacity of the Tyr(402) Factor H variant allows better and more efficient clearance and removal of cellular debris and reduces inflammation and pathology.

Beteiligte Forschungseinheiten

Infektionsbiologie Peter F. Zipfel Mehr erfahren

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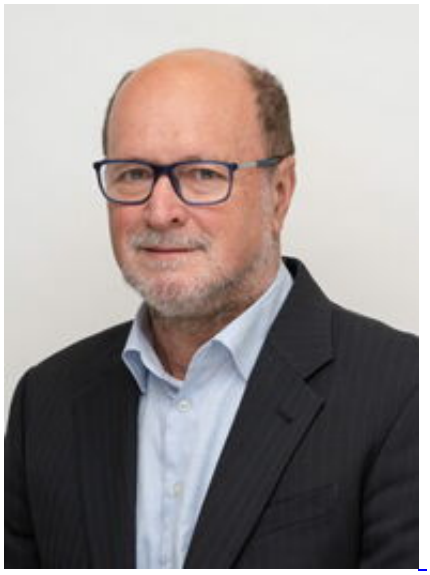

Peter F. Zipfel

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