Activation of endogenously expressed ion channels by active complement in the retinal pigment epithelium.

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Abstract

Defective regulation of the alternative pathway of the complement system is believed to contribute to damage of retinal pigment epithelial (RPE) cells in age-related macular degeneration. Thus we investigated the effect of complement activation on the RPE cell membrane by analyzing changes in membrane conductance via patch-clamp techniques and Ca(2+) imaging. Exposure of human ARPE-19 cells to complement-sufficient normal human serum (NHS) (25 %) resulted in a biphasic increase in intracellular free Ca(2+) ([Ca(2+)]i); an initial peak followed by sustained Ca(2+) increase. C5- or C7-depleted sera did not fully reproduce the signal generated by NHS. The initial peak of the Ca(2+) response was reduced by sarcoplasmic Ca(2+)-ATPase inhibitor thapsigargin, L-type channel blockers (R)-(+)-BayK8644 and isradipine, transient-receptor-potential (TRP) channel blocker ruthenium-red and ryanodine receptor blocker dantrolene. The sustained phase was carried by CaV1.3 L-type channels via tyrosine-phosphorylation. Changes in [Ca(2+)]I were accompanied by an abrupt hyperpolarization, resulting from a transient increase in membrane conductance, which was absent under extracellular Ca(2+)- or K(+)-free conditions and blocked

by (R)-(+)-BayK8644 or paxilline, a maxiK channel inhibitor. Single-channel recordings confirmed the contribution of maxiK channels. Primary porcine RPE cells responded to NHS in a comparable manner. Pre-incubation with NHS reduced H2O2-induced cell death. In summary, in a concerted manner, C3a, C5a and sC5b-9 increased [Ca(2+)]i by ryanodine-receptor-dependent activation of L-type channels in addition to maxi-K channels and TRP channels absent from any insertion of a lytic pore.

Beteiligte Forschungseinheiten

Infektionsbiologie Peter F. Zipfel Mehr erfahren

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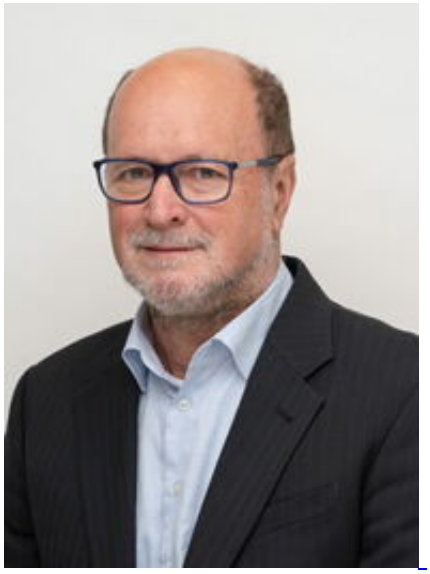
Details



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