Flotillin-dependent lipid-raft microdomains are required for functional phagolysosomes against fungal infections.

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Abstract

Lipid rafts form signaling platforms on biological membranes with incompletely characterized role in immune response to infection. Here we report that lipid raft microdomains are essential components of the phagolysosomal membrane of macrophages. Genetic deletion of the lipidraft chaperons flotillin-1 and flotillin-2 demonstrate that the assembly of both major defense complexes vATPase and NADPH oxidase on the phagolysosomal membrane requires lipid rafts. Furthermore, we discovered a new virulence mechanism leading to the dysregulation of lipid-raft formation by melanized wild-type conidia of the important human-pathogenic fungus *Aspergillus fumigatus*. This results in reduced phagolysosomal acidification. Phagolysosomes with ingested melanized conidia contain a reduced amount of free Ca^{2+} ions as compared to phagolysosomes with melanin-free conidia. In agreement with a role of Ca^{2+} for generation of functional lipid rafts, we show that Ca^{2+}-dependent calmodulin activity is required for lipid-raft formation on the phagolysosome. We

identified a single nucleotide polymorphism in the human *FLOT1* gene that results in heightened susceptibility for invasive aspergillosis in hematopoietic stem-cell transplant recipients. Collectively, flotillin-dependent lipid rafts on the phagolysosomal membrane play an essential role in protective antifungal immunity in humans.

Involved units

Molecular and Applied Microbiology Axel Brakhage Read more

Applied Systems Biology Marc Thilo Figge Read more

Leibniz-HKI-Authors



Axel A. Brakhage

Details



Zoltán Cseresnyés

Details



Marc Thilo Figge

Details



Marie Goldmann

Details



Thorsten Heinekamp

Details



Muhammad Rafiq

Details



Franziska Schmidt

Details



Hella Schmidt

Details



Andreas Thywißen

Details

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