CARD9+ microglia promote antifungal immunity via IL-1β- and CXCL1-mediated neutrophil recruitment.

Drummond RA, Swamydas M, Oikonomou V, Zhai B, Dambuza IM, Schaefer BC, Bohrer AC, Mayer-Barber KD, Lira SA, Iwakura Y, Filler SG, Brown GD, Hube B, Naglik JR, Hohl TM, Lionakis MS (2019) CARD9+ microglia promote antifungal immunity via IL-1β- and CXCL1-mediated neutrophil recruitment. *Nat Immunol* 20(5), 559-570.

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Abstract

The C-type lectin receptor-Syk (spleen tyrosine kinase) adaptor CARD9 facilitates protective antifungal immunity within the central nervous system (CNS), as human deficiency in CARD9 causes susceptibility to fungus-specific, CNS-targeted infection. CARD9 promotes the recruitment of neutrophils to the fungus-infected CNS, which mediates fungal clearance. In the present study we investigated host and pathogen factors that promote protective neutrophil recruitment during invasion of the CNS by Candida albicans. The cytokine IL-1β served an essential function in CNS antifungal immunity by driving production of the chemokine CXCL1, which recruited neutrophils expressing the chemokine receptor CXCR2. Neutrophil-recruiting production of IL-1β and CXCL1 was induced in microglia by the fungus-secreted toxin Candidalysin, in a manner dependent on the

kinase p38 and the transcription factor c-Fos. Notably, microglia relied on CARD9 for production of IL-1β, via both transcriptional regulation of Il1b and inflammasome activation, and of CXCL1 in the fungus-infected CNS. Microglia-specific Card9 deletion impaired the production of IL-1β and CXCL1 and neutrophil recruitment, and increased fungal proliferation in the CNS. Thus, an intricate network of host-pathogen interactions promotes antifungal immunity in the CNS; this is impaired in human deficiency in CARD9, which leads to fungal disease of the CNS.

Involved units

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Topics

Interactions with immune cells (MPM)

Damage to the host

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