Calcium sequestration by fungal melanin inhibits calcium-calmodulin signalling to prevent LC3-associated phagocytosis.

Kyrmizi I, Ferreira H, Carvalho A, Figueroa JAL, Zarmpas P, Cunha C, Akoumianaki T, Stylianou K, Deepe GS, Samonis G, Lacerda JF, Campos A, Kontoyiannis DP, Mihalopoulos N, Kwon-Chung KJ, El-Benna J, Valsecchi I, Beauvais A, Brakhage AA, Neves NM, Latge JP, Chamilos G (2018) Calcium sequestration by fungal melanin inhibits calcium-calmodulin signalling to prevent LC3-associated phagocytosis. *Nat Microbiol* 3(7), 791-803.

Details

Abstract

LC3-associated phagocytosis (LAP) is a non-canonical autophagy pathway regulated by Rubicon, with an emerging role in immune homeostasis and antifungal host defence. Aspergillus cell wall melanin protects conidia (spores) from killing by phagocytes and promotes pathogenicity through blocking nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-dependent activation of LAP. However, the signalling regulating LAP upstream of Rubicon and the mechanism of melanin-induced inhibition of this pathway remain incompletely understood. Herein, we identify a Ca2+ signalling pathway that depends on intracellular Ca2+ sources from endoplasmic reticulum, endoplasmic reticulum-phagosome communication, Ca2+ release from phagosome lumen and calmodulin (CaM) recruitment, as a master regulator of Rubicon, the phagocyte NADPH oxidase NOX2 and other molecular components of LAP. Furthermore, we provide genetic evidence for the

physiological importance of Ca2+-CaM signalling in aspergillosis. Finally, we demonstrate that Ca2+ sequestration by Aspergillus melanin inside the phagosome abrogates activation of Ca2+-CaM signalling to inhibit LAP. These findings reveal the important role of Ca2+-CaM signalling in antifungal immunity and identify an immunological function of Ca2+ binding by melanin pigments with broad physiological implications beyond fungal disease pathogenesis.

Beteiligte Forschungseinheiten

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