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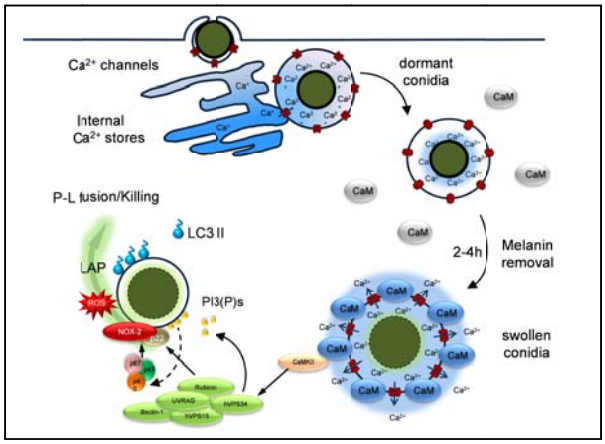
PRESS RELEASE

IMBB Researchers Identify a Novel Immunological Function of Melanin implicated in Pathogenesis of Human Fungal Diseases



IMBB-FORTH Researcher Irene Kyrmizi, working together with the head of the research team George Chamilos, and their collaborators, uncover a novel immunological function of fungal melanin mediated by inhibition of calcium (Ca^{2+}) signalling during phagocytosis.

The findings of this study have important implications in pathogenesis of human fungal diseases and are published today in *Nature Microbiology*

Melanins are ubiquitous macromolecular pigments of complex chemical composition and structure. The unique biological functions of these heterogeneous compounds are not fully understood, but seem to rely on their shared physicochemical properties. In medically important fungi, cell wall melanin is a major virulent factor that confers protection from killing by phagocytes via targeting a specialized autophagy pathway termed LC3 associated phagocytosis (LAP). LAP links two ancient processes, phagocytosis and autophagy, to coordinate degradation of extracellular particles, such as microbes or apoptotic cells, following their uptake by phagocytes. However, activation of LAP has distinct signalling requirements than canonical autophagy, which are incompletely characterized. In addition, the molecular mechanism that melanin pigments target the LAP pathway is currently unknown.

In the present study, the investigators infected primary human phagocytes with melanin competent and melanin defective (albino) mutants of the major human pathogenic fungus *Aspergillus fumigatus*, and applied high speed Ca^{2+} imaging, molecular biology and analytical chemistry tools to identify a novel Ca^{2+} signalling pathway that is targeted by melanin as the master regulator of LAP. Specifically, they demonstrated that during phagocytosis endoplasmic reticulum (ER)-phagosome communication triggers peri-phagosomal Ca^{2+} release that results in the recruitment of the Ca^{2+} effector protein calmodulin to the phagosome to activate LAP. Furthermore, they provided genetic evidence that this Ca^{2+}/calmodulin pathway has physiological importance in development of fungal pneumonia caused by *Aspergillus* in humans.

Next, the investigators systematically analyzed mechanisms of interference of melanin with the different molecular components of the Ca^{2+}/calmodulin signalling pathway regulating LAP. Importantly, they discovered that fungal melanin possess strong Ca^{2+} chelating properties that result in Ca^{2+} sequestration inside the phagosome, thus abrogating calmodulin recruitment and preventing activation of LAP. In proof of concept studies, the investigators showed that chemical ligation of synthetic beads and albino conidia with a Ca^{2+} chelator mirrored the effects of melanin on inhibition of calmodulin recruitment and LAP.

Although melanins have long been recognized as non-specific metal chelators, a clear biological role for their Ca^{2+} binding properties has not been previously assigned. This study shows for the first time that Ca^{2+} scavenging by fungal melanin has an immunological function and is specifically responsible for LAP blockade. Furthermore, this study has important implications in pathogenesis and management of fungal diseases, a major cause of infectious-related death in an expanding population of immunocompromised patients. In view of the mediocre activity of current antifungal therapies, harnessing activation of Ca^{2+} signaling regulating LAP could become a novel therapeutic strategy to combat fungal diseases. Finally, in view of the physiological importance of both melanins and the LAP pathway in humans, the findings of this study have broader implications in the pathogenesis of diseases beyond fungal infections.

Reference:

Kyrmizi I, Ferreira H, Carvalho A, Landero Figueroa JA, Zarmpas P, Cunha C, Akoumianaki T, Deepe, Jr GS, Samonis G, Lacerda JF, Campos Jr AC, Kontoyiannis DP, Mihalopoulos N, Valsecchi I, Beauvais A, Brakhage AA, Neves NM, Latge JP, Chamilos G. Calcium sequestration by fungal melanin inhibits calcium-calmodulin signalling to prevent LC3-associated phagocytosis (LAP). *Nat Microbiol*. 2018. doi: 10.1038/s41564-018-0167-x

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High-speed Ca^{2+} imaging of primary human monocytes infected with melanin competent (top panel) or melanin-deficient (lower panel) fungal strains. Arrows indicate peri-phagosomal Ca^{2+} signalling platforms and triangles indicate cytosolic Ca^{2+} spikes