Impaired phagocytosis directs human monocyte activation in response to fungal derived β -glucan particles

Giorgio Camilli¹, Elif Eren², David L. Williams³, Vishukumar Aimanian⁴, Etienne Meunier², and **Jessica Quintin**¹

¹ Immunology of Fungal Infections, Department of Mycology, Institut Pasteur, Paris, France.

² Institut de Pharmacologie et Biologie Structurale, IPBS, Université de Toulouse, CNRS, UPS, Toulouse, France.

³ Department of Surgery, Center of Excellence in Inflammation, Infectious Disease and Immunity, James H. Quillen College of Medicine, East Tennessee State University, Johnson City, Tennessee, USA.

⁴ Unité des Aspergillus Department of Mycology, Institut Pasteur, Paris, France.

Recognition of the fungal cell wall component β -glucan by the host receptor Dectin-1 display broad immunomodulatory properties. As such, stimulation of phagocytosis and activation of the oxidative burst are essential to engulf and kill the pathogens. Phagocytic cells, such as monocytes, are also key mediators of the early host inflammatory responses to infections. Whether an interplay exists between phagocytosis and the inflammatory response of human monocytes to fungal β -glucan remains to be characterized.

Figure 1. Phagocytosis impairment differentially affects the response of human monocytes towards whole *Candida albicans* and the cell wall fraction composed of branched β -glucan.

Figure 2. NLRP3-ASC-caspase-1 inflammasome is essential for β -glucan induced IL1 β .

Figure 3. Block of phagocytosis unleashes cytokine production by β -glucan via a Dectin-1/Syk/PI3K-dependent pathway.

Here we show that intact phagocytosis of heat-killed *Candida albicans* is essential to trigger inflammation and cytokine release. In contrast, inhibition of actin-dependent phagocytosis of particulate (1,3/1,6)- β -glucan induces a strong inflammatory signature. Activation of human monocytes results classical caspase-1 inflammasome formation, generation of strong oxidative burst, NF- κ B activation, as well as increased release of inflammatory cytokines. The sustained monocyte activation induced by the fungal β -glucan particles upon actin cytoskeleton disruption relies on Dectin-1 and can be finely regulated by specific inhibitors of the downstream signaling pathway. Our results highlight the mechanism by which phagocytosis tightly controls the activation of phagocytes by microbial pathogens and strongly suggest that actin cytoskeleton dynamic is an essential determinant of the host's susceptibility or resistance to invasive fungal infections.

Figure 4. Cytochalasin D/ β -glucan costimulation enhances I κ B α phosphorylation, I κ B α degradation and p65 nuclear translocation.

Figure 5. Cytochalasin D and β -glucan synergistically boost the production of ROS in human monocytes in a Dectin-1, PI3K and NADPH-dependent fashion.