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A novel mechanism that helps activated dendritic cells to initiate effective immunity

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Phagocytosis represents a critical innate barrier against infection and serves the clearance of extracellular microbes, infected and dying cells. Different immune cells use phagocytosis for microbial killing, but in dendritic cells (DCs) it mainly serves the processing and presentation of specific molecules (antigens) that are able to alert the immune system and to initiate immune responses. Researchers at VIB and UGent, in close collaboration with a research team of the Institute Curie in France, describe now a mechanism of how the fusion between phagosomes and lysosomes influences the presentation of antigens on major histocompatibility complex (MHC) I molecules to cytotoxic T cells, a process called cross-presentation. The results are published the 15the December issue of the prestigious journal *Immunity*.

An effective immune response

DCs patrol their environment for the presence of microorganisms and foreign particles. These cells are in a resting state and present antigens very poorly. For an effective induction of immune responses, DCs need to be activated through innate receptors, such as Toll-like receptors (TLRs), in a process called DC maturation.

Rudi Beyaert (VIB/UGent): "When the bacterial cell wall component lipopolysaccharide is sensed by TLR4 on the surface of DCs, it is known that this leads to the clustering of lysosomes. However, the functional consequences of this phenomenon are not understood. We analyzed the

pathways that are important for antigen degradation and cross-presentation after phagocytosis of antigens."

Eik Hoffmann (VIB/UGent): "We realized that depending on the duration of DC maturation, the cells displayed a strong and selective delay in the fusion activity between phagosomes and lysosomes. This delay prevents excessive degradation of internalized antigens and promotes their cross-presentation. We identified the organelle trafficking regulator Rab34 as the critical link, which induces lysosome clustering upon engagement of particular TLRs."

R. Beyaert: "This transient activity of mature DCs might restrict them in a way that they need to internalize and cross-present foreign antigens while pathogens are present, but before tissue destruction becomes too dominant. This is particularly important to avoid uptake and cross-presentation of 'self' antigens, which could otherwise represent a potential risk for the development of autoimmune diseases."

E. Hoffmann: "This study is a true and long-lasting collaboration between us and the lab of Sebastian Amigorena in Paris with many people involved. In addition, we received valuable help from others in Ghent, for example from Kris Gevaert's team that helped us uncovering the phagosomal proteome of resting and activated DCs."

More information: Andrés Alloatti et al. Toll-like Receptor 4 Engagement on Dendritic Cells Restrains Phago-Lysosome Fusion and Promotes Cross-Presentation of Antigens, *Immunity* (2015). DOI: 10.1016/j.immuni.2015.11.006

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