

How phagosome functions and cross presentation are controlled by innate sensing in dendritic cells

Sebastian Amigorena, Institut Curie, INSERM U932, Immunité et Cancer, 26 rue d'Ulm, 75248 Paris, Cedex 05, France.

Dendritic cells represent a highly specialized hematopoietic lineage, whose main role is to sense infections in tissues and to activate specific T lymphocytes in lymphoid organs to mount immune responses adapted to the threat. To activate T lymphocytes, dendritic cells need to present peptides derived from infectious antigens on MHC molecules on their plasma membrane. There are two main intracellular sites of peptide loading on MHC molecules: the endocytic pathway for class II and the ER for class I MHC molecules. Because of this localization, the former are mainly (not exclusively) loaded with peptides cleaved by lysosomal proteases from internalized antigens. Peptides to be loaded on class I MHC are mainly derived from proteins that are being translated in the cytosol and are cleaved by the proteasome, before translocation into the ER by dedicated TAP1/2 transporters.

In most cells types, the interchange of cargo and membranes between the two compartments is very limited. In dendritic cells, however, ER proteins are quite abundant in phagosomes. We showed recently that Sec22b controls the delivery of a subset of ER resident proteins to phagosomes. In the absence of Sec22b, the abundance of several ER residents in phagosomes is reduced, causing a defect in antigen cross presentation. Intriguingly, we also observed a marked acceleration of phago-lysosome fusion in the Sec22b-silenced dendritic cells, suggesting that the presence of ER in phagosomes delays phagosome maturation. Reduced levels of Sec22b also impaired antigen export from endosomes to the cytosol, suggesting a molecular link between export and the presence of ER-derived proteins in phagosomes. Interestingly, activation of dendritic cells by Toll-like receptor ligands modified both their antigen presentation capacities and their phagocytic functions, especially the fusion of phagosomes with lysosomes. Export to the cytosol, in contrast, seems to be regulated independently through other pathways of stress sensing. The contributions of factors that regulate phagosome functions in dendritic cells, and their relevance to antigen cross presentation will be discussed.