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MEMBRANE TRAFFICKING

Dampening down destruction in dendritic cells

Dendritic cells are a key component of the body's immunosurveillance squad. They internalize foreign proteins, tumour cells and pathogens into phagosomes, where they are partially degraded. The fragments are processed to antigenic peptides in the cytosol and presented on the plasma membrane as part of the major histocompatibility complex to cytotoxic T cells. In *Nature Cell Biology*, Jancic and colleagues report a molecular mechanism that ensures proteins are not entirely degraded in the proteolytic environment of the phagosome.

The study started from the authors' finding that dendritic cells from *Rab27a*-null mice (also known as ashen mice) display defects in cross-presenting antigens to T lymphocytes. RAB proteins are small GTPases that regulate membrane traffic, which is

highlighted by the fact that ashen mice have a lightened coat colour caused by a trafficking defect of pigment-containing organelles in skin cells.

The authors found that, in wild-type dendritic cells, RAB27a is recruited to phagosomes after engulfment. In ashen mice, the formation of phagosomes was not altered, and therefore the defect observed in cross-presentation might be caused by dysregulated processing of foreign proteins to antigens. The pH of phagosomes was found to be more acidic in ashen mice. Levels of protein degradation inside the phagosome were also increased, which is due to the pH-dependent activity of proteolytic enzymes found inside the phagosome. The authors also found that pharmacologically increasing the pH of the phagosomes to around wild-type levels restored the capability of the *Rab27a*-null dendritic cells to cross-present antigens. Together, these results indicate that deletion of *Rab27a* results in increased degradation of antigens, due to increased acidity of the phagosome.

This phenotype mirrors that of the previously reported one for mice that lack the NADPH oxidase NOX2. NOX2 is recruited to early phagosomes and inhibits the acidification

of the phagosome through the low-level production of reactive oxygen species (ROS) that mop up free protons. Could these two phenotypes be linked? RAB27a and NOX2 colocalized to intracellular vesicles that were also positive for lysosomal markers. Upon engulfment in ashen-mice-derived dendritic cells, the delivery of NOX2-containing lysosomal vesicles to phagosomes was delayed and ROS production was reduced.

The authors propose that NOX2-containing "inhibitory lysosome-related organelles" are recruited by RAB27a-dependent mechanisms to phagosomes soon after engulfment, thereby reducing phagosome acidity and protein degradation. As well as increasing our knowledge of how antigens are processed, which potentially could lead to more potent vaccines, this finding might help us to understand the immunological pathology of Griscelli syndrome, caused by mutations in the human form of *Rab27a*.

James Pickett

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...RAB27a is normally recruited to phagosomes after engulfment.

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ORIGINAL RESEARCH PAPER Jancic, C. et al. *Rab27a* regulates phagosomal pH and NADPH oxidase recruitment to dendritic cell phagosomes. *Nature Cell Biol.* 11 Mar 2007 (doi: 10.1038/ncb1552)

FURTHER READING Savina, A. et al. NOX2 controls phagosomal pH to regulate antigen processing during cross presentation by dendritic cells. *Cell* **14**, 205–218 (2006)