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AP3 links endosomal TLRs and antigen presentation

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AP3 facilitates the recruitment of TLR4 and MYD88 to phagosomes

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Toll-like receptor (TLR) signalling from phagosomes is required for the effective processing of phagocytosed antigens and their presentation to CD4⁺ T cells. Mantegazza *et al.* now show that the cargo-sorting protein AP3 (adaptor protein 3) has a central role in facilitating this process — it delivers TLR4 and the signalling adaptor molecule MYD88 to maturing phagosomes. TLR4–MYD88 signalling from the phagosome results in pro-inflammatory cytokine production and correlates with the export of phagocytosed peptide–MHC class II complexes to the cell surface.

Individuals with Hermansky–Pudlak syndrome type 2 — which is caused by a mutation in the β 3A subunit of AP3 — suffer from recurrent bacterial infections (among other symptoms), which suggests that AP3 has a

role in antibacterial responses. Here, the authors show that AP3-deficient dendritic cells (DCs) fail to efficiently activate antigen-specific CD4⁺ T cells and to induce interferon- γ (IFN γ) production by these cells following antigen uptake by phagocytosis, but not after endocytic antigen uptake. Accordingly, AP3-deficient mice had a defective T helper 1 (T_H1) cell response following *Listeria monocytogenes* infection.

This defect in T cell activation was not due to impaired antigen phagocytosis but reflected reduced surface expression of peptide–MHC class II complexes on AP3-deficient DCs compared with wild-type DCs. The degradation and MHC loading of phagocytosed antigens were unaffected, but peptide–MHC class II complexes were shown to be retained within punctate structures in AP3-deficient DCs. This suggests

that AP3 is required for the proper delivery of MHC complexes containing phagocytosed antigens to the cell surface.

However, because AP3 is dispensable for the MHC class II-mediated presentation of endocytosed antigens, it probably affects the presentation of phagocytosed antigens through an indirect mechanism. Compared with phagosomes from wild-type DCs, phagosomes from AP3-deficient mice had reduced recruitment of TLR4 and MYD88, which are required for pro-inflammatory signalling, but normal recruitment of the TLR4 adaptor molecule TRAM, which is required for type I IFN production. Furthermore, the levels of mRNAs encoding pro-inflammatory cytokines, but not of those encoding type I IFNs, were reduced in AP3-deficient DCs stimulated with the TLR4 ligand lipopolysaccharide in a particulate form (which is phagocytosed).

So, this study suggests that AP3 facilitates the recruitment of TLR4 and MYD88 to phagosomes and raises the possibility that the subsequent phagosome-intrinsic signals are required for effective MHC class II-mediated presentation of phagocytosed antigens.

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ORIGINAL RESEARCH PAPER Mantegazza, A. R. *et al.* Adaptor protein-3 in dendritic cells facilitates phagosomal Toll-like receptor signaling and antigen presentation to CD4⁺ T cells. *Immunity* 3 May 2012 (doi:10.1016/j.immuni.2012.02.018)