Sequence analysis of IKKα identified three putative hydrophobic LC3-interacting regions (LIRs). Mutation of the LIR-2 and LIR-3 carboxy-terminal sequences, but not the amino-terminal LIR-1 sequence, of IKKα abolished its interaction with LC3. In *Ikka*$^{-/-}$ cells, reconstitution with wild-type or LIR-1-mutant IKKα, but not with LIR-2- or LIR-3-mutant IKKα, restored IRF7 phosphorylation and IFNβ production.

The data indicate that LC3, which is recruited to the outer membrane of TLR9-ligated endosomes by the LAP process, anchors a signalling platform on the cytosolic face by directly recruiting IKKα through LIR-2 and/or LIR-3. The authors suggest that inhibiting this LAPosome signalling could be used to target the excess IFN production that occurs in autoimmune diseases triggered by self nucleic acids, such as psoriasis and systemic lupus erythematosus.

Kirsty Minton

ORIGINAL ARTICLE Hayashi, K. et al. The interaction between IKKα and LC3 promotes type I interferon production through the TLR9-containing LAPosome. *Sci. Signal.* **11**, eaan4144 (2018)

HIV-1 DNA sequences, which is indicative of viral reservoir stabilization through clonal T cell proliferation. Together, the results support a role for the OX40–BIRC5 pathway in maintaining the long-term survival of HIV-1-infected cells and suggest that targeting this pathway could reduce the size of the viral reservoir.

In keeping with this, co-culture of in vitro-infected CD4$^+$ T cells with YM155, a small molecule inhibitor of BIRC5, led to a reduced frequency of both latently and productively infected cells. Similarly, patient-derived in vivo-infected CD4$^+$ T cells exposed to YM155 had a reduced frequency of total HIV-1 sequences and of clonally expanded HIV-1 sequences. Next steps will be to determine what induces BIRC5 expression in infected cells and whether this is differentially regulated between cell subsets to explain their survival versus death.

Kirsty Minton

ORIGINAL ARTICLE Kuo, H.-H. et al. Anti-apoptotic protein BIRC5 maintains survival of HIV-1-infected CD4$^+$ T cells. *Immunity* https://doi.org/10.1016/j.immuni.2018.04.004 (2018)

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IMMUNE TOLERANCE

AHR ensures cells rest in peace

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor with important roles in xenobiotic metabolism and other immune responses. Shinde et al. now report that the AHR maintains immune tolerance to apoptotic cells by regulating the expression of the anti-inflammatory cytokine IL-10.

The authors initially assessed AHR activation in phagocytes co-cultured with apoptotic cells. They found that *Cyp1a1* and *Cyp1b1* mRNAs (which encode the AHR-induced cytochromes P4501A1 and P450B1) were upregulated in wild-type — but not AHR-deficient — bone marrow-derived macrophages (BMDMs) and dendritic cells cultured with apoptotic thymocytes. Imaging studies showed that exposure of phagocytes to apoptotic cells caused AHR to translocate from the cytoplasm to the nucleus. AHR activation required phagocytosis of apoptotic cells and was blocked by the inhibition of caspases or masking of phosphatidylserine in apoptotic cells.

Gene- and protein-expression analyses showed that AHR activation in BMDMs exposed to apoptotic cells was associated with the downregulation of pro-inflammatory cytokines (such as IL-1β, IL-6, IL-12p40 and TNF) and the upregulation of IL-10 and molecules associated with a regulatory phenotype. BMDMs cultured with apoptotic cells showed increased association of AHR with AHR-responsive elements in the *Il10* promoter, and blocking IL-10 in these cultures increased BMDM production of pro-inflammatory cytokines. Therefore, AHR activation seems to polarize macrophages to an immunoregulatory phenotype via the induction of IL-10. Pre-treatment of apoptotic cells with DNase prevented AHR activation; furthermore, Toll-like receptor 9 (TLR9)-deficient BMDMs did not show nuclear accumulation of AHR following apoptotic cell uptake. Therefore, activation of AHR in BMDMs in this system appears to require TLR9-mediated recognition of DNA from apoptotic cells.

The authors next examined whether AHR suppresses immune responses to apoptotic cells in vivo. Intravenous delivery of apoptotic cells to wild-type mice led to increased expression of IL-10 and TGFβ in splenic lysates. By contrast, delivery of apoptotic cells to mice with a myeloid cell-specific AHR deficiency led to the induction of IL-6 and IL-12p40, but not IL-10 or TGFβ. In line with this, splenic macrophages and dendritic cells from wild-type mice showed induction of *Cyp1a1* and *Il10* following intravenous injection of apoptotic cells, whereas in mice with a myeloid cell-specific AHR deficiency, these populations failed to upregulate *Cyp1a1* and *Il10* and instead expressed *Il6* and *Il12b*.

The uptake of apoptotic cells by tissue-resident phagocytes is important for limiting autoimmunity, and AHR blockade in mouse models of lupus was found to increase serum levels of pro-inflammatory cytokines and autoantibodies. Treatment of mice with established lupus with an AHR agonist decreased autoantibody levels and disease. Furthermore, ageing mice with a myeloid cell-specific AHR deficiency developed spontaneous systemic autoimmunity.

Finally, the authors showed that human macrophages cultured with apoptotic cells also upregulate *CYP1A1* and IL-10 in an AHR-dependent manner. Notably, they identified an AHR transcriptional signature in patients with systemic lupus erythematosus (SLE), who had higher expression of *AHR*, *CYP1A1* and *IL10* in peripheral blood mononuclear cells than healthy individuals. Finally, microparticles from the plasma of patients with SLE (but not from healthy individuals) were shown to have membrane-bound DNA and induced *CYP1A1* and *IL10* expression in macrophages via AHR activation. Therefore, apoptotic cells and DNA-containing microparticles can activate AHR in human macrophages to promote an anti-inflammatory response.

The authors propose that the AHR-related transcriptional signature seen in patients with SLE may reflect the upregulation of this anti-inflammatory pathway in an attempt to restrict tissue pathology. Their findings suggest that the AHR pathway could be targeted to treat systemic autoimmune diseases.

Yvonne Bordon

ORIGINAL ARTICLE Shinde, R. et al. Apoptotic cell-induced, TLR9-dependent AhR activity is required for immunological tolerance and suppression of systemic lupus erythematosus in mice and humans. *Nat. Immunol.* https://doi.org/10.1038/s41590-018-0107-1 (2018)