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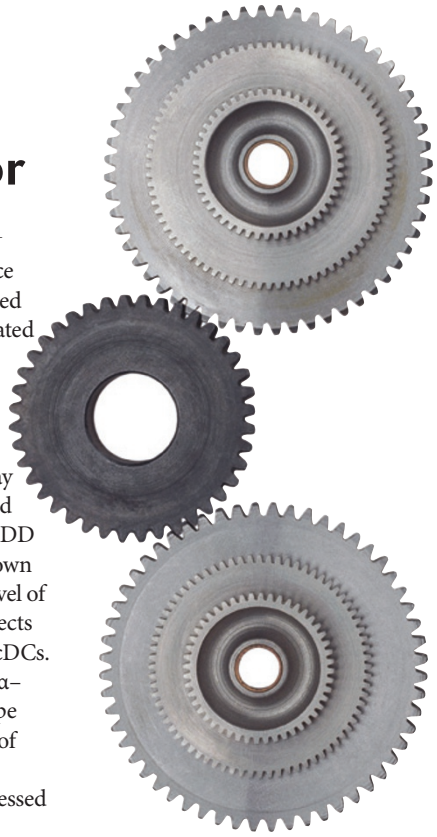
SIGNALLING

New roles for cell stress sensor



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Two studies published in *Nature Immunology* propose new functions for components of the unfolded protein response (UPR) in regulating the homeostasis of CD8α$^+$ conventional dendritic cells (cDCs) and the survival of plasma cells.

The UPR is a physiological response that helps cells to deal with cellular stress initiated by the accumulation of unfolded proteins in the endoplasmic reticulum (ER). Inositol-requiring transmembrane kinase/endonuclease 1α (IRE1α) is an initiator of the UPR and activates the transcription factor X-box-binding protein 1 (XBP1) through an mRNA splicing event. Osorio *et al.* found that IRE1α is constitutively activated in DCs, most notably in CD8α$^+$ cDCs, in the steady state. In addition, all DC subsets expressed spliced *Xbp1* mRNA, with the highest level of expression in CD8α$^+$ cDCs. Notably, this steady-state activation of IRE1α and XBP1 in cDCs occurred in the absence of the activation of other molecules associated with the UPR.

DC-specific deletion of *Xbp1* did not affect the differentiation of CD8α$^+$ cDCs, but these cells had an abnormal ER structure, although the ER secretory pathway remained functional. This suggests that basal activation of XBP1, in the absence of a general activation of the ER stress response, is required for ER homeostasis in these cells.

The expression of the genes encoding integrin β2 (a component of CD11c) and molecules involved in antigen presentation (including TAP-binding protein) was lower in XBP1-deficient CD8α$^+$ cDCs, but not in XBP1-deficient CD11b$^+$ cDCs, compared with controls. In keeping with this, XBP1-deficient CD8α$^+$ cDCs (but not XBP1-deficient CD11b$^+$ cDCs) had a lower level of surface expression of CD11c and impaired cross-presentation of cell-associated antigens.

In addition to cleaving XBP1, IRE1α can cleave other mRNA substrates in a process termed regulated IRE1α-dependent decay (RIDD). XBP1 deficiency resulted in a compensatory increase in RIDD in CD8α$^+$ cDCs, and this was shown to be responsible for the lower level of expression of CD11c and the defects in cross-presentation by CD8α$^+$ cDCs. These data suggest that the IRE1α–XBP1 axis regulates the phenotype and cross-presentation function of CD8α$^+$ cDCs in the steady state.

The study by Saini *et al.* addressed the role of the IRE1α–XBP1 axis in plasma cell survival. XBP1 has been shown to induce the synthesis of inducible nitric oxide synthase (iNOS; encoded by *NOS2*), and in several different experimental systems the authors showed that iNOS deficiency did not affect plasma cell development, but that it greatly compromised the survival of newly generated plasma cells. Interleukin-6 (IL-6) and APRIL (a proliferation-inducing ligand) provide survival signals to plasma cells in the bone marrow, but *Nos2*$^{-/-}$ plasma cells were unable to respond to either of these survival factors. This suggests that iNOS is an intermediate in some plasma cell survival pathways. In agreement with this, IL-6 was shown to induce *Nos2* transcription in wild-type plasma cells.

Further investigation showed that the positive effect of iNOS on plasma cell survival involved the activation of protein kinase G (PKG) through a pathway dependent on nitric oxide, soluble guanylyl cyclase and cyclic GMP (cGMP). In addition, the poor survival of *Nos2*$^{-/-}$ plasma cells was associated with a lower level of expression of *Xbp1* and other components of the UPR at the mRNA level, and with the enhanced activation of caspases. Both of these effects were shown to involve PKG activation. Thus, the survival of newly generated plasma cells involves the activation of a soluble guanylyl cyclase–cGMP–PKG pathway by iNOS, which modulates the UPR and inhibits caspase activation.

Taken together, these studies show how components of the UPR are necessary for maintaining the homeostatic functions of cDCs and plasma cells.

Olive Leavy

> “the IRE1α–XBP1 axis regulates the phenotype and cross-presentation function of CD8α$^+$ cDCs”

ORIGINAL RESEARCH PAPERS Osorio, F. *et al.* The unfolded-protein-response sensor IRE-1α regulates the function of CD8α$^+$ dendritic cells. *Nature Immunol.* http://dx.doi.org/10.1038/ni.2808 (2014) | Saini, A. S. *et al.* Inducible nitric oxide synthase is a major intermediate in signaling pathways for the survival of plasma cells. *Nature Immunol.* http://dx.doi.org/10.1038/ni.2806 (2014)