psoriasiform pathology. Further analysis of the inflammatory infiltrate indicated that T cells and mast cells accumulated at high levels in the inflamed skin of D6-deficient mice but not in that of wild-type mice. Infiltration of T cells into the epidermis was partially responsible for the subsequent accumulation of dermal mast cells, which contribute to development of the pathology through their release of granule products.

So, D6 functions *in vivo* as a decoy receptor, clearing away residual β-chemokines in inflamed skin, thereby helping to avoid aberrant recruitment of inflammatory cells and subsequent pathology.

Lucy Bird

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THYMIC DEVELOPMENT

TRAF6 distributes tolerance

Medullary thymic epithelial cells (mTECs) are important for the negative selection of thymocytes. However, the molecular regulation of mTEC differentiation and organization within the thymus is not well understood. New insight into this process has now been provided by a study published in *Science*, which shows that tumour-necrosis-factor receptor (TNFR)-associated factor 6 (TRAF6) is required for the differentiation and organization of mTECs and for the induction of T-cell self-tolerance.

TRAF6 is a cytoplasmic adaptor protein that transduces signals from several members of the TNFR superfamily, leading to the activation of transcription factors such as activator protein 1 (AP1) and nuclear factor-κB (NF-κB). Previous studies from Jun-ichiro Inoue's group have shown that the thymi of TRAF6-deficient mice are atrophied, leading the researchers to hypothesize that TRAF6 is important for thymic organogenesis. In this new study, the medulla was shown to be smaller in thymi from TRAF6-deficient mice than in thymi from wild-type animals, and the corticomedullary junction was ill defined. mTECs were present in the *Traf6*$^{-/-}$ thymi, but they were dispersed and not clustered in the medulla; they also failed to bind *Ulex europaeus* agglutinin-1 (UEA-1), a lectin that binds mature mTECs.

In addition to impaired maturation, TRAF6-deficient mTECs also expressed reduced levels of *Aire* mRNA, which encodes a protein that induces expression of tissue-specific antigens (TSAs) such that developing thymocytes are tolerized to these TSAs in the thymus. Consistent with this, TRAF6-deficient mice developed inflammation in several organs, including the lungs, liver and pancreas. Such inflammation in TRAF6-deficient mice was probably not only a result of decreased expression by mTECs of mRNA encoding TSAs but also a result of the reduced numbers of $CD4^+CD25^+$ regulatory T (T_{Reg}) cells. Similar inflammatory infiltrates were observed when TRAF6-deficient thymi depleted of haematopoietic cells were transplanted into nude mice, indicating that an intrinsic non-haematopoietic-cell defect was responsible for the autoimmune phenotype of TRAF6-deficient mice.

The phenotype of TRAF6-deficient mice was similar to that observed in mice lacking the NF-κB-family member REL-B. So, the authors examined fetal thymic stroma isolated from *Traf6*$^{-/-}$ mice and found decreased levels of REL-B in these cells compared with wild-type fetal thymic stroma. Furthermore, when TRAF6 was complemented in TRAF6-deficient mTEC lines, REL-B levels increased. Additional support for the idea that TRAF6 induces *Rel-b* transcription is provided by the presence of two NF-κB- and putative AP1-binding sites (transcription factors that are known to be activated downstream of TRAF6 signalling) in the *Rel-b* promoter.

This study identifies TRAF6 as a crucial molecular component of the signalling pathway that regulates mTEC differentiation and organization in the thymus. TRAF6 is also important in the development of self-tolerance, and future studies will focus on how TRAF6-induced REL-B regulates expression of *Aire* and development of T_{Reg} cells. Interestingly, the phenotype of TRAF6-deficient mice is also similar to that of mice lacking NF-κB-inducing kinase (NIK), which regulates the proteasomal processing of the NF-κB-family member p100 to generate the REL-B-binding partner p52. Understanding the relationship between NIK- and TRAF6-regulated activation of NF-κB-family members will help to define the molecular control of thymic organogenesis and central tolerance.

Karen Honey

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