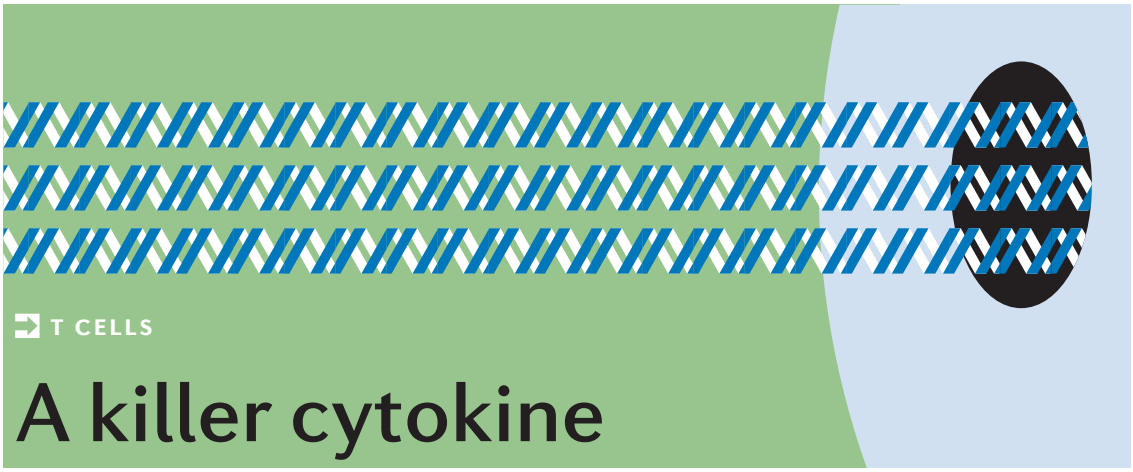

S.Bradbrook/NPG

T CELLS

A killer cytokine

T helper 17 (T_H17) cells have well-known antimicrobial and inflammatory functions, but exactly how these functions are mediated is unclear. New research shows that the human T_H17 cell-derived cytokine interleukin-26 (IL-26) functions like an antimicrobial peptide, directly lysing bacteria and promoting immunogenicity of DNA from dead bacteria and host cells.

Three-dimensional modelling of IL-26 showed that its structure is unlike that of other cytokines from the same family, and instead it shares features with antimicrobial peptides: specifically, an amphipathic structure, with clusters of cationic charges, and an ability to form multimers as well as dimers. Tests for antimicrobial activity showed that IL-26 can directly inhibit the growth of several Gram-negative and Gram-positive bacteria *in vitro* and can reduce bacterial titres in a mouse model of *Klebsiella pneumoniae* sepsis. In addition, supernatant from cultures of human T_H17 cells but not of T_H0 cells (which do not express IL-26) efficiently killed extracellular bacteria, an effect that was abrogated by the presence of blocking antibody specific for IL-26 or small interfering RNA against *IL26*. Similar to other cationic antimicrobial peptides, such as LL-37 and human β-defensin 3, recombinant IL-26 was shown to disrupt bacterial membranes by pore formation.

As LL-37 has been shown to form complexes with extracellular DNA, the authors next tested whether this was also the case for IL-26. Indeed, when mixed with bacterial DNA, IL-26 formed insoluble particles with DNA. Moreover, compared with IL-26 alone or bacterial DNA alone, IL-26–DNA complexes induced the production of interferon-α (IFNα) by plasmacytoid dendritic cells (pDCs). IL-26-lysed bacteria but not live bacteria also induced strong IFNα production, which could be inhibited when DNA was depleted by DNase treatment, suggesting that IL-26 binds bacterial DNA released from dead bacteria and promotes its immunogenicity.

So, what about human DNA? Recombinant IL-26 did not have any direct cytotoxic activity against human cells and did not induce IFNα production by pDCs when mixed with live human cells. However, when IL-26 was mixed with irradiated human cells to trigger cell death, IFNα production by pDCs was induced, and this was largely abrogated by DNase treatment. To investigate the mechanism of IFNα induction, the authors used fluorochrome-labelled DNA to track IL-26–DNA complexes in pDCs. They found that the complexes were internalized by pDCs through endocytosis following attachment to membrane heparin-sulfate proteoglycans. Once inside the cell, the IL-26–DNA complexes activated endosomal Toll-like receptor 9 (TLR9), which promotes IFNα production. Finally, the authors showed that supernatants from cultures of T_H17 cells that contain some dead cells or exogenous DNA induced IFNα production by pDCs in an IL-26-dependent manner, providing a new explanation for the known association of T_H17 cells with autoimmune disease.

Lucy Bird

> “IL-26 binds bacterial DNA released from dead bacteria and promotes its immunogenicity”

ORIGINAL RESEARCH PAPER Meller, S. *et al.* T_H17 cells promote microbial killing and innate immune sensing of DNA via interleukin 26. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3211 (2015)