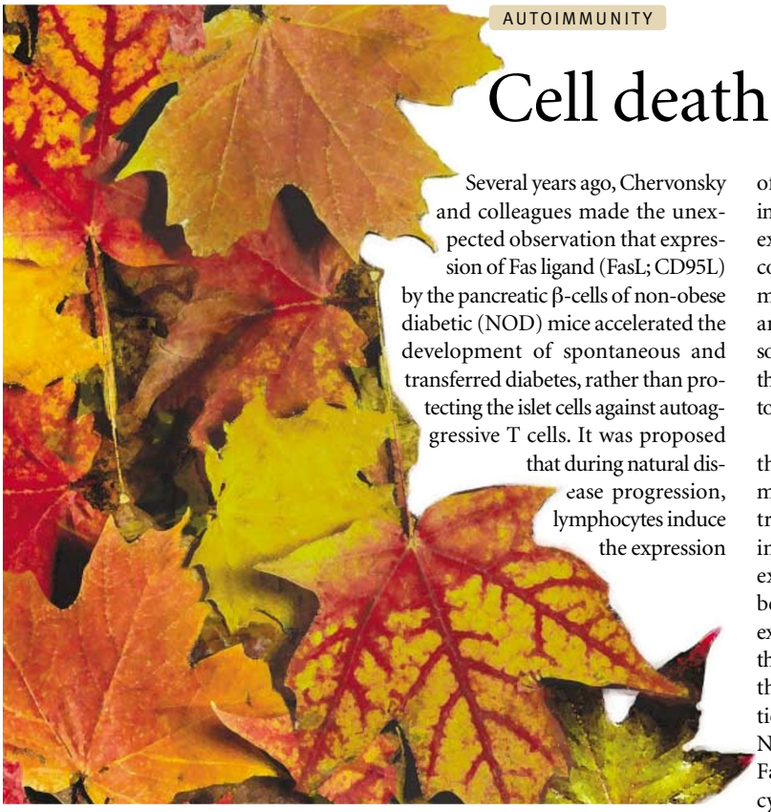

AUTOIMMUNITY

Cell death in diabetes

Several years ago, Chervonsky and colleagues made the unexpected observation that expression of Fas ligand (FasL; CD95L) by the pancreatic β-cells of non-obese diabetic (NOD) mice accelerated the development of spontaneous and transferred diabetes, rather than protecting the islet cells against autoaggressive T cells. It was proposed that during natural disease progression, lymphocytes induce the expression of Fas by β-cells, which are then induced to undergo apoptosis by FasL expressed by effector T cells. Using a combination of several transgenic mouse systems, Chervonsky, Flavell and colleagues have now clarified some of the controversies surrounding the precise role of Fas-mediated apoptosis in β-cell destruction.

Previous studies had shown that the expression of FasL by β-cells might stimulate neutrophils to infiltrate the pancreas, thereby resulting in islet destruction. Histological examination of spontaneously diabetic NOD.RIP-FasL mice (in which expression of FasL is under control of the rat insulin promoter) showed that there was no neutrophil accumulation compared with non-transgenic NOD mice. Furthermore NOD.RIP-FasL-*scid* mice, which lack lymphocytes but have normal numbers of neutrophils, did not develop spontaneous diabetes.

Next, it was shown that the induction of diabetes requires the expression of both Fas and FasL, as the transfer of insulin-specific $CD8^+$ T cells into NOD.RIP-FasL-*lpr* mice (which lack Fas) did not result in diabetes. But, it is possible that homozygous *lpr* mice upregulate expression of FasL by leukocytes, which could result in elimination of the transferred cells. However, NOD.RIP-FasL-*scid-lpr* mice, which lack endogenous lymphocytes expressing FasL, showed no acceleration of diabetes compared with NOD-*scid-lpr* mice when injected with splenocytes from diabetic NOD mice. Therefore, Fas participates in the killing of β-cells owing to the ectopic expression of FasL.

Finally, the authors used another transgenic system to manipulate Fas signalling in β-cells without systemic disruption. NOD.RIP-Fas^{cg} mice have a point mutation in the death domain of Fas that interferes with Fas oligomerization in islet cells in a

INNATE IMMUNITY

An ANGel in disguise

Antimicrobial molecules are well-recognised weapons in the armoury of the innate immune response to infection. In many host-defence settings, invading pathogens are exposed to a diverse array of defensive peptides, proteins and enzymes that have an important role in fending off infections of the respiratory and gastrointestinal tracts. Reporting in *Nature Immunology*, Jeffrey Gordon and members of his lab have now added to this diversity with the discovery that angiogenins are a new class of endogenous antimicrobial proteins.

Human angiogenin (ANG), better known for its proposed link with angiogenesis and as a promoter of tumour growth, has several unusual properties that indicated to researchers that its main function was something other than vascular development. In fact, observations that inflammation leads to an increase in the level of expression of messenger RNA encoding ANG and that members of the angiogenin family are subject to high rates of mutation both indicated that these molecules might contribute in some way to defending the host.

Using germ-free mice, the authors used microarrays to identify host genes that showed an increased level of expression in response to colonization of the small intestine by *Bacteroides thetaiotaomicron*, a member of the normal intestinal microflora. One molecule that emerged from this analysis was a previously uncharacterized member of the angiogenin family, Ang4. Further analysis showed that this molecule is expressed and secreted by Paneth cells and that normal intestinal bacteria induce its expression. The authors also showed that Ang4 has bactericidal activity against enteric pathogenic bacteria, including *Enterococcus faecalis* and *Listeria monocytogenes*. By contrast, the related family members mouse Ang1 and human ANG, which appear in the circulation during the acute-phase response to infection, have bactericidal and fungicidal activities against pathogens that are known to cause systemic infections. Interestingly, these molecules have little activity against enteric pathogens, which indicates that whereas Ang4 is a mediator of epithelial host defence in the intestine, Ang1 and ANG are unappreciated components of the systemic response to infection.

It is tempting to speculate that the pathogen-specific microbicidal activities of the different angiogenin-family members are a consequence of selective pressures on the host brought about by the presence of invading pathogenic bacteria at different sites in the body. What is also particularly intriguing is the ability of commensal bacteria in the gut to regulate expression of Ang4, a property that is unique, so far, to this specific intestinal microbicidal protein. As well as providing a mechanism by which the microflora of the host has the ability to shape the composition of the local environment, it also indicates that commensal bacteria of the intestine have a crucial role in the development of an effective innate immune response to the presence of their less-welcome compatriots.

David P. O'Connell,
Editor, Nature Reviews Microbiology

References and links

ORIGINAL RESEARCH PAPER Hooper, L. V. *et al.* Angiogenins: a new class of microbicidal proteins involved in innate immunity. *Nature Immunol.* 27 January 2003 (DOI: 10.1038/ni888)

WEB SITE

Jeffrey Gordon's lab: http://gordonlab.wustl.edu/