BACTERIAL PHYSIOLOGY

Sweet deception

Helicobacter pylori persists in the human stomach for many years using a range of tactics to counter host defences. Thomas Meyer, Christian Wunder and colleagues now report on a novel metabolic strategy used by *H. pylori* to evade host immunity.

The authors were intrigued by cholesterol metabolism in *H. pylori* — cholesterol is crucial for the growth of *H. pylori*, but the bacterium lacks the enzymes required to make the lipid, and how *H. pylori* detects and assimilates cholesterol has been a puzzle. Using a chemoattractant assay, Meyer and colleagues showed that *H. pylori* senses cholesterol and moves along a cholesterol gradient. Rather than absorbing secreted cholesterol, *H. pylori* associates with cholesterol-rich portions of the plasma membrane of gastric epithelial cells (called lipid-raft domains) and extracts cholesterol from the host cell. The incorporated sterol is then coupled to glucose through α-glycosidic bonding.

Although steryl glycosides are common in plants and in fungi, these chemical compounds are rare in bacteria. Also, most known bacterial cholesteryl glucosides are made up of β-glycosidic anomers rather than α-glycosidic anomers, suggesting that the unusual configuration of *H. pylori* cholesterol has functional significance.

To investigate this further, the research team asked whether unmodified cholesterol affected the immune response to *H. pylori*. They showed that excessive cholesterol *in vitro* enhanced the phagocytosis of *H. pylori* by antigen presenting cells (APCs) with subsequent T-cell activation. These findings were recapitulated *in vivo*: a high cholesterol diet in *H. pylori*-infected mice reduced the gastric bacterial load through a vigorous T-cell dependent inflammatory response.

By contrast, the conversion of cholesterol to cholesteryl α-glucoside markedly decreased the phagocytosis of *H. pylori* by APCs. The authors identified the gene encoding the cholesterol-α-glucosyltransferase enzyme (*hp0421*) and generated *H. pylori hp0421* mutants that lacked cholesteryl glucosides. These mutant strains were vigorously engulfed by macrophages, resulting in potent T-cell activation. Also, mice fed the

HIV

Relief for tired T cells

Earlier this year, researchers reported that virus-specific $CD8^+$ T cells in mice with chronic viral infection have an exhausted phenotype that is characterized by the expression of large amounts of the inhibitory receptor programmed cell death 1 (PD1). In a concerted effort by two groups, these findings have now been extended to humans.

In these two new studies, researchers used major histocompatibility complex (MHC) class I tetramers complexed with HIV-derived peptide epitopes to characterize virus-specific T cells in patients with chronic HIV infection. Both papers reported that PD1 expression was significantly upregulated by HIV-specific (tetramer-positive) $CD8^+$ T cells in untreated HIV-infected individuals compared with treated HIV-infected individuals. Moreover, longitudinal analysis of individuals before and after therapy with antiretroviral agents showed that PD1 expression correlated with viral load. This indicates that the presence of large amounts of viral antigen in individuals with chronic HIV infection might drive continuous high-level expression of PD1 by virus-specific T cells.

> “…the presence of large amounts of viral antigen in individuals with chronic HIV infection might drive continuous high-level expression of PD1 by virus-specific T cells.”

Consistent with previous reports, HIV-specific $CD8^+$ T-cell function in individuals with chronic HIV infection (either untreated or treated with antiretroviral agents) was shown to be impaired, with these T cells having a reduced capacity to produce cytokines and proliferate. In both studies, this impaired or ‘exhausted’ functional phenotype was shown to correlate with high PD1 expression.

Next, both groups asked whether this functional impairment could be reversed by blocking the interaction of PD1 with its ligand (PDL1), as Barber and colleagues had previously shown for mouse T cells (see Further Reading). Indeed, incubation of peripheral-blood mononuclear cells with PDL1-specific antibody following stimulation with HIV-derived peptides restored the proliferative capacity of these T cells, as indicated by increased numbers of tetramer-positive $CD8^+$ T cells. The production of cytokines and effector molecules, such as interferon-γ, tumour-necrosis factor and granzyme B, by HIV-specific $CD8^+$ T cells was also increased in the presence of PDL1-specific antibody compared with stimulation with HIV-derived peptides alone.

Day *et al.* went on to show that $CD4^+$ T cells, similar to $CD8^+$ T cells, are functionally impaired in individuals with chronic HIV infection and that the function of these T cells could similarly be restored following blockade of the PD1-signalling pathway.

Whether blockade of the PD1-signalling pathway to restore exhausted T cells is a realistic treatment approach for the effective control of viraemia in patients with chronic HIV infection awaits further study.

Lucy Bird, Associate Editor, *Nature Reviews Immunology*

ORIGINAL RESEARCH PAPERS Day, C. L. *et al.* PD-1 expression on HIV-specific T cells is associated with T-cell exhaustion and disease progression. *Nature* **443**, 350–354 (2006) | Trautmann, L. *et al.* Upregulation of PD-1 expression on HIV-specific $CD8^+$ T cells leads to reversible immune dysfunction. *Nature Med.* 20 Aug 2006 (doi:10.1038/nm1482)
FURTHER READING Barber, D. L. *et al.* Restoring function in exhausted CD8 T cells during chronic viral infection. *Nature* **439**, 682–687 (2006)