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Infection and autoimmunity: the glycolipid link

Although the association between bacterial infection and autoimmune disease is well known, there is little evidence for a specific mechanistic link. One hypothesis — the antigen non-specific theory — proposes that the widespread cellular damage inflicted by microbial infection might expose hidden self antigens to autoreactive T cells. Now, reporting in ***Immunity***, Gennaro De Libero and colleagues propose a more refined model in which bacterial infection induces the production of large amounts of endogenous glycosphingolipid (GSL) antigen by host cells. The authors suggest that the recognition of these GSLs by 'self-directed' T cells might contribute to autoimmune disease.

De Libero and co-workers focused their studies on T-cell clones that had been derived from patients with multiple sclerosis; these cells are specific for GSLs that are abundantly expressed in the central nervous system. As GSLs are presented to T cells by CD1 molecules — MHC class-I-like molecules that are implicated both in the activation of proinflammatory T-cell responses to mycobacterial products and the generation of autoreactive lymphocytes — the authors reasoned that further analysis of the CD1–T-cell interaction might reveal the mechanisms that link infection and autoimmunity.

Indeed, the self-GSL-specific T cells were activated by antigen-presenting cells (APCs) that had either been infected with bacteria or exposed to microbial products such as lipopolysaccharide (LPS). T-cell stimulation required ligation of the T-cell receptor by the CD1 complex, indicating an antigen-specific activation process. This led the authors to speculate that increased synthesis of endogenous GSLs might be the trigger that induces the autoreactive T-cell response. Further biochemical analysis proved that this was the case — APCs infected with bacteria or APCs that had been treated with LPS upregulated the synthesis of GSLs, and the authors propose that the increased numbers of CD1–GSL complexes on the surface of APCs activate the self-GSL-specific T cells.

These studies provide insights into the microbial-induced pathways that upregulate GSL synthesis. As different bacteria and bacterial products activated GSL-specific T cells, it is probable that several different pattern-recognition receptors and signalling pathways converge on the GSL biosynthesis machinery. Notably, only intact LPS was able to prime the APCs for optimal T-cell activation — lipid A or modified LPS was ineffective in this respect.

With regard to the physiological functions of GSL-specific T cells, these remain contentious, but as these cells respond to APCs that are primed by microbial infection, it is likely that they have a role in either promoting or modulating the initial immune response to infection. After resolution of infection, these self-GSL-specific T cells are a repository of potentially autoreactive lymphocytes.

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References and links

ORIGINAL RESEARCH PAPER De Libero, G. *et al.* Bacterial infections promote T cell recognition of self-glycolipids. *Immunity* **22**, 763–772 (2005)
FURTHER READING Kronenberg, M. & Kinjo, Y. Infection, autoimmunity and glycolipids: T cells detect microbes through self-recognition. *Immunity* **22**, 657–659 (2005)