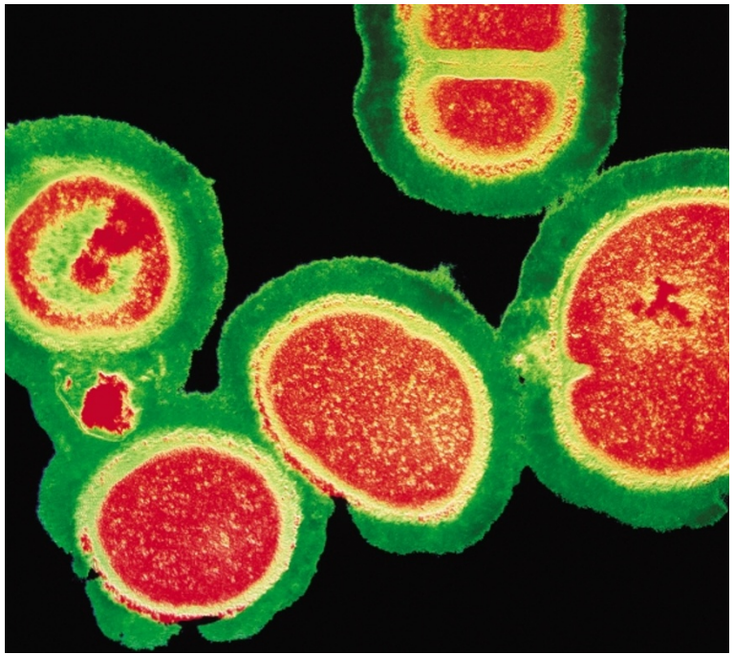
VACCINES

Dead or alive



Live vaccines usually give much better protection from infection than subunit vaccines or those based on preparations of dead or replication-defective microbes — but what is the immunological basis of this phenomenon? Increased antigen dose, altered antigen presentation and the nonspecific effects of inflammation are all possible mechanisms. Now, Gregoire Lauvau and co-workers, reporting in *Science*, have compared how live and killed vaccines interface with the immune system, using *Listeria monocytogenes* infection of mice as a model.

Although immunization with live *L. monocytogenes* induces long-lasting, $CD8^+$ T-cell-dependent protective immunity, vaccination with heat-killed *L. monocytogenes* (HKLM) is ineffective. To find out why, the authors tracked $CD8^+$ *L. monocytogenes*-specific T cells using MHC tetramers. They found that mice primed with live bacteria and HKLM-primed mice form recall $CD8^+$ T-cell responses of equivalent magnitude.

Why, then, does this $CD8^+$ T-cell memory response fail to protect HKLM-primed mice? One possible explanation is that $CD4^+$ T-cell memory, which is not elicited by HKLM vaccination, is crucial for protection. To test this, $CIITA^{-/-}$ mice (which are $CD4^+$ T-cell deficient) were immunized and challenged with live *L. monocytogenes*. These mice were immune to infection and their $CD8^+$ T-cell recall responses were indistinguishable from those of wild-type mice, indicating that protective immunity does not depend on $CD4^+$ T-cell memory.

The authors then took a closer look at the effects of live and HKLM vaccination on $CD8^+$ T-cell priming. Naive $CD8^+$ T cells from *L. monocytogenes*-specific TCR transgenic mice were transferred into an adoptive host which was then immunized. After immunization with live bacteria, the transgenic $CD8^+$ T cells were found to undergo expansion, develop cytotoxic activity, and downregulate the resting-cell marker CD62L. Conversely, following immunization

MUCOSAL IMMUNOLOGY

On guard!

The major histocompatibility complex (MHC) class I and II molecules present peptide antigen to $CD8^+$ and $CD4^+$ T cells, respectively. As well as classical MHC molecules, the mouse MHC encodes several non-classical MHC class I-like molecules, such as the thymus leukaemia (TL) antigen, whose functions remain incompletely understood. TL is expressed almost exclusively on intestinal epithelial cells and has been proposed to have a role in presenting antigen to intestinal epithelial lymphocytes (IELs). Reporting in *Science*, Hilde Cheroutre and colleagues now show that TL interacts with CD8αα homodimers on IELs, with important consequences for the mucosal environment.

Cheroutre *et al.* used TL tetramers to identify cells that bind to TL. Most IELs were stained by the tetramers, but not splenocytes, and only a minority of thymocytes were stained. Tetramers bound equally well to $TCR\alpha\beta^+$ and $TCR\gamma\delta^+$ IELs, and binding was irrespective of TCR specificity. Production of the TL tetramers in insect cells ensured that peptide–TL interactions were not possible, so peptide binding to TL molecules was not a requirement for the interaction with IELs.

As TL-tetramer binding is virtually specific for IELs, IELs express the CD8αα homodimer, and TL molecules contain a CD8α-binding motif, Cheroutre and colleagues reasoned that TL might bind CD8αα. This seemed to be the case — TL tetramers showed no staining on IELs from CD8α-deficient mice, and thymocytes from CD8β knockout mice, which express CD8αα homodimers, showed elevated TL-tetramer binding in comparison to wild-type mice. Studies using surface plasmon resonance, in which the binding of TL to CD8αα molecules immobilized on a chip was assessed, confirmed a preferential and high-affinity binding of TL to CD8αα.

So, what are the immunological consequences of TL–CD8αα interactions? This was tested by stimulating CD8α-deficient and CD8α-transfected T cells (expressing the same antigen-specific TCR) with TL^+ and TL^- forms of peptide-pulsed presenting cells. Increased interleukin-2 (IL-2) production by the CD8αα-expressing T cells was observed when they were stimulated with the TL-positive presenting cells. This enhanced cytokine production was confirmed using antigen-stimulated transgenic IELs, and intracellular cytokine staining revealed enhanced interferon-γ (IFN-γ) production. Polyclonally-stimulated wild-type IELs also showed increased IL-2 and IFN-γ production in the presence of TL. In contrast to the cytokine results, TL–CD8αα interactions decreased the proliferative and cytotoxic responses of IELs.

The results of this study indicate that CD8αα is not a TCR co-receptor and it affects T-cell function independently of TCR specificity. The authors speculate that TL–CD8αα interactions have a role in the maintenance of barrier function and homeostasis in the gut epithelium — inhibition of proliferation would ensure that cellular expansion would not disrupt the epithelial layer, and inhibition of cytotoxicity would ensure that the integrity of the epithelial layer is maintained. Further work will be required to elucidate the precise mechanisms by which TL–CD8αα interactions exert their regulatory effects in the intestine.

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References and links

ORIGINAL RESEARCH PAPER Leishman, A. J. *et al.* T cell responses modulated through interaction between CD8αα and the nonclassical MHC class I molecule, TL. *Science* **294**, 1936–1939 (2001)