Immunology

Killer T cells show their kinder side

The immune system protects the body by responding to invading organisms. But how is an attack on useful resident microbes prevented? A pathway used by immune cells to sense and respond to beneficial bacteria has now been identified.

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The immune system performs a difficult balancing act. It must respond rapidly to dangerous micro-organisms that threaten the host, yet also co-exist peacefully with the large array of micro-organisms that colonize barrier surfaces such as those of the skin and the gut. Writing in *Cell*, Linehan *et al*.[1] examine the interactions between immune cells and the bacteria that normally reside on the skin, and reveal the signalling pathway that governs the immune response to such bacteria.

Most immunity research has traditionally focused on how immune cells swiftly recognize and eliminate viral and bacterial pathogens, and the insights from such studies have increasingly led to the development of immune-based therapies. However, attention has now also turned to how microbial communities at barrier surfaces exert a longer-term influence on host immune responses. Linehan and colleagues examined the relationship between bacterial and immune cells present in the skin and reveal that a type of immune cell, called a cytotoxic $CD8^+$ T cell, that is best known for its role in killing unwanted cells also has an unexpected capacity to promote tissue repair.

The authors studied the bacterium *Staphylococcus epidermidis* using mouse and rhesus monkey hosts, as well as analysing clinical samples from patients. *S. epidermidis* usually colonizes human skin as part of a group of what are known as commensal organisms – those that exhibit long-term persistence and that don't usually cause disease. However, sometimes for newborns or patients who are in an immunosuppressed state, the same organism**,** *S. epidermidis*, can cause severe disease, and it can also create major chronic infection in artificial joints and vascular implants[2]. However, even though the bacteria are normally carried harmlessly, they are also not ignored. It has been reported[3] that the immune response to an initial encounter with specific strains of *S. epidermidis* is dominated by $CD8^+$ T cells in mouse skin. An immune response would be expected as a result of a bacterial challenge, but Linehan and colleagues asked two important questions about this response and the answers they obtained were illuminating.

The first question was how do T cells recognize the specific *S. epidermidis* strain. There are generally two ways of achieving this. A response to bacteria is thought to usually occur because a T cell recognizes bacterial peptide fragments bound to the 'classical' MHC1a protein that is part of the major histocompatibility complex (MHC) that presents such frgaments to immune cells. In these mouse experiments**,** however, a 'non-classical' protein, H-2-M3, of the MHC1b family was involved. The H2-M3 molecule can present[3] bacterial peptides that have a modification of the amino-acid residue methionine in which an *N*-formyl group is added. This result indicates that commensal bacteria can be sensed by an unconventional pathway i.e. not via conventional MHC1a molecules.

The other question was whether this non-classical immune-recognition pathway might also be coupled to possible 'unconventional' T-cell behavior**.** The team took an unbiased approach to address this question by analysing gene expression at a genome-wide level in the responding $CD8^+$ T cells and comparing these profiles to other related T-cell populations found in the mouse skin which did not respond to S. epidermidis**.** In contrast to the typical gene-expression profiles associated with the expected functions of responding $CD8^+$ T cells such as activation of the pathways involved in killing unwanted cells or in the release of pro-inflammatory signalling molecules, the authors instead surprisingly found that these $CD8^+$ T cells expressed genes that are associated with the processes of wound healing and tissue repair. The authors tested whether this gene-expression signature was indeed indicative of a healing response *in vivo* and in a mouse model of skin wound healing in association with S. epidermidis colonisation demonstrated a clear association between this unconventional T-cell response and the promotion of wound healing. Thus, the immune recognition of bacterial resident of the skin can induce a striking form of immunity that does not directly retaliate against that bacteria but instead aids tissue repair**.**

Thinking about the bigger picture, this finding by Linehan and co-workers adds to a growing recognition of the diverse functions of unconventional T cells, which are enriched at barrier sites and can recognize evolutionarily conserved microbial proteins. Such T cells include, for example, mucosa-associated invariant T (MAIT) cells, which are abundant in humans and induced by commensals, and share several of the key features (e.g. production of the signaling molecule Interleukin-17) of the T-cell population studied by Linehan and colleagues[4,5]. These, and other T cell populations in humans and mice such as invariant natural killer T (iNKT) cells and germline encoded mycolyl-reactive (GEM) T cells also share the property action in response to MHC1b recognition[6,7]. A human equivalent to mouse H2-M3 has not been identified so far. It is possible that if such an equivalent is found, novel human T cell populations might fulfil a similar role to that of the $CD8^+$ T cells which were observed by Linehan and colleagues during their studies of mouse skin, or alternatively this role may be taken by a related unconventional T cell type.

As the authors mention, many day-to-day interactions of the immune system with microbes are likely with commensals in the skin, gut or airways. Therefore the induction of a host immune response to such bacteria that keeps the status quo rather than drives elimination of the microbe, which is usually accompanied by inflammation and tissue damage, could be a beneficial response. But should we really consider this response to be unconventional? Although the roles of classical MHC molecules and responding cells were defined first, non-classical MHC and MHC-like proteins are considered to be more ancient[8,9], in evolutionary terms, than MHC 1a. Because Linehan and colleagues show a direct link between the role of MHC 1b molecules and tissue homeostasis perhaps these functions evolved in parallel and represent the broadly 'conventional' functions of the immune system, with additional specializations of the immune system subsequently evolving over time.

This study hints at the potential broad, long-term effects of microbial residents on the immune system. If future studies mechanistically link individual microorganisms to specific immune responses, it might be possible to understand not only the roles of some abundant and relatively unexplored immune-cell populations, but ultimately determine how resident microbes affect health and disease in a way that might point us towards new treatment approaches.

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