MATERIALS SCIENCE

Wing origami

Origami-based design techniques have applications ranging from nanoscale devices to architectural structures. But conventional techniques have a limited range of folding patterns. Writing in *Science*, Faber *et al.* report an approach that overcomes this restriction (J. A. Faber *et al. Science* **359,** 1386–1391; 2018).

The authors were inspired by the amazing folding abilities of earwig wings (pictured). They discovered that protein-rich joints in the wings behave like springs, and mimicked this design in synthetic structures using mechanical springs. Such structures show folding patterns and functionalities that were impossible using previously available methods. **Ryan Wilkinson**

PANTHER MEDIA GMBH/ALAMY

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 has now been identified that allows immune cells to sense and respond to beneficial bacteria.

PAUL KLENERMAN & GRAHAM OGG

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

Most immunological research has focused on how immune cells recognize and eliminate viral and bacterial pathogens, and the insights obtained have led to the development of many immune-based therapies. However, attention has also turned to microbial communities at barrier surfaces and the long-term influence they exert on host immune responses. Accordingly, Linehan and colleagues studied the skin-dwelling bacterium *Staphylococcus epidermidis* in mice and rhesus monkeys, as well as analysing human-tissue samples from the clinic.

Staphylococcus epidermidis belongs to a group of microorganisms termed commensals, and usually colonizes human skin without causing disease. However, in premature newborns and people who are in an immunosuppressed state or who have received artificial joints, *S. epidermidis* can cause severe disease or chronic infection[2]. Furthermore, even though the bacterium is normally harmless, it is not ignored by the immune system. In mouse skin, the response[3] to an initial encounter with certain strains of *S. epidermidis* is dominated by a type of immune cell called a cytotoxic $CD8^+$ T cell, also known as a killer T cell. Linehan and colleagues asked two key questions about this response, and the answers they obtained are illuminating.

The first question was, how do T cells recognize *S. epidermidis*? A response to bacteria is thought to occur when a T cell recognizes a bacterial peptide fragment bound to the 'classical' class Ia protein component of the major histocompatibility complex (MHC), which presents such fragments to immune cells. However, using a mouse model system, Linehan and colleagues found that a 'non-classical' protein, H2-M3, which belongs to the MHC class Ib family, was instead involved in MHC presentation in the response to *S. epidermidis*. H2-M3 can present[4] bacterial peptides in which the amino-acid residue methionine has been modified by addition of an *N*-formyl group.

The other question Linehan and colleagues sought to answer was whether this non-classical immune-recognition pathway might also be coupled to 'unconventional' T-cell behaviour. The team investigated this by comparing gene-expression patterns of $CD8^+$ T cells responding to *S. epidermidis* with those of other types of T-cell population in the mouse skin that did not respond to the bacterium. The authors found that the responsive $CD8^+$ T cells expressed genes associated with wound healing and tissue repair (Fig. 1). This was surprising because responding $CD8^+$ T cells would be expected to express genes associated with activation of the pathways involved in killing unwanted cells or in the release of pro-inflammatory signalling molecules.

Using an *in vivo* mouse model of skin-wound healing in association with *S. epidermidis* colonization, the authors demonstrated that the tissue-repair gene-expression signature in responding T cells was linked to promotion of a healing response. Thus, immune recognition of bacterial residents of the skin can induce a form of immunity that does not directly retaliate against the bacterium, but instead aids tissue repair.

The authors' finding adds to a growing recognition of the diverse functions of other unconventional T cells that are found at barrier sites and that can recognize evolutionarily conserved microbial molecules. These cells include, for example, mucosal-associated invariant T cells, which are abundant in humans and induced by commensals, and which share several features[5] of the T-cell population studied by Linehan and colleagues — such as the production of the signalling molecule interleukin-17A.

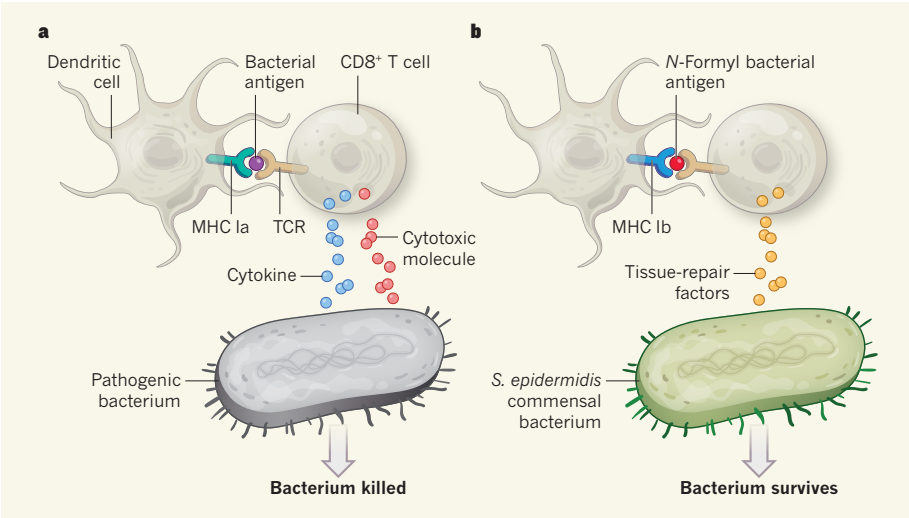

Figure 1 | Response of killer T cells to bacterial infection. **a**, An immune cell called a $CD8^+$ T cell (killer T cell) can help to control infection by a pathogenic bacterium. The T-cell receptor (TCR) recognizes infection when a bacterial peptide called an antigen is presented on dendritic cells of the immune system by an MHC class Ia protein. A conventional T-cell response is then unleashed, and the release of cytokine and cytotoxic molecules triggers inflammation and bacterial destruction. **b**, Linehan *et al.*[1] report an analysis of the killer-T-cell response to *Staphylococcus epidermidis* using mouse models and human cells. This type of bacterium, called a commensal, can become a long-term, non-pathogenic resident of the body. Killer T cells recognize *S. epidermidis* when an MHC class Ib molecule presents an antigen containing an *N*-formyl modification of an amino-acid residue. The T cell expresses genes associated with tissue repair, and the bacterium survives this 'unconventional' response. However, such immune responses are probably not neatly divided into these categories, and conventional T-cell responses might in some cases aid tissue repair and unconventional T-cell responses might aid host defence against pathogens.

These and other T-cell populations in humans and mice, such as invariant natural killer T cells and germline-encoded mycolyl-reactive T cells, also act in response to MHC class Ib-mediated bacterial-peptide 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, a human T-cell population might fulfil a similar role to that of the $CD8^+$ T cells observed by Linehan and colleagues.

As the authors note, many of the day-to-day interactions between immune-system cells and microbes are probably with the commensals in the skin, gut and airways. Therefore, an immune response that maintains the status quo, rather than driving bacterial elimination, which is usually accompanied by inflammation and tissue damage, could be beneficial. But should such a response really be considered unconventional? Although the roles of classical MHC molecules and responding immune cells were identified first, non-classical MHC and MHC-like proteins are evolutionarily older[8,9] than MHC class Ia molecules. Linehan and colleagues reveal a direct link between the role of MHC class Ib molecules and tissue homeostasis. Therefore, these functions might have evolved in parallel and represent the broadly 'conventional' functions of the immune system, with additional immune-system specializations evolving over time.

The authors' 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 types of immune response, it might be possible not only to understand the roles of some abundant and relatively unexplored immune-cell populations, but also to determine how resident microbes affect health and disease in a way that might lead to new treatment approaches. ■

Paul Klenerman *and* **Graham Ogg** *are in the NIHR Biomedical Research Centre, Oxford OX1 3SY, UK.* **P.K.** *is also in the Translational Gastroenterology Unit, Nuffield Department of Medicine, University of Oxford.* **G.O.** *is also in the MRC Human Immunology Unit, University of Oxford.*
e-mails: paul.klenerman@ndm.ox.ac.uk; graham.ogg@ndm.ox.ac.uk

1. Linehan, J. L. *et al. Cell* **172,** 784–796 (2018).
2. Sabaté Brescó, M. *et al. Front. Microbiol.* **8,** 1401 (2017).
3. Naik, S. *et al. Nature* **520,** 104–108 (2015).
4. Wang, C.-R. *et al. Cell* **82,** 655–664 (1995).
5. Legoux, F., Salou, M. & Lantz, O. *Annu. Rev. Cell Dev. Biol.* **33,** 511–535 (2017).
6. Van Rhijn, I. *et al. Nature Immunol.* **14,** 706–713 (2013).
7. Godfrey, D. I., Uldrich, A. P., McCluskey, J., Rossjohn, J. & Moody, D. B. *Nature Immunol.* **16,** 1114–1123 (2015).
8. Rodgers, J. R. & Cook, R. G. *Nature Rev. Immunol.* **5,** 459–471 (2005).
9. Goyos, A., Sowa, J., Ohta, Y. & Robert, J. *J. Immunol.* **186,** 372–381 (2011).

This article was published online on 26 March 2018.

METABOLISM

The healthy diabetic cavefish conundrum

Some Mexican cavefish have a mutation in an insulin receptor protein that affects blood-glucose regulation. The same mutation causes diabetes and health problems in humans, but the diabetic cavefish thrive. SEE LETTER P.647

SYLVIE RÉTAUX

Blind Mexican cavefish (*Astyanax mexicanus*) live in dark caves, a challenging environment that has shaped their evolution. On page 647, Riddle *et al.*[1] reveal the surprising way in which cavefish regulate their glucose metabolism, a finding that might have implications for our understanding of human diabetes.

Blood-glucose regulation is essential for the body to function normally. In humans, this is achieved by a complex network of interactions between several organs that is mediated by hormones and neuropeptide molecules. After a meal, glucose levels rise, and β-cells in the pancreas release the hormone insulin. Insulin binds to its receptor on the surface of liver, muscle and fat cells, stimulating them to take up glucose from the bloodstream, and thereby returning blood glucose levels to normal. Conversely, if blood glucose levels drop, for example between meals, pancreatic α-cells release the hormone glucagon, which stimulates the liver to break down its reserves of a glucose polymer called glycogen. The release of this glucose into the bloodstream once again returns blood glucose levels to normal.

Disturbance in these interplays can cause severe metabolic disorders, such as diabetes, which results in high blood-glucose levels and a range of deleterious effects. In type I diabetes, β-cells are destroyed by immune cells, and insulin is not produced. In type II diabetes, insulin is produced, but its levels are too low