IMMUNOTHERAPY

A gut punch fights cancer and infection

Microorganisms in the human gut can affect immune-system cells. Gut bacterial strains have been discovered that boost immune cells that have cell-killing capacity and that can target cancer and protect against infection. SEE ARTICLE P.600

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The bacteria that live in our bodies have a pivotal role in the maintenance of our health, and can influence a range of conditions, such as obesity and cancer[1–6]. Perhaps the most important role for the community of microorganisms that live in our gut — termed the microbiota, which include bacteria, fungi and archaea — is to aid immune-system development[7]. On page 600, Tanoue *et al.*[8] report the identification of 11 strains of bacteria that reside in the guts of some healthy humans and that can boost immune responses that fight infection and cancer.

A particularly potent type of immune cell that recognizes and kills infected and cancerous cells is the cytotoxic $CD8^+$ T cell. These cells identify target cells through interactions between their T-cell receptor proteins (TCRs) and peptide fragments called antigens from the target cell. Harnessing an approach used previously[9,10] to identify bacterial strains that can boost certain subsets of T cell, Tanoue and colleagues used mouse models in their search for bacteria that drive production of the subset of $CD8^+$ T cells that produce a potent immunostimulatory protein called interferon-γ (IFN-γ) and are known as $CD8^+$ IFN-γ^+ T cells. They found that mice housed under normal laboratory conditions had this type of T cell in their colons, but that such cells were mainly absent in mice raised in a germ-free environment.

To try to identify bacteria that might be responsible for boosting $CD8^+$ IFN-γ^+ T cells, the authors transferred the microbiota in faecal samples from healthy humans into mice raised under germ-free conditions. This approach, and the subsequent analysis of the subsets of bacteria that grew in the mice, allowed the authors to identify a mixture of 11 bacterial strains that drive the accumulation of $CD8^+$ IFN-γ^+ T cells in the mouse colon (Fig. 1). Such accumulation of these cells might result from proliferation and differentiation of existing T cells in the colon, recruitment of the cells from elsewhere in the body, or a combination of both. These $CD8^+$ IFN-γ^+ T cells specifically recognized bacterial antigens found in a mixture of the 11 strains. The authors found that immune cells called dendritic cells help to present these bacterial antigens to T cells. This type of interaction between dendritic cells and T cells can help to prime T-cell responses.

Tanoue and colleagues investigated whether this increase in $CD8^+$ IFN-γ^+ T cells, which can have a key role in defence against infections, could protect against a disease-causing bacterium called *Listeria monocytogenes*. This was indeed the case, and mice that received the 11 bacterial strains had a greater ability to combat an *L. monocytogenes* infection than did control mice that did not receive the strains. Moreover, if *L. monocytogenes* was injected directly into a cavity in the mouse abdomen, the animals that received the strains were protected from *L. monocytogenes* infection of their spleen or liver, suggesting that the protective effects of the bacteria extend to generating immune responses beyond just the gut.

The authors investigated the role of $CD8^+$ IFN-γ^+ T cells in anticancer responses. A current trend in cancer immunotherapy is to target proteins that inhibit the immune system. Such an approach is termed immune-checkpoint blockade, and it can invigorate the immune response in a way that enables $CD8^+$ T cells to target and kill tumours. This method has generated much interest because, in certain cases, it can cause sustained tumour shrinkage in people who otherwise do not respond to treatment[11–13]. Most cancers, however, are unresponsive to these checkpoint-blockade therapies. The microbiota can affect responses to these treatments[5,6,14–16], but there is no consensus regarding which species and strains of microorganisms are the most effective at boosting an immune response.

Tanoue *et al.* report that the administration of their defined set of bacteria enhances the efficiency of checkpoint-blockade treatment in two tumour models in which cancer cells were transplanted into the skin of mice. As they had observed with their *L. monocytogenes* studies, administration of the 11 bacterial strains caused an increase in $CD8^+$ IFN-γ^+ T cells at the sites of disease rather than only in the colon. The authors found that T cells were generated that had specificity for tumour antigens rather than for antigens in the bacterial mixture. Yet how changes in the microbiota affect T cells in the body's periphery is unknown. Surprisingly, the T cells in the transplanted tumours were of distinct origin from those in the colon, and did not arise from the movement of either T cells or dendritic cells between those organs. Furthermore, the authors found that the 11 bacterial strains did not leave the gut and move to other sites. Instead, the authors suggest that metabolite molecules secreted by these bacteria might circulate in the host's body and boost T cells elsewhere.

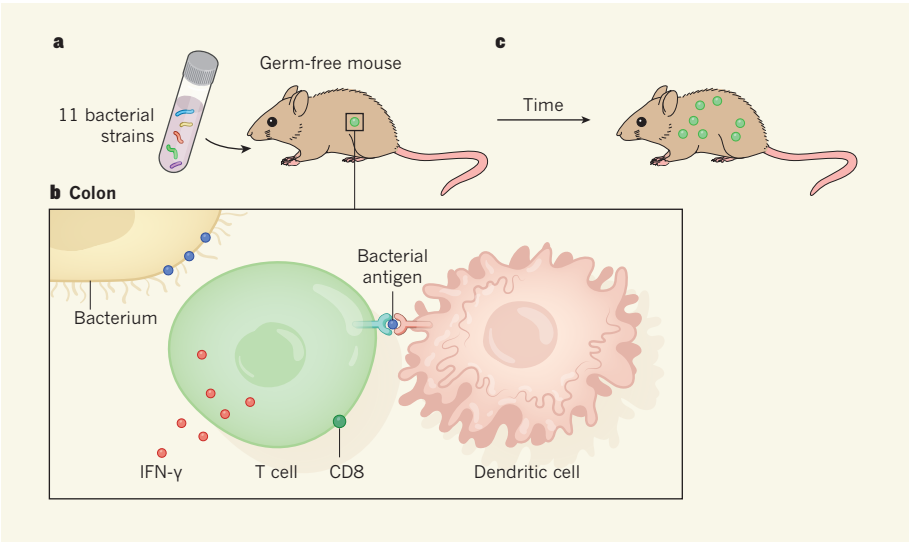

Figure 1 | Bacteria that boost immune defences. **a**, Tanoue *et al.*[8] report the identification of 11 bacterial strains that naturally colonize the gut of certain people, and that augment the immune responses of germ-free mice that ingest these strains. **b**, The authors report that fragments of proteins, called antigens, from these ingested bacteria are presented by a type of immune cell called a dendritic cell to another type of immune cell called a T cell. Such interactions can boost T-cell responses. The type of T cell that accumulates in the colon after treatment with the 11 strains makes the protein CD8 and secretes the immune-stimulating protein IFN-γ. **c**, Over time, this type of T cell accumulated in other locations beyond the gut. However, these T cells did not arise from those in the gut, and how they are generated is unknown. The authors' studies of mice indicated that these T cells can fight infection by a disease-causing bacterium and enhance the effectiveness of a type of anticancer immunotherapy treatment.

Further work will be needed to determine how the presence of these gut bacteria can influence immune cells at distant sites.

Although faecal transplantation is effective as a treatment for a variety of human illnesses[17], for microbiota-based therapies to be more widely adopted in the clinic, the use of defined bacterial strains will probably be preferred. Generating therapeutics that contain defined strains might increase the robustness of responses and reduce the risks associated with the transplantation of faecal samples of unknown bacterial composition.

Previous studies aimed at evaluating the effects of perturbing the microbiota to augment checkpoint-blockade responses have mainly focused on trying to identify differences between the microbiota of responders and non-responders. By contrast, Tanoue and colleagues demonstrated a way to define a subset of bacterial strains that can specifically boost tumour-reactive $CD8^+$ T cells. These strains were not present in most healthy individuals whom the authors tested, and were of low abundance in the faecal sample in which they were identified. This potentially explains why previous studies have not identified these bacteria as having a role in boosting immune responses.

When checkpoint blockade is used to invigorate an immune response, it frequently causes an adverse state of inflammation and an autoimmune reaction, particularly in gut tissues[18,19]. The 11 bacterial strains had a minimal effect on reducing cancer growth in the absence of accompanying checkpoint-blockade treatment, and it remains to be determined whether the induction of $CD8^+$ IFN-γ^+ T cells might exacerbate such adverse immune reactions in people receiving checkpoint-blockade therapy. Furthermore, mouse recipients of the strains had to be pretreated with antibiotics before administration to enable the bacteria to colonize the host. This method might place individuals at risk of infection by disease-causing organisms such as *Clostridium difficile*, which typically thrive only in the absence of the normal gut bacteria.

Yet, despite this possible risk, there is reason to be cautiously hopeful. The authors found little or no evidence of colonic inflammation in mice or monkeys treated with the 11 bacterial strains. Perhaps this defined set of normal bacterial residents specifically activates only infection- and tumour-reactive T cells without triggering self-reactivity. More studies will be needed to evaluate the effects of these bacteria on inflammation and autoimmune reactions, but these promising data suggest that we are making progress in efforts to harness the microbiota to fight infection and cancer. ■

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ATMOSPHERIC CHEMISTRY

Aerosol formation assumptions reassessed

Experiments show that the amount of atmospheric particles produced from plant emissions could be lower than was thought — challenging our understanding of the processes that affect air quality and climate. SEE ARTICLE P.587

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Plants take up carbon dioxide and release volatile organic compounds (VOCs), in a similar way to how other organisms breathe in oxygen and exhale CO_2. These VOCs are oxidized in the atmosphere and then contribute substantially to the burden of tiny particles suspended in the air, which are known as aerosols. Aerosols produced from VOCs are known as secondary organic aerosols (SOAs), and affect both air quality and Earth's climate. The total rate of SOA production was thought to be the sum of the individual rates associated with the oxidation of each VOC. But on page 587, McFiggans *et al.*[1] show that a more accurate description is needed to improve the representation of SOAs in computational models of air quality and climate.

The atmosphere contains a complex mixture of VOCs, originating from biological sources and from human activities. Natural VOC emissions are globally dominated by the compound isoprene, produced by trees and shrubs[2]. However, the ability of isoprene to form SOAs is limited. Monoterpene compounds — the main components of the perfumes produced by flowers, leaves and

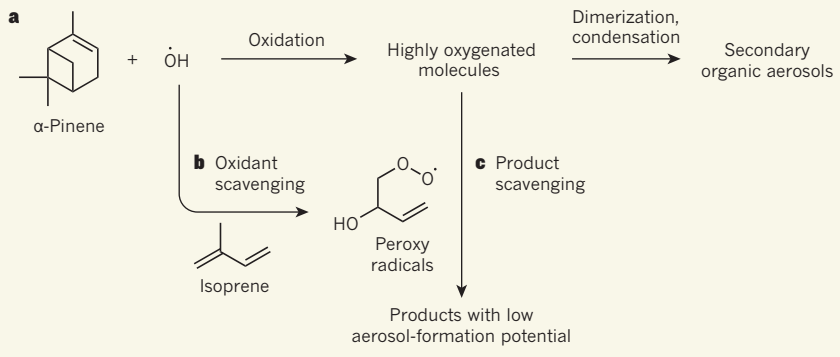

Figure 1 | Processes that affect aerosol formation from plant emissions. **a**, Many plants emit compounds known as monoterpenes (such as α-pinene) to the atmosphere, where they are oxidized by hydroxyl radicals (ȮH) to form highly oxygenated molecules (HOMs). These molecules can form dimers and contribute to the condensation of tiny particles known as secondary organic aerosols (SOAs), which affect cloud formation and air quality. **b**, Another plant emission, isoprene, can react with — and thereby scavenge — hydroxyl radicals to form peroxy radicals, suppressing SOA formation from monoterpenes[5,6]. **c**, McFiggans and colleagues' laboratory experiments[1] show that peroxy radicals formed from isoprene oxidation react with, and thus scavenge, oxidation products such as HOMs that have high SOA-formation potential, further lowering SOA production. They also find that methane and carbon monoxide suppress SOA formation through product scavenging (not shown).