forefront of tumour-antigen discovery and cancer-immunotherapy development[7–9]. It is thus fitting that Kalaora *et al.* use melanoma samples to describe another potential class of tumour antigen.

The authors set out to investigate the bacterial composition of 17 melanoma metastases (tumours formed when a cancer spreads from its original site to other regions of the body) from 9 people. They found that the composition of bacteria was highly similar in different metastases from the same individual, and sometimes in samples from different people. This finding indicates that particular bacterial species are common to melanoma, in line with a previous study reporting tumour microbiota specific to different types of cancer[1]. The authors also confirmed that these bacteria were present in melanoma cells, rather than in the surrounding extracellular microenvironment.

Kalaora and colleagues went on to investigate whether peptides from these intracellular bacteria are presented to the immune system in the same way as are other intracellular antigens. To this end, they used an approach based on mass spectrometry called immunopeptidomics, which allows direct detection of HLA-presented peptides. They found close to 300 peptides in their samples, from 33 bacterial species. Several peptides were found in more than one tumour from the same person and in tumours from different people.

The authors next asked whether the bacterial peptides are truly presented by melanoma cells, rather than by immune cells called antigen-presenting cells (APCs) that detect, take up and present pathogens to other cells of the immune system. The authors used an immune-cell marker protein to separate cells from two melanoma samples into APCs and tumour cells. Immunopeptidomics revealed that both groups of cell presented bacterial peptides. A subset of the peptides was presented by both APCs and tumour cells, indicating that the same peptide can both initiate an immune response through presentation on APCs and be a target for immune attack on tumour cells. The researchers then showed that T cells (which recognize HLA-presented peptides) isolated from the melanomas reacted to the identified bacterial peptides, including some of the peptides shared between tumours and individuals.

Taken together, Kalaora and colleagues' results point to the possibility that tumour-displayed bacterial peptides are a previously unidentified class of tumour antigen (Fig. 1). However, several questions remain. To be bona fide tumour antigens, the identified bacterial species should not invade non-tumour tissue and their peptides should not be presented on HLAs on non-tumour cells. If this presentation were detected, the peptides would not qualify as immunotherapy targets. In addition, the bacterial peptides seem to be quite abundant (at least, compared with the numbers of identified melanoma neoepitopes[7]), so why does the body not mount an effective immune response against melanomas? Further studies of tumour-displayed bacterial peptides in combination with patient information will be needed to elucidate the potential clinical role of the peptides. Such data might help researchers to select suitable bacterial targets for cancer-immunotherapy approaches.

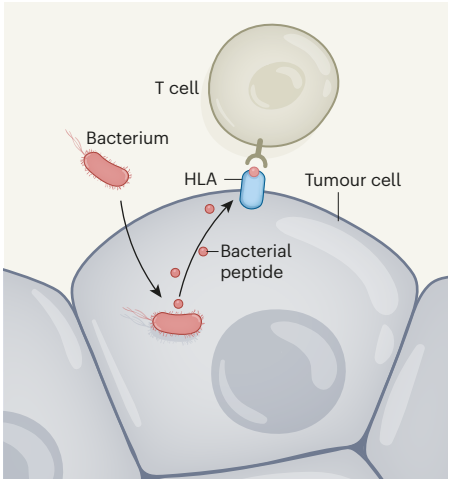

Figure 1 | A route to antitumour immunity triggered by bacteria. Kalaora *et al.*[4] report that certain bacteria can invade cells from a type of tumour called melanoma. Peptide fragments from bacterium-derived molecules are presented on the tumour cell surface by proteins called human leukocyte antigens (HLAs). Immune cells called T cells recognize and are activated against these presented peptides. Thus, bacterial peptides might be a previously unidentified class of tumour antigen – a type of molecule that enables T cells to distinguish tumour cells from normal tissue.

In conclusion, the bacterial peptides identified by Kalaora *et al.* could be attractive targets for immunotherapy. As bacterial peptides are 'non-self', it should be comparatively easy to elicit strong immune responses against them, and there would be no concerns about autoimmunity if it could be ascertained that they are not presented on any normal tissue. Thus, tumour-displayed bacterial peptides could serve as tumour-specific antigens shared between people – a rare and useful combination for therapeutics, so far seen only in virally induced tumours, in which epitopes can be derived from viral cancer-causing proteins[5]. Recent data indicate that tumour-invading bacteria might be a common phenomenon[1,2]. Kalaora and colleagues' work could therefore lay the foundation for identifying shared tumour-specific antigens in a wide range of tumour types.

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1. Nejman, D. *et al. Science* **368**, 973–980 (2020).
2. Xavier, J. B. *et al. Trends Cancer* **6**, 192–204 (2020).
3. Geller, L. T. *et al. Science* **357**, 1156–1160 (2017).
4. Kalaora, S. *et al. Nature* **592**, 138–143 (2021).
5. Coulie, P. G., Van den Eynde, B. J., van der Bruggen, P. & Boon, T. *Nature Rev. Cancer* **14**, 135–146 (2014).
6. Schumacher, T. N. & Schreiber, R. D. *Science* **348**, 69–74 (2015).
7. van der Bruggen, P. *et al. Science* **254**, 1643–1647 (1991).
8. Bassani-Sternberg, M. *et al. Nature Commun.* **7**, 13404 (2016).
9. Waldman, A. D., Fritz, J. M. & Lenardo, M. J. *Nature Rev. Immunol.* **20**, 651–668 (2020).

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Microbiology

Gut microbes regroup to aid defence after infection

Melissa M. Kendall & Vanessa Sperandio

Resident gut microbes can help to block infection, but the mechanisms involved are not fully understood. It has now been found that changes in the microbial community after infection boost the level of a molecule that combats harmful bacteria.

Complex interactions between a mammalian host and its intestinal microbiota (the community of microorganisms that reside in the small and large intestines) influence host health and disease susceptibility. A major challenge in delving into the mechanistic relationships driving such interactions is the high diversity of species in the microbiota, which gives rise to a microbial profile that is unique to each individual[1], much as a fingerprint is. There is a growing appreciation that the gut microbiota is implicated in generating resistance to gut colonization by disease-causing microorganisms (pathogens). However, many

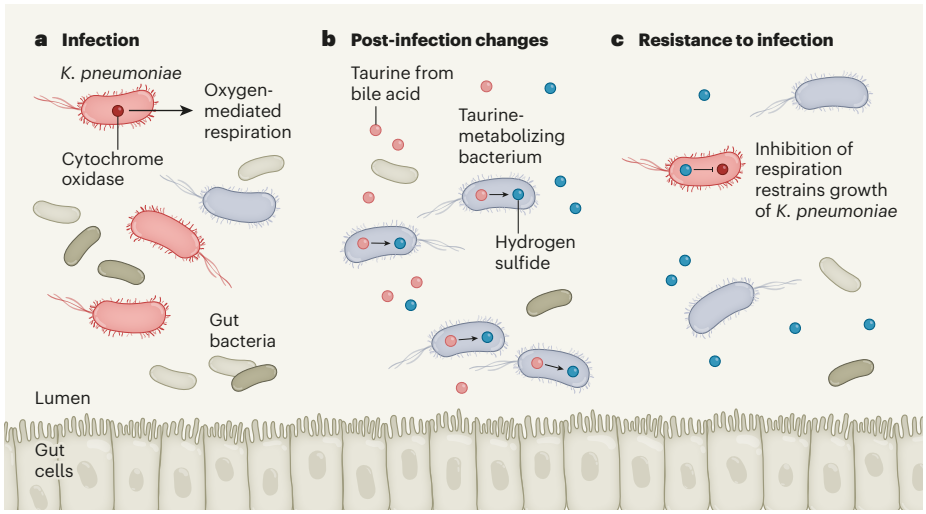

Figure 1 | How gut infection leads to changes that boost defence. Stacy *et al.*[3] report how infection by harmful bacteria such as *Klebsiella pneumoniae* in mice affects the resident gut bacteria. **a**, *Klebsiella pneumonia* can grow and establish an infection in the lumen of the mammalian gut, thanks to the enzyme cytochrome oxidase. This enzyme enables the bacterium to generate energy by aerobic respiration using oxygen in the host's gut. **b**, After infection by *K. pneumoniae*, the level of the molecule taurine rises in the gut. Taurine is produced from the metabolism of bile acids, which are secreted into the gut from the liver. Stacy and colleagues present genetic evidence indicating that, after infection, resident bacteria that can use taurine become more common in the gut. When bacteria metabolize taurine, they produce hydrogen sulfide gas. **c**, Hydrogen sulfide inhibits aerobic respiration, and can thereby block the growth of harmful bacteria.

studies of this phenomenon have been largely descriptive, and have tended to correlate only particular microbiota compositions with a state of health or disease[2]. Writing in *Cell*, Stacy *et al.*[3] present a detailed mechanism that reveals how changes to the microbiota drive resistance to invasion by pathogens.

It is generally accepted that the microbiota can hinder colonization by intestinal pathogens[4], and several lines of evidence support the idea that the gut microbiota can have a role in limiting pathogen growth. For example, prolonged and/or high levels of antibiotic use in people promotes expansion of *Clostridium difficile*[5], a bacterium that causes severe diarrhoea and inflammation of the colon, leading to a high risk of disease and death. Low complexity in the diversity of species present in the microbiota, a characteristic commonly observed for inhabitants of industrialized nations, is associated with enhanced susceptibility to infectious diseases[6]. Moreover, mice that have either been treated with antibiotics or raised in germ-free conditions, and thus lack a microbiota, are more susceptible to intestinal pathogens than are mice with a normal microbiota[7].

Conversely, certain microbiotas might lead to the promotion of pathogen growth or infection at a higher level of virulence. For example, different mouse microbiotas determine susceptibility to the pathogen *Citrobacter rodentium,* which causes a type of abnormal growth in the colon called hyperplasia[8]. Microbiota transplantation from susceptible to non-susceptible mice induces susceptibility to *C. rodentium* infection, whereas microbiota transplantation from non-susceptible to susceptible animals generates resistance to infection[8]. Epidemiological evidence indicates that susceptibility to infections by the food-borne pathogen *Campylobacter jejuni* in people in Sweden depended on the species composition of their microbiota[9]. And reports have highlighted how certain gut pathogens, such as *Salmonella enterica* and *C. rodentium*, exploit host–microbiota cues to precisely modulate their metabolism and, through the process of respiration, their energy generation. By sensing and responding to these cues, pathogens can also increase or decrease expression of components of their virulence repertoire, which are used to colonize the host[10–12].

Exciting research is starting to investigate the role of the microbiota in infection. Such work is going beyond just documenting correlations between infection and the presence or absence of species, or differences in species composition. It is beginning to unravel the mechanisms by which particular compositions of microbiota offer resistance to infection or aid invading pathogens.

Stacy and colleagues report that, after infection with the gut pathogen *Klebsiella pneumoniae*, mice have an enhanced ability to resist subsequent infection by this bacterium (Fig. 1). To try to understand the pathway responsible, the authors analysed microbial DNA, assessing the metagenomes (all of the microbial genes detected in the community) from post-infection microbiotas and naive microbiotas (those not previously exposed to the bacterium), to determine how microbes might contribute to colonization resistance. The team found that genes encoding proteins needed for the metabolism of sulfur-containing molecules, including taurine, were much more enriched in the post-infection microbiotas than in the naive microbiotas.

Bile acids are made in the liver and stored in the gall bladder, and they are the main source of taurine in the gut. They are secreted into the intestine to aid the digestion of fatty foods and oils. Specific members of the microbiota break down bile acids, releasing taurine, which can serve as an energy source for other gut bacteria. The use of taurine in bacterial metabolic pathways generates the compound hydrogen sulfide as a by-product. At high concentrations, hydrogen sulfide can inhibit the activity of cytochrome oxidase enzymes, which catalyse reactions that occur during oxygen-dependent (aerobic) respiration.

Invading intestinal pathogens often exploit host-generated oxygen to obtain energy by aerobic respiration and thus gain a foothold in their efforts to colonize the host[13]. Stacy and colleagues report a correlation between taurine-mediated production of sulfide molecules, including hydrogen sulfide, by the microbiota after infection and the concomitant inhibition of pathogen respiration, which would ultimately inhibit infection by the pathogen. The authors demonstrated this effect for two pathogens, *K. pneumoniae* and *C. rodentium*, which suggests that the post-infection microbiota provides broad protection against invaders. Notably, Stacy *et al.* report that taurine supplementation in the animals' drinking water led to similar effects. Taurine is a common component of energy drinks, and this discovery of its role in the gut is intriguing. A deeper understanding of such mechanisms could open the door to precision manipulation of the microbiota to combat certain infectious diseases.

These results suggest that dietary supplementation of certain metabolites, such as taurine, might offer a way to reprogram the microbiota's 'metametabolism' to enhance resistance to pathogens. This and other studies defining the mechanisms by which the microbiota affects the metabolism, respiration and virulence of intestinal pathogens represent a key step forwards in the field of host–microbiota–pathogen interactions.

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1. Franzosa, E. A. *et al. Proc. Natl Acad. Sci. USA* **112**, E2930–E2938 (2015).
2. Bäumler, A. J. & Sperandio, V. *Nature* **535**, 85–93 (2016).
3. Stacy, A. *et al. Cell* **184**, 615–627 (2021).
4. Sassone-Corsi, M. & Raffatellu, M. *J. Immunol.* **194**, 4081–4087 (2015).
5. Theroit, C. M. & Young, V. B. *Annu. Rev. Microbiol.* **69**, 445–461 (2015)
6. Ducarmon, Q. R. *et al. Microbiol. Mol. Biol. Rev.* **83**, e00007-19 (2019).
7. Sorbara, M. T. & Pamer, E. G. *Mucosal Immunol.* **12**, 1–9 (2019).
8. Willing, B. P., Vacharaksa, A., Croxen, M., Thanachayanont, T. & Finlay, B. B. *PloS ONE* **6**, e26988 (2011).
9. Kampmann, C., Dicksved, J., Engstrand, L. & Rautelin, H. *Clin. Microbiol. Infect.* **22**, 61.e1–61.e8 (2016).
10. Winter, S. E. *et al. Nature* **467**, 426–429 (2010).
11. Ellermann, M. *et al. Cell* **183**, 650–665 (2020).
12. Anderson, C. J., Clark, D. E., Adli, M. & Kendall, M. M. *PLoS Pathog.* **11**, e1005278 (2015).
13. Lopez, C. A. *et al. Science* **353**, 1249–1253 (2016).

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Materials science

Atomic structure of a glass imaged at last

Paul Voyles

The positions of all the atoms in a sample of a metallic glass have been measured experimentally — fulfilling a decades-old dream for glass scientists, and raising the prospect of fresh insight into the structures of disordered solids. **See p.60**

If the chemical element and 3D location of every atom in a material are known, then the material's physical properties can, in principle at least, be predicted using the laws of physics. The atomic positions of crystals have long-range periodicity, which has enabled the development of powerful methods that combine diffraction experiments with the mathematics of symmetry to determine the precise atomic structure of these materials. Moreover, deviations from periodicity that create defects in crystals can be imaged with sub-ångström resolution. But these methods do not work for glasses, which lack long-range periodicity. Our knowledge of the atomic structure of glasses is therefore limited and acquired indirectly. On page 60, Yang *et al.*[1] report the experimental determination of the 3D positions of all the atoms in a nanometre-scale sample of a metallic glass.

The authors accomplished this feat using atomic-resolution electron tomography. In this method, 2D projections of the 3D atomic structure of a sample are acquired by passing a beam of electrons through the sample: a series of 2D images is produced by altering the orientation of the sample to the beam, and these images are then reconstructed into a 3D image of the whole sample. This technique has been used to determine the atomic structure of crystals for a decade[2,3]. However, most of the information required to construct the full 3D atomic structure of a crystal is contained in just a few of the 2D images, which are acquired when the sample is oriented in ways that cause the atoms to line up in rows, one behind the other, with empty space between them[4]. Unfortunately, such orientations do not exist for glasses.

Special orientations are also lacking for non-crystalline biomolecules. Electron microscopists have overcome this problem by studying millions of nearly identical copies of the same biomolecule, thereby achieving single-atom resolution in tomographic reconstructions[5]. By contrast, every cubic nanometre of a glass has a unique structure, which means that Yang *et al.* had to adopt a different strategy. They used a combination of state-of-the-art computational imaging techniques — including sophisticated methods to correct distortions and to reduce noise that obscures the image signal — to produce a series of high-quality 2D images that capture subtle variations in contrast when the glass is viewed in different orientations. They then used an original approach to reconstruct the final, atomically resolved 3D image (Fig. 1). Although the authors cannot specifically identify the element for each atom, they do assign each atom to one of three categories, each of which includes either two or four of the eight elements in the glass.

Theoretical descriptions of glass structure rely on long-standing principles that define motifs of atoms. For glasses in which the atoms are covalently bonded, such as commonplace window glass, the principle is preservation of bond lengths and angles, and the motif is a continuous random network of bonds[6] (Fig. 1a). The random-network motif has been elaborated to accommodate, for example, atoms that have varying numbers of bonds[7].

For glasses in which the atoms exhibit metallic bonding, the principle is to achieve dense,

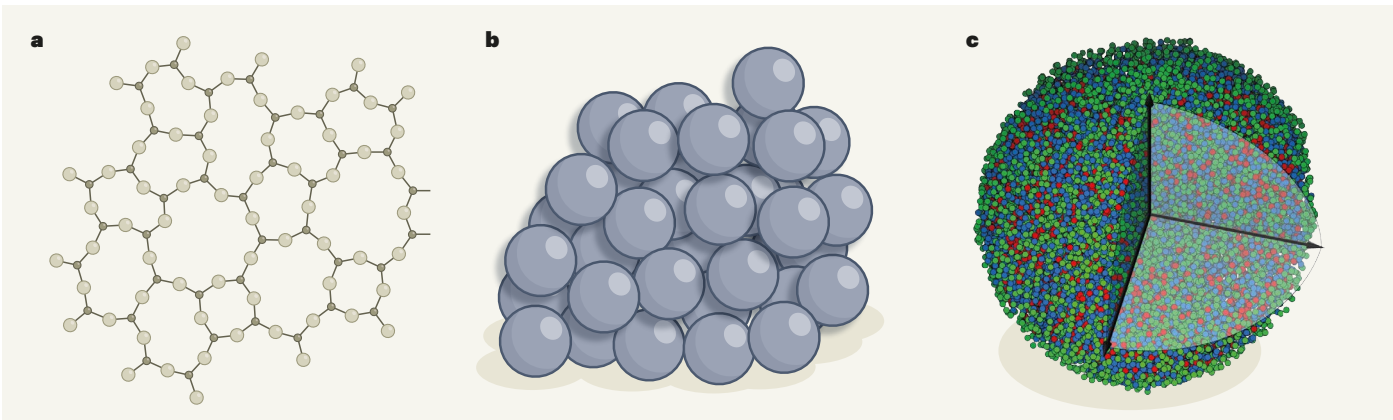

Figure 1 | The atomic structure of glasses. Knowledge of glass structure has been based on long-standing models developed from simple physical principles. **a**, For glasses in which the atoms are covalently bonded, a continuous random network of atoms has been proposed to form[6], in which bond lengths and angles between atoms are preserved. **b**, For metallic glasses, the structure was thought to involve the dense random packing of spherical atoms[8]. **c**, Yang *et al.*[1] have used a method called atomic-resolution electron tomography to determine the position of every atom in a nanometre-scale sample of a metallic glass. Although the authors could not specifically identify the element for each atom, they did assign each atom to one of three types, each including either two or four of the eight elements in the glass. The availability of fully resolved atomic data for glasses represents a step change in understanding compared with **a** and **b**.