over the past decade or so, researchers have learnt that this picture needs to be amended in fundamental ways. This realization has led to the discovery of materials known as topological insulators, which are insulating in their interior but robustly conducting on their boundaries[4]. Correspondingly, these materials have an energy gap in their interior, but are gapless on their boundaries. This behaviour reflects beautiful, albeit somewhat abstract, topological properties of the materials' electronic states.

Rizzo *et al.* and Gröning *et al.* have experimentally demonstrated that graphene nanoribbons can be used to produce such topological states. Defect-free graphene nanoribbons can be grown on metallic substrates in a remarkably flexible manner[5]. Starting with cleverly designed precursor molecules, the nanoribbons' terminations and widths can be controlled with single-atom precision. The authors used this synthesis technique to grow nanoribbons that alternate in width (Fig. 1a).

The widths were chosen such that the nanoribbons consist of alternating topologically trivial and non-trivial segments. Whenever two materials of different topology are brought into contact, gapless states must form at the interface. Consequently, such states are produced at the junctions between the nanoribbon segments. Because nanoribbons are essentially one-dimensional, each of these gapless junction states is simply an individual electron orbital localized in the vicinity of the intersection.

But the topology of the nanoribbons does not stop here. Rizzo *et al.* and Gröning *et al.* used the junction states as building blocks to engineer yet another system. This system is closely related to an archetypal model of electronic topology known as the Su–Schrieffer–Heeger (SSH) model, which emerged in the late 1970s from the study of organic conductors such as polyacetylene[6].

Although the SSH model is simple, it has remarkable properties. In particular, a finite chain of electronic orbitals described by the SSH model can have gapless topological states localized at its ends. The crucial ingredient in the model is an alternation of weak and strong bonds between neighbouring electron orbitals.

In the authors' nanoribbons, adjacent gapless junction states straddle narrow or wide regions of the material. The coupling of these states is stronger across the wide regions than across the narrow regions, producing exactly the bond alternation that underlies the SSH model. Such a coupling is therefore expected to generate topological states at the ends of the nanoribbons, assuming that these materials are suitably designed[1].

Rizzo *et al.* and Gröning *et al.* confirmed this theoretical prediction to an impressive degree. The authors used a combination of scanning tunnelling microscopy and spectroscopy to probe and visualize the electronic properties of the nanoribbons with atomic-scale spatial resolution (Fig. 1b). They observed the junction states — which formed broadened energy bands as a result of their coupling — and the end states associated with the bond alternation. Of note is the fact that the authors grew and probed their nanoribbons on a highly conducting gold substrate, which effectively weakens the electric forces between the electrons in the nanoribbons. Without such a conducting substrate, these forces could be substantial, and might produce additional interesting physics[1].

Beyond fabricating these specific nanoribbons and exploring their electronic topologies, the two studies reveal several key insights. For instance, the production of topological electronic materials is often hampered by sample imperfections. Frequently, defects induce a large internal conductivity, even if the material is nominally a topological insulator. This problem is particularly severe in 1D systems, in which the electrons cannot circumvent defects. Such systems are often fabricated using a top-down approach, in which the materials are patterned from larger structures. A promising avenue for alleviating the issue of sample imperfections is to produce the systems by means of a bottom-up method, such as that used by the authors, in which the materials are made by chemical processes.

These studies also highlight the potential of using topological boundary states for materials engineering. This idea can be extended to higher dimensions than the authors' 1D system, for instance to periodic 'superlattices' made of alternating topologically trivial and non-trivial layers. Finally, the authors suggest that, when in contact with a superconductor, the nanoribbons could act as a topological superconductor — another fascinating class of topological electronic state that might have applications in quantum computing. ■

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IMMUNOLOGY

Making mitochondrial DNA is inflammatory

Activation of the inflammasome protein complex in immune cells is a key step that triggers an innate immune response. It emerges that the synthesis and oxidation of mitochondrial DNA drives this activation step. SEE ARTICLE P.198

MICHAEL P. MURPHY

The innate immune response mounts a defence when immune cells recognize general hallmarks of infection, such as lipopolysaccharide (LPS) molecules, which are present in many types of bacterium. However, the inappropriate unleashing of an innate immune response can lead to autoimmune disorders. Gaining a better understanding of how innate immune responses are regulated might lead to improvements in clinical treatments for such disorders. On page 198, Zhong *et al.*[1] report that DNA synthesis in organelles called mitochondria has a key role in triggering an innate immune response

Mitochondria can regulate how immune cells respond to infection and tissue damage. For example, these organelles can produce pro- or anti-inflammatory signals by altering the levels of metabolites produced in the Krebs cycle[2,3], or by changing the level of production of reactive oxygen species (ROS)[4,5]. More and more examples are being found of mitochondrial functions being repurposed in unexpected ways to contribute to inflammatory signalling[2–5].

The inflammasome is a multiprotein complex that assembles in immune cells during an innate immune response. It provides defensive functions when the inflammasome-associated enzyme caspase-1 cleaves and activates inflammatory proteins such as IL-1β. Inflammasomes that contain the protein NLRP3 can form in immune cells called macrophages, and the initial steps in the assembly or priming of this type of inflammasome are reasonably well understood: if LPS binds to the receptor protein TLR4 on the macrophage surface, there is an increase in signalling by the NF-κB pathway. This causes an increase in expression of NLRP3 and of the precursor form of IL-1β.

However, the process that triggers inflammasome activation, which occurs when the enzyme caspase-1 is recruited to

the inflammasome and aids the production of inflammatory proteins, is not fully understood. It was puzzling that many highly diverse molecular cues can trigger this step. Yet hints from experimental studies have suggested that these cues might ultimately act through a mitochondrial pathway associated with high levels of mitochondrial ROS[3,6,7] — which are required to oxidize mitochondrial DNA — and the release of oxidized mitochondrial DNA, which binds to the inflammasome[8].

The binding of mitochondrial DNA to an NLRP3-containing inflammasome is essential for inflammasome activation[9,10]. Zhong and colleagues studied mice to assess whether the availability of this mitochondrial DNA might regulate inflammation. The authors engineered animals so that their immune cells lack the protein TFAM, which is required for mitochondrial DNA replication. This led to a loss of mitochondrial DNA, resulting in defective inflammasome activation. When the authors transferred synthetic oxidized mitochondrial DNA into macrophage cells grown *in vitro* from the animals lacking TFAM, this triggered inflammasome activation in response to an LPS signal.

The authors investigated how mitochondrial sensing of innate-immunity triggers might lead to mitochondrial-DNA synthesis. They report that LPS binding to TLR4 activates a pathway that drives expression of the enzyme CMPK2, which is required to produce the nucleotide cytidine triphosphate (CTP) (Fig. 1). Zhong and colleagues engineered mouse macrophage cells to lack CMPK2, and found that such cells were deficient in inflammasome activation. It is unknown how CMPK2 and the mitochondrial CTP pool operate as a control point for mitochondrial-DNA synthesis in macrophages.

To track newly made mitochondrial DNA, the authors introduced a labelled building block of DNA into macrophage cells grown *in vitro*. When these cells received an inflammasome-activating cue, such as LPS, newly made DNA was found to be associated with the inflammasome, and DNA-sequence analysis confirmed its mitochondrial origin. Intriguingly, the authors did not find evidence that the oxidized DNA had to be mitochondrial DNA to bind to the inflammasome. The introduction of oxidized nuclear DNA could do the job just as well, suggesting that oxidized DNA is the key signal.

Zhong and colleagues' work fills in the gap between the priming and activation of the inflammasome by indicating that newly synthesized mitochondrial DNA can give rise to oxidized mitochondrial DNA fragments that exit the organelle to activate NLRP3-containing inflammasomes. Their core conclusions are convincing; however, the solidity of these findings inevitably focuses our attention on those points that are still uncertain. One intriguing issue is the nature of the newly synthesized mitochondrial DNA. The authors' findings suggest that this is produced by the polymerase enzyme that normally replicates mitochondrial DNA, but it is unclear whether the entire mitochondrial DNA sequence is replicated or whether replication terminates prematurely once sufficient DNA is made to generate an inflammatory signal. And is newly formed mitochondrial DNA particularly susceptible to oxidative damage? Could it be that the newly synthesized DNA lacks protection from the nucleoid proteins that normally bind to mitochondrial DNA, thereby increasing its exposure to ROS?

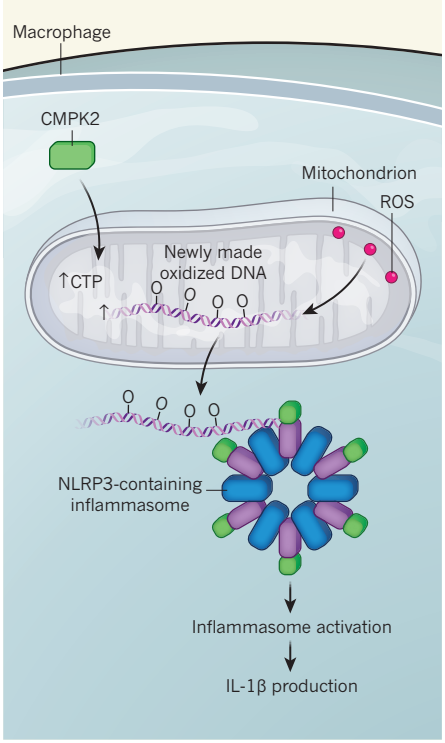

Figure 1 | Newly synthesized oxidized mitochondrial DNA triggers inflammasome activation. The inflammasome is a multiprotein complex that has a key role in generating a defence response and is found in immune cells such as macrophages. How inflammasomes that contain the protein NLRP3 are activated was not fully understood. Zhong *et al.*[1] studied inflammasome activation in mice and report that, when macrophages sense a foreign molecular cue, levels of the enzyme CMPK2 increase. CMPK2 localizes to an organelle called a mitochondrion and drives an increase in the levels of the nucleotide cytidine triphosphate (CTP). This event is linked to synthesis of mitochondrial DNA, and this freshly generated DNA is thought to be oxidized (O denotes oxidized DNA) by reactive oxygen species (ROS). The authors find that oxidized DNA exits the mitochondrion, binds to the NLRP3-containing inflammasome and activates it. This leads to the production of inflammatory proteins such as IL-1β.

The authors incorporated the oxidized nucleotide 8-hydroxy-2′-deoxyguanosine into cells grown *in vitro* as a way to generate oxidized mitochondrial DNA. This type of nucleotide is frequently found in oxidized DNA, but there are many other types of oxidative DNA modification, and it would be interesting to explore which of these can activate inflammasomes.

How do the ROS needed for DNA oxidation arise? The tacit assumption is that non-specific organelle damage generates ROS. Yet this is debatable[11]. I suspect that the mitochondrial ROS production during NLRP3-inflammasome activation might be just as regulated as the process of mitochondrial DNA synthesis. Perhaps the succinate molecules that accumulate after LPS stimulation are oxidized to drive mitochondrial ROS production[4].

Another area worthy of future investigation is how oxidized mitochondrial DNA is released into the cytoplasm. The authors make the plausible proposal that a large mitochondrial pore might provide an exit route. One candidate is the mitochondrial permeability transition pore, which forms in response to increased levels of ROS[12]. However, there are also other possibilities to consider: for example, mitochondria can release microvesicles containing oxidized DNA and protein[13].

The authors' insights into the activation of NLRP3-containing inflammasomes immediately suggest targets for the development of anti-inflammatory drugs. One area to explore is inhibition of CMPK2 during inflammation, and other parts of the pathway that the authors uncovered are worth considering as targets, too.

This finding of yet another fascinating link between mitochondria and inflammatory signalling in the innate immune system might reflect the organelle's early evolutionary origins as a bacterial cell. This inherent otherness could give mitochondria a head start in being recognized as foreign by the innate immune system.

On page 238, Dhir *et al.*[14] report that the release of double-stranded RNA from mitochondria acts as an antiviral signal. This provides an additional example that the release of mitochondrial nucleic acids to the cytoplasm can act as a signal that triggers a defence response. ■

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