They also saw that the influence of a neuron on the surrounding network changed with distance: it exerted an excitatory influence on a small population of neurons at short distance (25–70 micrometres); an inhibitory influence at medium distance (70–300 μm, with maximum suppression at about 110 μm), affecting most of the neighbouring neurons; and had little influence at long distance (greater than 300 μm).

The authors' subsequent in-depth analysis revealed a much more complex pattern than a general inhibition of neural activity. They found that the extent of the influence of neurons on other neurons was related to how they responded to certain features of visual stimuli, such as orientation and temporal frequency. When a neuron was activated, neurons that were tuned to respond to similar features to that neuron were more strongly suppressed than were neurons with a different tuning. This inverse relationship remained true regardless of the distance between neurons. However, scattered within the ripples of influence, the authors also found a sparsely distributed group of neurons that were similarly tuned to the target neuron and strongly excited by it (Fig. 1). The response patterns of these neurons were also well correlated in time with that of the target neuron (that is, their moment-to-moment electrical activities closely resembled each other).

The authors' findings suggest that the complex network of the central nervous system works by balancing two parallel modes of computation. A predominant inhibitory influence between neurons that have similar tuning (which the authors call feature competition) is peppered with sparsely distributed pockets of excitatory influence among well-correlated neurons (which they call feature amplification). The model beautifully illustrates how feature competition reduces redundancy and enables inputs that are meaningful signals to be separated from those that are muddling noise, whereas feature amplification further improves the ability of select neurons to effectively carry information about the stimulus.

The work by Chettih and Harvey raises several questions. What are the cellular underpinnings of the widespread neuronal suppression that promotes feature competition? Inhibitory interneurons act locally to suppress other neurons' activity, and distinct types of interneuron have different responses to stimulation. For example, a burst of more than five action potentials in a neuron can induce a spiking response in approximately 30% of the neighbouring somatostatin-expressing (SOM^+) interneurons, whereas parvalbumin-expressing (PV^+) interneurons do not seem to respond to such stimulation[3] (although contrasting findings have been reported[4]). Chettih and Harvey added, on average, six action potentials to target neurons using optogenetics. This profile of stimulation might make the activation of SOM^+ interneurons more likely than that of PV^+ interneurons. Notably, the SOM^+ interneurons are more selectively tuned than PV^+ interneurons[10]. A preferential recruitment of the tuned inhibitory neurons could potentially bias the network response towards feature competition.

Finally, how is the encoding of stimuli by the brain affected by the animal's behavioural state? Does the cortical network use different coding schemes for different behavioural or environmental contexts, in a way that affects the pattern of the neuronal responses[9]? Would the 'ripples' in a neural network change dramatically under a greater impact, much like the behaviour of a non-Newtonian fluid, like ketchup? That remains to be seen. ■

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IMMUNOLOGY

Inflammation clues in STING protein structure

The STING protein aids intracellular defences by triggering inflammation. Studies that uncover how STING is activated might lead to strategies for targeting this protein in the treatment of cancer or autoimmune diseases. SEE LETTERS P.389 & P.394

ANDREA ABLASSER

The branch of the immune system called innate immunity has a pivotal role in host defence by recognizing general hallmarks of disease-causing agents. The intracellular protein STING, a transmembrane protein usually located on an organelle called the endoplasmic reticulum, is a key regulator of this type of immune response[1]. Writing in *Nature*, Shang *et al.*[2] (page 389) and Zhang *et al.*[3] (page 394) report full-length structures of STING, including STING in complex with the kinase protein TBK1, which initiates the downstream signalling pathway that is triggered on STING activation.

The abnormal presence of double-stranded DNA in the cytoplasm is a potent danger signal that activates STING. If the enzyme cGAS senses such DNA[4,5], it makes the molecule cGAMP; when this binds and activates STING, a signalling cascade begins that eventually alters gene expression to generate proinflammatory molecules. Abnormalities in this defence mechanism can underpin a spectrum of conditions, including cancer, autoinflammatory syndromes or neurodegenerative diseases[6–9]. STING is thus a highly promising drug target[10], but for such efforts to succeed, it is essential to understand how STING activity is regulated.

Previous studies[11–13] have illuminated how the cytoplasmic domains of STING interact with cGAMP and how the downstream signalling events that follow STING activation are triggered. For example, cGAMP binds to a V-shaped pocket that is formed by the cytoplasmic domains of two STING proteins that make a dimer[11] and, after undergoing a conformational change, STING is transported to an organelle called the Golgi complex, where it recruits TBK1 (ref. 12). Despite such progress, how cGAMP binding causes STING activation and facilitates the subsequent downstream signalling events was unknown.

Shang and colleagues used the technique of cryo-electron microscopy (cryo-EM) to generate near atomic-resolution structures of full-length human STING without cGAMP bound to it, and full-length chicken STING with and without cGAMP bound. Without cGAMP bound, the STING dimer is stabilized by interactions between different domains in each STING protein and between domains of the two different STING proteins.

A transmembrane helix is linked to the cGAMP-binding domain through a connector element — made up of a connector helix and a connector loop — that forms a crossover point between the two STING proteins. In the cGAMP-bound state, the connector elements and the cGAMP-binding region of each subunit unwind, causing a 180° rotation

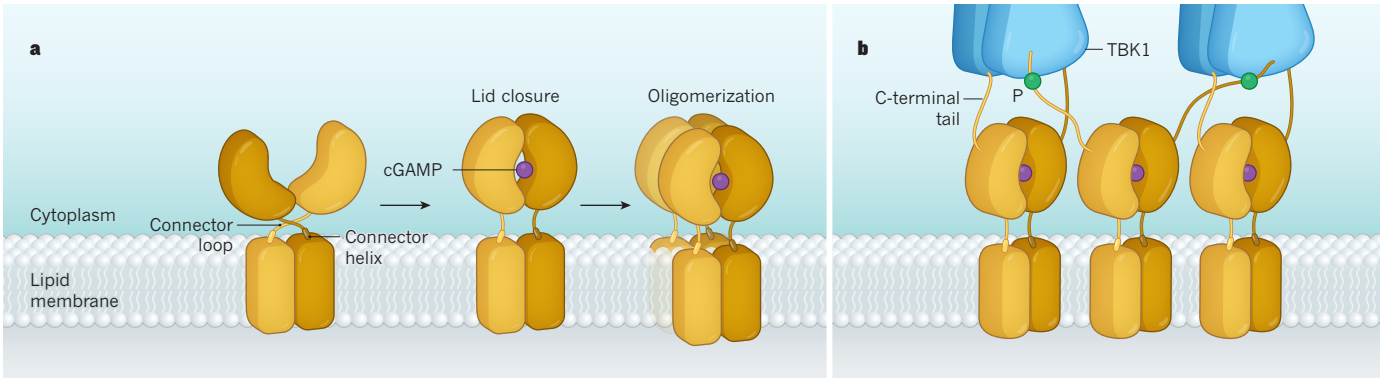

Figure 1 | Structures of the STING protein. **a**, Shang *et al.*[2] report cryo-electron microscopy (cryo-EM) structures of full-length human and chicken STING protein bound to the cGAMP molecule, which activates STING to trigger inflammation. STING is a transmembrane protein that forms dimers (the two STING proteins in each dimer are shown in different shades of yellow). When cGAMP binds, the cytoplasmic domains of the STING proteins undergo a 180° rotation and unwind around the crossover point between the proteins, at which there is a connector loop and a connector helix. This conformational change enables tight binding between adjacent STING dimers and, thereby, the formation of STING oligomers. **b**, Zhang *et al.*[3] present a cryo-EM structure of STING in complex with the kinase protein TBK1, which has a key role in the signalling cascade that follows STING activation. The authors find that a TBK1 dimer binds above the cGAMP-binding pocket of a STING dimer. Their model suggests that the carboxy-terminal (C-terminal) 'tail' region of a given STING protein is phosphorylated (P denotes a phosphate group) by the TBK1 dimer bound to the adjacent STING dimer. (Graphic based on Fig. 4 of ref. 2 and Extended Data Fig. 7 of ref. 3.)

(see Supplementary Video 1 of ref. 2) of the cGAMP-binding domain (Fig. 1). This movement is probably initiated by cGAMP, which might push apart the junction of the connector element and the cGAMP-binding domain. Some disease-causing mutations of STING are in this junctional region, suggesting that these mutations might cause this rotation to occur even in the absence of cGAMP.

The cryo-EM data for cGAMP-bound STING generated by Shang *et al.* offers some intriguing clues about how this unwinding and 180° rotation trigger STING activation. In an activated, cGAMP-bound state, STING dimers are tightly packed and arranged side by side in the lipid membrane. The dimers can make connections with adjacent dimers, and these connections are stabilized by a loop that connects the dimers at their interface. The authors' modelling suggests that, in the absence of cGAMP binding, this interface loop would be in an orientation that would block tight binding between adjacent STING dimers. The connector element probably stabilizes this inhibitory orientation of the interface loop when cGAMP isn't bound, suggesting that the rearrangement of the connector element on cGAMP binding could promote tetramerization and is associated with STING activation. The authors observed the formation of activated STING tetramers, and it is probable that oligomers of activated STING form that are larger than this.

Zhang *et al.* investigated the interaction of STING with TBK1. Their cryo-EM data reveal that a dimer of TBK1 proteins is located on top of the cGAMP-binding domain of the STING dimer. This interaction between STING and TBK1 is mediated by an evolutionarily conserved stretch of eight amino-acid residues in the carboxy-terminal 'tail' of STING — a part of the protein that was not visible in earlier STING structures. This C-terminal part of STING is tethered to the cGAMP-binding domain by a flexible linker region, allowing STING and TBK1 to adopt different orientations relative to each other and to interact independently of whether cGAMP has bound STING. This suggests that the role of cGAMP binding in promoting the interaction between STING and TBK1 is probably indirect; it might enforce an oligomeric state of STING or initiate STING movement to the Golgi complex.

The structure of STING in complex with TBK1 suggests that the autophosphorylation of TBK1 (the addition of a phosphate group to one TBK1 by another TBK1) that is necessary for TBK1 activation cannot be carried out by TBK1's dimer partner. Moreover, although activated TBK1 phosphorylates STING, the structural information indicates that the phosphorylation site on STING is probably located beyond the reach of the catalytic domains of a TBK1 dimer bound to a STING dimer. Together, these features suggest that a complex of one STING dimer and one TBK1 dimer would fail to phosphorylate the constituent proteins, and supports a model in which oligomerization of activated STING leads to the phosphorylation of neighbouring TBK1 dimers, which, in turn, phosphorylate neighbouring STING molecules. The authors speculate that the flexibility in the possible orientations for interaction between TBK1 and STING could aid this activation process.

Shang, Zhang and their respective colleagues have pushed the limits for high-resolution cryo-EM of transmembrane proteins. Solving the structure for this type and size of protein complex is a major challenge[14], but their success will probably motivate others to try to solve the cryo-EM structures of similarly sized (about 80-kilodalton) transmembrane protein complexes.

The structural models emerging from the authors' studies might aid investigations that seek to answer other questions about how STING functions. For example, the mechanism that regulates STING movement from the endoplasmic reticulum to the Golgi complex remains to be determined. STING also has functions that do not require TBK1 activity, including the initiation of a degradation process called autophagy, and how such processes are controlled is not fully understood. Moreover, the structures will certainly be useful for drug-discovery programmes by pinpointing protein regions that might offer a targeting opportunity to precisely manipulate STING activity. Such efforts might result in STING-targeting therapies for the treatment of human disease. ■

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