force-gating mechanism), along with several other domains (dubbed the latch, clasp and anchor) and the carboxy-terminal domain (CTD), which extends from the 'inner helix' formed by the pore-lining TM38. Saotome *et al.* and Zhao *et al.* performed mutagenesis experiments in which they replaced amino acids in these key regions with other amino acids to observe the effects on channel behaviour. These structure-based mutagenesis studies provide insight to the machineries involved in ion permeation through the channel and force gating.

The long central pore of mPiezo1 seems to connect to the aqueous surroundings of the channel through lateral portals that serve as ion-access pathways; additional windows possibly open to the membrane interior. These features are reminiscent of the structures of trimeric acid-sensing ion channels and P2X receptors[7]. Zhao *et al.* report that negatively charged amino-acid residues in the lateral portals influence the ion selectivity and other properties of the pore, supporting the notion that the portals form part of the ion-permeation pathway.

Also notable is Saotome and colleagues' finding that a phenylalanine residue at a pore constriction affects both permeation and the rate at which the channel is inactivated when subjected to a prolonged stimulus. As pointed out by Saotome *et al.* and Zhao *et al.*, inactivation is also modified by disease-causing mutations of multiple charged residues that are involved in the interactions of the anchor with the pore-lining inner helix and the CTD. Taken together with a recent biophysical study[8] that suggests the existence of intricate connections between the ion-permeation pathway and channel inactivation, the structures of mPiezo1 provide hints about the coupling between the pore and the machinery that opens the channel in response to force.

Additional structure-guided studies using mutagenesis and electrophysiology are now needed to further investigate the function of mPiezo1. Other approaches, such as molecular-dynamics simulations, should help to reveal the force-gating mechanisms. Zhao and colleagues' findings, along with those of others[8,9], suggest that multiple parts of mPiezo1 are involved in force gating, including its N-terminal region. A more complete structure that includes the currently unresolved 1,100 amino-acid residues at the N-terminal end of the protein is therefore needed. Moreover, the reported structures seem to show a closed channel. The structure of an open channel could provide valuable clues to the permeation and gating mechanisms.

Guo and MacKinnon observed that the unusual dome shape of the mPiezo1 trimer causes deformation of synthetic membrane vesicles. They suggest that the curvature of the arms induces deformation of the cell membrane that changes with membrane tension and on channel opening. It will be interesting to see whether mPiezo1-induced membrane deformation is detectable *in vivo*, and how it responds to mechanical stimuli.

Apart from mPiezo1, structural information is available for three other families of bona fide mechanically activated channels. The molecules and gating mechanisms all seem to be distinct. The bacterial MscL protein is a homopentamer, and responds to membrane tension by opening a wide pore[10]. The dimeric TRAAK and TREK channels have windows that might allow lipid fatty-acid chains to extend into the pore, and they respond to membrane tension by simultaneously opening the channel and expanding the area of the membrane that is occupied by the channel, although the tension range needed for channel activation differs from that of MscL[11]. The homotetrameric NompC channel found in the fruit fly *Drosophila* contains a bundle of four helices that looks like a coiled spring; this is thought to tether the channel to microtubule structures in the cytoskeleton for force gating[12]. It is to be hoped that some general principles that unite these seemingly disparate structures will emerge as we learn more about each system. ■

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PANCREATIC DISEASE

An inflammatory transcriptional switch

The mouse pancreas adopts a pre-inflammatory state in response to a chemical injury or the loss of one copy of the gene *Nr5a2*. This state might predispose mice, and possibly humans, to pancreatitis and pancreatic cancer. SEE LETTER P.533

L. CHARLES MURTAUGH & RAYMOND J. MACDONALD

Inflammation can initiate the repair of injured tissue, but, if it persists, can also be a fertile ground for disease and cancer[1]. For instance, chronic inflammation is central to pancreatitis, in which digestive enzymes produced by the pancreas's acinar cells are inappropriately activated, causing tissue digestion and cell death[2]. In mice, transient downregulation of acinar-cell-specific transcription factors and their targets aids recovery from pancreatitis, perhaps by reducing further enzyme production[3]. But irreversible downregulation of these factors is associated with tumours in mice[4–6], and people with pancreatitis have an increased risk of pancreatic cancer[2]. Until now, the causal link between pancreatic inflammation, gene-expression changes and cancer has not been understood. On page 533, Cobo *et al.*[7] describe how repurposing of the pancreatic transcription factor Nr5a2 controls the acinar-cell inflammatory response.

The same research group had previously discovered[8] that loss of one of the two copies (alleles) of the *Nr5a2* gene in mice impairs pancreatic regeneration after mild inflammation, and sensitizes acinar cells to a cancer-causing protein. It seemed likely, therefore, that decreased levels of Nr5a2 diminish the resilience of pancreatic cells.

In the current study, Cobo *et al.* explored this theory by analysing NR5A2-protein levels in samples from humans with a type of cancer called pancreatic ductal adenocarcinoma (PDAC). Consistent with their theory, the researchers found that NR5A2 levels in tumour cells tended to be low in people who had a history of pancreatitis. These patients were also more likely to carry a common single-nucleotide mutation linked to the *NR5A2* gene, associated with increased risk of PDAC, than were people whose tumour cells had high levels of NR5A2. These observations support the idea that low NR5A2 levels increase PDAC risk by raising the

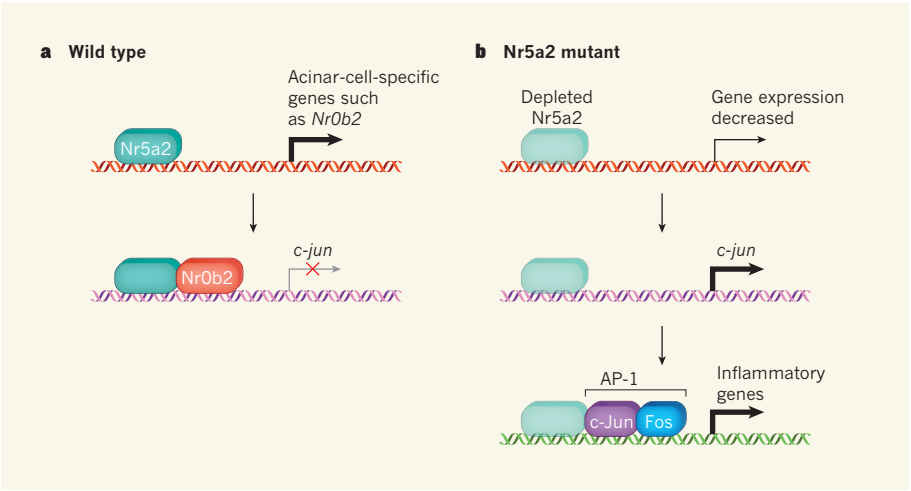

Figure 1 | A transcriptional shift in the pancreas. Cobo *et al.*[7] describe how loss of one of the two copies of the gene *Nr5a2*, which encodes a transcription factor, affects gene expression in the mouse pancreas. **a**, In wild-type animals, the Nr5a2 protein binds to promoter DNA that drives the expression of genes specific to pancreatic acinar cells. These targets include *Nr0b2*, which encodes a transcriptional repressor. Both Nr5a2 and Nr0b2 bind to the promoter of the gene *c-jun*, repressing its expression. **b**, When one copy of *Nr5a2* is deleted, there is less Nr5a2, and so its target genes, including *Nr0b2*, are expressed at lower levels. Under these conditions, Nr0b2 does not associate with Nr5a2, leading to derepression of *c-jun*. The c-Jun protein binds another protein, Fos, to form the transcription factor AP-1. Together, Nr5a2 and AP-1 promote the expression of genes involved in pancreatic inflammation.

propensity for pancreatic inflammation.

Next, the group investigated mice genetically engineered to lack one *Nr5a2* allele. They showed that this mutation triggers a cascade of regulatory events that leads to the upregulation of inflammation-promoting genes. This occurs without infiltration of inflammatory white blood cells into the pancreas, indicating that reduced Nr5a2 expression produces a 'primed' pre-inflammatory state that is a precursor to inflammation. The researchers found that these gene-expression changes are very like those seen shortly after treating mice with caerulein, a chemical inducer of inflammatory pancreatitis in mice.

In a normal pancreas, Nr5a2 binds to promoter DNA sequences that drive the expression of acinar-cell-specific genes to promote cell differentiation, and Cobo and colleagues found that the protein was absent at promoters of inflammatory genes. Therefore, a simple explanation for the pre-inflammatory characteristics observed in Nr5a2-mutant mice might be decreased Nr5a2 binding to the promoters of one or more anti-inflammatory target genes, and so reduced expression of these genes. However, the reality is much more interesting — the authors observed recruitment of Nr5a2 to the promoters of inflammatory genes in mutants.

Many of these inflammatory genes are targets of AP-1, a transcription factor consisting of two proteins: one from each of the Jun and Fos families. Cobo *et al.* found that Nr5a2 interacts physically with one Jun protein, c-Jun, and co-occupies AP-1 target sites on DNA. They then demonstrated the importance of this interaction by showing that pancreas-specific deletion of c-Jun restores Nr5a2 binding to its typical target genes. Furthermore, they showed that Nr5a2-mutant mice are hypersensitive to caerulein-induced pancreatitis, and that this hypersensitivity can be eliminated by *c-jun* deletion. Next, the authors found that the switch of Nr5a2 to AP-1 binding sites also occurs in wild-type mice during early pancreatitis — this, too, depends on c-Jun.

How might reduced expression of a transcription factor cause its redistribution across target genes? One target of Nr5a2 in uninjured tissue is the gene *Nr0b2* (ref. 9), which encodes a transcriptional co-repressor. Cobo *et al.* demonstrate that, in normal conditions, both Nr5a2 and Nr0b2 bind directly to the *c-jun* promoter, ensuring that the gene is only weakly expressed (by contrast, no Nr0b2 binding occurs at Nr5a2's highly expressed targets). When Nr5a2 levels are low, as in mutant mice, Nr0b2 levels decrease rapidly, such that it no longer associates with Nr5a2 at the *c-jun* promoter. The loss of Nr0b2 repressor activity results in increased c-Jun expression, and so higher levels of AP-1. AP-1 then recruits Nr5a2, even at its diminished levels, to different, inflammatory target genes (Fig. 1).

The authors found that, although AP-1 is present at modest levels in the wild-type, uninjured pancreas, it does not bind Nr5a2. Perhaps Nr5a2 binding to Nr0b2 blocks its interaction with c-Jun, and the loss of Nr0b2 during inflammation exposes a high-affinity site for c-Jun, enabling recruitment of Nr5a2 by AP-1. Biochemically focused studies will be required to unravel the complex and

50 Years Ago

Hovermarine, a small firm based in Southampton, has now produced its first hovercraft … The design is particularly interesting; the hovercraft has submerged sidewalls, so that in motion it looks much like a conventional boat … The makers suggest that this sort of craft will be best suited to use in estuaries or rivers, where very large seas are not often experienced. At a speed of 28 knots, the craft will comfortably accommodate seas of up to 3 ft. in height; in more severe conditions, the company says, the maximum speed attainable will depend on the state of the sea and the amount of discomfort which the passengers are prepared to accept.
From *Nature* 24 February 1968

100 Years Ago

Mr. T. J. Westropp … has republished from the Proceedings of the Royal Irish Academy … a paper entitled "The Ancient Sanctuaries of Knockainey and Clogher, Co. Limerick". Here a cairn commemorates the cult of the goddess Aine, of the god-race of the Tuatha de Danann. She was a water spirit, and has been seen, half-raised out of the water, combing her hair. She was a beautiful and gracious divinity … and is crowned with meadowsweet (Spiraea), to which she gave its perfume. She is a powerful tutelary spirit, protector of the sick, and connected with the moon, her hill being sickle-shaped, and men … used to look for the moon — whether risen or not — lest they should be unable to find their way back. They used to visit her shrine on St. John's Eve, carrying wisps of lighted straw, in order to bring good luck to crops and herds … Her son, the magic Earl of Desmond, is still seen riding over the ripples of Loch Gur until his horse's golden shoes are worn out.
From *Nature* 21 February 1918

changeable network of Nr5a2 interactions.

Other questions are raised by this work, too. For instance, how does caerulein treatment modulate Nr5a2 function? Cobo *et al.* find that Nr5a2 is redistributed to inflammatory-gene targets within 30 minutes of a single caerulein dose, and that expression of these targets is fully induced within one hour. This implies a rapid mechanism, possibly not dependent on increased c-Jun expression. In addition, this work does not prove that Nr5a2 is required to activate the inflammatory genes that it binds — this will require comparison of mouse pancreases lacking one *Nr5a2* allele with those lacking both (null), in which there is no Nr5a2. It is notable that a previous comparison of *Nr5a2* wild-type and null pancreases did not identify differences in inflammatory-gene expression[9], potentially confirming that residual Nr5a2 is needed to activate inflammatory genes.

Inflammation promotes tumour development in many tissues[1], and Cobo and colleagues' study suggests that altering susceptibility to inflammation may be one way in which common single-nucleotide mutations contribute to the risk of cancer. If future work reveals that human NR5A2 mutations associated with PDAC risk reduce NR5A2 levels in the healthy pancreas, it might be possible to offset the cancer risk using anti-inflammatory drugs. A more targeted approach could take advantage of the potential for NR5A2 to bind and be activated by small organic molecules[10,11]. Such an activating drug might decrease the severity or frequency of pancreatitis in people with insufficient NR5A2, by raising the transcriptional activity of the residual protein. ■

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ENGINEERING

Neurons mimicked by electronics

Electronic devices can currently emulate only basic functions of biological neurons. Devices called memtransistors could overcome this limitation and give rise to improvements in artificial-intelligence systems. SEE LETTER P.500

DA LI & XIAOGAN LIANG

The human brain contains billions of neurons that are linked to one another by trillions of tiny contacts called synapses. Designing electronic devices that approach this level of connectivity remains challenging, but, on page 500, Sangwan *et al.*[1] report a breakthrough in this quest. They present a multi-terminal device called a memtransistor, which is made using a single layer of the semiconductor molybdenum disulfide (MoS_2). Such devices could enable the construction of neural-network systems that have a high degree of connectivity and that can execute complex neural functions. This envisaged network technology, if eventually created, would have a great impact on the development of hardware-based artificial intelligence (AI).

For a long time, AI was regarded as science fiction, presented in a variety of forms from humanoid robots to supercomputers. However, the past few years have witnessed rapid progress towards the realization of these fictional machines. For example, in 2016, AlphaGo became the first AI program to defeat a world champion at the game of Go — a victory that greatly increased public interest in AI research (see go.nature.com/2g9kruc).

Neural networks could enable the generation of AI systems that have unprecedented analytical and computational capabilities. However, these networks are typically constructed using electronic components called complementary