than that of our Sun, but their inner structure is very different. They have long been known to have complicated, low-amplitude light curves[7]. One might think that the large number of detected frequencies would make these stars ideal targets for asteroseismology.

The theoretical models of δ Scuti stars predict many possible excited eigenmodes and corresponding frequencies. In fact, there are many more such frequencies in models than have been observed[8], and usually we do not know which of the possible modes are seen. If there were some regular structure to the frequencies (such as frequencies with comb-like regular differences), we would have a better chance of identifying them. But the theoretical models generally do not predict regular frequency structure for these stars.

Bedding *et al*. have identified a special subgroup of δ Scuti stars that pulsate at higher frequencies than do most such stars. For this subgroup, both theory and observations suggest the existence of regular frequency structures. Other researchers have previously found regular structures in observed data for some δ Scuti stars (see refs 9–14, for example), but did not identify the oscillating modes conclusively, if at all. Bedding *et al*. provide unambiguous mode identification for a uniform and relatively large sample of these stars.

A key factor in the authors' success is that many of the stars in the subgroup rotate more slowly than do other δ Scuti stars. (Alternatively, it could be that some of the stars are observed almost pole-on, resulting in apparently small rotation velocities.) Theoretical models predict that the frequency spectra of stars that have low rotation velocities are less complicated than those with higher rotation speeds[14], which makes it easier to recognize their regular frequency structures. Bedding *et al*. not only identified these structures, but also associated the frequencies with the corresponding eigenmodes.

Sky surveys now and in the near future will target many thousands of δ Scuti stars, including many that are similar to those described by Bedding and co-workers. This is not merely an opportunity to understand the physics of a special group of δ Scuti stars better. The authors show that these are young stars, which means that they can be used as tracers to estimate the age of open star clusters or of young stellar associations in our Galaxy. In this way, we might learn more about the evolution of the Milky Way. Bedding and colleagues' study is therefore not the last word on δ Scuti stars. Rather, it opens up avenues of investigation for this important stellar group.

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Immunology

Brain–spleen connection aids antibody production

Flurin Cathomas & Scott J. Russo

Elucidating how the brain controls peripheral organs in the fight against infection is crucial for our understanding of brain–body interactions. A study in mice reveals one such pathway worthy of further investigation. **See p.204**

Interactions between the mind and the body have sparked the interest of scientists and philosophers for centuries. In ancient Greece, the physician Galen described the spleen as being the source of black bile, which was thought to cause melancholy when secreted in excess. Today, research is uncovering complex ways in which the brain and body interact to affect diverse aspects of health, from mood to immune function. The spleen aids immune defences by functioning as part of the lymphatic system; the organ is a major hub of activities needed to initiate responses in the adaptive branch of the immune system, which handles defences that are tailored to a specific disease-causing agent.

The spleen is a target of top-down control from the brain[1]. Zhang *et al.*[2] have taken our understanding of brain–spleen connections to the next level by revealing on page 204 an aspect of top-down control that regulates the adaptive immune system.

The spleen's contribution to immune responses occurs mainly in its white-pulp region, where immune cells that have arrived from elsewhere in the body present peptide fragments called antigens to immune cells called T cells. If a T cell binds to and recognizes such an antigen, which might indicate the presence of an abnormal cell or a foreign invader, this activates the T cell, which in turn activates immune cells called B cells. B cells differentiate to form plasma cells (Fig. 1) that secrete antibodies specific for the antigen presented, and these antibodies are released into the bloodstream to fight infection[3].

Spleen activity is controlled by the autonomic nervous system — a part of the nervous system that regulates organs. More specifically, the spleen is controlled mainly by the sympathetic branch of the autonomic nervous system, which is associated with the 'fight-or-flight' response[4]. However, little was known previously about possible upstream brain regions that might connect to the autonomic nervous system in the spleen to control it and, by extension, adaptive immunity. An earlier study in mice[5] revealed that stimulation of a brain region called the ventral tegmental area, a part of the brain's reward circuit, boosts immune responses and protection against harmful bacteria.

Zhang and colleagues developed a surgical technique to remove nerves from the spleen in mice. This mainly removed inputs from the autonomic nervous system and prevented top-down control from the brain to the spleen. After surgery, the animals were injected with an antigen. Plasma cells that made antibodies targeting that antigen arose in abundance in control mice that had undergone a 'sham' operation that did not remove nerves. Such an increase did not occur in the denervated mice, indicating that splenic-nerve activity regulates the formation of plasma cells and thus adaptive immunity.

The authors investigated which molecular mechanisms might be needed for plasma-cell formation in this context. They studied the expression of various types of receptor that can bind the neurotransmitter molecule acetylcholine, which is a key signalling component of the autonomic nervous system. Zhang *et al.* report that B cells express a type of acetylcholine receptor called a nicotinic receptor, and the authors pinpointed protein subunits

of this receptor, including one called Chrna9. To test the role of nicotinic receptors containing Chrna9 in plasma-cell formation, Zhang *et al.* transplanted haematopoietic stem cells, which can generate immune cells, into mice that had undergone a treatment to remove their own haematopoietic stem cells. When the transplanted stem cells came from mice engineered to lack the gene encoding Chrna9, these animals generated fewer plasma cells after an injection of antigens than did animals that received antigen injections and transplants of stem cells with the gene intact. This result indicates that plasma-cell formation requires the presence of nicotinic receptors.

When a type of T cell called a $CD4^+$ T cell is activated by antigen recognition, it secretes acetylcholine in response to the hormone noradrenaline[6]. The authors reveal that such T cells serve as a 'relay' between the release of noradrenaline from the splenic nerve and the subsequent acetylcholine-dependent[6] formation of plasma cells (Fig. 1).

To map the neural circuit that connects the spleen and brain, the authors used a method termed retrograde tracing, which relies on monitoring the expression of a fluorescent protein encoded by a virus that can 'jump' across the synapses that connect neurons. This enabled Zhang and colleagues to track all upstream inputs to a given nerve cell in the spleen. The authors thereby identified two key brain regions (the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus) that contain neurons that connect to splenic nerves. These regions are major centres involved in the response to psychological stressors such as fear or threatening situations[7], and they have essential roles in regulating the production of neuroendocrine hormones, for example, by a pathway called the hypothalamic-pituitary-adrenal axis[8].

One population of nerve cells in these two regions releases the hormone corticotropin, which is thought to have a key role in initiating the body's response to stress[9]. To determine whether corticotropin-producing neurons affect the spleen, Zhang *et al.* stimulated these neurons using a technique called optogenetics, and assessed whether this affected the activation of splenic nerves by monitoring their firing using electrophysiological recording. This provided crucial functional evidence for a brain–spleen connection, because such stimulation increased the firing of splenic-nerve cells. The authors also report that the inhibition or ablation of corticotropin-producing neurons in either of the two brain regions impaired the formation of plasma cells after antigen injection. Conversely, activation of the neurons stimulated such plasma-cell formation.

Although these circuit-based experimental approaches provide key proof for the existence of the brain–spleen axis, the authors also needed to test their model using suitable interventions that activate the 'stress centres' in the brain. However, neurons in the central nucleus of the amygdala and the paraventricular nucleus function in a pathway that causes the adrenal gland to secrete the hormone glucocorticoid in response to stress, and glucocorticoids are potentially immunosuppressive[10].

The authors therefore considered whether the concentration of glucocorticoids secreted by the adrenal gland might depend on the severity of the stress. To avoid possible glucocorticoid-driven immunosuppression that might interfere with their analysis of antibody production, Zhang *et al.* studied mice that had been placed on an elevated, transparent platform; this provided a behavioural situation that induced only moderate stress. Following antigen injection, this scenario, but not another set-up that caused more-severe stress, led to the generation of antigen-specific antibodies. The authors showed that this antibody production depends on corticotropin-producing neurons in the brain circuit that they had described.

There is growing evidence that dysregulation of the immune system has a bottom-up role in promoting several behaviours relevant to neuropsychiatric disorders[11]. Zhang and colleagues' study provides insights in the other direction — how the brain exerts top-down control of immune-system function. Future research will be needed to investigate whether this particular brain–spleen circuit exists in humans. The authors' work opens up the exciting possibility that activating certain brain regions (through behavioural interventions or by selective stimulation using neuromodulatory techniques such as transcranial magnetic stimulation) could modulate the immune system. To return to Galen, he was right that the spleen is a key site of connection between the brain and the body, but his ideas about how the spleen induces melancholy now give way to this new perspective on how the mind might modulate resilience-promoting antibodies.

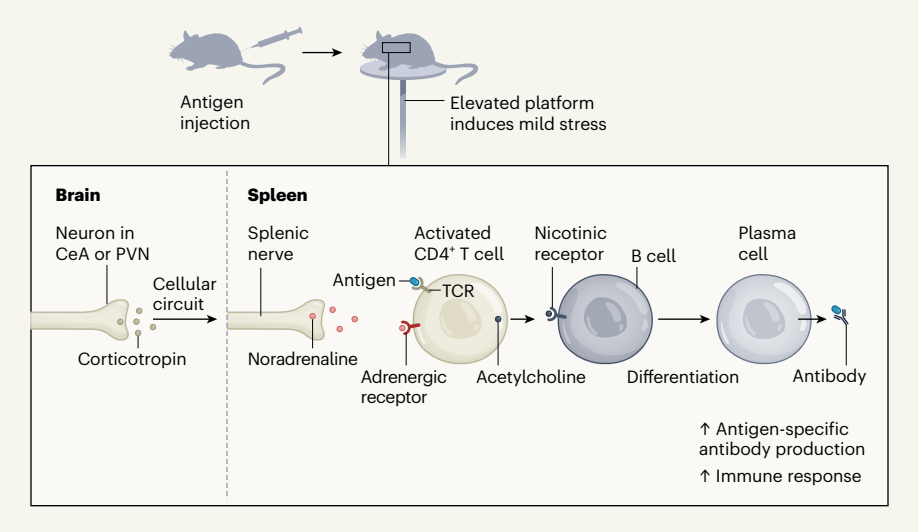

Figure 1 | Brain control of antibody production. Zhang *et al.*[2] describe a circuit between the brain and the spleen that aids immune defences. The authors injected animals with an antigen (a peptide fragment) that can be recognized by immune cells. Placing the animal on a high platform activated neurons that produce the molecule corticotropin. These neurons are located in brain regions that respond to stress, called the central amygdala (CeA) and the paraventricular nucleus (PVN) of the hypothalamus. A cellular circuit connects these activated neurons to the splenic nerve and drives it to release the molecule noradrenaline. An immune cell termed a $CD4^+$ T cell is activated when its T-cell receptor (TCR) binds to antigen. When such a cell encounters the noradrenaline released in the spleen (which binds to what is termed an adrenergic receptor), this leads the T cell to secrete the molecule acetylcholine[6]. This molecule binds to a nicotinic receptor on an immune cell called a B cell, causing it to differentiate into a plasma cell. The plasma cell boosts immune defences by making antibodies that recognize the specific antigen that activated the T cell.

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