Silicon carbide is expected be phonon matched to silicon, but there is no evidence that it is also matched to gallium nitride. The interface between diamond and silicon carbide displayed the lowest thermal boundary resistance, owing to the well-matched phonon modes of these materials, and the thermal boundary resistance at the interface between the silicon and silicon carbide was relatively low, too. But phonon matching at the interface between gallium nitride and silicon carbide is yet to be fully investigated. Engineering this interface could well reduce the 3.1 m^2 K GW^{-1} resistance observed for gallium nitride devices.

It is not yet clear whether the performance of these semiconductor devices will be affected by silicon carbide interface engineering, so the device properties must be carefully evaluated before the phonon bridges developed by Woo and colleagues can be deployed widely. Nevertheless, the team's strategy for maximizing heat dissipation in semiconductor transistors will help to realize the full potential of both silicon and gallium nitride technologies.

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Immunology

Astrocyte cells in the brain have immune memory

Michael V. Sofroniew

The central nervous system's astrocyte cells respond to injury and disease. The finding that they form molecular memories of certain responses, and that these modify inflammatory signalling, sheds light on autommunity. **See p.865**

A history of infection, traumatic injury or disease can influence the onset, progression or severity of central nervous system (CNS) disorders, such as autoimmune disease, stroke and neurodegenerative disease. How this occurs is poorly understood. An emerging potential mechanism is a form of intracellular molecular memory that is mediated by what are called epigenetic changes — modifications of proteins that control the accessibility of DNA for gene expression. Epigenetic immune memory is well characterized in cells of the 'innate' branch of the immune system after defence responses, and the process heightens subsequent defence responses[1]. On page 865, Lee *et al.*[2] reveal that a CNS cell called an astrocyte can acquire epigenetic immune memory that amplifies the cell's pro-inflammatory signalling in response to specific molecular stimuli and during autoimmune disease. The findings open doors to understanding and potentially ameliorating various CNS disorders.

Astrocytes are ubiquitous cells that are present throughout the entire CNS and engage in multiple activities that are essential for healthy CNS function[3]. These cells also respond to all forms of CNS injury and disease. The past few years have seen an explosion of interest in the role of astrocytes in neurological and behavioural disorders, and mounting evidence shows that astrocytes can exert beneficial or detrimental effects that powerfully influence the outcome of these disorders[3]. In this context, astrocytes are emerging as important tissue-resident responders that are directly involved in innate-immune defences and that regulate CNS inflammation in response to infection, injury and disease[4,5].

Vertebrate immunity has long been divided into innate and adaptive arms that comprise different sets of bone-marrow-derived immune cell. Innate immune cells respond rapidly to disease-causing agents and tissue damage through receptors that can recognize general hallmarks of trouble, such as proteins that are common to a range of viruses and bacteria. Adaptive immune cells respond more slowly by comparison and show classic immunological memory by boosting populations of immune cell that can recognize, in a highly specific way, a protein that might be unique to a particular bacterial species, for example.

It has emerged that innate immune cells can also demonstrate a form of cellular memory by undergoing long-term functional reprogramming through epigenetic modification of proteins that control DNA accessibility. This alters subsequent gene expression and functional responses[1,6]. There is a growing appreciation that in addition to bone-marrow-derived cells, there are tissue-resident innate immune cells that can also show such epigenetic immune memory[1,6]. Lee and colleagues' work demonstrates this capacity in CNS astrocytes and identifies underlying molecular mechanisms that could be targeted.

Lee and colleagues first asked whether exposure to an initial pro-inflammatory stimulus might alter the way that astrocytes respond to a second stimulus (a rechallenge) that is identical to the first stimulus. The authors exposed mouse brains *in vivo*, or mouse astrocytes in cell cultures *in vitro*, to the proteins IL-1β and TNF, which are molecules known as cytokines that stimulate pro-inflammatory responses. These particular cytokines were used because previous studies have implicated them in the autoimmune disease multiple sclerosis and a mouse system used to model multiple sclerosis, termed experimental autoimmune encephalomyelitis (EAE). Using RNA sequencing to assess gene expression, the authors found that rechallenge with a second stimulation of IL-1β and TNF caused significantly more potent astrocyte pro-inflammatory responses, which were reflected in both the number and expression levels of upregulated pro-inflammatory genes compared with a single stimulation alone (Fig. 1a). Notably, inflammatory gene expression returned to baseline before the second stimulation, indicating that the increased expression was not simply a cumulative additive effect, but was a true augmentation from baseline.

To examine any potential relevance to autoimmunity, the authors studied the mouse model system of EAE. Astrocytes grown *in vitro* from mice with EAE showed enhanced responses after a single stimulation with IL-1β and TNF compared with that of astrocytes derived from healthy mice. This resembled the response of cultures from healthy mice to a second cytokine challenge, suggesting that EAE exerts a priming effect that amplifies astrocyte pro-inflammatory signalling.

How might exposure to cytokines or autoimmune disease alter astrocyte responses on rechallenge? The authors explored whether

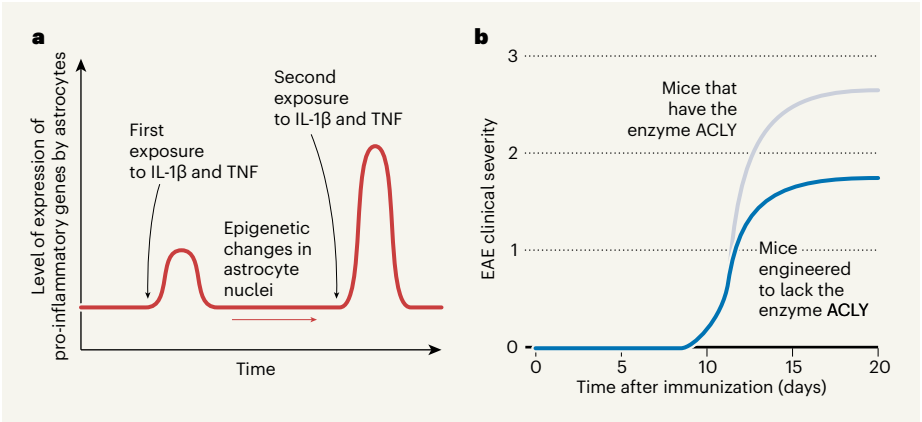

Figure 1 | The effect of previous exposure of astrocyte cells to inflammatory stimuli. Lee *et al.*[2] investigated what factors might influence the defence response of cells in the brain and spinal cord, called astrocytes. The data indicate that these cells gain a memory of inflammatory challenges that boosts their subsequent defence responses on rechallenge. **a**, When mice were exposed to inflammatory stimuli (the proteins IL-1β and TNF) twice, the second exposure resulted in astrocyte cells showing enhanced expression of pro-inflammatory genes, such as *Nfkb*, *Il6* and *Ccl2*. The authors provide evidence that this higher level of gene expression arises because the initial exposure results in changes (called epigenetic modifications) in the nucleus of the astrocyte to the complex of DNA and histone proteins. **b**, The authors examined a mouse model of multiple sclerosis called experimental autoimmune encephalomyelitis (EAE), which is associated with inflammatory signalling. If mice were engineered to lack components associated with mediating epigenetic changes that boost pro-inflammatory gene expression in astrocyte cells, such as the histone-modifying enzyme ACLY, they had less severe disease than did the mice that had the components.

epigenetic remodelling of proteins that control DNA accessibility might underlie the differences observed. DNA is wrapped in, and isolated by, proteins called histones. DNA accessibility for gene expression can be modified epigenetically by the addition or removal of acetyl groups attached to histones. The acetylation or deacetylation of histones is mediated by enzymes known as histone acetylases (HATs) or histone deacetylases. Lee *et al.* found that rechallenge with cytokines increased astrocyte expression of *Ep300*, the gene encoding the HAT p300. Moreover, increased p300 was associated with gene-expression responses linked to histone acetylation, including increased DNA accessibility in inflammation-related genes. Histone modification by p300 occurs by acetylation of the histone protein histone 3 using the molecule acetyl coenzyme A, which is produced by the enzyme ATP citrate lyase (ACLY).

To test whether the EAE-associated increase in astrocyte pro-inflammatory responses might occur through histone modification mediated by p300, the authors engineered the deletion of *Ep300* or *Acly* selectively from astrocytes. Deletion of either *Ep300* or *Acly* attenuated EAE clinical symptoms (Fig. 1b) and reduced astrocyte pro-inflammatory changes in gene expression. This provided strong evidence that the pathway for epigenetic memory boosts astrocyte pro-inflammatory responses in EAE. Echoing their findings for EAE, the authors identified large populations of astrocytes that express ACLY and p300 in people who have multiple sclerosis compared with people who did not, suggesting that astrocyte epigenetic memory driven by ACLY and p300 might contribute to pathological pro-inflammatory responses in this autoimmune disorder.

Innate immune memory that boosts pro-inflammatory responses probably evolved as a beneficial means of dealing with repeated infections, but such responses have the potential to become detrimental in the context of other disorders[1]. This also might be the case for innate immunity in astrocytes, which are strong responders to microbial infections. As the findings by Lee *et al.* now show, innate immune memory in some astrocytes can amplify their pro-inflammatory responses in ways that might contribute to disease in autoimmune disorders, such as multiple sclerosis.

Beyond autoimmunity, inflammation is emerging as a key potential modifier of many CNS disorders in animals and people[7]. Moreover, it is becoming clear that repeated exposure to insults of the CNS that involve inflammation, such as traumatic injuries, stroke and infections, can modify subsequent responses and can in some cases predispose to degenerative changes, whereas in other cases can confer protection. For example, CNS inflammatory responses are augmented by repetitive head trauma, which also predisposes to neurodegenerative disease[7].

By contrast, exposure to a mild case of reduced blood flow (ischaemia) can confer protection against subsequent ischaemic events through mechanisms that might involve astrocytes[8,9]. In this context, innate immune memory need not always be detrimental. For example, repeated multiple exposures to the same inflammatory stimulus in microglia cells, another type of CNS innate immune cell, can induce innate immune tolerance that attenuates responses to the same inflammatory stimulus or to subsequent ischaemia or neurodegeneration similar to that seen in Alzheimer's disease[6].

Could innate immune memory implemented through innate immune memory in astrocytes more broadly influence CNS disorders? Several lines of evidence make it tempting to speculate that this might be the case. For example, p300 has been identified as a regulator of astrocyte responses in a broad cross-section of CNS disorders, including stroke, trauma and neurodegeneration[10]. Notably, innate immune memory can be context dependent, such that different stimuli evoke different responses[1] and astrocytes have diverse context-dependent signalling mechanisms that might enable such differential responses[10]. Astrocytes can undergo remarkably different changes in epigenetically regulated DNA accessibility in different disorders, and these cells have at their disposal an impressive arsenal of molecular regulators that can influence DNA accessibility in diverse ways[10].

Given that some disorders might trigger distinct forms of innate immune memory, it will be interesting to explore whether innate immune memory triggered in astrocytes by one disorder, for example infection, can alter responses to a subsequent disorder, such as a traumatic injury. There is much work to be done. Nevertheless, the concept that innate immune memory can alter astrocyte inflammatory responses adds to the growing awareness that astrocytes can powerfully influence CNS disorders[3], and points towards the need to identify additional astrocyte mechanisms that might represent potential therapeutic targets.

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