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NEUROINFLAMMATION

Synapses pruned in lupus

Lupus is an autoimmune disease that can cause brain dysfunction. Studies in mouse models of lupus find that interferon proteins can cause the brain's immune cells to trim the synaptic connections between neurons. SEE LETTER P. XXX

SARAH MCGLOSSON & DAVID HUNT

Lupus is a complex autoimmune disease that can affect almost any organ in the body¹. Brain dysfunction develops in many people with the disease, but the molecular and cellular basis for this aspect of the condition are poorly understood, and there are no therapies that target it. In a paper online in *Nature*, Bialas *et al.*² provide insight into how brain disease can occur in mouse models of lupus, and bring a potential therapeutic target into focus.

Type I interferon proteins and their receptor are part of a pathway that has a pivotal role in the immune response against viral infection. Compared with healthy individuals, people who have an impaired type I interferon response can be prone to infections, whereas individuals who have an overactive response might have autoimmune disease or organ damage associated with inflammation^{3,4}. Abnormal activation of the type I interferon response is observed in most people with lupus, and a clinical study⁵ found that interferon-related gene expression correlates with specific disease features.

Bialas and colleagues investigated previously established mouse models of lupus in which there is activation of the type I interferon response⁶. The authors observed that such mice show significant neurological deficits, including poor performance on cognitive and behavioural tasks compared with wild-type animals. However, treating the model mice with an antibody that blocks signalling through the type I interferon receptor prevents these neurological symptoms.

The authors sought to determine which cells might be responsible for this phenomenon. In many diseases associated with neuroinflammation, immune cells enter the brain. However, Bialas *et al.* found no evidence of such infiltration in the brains of the model mice. This finding indicates that the cells causing neurological damage might originate in the brain itself.

Microglia, the resident immune cells of

the brain, were considered a prime suspect. These cells perform many immunological roles, including the active surveillance of their environment, and through a process called engulfment they can ingest cellular material. Inflammation and the presence of cellular damage can stimulate microglia to adopt an activated state associated with an increase in the activity of immune functions, including engulfment. The authors found that microglia were in an activated state throughout the brains of the model mice, and were responding to signalling by type I interferon.

Using the model mice, Bialas and colleagues purified microglial cells and sequenced the cellular RNA. Relative to the expression patterns observed in wild-type mice, the model mice showed upregulation of a broad set of interferon-dependent genes, including those involved in pathways associated with environmental sensing and the engulfment

of cellular material. In a series of elegant experiments, the authors demonstrated an association between the observed microglial activation and an increased engulfment of neuronal material, particularly of material from synapses, which form the junctions between two neurons. The use of electron microscope imaging enabled the authors to catch microglia in the act of synaptic ingestion.

The number, or density, of synapses was found to be decreased in the brains of the lupus-model mice, when compared with the synaptic density in wild-type mice (Fig. 1). These abnormalities could be prevented by blocking interferon signalling. Although determining whether this mechanism causes disease in humans remains a challenge for the future, the authors do show evidence of widespread activation of an interferon response in microglia and other cell types in the brains of people with lupus. Perhaps, in addition to the microglia-mediated mechanisms seen in the mouse models, humans have other cellular targets through which interferon can cause brain disease.

These findings have implications for understanding core neurobiological processes, as well as offering insights of clinical relevance. Synaptic pruning by microglial cells was originally described as a mechanism that helps to sculpt neuronal circuits in the developing brain⁷. Subsequent discoveries have implicated synaptic pruning as a pathological mechanism associated with the early stages of some neurodegenerative diseases⁸. The

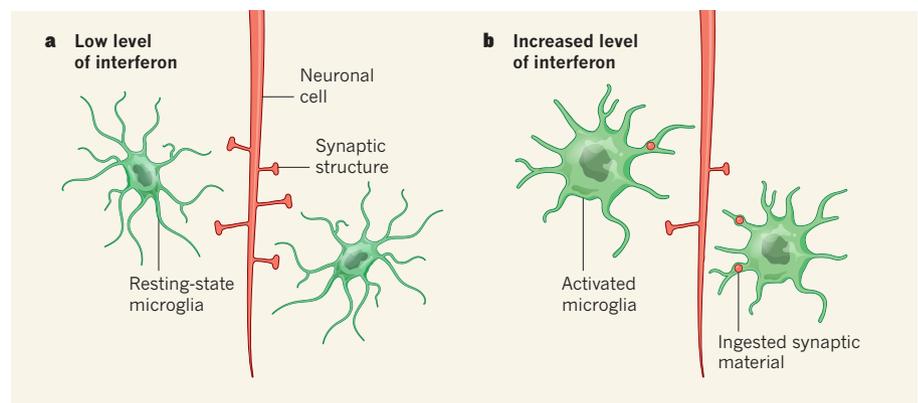


Figure 1 | Synaptic pruning in autoimmunity. **a**, In healthy, wild-type animals, resident immune cells in the brain known as microglia are usually in a resting state as they patrol the areas around neuronal cells and the cellular regions that form synaptic connections. These animals express a low level of interferon proteins, which are key regulators of an immune response. **b**, Bialas *et al.*² investigated the brain inflammation that can occur as a feature of an autoimmune disease called lupus. The authors used previously established⁶ mouse strains that provide models for studying the disease. These animals have a higher level of interferon than do wild-type animals. Bialas and colleagues observed that the microglial cells in the model mice adopted an activated state that involved activation of immune functions, including the ingestion of cellular material through a process known as engulfment. Using image analysis, the authors observed that the activated microglial cells ingested synaptic material from neurons, resulting in a reduced synaptic density compared with that of wild-type animals. This change to the synapses could be prevented by blocking activation of the interferon pathway (not shown).

finding that inflammatory factors such as type I interferon can modulate neuronal connectivity will doubtless provoke further debate surrounding the expanding list of potential roles for microglial-mediated synaptic pruning in brain health and disease.

This study adds to the growing scientific rationale for classifying lupus brain disease according to the molecular mechanism involved⁵. This is because it is becoming increasingly clear that neurological disease in lupus is heterogeneous and can be driven by distinct molecular mechanisms. For example, some people with lupus develop brain disease associated with antibodies that bind to proteins expressed on the surface of neuronal cells⁹, whereas the work by Bialas and colleagues adds to an increasing body of evidence pointing to type I interferon as having a neurotoxic role^{3,4,10}. Clinical trials of targeted therapies are much needed for lupus-associated neurological disease. The ability to group patients according to the molecular mechanisms that drive their disease should facilitate such studies and maximize the chance of

treatment success.

The tools for studying the therapeutic modulation of type I interferon signalling in people with lupus continue to increase in precision¹¹. Consideration should be given to the most effective strategy for modulating this pathway in the human brain, because the blood–brain barrier poses particular challenges for the access of drug treatments. Moreover, therapeutic blockade of type I interferon signalling in the brain is not without potential risks, given the pivotal role of this pathway in host defence and the need for a basal level of interferon signalling to maintain neuronal health¹².

Bialas and colleagues' work identifies an intriguing and previously unknown cause of brain damage in mouse models of lupus. But perhaps more importantly, it provides a timely impetus to consider targeted clinical studies that tackle the often-neglected problem of brain disease in people with lupus. ■

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