To initiate assembly, the researchers made use of electron catalysis — a widely used strategy for inducing the formation of covalent bonds in synthetic organic chemistry[4,5]. Introduction of an electron into one of Jiao and colleagues' molecules lowers the Coulombic repulsion to such an extent that the dumb-bell can enter the macrocycle. In other words, the configuration of the key (the guest) is set so that it fits perfectly into the lock (the host) — or vice versa, if an electron is added to the host, rather than to the guest (Fig. 1b).

Once the dumb-bell is situated in the macrocycle, the binding sites in the host and guest can dock with each other through non-covalent interactions. In this case, the interactions are produced by the pairing up of radicals, and of electron donor and acceptor groups. Moreover, the resulting complex can now pass the activating electron on to another unbound molecule. This electron-transfer step locks the dumb-bell into the macrocycle and simultaneously sets off a chain of further transfers, leading to the formation of more complexes.

Jiao *et al*. first demonstrated this catalytic concept by using chemical reagents (reductants) as the electron source, but then went on to replace the reductants with electric current. In the latter approach, electrons are injected into molecules at the cathode surface in an electrochemical cell. Notably, the rate of molecular self-assembly can be conveniently controlled by the current intensity, and the process can be initiated and interrupted as desired by switching the current on and off.

Another advantage of the cathode-driven process is that it is clean — no waste is produced from the electron source, unlike when chemical reductants are used. And, in contrast to conventional molecular-recognition processes, the ratio of molecular assemblies to free molecules can be adjusted at will. A strength of the work is that the authors combined a wide variety of techniques to collect conclusive evidence for the proposed catalytic mechanism.

Electron-catalysed self-assembly is a pivotal addition to the toolbox of supramolecular chemistry, and will inspire chemists to develop new means of controlling non-covalent binding events and to orchestrate molecular assembly at extended length scales. Furthermore, Jiao and colleagues' work might serve as a starting point for the development of new forms of complex matter[6].

One of the current limitations is that the assembly process cannot yet be reversed under the given conditions. A future challenge could therefore be to develop a bidirectional approach, in which two different stimuli (such as positive and negative currents) can be used to switch between assembly and disassembly. This could, for example, eventually enable the synthesis of supramolecular materials whose properties can be controlled by electrical pulses. Exciting developments in the field of electrically stimulated self-assembly are to be expected in the future.

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Medical research

Multiple sclerosis sparked by virus-led autoimmunity

Hartmut Wekerle

Understanding factors that lead to the development of multiple sclerosis might aid efforts to develop new therapies. Clinical data now implicate a viral culprit and immune-system dysfunction as underlying factors in this condition. **See p.321**

Most people who study multiple sclerosis (MS) propose that the factors underlying initiation of the disease enter the central nervous system (CNS) from outside the brain. The debate about the nature of these factors has split researchers into two main camps. Most see autoimmunity as the driving factor for the illness, but a minority invoke viral culprits. On page 321, Lanz *et al*.[1] report evidence that might settle this debate through a compromise solution.

Supporters of the autoimmunity thesis point to compatible evidence such as the particular patterns of inflammatory injuries in MS; genetic risk factors involving immune-related genes; and immunotherapy treatments that help to relieve the condition[2]. However, a universally accepted culprit that could be the prompt for an abnormal immune response leading to MS has been missing until now. For the proponents of a viral origin, analysis of human populations using epidemiological evidence from the clinic provides compelling data coupling MS with the Epstein–Barr virus[3]. But this associative connection lacked a causal, disease-triggering link.

Lanz *et al*. examined antibodies obtained from the cerebrospinal fluid (CSF) of people with MS, and identified antibodies that recognize small regions of protein (antigens) corresponding to proteins of the Epstein–Barr virus. The authors report that such antibodies also recognize the protein GlialCAM, which is a component of glial cells in the brain. This result indicates that GlialCAM can act as a target of these antibodies, providing an 'autoantigen' for self-directed autoimmunity; it also suggests that this contributes to the events leading to MS.

Importantly, Lanz and colleagues' data indicate that these crossreactive antibodies evolve from ones that recognize only the virus, through a process of antibody refinement. In samples of CSF from people with MS, the level of immunoglobulin proteins (which form antibodies) are higher than those in the CSF of healthy people, and this is a diagnostic sign of MS. A technique called electrophoretic separation shows that these immunoglobulins form discrete bands in the electrophoresis analysis, which are produced by individual families (clones) of B cells. These bands, called CSF-specific oligoclonal bands (OCBs), are absent from blood plasma samples. The nature of the antigens that these immunoglobulins recognize is debated. Previous studies indicated that these OCB antibodies bound to various ubiquitous intracellular proteins, but not to CNS-specific autoantigens, raising doubts about whether such antibodies cause disease[4].

Lanz *et al*. revisited this topic taking a straightforward and powerful approach. They isolated antibody-producing B cells of the immune system called plasmablasts from CSF samples of people with early-stage MS (Fig. 1). The authors characterized the cells individually and assessed their antigen receptors; the genes encoding these receptors provide an initial blueprint that is modified to form the antibodies that the mature, activated cells produced. The plasmablasts expressed markers on their surface indicating ongoing activation of these cells, possibly indicating antigen recognition — but they did not express proteins required for cell migration, which qualified them as being CNS residents. Key

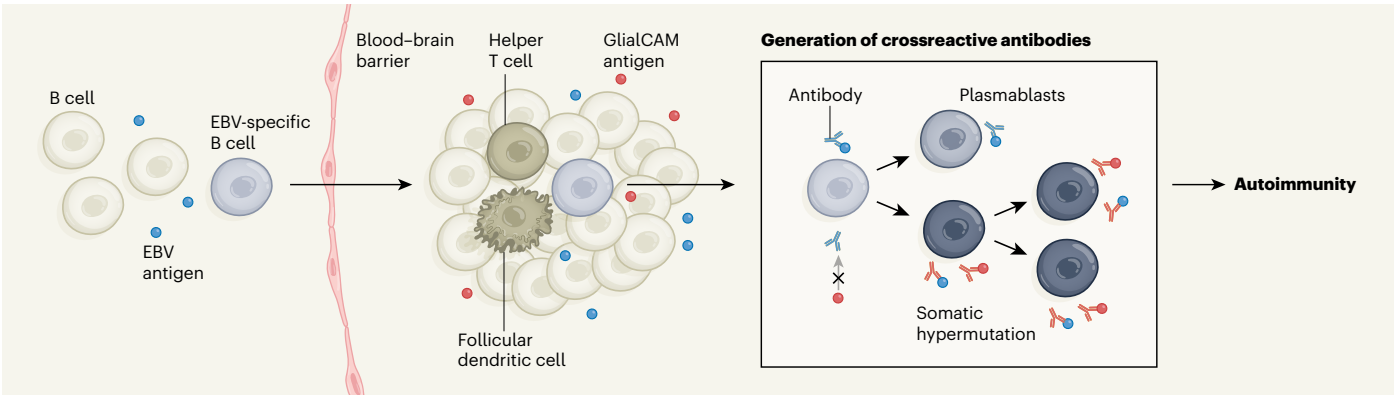

Figure 1 | A link between viral infection and immune dysfunction in multiple sclerosis. Lanz *et al.*[1] analysed antibody-producing immune cells called B cells in blood samples from people with multiple sclerosis (MS). Some of the B cells make antibodies that recognize a protein fragment, termed an antigen, of Epstein–Barr virus (EBV). EBV infection is implicated[3] in MS. Lanz and colleagues' evidence indicates that, after EBV-specific B cells enter the brain, they undergo a process that modifies target recognition by antibodies. During this process, aggregated B cells might form a site at which EBV-specific B cells recognize antigen, aided by immune cells called helper T cells and follicular dendritic cells. Antigen recognition would activate the cells and cause them to proliferate and differentiate to form antibody-producing cells called plasmablasts. EBV-specific B cells in the brain undergo a change called somatic hypermutation. This alters the specificity of the antibodies they produce from an antibody (blue) that recognizes only EBV antigen to an antibody (red) that recognizes the antigens of both EBV and a brain protein called GlialCAM. Targeting of GlialCAM could lead to autoimmunity, which is a hallmark of MS.

observations of Lanz and colleagues' study came from the authors' analysis of the genes encoding immunoglobulin, which shed light on the origin of the cells, and on their target antigens.

A B cell that has not yet encountered an antigen that it recognizes 'shuffles' (recombines) sets of gene segments representing parts of immunoglobulin, thereby creating a sequence corresponding to a 'primordial' antibody that can be termed a germline ancestor antibody. On antigen recognition, and with the support of other immune cells called cognate T helper cells (which recognize the same antigen), the immunoglobulin-encoding gene is modified through mutation by what is known as somatic hypermutation; ultimately, this boosts the antibody's antigen-binding strength — a process referred to as affinity maturation[5]. The CNS-resident plasmablasts studied by Lanz *et al.* had immunoglobulin genes showing numerous signs of somatic hypermutation. Successive modifications of immunoglobulin-encoding genes mediated by somatic hypermutation could be traced in the formation of cellular lineages (clonal pedigrees) that could be tracked, starting from single initial progenitor cells, using RNA sequencing.

Furthermore, Lanz and colleagues confirmed that the plasmablasts produced OCB antibodies, as previous work had indicated[6]. However, the antigen specificity and the affinity of the antibodies could not be deduced merely by RNA sequencing, because antigen binding is a function of a properly folded protein translated from RNA. Consequently, in pursuit of the target antigens, the investigators harnessed their transcriptional information to establish a library of 148 antibodies corresponding to those from the plasmablasts. When confronted with proteins from different viruses, one-third of the antibodies tested bound to proteins from Epstein–Barr virus. And much of the response against that virus was directed towards the transcription-factor protein EBNA1, a result that was observed in samples from six out of nine individuals with MS.

Most interestingly, the data reveal that affinity maturation in the brain led to a change in reactivity of a prominent B-cell clone; instead of displaying antibody-mediated reactivity solely against Epstein–Barr virus, it exhibited crossreactivity against a brain autoantigen. A representative plasmablast-derived anti-EBNA1 antibody was tested for binding to potential target autoantigens using a library of more than 16,000 human proteins. The antibody recognized GlialCAM. By contrast, the version of the antibody produced by this cell lineage before somatic hypermutation occurred bound to EBNA1, but ignored GlialCAM.

"This mechanism might be relevant to other viruses and autoimmune diseases."

These data are intriguing and will certainly spawn many new lines of research. Where and how in the brain does affinity maturation develop? The process typically requires availability of the recognized antigen(s); aid from cognate T helper cells; and, ideally, a favourable microenvironment. Some of these prerequisites are provided in the brains of people with MS, especially when abnormal aggregates of B cells are present in leptomeningeal and perivascular brain compartments. Such aggregates are frequently found in the brains of people with MS. They can contain EBNA1, and provide a suitable milieu for B-cell differentiation during the maturation process that generates antibody-producing cells[7]. EBNA1-reactive helper T cells have also been described in MS, and some of these crossreact with peptides of myelin; this substance, which wraps around parts of neurons, is the main target of the autoimmune attack in MS[8].

The antibody with observed crossreactivity of EBNA1 and GlialCAM is a tantalizing discovery. GlialCAM is expressed mostly in a type of glial cell called an astrocyte, which, among other functions, controls the balance of water and electrolyte molecules in the brain. Mutations that generate a dysfunctional version of GlialCAM cause a rare human brain disorder called megalencephalic leukoencephalopathy[9]. Are these double-reactive antibodies responsible for disease? Lanz and colleagues report that the patterns seen when this dual-purpose antibody binds to samples of mouse brain sections, and to permeabilized glial cells grown *in vitro* are reminiscent of those observed when antibodies bind to the protein aquaporin-4; this protein is the target of disease-causing antibodies in a condition called neuromyelitis optica spectrum disorder[10], which is associated with autoimmune destruction in the brain.

The authors report that exposing mice to EBNA1 peptides, an intervention that could boost production of EBNA1-targeting antibodies, aggravates the condition of animals used as a mouse model for aspects of MS. However, it is worth remembering that the antigens possibly recognized by most antibodies are intracellular. They would therefore be inaccessible to antibodies, which bind directly to the antigen that they recognize when it is an integral part of a protein, but not to antigens presented on the cell surface bound to major histocompatibility complex receptors. The crossreactive antibody

identified by Lanz *et al.* recognizes intracellular targets — EBNA1 is a transcription factor, and the intracellular portion of GlialCAM contains the antibody-binding region.

As was impressively corroborated by an epidemiological study[3] reported this year, infection by Epstein–Barr virus is tightly associated with the development of MS, and, indeed, such infection can be considered as a risk factor[11]. Should we now see MS as an autoantibody-driven autoimmune disease with EBNA1/GlialCAM antibody crossreactivity as a general mechanism triggering the disease? A definitive answer to this question would be premature at present.

Instead, we need to await the outcome of studies that examine more people, from a diverse range of ethnicities. Regarding the highlighted crossreactive antibodies, critics might point to the relatively small numbers of individuals studied, which could mean that this result is not applicable to a wide population of people with MS. Also worth mentioning is that the individuals studied were selected on the basis of the high numbers of immune cells found in their CSF, and this might have introduced a bias towards people with a particular subset of MS.

There is generally scant direct evidence of autoantibodies causing tissue destruction in MS. For many people with the disease, treatment to deplete B cells is highly effective, although it seems to have almost no effect on CSF OCBs or peripheral blood immunoglobulin[12]. However, there are subgroups of people with MS who have antibodies that bind to decaying brain cells, and who respond to the elimination of plasma (auto-)antibodies by a method known as plasmapheresis[13]. Even if the crossreactive antibodies identified by Lanz and colleagues are not a universal marker of MS, they might turn out to be useful as markers of a particular subtype of MS.

Despite these limitations, the new study provides a concrete, striking example of how a B cell that initially provides a defensive function by recognizing a viral antigen might acquire potentially dangerous self-reactivity. Beyond MS, this mechanism might be relevant to other viruses and autoimmune diseases. Will the present work pave the way to antiviral vaccination approaches as a means of protecting against MS? This would be the sort of advance hoped for by numerous people who either have the disease or are at high risk of developing it. The jury is out.

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Photonics

Light measures up on a chip the size of a fingertip

H. Y. Fu & Qian Li

An optical device enables high-speed, high-resolution distance measurements to be made over a large field of view. Clever switching gives the integrated design a tiny footprint and keeps its power consumption low. **See p.253**

Our eyes use 3D information to sense our surroundings, but few imaging systems are capable of emulating this feat. Light detection and ranging (lidar) systems are an exception: they use 3D imaging to measure targets over long distances with high precision, and for this reason, they have been widely applied in technologies ranging from autonomous driving to complex cartography[1]. The next challenges for lidar methods are miniaturization and integration into a single chip. But these advances can come at the cost of a limited field of view and low resolution. On page 253, Zhang *et al.*[2] report an integrated lidar system that offers an exceptional field of view and high resolution in a compact, low-power device.

Light waves have a similar role in lidar to that of radio waves in radar: a lidar sensor sends out and receives information encoded in light pulses, and the system uses this information to make a map of its surroundings. To capture 3D information in this map, a laser beam must be steered around the space, and this is typically achieved using mechanical beam scanners with moving parts. However, these methods can be unstable, slow, bulky and expensive. Over the past decade, mechanical beam scanners have begun to be replaced by non-mechanical scanners with fast steering speeds and improved stability[3,4]. The optical-phased array and the focal-plane switch array are two such devices.

An optical-phased array works by controlling the optical properties of the light waves emitted by antennas in an array — specifically, their relative phase, which is the degree to which the waves are in step with each other. To achieve high performance, the antennas must be large, and closely spaced on a single chip. However, controlling the phase of a large number of elements is challenging when they are tightly packed, and the power consumption is high, which makes integration difficult. This means that 2D optical-phased arrays are limited to a 46° field of view in one direction and 36° in the other[5], although some 2D optical-phased arrays with high resolution and large fields of view have also been demonstrated[6].

By contrast, a focal-plane switch array maps each angle in the field of view to a pixel in the focal plane of a lens, which then performs imaging like a camera. Instead of controlling the phase of each pixel, a focal-plane switch array uses switches to turn each pixel on and off. The optical antenna corresponding to each pixel is independent of the other antennas, making it possible to integrate a large array on a single chip. Nevertheless, focal-plane switch arrays can still require high power consumption and a large footprint because of the size of the switches and the energy needed to tune them[7].

For all of these reasons, integrating a large-scale focal-plane switch array into a single chip is a challenging task, yet Zhang *et al.* succeeded in fitting an antenna array corresponding to 128 × 128 pixels on a chip the size of a fingertip, just 10 × 11 millimetres. With a large-aperture lens, this means that their device can aim a laser beam in 16,384 distinct directions in a field of view of 70° by switching the beam to different antennas.

The team's chip achieves this remarkable performance with the help of microelectromechanical silicon photonic switches that control the optical antennas. The elaborate design of these switches is key,