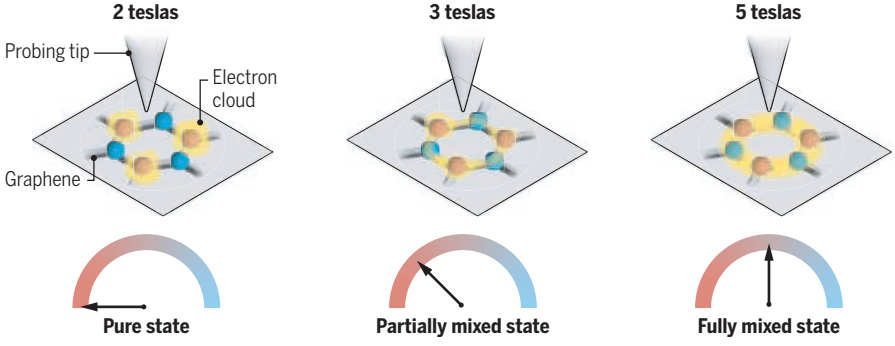
Liu *et al.* used scanning tunneling microscopy to determine the valley labels of the electrons. The percentage of the valley superposition is directly visible as the relative occupation of the two types of atoms in the mapped electron density (see the figure). The authors tracked this percentage and the phase factor of the superposition, when increasing the magnetic field, and observed that the percentage changes continuously from a 100% K valley occupation to a 50/50 mixed superposition state of K and K'. Moreover, the magnetic field where the transition between these two types of valley ferromagnets takes place depends on the substrate on which the graphene is deposited. The reason is the substrate's different influence on the two types of carbon sites in graphene.

Besides revealing unprecedented details of the change in electron arrangement when changing the magnetic field, Liu *et al.* probed the electron system around positions where more electrons are located than on average. It has long been conjectured that such areas are surrounded by a well-defined distribution of the percentage and of the quantum-mechanical phase factor of the valley label (*6*, *7*, *8*). On each circle around the charge center, percentage and phase factor change in a way that eventually leads to a new particle—the charged skyrmion (*6*), which is a localized structure made of many interacting electrons. Although there have been indirect experimental observations for charged skyrmions (*9*), they have never been observed in real space. Liu *et al.* mapped out the percentage and phase factor of the valley label and found the whirlpool-type texture around a charged position. The valley skyrmion has a size of 7 nm and shows excellent agreement with model calculations (*7*, *8*). As particles, such skyrmions are robust, although they are made of a complex distribution of the constituting electrons. The emergence of such new particles from the ensemble of electrons is a central beauty of many-particle electron systems.

The experiments by Liu *et al.* mark a milestone for probing real-space patterns of electron arrangements occurring as a result of strong interactions. This can be extended by mapping the spin degree of freedom using spin-polarized scanning tunneling microscopy (*10*). Hence, details of all four degrees of freedom in the ground state arrangement could be disclosed as crucial to decipher other ground states where the spin labels also exhibit a superposition (*11*). Moreover, the authors found well-known indications of even more-complex electron arrangements in their experiments. In these arrangements, some of the emergent particles carry only one-third of the charge of a single electron (*12*). Using the approach of Liu *et al.*, one could begin to tackle the mysteries of these and many other emergent particles by direct imaging (*13*). ■

How electrons rearrange themselves in graphene

The tip of a scanning tunneling microscope maps the electron distribution (shown as a yellow haze) on the two different types of carbon sites (shown as red and blue balls) at different magnetic fields. The distribution changes continuously from being only on the red sites to being equally distributed on both types of sites, marking a quantum-mechanical transition of the electron arrangement.



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DISEASE

Epstein-Barr virus and multiple sclerosis

Infection with Epstein-Barr virus is the trigger for the development of multiple sclerosis

By **William H. Robinson**[1,2] *and* **Lawrence Steinman**[3]

Infection with the Epstein-Barr virus (EBV) has long been postulated to trigger multiple sclerosis (MS) (*1*). Prior analyses demonstrated increased serum antibodies to EBV in ~99.5% of MS patients compared with ~94% of healthy individuals (*2*). On page 296 of this issue, Bjornevik *et al.* (*3*) analyzed EBV antibodies in serum from 801 individuals who developed MS among a cohort of >10 million people active in the US military over a 20-year period (1993–2013). Thirty-five of the 801 MS cases were initially EBV seronegative, and 34 became infected with EBV before the onset of MS. EBV seropositivity was nearly ubiquitous at the time of MS development, with only one of 801 MS cases being EBV seronegative at the time of MS onset. These findings provide compelling data that implicate EBV as the trigger for the development of MS.

How does a virus with tropism for B cells develop into a disease of the central nervous system (CNS)? In MS, there is an inflammatory attack against the myelin sheath and the axons that it insulates. Ultimately, neurons themselves are injured. In MS, B cells and their activated progeny, plasmablasts, express integrin α4, which has adhesive properties that allow these antibody-producing cells to move from the bone marrow to the peripheral circulation and then across the blood-brain barrier (BBB), where they take residence inside the brain and its internal lining (*4*). A distinct feature of MS is the synthesis of

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immunoglobulins by clonal expansions of plasmablasts within the brain. When these immunoglobulins, found in cerebrospinal fluid (CSF) from patients with MS, are applied to an electrophoretic gel, they form bands of restricted mobility, called oligoclonal immunoglobulin bands, representing clonal expansions of plasmablasts. These antibodies target myelin-producing glial cells, thereby damaging them (*4*).

Multiple studies have identified EBV-infected B cells in the brains of MS patients (*5*, *6*). Understanding how infection of B cells with EBV initiates the pathology seen in MS is now ripe for a deeper understanding of the roles of these clonally expanded B cells and plasmablasts. Depletion of B cells with monoclonal antibodies targeting CD20 has emerged as one of the most efficacious therapies for MS (*7*). However, because of the BBB, CD20 monoclonal antibody therapies do not reach the CNS in sufficient amounts, and moreover, antibodies to CD20 do not deplete their progeny, antibody-producing plasmablasts and plasma cells, which lack CD20.

The mechanism (or mechanisms) of EBV-mediated MS development remains elusive. Possibilities include molecular mimicry, through which EBV viral protein sequences mimic human myelin proteins and other CNS proteins and thereby induce autoimmunity against myelin and CNS antigens (*8*). EBV transformation of B cells could also lead to clonal expansion of pathogenic plasmablasts. EBV may transform B cells through disruption of several pathways: EBV latent membrane protein 2A (LMP2A) mimics B cell receptor (BCR) signaling. LMP1 mimics CD40 receptor signaling, a costimulatory pathway that is important for B cell–T cell interaction. Additionally, EBV encodes an interleukin-10–like protein, which activates B cells (*9*). EBV might also mediate bystander damage to the axon and its surrounding sheath, or defective clearance of infected B cells. $CD8^+$ T cells specific for EBV lytic proteins are present in MS brain lesions, and a persistent EBV infection in the CNS might stimulate $CD8^+$ T cell responses that mediate CNS injury (*4*–*8*) (see the figure).

There are multiple reports suggesting that molecular mimicry might induce MS. Serum antibodies from MS patients to the EBV small capsid protein BFRF3 cross-react with the cytoplasmic protein septin-9 and are associated with demyelination (*10*). Another study showed serum antibodies from MS patients are cross-reactive between amino acids 411–440 of the viral protein EBV nuclear antigen 1 (EBNA-1) and the human chloride-channel protein, anoctamin 2 (ANO2), which is associated with electrical conduction in axons (*11*). MS serum antibodies targeting EBNA-1 residues 411–426 that cross-react with myelin basic protein have also been identified (*12*). Clonally expanded antibodies in the CSF of MS patients targeting EBNA-1 residues 386–405 that cross-react with the CNS cell adhesion molecule, glialCAM, have also been described (*4*). It is intriguing that three contiguous regions of mimicry have been reported in a small region of the EBNA-1 protein; this may arise through immune surveillance in a process called epitope spreading.

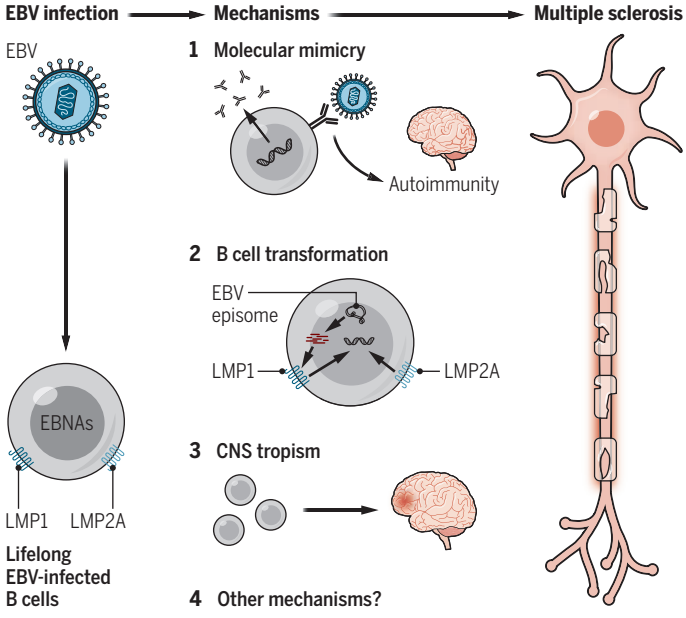
Increased incidence of EBV infection is associated with other autoimmune diseases, including systemic lupus erythematosus (SLE). Serologic reactivation of EBV (production of EBV serum antibodies after resolution of acute infection) is associated with transition to clinical SLE. EBNA-1, through amino acid regions distinct from those implicated in MS, has been shown to mediate molecular mimicry of nuclear antigens associated with SLE pathogenesis (*13*, *14*). Mice engineered to express a CD40-LMP1 fusion protein exhibited increased EBNA-1–mediated molecular mimicry and lupus-like clinical features (*15*). Whether EBV infection activates other inflammatory mechanisms common to MS and other autoimmune diseases, including SLE, is under investigation.

Nearly everyone is infected with EBV, but only a small fraction develop MS. Thus, other factors, such as genetic susceptibility, are important in MS pathogenesis. Certain genes, such as those encoding the antigen-presenting human leukocyte antigen (HLA) proteins, determine the portion of a protein that is presented to the immune system. Other genes control modifications in EBV-associated proteins, including phosphorylation. Such genes are critical for modulating molecular mimicry (*4*, *11*). Thus, given these additional gating factors in MS pathogenesis, infection with EBV is likely to be necessary, but not sufficient, to trigger development of MS. Infection with EBV is the initial pathogenic step in MS, but additional fuses must be ignited for the full pathophysiology.

There may be new opportunities for therapy: Would a vaccine against EBV protect against MS? Can the B cells that dwell in the CSF be killed or inactivated with therapeutics? Would antivirals that target EBV provide effective therapy, especially when given early in the course of disease? Now that the initial trigger for MS has been identified, perhaps MS could be eradicated. ■

Model for multiple sclerosis development

In at-risk individuals, Epstein-Barr virus (EBV) infection of B cells promotes the development of multiple sclerosis through several possible mechanisms. These include molecular mimicry (**1**) by EBV nuclear antigen 1 (EBNA-1), B cell transformation (**2**) through latent membrane protein 1 (LMP1) and LMP2A, induction of B cell trafficking (**3**) to the central nervous system (CNS), and/or other unknown mechanisms (**4**).



GRAPHIC: A. MASTIN/*SCIENCE*

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