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Cytomegalovirus: a culprit or protector in multiple sclerosis?

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Multiple sclerosis (MS) is a chronic disabling autoimmune disease of the central nervous system (CNS). Cytomegalovirus (CMV), a β herpes virus, may have a detrimental or beneficial role in MS pathology. Accumulating evidence indicates that CMV contributes to MS disease via interplay of different mechanisms such as molecular mimicry, bystander activation, and epitope spreading. The activation and expansion of a specific T cell subset, $CD4^+CD28^{null}$ T cells, via CMV infection could also contribute to MS pathology. Various additional observations also indicate a protective effect of CMV on autoimmune diseases. CMV immune evasion may mitigate the autoimmune reactions and proinflammatory milieu that contribute to MS.

Hurdles in CMV and MS research

In this article we focus on cytomegalovirus (CMV), a member of the β herpes family that establishes lifelong latent infections in ≥70% of the human population [1]. CMV infection was considered 'innocent' in immunocompetent persons, but evidence is now emerging about the large impact of CMV infection on the aging immune system. In addition, the possible involvement of CMV in a wide range of diseases is now being recognized, including in autoimmune diseases such as multiple sclerosis (MS).

MS is a chronic disabling autoimmune disease of the CNS (Box 1). Autoreactive immune cells attack the CNS myelin, leading to demyelination, axonal injury, and ultimately neural cell loss. A wide range of symptoms can occur, including fatigue, muscle weakness, and visual difficulties. MS is often preceded by clinically isolated syndrome (CIS), where patients experience a first episode of neurologic symptoms, such as optic neuritis, without a second event. Another disease, namely acute disseminated encephalomyelitis (ADEM), is clinically and pathologically similar to MS, and often manifests after an infection [2].

The role of CMV in MS disease is disputed. Our own research, together with that of others, supports a detrimental role of CMV, where the virus contributes to MS pathology, whereas others believe that CMV is disease-limiting. We discuss here viral mechanisms that are suggestive for promotion of autoimmunity and we summarize evidence arguing in favor of and against CMV involvement in MS etiology and progression.

Possible mechanisms of viral contribution to autoimmune disease

There are several different mechanisms by which viruses such as CMV could drive autoreactive T cell activation and thus lead to autoimmune disease (Figure 1). Two hypotheses rely on the fact that potentially autoreactive T cells are already present in low numbers in each individual. These cells seem to escape negative selection in the thymus during normal T cell development (see Glossary) [3,4].

Glossary

Brain atrophy: decreased brain volume. In MS this is due to the loss of neurons and axons.
Cryptic epitopes: self-epitopes that are not easily accessible to the immune system. T cells specific for these cryptic epitopes are present because they are not deleted in the thymus by negative selection, and might become activated in the periphery if these epitopes are made available via systemic release.
Heterologous immunity: established immunity to previously encountered viruses can alter responses to unrelated pathogens, thereby impacting upon the course and outcome of this new infection. Heterologous immunity may be beneficial by boosting protective responses, but can also result in severe immunopathology.
Immunosenescence: age-dependent decrease in immunological competence, due to the ongoing deterioration of innate and adaptive immune responses.
Inbred/SPF laboratory mouse strains: inbred strains are created by inbreeding (brother × sister mating) to achieve genetic homozygosity. Specific pathogen-free (SPF) animals are, as their name implies, not contaminated with specific pathogens (in contrast to conventional animals) because they are maintained in facilities that incorporate barriers to prevent contamination.
Mitogen or superantigen: microbial proteins (from e.g., viruses, bacteria) that strongly stimulate immune cells without prior antigen processing. They elicit massive T cell activation and release of numerous cytokines, resulting in systemic shock (e.g., toxic shock syndrome). By activating autoreactive T cells, superantigens could contribute to autoimmunity.
Negative selection of T cells: in the thymus, this process deletes T cells that bind strongly with self-peptides, by inducing apoptosis. Thus, negative selection prevents the formation of mature self-reactive T cells that are capable of inducing autoimmunity. Even so, not all autoreactive T cells are removed. Those T cells with weak binding capacities can bypass the selection process and are present in the periphery of each individual. Upon activation (e.g., during infection), these cells could cause an autoimmune reaction.
Oligoclonal expansion: expansion of a limited number of T cell clones, thus strongly skewing the T cell receptor (TCR) and T cell repertoire.
White and gray matter lesions: lesions most frequently occur in the white matter, including areas within the spinal cord, the brainstem, the periventricular white matter of the cerebrum, and the optic nerves. However, lesions also arise within the cortex (gray matter). Differences between white- and gray-matter lesions are the amount of inflammation and disruption of the cytoarchitecture, which occur to a far lesser extent in gray-matter lesions. Nevertheless, neuronal and axonal pathology also arise in these gray-matter lesions.

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Box 1. Disease course and types of MS

Patients often present to the clinic with a first episode of neurologic symptoms, and are diagnosed with clinically isolated syndrome (CIS) until a second event occurs. After this second event, the McDonald criteria are fulfilled and the diagnosis is changed to clinically definite MS. With this second event we imply either a second clinical attack or secondary lesions that are disseminated in time and space, established via MRI.

The majority of MS patients (85%) develop RRMS disease with a duration ranging from several years to decades. In most patients, the episodes of recovery (remissions) gradually become less frequent and finally disappear completely, while their symptoms become more pronounced and their disability worsens. At this stage the disease converts to the secondary progressive (SP) phase.

In a minority of patients (10%), those with primary progressive MS (PPMS), the disease is progressive from onset.

A relatively rare (5%) form of MS, progressive relapsing MS, consists of steadily worsening of the disease, but also comprises relapses. In some cases there is no recovery, although in other cases there is. Thus the periods between relapses involve continuing progression of the disease instead of remission as in RRMS.

The lesions in RRMS are usually located in the white matter around ventricles and blood vessels, and are characterized by sharply edged focal areas of inflammation with a variable degree of demyelination, remyelination, and axonal injury. Lesions in progressive MS are also found in the gray matter and are characterized by intensive demyelination with little inflammation but pronounced degeneration of oligodendrocytes and neurons.

One hypothesis suggests the direct triggering of autoreactive T cells by infectious pathogens which express antigenic epitopes that structurally resemble epitopes of self-antigens [5]. A well-known example of this molecular mimicry is the T cell crossreaction between the MS related autoantigen myelin basic protein and Epstein–Barr virus (EBV) [6]. A second hypothesis, proposed by 't Hart *et al.*, is a variation of the molecular mimicry paradigm, namely a 'delayed molecular mimicry' model in which latent chronic infections create a repertoire of long-living virus-specific memory T cells. These cells can be reactivated at any moment in time when they encounter molecular mimicry motifs present in self-antigens that are shed from injured tissues [7]. Another hypothesis entails bystander activation, and comprises a variety of antigen-nonspecific theories. First, cytokines produced by virus-specific immune cells could lead to the accidental activation of autoreactive T cells. Second, host cell destruction by viral infection leads to the release of cryptic epitopes, including self-antigens that normally are not accessible to the immune system. Finally, a mitogen or superantigen, released from the infectious pathogen, could lead to polyclonal lymphocyte activation [3,8]. Thus, the inflammatory setting of a viral infection could elicit the activation and clonal expansion of autoreactive T cells, resulting in autoimmune disease [9]. McCoy *et al.* suggest a combination of both aforementioned hypotheses: viral epitopes crossreact with self-antigens (molecular mimicry) to prime genetically susceptible individuals. After this priming a non-specific immunologic challenge, leading to cytokine production (bystander effect), could provoke autoimmunity [10].

Another process closely linked to molecular mimicry and bystander activation is epitope spreading. After the initial reaction to a pathogen, antigens released from 'primary lesions' in the target tissue will prime an expanding range of potentially autoreactive T cells as a consequence of T cell receptor (TCR) diversity [11,12]. This cascade of self-recognition events provides a continuous inflammatory state that leads to chronic autoimmunity [13]. Delogu *et al.* suggest that the three processes are linked, thus adding epitope spreading to the McCoy *et al.* hypothesis. Molecular mimicry would occur early in the development of autoimmunity, whereas bystander activation and epitope spreading occur later on, exacerbating the autoimmune responses [9].

The hypotheses of 't Hart *et al.* and McCoy *et al.* also comply with the so-called 'fertile field' concept described by Fujinami *et al.* [14]. The fertile field concept states that exposure to a potential immunogen is normally without consequence, but that under particular circumstances (e.g., viral infection) the immunological environment changes, leading to a dysregulated immune reaction. Thus the viral infection would create a fertile field in which immune responses to antigens could develop. Primed autoreactive T cells (by viral infections) also create a fertile field because later events might trigger the expansion and activation of these cells leading to autoimmune disease.

Evidence in favor for the involvement of CMV in MS disease

The interaction of environmental and genetic factors is thought to play a dominant role in the etiology of MS. It is envisaged that some environmental factors (e.g., viruses) are potential triggers of the disease, while others (e.g., vitamin D or smoking) may also influence the disease course. Several observations support a viral trigger for MS or ADEM. Many viruses are associated with encephalomyelitis, axonal damage, and other demyelinating processes [15,16].

Animal models

Most animal models used in translational MS research are based on inbred/SPF (specific pathogen free) laboratory strains of mice and rats. A minority of the research is based on non-human primates, man's closest kin in nature.

Rodents. In several mouse models, viral infection elicits an MS-like disease. Examples include Theiler's murine encephalomyelitis virus (TMEV), mouse hepatitis virus (MHV), Semliki Forest virus (SFV), and canine distemper virus (CDV) (Box 2). These models provide compelling evidence for a possible viral cause, or at least as part of the multifactorial and complex etiology of MS [7,17].

One of the most convincing mechanisms via which CMV could play a role in MS is molecular mimicry. Crossreactivity between $hCMV_{981–1003}$ and myelin oligodendrocyte glycoprotein (MOG) residues 35–55 ($MOG_{35–55}$) in Lewis rats was found [18]. Furthermore, sensitization of the rats against $MOG_{35–55}$ triggered $CMV_{981–1003}$-specific lymphocytes, leading to clonal expansion and migration towards the spleen. This study provides further evidence of the 'delayed molecular mimicry' theory.

In another animal model, SJL/J mice were primed with vaccinia virus encoding proteolipid protein and were subsequently challenged with murine CMV (mCMV) [14]. These mice developed white-matter lesions and had impaired