Commentry

Pathogenesis of Multiple Sclerosis: How Much Space is Left for Autoimmunity?

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Abstract

Multiple Sclerosis (MS) is generally considered an autoimmune disease, mainly because the preferred and well-studied animal models for the disease are autoimmune models. In human disease, however, evidence for autoimmunity in MS has been sought for a long time with marginal results. On the other hand, two viruses, EBV and HHV-6A, play an etio-pathogenic role and, as recently discussed, their mutual interaction might be a key element in the pathogenesis of MS. This short review summarizes evidence that supports this view of changing the paradigm about the etio-pathogenesis of MS from autoimmunity to viral.

Introduction

Hohlfeld and Steinmann [1] recently reviewed the history of a very useful animal model of autoimmune T-Cell transfer that significantly contributed as the basis of thinking about pathogenic mechanisms in Multiple Sclerosis (MS) for many years. They conclude with:

"Ever since autoimmunity was considered to play a decisive role in the pathogenesis of MS, the search for the responsible antigens was one of the main domains in MS research and still is. Nevertheless, in contrast to the situation in experimental models of the disease, where there has emerged a gradually increasing wealth of information about the nature of antigens involved, we still are virtually ignorant about antigens in MS" [1]. Where are we today?

In a recent article, the author has formulated a hypothesis claiming that the interaction of two well-studied viruses, i.e., HHV-6A and EBV, is crucial to the pathogenesis of MS [2]. The basic tenet is that HHV-6A infection in the CNS of genetically susceptible individuals leads to transformation of latently EBV-infected B-cells in the CNS leading to the well-known production of oligoclonal immunoglobulins and free kappa light chains on one side and to T-cell responses to the transformed B-cells on the other side. But again, the question remains whether autoimmunity could secondarily be created by this inflammatory process.

Experimental Evidence for Autoimmunity

Autoimmunity has been studied in many experimental animal models and T-cells have been found to play a central role in the pathogenesis of these experimental diseases [3]. Particularly, T-cells that are specific for auto-antigens of the CNS, like myelin basic protein (MBP) or auto-antigens of the PNS, like myelin protein P2, can be grown *in vitro* as T-cell lines and are able to elicit an inflammatory pathology when injected into naive animals resulting in overt clinical paralysis [1,4,5]. However, T-cells alone are not sufficient for establishing the full pathological picture resembling human disease and injection of autoantibodies to galactocerebroside or a myelin oligodendroglial glycoprotein (MOG) might in addition be necessary in a synergistic pathogenic mechanism [6,7]. In any case, however, autoimmunity is deliberately induced in these models by using auto-antigens as immunizing agents. Spontaneous development of autoimmunity [8] or autoimmunity as a corollary of viral infection is more difficult to study in experimental models. One proposed mechanism is epitope spreading after tissue damage leading to autoimmunity [9,10], other mechanisms are molecular mimicry and bystander activation [11-13]. Nevertheless, valuable pathogenic autoimmune mechanisms can be studied in these models. However, despite of the autoimmune nature of these experimental animal models, the question stays unanswered: How much autoimmunity is involved in MS? Or more bluntly, is MS an autoimmune disease? [14].

Evidence for Autoimmunity in MS?

Antibodies

If autoantibodies exist as pathogenic items in the CNS of MS patients, they should be found in the cerebrospinal fluid (CSF) of the patients. However, the search for such MS-specific autoantibodies has so far not yielded conclusive results [15]. Recently, two new candidates for MS-specific antibodies have been reported: KIR4.1 antibodies in the serum and RBPJ antibodies in the CSF. KIR4.1 (KCNJ10) is a potassium channel subunit expressed by astrocytes. It has recently been described as a target of the autoantibody response in a subgroup of persons with multiple sclerosis [16]. However, the specificity for MS is debated [17], but it could be a marker of inflammatory disease activity [18]. RBPJ is a ubiquitous protein of the Notch signaling pathway that plays an important role in Epstein-Barr virus infection. It has recently been described as a MS auto-antigen candidate that is recognized by CSF-derived immunoglobulin G in a subset of patients with MS [19].

A newer study examined recombinant human immunoglobulin from a series of expanded B cell clones that have been isolated from the CNS tissue of six MS brains. Using multiple methodologies none of the detected antigen specificities were unique to MS [20]. One explanation for these findings would be that such specificities are random as one would expect from EBV-transformed and immortalized B-cells [21].

T-cells

Autoantigen-specific T-cells are present in patients with autoimmune disease but also in healthy subjects. Similarly, myelin-specific T-cells are found in MS as well as in controls [22]. They belong to both subtypes, CD4+ and CD8+ [23]. Their fine-specificity is not always established but might be important to their functional role [24]. Particularly, the involvement of different MHC molecules for peptide recognition could be crucial. Therefore, it is difficult to establish the role of auto-reactive T-cells that may range from pathogenic to protective [25].

Auto-reactive T-cells can be stimulated specifically by auto-antigens or non-specifically by superantigens. Superantigens are microbial antigens that have the ability to stimulate large numbers of T-cells of certain T-cell receptor families in a manner that is class II major histocompatibility complex (MHC) unrestricted. Superantigens may play a role during viral infections of the CNS. Both, HHV-6A and EBV induce expression of the human endogenous retrovirus HERV-K18-encoded superantigen [26,27]. The HERV-K18.3 env genotype is a known potential risk factor for MS [28]. Interestingly, the HERV-K18-encoded super antigen stimulates T-cells carrying receptors of the Vβ13 family [27] in which also T-cell clones with specificity for an immunodominant peptide of MBP have been found in MS patients [29]. This example demonstrates how a viral infection might lead to or enhance an autoimmune reaction.

Diseases of the CNS with Evidence for Autoimmunity

In contrast to the marginal evidence for autoimmunity in MS, an increasing number of CNS diseases are discovered where autoimmune pathogenesis is more evident [30-32]. Basically, two types of autoantibodies are involved, those against cell surface antigens [33] and those against intracellular antigens. In the latter case, a T-cell mediated pathogenicity is postulated [34]. Both types of encephalitides can be paraneoplastic or non-paraneoplastic.

A special case of CNS autoimmunity is Neuromyelitis Optica (NMO) where autoantibodies against aquaporin 4 [35] play an important diagnostic [36] and pathogenic role. Also aquaporin 4-specific T-cells are probably involved in the development of the astrocyte-destructive lesions [37]. The aquaporin 4-IgG-mediated damage to astrocytes might secondarily also lead to demyelination [38]. So, CNS autoimmunity is basically not difficult to detect.

So, How is Demyelination Caused in MS? A Role for HHV-6A?

Evidence for infectious agents leading to myelin destruction goes back many years. Mice with naturally occurring or experimentally induced Theiler's virus infection leading to demyelination were the first models of MS [39-42]. In humans, it has been found that in CNS lesions of patients with AIDS, demyelination is closely related to active HHV-6 infection [43], similar to demyelinative lesions of progressive multifocal leukoencephalopathy [44] and HHV-6-associated demyelination has even been found in an immunocompetent adult [45]. A central role in such demyelinating processes seems to be attributable to astrocytes but also remyelination depends on astrocytic functionality [46,47]. Since HHV-6A infects astrocytes [48], it may well disturb their functional relation to myelination. Furthermore, HHV-6A infection of glial precursor cells disrupts their properties that probably are crucial for remyelination [49]. So, autoantibodies to myelin antigens, as they have been unsuccessfully sought for a long time in MS patients, probably are not needed for demylination.

Conclusion

Experimental Autoimmune Encephalomyelitis is an elegant animal model of Multiple Sclerosis that closely resembles the human disease MS in many pathological features. Even autoimmune encephalitis in humans that rarely occurred after active sensitization with brain tissue or brain cells during rabies vaccination show a pathology that closely but not completely resembles the pathology in MS [50]. Based on these findings MS is considered an autoimmune disease. However, when looking for autoimmune phenomena in clinical MS, the results so far are disappointing [51]. This in contrast to autoimmune encephalitides where autoantibodies are readily found and successfully used in diagnostics.

Therefore, a change of paradigm is timely. According to evidence reviewed by the author [2] about the combined pathogenic role of HHV-6A and EBV in MS and the lack of autoimmune phenomena specific for the disease as discussed above, it is suggested that MS is considered an infectious disease caused by two interacting herpes viruses, HHV-6A and EBV, in genetically susceptible individuals and not an autoimmune disease.

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