Review

Mechanistic biology linking traumatic brain injury to multiple sclerosis susceptibility

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ABSTRACT

Multiple sclerosis (MS) is a major, immune-mediated, demyelinating disease and the major cause of non-traumatic disability in young adults. Susceptibility to disease is controlled by a variety of interacting features that include genetic and notably environmental factors. One of these risk factors appears to be the occurrence of traumatic brain injury. In a follow-on to previous analysis of head injury-induced risk factors for MS, analysis of Swedish Registry data of MS and matched controls demonstrates enhanced susceptibility to MS, notably when stratified for the presence of HLA-DRB1*15.01, absence of HLA-A*02.01 and occurrence of smoking, which are known risk factors, the risk of MS increases to OR 65.4 (95% CI 8.35 to 512). This can be mechanistically supported by a number of routes whereby brain injury can lead to expression of autoantigenic targets, or damage-related release of neuroantigens that could generate a novel autoantigenic response in draining lymph nodes following glymphatic/meningeal lymphatic drainage. These may be different from other mechanisms that are relevant to susceptibility due to human leucocyte antigen expression and smoking.

RISK OF MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a major, immune-mediated demyelinating disease and the major cause of non-traumatic disability in young adults affecting about 3 million people worldwide.[1] Susceptibility to MS is controlled by a variety of interacting features that include genetic and notably environmental factors as seen by the elevated but relatively low frequency of disease concordance in monozygotic twins compared with the general population.[1 2] However, it is evident there are inheritable factors controlling MS and there are elevated risks for people with family members who have the disease.[1 3] Indeed, it is clear that MS is polygenic and over 230 genetic variants associated with susceptibility to MS have been identified, none of which, however, appear to be absolutely necessary for disease development.[4] Most are related to immune function and each variant carries a small increased risk, with sex genes and *HLA-DR B1*15.01* (associated with increased risk) and *HLA-A*0201* (associated with decreased risk) variants exhibiting the strongest associations.[4 5] The *HLA-DRB1*15:01* risk gene variant is common in northern Europeans, due to ancestry, where the frequency of MS is relatively high[6] and is associated with increased viral load following Epstein-Barr virus (EBV) infection which is another risk factor for MS.[7 8] Again, while being increasingly viewed as a causal factor of MS, this common infection is associated with other autoimmunities.[7 9] The EBV-associated risk is not only associated with infection, but time of infection, typically later in European and Western societies, and the presence of mononucleosis.[9–11] In addition, there is evidence that potentially ultraviolet light sun exposure and dietary and sunlight-induced vitamin D levels can influence susceptibility, possibly during gestation and the geographical distribution of MS to be present in areas further from the equator.[12 13] The importance of environmental elements is further supported by the increasing occurrence of MS in second-generation immigrants to MS-endemic geographical regions.[14] Genetics and geography are more difficult elements to control risk in MS or other autoimmunities however, some risk factors that affect MS are modifiable, with variable degrees of supportive evidence including: diet; childhood obesity and body mass index, organic solvent exposure and smoking tobacco.[15–20] These risk features also include head trauma.[21 22]

HEAD TRAUMA AND THE RISK OF MS

Traumatic brain injury (TBI) results from the alteration of normal brain function caused by an external force. TBI is a common condition affecting about 69 million (95% CI 64 to 74×10^6) people each year and is frequently caused by road traffic accidents.[23 24] Moderate to severe TBI is associated with loss of consciousness from several minutes to many hours but many people experience mild TBI such as concussion following blows to the head.[25] It is of interest that TBI has been associated as a risk factor for a number of degenerative, neurological conditions which indicates the risk of the development of any neurological illness such as Alzheimer's disease, Parkinson's disease and other types of dementia subsequent to mild TBI was 1.67 (95% CI 1.44 to 1.93, p<0.0001), including both neurological (OR 1.55, 95% CI 1.31 to 1.83, p<0.0001) and psychiatric (OR 2.00, 95% CI 1.50 to 2.66, p<0.0001) outcomes.[26] This may increase in amyotrophic lateral sclerosis (OR 3.1, 95% CI 1.2 to 8.1) also.[27] Likewise, there is supportive data to suggest that previous TBI is a risk factor for MS[21] and Guillain-Barre syndrome.[28] Meta-analysis of high-quality case–control studies suggests there are statistically significant associations between sustaining head trauma in childhood (OR 1.27, 95% CI 1.12 to 1.44, p<0.001) and adulthood (>20 years) head trauma (OR 1.40, 95% CI 1.08 to 1.81, p=0.01) and the risk of being diagnosed

with MS.[22] In adult studies, about half of the cases (n=10/21) indicated an elevated risk with an OR over 2, and some had marked upper limits of the OR.[22] This view has continued to be underpinned by subsequent studies in adolescents (11–20 years old), that demonstrated increased MS risk (HR=1.29, p=0.03), notably in males (HR=1.41, p=0.04).[29] This risk was increased further by multiple trauma (OR 2.33, 95% CI 1.35 to 4.04, p=0.002) compared with single events (OR 1.22 (95% CI 1.05 to 1.42, p=0.008)) including later diagnosis.[30 31] However, this association has not been universally confirmed[32–34] and may depend on the perceived quality of the studies.[21] The risks of this could be influenced by the presence of comorbidities, such as thyroid disease and type 2 diabetes, and the genetics of susceptible individuals.[31 35] As such, in a recent study showing increased risk of subsequently people developing MS (OR 1.34, 95% CI 1.17 to 1.53), if people were stratified to both the expression of *HLA-DRB1*1501* and absence of *HLA-A*0201* rendered an 18-fold increased risk of MS, compared with those with neither the genetic risk factors nor a history of head trauma (OR 17.7, 95% CI 7.13 to 44.1).[31] As such, it was considered to be of interest to determine whether further stratification for the presence of other risk factors, such as smoking, would affect the risk of MS further, as seen with exposure to organic solvents and smoking where the risk in exposed *HLA-DRB1*1501* positive, *HLA-A*0201* negative non-smoker increased from OR 6.7 (3.7 to 12.1) to OR 30.3 (11.7 to 78.3) in smokers compared with *HLA-A*0201* positive individuals lacking the three risk factors.[31] Therefore, further similar analysis was undertaken to assess the impact of smoking on head trauma-related risk of MS (table 1). Although the numbers are small, the data indicate the risk of MS in TBI with HLA-DRB1*15.01 and HLA-A*02.01 in never-smokers versus smokers, increased from OR 12.7 (95% CI 4.47 to 36.0) to OR 65.4 (95% CI 8.35 to 512), compared with those expressing the HLA-A*02.01 and lack of HLA-DRB1*1501 expression or a history of smoking or TBI (table 1). This suggests that the genetics of recipients and their life history can impact the results of subsequent TBI. However, it is important that such statistical associations can be supported by plausible biology.

During ischaemic stroke, neurological damage will also release neuroantigens, but in contrast to head trauma, there is a lack of evidence for stroke as a risk factor for MS, although it can occur.[36] Conversely, stroke appears to be more common in MS and could perhaps relate to altered vascular biology in MS.[37 38] However, the age demographic for MS is typically much younger than for stroke.[39] There is immune senescence with ageing, and it does not appear that sequestration of the immune system in the CNS, as occurs in MS, develops following acute ischaemia,[40] suggesting that key aetiological features required for MS development are lacking, possibly accounting for lack of a reported relationship.

PATHWAYS TO AUTOIMMUNITY

While the cause of MS is currently unproven, it is thought to represent an autoimmune disease of the central nervous system (CNS).[1 3] MS is associated with the generation of mononuclear cell infiltrates around blood vessels leading to white cell entry into the CNS, damage of myelin and oligodendrocytes, and nerve loss and disability accumulation.[1 3] Importantly, the response to early effective immunotherapy, which prevents peripheral immunity from entering the CNS, controls the accumulation of disability in relapsing and progressive MS and demonstrates that this is a central part of the pathology, rather than a secondary phenomenon.[41–43] This limits the development of mechanistically distinct neurodegenerative processes that respond slowly and poorly to relapse-inhibiting agents following exhaustion of the neurological reserve as seen in humans and animal models.[44–47]

Although self-reactive lymphocytes are typically deleted as part of the homeostatic, immune-tolerance mechanism, potentially autoreactive lymphocytes are generated in everybody, but are typically controlled.[48–50] Lymphocytes are produced in the bone marrow and are educated in primary (thymus) and secondary (spleen, Peyer's patches, tonsils, appendix and lymph nodes) lymphoid organs to avoid autoimmunity.[50] Naïve cells express adhesion molecules such as L-selectin (CD62L), which promote

Table 1 OR with 95% CI of multiple sclerosis among subjects categorised by HLA-DRB1*15.01 status, a reported history of smoking and head trauma

HLA-DRB1*15.01 $^{+}$	HLA-A*02.01^{-}	Ever smoking	Recent TBI	Cases/controls	OR (95% CI)
–	–	–	–	159/591	1.0 (reference)
–	–	+	–	195/475	1.50 (1.17 to 1.91)
–	+	–	–	252/534	1.73 (1.37 to 2.19)
–	+	+	–	288/419	2.42 (1.91 to 3.07)
+	–	–	–	214/236	3.83 (2.92 to 5.04)
+	–	+	–	249/210	4.99 (3.79 to 6.55)
+	+	–	–	301/197	6.56 (4.99 to 8.62)
+	+	+	–	308/136	9.62 (7.21 to 12.8)
–	–	–	+	5/15	1.14 (0.40 to 3.23)
–	–	+	+	8/19	1.59 (0.67 to 3.78)
–	+	–	+	10/20	1.86 (0.84 to 4.10)
–	+	+	+	18/13	5.22 (2.45 to 11.2)
+	–	–	+	9/4	9.80 (2.94 to 32.7)
+	–	+	+	13/12	4.93 (2.16 to 11.2)
+	+	–	+	15/5	12.7 (4.47 to 36.0)
+	+	+	+	13/1	65.4 (8.35 to 512)

The study group comprised the Swedish population aged 16–70 years. Incident cases of McDonald criteria positive MS were recruited via hospital-based and privately run neurology units throughout the country. For each case, two controls were randomly selected from the national population register in close temporal alignment with the case's inclusion, matched by age in 5-year age strata, sex and residential area.[31]

recirculation and migration through high endothelial venules into lymphoid tissue where they are most likely to contact infection-related antigens, presented by antigen-presenting cells, which drain via the lymphatics from the surrounding tissues[50 51] (figure 1). Once activated by their target antigens, naïve cells proliferate and differentiate to become memory/effector cells that express new adhesion molecules such as alpha4 (CD49d), beta1 (CD29) integrins and chemokine receptors that allow them to circulate and surveil tissues for infection or in the case of B cells to secrete protective antibodies.[50 51] This process provides lifelong control of infection that is central to immune function. However, if these immune cells recognise self-targets then uncontrollable autoimmunity may develop.[48 50 52] Once sufficient memory cells are generated, relatively innocuous environmental stimuli can trigger their activation, circulation and entry into the CNS, as seen in animal models of MS[52–55] (figure 1). Although there has been some concern over whether the initial response in MS is generated within the CNS or periphery,[41] given the recent discovery of glymphatics and meningeal lymphatics that allow drainage of brain proteins and cells into peripheral lymph nodes,[56–58] even centrally derived triggers can generate peripheral immunity that later enters the CNS to deliver effector function. As such, myelin antigens and maturing B cells that accumulate in the brain during disease can be detected in draining lymph nodes in MS.[59 60] Meningeal lymphatic activity is important during recovery from TBI and therefore this pathway is operational during TBI.[61]

Highly effective therapy in MS is associated with depletion or functional inhibition of memory B and T cell activity, which limits blood–brain barrier dysfunction, cellular inflammation and nerve damage.[42 62] Memory B cells are not only formed in response to antigen-driven expansion and maturation signals, but can be created independently of antigen-driven events following EBV infection due to the capacity of EBV to mimic B cell receptor and CD40 stimulatory/costimulatory signals.[62] The genetics of the host may facilitate this in both positive or negative ways, such as, in the case of increased (*HLA-DRB1*15.01*) or decreased (*HLA-A*02.01*) cellular viral loading due to expression of MS-risk associated human leucocyte antigens (HLA) variants either involved in, or protective against, EBV infection.[5 62] Once generated, memory B cells have the potential to present autoantigen to T cells to create T cell memory, secrete cytokines that influence blood–brain barrier, myelination and neuronal survival, but are also precursors for plasmablasts and plasma cells that can that may drive pathology either directly or indirectly via activation of the local glial response.[42 62–67] While there

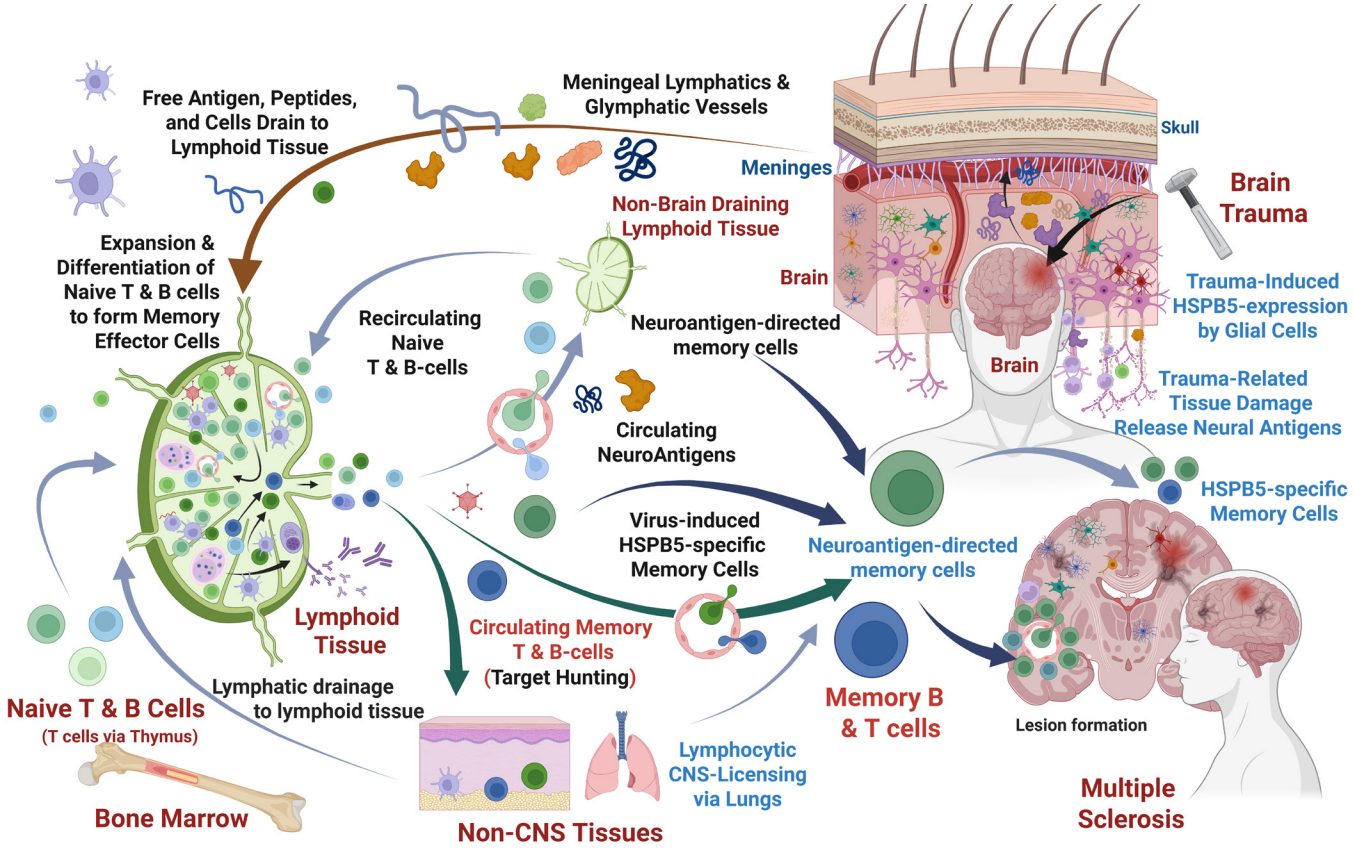

Figure 1 Mechanistic pathways explaining traumatic brain injury (TBI) as a risk factor for the development of multiple sclerosis (MS). MS is associated with the entry of pathogenic immune cells into the central nervous system (CNS) due to signals from within the peripheral immune system, possibly following additional activation signals acquired during re-circulation in tissues, such as the lungs. This activation is possibly due to molecular mimicry between infection-targeted immunity and brain tissue or autoantigen-induced immunity. This could occur following neuroantigen release within the CNS that drains into the lymphoid tissue where neuroantigen-specific naïve cells may be activated to become memory/effector cells and circulate through tissues. TBI may initiate immune exposure to neuroantigens that are released during damage or produced during the removal of debris during repair. Alternatively, the damage may cause upregulation of novel antigens, such as HSPB5 that most people are immune to, and autoimmunity develops when their target antigen is contacted within the CNS. In addition, reduced blood–brain barrier function due to injury may allow neuroantigen-specific cells to enter the CNS and immunity will develop following contact with antigen. Produced with www.biorender.com.

is evidence for the formation of pathogenic antibodies in MS, possibly as a consequence of damage,[68] these could be generated locally following differentiation of mononuclear cells entering the CNS or by entry from the periphery due to mononuclear cell-induced blood–brain barrier dysfunction. Therefore, delivering antigen to lymph nodes and the generation of effector memory cells capable of responding to CNS antigens are probably key components in the generation of CNS autoimmunity (figure 1).

PATHWAYS OF CNS AUTOIMMUNITY AFTER TBI

It is evident that a prodromal phase of MS occurs where clinically silent disease develops, as seen in the chance detection of a radiologically isolated syndrome showing typical MS imaging and immune-pathology seen following biopsy and/or lumbar puncture, which is evident years before clinically definite MS occurs.[69 70] Likewise, exposure to potential aetiological triggers, such as EBV, occurs sometime (median 5–8 years, range 0–12 years) before diagnosis.[7 8] This indicates that it may take some time for TBI to trigger MS. Furthermore, given the high frequency of TBI and low frequency of MS, the conditions that trigger MS after TBI will be a rare event, in MS-susceptible individuals. However, there is biology that can support this causal link.

In MS, it is widely believed that immunity to infections such as EBV can induce memory T and B cells which in turn induce a pathogenic response due to cross-reactivity with myelin proteins including: myelin basic protein, glialcam/hepacam, myelin oligodendrocyte glycoprotein following *molecular mimicry* between the amino acid sequences shared between proteins.[71–74] While TBI is associated with post-traumatic infections,[75] it is not clear if such mimicry-related response occurs. However, *epitope/determinant spread* is a simpler plausible mechanism by which CNS injury liberates neural antigens that generate an autoimmune response (figure 1). This was first shown in animals where viral-induced damage liberated neuroantigens that created and drove a pathogenic autoimmune disease in the CNS.[76] This was further shown to occur during CNS-autoimmunity, where it was also shown that removal of draining lymph nodes could inhibit epitope spreading.[76–79] Epitope spread also occurs at the T cell and antibody level during MS.[80 81] Although the target antigen(s) in MS are unknown/unproven and may be diverse, there is ample evidence that TBI can create damage that liberates antigens, implicated in the pathogenesis of MS and other neurological conditions, that reach the circulation and may target cells in many lymphoid tissues including: myelin protein, myelin lipids, astrocytic and neuronal antigens.[82–88] The pathological process during TBI, following a physical impact to the head, may result in long-lasting dysfunction of the blood–brain barrier and neuroinflammation,[89–91] which will facilitate immune access to the CNS, and also the release of neuroantigens into the circulation. As such, it is evident from examining neurofilament release that neuroantigen is being chronically released into the circulation for months or even years following severe TBI,[83] suggesting the damage and remodelling occurring following TBI acts as an *antigen depot* providing similar low antigen release akin to that occurring in adjuvants used in CNS-autoimmunity in animals.[44] This may contribute to the development of MS. While the functional significance of this remains hypothetical, CNS injury has been associated with the generation of neural autoantibodies, indicating that TBI can be associated with autoimmunity.[85 92] Increased blood–brain barrier function may facilitate entry of pathogenic memory/effector cells into the CNS and may facilitate entry of naïve cells that may encounter their cognate antigen and become sensitised. While the lymphoid tissue is specialised for this activity and is, thus, perhaps the more likely location for activation, it has been suggested that epitope spread can be centrally generated.[93] Importantly, TBI induces *alpha B crystallin* (CRYAB/HspB5) within the CNS, often in astrocytes.[87] This is of significance since this small heat shock protein is the most abundant, dominant autoantigen upregulated in MS brain tissue.[94] It is induced in antigen-presenting B cells following infection with viruses such as EBV, which can activate CRYAB-reactive T cells that are not typically eliminated due to a lack of thymic expression that induces negative selection of reactive lymphocytes.[63] CRYAB-specific antibodies are also induced during MS.[73] This provides another mechanistically relevant approach that could lead to autoimmunity in MS following TBI.

It seems that a history of smoking, a well-known risk factor for MS susceptibility and poorer prognosis,[95 96] increases the risk of TBI-related MS (table 1). How these features interact is unproven, but it is likely that the mechanisms of smoking-related MS risk are distinct from those suggested above to relate to TBI-associated MS. Although smoking clearly can exert CNS-directed effects: such as the production of free radicals, oxidative stress, carbon monoxide, vascular changes and hypoxia that can damage the nervous system,[97 98] it induces many systemic effects, including the induction of pro-inflammatory cytokines, increases in, and reduced regulation of, lymphocytes and lung inflammation, which may increase the likelihood of autoimmunity.[99] The latter is important since evidence in animal models of MS suggests that the lung contains a niche for the generation of potentially auto-aggressive lymphocytes, which can become activated and licensed to migrate into the CNS where they can induce autoimmunity.[100 101] However, while there are sound mechanistic reasons of how TBI could impact on MS susceptibility, these remain hypothetical and will require further study, and effective disease manipulation following the targeting of the relevant pathways, to assess causality.

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Anonymised data will be shared following request from any qualified investigator wishing to analyse questions related to this article.

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