Multiple sclerosis (MS) is a common neurological disease characterised by sclerotic plaques of dead and dying oligodendrocytes and neurons in the central nervous system, usually with evidence of accompanying inflammatory activity. Infectious agents might cause or contribute to this cell death, but none have yet been established as doing so. Instead, MS is regarded as predominantly an autoimmune disease, responsive to immunomodulators. However, there is compelling epidemiological and empirical evidence implicating Epstein–Barr virus (EBV), with minor support for other viruses, as contributing to the pathogenic immune response in MS. Now the recent dramatic advances in identifying the genetic risk factors for MS have provided some tantalising leads to microbe involvement. If conclusive evidence is found, vaccines, antivirals/antibiotics or pathogens themselves might prove useful therapeutics.

**Biography**

**Professor Andrew Lloyd** AM, BBS, MD, FRACP is an infectious diseases physician and immunology researcher. He leads a multidisciplinary team of clinicians and scientists in research studying the biological basis of inflammation in human infectious diseases, including studies of hepatitis C infection and post-infective fatigue states. He is a NHMRC Practitioner Fellow and his research is supported by a NHMRC Program, Partnership and Project Grants. He is the Director of Infection and Inflammation Research Centre (II RC) in the School of Medical Sciences at the University of New South Wales. Professor Lloyd was awarded an Australia Medal (AM) for his research achievements in infectious diseases and for his work in establishing the hepatitis service in the NSW prisons.
countries, but also in Asia and elsewhere (because MS is described worldwide), infect children (because MS risk reflects childhood environment), cause chronic infection (because the disease is usually late onset and persistent) and is more likely in the higher latitudes (because MS prevalence increases with latitude).

The strongest candidate to date is EBV, which fulfils all these criteria. Although typically 90% of the general population carry EBV, virtually 100% of people with MS do. Notably, though, other common chronic viruses, such as HHV6, chicken pox, measles and cytomegalovirus have also been described as more prevalent in MS, such that exposure to these viruses might also render people susceptible to MS and the virus is not causative but associative. More compellingly, late infection or severe infection with EBV increases risk of MS by up to 20-fold, an increase not yet found for other pathogens. People with MS have poor CD8 responses to EBV, T cells recognizing myelin proteins can be activated by EBV, high titres of EBV antibodies are associated with relapses and paediatric MS. A prospective study of 915 individuals found the 10 who were EBV negative and later developed MS were all EBV positive before they developed MS, whereas of the 28 EBV negative controls only 35% became EBV positive over the same time period. High EBV antibody titres, in combination with the first MS susceptibility gene, and variant of largest effect yet known, HLA DRB1*1501, increases the risk of MS, additively and independently, not interactively. Oligoclonal bands found in the CSF of many with MS can be reactive to EBV and other herpesviruses.

EBV infects B cells through CD21, and possibly CD35. Both of these genes are not among those known to affect susceptibility to MS. The infected B cells proliferate through signaling through EBVs own analogue of human CD40. Strikingly, genetic variants of CD40 are associated with MS, and the genotype with higher expression of CD40 decreases MS risk. Because CD40 is a costimulatory molecule required for T cell activation, it would be expected that higher expression would increase the risk of MS. A potential explanation for this paradox is that low host CD40 expression on B cells favours proliferation/survival of EBV infected B cells, using their EBV CD40. In support of this, anti-CD20 B-cell-depleting drugs such as Rituximab, which are used as a therapies to reduce EBV infection, are effective in MS, but those targeting terminally differentiated B cells are not. The effect of more specific depletion of EBV infected B cells on MS needs to be investigated.

Genome wide analysis studies have implicated specific viruses for some autoimmune conditions. Individuals homozygous for the Crohn’s diseases risk allele rs601338 of FUC2, the receptor for noroviruses, are protected against norovirus infection, but are more likely to develop Crohn’s and other autoimmune diseases such as type 1 diabetes and inflammatory bowel disease, consistent with the ‘hygiene hypothesis’. The MS risk gene TNFSF14 (also known as herpesvirus entry mediator ligand or LIGHT) is an entry receptor for Herpes simplex 1 (HSV1), a neurotropic virus. A ligand for TNFSF14, TNFRSF6B, is also a MS risk gene. SLAM family proteins are used by morbilliviruses to facilitate cell entry. These viruses then circumvent the interferon response by blocking Tyk2 signalling. Both SLAMF7 and TYK2 are risk genes for MS. Measles and canine distemper virus, both implicated in the Faroe Island MS ‘epidemics’, are morbilliviruses. Further viral receptors and genes important in their infection might be in the list of MS genes. But as TNFSF14/TNFRSF6B and SLAMF7/TYK2 also have roles affecting other aspects of the immune response, further implication of a HSV1/morbillivirus contribution to MS might follow if the MS susceptibility genotype can be shown to increase tissue damage or other infectious consequences due to these viruses.

The genes affecting MS susceptibility support a role for immune response in MS, but although they, as yet, provide no smoking gun for particular viruses, the evidence that most of these genes are under recent positive selection is consistent with the genetic variants affecting selection against pathogens. Most of these genes are also predominantly expressed in T cells or antigen-presenting cells, consistent with a role for molecular mimicry or bystander activation contributing to disease aetiology, but also with excessive reaction to self antigen independently of pathogen effect.

A ‘smoking gun’ for one environmental trigger was found. This is vitamin D. Low vitamin D has been implicated as contributing to MS development and progression from epidemiological and empirical studies. It now seems that genetic variants of the two genes regulating its activation in antigen presenting cells, CYP27B1 and
and CYP24A1, affect MS risk. As well as regulating DC tolerisation, vitamin D can be antimicrobial, through its upregulation of cathelicidin.

Current successful therapies for MS alter leukocyte survival, modulation or trafficking. Further manipulation of the immune response might be beneficial if a microbial effect on MS aetiology is defined. Vaccination might be a useful strategy whether viruses such as EBV increase susceptibility (especially if late infection) or protect (especially if early infection) against MS. This might include use of the pathogen itself. To support such approaches, experimental studies are needed to determine if genes associated with MS function through their effect on infections. Novel approaches to establishing if viruses are pathogenic include sequencing of non-host DNA/RNA, especially in plaques, and amplified endogenous retroviruses. Such studies could use historic samples from the Faroe islands and elsewhere. If pathogens contribute to autoimmunity, even if in only a subset of patients, it is highly likely that their identification will provide significant clinical benefits.

References

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Biography

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