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Commentary

Kissing genetic MS risk loci to life

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ABSTRACT

Multiple sclerosis (MS) is an inflammatory autoimmune demyelinating disease of the central nervous system (CNS) [1]. Its debilitating effects on sensory, motor, autonomic, and neurocognitive functions affect primarily young adults, especially women (two to three times more frequent than in men), and is most frequent in northern countries, affecting more than 150 individuals of every 100,000 inhabitants e.g. in Canada and the Scandinavian countries. The development of this often initially relapsing/remitting and later progressive disease is associated with genetic and environmental risk factors [1, 3]. The major histocompatibility complex (MHC) class II gene locus is by far the most prominent genetic risk factor, and altered immune responses to the Epstein Barr virus (EBV), the causative infectious agent of most cases of infectious mononucleosis or "kissing disease", have in recent years emerged as the most prominent environment induced risk factors for MS [1]. Interestingly, particularly infectious mononucleosis as symptomatic primary EBV infection, caused by a lymphocytosis of mainly lytic EBV antigen specific $CD8^+$ T cells, and elevated antibody responses against EBV have been found to synergize with the MS associated MHC class II molecule HLA-DRB1*1501 to increase MS risk seven- to fifteen-fold, respectively [1]. Moreover, EBV infection seems to precede MS onset by several years in nearly all patients. Thus, EBV infection currently appears as a prerequisite for MS development that increases the risk for this autoimmune disease in genetically susceptible individuals.

In the study by Keane et al. in this article of *EBioMedicine* the authors shed more light on possible mechanisms of this interaction [4]. They focus on six MS associated genetic polymorphisms outside the MHC class II locus that are adjacent to genes that they and others have previously identified to be altered in their expression by EBV infection [5,6]. Interestingly, these include five that influence tumor necrosis factor (TNF) receptor signaling for NF-κB dependent gene transcription (TRAF3/RCOR1, CD40, TNFAIP8, TNFRSF1A, and TBX6) and one C-type lectin receptor (CLECL1) of so far poorly described function. The authors describe that EBV nuclear antigen 2 (EBNA2) dependent transcription of these is MS risk allele specific, and that this transcription can be blocked with an EBNA2 peptide that interferes with EBNA2 binding to RBP-Jκ which is in addition to EBF1 the main transcription factor for EBNA2 dependent transcriptional regulation [7]. EBNA2 drives both viral and host gene transcription during B cell transformation after EBV infection, and accordingly Keane et al. detect decreased proliferation of EBV transformed B cells (lymphoblastoid cell lines or LCLs) after EBNA2 peptide treatment. They had previously shown that LCL proliferation is increased upon EBV infection of B cells that carry MS risk alleles [5]. These data suggest that differential regulation of EBNA2 dependent gene transcription by adjacent MS associated genetic polymorphisms enhances EBV associated B cell transformation. Interestingly, five of the six differentially regulated genes (TRAF3/RCOR1, CD40, TNFAIP8, TNFRSF1A and TBX6) seem to influence the signaling pathway that is engaged by latent membrane protein 1 (LMP1), considered to be the main EBV oncogene, a viral CD40 homologue with regards to its TNF receptor-like signaling, itself under the transcriptional control of EBNA2, and taking over from EBNA2 to drive B cell proliferation several days after EBV infection of B cells [7]. The resulting accumulation of EBV transformed B cells might facilitate MS development.

Together with this study in *EBioMedicine* a picture emerges that genetic MS susceptibility is exploited by EBV for more efficient B cell transformation and decreased EBV specific immune control [1,3]. Accordingly, HLA-DRB1$\times$1501, the main genetic risk factor of MS, allows only for attenuated EBV specific immune control despite higher T cell expansion after EBV infection of mice with reconstituted human immune system components [8]. This genetic context results also in elevated antibody responses against EBV nuclear antigen 1 (EBNA1) which in part cross-react with the autoantigen anoctamin 2 [9]. Furthermore, cross-reactivity of HLA-DRB1*1501 restricted EBNA1 specific $CD4^+$ T cells with the myelin antigen myelin basic protein (MBP) and their elevated frequency in MS patients have been reported [10]. Thus, genetic risk factors for MS might allow EBV infection to establish more transformed B cells that then efficiently

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stimulate autoimmune T cell responses, some of which are cross-reactive to myelin antigens, and thereby drive autoimmunity in the CNS. This hypothesis would justify targeting EBV infection in MS patients to decrease EBV transformed B cells that are possibly also located in the brain [2]. Only such EBV directed therapies could, however, definitively prove an involvement of poorly controlled EBV infection in MS pathoetiology.

Contributors

C.M. wrote the article.

Declaration of Competing Interest

The author declares no conflict of interest.

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