

EBV is a γ 1-herpesvirus that belongs to the large genus of primate lymphocryptoviruses (LCV) (Wang et al., 2001; Carville and Mansfield, 2008). EBV and related LCV have similar functions, including infection of B lymphocytes leading to their constitutive activation and transformation. Of the adult human population, > 90 % is infected with EBV; although in healthy individuals only a small proportion of the B cells, about 1 per 100.000 memory B cells, carries the virus in the form of episomal DNA in the nucleus. The vast majority of infected B cells are found in the lymphoid system, especially in the vicinity of the tonsils; in the blood about one infected B cell per 5 ml can be found (Laurence and Benito-Leon, 2017). Infection usually occurs during childhood via salivary transmission and remains asymptomatic. Infection at adolescent age can lead to infectious mononucleosis (IM) a.k.a. morbus Pfeiffer, a disorder characterized by flu-like symptoms – e.g., fever, sore throat, swollen glands, headaches and fatigue – that can last for several weeks. During IM EBV can be detected in up to 50 % of all memory B cells, but this oligoclonal expansion declines to 0.001% by the action of cytotoxic T cells.

A plethora of data support a strong association of EBV infection with increased MS risk. The risk to develop MS is very low or absent in individuals who are seronegative for EBV (Pakpoor et al., 2013). EBV seropositivity increases MS risk about 5-fold; presence of high antibody serum titer against the EBV latency marker, EBNA-1, further increases the risk about 30-fold and past experience of IM ± 2-fold. Nevertheless, it is poorly understood via which mechanism(s) EBV influences MS risk, especially with regard to the discrepancy between the high infection rate in the human population (>90%) and the much lower MS incidence (0.1%). Proposed mechanisms include the following: reactivation of memory B cells within the CNS, induction of cross-reactive T- and/or B-cell responses between EBV and self-antigens, facilitation of forbidden B memory responses against CNS antigens or infection of autoreactive B cells (Laurence and Benito-Leon, 2017). Several of these mechanisms assume the presence of EBV-infected B cells within the CNS, although undisputed evidence is lacking (Lassmann et al., 2011). This means that also pathogenic concepts based on the presence of EBV-infected B cells in the periphery need to be considered.

Our own work in the marmoset EAE model indicates that LCV infection endows B cells with the capacity to reactivate strongly autoreactive effector memory CD8+ T cells present in the normal immune repertoire ('t Hart et al., 2016). These T cells can directly induce EAE pathology ('t Hart et al., 2017a). Further details can be found in Boxes 4 and 6.