The sequence 34-56 of MOG is localized in the evolutionary conserved domain 20-50 and represents the immunodominant T cell epitope of human MOG. An important question is why are these potentially autoaggressive T cells not depleted in the thymus? One possibility, discovered in NOD mice, is that the epitope is destroyed by the thymus-specific serine protease TSSP, a proline-specific endopeptidase expressed in expressed in thymic epithelial cells (Serre et al., 2017). We posit that activation of autoaggressive T cells that have escaped thymic selection in the periphery is prohibited by a similar destructive epitope processing mechanism operational in peripheral APCs. The primary sequence, GMEVGWYRPPFSRVVHLYRNGKD, contains multiple targets for the serine protease cathepsin G (catG), which has tryptic (R, K, H) as well as chymotryptic (W, F, Y, L, M) substrate specificity (Raymond, 2010). Our studies in lysates of non-infected and LCV-infected B cells from marmosets and rhesus monkeys revealed catG as the leading protease and the arginine (Arg/R) residues at positions 41, 46 and 52 as principle targets (Jagessar et al., 2016). As two of these are localized within the octamer epitope MOG40-48 and are potential TCR contact residues, as shown in mice (Carrillo-Vico et al., 2010), we speculated that the epitope might be degraded in B cells.

Interestingly, degradation of the peptide by catG can be prohibited by substitution of the Arg residues for citrulline. This peptide citrullination is a common post-translational modification that is catalyzed by peptidyl-arginine deïminases (PAD) and has been associated with autoimmune diseases, including rheumatoid arthritis (van Venrooij and Pruijn, 2000) and MS (Chirivi et al., 2013). One of the five isoforms of PAD (PAD2) was found to be upregulated in LCV-infected B cells. In both conditions (epitope cleavage or citrullination) activation of T cells specific for the native peptide will be prohibited. However, Anderton et al. found that CD4+ T cells specific for citrullinated MOG34-56 can be induced in mice and that transfer of these T cells into littermates exacerbates EAE induced with the non-citrullinated peptide (Carrillo-Vico et al., 2010).