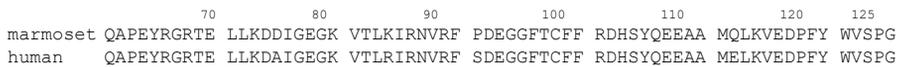
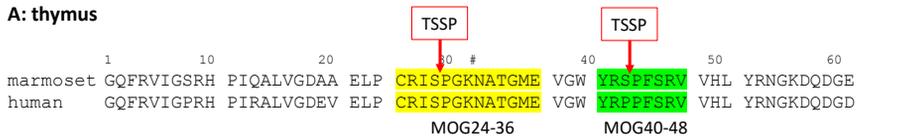


Two epitopes are immunodominant in the marmoset EAE model, namely the CD4+ T cell epitope MOG24-36 and the CD8+ T cell epitope MOG40-48. The concept that autoimmunity is due to hyper-reactivity of certain T cell specificities raises questions about the immunodominance of exactly these epitopes. We posit that the immunodominance of the mentioned epitopes can be explained by the escape of T cells reactive with these epitopes from thymic selection. A recent paper reports that intrathymic processing of MOG occurs within thymic epithelial cells and DCs, where the leading protease is TSSP, a proline-specific dipeptidyl peptidase (Serre et al., 2017). TSSP cleaves at SP/PP dipeptide motifs (A). The extracellular domain of human and marmoset MOG contains these motifs within the MOG24-36 and MOG40-48 epitopes and at far the C-terminal end. This may imply that both T cell epitopes can be destroyed by TSSP, thus abrogating the negative thymic selection of both T cell specificities; this needs to be proven however. Hypothetically, there should be a back-up system in the periphery to prevent that these T cell specificities are activated, leading to autoimmunity. Such a potential mechanism was found in the atypical marmoset EAE models induced with rhMOG or MOG34-56 in IFA (Jagessar et al., 2015). We observed that in this model T cell and antibody reactivity against MOG24-36 is present, while reactivity against MOG40-48 is absent; although the MOG34-56/IFA model shows that CD8+ T cells against this epitope are present in the repertoire. We showed that in the periphery MOG is processed in B cells, where the endolysosomal serine protease cathepsin G (catG) is leading. CatG cleaves at arginine (R) residues, which are present at positions 25, 40 and 48 in the epitopes.

A second question is why are the MOG34-56 reactive T cells present themselves as antigen-experienced cells, suggesting they have been activated after an earlier encounter with antigen, e.g., a viral infection. To test this, we first determined the CD8+ T cell epitope, which was the peptide sequence 40-48, and then used Blast search to find sequence similarity with known pathogens. Interestingly, we found striking similarity between MOG40-48 and a peptide derived from the UL86 ORF-encoded major capsid protein of human/rhesus monkey cytomegalovirus.

A: thymus



B: periphery

