



UKE Paper of the Month December 2024

Protective effect of TCR-mediated MAIT cell activation during experimental autoimmune encephalomyelitis

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ABSTRACT:

Mucosal-associated invariant T (MAIT) cells express semi-invariant T cell receptors (TCR) for recognizing bacterial and yeast antigens derived from riboflavin metabolites presented on the non-polymorphic MHC class I-related protein 1 (MR1). Neuroinflammation in multiple sclerosis (MS) is likely initiated by autoreactive T cells and perpetuated by infiltration of additional immune cells, but the precise role of MAIT cells in MS pathogenesis remains unknown. Here, we use experimental autoimmune encephalomyelitis (EAE), a mouse model of MS, and find an accumulation of MAIT cells in the inflamed central nervous system (CNS) enriched for MAIT17 (ROR γ t+) and MAIT1/17 (T-bet+ROR γ t+) subsets with inflammatory and protective features. Results from transcriptome profiling and Nur77GFP reporter mice show that these CNS MAIT cells are activated via cytokines and TCR. Blocking TCR activation with an anti-MR1 antibody exacerbates EAE, whereas enhancing TCR activation with the cognate antigen, 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil, ameliorates EAE severity, potentially via the induction of amphiregulin (AREG). In summary, our findings suggest that TCR-mediated MAIT cell activation is protective in CNS inflammation, likely involving an induction of AREG.

STATEMENT:

This study shows the protective and regenerative potential of T cell receptor activation of MAIT cells in EAE, the mouse model of multiple sclerosis (MS). All MAIT cells in mice and men recognize an exclusive class of antigens, metabolites of the riboflavin pathway present in many commensal bacteria and yeast and presented by the highly conserved, non-polymorphic MR1. Therefore, specific therapeutic targeting of MAIT cells by application of the antigen 5-OP-RU or manipulation of the microbiome to increase the level of MAIT cell antigens holds the promise to be translatable to human MS or other autoimmune diseases.

BACKGROUND:

This work was conducted at the Institute of Neuroimmunology and Multiple Sclerosis (INIMS) under the supervision of Prof. Manuel A. Frieze and Dr. Anne Willing. It was mostly performed by Mark Walkenhorst as a PhD student and early career post doc. The INIMS' main interest is to study the interactions of the immune and nervous system. This work was supported by the Deutsche Forschungsgemeinschaft (Grant No. 470154978; WI 5322/2-1 to A.W.) and Bundesministerium für Bildung und Forschung (Grant No. 01G1605C to M.A.F.).