A113 CONSTITUTIVELY ACTIVE RAP1 PROTECTS FROM EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS (EAE) BY QUANTITATIVE AND QUALITATIVE MODULATION OF AUTO-REACTIVE T CELLS

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Background and objectives Rap1 is an important signalling molecule downstream of the T-cell receptor (TCR), which can modulate T lymphocyte function upon antigen stimulation. The authors recently demonstrated that transgenic mice with constitutively active Rap1 (RapV12) are protected from experimental arthritis (*Abreu, Arthritis Rheum, 2010*). Here, the authors aimed to identify the mechanisms of protection by using a TCR transgenic model of myelin oligodendrocyte glycoprotein (MOG)–induced experimental autoimmune encephalomyelitis (EAE) (2D2 mice).

Methods Flow cytometry and ELISA were used to analyse the phenotype and cytokine profile of MOG-specific autoreactive T cells in 2D2xRapV12, 2D2, RapV12 and wild type (WT) mice (n=5 per genotype), either in basal conditions or after in vivo priming with MOG peptide. In addition, clinical EAE was monitored for 30 days (n=19 mice per genotype)

Results In basal conditions, there was a strong reduction in the number of autoreactive T cells in 2D2xRapV12 versus 2D2 animals in the naïve and memory compartment (42 vs 24%, p=0.03), indicating that constitutive Rap1 activation enforces central tolerance. Qualitative analysis of the autoreactive T cells that escaped tolerance showed no differences in T cell subsets, proliferation, apoptosis, expression of costimulatory molecules and production of pro-inflammatory cytokines. After in vivo priming with MOG, however, the authors observed a profound inhibition of tumour necrosis factor production by T cells constitutively expressing Rap1 (19% of 2D2 RapV12 CD4s vs 0.4% in 2D2 controls, p=0.002), whereas there was a slight increase in IFN-γ and IL-17 production. To

evaluate the pathophysiological relevance of these quantitative and qualitative alterations of the autoreactive T cells, EAE was induced in 2D2xRapV12 versus 2D2 and in RapV12 and WT littermates. In the 2D2 model, where a significant number of autoreactive T cells are still present despite the constitutive RapV12, the authors observed no difference in EAE scores but an improved survival in the 2D2xRapV12 versus 2D2 mice (42 vs 16%; p=0.04). In wild-type mice, constitutive Rap1 expression led to increased survival (100 vs 74%; p=0.02) as well as lower EAE scores (p=0.07).

Conclusion Constitutive activation of Rap1 reduces the autoreactive T cell pool and affects pro-inflammatory cytokine production by the remaining autoreactive T lymphocytes. As in experimental arthritis, these quantitative and qualitative effects are associated with a protection from autoimmune disease in EAE.