A168 MAINTENANCE OF T CELL RAP1 SIGNALLING PROTECTS MICE AGAINST COLLAGEN-INDUCED ARTHRITIS

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Background Activation of the small GTPase Rap1 in T lymphocytes regulates cell adhesion, cytokine production and reactive oxygen species production. The authors have recently identified blocked Rap1 activation as one of the T cell receptor proximal signalling defects in rheumatoid arthritis (RA)

synovial fluid T cells. The goal of this study was to determine if maintaining Rap1 signalling in murine T cells could modify disease in collagen-induced arthritis.

Methods Arthritis was induced in wild-type (WT) and RapV12 transgenic (expressing constitutively active Rap1 in the T cell compartment) C57BL/6 mice by immunisation with chicken collagen type II emulsified in complete Freund's adjuvant. Arthritis and paw swelling was monitored three times weekly until killing at day 60. In a second experiment, mice were killed at day 40 and blood, spleen and lymph nodes harvested. Serum anticollagen antibodies were measured by ELISA. Splenic and lymph node cells were assessed for expression of T cell surface markers and FoxP3. Cytokine production and co-stimulatory protein expression following ex vivo stimulation were also assessed by fluorescence activated cell sorting analysis. In an acute inflammation model, mice were challenged with primary and secondary flu infections.

Results Disease incidence in RapV12 mice (30%) was severely reduced compared with WT mice (100%). Arthritis scores observed in WT mice were also significantly reduced in RapV12 mice ($p < 0.001$). Infiltration of synovial tissue and cartilage erosion were not detected in RapV12 mice. Radiological scores in RapV12 mice were significantly reduced compared with WT mice ($p < 0.001$), and anticollagen immunoglobulin G2 α (IgG2 α) and IgG2 β titres were reduced by 75% in RapV12 mice at day 40 compared with WT mice ($p < 0.05$). Numbers and percentages of T cells (naive/effector/memory), FoxP3+ Tregs and Th17 cells were equivalent in WT and RapV12 mice, but the percentage of tumour necrosis factor-secreting T cells was decreased in RapV12 mice ($p < 0.05$), and defective expression of inducible co-stimulator and CD40L proteins needed to promote B cell Ig class switching was noted. No differences were observed between WT and RapV12 with regard to primary or secondary responses to flu infection.

Conclusion Maintenance of T cell Rap1 signalling in murine T cells reduces disease incidence and severity in the collagen-induced arthritis model. Protection against disease is associated with decreases in the function of cytotoxic T cells, T helper cytokines used in autoantibody class switching, and development of IgG2 α and IgG2 β autoantibodies. Strategies aimed at restoring Rap1 function in RA synovial T cells may have therapeutic benefit in RA without jeopardising normal immune responses.