

## Analysis of partial ZAP-70 deficiency in a murine model of rheumatoid arthritis

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Recombinant human G1 (rhG1) induced arthritis (GIA) model resembles human rheumatoid arthritis (RA) both in immunological characteristics and clinical parameters. Immunization of BALB/c mice with rhG1 domain of human proteoglycan aggrecan induces arthritis. T cells are involved in the pathogenesis of arthritis; their activation is regulated by ZAP-70, a key molecule in T cell receptor signaling.

The aim of our study was to assess the effect of partial ZAP-70 deficiency on autoimmune arthritis in the GIA model.

Wild-type BALB/c (WT) and ZAP-70 heterozygous knockout ( $ZAP-70^{+/-}$ ) mice were immunized with rhG1 side-by-side. Surprisingly, partial ZAP-70 deficiency did not inhibit the development of GIA; moreover, the arthritis was more severe in  $ZAP-70^{+/-}$  mice than in WT as assessed by the physical scoring system. Luminescence imaging confirmed the increased inflammatory activity in affected limbs of  $ZAP-70^{+/-}$  mice compared to WT animals. There was a clear correlation between the results of the functional test (hanging time measurements) and the clinical scores. Alterations in the physical performance preceded the clinical onset of arthritis. Investigation of the T cell mediated immune response indicated decreased T cell proliferation and IL-4,-6 production accompanied by significant IL-17,  $IFN\gamma$  and  $TNF\alpha$  production measured from *in vitro* splenocyte cultures.

Contrary to our expectations partial deficiency of ZAP-70 did not ameliorate the severity of arthritis in GIA model, which may be due to alterations in T cell activation and apoptosis.

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