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

Reka Kugyelka, Katalin Olasz, Zoltan Kohl, Sohn Hee Seung, Oktavia Tarjanyi, Peter Nemeth, Timea Berki, Ferenc Boldizsar

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, IFNγ and TNFα 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.

This work was funded by OTKA, K101493. and Bolyai Janos Reseach Scholarship of the Hungarian Academy of Sciences to FB.