Cím:	THE ROLE OF ZAP-70 KINASE IN THE FINE-TUNING OF TCR SIGNALLING: IMPL AND –THERAPY
Szerzõ:	Boldizsár Ferenc
További szerzõk:	Szabó Mariann, Kohl Zoltán, Prenek Lilla, Kugyelka Réka, Németh Péter, Berki Tímea
Munkahely:	University of Pécs, Department of Immunology and Biotechnology

ZAP-70 (zeta-chain associated 70 kDa) kinase is a key regulator of T cell receptor signaling. After ligand binding of the T cell receptor (TcR), Lck kinase phosphorylates tyrosine (Y) residues of the CD3 ζ chains and ZAP-70, which, in turn, phosphorylates a number of downstream target proteins (eg. LAT, SLP-76, PLCγ, Cbl).

ZAP-70 itself contains a number of Y residues, which can be phosphorylated. Using an array of mutant cell lines where targeted Y-Phenylalanine (F) mutations were introduced into ZAP-70, we were able to characterize the fine details of TcR signaling. Our data confirmed the function of earlier described activator (Y315, Y493) and inhibitory (Y292, Y492) residues; moreover, we described the regulatory role of previously less-known (Y069, Y126, Y178) positions.

Glucocorticoid treatment is widely used for suppressing the immune response, primarily through the inhibition of T cell functions. Our earlier work demonstrated, that ZAP-70 is also involved in non-genomic (rapid) GC signaling mechanisms. Using our Y-F mutant ZAP-70 expressing cell line array, we identified that Y315 and Y492 were phosphorylated upon short-term high dose GC analogue treatment. These results confirmed that ZAP-70 represents an important link between the non-genomic GC and TcR/CD3 signaling pathways.

Moreover, potential role of ZAP-70 kinase was implicated in chronic lymphoid leukemia (CLL) and autoimmune arthritis. It has been shown in a subgroup of patients with CLL that the malignant B-lymphocytes express ZAP-70 kinase, which was associated with inferior clinical outcome and prognosis. Using two ZAP-70 specific antibodies recognizing different epitopes in the kinase, we performed intracellular staining of malignant B cells from CLL patients. Based on our preliminary experiments, it seems possible that the ZAP-70 molecule expressed in the tumorous B-cells is structurally different from that found in normal T-cells, as some patients showed positivity with either one or the other antibody, while the normal T-cells were positive with both antibodies, just as expected.

A spontaneous single point mutation at 163 from Triptophane (W) to Cysteine (C) in the SH2 domain of ZAP-70 caused altered thymic selection and leads to the development of autoimmune arthritis in SKG mice. Another study has shown that targeted simultaneous mutation at positions Y315 and Y319 to Alanine led to similar defects in T cell development than in SKG mice, interestingly, however, these mice did not develop autoimmune arthritis despite the presence of rheuma factor in the sera, increased IL-17 production and impaired Treg development.

These data clearly show, how our understanding about ZAP-70 kinase has emerged from being exclusively a T cell specific signaling molecule to an important therapeutic target and potential regulator of pathologies like CLL or autoimmune arthritis.