13. KEY NON-RECEPTOR TYROSINE KINASES IN ADAPTIVE IMMUNITY

Author: Osoianu Inesa

Scientific advisor: Simionică Eugeniu, Doctor of Biology, Department of Biochemistry and Clinical Biochemistry, *Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova

Introduction. Non-receptor tyrosine kinases (NRTKs) are cytosolic enzymes, grouped together as a subclass of protein tyrosine kinases (TKs) due to their lack of an extracellular and transmembrane domain, unlike receptor tyrosine kinases (RTKs) – another sub-class of TKs. By means of protein phosphorylation NRTKs activate different signaling pathways, thus regulating a number of cellular functions: growth, proliferation, differentiation, adhesion, migration and apoptosis. Crucial is NRTKs involvement in the adaptive immune system by regulation of B and T cells activation and response.

Aim of study. This study aims to identify NRTKs that are specifically involved in the activation and regulation of adaptive immunity cells.

Methods and materials. A literature review has been performed using PubMed, Elsevier and Hinari databases. A number of 45 scientific articles related to the keywords have been identified, out of which only 37 met the inclusion criteria in the research topic.

Results. Non-receptor tyrosine kinases include 10 families, classified according to their structural and functional differences. Among these, several NRTKs from SYK (ZAP-70, SYK), TEC (ITK, TXK, BTK) and SRC (LCK, FYN, LYN) families have shown to play a critical role in adaptive immunity. In T cells, a signaling cascade is initiated when a T cell receptor (TRS) recognizes a foreign antigen associated with a major histocompatibility complex (MHC). This results in the activation of LCK and FYN, which phosphorylates the ITAM motifs present in the signal-transducing CD3 subunit of the TRC. The recruitment of ZAP-70 then takes place and a series of signaling events are initiated by phosphorylation of two adaptor proteins – LAT and SLP-76. These adaptors create a signaling complex by recruiting several important signaling molecules, including ITK, that activates phospholipase (PLC) γ1. The subsequent activation of downstream signaling pathways leads to the activation of second messengers and an increase in intracellular Ca2+. Transcriptional modifications are triggered following these events, leading to the production of interleukin-2 (IL-2) and T cell proliferation. ITK and TXK are also involved in T helper cell differentiation, with ITK being expressed in both Th1 and Th2 cells and TXK expression being limited to the Th2 cells only. Unlike T cells, B cells don't require an intermediate MHC for antigen recognition. Thus, after B cell receptor (BCR) binds to the antigen, ITAM domain is exposed and phosphorylated by the LYN kinase. SYK is then recruited and phosphorylates BLNK to form a multi molecular signaling complex with PLC-γ2 and BTK. This activates PIP2 and, similar to TCR signaling, leads to second messengers production and intracellular Ca2+ increase, the net result being B-cell proliferation and antibody production.

Conclusion. Non-receptor tyrosine kinases play a central role in B and T cells proliferation and regulation, thus knowledge of NRTKs effects and site of action opens new possibilities for addressing the immune disorders.