Session 2. Approaches to chronic viral infection and cancer cure

**Identification of the “missing” transcription factors in Chronic leukocytic leukemia B-cells**

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**Background:** It is known that the Epstein-Barr virus (EBV) can infect any type of B-cells, expressing the Complement receptor type 2 (CR2, also known as CD21) on a surface of the cells, including B-cell of Chronic lymphocytic leukemia (CLL). *In vivo*, EBV-infected CLL cells makes less than 0.01% of a total B-cell count. *In vitro*, infected cells usually do not proliferate, due to lack of expression of the EBV-encoded Latent membrane protein1 (LMP1). LMP1 is transactivated by the EBV-encoded nuclear antigen 2 (EBNA-2), together with cellular transcription factors. Some of them are known, such as NOTCH1, RBPj-kappa, and PU.1. Other factors are waiting to be discovered.

**Materials & Methods:** a bioinformatic analysis of the open expression databases and of the LMP1 promotor region; study of gene expression at MRNA (qPCR) and protein (FACS, western-blotting, immunofluorescence, immunocytochemistry) levels; a statistical analysis with the help of GraphPad Prism (v.9).

**Results:** after bioinformatic analysis and the literature search we found several genes that might take part in the formation of transactivation and/or inhibition protein complexes, bound to the LMP1 promotor. Thus, dimers of the NFkB subunits – RELA-RELB or RELB-RELB, and also dimers ATFF2-c-JUN and PAX5-TFAP2 can activate *LMP1*. Noteworthy, according to our data, expression of TFAP2 is almost 20 folds lower in CLL cells, compared to normal B-cells, activated with anti-CD40 and IL4 (*Matveeva et al, Oncology, 2016*). Importantly, the TGFB-SMAD2/3 and IL-2-STAT2/5 (JAK-STAT5) pathways are not functional at the basal level in B-lymphocytes of patients with CLL. This is due to very low expression of the SMAD2 and the absence of SMAD3-SMAD4 heterodimers in the nucleus. The IL-2-STAT (JAK-STAT5) signaling pathway is inhibited at the basal level in CLL cells, most probably due to low levels of phosphorylation, or its complete. A number of questions arise from the accumulated knowledge: whether is it possible to make cells respond to signals through IL-2, TGFB, and TNFB receptors after transfections with the missing in CLL transcription factors.

**Conclusions:** The study on the molecular mechanisms of the regulation of cellular signaling pathways in CLL cells is vitally important for the development of individualized therapies.

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