REGULATION OF TOLL-LIKE RECEPTOR 9-DEPENDENT ANTIVIRAL RESPONSE BY MAL ADAPTOR PROTEIN

Toll-like receptors (TLRs) are an important group of proteins involved in activation of innate immune response. By binding structures known as pathogen-associated molecular patterns (PAMPs), they activate plethora signaling pathways leading to the induction of expression e.g. proinflammatory cytokines or type I interferons. TLRs are receptors anchored to the cell membrane or endosomes. Endosomal receptors are mainly responsible for the recognition of the nucleic acids of pathogens internalized by phagocytosis or endocytosis. They include, among others, TLR9 that binds fragments of bacterial and viral DNA rich in unmethylated cytosine-guanine dinucleotides (CpG). Correct ligand recognition depends on the multilevel process of receptor maturation and enables the recruitment of a protein complex called Myddosome. Until recently, it was suggested that MyD88 is recruited to TLR9 due to the direct TIR-TIR interaction, excluding the involvement of adapter proteins in this process. Membrane TLRs incl. TLR2 and TLR4 anchors the Myddosome engaging the Mal adapter protein. Participation of Mal in endosomal TLR-dependent cascades was excluded, due to the preferential binding of $PI(4,5)P_2$, which is present predominantly in the cell membrane, by the adaptor protein.

The signal transmission from Myddosome in TLR9-dependent pathway allows the activation of transcription factors, namely NF-κB, AP-1 and IRF family, which initiate the expression of genes encoding a repertoire of pro-inflammatory cytokines such as TNFα or IL-6, as well as type I interferons

The aim of this study was to investigate the effect of the Mal protein on the regulation of the signaling pathway initiated by the endosomal TLR9 receptor.

The results of the research allowed to identify the mechanism of regulation of the endosomal TLR9 receptor signaling pathway by the Mal protein, which until now has been associated mainly with receptors anchored in the cell membrane. In the first step, it was found that activation of TLR9 by both HSV-1 virus and synthetic CpG leads to *IFNB1* and *TNF* expression in an Mal-dependent pathway. Observations suggest that this protein is involved in the regulation of phosphorylation of the MAP family kinases, namely ERK1/2. The presence of the Mal protein regulates the non-canonical NF-κB signaling cascade by activating the cytoplasmic-nuclear translocation of the c-Rel/p50 heterodimer, as manifested by decreased expression of the genes encoding IFNβ and TNFα in Mal-deficient cells. In addition, a novel interaction of the Mal with the Atg16L1 protein involved in the autophagy process was identified.

Due to the participation of the TLR9 receptor in many disease processes, including in the course of encephalitis associated with HSV-1 infection (HSE - Herpes Simplex-1 Encephalitis), but also in autoimmune diseases, such as systemic lupus erythematosus and psoriasis, it seems important to understand new mechanisms of innate immune response regulation, including TLR9-dependent response, which will enable the development of new antiviral therapies.