POLISH ACADEMY OF SCIENCES
INSTITUTE OF IMMUNOLOGY AND EXPERIMENTAL THERAPY
LABORATORY OF SIGNALING PROTEINS

EWA KOWALCZYK

Adaptor protein Mal/TIRAP and its role in TLR7 signaling pathway

(dissertation)

Supervisor:
Jakub Siednienko, PhD

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ABSTRACT

Toll – like receptors (TLRs) constitute a crucial element of the innate immune response. Their function is ensured by the capability to recognize a wide variety of pathogen-associated molecular patterns (PAMP`s) followed by triggering a signaling cascade upon binding of a ligand. TLRs activation results in the release of a variety of cytokines that orchestrate complex action of the immune system. The well-known example is the production of pro-inflammatory and antiviral cytokines including TNFα, CCL5, IFN and priming naive cells of the adaptive immune system in response to microbial and viral stimuli. However, in some instances e.g. following tissue damage, TLRs can also be activated by molecules of endogenous origin and instigate an immune response that leads to autoimmune diseases.

TLR`s dependent activation of the immune response to viral infection proceeds via induction of anti-viral type I interferons (IFN) and chemokines i.e. IP-10. Virus-derived molecules including DNA, ssRNA or dsRNA are recognized by intracellular TLRs including TLR3, 7/8 and 9. Particularly TLR7 has emerged in the light of recent research as a key sensor of viral ssRNA, as has been shown in examples including Influenza, HIV or Sendai viruses. TLR7 also recognizes imidazoquinolines, such as R848 and R837, which mimic single-stranded RNA.

The results presented in this dissertation indicate that the R848 triggered TLR7 signaling requires the adaptor protein Mal. Mal, a key component of the TLR4 signaling pathway, facilitates TLR7-induced IFNβ production but is not necessary for TNFα expression in macrophages and plasmacytoid dendritic cells. Moreover it was shown that both ERK1/2 and IRF7 activation following TLR7 engagement are dependent on the expression of Mal. Additionally results indicate that TLR7 and Mal-dependent ERK1/2 phosphorylation requires PI3K (phosphoinositide 3-kinase) activity, a key enzyme involved in the autophagosome formation. The hypothesis considering PI3K as a link between TLR7 signaling and the autophagy process seems to appear as an interesting research topic since TLR signaling pathways are complex and integrate many different molecules and mechanisms - still not fully understood. Elucidation of the new aspects of TLR`s functionality may also provide insight into the mechanism of autoimmune disorders and contribute to the development of targeted therapies.