Pellino3 ligase and its role in type I IFN signalling pathways.

Abstract:

The body protection against viral infection is inducing and regulating innate and acquired immune mechanisms. One of such a mechanism is stimulating immune cells to produce antiviral cytokines such as interferons (IFNs), which provide a high level of protection against the development of viral diseases. In the IFN I gene expression, regulation pattern recognition receptors (PRRs) are involved, that detect the nucleic acids of pathogens. One of such a receptor is the Toll-like receptors (TLRs) and their induction leads to the ubiquitin ligase Pellino3 activation, which regulates signaling pathways induced by ligand binding to TLR3 and TLR4 receptors, resulted in the secretion of type I IFN. Considering the fact, that Pellino3 indirectly influences the level of produced IFNβ in TLR pathways, this work focused on understanding the role of Pellino3 in signaling cascades activated by IFNβ interactions with IFNAR.

The studies were carried out on murine bone marrow derived macrophage and human monocytes using murine and human recombinant interferon β. The results obtained in the first stage of this study showed that the ubiquitin ligase Pellino3 is involved in the expression regulation of the interferon-stimulated genes (ISG), activation and the secretion of cytokines like Cxcl10, CXCL10 and Cxcl11.

In the next stage of the research, it was shown that Pellino3 influences the key proteins phosphorylation of the JAK-STAT signaling pathway, such as TYK2 kinase and STAT1 transcription factor. In addition, Pellino3 ligase is involved in the translocation into the nucleus of STAT1 and the regulatory factor IRF9.

In further experiments, the Pellino3 participation in the signaling cascade, transduced with type I IFN, that activates the transcription factor - NFκB was shown. It has been shown that the Pellino3 protein presence is required for the phosphorylation and degradation of the NFκB inhibitor subunit, IκBα and is also required for translocation into the nucleus of the NFκB family proteins: p65, RelB and cRel.

The obtained results with use of the NFκB and the 26S proteasome inhibitors and literature data allowed to propose two models in which Pellino3 is involved in the NFκB activation process, where TRAF proteins play a key role. The first model suggests that Pellino3 interacts with TRAF6, leading to the activation and degradation of IκBα in the 26S proteasome,

resulting in p65 / p50 proteins translocation into the nucleus. The second model suggests that Pellino3 interacts with TRAF2, consequently this ligase affects the RelB protein translocation to nucleus.