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Perspective

Regulation of *TPL2* Gene in Viral Infection

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DESCRIPTION

Signals from Toll-Like Receptor (TLRs) 3 and 9 did not initiate early activation of the IKKβ-*TPL2*-ERK pathway. Instead, delayed NADPH oxidase-dependent ERK phosphorylation and TNF-α secretion were induced *via* autocrine ROS signaling. Surprisingly, *TPL2* gene is a key regulator of ROS production during TLR signaling. Due to defective IL-1β induction in *TPL2*$^{-/-}$ macrophages, ROS are essential for IL-1β production in response to LPS. In addition to ROS-mediated ERK phosphorylation in TLR3 and TLR9 signaling, this study also identified *TPL2* as a key regulator of ROS production in TLR signaling. Immediate activation of *TPL2* and ERK during TLR7 signaling also suggests that *TPL2* likely plays a preferential role in host defense against TLR7-triggering RNA viruses. A recent study showed that Vesicular Stomatitis Virus (VSV) replication was increased in embryonic fibroblasts of *TPL2*-deficient mice. However, MAP3K8/*TPL2* is a positive regulator of murine gamma herpesvirus 68 lytic gene expression and replication, and *TPL2* upregulates lytic gene expression and viral lytic gene promoter activity, thereby inhibiting Murine gamma Herpes Virus (MHV)-68 enhanced lytic replication. Therefore, the *TPL2*/AP-1 signaling pathway was confirmed to be a positive regulator of lytic replication of MHV-68. Regulation of downstream NF-κB and MAPK signaling pathways by the p105-ABIN2-*TPL2* complex was essential for host cell responses to pathogens. Interestingly, M protein interacted not only with RelAp43, but also with *TPL2* and ABIN2. The M protein then interacts with the complex to promote ABIN2 release, promoting the production of RelAp43-p50 NF-κB dimers and controlling the expression of IFNβ, TNF and CXCL2 during rabies infection.

Mitogen-Activated Protein (MAP) kinase cascades not only activate key intracellular signaling pathways in response to various external stimuli, but also immune and inflammatory factors during infection. Various intracellular signaling pathways, including NF-κB1, MAP kinase and IRF, are activated by viral infection with receptors that regulate the induction of antiviral IFNs. Therefore, MAPs are important for regulating IFN production and participating in antiviral immunity. In MAP kinases, *TPL2*/MAP3K8 plays an important role in regulating IFN by promoting the ERK-dependent c-fos induction. *TPL2* is essential for IFN-α production from Plasmacytoid Dendritic Cells (pDC) and IFN-γ production from CD4$^+$ T cells. Therefore, *TPL2* is essential for inducing an effective immune response during infection. Mechanistically, *TPL2* enhances induction of ISG and virus-specific CD8$^+$ T cells to purify virus and exert specific effects, whereas deficient CD8$^+$ T cells mediate reduced ISG expression. This phenomenon increases susceptibility, as deficient phenotypes of antiviral factors such as IFITM3 can alter the infection process. Moreover, the effects of *TPL2* on the induction of IFN-γ in T cells is associated with *TPL2* in a manner that is dependent on the Akt-FOXO1 cascade. Regulation of *TPL2* on Akt-FOXO1 signaling in CD8$^+$ T cells also revealed anamnestic responses and antiviral effects of *TPL2* in chronic viral infections.

TPL2 plays an important role in regulating Aktser473 phosphorylation and PI3K/mTOR-mediated IFN-λ production. In addition, *TPL2* directly transduces type I IFN signaling, causes phosphorylation of ERK and STAT1 Ser727, and regulates the induction of ISGs, which are important for limiting viral replication. In addition to early innate immune responses, *TPL2* also induces proliferation of specific CD8$^+$ T cells, which may facilitate virus clearance from infected lungs.

CONCLUSION

IRF7 is thought to be the 'master regulator' for the induction of type I IFNs in influenza virus infection, suggesting an important role for IRF7 in the induction of IFNα/β production. In addition to regulating ISG transcription, the TPL2-ERK signaling pathway also regulates the phosphorylation of the translation initiation factor eIF4E. It is involved in the translation of various genes. Thus, the *TPL2*-ERK pathway regulates the biological effects of IFNs at the transcriptional and post-transcriptional level, whereas *TPL2* not only restricts viral replication but also modulates immune responses in the lung. *TPL2* also promotes host protective immunity during influenza virus infection by integrating innate and adaptive antiviral immune responses.

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