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"PTPN13 CONTRIBUTES TO EBOLA VIRUS INDUCED IMMUNE DYSREGULATION VIA DEPHOSPHORYLATION OF IRF3 AND PI3K-p85β"

By

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Department of Medicine

Wednesday, March 25th, 2026
Cancer Center, G1196
12:00 P.M.

Join Zoom presentation
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ABSTRACT

Ebola virus (EBOV) infection can trigger a cytokine storm and immune dysregulation leading to immunopathology. Despite being the main cause of disease and resulting mortality, the immune signaling pathways and regulatory mechanisms targeted during EBOV infection remain incompletely defined. We focused on investigating post-translational modification (PTM) enzymes, identifying how their expression and activity regulate key on and off signals for the immune response. Phosphorylation has known roles in regulating the expression and production of antiviral type-I Interferons (IFN-I) and other cytokines, prompting us to examine phosphatases and their potential differential expression over the course of viral infection. We identified Protein Tyrosine Phosphates Non-receptor Type 13 (PTPN13), whose expression was increased transiently early during infection followed by a rapid decrease. PTPN13 knockout cells showed increased IRF3 phosphorylation and subsequent IFN-β and IFN-stimulated genes (ISGs) induction upon dsRNA Poly(I:C) stimulation. Additionally, we detected binding between PTPN13 and IRF3, specifically an IRF3-5D mutant, through co-immunoprecipitation assays. Using an IFN-β luciferase reporter assay, we show that ectopic expression of WT IRF3 has increased IFN reporter activity in PTPN13 KO cells as compared to WT cells. In contrast, IRF3 encoding a mutation that lacks phosphorylation on Y292 (Y292F) is inactive in both WT and PTPN13 KO cells, indicating that Y292 is the target site for dephosphorylation by PTPN13. RNA sequencing (RNAseq) analysis showed that PTPN13 KO cells infected with EBOV had an early spike in IFN-I production followed by reduced ISG induction at a later time point that correlated with a small but significantly higher level of EBOV titers during infection. In addition, PTPN13 KO cells also showed a significant decrease in AKT phosphorylation, which correlated with reduced induction of the neutrophil chemoattractant CXCL1 due to an increase in the p85β regulatory subunit of PI3K. Together, these data suggest that PTPN13 regulates multiple immune inflammatory signaling pathways and identifies IRF3 as a target of PTPN13. We propose that the decrease in ISGs observed during EBOV infection in PTPN13 knockout cells is due to another pathway either targeted by the virus or indirectly regulated by PTPN13 that further dampens the IFN response.