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Identification of PP1 as the First Phosphatase for IRF7

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Commentary

Interferon (IFN) regulatory factor 7 (IRF7) is phosphorylated and activated in response to pathogenic infections for production of type I IFNs. The IFN production has to be turned off soon after infection. While there are a panel of kinases have been identified for IRF7 phosphorylation, no phosphatase has been reported for IRF7 dephosphorylation that may play a pivotal role in turning off IFN production. We have recently addressed this critical question by identification of protein phosphatase 1 (PP1) as the first phosphatase for IRF7.

Main content: The host innate immune system defends against invading pathogens initially by triggering signaling pathways mediated by the transmembrane receptors TLRs [1], and cytoplasmic receptors that include RLRs [2,3], NLRs [4], cGAS [5,6], IFI16 [7], DDX41 [8,9], DHX9/36 [10,11], RNA polymerase III [12], TRIM5α [13], ISG56 [14], LRRFIP1 [15], MRE11 [16], amongst others. Interferon (IFN) regulatory factor 7 (IRF7) is phosphorylated and activated downstream of many of these innate immune pathways for induction of IFN-I gene expression (especially IFNαs) [17]. The innate immune system also comprises of lymphocytes-mediated epigenetic memory, which defends reinfection and involves ATF7-mediated chromatin regulation [18,19].

IRF7 is required not only for IFN priming at early stage, but also for IFN amplification at later stages when robust IFN-I production depends on a positive regulatory circuit between IRF7 and IFN-I [20-22]. This robust reaction is turned off soon after infection under normal physiological conditions, but excessive production of IFN-I is fatal to the cell. Thus, regulation of IRF7 phosphorylation is of paramount importance for controlling antiviral innate immunity. However, no phosphatase for negative regulation of IRF7 phosphorylation and activity has been reported.

In our recent study [23], we have identified a conserved protein phosphatase 1 (PP1)-binding motif in human and mouse IRF7 proteins, and shown that PP1 physically interacts with IRF7. Exogenous expression of PP1 subunits (PP1α, β or γ) ablates IKKε-stimulated IRF7 phosphorylation and dramatically attenuates IRF7 transcriptional activity. Inhibition of PP1 activity significantly increases IRF7 phosphorylation and IRF7-mediated IFNα production in response to NDV infection or Toll-like receptor 7 (TLR7) challenge, leading to impaired viral replication. In addition, IFN treatment, TLR challenges and viral infection induce PP1 expression.

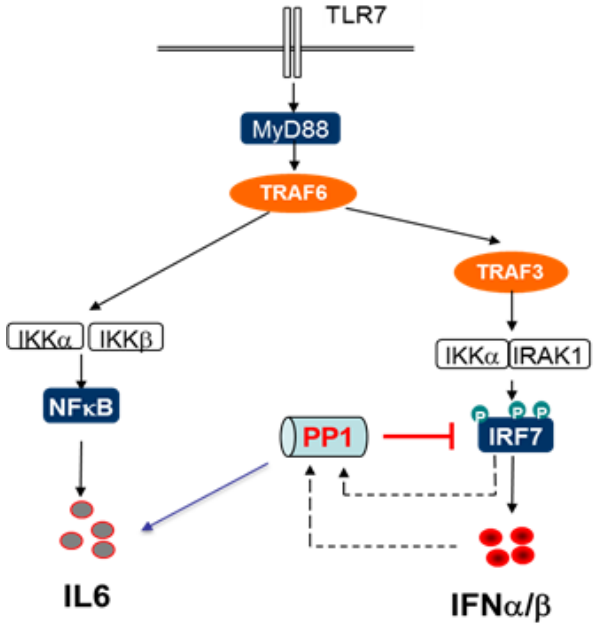

Figure 1: PP1 abrogates IRF7-mediated type I IFN response in antiviral immunity. IRF7 is phosphorylated by IKKs or IRAK1 downstream of TLR signaling pathways in response to viral infection. PP1 targets IRF7 for dephosphorylation and attenuates type I IFN production in these signaling pathways. Also, PP1 promotes IL6 production. In addition, IFN treatment, TLR challenges and viral infection induce PP1 expression. Correspondingly, we have identified IFN-responsive elements and IRF-binding motifs in the PP1 gene promoters, and the transcriptional regulation is currently under investigated.

Our results are the first to identify PP1 as a phosphatase that targets key activating phosphorylation sites of IRF7, attenuating its activity and blocking the IFN-I response during viral infection (Figure 1). Thus, our study has addressed an important knowledge gap regarding IRF7-mediated IFN-I innate immune response, and has broad significance in IFN-mediated antiviral innate immunity and IRF7-mediated pathogenesis [17]. In future follow-up studies, we will validate our findings in *in vivo* systems, and develop strategies to control PP1 phosphatase activity during viral infection for potential clinical interventions.

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