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], TRIM5a [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 reinfecion 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 reacition 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 IKKe-stimulated IRF7 phosphorylation and dramatically attenuates IRF7 transcriptional activity. Inhibition of PP1 activity significantly increases IRF7 phosphorylation and 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.

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.
References