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Commentary OMICS International

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.

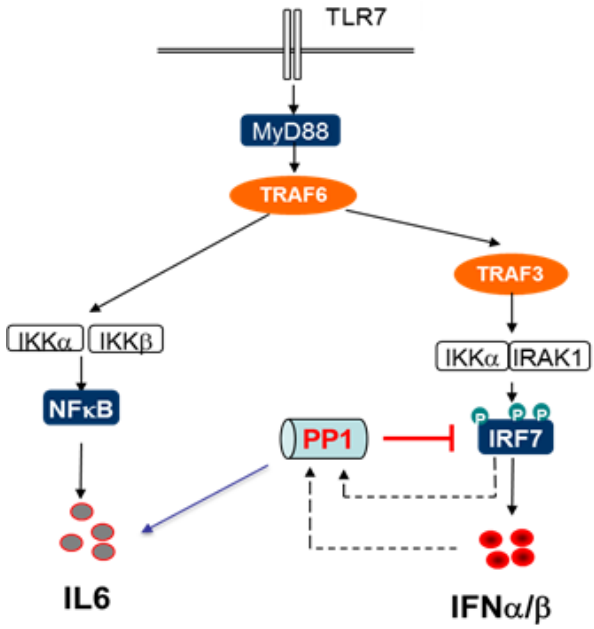

Figure 1: PP1 abrogates IRF7-mediated type I IFN response in antiviral immunity. IRF7 is phosphorylated by IKKs or IRAK1 downstream of TLR signaling pathways in response to viral infection. PP1 targets IRF7 for dephosphorylation and attenuates type I IFN production in these signaling pathways. Also, 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.

References

1. Kawai T, Akira S (2010) The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol 11: 373-384.
2. Rehwinkel J, Reis e Sousa C (2010) RIGorous detection: exposing virus through RNA sensing. Science 327: 284-286.
3. Hornung V, Latz E (2010) Intracellular DNA recognition. Nat Rev Immunol 10: 123-130.
4. Sha W, Mitoma H, Hanabuchi S, Bao M, Weng L, et al. (2014) Human NLRP3 inflammasome senses multiple types of bacterial RNAs. Proc Natl Acad Sci U S A 111: 16059-16064.
5. Sun L, Wu J, Du F, Chen X, Chen ZJ (2013) Cyclic GMP-AMP synthase is a cytosolic DNA sensor that activates the Type I interferon pathway. Science 339: 786-91.
6. Wu J, Sun L, Chen X, Du F, Shi H, et al. (2013) Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. Science 339: 826-830.
7. Unterholzner L, Keating SE, Baran M, Horan KA, Jensen SB, et al. (2010) IFI16 is an innate immune sensor for intracellular DNA. Nat Immunol 11: 997-1004.
8. Parvatiyar K, Zhang Z, Teles RM, Ouyang S, Jiang Y, et al. (2012) DDX41 recognizes the bacterial secondary messengers cyclic di-GMP and cyclic di-AMP to activate a type I interferon immune response. Nat. Immunol 13:1155-61.
9. Zhang Z, Yuan B, Bao M, Lu N, Kim T, et al. (2011) The helicase DDX41 senses intracellular DNA mediated by the adaptor STING in dendritic cells. Nat Immunol 12: 959-965.
10. Kim T, Pazhoor S, Bao M, Zhang Z, Hanabuchi S, et al. (2010) Aspartate-glutamate-alanine-histidine box motif (DEAH)/RNA helicase A helicases sense microbial DNA in human plasmacytoid dendritic cells. Proc Natl Acad Sci USA 107: 15181-6.
11. Zhang Z, Kim T, Bao M, Facchinetti V, Jung SY, et al. (2011) DDX1, DDX21, and DHX36 Helicases Form a Complex with the Adaptor Molecule TRIF to Sense dsRNA in Dendritic Cells. Immunity 34: 866-78.
12. Chiu YH, Macmillan JB, Chen ZJ (2009) RNA polymerase III detects cytosolic DNA and induces type I interferons through the RIG-I pathway. Cell 138: 576-591.
13. Pertel T, Hausmann S, Morger D, Züger S, Guerra J, et al. (2011) TRIM5 is an innate immune sensor for the retrovirus capsid lattice. Nature 472: 361-365.
14. Pichlmair A, Lassnig C, Eberle CA, Górna MW, Baumann CL, et al. (2011) IFIT1 is an antiviral protein that recognizes 5'-triphosphate RNA. Nat Immunol 12: 624-630.
15. Yang P, An H, Liu X, Wen M, Zheng Y, et al. (2010) The cytosolic nucleic acid sensor LRRFIP1 mediates the production of type I interferon via a beta-catenin-dependent pathway. Nat Immunol 11: 487-494.
16. Kondo T, Kobayashi J, Saitoh T, Maruyama K, Ishii KJ, et al. (2013) DNA damage sensor MRE11 recognizes cytosolic double-stranded DNA and induces type I interferon by regulating STING trafficking. Proc Natl Acad Sci USA 110: 2969-74.
17. Ning S, Pagano JS, Barber GN (2011) IRF7: activation, regulation, modification and function. Genes Immun 12: 399-414.
18. Yoshida K, Maekawa T, Zhu Y, Guillet CR, Chatton B, et al. (2015) The transcription factor ATF7 mediates lipopolysaccharide-induced epigenetic changes in macrophages involved in innate immunological memory. Nat Immunol16: 1034-43.
19. Fang TC, Schaefer U, Mecklenbrauker I, Stienen A, Dewell S, et al. (2012) Histone H3 lysine 9 di-methylation as an epigenetic signature of the interferon response. JEM 209: 661-9.
20. Marie I, Durbin JE, Levy DE (1998) Differential viral induction of distinct interferon-à genes by positive feedback through interferon regulatory factor-7. EMBO J 17: 6660-9.
21. Sato M, Hata N, Asagiri M, Nakaya T, Taniguchi T, et al. (1998) Positive feedback regulation of type I IFN genes by the IFN-inducible transcription factor IRF-7. FEBS Lett 441: 106-110.
22. Honda K, Taniguchi T (2006) IRFs: master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. Nat Rev Immunol 6: 644-58.
23. Wang L, Zhao J, Ren J, Hall KH, Moorman JP, et al. (2016) Protein phosphatase 1 abrogates IRF7-mediated type I IFN response in antiviral immunity. Eur J Immunol 46: 2409-2419.