# MAPK Phosphatase 5 Expression Induced by Influenza Virus Negatively Regulates IRF3 Activation and Type I Interferon Response

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**Background/Objective**
Type I interferons (IFNs) are essential for host defence against viral infection such as influenza A virus infection which is a major threat to public health globally. Type I IFNs are the major targets of viral immune evasion strategies. The interferon regulated factor 3 (IRF3) is known as a master regulator of type I IFNs. MAP kinase phosphatases (MKPs) has been implicated a role in regulation of type I interferon expression. However, if MKPs regulate IRF3-type I interferon is unclear. In this study, we investigated the regulatory role of MKP5 in innate immune response, particularly in the IRF3-type I interferon axis, to influenza infection.

**Method**
Mice deficient in MKP5 were infected with H1N1 and H3N2 influenza viruses to examine the function of MKP5 in immune response to influenza infection. Wild-type and MKP5 knockout bone marrow-derived macrophages and dendritic cells were generated to investigate the regulatory mechanism of this protein in IRF3-type I interferon signaling upon influenza infection.

**Result**
Mice deficient in MKP5 were resistance to PR8 (H1N1) influenza virus infection compared with wild-type mice, which is associated with increased IRF3 activation and type I IFN expression in the lung. Mechanistically, MKP5 directly interacts with and dephosphorylates IRF3 at Ser396 and Ser386 residues to inhibit IRF3 activation and type I IFN expression in response to virus infection. Interestingly, the non-structure protein 1 (NS1) from H1N1 and H3N2 influenza viruses induces the expression of MKP5. However, the inhibition of MKP5 on type I interferon expression is independent of NS1.

**Conclusion**
MKP5 is a novel negative regulator of IRF3-type I IFN system. Our study for the first time reveals a critical function of a dual specificity phosphatase in the negative regulation of IRF3 activity and demonstrates a novel mechanism by which influenza inhibit type I interferon response in host through MKP5.