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Understanding inhibition of viral proteins on type I IFN signaling pathways with modeling and optimization

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ABSTRACT

The interferon system provides a powerful and universal intracellular defense mechanism against viruses. As one part of their survival strategies, many viruses have evolved mechanisms to counteract the host type I interferon (IFN-α/β) responses. In this study, we attempt to investigate virus- and double-strand RNA (dsRNA)-triggered type I IFN signaling pathways and understand the inhibition of IFN-α/β induction by viral proteins using mathematical modeling and quantitative analysis. Based on available literature and our experimental data, we develop a mathematical model of virus- and dsRNA-triggered signaling pathways leading to type I IFN gene expression during the primary response, and use the genetic algorithm to optimize all rate constants in the model. The consistency between numerical simulation results and biological experimental data demonstrates that our model is reasonable. Further, we use the model to predict the following phenomena: (1) the dose-dependent inhibition by classical swine fever virus (CSFV) N^{pro} or E^{rns} protein is observed at a low dose and can reach a saturation above a certain dose, not an increase; (2) E^{rns} and N^{pro} have no synergic inhibitory effects on IFN-β induction; (3) the different characters in an important transcription factor, phosphorylated IRF3 (IRF3p), are exhibited because N^{pro} or E^{rns} counteracted dsRNA- and virus-triggered IFN-β induction by targeting the different molecules in the signaling pathways and (4) N^{pro} inhibits the IFN-β expression not only by interacting with IFR3 but also by affecting its complex with MITA. Our approaches help to gain insight into system properties and rational therapy design, as well as to generate hypotheses for further research.

1. Introduction

Type I interferons (IFN-α/β) represent the first line of defense for the innate immune system (Kawai and Akira, 2006), which play essential role in immunity to viral infection (Bekisz et al., 2004; Schindler, 2002; Taniguchi and Takaoka, 2001). Virus and double-strand RNA (dsRNA) induce IFN-α/β production by Toll-like receptor 3 (TLR3)-dependent and/or TLR3-independent signaling pathways (Levy and Garcia-Sastre, 2001; Levy and Marie, 2004). The latter is associated with the two RNA helicases, retinoic acid-inducible gene-I (RIG-I) (Yoneyama et al., 1998) and melanoma differentiation-associated gene 5 (MDA5) (Andrejeva et al., 2004). These two parallel signaling pathways converge by activating the transcription factors IRF3 and NF-κB, ultimately leading to IFN-α/β production and establishment of an antiviral state in host cells. Signaling pathways for virus- and dsRNA-triggered IFN-α/β gene expression are summarized in Fig. 1.

As seen in Fig. 1, upon viral infection, dsRNA (a replication intermediate of RNA viruses) interacts with the RNA helicase domain of RIG-I or MAD5. The caspase-recruitment domain of RIG-1 or MAD5 then transmits signals to the CARD modules of VISA (also known as CARDIF, IPS1 and MAVS) in the mitochondrial membrane (Hornung et al., 2006; Kato et al., 2006; Meylan et al., 2004; Seth et al., 2005; Xu et al., 2005). In the outer mitochondrial membrane, an another adaptor protein, MITA interacts with the signaling molecules VISA and IRF3 (Zhong et al., 2008), to form MITA–VISA and MITA–IRF3 complexes, respectively. Two complexes can get together by MITA–MITA interaction. As a TANK-binding kinase 1 (TBK1) substrate, the phosphorylated MITAs are significantly increased during viral infection, which triggers the subsequent phosphorylation of IRF3 and IRF7. Phosphorylated IRF3 (IRF3p), in turn, forms a homodimer or a heterodimer with phosphorylated IRF7 (IRF7p). The dimeric complexes then translocate to the nucleus, leading to the expression of IFN-α/β genes. Generally, IRF7 is expressed in low level in most cells. After

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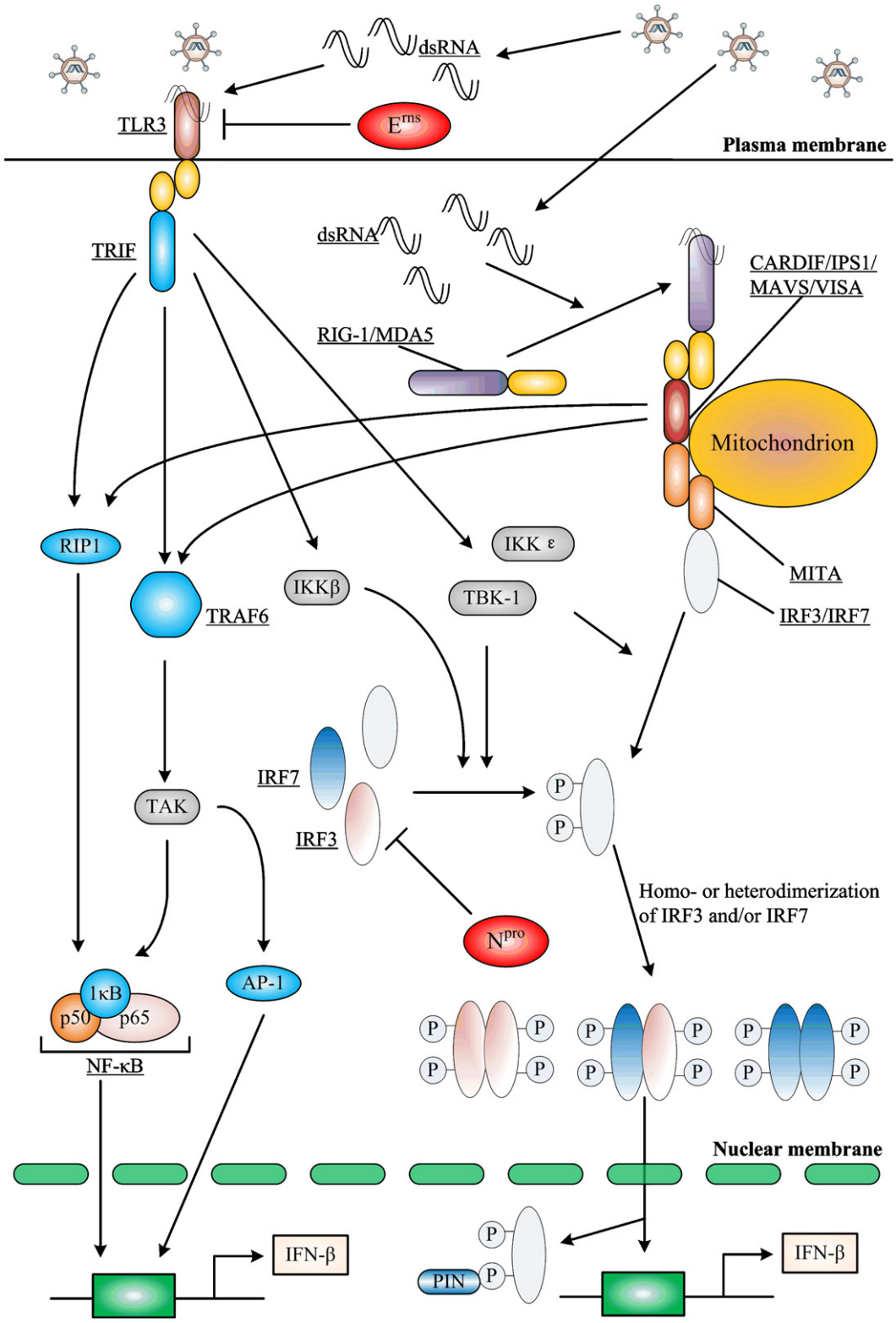

Fig. 1. Schematic diagram of dsRNA- and virus-triggered type I IFN signaling pathways, including all key components considered in the model. dsRNA in the cytoplasm activates the RIG-I/MDA5-mediated signaling pathway. Exogenous dsRNA triggers the Toll-like receptor 3 (TLR3)-mediated signaling pathway. Both signaling pathways result in the activation of transcript factor NF-kB, AP-1 and IRF3/7, leading to the transcription of type I IFN gene (IFN-α/β). CSFV N^{pro} and E^{rns} proteins are also shown to negatively modulate type I IFN signaling pathways.

viral infection, IRF7 is up-regulated and phosphorylated. IRF7p positively regulates the expression of IFN-α/β, which is responsible for the high level of IFN-α/β at the late phase of viral infection (Marie et al., 1998; Sato et al., 1998).

The exogenous dsRNA-triggered IFN-α/β induction is mediated by TLR3, which sensors extracellular dsRNA (Oshiumi et al., 2003; Yamamoto et al., 2002; Yoneyama et al., 2004). Binding of dsRNA to TLR3 initiates a unique signaling cascade that depends on the