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REVIEW

Novel functions of type I interferons revealed by infection studies with *Listeria monocytogenes*

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Abstract

Infection of cells and mice with *Listeria monocytogenes* stimulates production of type I interferons (IFN). These in turn sensitise the Listeria host to lethal sequelae of infection with these bacteria. Here, we summarise recent findings on the production and biological effects of type I IFN in the course of *L. monocytogenes* infection.

Keywords: Infection; Intracellular bacteria; *Listeria monocytogenes*; Type I interferons; TLR

Contents

Introduction

Type I interferons (IFNs) were described more than 50 years ago for their ability to 'interfere' with viral infections. These cytokines exert their antiviral ability by inducing hundreds of IFN-stimulated genes (ISGs), which can impede viral propagation at different stages of the infectious cycle. The family of type I IFN genes comprises more than 15 members in humans and mice, with 14 IFNα subtypes and one single IFNβ species being the most studied ones. Binding of IFNα/β to the

Abbreviations: IFN, interferon; IRF, interferon regulatory factor; ISGF3, interferon-stimulated gene factor 3; Jak, Janus kinase; MyD88, myeloid differentiation factor 88; SH2, Src homology 2 domain; STAT, signal transducer and activator of transcription; TLR, Toll-like receptor; TRAM, TRIF-related adaptor molecule; TRIF, Toll/IL-1 receptor (TIR)-domain-containing adaptor inducing IFN-beta; TUNEL, terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling; Wt, wild-type.

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type I IFN receptor (IFNAR) leads to the activation of the receptor-associated tyrosine kinases Jak1 (Jak – Janus kinase) and Tyk2, which in turn phosphorylate the receptor-chains and thus create docking sites for the transcription factors STAT 1 and 2 (STAT – signal transducer and activator of transcription). STAT1 and 2 are phosphorylated by the Jaks at their tyrosine residues 701 and 689, respectively, and heterodimerise via reciprocal association of their Src homology 2 (SH2) domains (see Fig. 1). Together with IRF-9 (IRF – interferon regulatory factor), this protein complex forms the transcription factor ISGF3, which binds to DNA at the interferon-stimulated response elements (ISRE) and induces transcription of ISGs (Decker et al., 2002; Decker et al., 2005; Darnell, 2007; Stark, 2007).

Studies in the field of innate immune recognition extended the function of type I IFNs beyond their role in inducing an antiviral response. With the discovery of the myeloid differentiation factor 88 (MyD88)-independent pathway downstream of TLR4 (TLR – Toll-like receptor) it became clear that also bacterial products can induce copious amounts of type I IFN (Perry et al., 2005; Pietras et al., 2006; Stetson and Medzhitov, 2006a). The MyD88-independent pathway leading to type I IFN synthesis downstream of TLRs 3 and 4 requires a distinct adapter protein, Toll/IL-1 receptor (TIR)-domain-containing adaptor inducing IFN-beta (TRIF), which in the case of TLR4 is aided by its interactor TRIF-related adaptor molecule (TRAM). TRIF-dependent signalling stimulates activity of the protein serine threonine kinase Tank-binding kinase 1 (TBK1) and/or its kin, IKKε. Both TBK1 and IKKε belong to the larger family of IκB kinases. Their activity concerning IRF3 activation is redundant in some, but not all cell types (Hemmi et al., 2004; Matsui et al., 2006). These kinases phosphorylate transcription factors belonging to the IRF family, most prominently IRF-3 and IRF-7. Whereas IRF-3 activity is limited to the IFN-β promoter, IRF7 is capable of stimulating all type

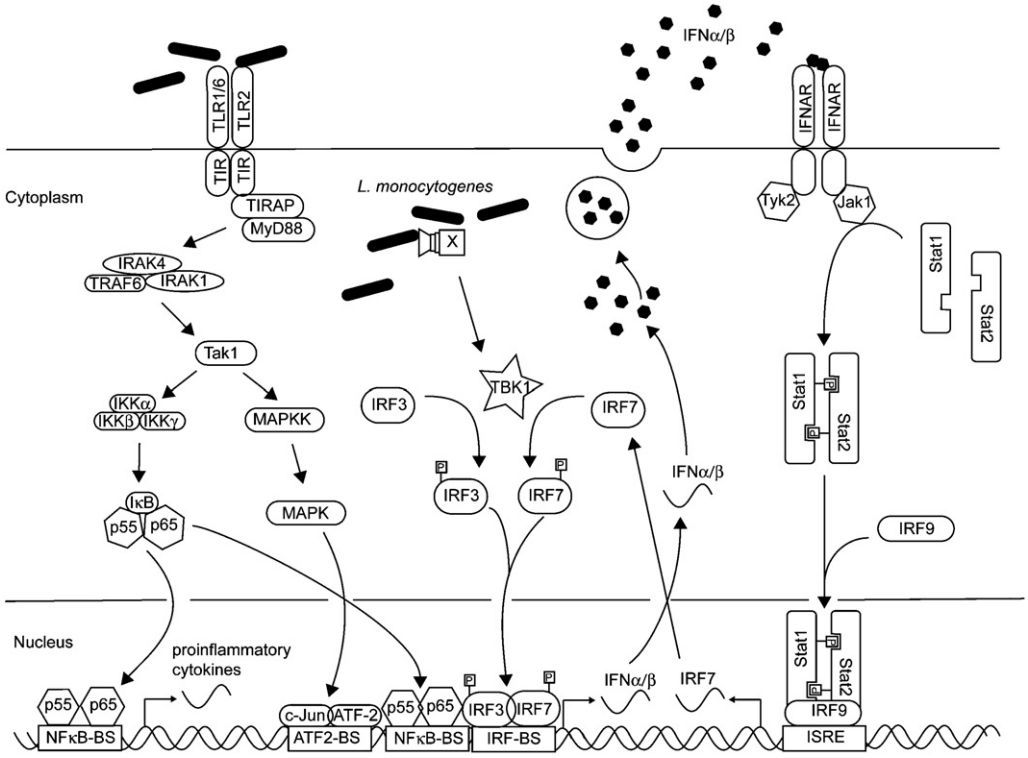

Fig. 1. Signalling pathways stimulated by *L. monocytogenes*. TLR2 stimulation by membrane components of *L. monocytogenes* leads to activation of the MAPK and NFκB pathways and the synthesis of proinflammatory cytokines. The signal diverges at the level of TAK1, which stimulates the IKK-complex leading to degradation of IκB and release of NFκB, and which activates MAPKK resulting in the activation of the transcription factors c-Jun and ATF-2. After escape to the cytoplasm, and recognition by an unknown receptor X, *L. monocytogenes* triggers the activation of TBK1, which in turn phosphorylates IRF-3. Following translocation to the nucleus, activated IRF-3 stimulates the synthesis of IFN-β. The IFN-β promoter additionally contains binding sites for NFκB and c-Jun/AFT2. IFN-β is secreted and binding to its receptor activates the Jak kinases Jak1 and Tyk2. Phosphorylation of STAT1 and STAT2 via the Jaks enables the heterodimerisation of these two proteins by reciprocal recognition of their SH2 domains. Together with IRF-9, the proteins form the transcription factor ISGF3, which triggers the synthesis of ISGs. One of these genes, IRF-7, can again be activated by TBK1 and induce a second wave of type I IFN synthesis, thus leading to a positive amplification loop.