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Review

Putting the brakes on the anti-viral response: negative regulators of type I interferon (IFN) production

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Abstract

Type I IFNs (IFNα/β) are essential anti-viral cytokines produced in response to the detection of viral components by host pattern recognition receptors. IFNα/β production is transient, and aberrant activation can be hazardous to the host. In this article, we review our current understanding of host negative regulatory mechanisms that control IFNα/β production.
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Keywords: Interferon; Virus; Negative regulation

1. Introduction

The anti-viral innate immune response depends upon the production of a family of cytokines called type I interferons, composed of IFNβ and several IFNα species [1]. IFNα/β are produced in direct response to virus infection and promote an anti-viral environment in cells. Initiation of the IFNα/β driven anti-viral state requires their *de novo* transcription, which is ultimately dependent upon the detection of viral pathogen-associated molecular patterns (PAMPS) by germ line encoded pattern recognition receptors (PRR). These PRRs include members of the Toll-like receptor (TLR) and RIG-I-like receptor (RLR) families [2]. Engagement of PRRs with PAMP ligands results in the orchestrated activation of numerous signalling pathways that culminate in the nuclear translocation of a number of transcription factors, including NFκB and interferon regulatory factors (IRF3/IRF7) [3]. These form an enhanceosome complex and initiate transcription from IFNα/β genes. Secreted IFNα/β proteins act in both an auto- and paracrine fashion, alerting the surrounding cells to the presence of pathogens. They bind to IFNAR1/2 receptors on the cell surface and initiate a signalling cascade resulting in the activation of over 300 interferon-stimulated genes (ISGs) in the target cell, including the dsRNA activated protein kinase (PKR) and 2′-5′oligoadenylate synthase (2′-5′-OAS). PKR suppresses protein synthesis in infected cells, whilst 2′-5′-OAS activates RNAse L, which degrades virus genomes. In addition they enhance the immune response to virus infection by activating effector cell function and promoting an adaptive immune response.

The potency of the IFNα/β response is illustrated by numerous inflammatory disorders, including Systemic Lupus Erythromatosus, dermatomyositis and psoriasis, in which enhanced IFNα/β expression is associated with inflammation and tissue damage. Accordingly, the negative regulation of IFNα/β production by host proteins is of paramount importance and over recent years increasing number of these proteins has been identified. These have been shown to target multiple signalling pathways to prevent inappropriate inflammation (Table 1). Here we provide an overview of the proteins known to inhibit PRR-mediated IFNα/β production and describe the various mechanisms employed to achieve suppression of this response. Understanding how anti-viral signalling is regulated may lead to new strategies for the control of both viral and inflammatory diseases.

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Table 1
Regulators of type I IFN production.

Inhibitor	Target(s)	Mechanism	Regulation	Ref
TRIAD3a	TLR9/TRAF3	Lys-48 polyubiquitylation and degradation	Steady state and negative feedback	[8, 59]
Rab7b	TLR9	Lysosomal degradation of MyD88	Steady state	[9]
ST2	MyD88	Sequestration of MyD88	Steady state	[13]
SIGIRR	MyD88	Sequestration of MyD88	Steady state	[12]
MyD88s	MyD88	Dimerisation with MyD88	Negative feedback	[14]
SARM	TRIF	Sequestration of TRIF	Negative feedback	[15]
SQSTM1/HDAC6	MyD88	Sequestration of MyD88	Steady state	[16]
TRAF1	TRIF	Sequestration of TRIF	Negative feedback	[17]
LGP2	RIG-I/IPS-1	Sequestration of RNA	Steady state	[23]
RIG-I kinase X	RIG-I	Phosphorylation preventing interaction with TRIM25	Steady state	[24,25]
CYLD	RIG-I/TRAF2/TRAF6/RIP1/TBK1	Deubiquitylation of targets	Steady state, levels reduced during infection	[26,43]
RNF125	RIG-I	Lys-48 polyubiquitylation and degradation	Negative feedback	[27]
ISG15	RIG-I	Sequestration of RIG-I	Negative feedback	[28]
Atg5–Atg12	RIG-I/Mda-5/IPS-1	Binds RLRs and IPS-1 adaptor	Steady state	[34]
DAK	Mda-5	Sequestration of Mda-5	Steady state	[29]
Mfn2	IPS-1	Sequestration of IPS-1	Steady state	[36]
gC1qR	IPS-1	Competes with RLR for IPS-1	Negative feedback	[38]
NLRX1	IPS-1	Competes with RLR for IPS-1	Steady state	[37]
PCBP2/AIP4	IPS-1	Lys-48 polyubiquitylation of IPS-1	Negative feedback	[40]
PSMA7	IPS-1	Mediates proteasomal degradation of IPS-1	Negative feedback	[41]
PLK1	IPS-1	Sequestration of IPS-1 from TRAF3	Negative feedback	[35]
A20	RIP1/TBK1	Proteolytic degradation of RIP1 and blocks interaction between TRAF3-TBK1	Negative feedback	[56,72]
OTUB1/OTUB2	TRAF6	Deubiquitylate TRAF6	Negative feedback	[45]
TANK	TRAF6	Unknown	Steady state and negative feedback	[47]
FLN29	TRAF6/TRAF3	Unknown	Negative feedback	[46]
Optineurin	RIP1/TBK1/TRAF3	Competes with NEMO for RIP1 and complexes with TBK1-TRAF3	Negative feedback	[48,49]
TRIM30α	TAB2/TAB3	Probable lysosomal degradation of TAB2/TAB3	Negative feedback	[50]
NLRC5	IKKα/IKKβ	Sequesters IKK complex into inactive form	Steady state	[51]
SHIP-1	TBK1	Dephosphorylates TBK1	Negative feedback	[58]
DUBA	TRAF3	Deubiquitylates TRAF3	Negative feedback	[60]
SIKE	TBK1/IKKε	Sequesters TBK1/IKKε in inactive complex	Steady state	[61]
Pin1	IRF3/IRF7	Phosphorylation isomerisation	Negative feedback	[63]
Cullin E3 ligase	IRF3/IRF7	Phosphorylation dependent Lys-48 polyubiquitylation and degradation	Negative feedback	[65]
RBCK1	IRF3	Lys-48 polyubiquitylation and degradation	Steady state and activated	[64]
TRIM21/Ro52	IRF3/IRF7	Lys-48 polyubiquitylation and degradation	Negative feedback	[66]
SUMO	IRF3/IRF7	SUMOylation	Steady state and negative feedback	[69]
HDAC1/HDAC8	IRF3/IRF7	Transcriptional repression	Negative feedback	[70]
MafB	RF3/IRF7	Sequestration from CBP	Steady state	[71]

2. Toll like receptors: gatekeepers of the innate immune response

Ten TLRs have been identified in humans and these recognise specific molecular patterns on invading microorganisms. TLRs are type I trans-membrane proteins characterised by an extracellular leucine-rich repeat region that binds ligands and a cytoplasmic Toll-interleukin (IL) 1-Receptor homology (TIR) domain, responsible for initiating signal transduction. This review discusses TLRs implicated in the response to virus infection: TLR3 detects dsRNA, TLR7 recognises ssRNA and TLR9 binds to hypomethylated CpG-rich DNA [3]. As there are several excellent reviews on the regulation of TLRs [4,5], we provide only a brief description of some of the strategies adopted by the cell to prevent inappropriate TLR activation.

An abundance of evidence highlights the importance of TLR localisation for the correct recognition of ligand [6]. Given that host nucleotides can act as TLR ligands and potentially induce an autoimmune response, the anti-viral TLRs are compartmentalised to avoid such an event. TLR3, TLR7 and TLR9 contain retention signals that maintain them in the ER until cells are stimulated with the appropriate ligand, at which point they are specifically chaperoned to the correct endosomal compartment and couple to components of the signalling machinery to initiate down-stream signalling. For TLR9, correct signalling is only achieved when the immature form of the receptor is cleaved

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