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Interferons and interferon stimulated genes - role in RNA viral infections

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Abstract
Interferons and interferon-stimulated genes (ISGs) play a crucial role in the immune response against viral infections. Interferons are signaling proteins that are released by infected cells to alert neighboring cells of the presence of a viral invader. Upon binding to their receptors on neighboring cells, interferons induce the expression of ISGs, which have various antiviral functions. These ISGs can inhibit viral replication, enhance antigen presentation, and activate immune cells to eliminate the virus. Understanding the intricate interplay between interferons and ISGs is essential for developing effective antiviral therapies.

Keywords: Interferon, interferon stimulated genes (ISGs), viral infection, pattern recognition receptors (PRRs)

Introduction
Interferons and interferon-stimulated genes (ISGs) play a crucial role in the immune response against viral infections. Interferons are a group of signaling proteins that are produced by host cells in response to viral invasion. They are part of the innate immune system and act as a first line of defense against viruses. Upon detection of viral components, infected cells release interferons to alert neighboring cells of the impending threat. These interferons bind to specific receptors on surrounding cells, triggering a cascade of events that result in the expression of various ISGs.

ISGs are genes that are upregulated in response to interferon signaling. They encode proteins that have antiviral properties and play a key role in limiting viral replication and spread. ISGs can be broadly categorized into two groups: those that directly inhibit viral replication and those that modulate the immune response. Some ISGs encode enzymes that target different steps of the viral life cycle, such as viral entry, replication, and assembly. These enzymes can interfere with essential viral processes, preventing the virus from replicating efficiently. Other ISGs are involved in the activation and regulation of immune cells, enhancing the immune response against the virus.

The induction of interferons and ISGs is tightly regulated to ensure an appropriate immune response. The production of interferons is triggered by the recognition of viral components by pattern recognition receptors (PRRs) within infected cells. PRRs can detect various viral molecules, such as viral RNA or DNA, and initiate a signaling pathway that leads to interferon production. Once released, interferons bind to their receptors on neighboring cells, activating intracellular signaling pathways that result in the upregulation of ISGs.

The role of interferons and ISGs in viral infections extends beyond their direct antiviral effects. They also play a crucial role in shaping the adaptive immune response. Interferons can enhance antigen presentation by infected cells, leading to a more efficient recognition of viral antigens by T cells. Additionally, they can regulate the differentiation and function of various immune cell types, such as dendritic cells and natural killer cells, further contributing to the elimination of viruses.

Different components of innate immune system involved in active immunity against viral infections are discussed here.

Pattern recognition receptors

The presence of viral nucleic acids and PAMPs (pathogen associated molecular patterns) in the host cells are recognized by PRRs (Pattern recognition receptors). The PRRs are distributed in the cytoplasm, endosomes and on the cellular surface. The recognition of PAMPs by PRRs leads to activation of a cascade of reactions leading to the increased expression of type I Interferons as well as inflammatory cytokines and chemokines.

Of all the PRRs involved in sensing RNA viral genomes, Toll-like receptors (TLRs) and RLRs have remarkable role. TLRs such as TLR2, TLR4 and TLR5 are expressed on the surface, while TLR3, TLR7, TLR8 and TLR9 are present on the endosomal compartments of some cell types. Retinoic acid-inducible gene-I (RIG-I)- like receptors (RLRs) are ubiquitous and recognize cytosolic RNA helicases. TLR3 recognises double stranded RNA (dsRNA) where as TLR7 and 8 detect single-stranded RNA (Said *et al.*, 2018) [31].

TLRs, which belong to type I transmembrane proteins, have extracellular N-terminal with three major domains: N-terminal extracellular domain (ECD), which is rich in leucine-rich repeats (LRRs) undergoes dimerization upon binding with the dsRNA of the pathogen and initiates the signal transduction cascade that is mediated through the transmembrane alpha helix domain. The third domain, C-terminal cytoplasmic toll-interleukin 1 receptor (TIR) domain-contains adaptor protein-inducing IFN-β (TRIF) is then recruited, which, upon undergoing slight conformational changes form a signalling complex with TNF receptor-associated factor 6 (TRAF6), TRAF3 and TBK1. This signalling complex activates NF-κB pathway leading to the production of type 1 IFNs and cytokines, respectively (Said *et al.*, 2018) [31].

RLRs, which form the second group of PRRs involved in sensing viral RNA, belong to the family of cytosolic RNA helicases that specifically detects either double stranded or single stranded RNA species derived from viruses in the cytoplasm. Till date, three RLRs such as RIG-I (Retinoic acid inducible gene I), MDA-5 (Melanoma differentiation associated factor 5) and LGP2 (Laboratory of Genetics and Physiology 2) have been identified. Basal or low levels of RLR expression is maintained in normal uninfected cells; however, the expression is upregulated following exposure to IFN or viral infection (Yoneyama *et al.*, 2004) [45]. They are involved in activating the innate immune response in myeloid cells, epithelial cells, and cells of central nervous system. Further, MDA-5 is reported to be upregulated in cells lacking IFN receptor upon virus infection indicating that the virus can directly upregulate RLR expression (Yount *et al.*, 2007) [46].

Once viral RNA PAMPs is recognized by the C terminal domain, RIG-I or MDA-5 undergoes a conformational change and the latent CARD domains are exposed, leading to an association with CARD adaptor protein mitochondrial antiviral signalling (MAVS) through homotypic CARD-CARD interactions leading to dimerization of MAVS. The dimerization of MAVS recruits TNF receptor-associated factors (TRAFs), resulting in the activation of transcription factors such as nuclear factor-κB (NF-κB) and IFN regulatory factor (IRF)-3/7. Homodimerized IRFs and activated NF-κB translocate to the nucleus and activate the production of pro-inflammatory cytokines and type I IFN transcripts (Chiba *et al.*, 2015) [5].

Members of RLR family are involved in recognizing a variety of viruses. For instance, RIG-I senses hepaciviruses and the members of *Paramyxoviridae*, *Rhabdoviridae* and *Orthomyxoviridae.* Both MDA-5 and RIG-I are involved in recognition of certain viruses like West nile virus, Dengue virus and Reo viruses (Kato *et al.*, 2006) [17]. Studies have suggested that innate immune responses in Picornavirus infection is triggered by MDA-5. MDA-5 recognises large dsRNA fragments, representing either part of a viral genome or a viral replication product (Feng *et al.*, 2012) [10]. During the course of viral replication, negative strand RNA and double stranded RNA (dsRNA) are formed, known as the replicative form (RF), triggers a significant IFN α/β response (Kato *et al.*, 2006) [17].

Interferons

Interferons (IFNs), the first line of host innate immune defenses against viral infections, were discovered by Issacs and Lindenmann in 1957 [16] during the infection of chick chorio-allantoic cells with influenza virus. The authors demonstrated that infected cells produced a secreted factor that induced a virus resistant state. IFNs belong to a large family of multifunctional, secreted proteins involved in antiviral defense, cell growth, differentiation, apoptosis and modulation of immune function through autocrine and paracrine mechanisms (Samuel, 2001) [32].

The IFNs are classified into three distinct types depending on the receptor complex they signal through- type I, II and III. Type I IFNs, also called viral IFNs include many subtypes like IFN-α, IFN-β, IFN-ε, IFN-κ and IFN-ω, that signals through the type I IFN heterodimeric receptor complex comprising IFNAR1 and IFNAR2. Type I IFNs are primarily induced by virus infections and can be synthesized by almost all cell types particularly upon viral infection. They have antiproliferative and immunomodulatory activities along with the antiviral activity. Type II IFNs are also known as immune IFN with IFN γ as the only member. They are stimulated by mitogen or antigen stimuli and are synthesized by cells of immune system. Type II IFNs mainly have pro-inflammatory and immunomodulatory functions that are distinct from type I and type III IFN functions (Lee and Ashkar, 2018). Type III IFNs include IFN λ1, IFN λ2and IFN λ3 and are stimulated by similar pathogen sensing pathway as of type I IFN and elicits antiviral, anti-proliferative and immunomodulatory activities. These class of IFNs confer antiviral activity at epithelial surfaces and provides a front-line defence that confers less collateral damage than type I IFNs (Lazear *et al.*, 2019) [22]. Type III IFNs signal through heterodimeric receptor, IFNLR, and forms a signalling-component ternary complex upon binding. Despite the differences in their receptors, all the IFNs signal through JAK-STAT pathway. Upon binding, IFN induces phosphorylation of JAK1/TYK2 kinases that in-turn activate the latent cytoplamsic proteins STAT1 and STAT2. The phosphorylated STATs heterodimerize and bind to IRF9 forming the ISGF3 complex, which translocate to the nucleus to activate IFN stimulated genes through ISRE dependent promoters (Dussurget *et al.*, 2014) [8]. Though type III IFNs binding to their cognate receptor, IFNLR1, induces similar signalling cascade, it activates GAS-dependent promoters in the nucleus. Expression of genes during IFN signalling include ISGs, the Interferon stimulated genes, which are involved in wide range of activities (Schneider *et al.*, 2014) [33].

Interferon Stimulated Genes

Interferon stimulated genes (ISGs), the effectors of IFN signalling, are engaged in a wide array of activities in the cell especially during viral infection. Over 300 ISGs are identified

till date and often detects viral molecules and modulate signalling pathways. ISGs activate transcription factors of JAK-STAT pathway to augment IFN production and protection from virus (Sadler and Williams, 2008) [30]. Some ISGs act in synergistic manner to augment specific PRR signalling pathways. Some important ISG candidates pertaining to antiviral activity are OAS/*RNaseL*, viperin, PKR (Protein kinase R), ISG-15, Mx-proteins, Cholesterol 25 hydroxylase (Ch25H), TRIM, IFIT, IFITM.

Some ISGs like OAS and PKR can recognize double stranded RNA in the cells. OAS is expressed at constitutive levels in the cytosol and are also induced by IFNs. Cytosolic PAMP (viral RNA) detection by OAS leads to the synthesis of 2'-5'-oligoadenylates, which then act as intracellular second messengers to activate latent *RNaseL* (Hovanessian and Justesen, 2007) [14-15] resulting in widespread cleavage of both host and viral RNA. And, the production of additional PAMPs reinforce the innate immune response. In addition to the OAS/*RNaseL* system, activation of protein kinase R (PKR) by cytosolic PAMPs leads to a dramatic reduction in host cell translation as well as to the degradation of the inhibitor of κB (KB) that results in activation of the NF-κB signalling pathway.

Antiviral Effectors

To complete their life cycle, viruses must enter cells, translate and replicate their genomes and exit in order to infect new cells. Every stage of the virus life cycle is a potential target for ISG intervention and there are examples of ISGs targeting each one. The antiviral can be categorized depending on the stage of viral life cycle at which they act, as follows (Schneider *et al.,* 2014) [33]

1. Inhibition of virus entry: Mx proteins, Ch25H, IFITM proteins, TRIM proteins
2. Inhibition of viral RNA replication and translation: ISG-15, ZAP, OAS/*RNaseL* and PKR.
3. Inhibitors of viral egress: Viperin and tetherin.

Inhibition of viral entry

Myxovirus resistance (Mx) proteins, Mx1 and Mx2 belong to a small family of dynamin-like large guanosine triphosphatases (GTPases), which is closely related to the dynamin GTPase family. They have N-terminal GTPase domain, central interacting domain and C-terminal leucine zipper. Both the central domain and leucine zipper are required for recognition of viruses (Sadler and Williams, 2008) [30]. Mx1 is broadly inhibitory and traps incoming viral components, such as nucleocapsids, and prevents them from reaching their cellular destination.

Mx1 proteins have been shown to interfere with the replication of FMDV O serotype at early stages post infection in BHK-21 cells. The expression of bovine Mx1 protein reduced viral yields by 90% and viral VP1 mRNA by 60% (Cai *et al.,* 2013) [4]. In another study, insertion of internal ribosome entry site (IRES) of FMDV-Mx1 construct between promoter and ORF of porcine Mx1 showed protection against FMDV infection in PK-15 cells (Yuan *et al.,* 2015) [47]. Other viruses that are susceptible to Mx proteins include Coxsackie virus (*Picornaviridae*), Hepatitis B virus (*Hepadnaviridae*); *Bynyaviruses*, *Orthomyxovirus* and *Paramyxovirus*. Bovine Mx1 localized in the cytoplasm elicits antiviral activity against vesicular stomatitis virus of *Rhabdoviridae* family (Verhelst *et al.,* 2013) [42].

Ch25H converts cholesterol to soluble factor, 25-hydroxy cholesterol and the expression levels of Ch25H is upregulated by both type I and type II IFNs. Ch25H mediated protection occurs at the stage of virus - host membrane fusion of the infectious cycle. High concentrations of 25 hydroxy cholesterol result in the changes in physical properties of membrane and as a soluble oxysterol, 25HC inhibits viral entry by blocking membrane fusion between virus and cell (Liu *et al.,* 2013) [26]. Also, 25 hydroxy cholesterol inhibits the sterol biosynthesis by negative feedback mechanism. The sterol biosynthesis pathway generates isoprenoids (farsenyl and geranyl and geraniol) which are critical for protein prenylation. Protein prenylation plays a critical role in life cycle of several viruses (Einav and Glenn, 2003) [9]. 25HC can exert its antiviral effects by multiple mechanisms like altering the membrane properties directly (for enveloped viruses) by inhibiting sterol biosynthesis through negative feedback and affecting prenylation of both virus and host proteins. 25HC can broadly inhibit the replication of viruses like Herpes simplex virus, HIV, Ebola virus, Vesicular stomatitis virus (Liu *et al.,* 2013) [26], Porcine reproductive and respiratory syndrome virus, Reovirus (Doms *et al.,* 2018) [6].

Interferon induced transmembrane proteins (IFITM) composed of four proteins IFITM 1, 2, 3 and 5. These proteins function at the stage of viral entry into the cell. IFITM proteins prevent virus from traversing the lipid bilayer of the cell and accessing the cytoplasm (Bailey *et al.,* 2014) [2]. They also inhibit endocytic fusion events *i.e.* restriction occurs at endosomes and lysosomes of broad spectrum of viruses, but the actual mechanism of how these proteins act is still not clear. IFITM proteins are mainly involved in restricting enveloped viruses and some non-enveloped viruses like reovirus (Anafu *et al.,* 2013) [1].

The tripartite motif (TRIM) family of proteins is large and contain more than 80 members. The members of this family play central role in host defense against viral infections. The structure of TRIM proteins has N-terminal RING domain, followed by B-box domain and a C-terminal coiled coil domain. RING domain and B-box domain are important for TRIM protein role as E3-ubiquitin ligases., TRIM proteins are associated with virus-induced autophagy and autophagy-mediated viral clearance. TRIM25, TRIM65 regulates RLR signalling; TRIM 6, 24 and 28 are implicated in the regulation of IFNAR signal transduction. Several TRIM proteins showed direct antiviral activity on retrovirus, Japanese encephalitis virus, Flavivirus. Further, recent studies have identified that TRIM25 acts as a key regulator of ZAP's antiviral activity by mediating both K48- and K63-linked polyubiquitination of ZAP (Zheng *et al.,* 2017) [48].

Inhibition of viral replication and translation

The first member in this group, ISG-15, is a ubiquitin like protein. It covalently attaches to the target proteins by isopeptide bond through ISGylation. ISGylation does not drive protein degradation, but rather parallels ubiquitin's activating effects. ISG15 prevents virus mediated degradation of the IFN regulatory factor 3 (IRF3), thereby enhancing induction of IFNβ (Shi *et al.,* 2010) [34]. ISGylation modulates enzyme function; for instance, ISGylation of host protein 4EHP (negative regulator of translation) increases its affinity for the 5′ cap structure of RNA thereby enhancing its ability to block translation initiation (Okumura *et al.,* 2007) [28]. Conversely, conjugation of ISG15 to the Protein Phosphatase 1B (PPM1B) suppressed enzyme activity, thereby enhancing NF-κB signalling. In addition, co-translational attachment of ISG-15 to viral capsid proteins inhibits the assembly of virus

particles.

ZAP, zinc finger antiviral protein was originally identified as host restriction factor that inhibits the replication of Moloney murine leukaemia virus (MMLV). CCCH type zinc finger motifs present in the N-terminal end of ZAP directly binds to viral RNA, removes poly A tail using the cellular poly A ribonuclease (PARN) and degrades the RNA body from the 3'-end by recruiting the 3'-5' exoribonuclease complex exosome. The optimal antiviral effects of ZAP is determined by DEAD box RNA helicase p72. Apart from degrading viral transcripts, ZAP also represses their translation (Sun *et al.*, 2012) [36]; however, the mechanistic basis of translational inhibition of ZAP is yet to be unravelled.

Protein kinase R (PKR), which is ubiquitous and constitutively expressed, is linked with the regulation of cell growth and proliferation with tumor suppressor functions. Type I and III IFNs induce the expression of PKR and the resulting serine/threonine kinase activity initiates the signalling cascade. Members of PKR kinase family prevent recycling of GDP, by phosphorylating the translation initiation factor EIF2α at serine 51. This results in the sequestration of the limiting guanine nucleotide exchange factor, EIF2β. Overall, it halts translation and allow the cell to reconfigure gene expression. Much of the antiviral and antiproliferative activities of PKR can be attributed to its phosphorylation of EIF2α (Sadler and Williams, 2008) [30]. Apart from inhibiting the translation, PKR interacts with IKK complex and regulates the signal transduction and transcription by activating the NF-κB pathway (Kumar *et al.*, 1994) [21].

Inhibition of viral egress

Tetherin, also called Bst-2 exhibits antiviral activity primarily against enveloped viruses. The antiviral activity of tetherin was demonstrated in HIV where the protein retains nascent viral particles at the cell surface by linking them to cell surface or to each other and blocking the release of virus from the cell (Perez-Caballero *et al.*, 2009) [29]. The trapped viral progeny on the surface of infected cells undergoes degradation. The second mode of action is that tetherin was identified as an activator of NF-κB suggesting that tetherin is an intermediate in the signal transduction process. A variety of enveloped viruses have been shown to be restricted by tetherin like simian immunodeficiency virus, Rous sarcoma virus, Ebola virus, filo viruses and Herpes virus (Kuhl *et al.*, 2011) [20].

Conclusion

In conclusion, interferons and interferon stimulated genes play a crucial role in the immune response against viral infections. Interferons are cytokines that are produced by infected cells as a defense mechanism to limit viral replication and spread. They act by inducing an antiviral state in surrounding cells, which helps to inhibit viral replication and prevent the spread of infection. Additionally, interferon stimulated genes are activated by interferons and play a key role in the antiviral response. These genes produce proteins that have various antiviral activities, such as inhibiting viral replication, degrading viral RNA, and activating immune cells. Together, interferons and interferon stimulated genes form a potent defense system against viral infections. In summary, understanding the role of interferons and interferon stimulated genes in viral infections is critical for the development of effective antiviral therapies. Further research is needed to explore the specific mechanisms by which these molecules exert their antiviral effects and to identify potential interventions that can enhance their activity. By harnessing the power of interferons and their downstream targets, we can hope to improve our ability to combat viral infections and protect public health.

Conflict of Interest

Not available

Financial Support

Not available

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