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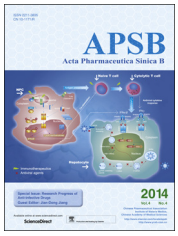

REVIEW

Recent advances in the anti-HCV mechanisms of interferon

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Abstract Interferon (IFN) in combination with ribavirin has been the standard of care (SOC) for chronic hepatitis C for the past few decades. Although the current SOC lacks the desired efficacy, and 4 new direct-acting antiviral agents have been recently approved, interferons are still likely to remain the cornerstone of therapy for some time. Moreover, as an important cytokine system of innate immunity, host interferon signaling provides a powerful antiviral response. Nevertheless, the mechanisms by which HCV infection controls interferon production, and how interferons, in turn, trigger anti-HCV activities as well as control the outcome of HCV infection remain to be clarified. In this report, we review current progress

Abbreviations: CHC, chronic hepatitis C; DCs, dendritic cells; DNAM1, DNAX accessory molecule-1; dsRNA, double-stranded RNA; E2, envelop 2; GAS, IFN-γ-activated site; GWAS, genome-wide association studies; IFN, interferon; IFN-α, interferon-α; IFNAR1, interferon-alpha receptor 1; IFNAR2, interferon-alpha receptor 2; IFNGR1, interferon gamma receptor 1; IFNGR2, interferon gamma receptor 2; IFNL4, IFN-lambda 4; IL-10R2, interleukin-10 receptor 2; IL-29, interleukin-29; IRF-3, interferon regulatory factor 3; IRGs, IFN regulatory genes; ISG15, interferon-stimulated gene 15; ISGs, IFN-stimulated genes; ISGF3, IFN-stimulated gene factor 3; ISREs, IFN-stimulated response elements; JAKs, Janus activated kinases; MAVS, mitochondrial antiviral signaling protein; MDA-5, melanoma differentiation-associated gene-5; MHC, major histocompatibility complex; NKCs, natural killer cells; NKTCs, natural killer T cells; OAS, 2′-5′-oligoadenylate synthetase; PAMPs, pathogen-associated molecular patterns; PBMCs, peripheral blood mononuclear cells; pDC, plasmacytoid dendritic cell; PKR, protein kinase R; PRRs, pattern recognition receptors; RdRp, RNA dependent RNA polymerase; RIG-I, retinoic acid-inducible gene-I; RLRs, RIG-I-like receptors; SNPs, single-nucleotide polymorphisms; SOC, standard of care; STAT1, signal transducer and activator of transcription 1; STAT2, signal transducer and activator of transcription 2; SVR, sustained virological response; TH1, T-helper-1; TH2, T-helper-2; TLRs, Toll-like receptors; TYK2, tyrosine kinase 2; USP18, ubiquitin specific peptidase 18

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in understanding the mechanisms of IFN against HCV, and also summarize the knowledge of induction of interferon signaling by HCV infection.

1. Introduction

Interferons (IFNs) are a family of cytokines secreted by host cells in response to various pathogens like viruses, bacteria, fungi, or parasites which trigger the protective defenses of the immune system[1]. To defend against invading viral pathogens, the interferon signatures activate the transcription of numerous IFN-stimulated genes (ISGs) and thus promote a broad-spectrum of antiviral responses[2].

In 1986, interferon-α (IFN-α) was first approved as a treatment for patients with non-A non-B (now renamed type C) chronic hepatitis. After this landmark study, further improvements in research technologies led to increased sustained virological response (SVR) rates. These included addition of the guanosine analog ribavirin to IFN treatment[3], followed by pegylation of the IFN molecule. Pegylated IFN-α, which was developed to extend the interdose interval to at least one week, offered improved convenience, decreased side effects, and superior clinical efficacy when compared with IFN-α. Presently, the standard treatment of chronic hepatitis C remains the combination of pegylated IFN-α and RBV. Recently, three NS3-4A protease inhibitors, telaprevir (Vertex/Janssen)[4], boceprevir (Merck) and simeprevir (Janssen)[5,6], and one NS5B RNA dependent RNA polymerase (RdRp) inhibitor sofosbuvir (Gilead)[6], have been approved in combination with pegylated IFN-α and ribavirin for the treatment of chronic HCV infection. These agents will improve the rate of SVR, but their toxicities combined with Pegylated IFN-α and RBV may limit their overall efficacy. For this reason, interferons are still likely to remain the cornerstone of therapy for some time.

Since the first use of the standard therapeutic paradigm against chronic hepatitis C more than 20 years ago, fundamental biomedical research has greatly improved our understanding of the underlying molecular mechanisms of IFN production, regulation and antiviral action. This has been accompanied by substantial progress in understanding the HCV life cycle.

Presently, we review the current information on the mechanisms of IFN actions against HCV, and summarize the latest knowledge of induction of interferon signal by HCV infection (Fig. 1).

2. Induction of interferon

It is well known that the innate immune response is the first line of defense against viral infections, and IFNs are the central cytokines responsible for the induction, activation and regulation of the antiviral state in innate immune cells like natural killer cells (NKCs)[7]. Based on their structural features, receptor usage and biological activities, three distinct types of IFNs are now recognized. Type I IFNs (IFN-α, IFN-β and IFN-ω) and type III IFNs (IFN-λ1, IFN-λ2 and IFN-λ3; also named as IL29, IL28A, and IL28B respectively) are produced by most types of cells which are infected with virus and also by key sentinel cells of the innate immune system: macrophages and dendritic cells (DCs). However, the type II IFNs (IFN-γ) are only produced by certain cells of the immune system, including NKCs and natural killer T cells (NKTCs), which belong to a part of the innate immune response, as well as antigen-specific T cells (both CD4+ T helper 1 and CD8+ cytotoxic T cells).

It is now clear that there are several families of pattern recognition receptors (PRRs) surveying the cellular micro-environment for viral infection. The two important characterized families of PRRs that detect viral genomes and then induce type I and type III IFNs are the Toll-like receptors (TLRs) and the retinoic acid-inducible gene-I (RIG-I)[8]. After recognizing viral infection, these receptors initiate intracellular signaling cascades, which are responsible for the production of type I and type III IFNs and proinflammatory cytokines, and mediate the antiviral immune response finally. TLRs are a family of transmembrane pattern recognition receptors that recognize microbial pathogen-associated molecular patterns (PAMPs) and activate the expression of genes involved in inflammatory and immune responses[9]. There are at least 10 human TLRs, and 5 of them are involved in the recognition of viral infections. TLR3, TLR7 and TLR9 represent a TLR subfamily that recognize viral nucleic acids and induce an endogenous interferon response, while viral glycoproteins have been shown to interact with TLR2 and TLR4. TLRs are expressed on several types of immune cells including macrophages, DCs, B cells, as well as fibroblasts and epithelial cells. When the HCV invades, the TLR2 will recruit TLR1 and TLR6 as coreceptors for HCV core- and NS3-mediated activation of macrophages and innate immunity in humans[10]. Meanwhile, HCV infection directly induces TLR4 expression and thereby activates B cells, which may contribute to the host's innate immune responses[11]. Along with TLR3, TLR7 and TLR9 are localized in intracellular compartments such as endosomes. The latest reports show that TLR3 and TLR7 play highly significant roles in the recognition of HCV RNA[12–15]; TLR3 senses double-stranded RNA (dsRNA), which is an essential intermediate in the HCV replication cycle, and then initiates signaling that activates NF-κB and interferon regulatory factor 3 (IRF-3), thereby inducing the synthesis of type I IFN[16]. TLR7, expressed on the DCs and Kupffer cells, shows a very good ability to sense the HCV RNA, subsequently leading to the synthesis of type I IFNs[12,17].

Importantly, macrophages and DCs do not have to directly infect themselves by HCV in order to produce IFNs. Instead, they constantly screen materials from the outside, including intact viral particles and cellular remnants containing viral fractions. After the degradation in the endosomes, viral nucleic acids are exposed and recognized by TLRs. In addition, viruses escaping the endosomal entry pathway can be detected by the cytosolic pathways and then induce types I and III IFNs. In general, viral RNA genomes or viral replication intermediates can be sensed in cytoplasm or endosomes by the related cytoplasmic RNA helicases RIG-I and melanoma differentiation-associated gene-5 (MDA-5). Accumulating evidence suggests that RIG-I-like receptors (RLRs), particularly RIG-I and MDA5, are responsible for the recognition of HCV RNA[18]. It has been reported that RIG-I senses HCV RNA in the early stage of infection and activates downstream pathways of the innate immune response[19]. After sensing the viral RNA, these sensors utilize the mitochondrial antiviral signaling protein (MAVS, also known as