Cytokine and Growth Factor Reviews xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

journal homepage: www.elsevier.com/locate/cytogfr

ADAR1 and PKR, interferon stimulated genes with clashing effects on HIV-1 replication

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ARTICLE INFO

Keywords:
Interferon
PKR
ADAR1
HIV
Interferon stimulated genes

ABSTRACT

The induction of hundreds of Interferon Stimulated Genes (ISGs) subsequent to virus infection generates an antiviral state that functions to restrict virus growth at multiple steps of their replication cycles. In the context of Human Immunodeficiency Virus-1 (HIV-1), ISGs also possess antiviral functions, but some ISGs show proapoptotic or proviral activity. One of the most studied ISGs, the RNA activated Protein Kinase (PKR), shuts down the viral protein synthesis upon activation. HIV-1 has evolved to evade its inhibition by PKR through viral and cellular mechanisms. One of the cellular mechanisms is the induction of another ISG, the Adenosine Deaminase acting on RNA 1 (ADAR1). ADAR1 promotes viral replication by acting as an RNA sensing inhibitor, by editing viral RNA and by inhibiting PKR. This review challenges the orthodox dogma of ISGs as antiviral proteins, by demonstrating that two ISGs have opposing and clashing effects on viral replication.

1. Introduction

1.1. Interferon pathway in the cell

Interferons (IFNs) are cytokines which belong to the antiviral innate immune system that eukaryotic cells developed through evolution to survive viral infections. IFNs are classified into three groups (types I, II and III) based on their structure, complementary receptors and biological activity [1]. As outflowed in Fig. 1, the production of type I IFNs (IFN-I) is a result of interaction of pathogen-associated molecular patterns (PAMPs) with germline-encoded cellular receptors called Pattern Recognition Receptors. Viral PAMPs include single-stranded (ss) and double-stranded (ds) DNA or RNA molecules, as well as viral glycoproteins [2,3]. Their detection by Toll-like Receptors (TLRs), nucleotide oligomerization domain proteins, C-type lectin receptors and retinoic acid-inducible gene I (RIG-I)-like receptors leads to the release of soluble IFNs [4,5]. Once in the extracellular space, secreted IFNs interact with their corresponding cell surface receptors in either an autocrine or paracrine manner. After binding to IFN-α receptor 1 (IFNAR1), IFN-I immediately activates the Janus kinases/signal transducers and activators of transcription (JAK/STAT) signalling pathway, which results in the formation of a trimer composed of IFN regulatory factor (IRF)-9 and the phosphorylated proteins STAT1 and STAT2 [6,7]. This complex translocates to the nucleus and binds to the IFN Stimulated Response element on responsive promoters to stimulate the induction of hundreds of IFN-stimulated genes (ISGs) [8,9]. This sets up an environment that prevents viral replication and spread, subsequently leading to adaptive immunity [10,11].

Abbreviations: ADAR1, adenosine deaminase acting on RNA 1; AGS, Aicardi-Goutières syndrome; APOBEC3, apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3; ds, double-stranded; dsRBD, dsRNA binding domains; eIF2α, translation initiation factor2; HIV-1, human immunodeficiency virus-1; HLA, human leukocyte antigens; IFITM, interferon-induced transmembrane; IFITs, IFN-induced proteins with tetratricopeptide repeats; IFN-I, type I IFNs; IFNAR1, IFN-α receptor 1; IFNs, Interferons; IP-10, IFNγ inducible protein 10; IRF, IFN regulatory factor; ISGs, interferon stimulated genes; IV, influenza virus; JAK/STAT, Janus kinases/signal transducers and activators of transcription; LCMV, lymphocytic choriomeningitis; MAVS, mitochondrial antiviral-signaling protein; MDA-5, melanoma-differentiation-associated 5; MHCs, major histocompatibility complexes; MV, measles virus; Mx, myxovirus resistance; NK, natural killer; NF-κB, nuclear factor kappa B; OAS, oligoadenylate synthetase; PACT, PKR activator; PAMPs, pathogen-associated molecular patterns; PBMCs, peripheral blood mononuclear cells; PKR, RNA activated protein kinase R; RLI, RNAse L inhibitor; RVFV, Rift valley fever virus; SAMHD1, sterile alpha motif and HD-domain containing protein 1; SIV, simian immunodeficiency virus; SLFN, Schlafen; ss, single-stranded; TAR, trans-activation response; TLRs, toll-like receptors; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; TRIM, tripartite motif; TRBP, TAR RNA binding protein; Tsg101, tumor susceptibility gene 101; Vif, virion infectivity factor; Vpu, viral protein U; Vpx, viral protein X; VSV, vesicular stomatitis virus; VV, vaccinia virus; WNV, West Nile virus

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https://doi.org/10.1016/j.cytogfr.2018.03.007
Received 8 March 2018; Received in revised form 19 March 2018; Accepted 19 March 2018

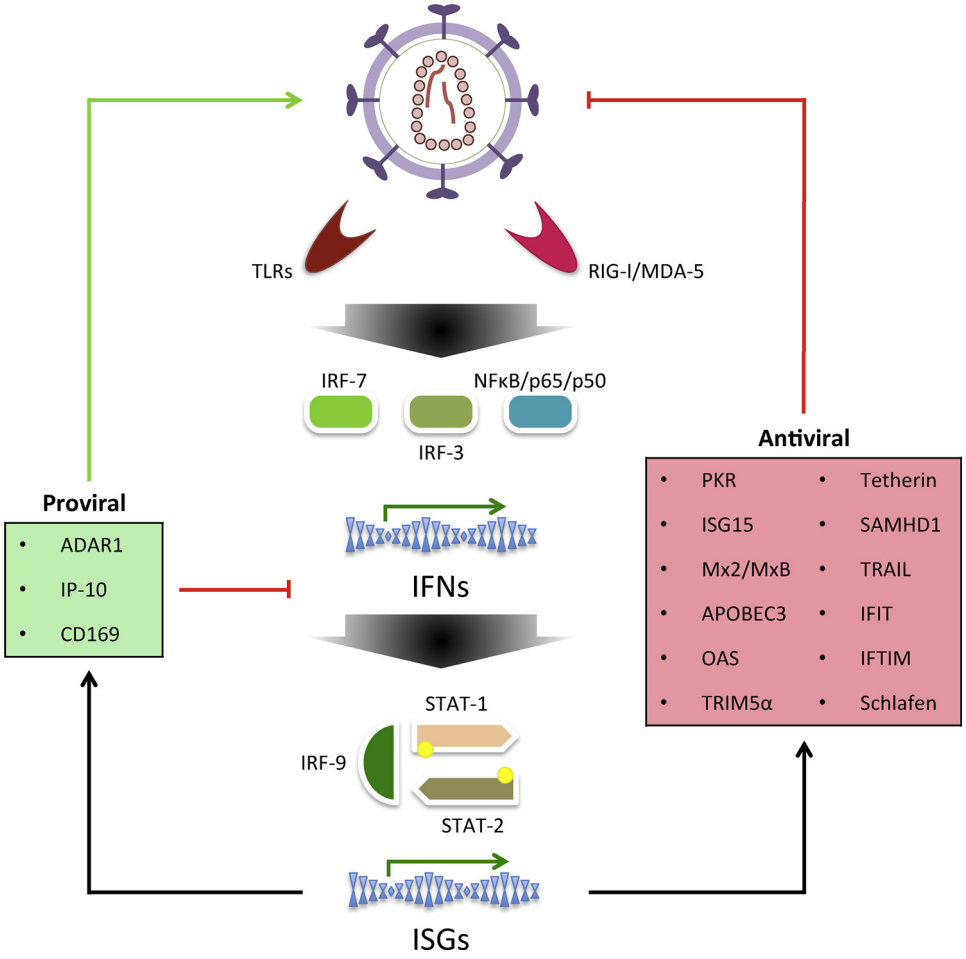

Fig. 1. From PAMPs to ISGs, the induction of antiviral and proviral molecules by the innate immune response to an HIV-1 infection. Toll-like and RIG-I receptors activate transcription factors, IRF-7,-3 or NFκB, upon sensing viral antigens. Newly induced IFN-I triggers the assembly of STAT-1/2 and IRF-9 complex which then promotes the expression of Interferon Stimulated Genes. Antiviral ISGs inhibit HIV-1 propagation at multiple steps of viral life cycle. Proviral ISGs can either inhibit the production of IFNs in infected cells or directly enhance the virus.

1.2. Interferon is needed for viral clearance

IFN treatment of virally infected cells can clear the infection through multiple mechanisms [12]. IFN inhibits Human Immunodeficiency Virus-1 (HIV-1) replication in primary macrophages and lymphocytic T cells, and induces the production of ISGs, blocking several steps, including entry, reverse transcription, protein synthesis, virion assembly and release [13–15]. Several IFN types are used therapeutically against hepatitis C and B viruses, Kaposi's sarcoma-associated herpes virus and papillomaviruses [16,17]. Approaches using combination therapy with pegylated IFN in HIV-1-infected patients with coinfections and IFN treatment during interruption of antiretroviral therapy have also been assessed and have shown lower viral rebounds in the patients receiving IFN [18,19]. Additional evidence of IFN's role comes from the increased influenza virus (IV) replication, dissemination and lethality in mice deleted of IFNAR1 or STAT1 genes [20,21]. For individuals with reduced production of IFN-I and -III in myeloid and peripheral dendritic cells, a seasonal flu can be life-threatening [22]. In the same manner, mice lacking the IFNAR1 were acutely susceptible to West Nile virus (WNV), lymphocytic choriomeningitis virus, vesicular stomatitis virus (VSV) and vaccinia virus (VV) [23–26]. So far, due to viral and cellular counteractions of the ISGs, IFN cannot clear HIV-1 infection, but therapeutic administration of IFNα in infected patients has shown a significant reduction in plasma HIV-1 viral load [27,28].

1.3. IFN can be detrimental in the chronic phase

Production of IFNs is generally very prominent at the beginning of the infection and goes down in the following days regardless of viral clearance to prevent excessive immunopathology. Indeed, when they persist during the chronic phase of infection, IFNs can be detrimental to the cell [11]. During chronic simian immunodeficiency virus (SIV) infection, its natural host, the African green monkey, exhibits low IFN-I levels and does not progress to Acquired Immunodeficiency Syndrome (AIDS), while the Rhesus macaque, the non-natural host, develops AIDS and manifests high levels of IFN-I signaling signatures [29,30]. Equivalently, chronic HIV-1 infection is characterized by elevated levels of pro-inflammatory cytokines, including IFN-I and is correlated to immune activation and a poor prognosis for AIDS progression [31,32]. Therefore, these deleterious effects, mainly in the chronic phase, preclude long-term therapeutic usage of IFNs [33,34].

1.4. The balance between ISGs and their antagonistic actions

Although IFN response proves to be crucial for the initial and subsequent control of a viral infection, many viruses are able to evade it and successfully propagate in the host. This can be due to viral countermeasures that affect IFN production, signaling or the activity of ISGs [16,35]. HIV-1 is an example of such viruses and has evolved ways of countering different ISGs aimed at it [36]. In this review, we will discuss the most studied ISGs that are known to target HIV-1. The main