Virus Research 193 (2014) 65–77

Contents lists available at ScienceDirect

Virus Research

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

HIV-1 translation and its regulation by cellular factors PKR and PACT

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ARTICLE INFO

Article history:
Available online 23 July 2014

Keywords:
HIV
Translation
Protein kinase R
PKR activator

ABSTRACT

The synthesis of proteins from viral mRNA is the first step towards viral assembly. Viruses are dependent upon the cellular translation machinery to synthesize their own proteins. The synthesis of proteins from the human immunodeficiency virus (HIV) type 1 and 2 RNAs utilize several alternative mechanisms. The regulation of viral protein production requires a constant interplay between viral requirements and the cell response to viral infection. Among the antiviral cell responses, the interferon-induced RNA activated protein kinase, PKR, regulates the cellular and viral translation. During HIV-1 infection, PKR activation is highly regulated by viral and cellular factors. The cellular TAR RNA Binding Protein, TRBP, the Adenosine Deaminase acting on RNA, ADAR1, and the PKR Activator, PACT, play important roles. Recent data show that PACT changes its function from activator to inhibitor in HIV-1 infected cells. Therefore, HIV-1 has evolved to replicate in cells in which TRBP, ADAR1 and PACT prevent PKR activation to allow efficient viral protein synthesis. This proper translation will initiate the assembly of viral particles.

1. Introduction

Eukaryotic translation is regulated from initiation to elongation and termination steps (Dever and Green, 2012; Fraser, 2009; Hinnebusch and Lorsch, 2012). The co-evolution between viruses and their hosts results in a mutual interplay between their regulatory mechanisms. Viruses are entirely dependent on cellular translation factors for the production of their proteins. Viruses interfere with host translation mechanisms by subverting cellular factors for their own use, but have also evolved mechanisms to either shut-off or modify cellular translation, which may contribute to their pathogenicity (Li et al., 2013; Mohr and Sonenberg, 2012; Walsh et al., 2013). In addition, the development of specific mechanisms for the production of their own proteins ensures their replication within the cell (Firth and Brierley, 2012; Komarova et al., 2009; Reineke and Lloyd, 2011; Roberts et al., 2009).

In response to virus invasion, cells have evolved mechanisms to counteract the negative impact of viruses and ensure their survival. The immediate innate immune response is mediated by external and internal sensors (Kumar et al., 2011), which recognize the viral components and trigger mechanisms leading to the production of cytokines and interferon (IFN)α/β proteins (Borden et al., 2007; Randall and Goodbourn, 2008). IFNs are secreted, bind to receptors in a paracrine and autocrine manner on different cell types to trigger signalling cascades leading to the production of IFN-stimulated

Abbreviations: ADAR, adenosine deaminase acting on RNA; ds, double-stranded; dsRBD, dsRNA binding domain; dsRBP, dsRNA binding protein; eIF, eukaryotic translation initiation factor; HCV, Hepatitis C virus; HDV, Hepatitis D virus; HIV, human immunodeficiency virus; HTLV, Human T-cell leukaemia virus; IFN, Interferon; IRES, internal ribosome entry site; IKK, inhibitor of nuclear factor kappa-B kinase; IP, immunoprecipitation; ISRE, IFN Stimulated Response element; IRF, IFN regulatory factor; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MDA-7, melanoma-associated gene 7; MEK, MAPK kinase; miRNA, micro RNA; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OAS, 2′-5′oligoadenylate synthetase; PABP, PolyA binding Protein; PAMPs, pathogen-associated molecular patterns; PACT, PKR Activator; PDCs, plasmacytoid dendritic cells; PKR, Protein Kinase RNA activated; RAX, PKR-associated protein X; RHA, RNA Helicase A; RT, reverse transcription; RLR, RIG-I like receptor; RNAi, RNA interference; RRE, Rev Response Element; S-HDag, small delta antigen; slfn, Schlafen; ss, single-stranded; SIV, simian immunodeficiency virus; siRNA, small interfering RNA; STAT, signal transducers and activators of transcription; TAR, trans-activation responsive element; TLRs, Toll-like receptors; TRAF, TNFR-associated factor; TRBP, TAR RNA Binding Protein; UTR, untranslated region; VHS, virus host shutoff; VSV, Vesicular stomatitis virus; ZBD, Z-DNA binding domain.

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http://dx.doi.org/10.1016/j.virusres.2014.07.014
0168-1702/

genes (ISGs) (Randall and Goodbourn, 2008; Sadler and Williams, 2008). Most ISGs have antiviral activities, but some of them, like the adenosine deaminase acting on RNA (ADAR1) have both antiviral and proviral functions (Gélinas et al., 2011; Samuel, 2011). Among the ISGs, the protein kinase RNA-activated (PKR) and the 2′-5′ oligoadenylate synthetases (OAS) are activated by double-stranded (ds)RNA. They block the initiation of translation or activate a latent endoribonuclease, RNAse L, respectively, both resulting in inhibition of cellular and viral protein synthesis (Hovanessian, 2007). To ensure viral replication and cell survival, the activity of these enzymes is regulated by viral and cellular factors (Dabo and Meurs, 2012; Garcia et al., 2006, 2007).

In this review, we will analyze the mechanisms involved in the translation of *Human immunodeficiency viruses* (HIV)-1 and -2 and their regulation by viral and cellular factors by comparison with other viruses. The innate immunity pathway leading to control of viral translation will also be described. Recent data on the role and regulation of PKR and the unexpected change in the function of its regulator, the PKR activator (PACT) during HIV-1 replication will be described in more detail.

2. HIV-1 and HIV-2 translation

HIV replication requires constant interactions between the virus and its host and cellular mechanisms of gene expression are diverted to produce viral RNA and proteins. Once produced, HIV RNA undergoes multiple splicing to produce mRNAs for the synthesis of its proteins. In the early phase, HIV mRNA is multiply spliced into 2 kb mRNAs which are exported to the cytoplasm and translated to produce Rev, the trans-activator of transcription (Tat) and Nef. Tat and Rev go to the nucleus, where Tat increases the rate of transcription (Gatignol, 2007). In the late phase, the viral protein Rev, its RNA target Rev Response Element (RRE), and cellular factors are essential to bring the singly spliced and the genomic RNA out of the nucleus for translation (McLaren et al., 2008; Pollard and Malim, 1998; Suhasini and Reddy, 2009). HIV translation initiation occurs mainly through the cap-dependent scanning mechanism, but other mechanisms occur, including the use of an internal ribosome entry site (IRES) in the 5′UTR and in gag RNA as well as various specialized mechanisms to translate the large number of singly and doubly spliced RNAs (Bolinger and Boris-Lawrie, 2009; de Breyne et al., 2013; Purcell and Martin, 1993). Furthermore, the regulation of translational elongation involves a programmed −1 ribosomal frameshift to produce Gag–Pol from the full-length mRNA (Bolinger and Boris-Lawrie, 2009; Brakier-Gingras et al., 2012). In addition, as part of the virus-induced detrimental effects, HIV-1 reduces cellular translation by impairing eIF4E with Vpr and by cleaving eIF4G and PABP with its Protease (Castello et al., 2009; Ohlmann et al., 2002; Perales et al., 2003; Sharma et al., 2012).

2.1. cap-dependent translation

Like other viruses, *Retroviruses* use the cellular translational machinery for the synthesis of their proteins and have evolved diverse strategies to produce the appropriate amount of each protein for efficient replication (Bolinger and Boris-Lawrie, 2009; Chamond et al., 2010; de Breyne et al., 2013). HIV translation occurs mainly through a cap-mediated scanning mechanism from its 5′ end. It starts with the recognition of the 7-methyl-guanosine cap by eukaryotic translation initiation factor eIF4E cap-binding protein, which forms a complex with eIF4G and eIF4A (de Breyne et al., 2012). The 40S ribosomal subunit associated with eIF3, eIF2, GTP and Met-tRNA forms the 43S ribosome complex, binds the capped mRNA and scans it until an initiator AUG codon is found (Bolinger and Boris-Lawrie, 2009; de Breyne et al., 2013; Kozak, 1989). HIV translation initiation is slowed down by the highly structured sequence in the 5′ untranslated region (UTR) (Dorin et al., 2003; Dugré-Brisson et al., 2005; Soto-Rifo et al., 2012a; Svitkin et al., 1994). All HIV transcripts start with the formation of the trans-activation responsive element (TAR) RNA at their 5′ end. In HIV-1, the TAR RNA is composed of a stable stem-bulge-loop structure, whereas in HIV-2 RNA, this structure is duplicated (Bannwarth and Gatignol, 2005; Berkhout et al., 1990; Jeang and Gatignol, 1994; Soto-Rifo et al., 2012a). The TAR structure constitutes a block to translation, which is stronger for HIV-2 (Soto-Rifo et al., 2012a). For HIV-1, this block can be alleviated by the TAR RNA Binding protein (TRBP), by the autoantigen La, by Staufen or by DEAD box polypeptide 3 (DDX3) (Chang et al., 1994; Dorin et al., 2003; Dugré-Brisson et al., 2005; Soto-Rifo et al., 2012b; Svitkin et al., 1994), but these factors have not been studied in the context of HIV-2 for which the IRES may play an important function (Soto-Rifo et al., 2012a). Furthermore, the cellular proteins, PKR, 5′OAS, Schlafen and GCN2 negatively impact HIV-1 translation in response to IFN, stress and dsRNA (Clerzius et al., 2011; Cosnefroy et al., 2013; del Pino et al., 2012; Jakobsen et al., 2013; Li et al., 2012; Silverman, 2007). In contrast, cellular factors such as the RNA helicase A (RHA), upframeshift protein 1 and the Rev co-factors Sam68, eIF5A, human Rev-interacting protein (hRIP) and DDX3 increase cap-dependent translation efficiency of HIV-1, although eIF5A, hRIP and DDX3 also act on IRES-mediated translation (Ajamian et al., 2008; Bolinger et al., 2010; Liu et al., 2011; Soto-Rifo et al., 2012b).

2.2. IRES

IRES elements, which directly recruit the 40S ribosomal unit, have been observed in several retroviruses (Berlioz and Darlix, 1995; Camerini et al., 2008; Deffaud and Darlix, 2000; Nicholson et al., 2006; Ohlmann et al., 2000; Vallejos et al., 2012). In the *simian immunodeficiency virus* (SIV), HIV-1 and HIV-2, IRESes have been identified before or within Gag and promote the translation of transcripts expressing Gag and Gag-Pol proteins (de Breyne et al., 2013). In HIV-1, an IRES element, active during the G2/M phase has been identified in the 5′UTR, upstream of the HIV-1 Gag AUG (Brasey et al., 2003; Vallejos et al., 2011). This IRES was confirmed in various HIV-1 strains, primary HIV-1 isolates and its strength is cell-type specific (Gendron et al., 2011; Plank et al., 2013; Vallejos et al., 2012). Furthermore, it is stimulated by oxidative stress and is most functional when the cap-dependent translation is shut down by the co-expression of the *Picornavirus* proteases (Amorim et al., 2014; Gendron et al., 2011; Monette et al., 2013). Another IRES has been identified within the Gag coding region of HIV-1, driving the synthesis of a low-abundance 40-kDa Gag isoform (Buck et al., 2001). In HIV-2 and SIV, an IRES element has been identified only downstream of the Gag AUG in the genomic RNA for efficient translation of Gag and GagPol proteins. This IRES promotes the synthesis of shorter, N-truncated isoforms of Gag (Herbreteau et al., 2005; Locker et al., 2011; Nicholson et al., 2006). These IRESes within Gag of HIV-1, HIV-2 and SIV initially bind the 40S subunit and eIF3, require the function of the DEAD-box helicase eIF4A and have the specificity to recruit three initiation complexes on a single molecule to mediate the synthesis of full-length and N-truncated Gag molecules (Locker et al., 2011; Weill et al., 2010). The requirements of each IRES for specific eIFs and associated factors will likely identify conserved and different features of their translation initiation and role during the viral replication cycle.

2.3. Frameshifting

The synthesis of the Pol protein in HIV-1 and -2 is dependent on a ribosomal −1 frameshifting to produce the Gag–Pol fusion protein (Jacks et al., 1988; Wilson et al., 1988). The frameshifting