Available online at www.sciencedirect.com
SCIENCE DIRECT
Virus Research 119 (2006) 100–110
Virus Research
www.elsevier.com/locate/virusres

Inhibition of PKR by RNA and DNA viruses

Jeffrey O. Langland [a], Jason M. Cameron [a,b], Michael C. Heck [a], James K. Jancovich [a,b], Bertram L. Jacobs [a,b,*]

[a] *Center for Infectious Disease and Vaccinology, The Biodesign Institute, Arizona State University, Tempe, AZ 85287-5401, USA*
[b] *School of Life Sciences, Graduate Program in Molecular and Cellular Biology, Arizona State University, Tempe, AZ 85287-4501, USA*

Abstract

Interferons were the first of the anti-viral innate immune modulators to be characterized, initially characterized solely as anti-viral proteins [reviewed in Le Page, C., Genin, P., Baines, M.G., Hiscott, J., 2000. Inteferon activation and innate immunity. Rev. Immunogenet. 2, 374–386]. As we have progressed in our understanding of the interferons they have taken a more central role in our understanding of innate immunity and its interplay with the adaptive immune response. One of the key players in function of interferon is the interferon-inducible enzyme, protein kinase (PKR, activatable by RNA). The key role played by PKR in the innate response to virus infection is emphasized by the large number of viruses, DNA viruses as well as RNA viruses, whose hosts range from insects to humans, that code for PKR inhibitors. In this review we will first describe activation of PKR and then describe the myriad of ways that viruses inhibit function of PKR.

Keywords: PKR; Interferon; Interferon-resistance; RNA viruses; DNA viruses; Innate immune evasion

1. Introduction

Interferons were the first of the anti-viral innate immune modulators to be characterized, initially characterized solely as anti-viral proteins (reviewed in Le Page et al., 2000). As we have progressed in our understanding of the interferons they have taken a more central role in our understanding of innate immunity and its interplay with the adaptive immune response. One of the key players in function of interferon is the interferon-inducible enzyme, protein kinase (PKR, activatable by RNA). The key role played by PKR in the innate response to virus infection is emphasized by the large number of viruses, DNA viruses as well as RNA viruses, whose hosts range from insects to humans, that code for PKR inhibitors. In this review we will first describe activation of PKR and then describe the myriad of ways that viruses inhibit function of PKR.

Activation of PKR appears to occur concomitantly with protein homodimerization and intermolecular phosphorylation (Kostura and Mathews, 1989; Langland et al., 1994; Patel et al., 1995; Thomis and Samuel, 1995). The PKR enzyme is composed of two well characterized domains consisting of an N-terminal regulatory domain that consists of consensus dsRNA-binding motifs and a C-terminal catalytic domain that contains conserved motifs for protein kinase activity (Meurs et al., 1990). Activation of PKR by RNA is dependent on the dsRNA structure, rather than the nucleotide sequence. Approximately 50 bp of duplexed RNA are required for full activation (Robertson and Mathews, 1996), although shorter stretches of secondary structure on predominantly single stranded RNA can activate PKR (Ben-Asouli et al., 2002). The role of binding to dsRNA may be to induce dimerization which then leads to intermolecular autophosphorylation and activation (Romano et al., 1998a). PKR can also be activated by a related dsRNA-binding protein, PACT (Patel and Sen, 1998). Activation of PKR is likely associated with phosphorylation of T446 and T451 with-in the so-called activation loop of PKR (Galabru and Hovanessian, 1987; Kostura and Mathews, 1989).

Activated PKR is involved in a number of cellular regulatory roles. Most well characterized is PKR's involvement in the phosphorylation of eukaryotic translation initiation factor, eIF2 (Clemens and Elia, 1997; Meurs et al., 1992). eIF2 containing an α subunit phosphorylated on S51 becomes a potent inhibitor of eIF2B, the nucleotide exchange factor necessary for recycling of eIF2. Therefore, the phosphorylation of eIF2 by PKR during virus infection ultimately leads to an inhibition in protein synthesis and a block in viral replication.

* Corresponding author. Tel.: +1 480 965 4684; fax: +1 480 727 7615.
E-mail address: bjacobs@asu.edu (B.L. Jacobs).

0168-1702/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.virusres.2005.10.014

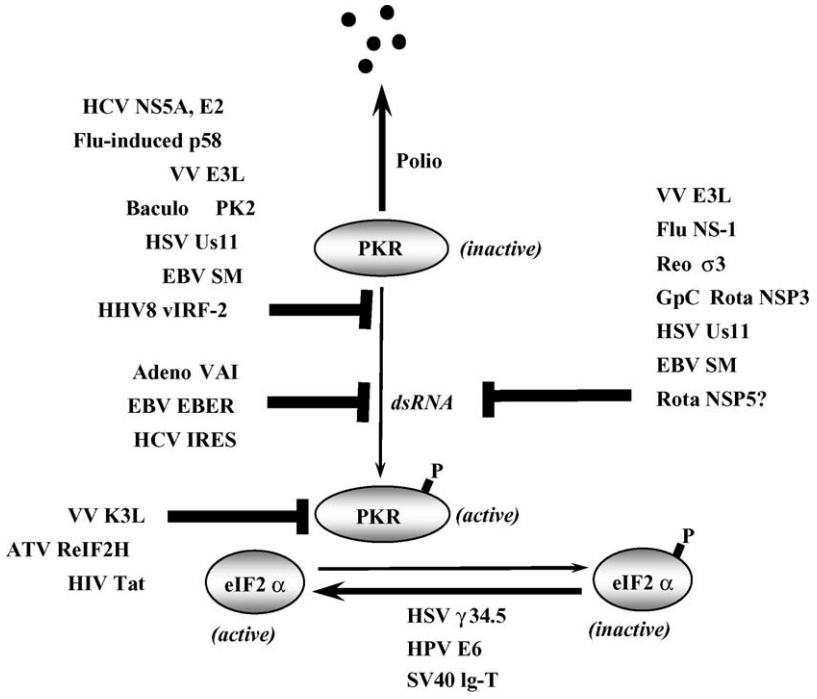

Fig. 1.

PKR also plays a role in regulating several signal transduction cascades in the cell. The transcription factor NF-κB, which leads to expression of many pro-inflammatory genes, can be activated indirectly by PKR via association with TRAF and activation of the I kappa B kinase (IKK) complex (Gil et al., 2004). PKR has also been shown to play a role in the activation of p38 MAP kinases and the stress-activated protein kinase (SAPK)/c-Jun amino-terminal kinases (JNKs) (Goh et al., 2000). Interestingly, the activation of transcription factors IRF-3 and IRF-7, which lead to the expression of interferon-β, can occur in the presence of dsRNA, but this induction does not appear to require PKR suggesting the presence of additional dsRNA-responsive enzymes present in the cell (Smith et al., 2001).

Many viruses have evolved elaborate mechanisms to inhibit the PKR response. These viral countermeasures have been shown to block the PKR response at virtually every step in the pathway, from activation through substrate phosphorylation (Fig. 1; Table 1). For many viruses, multiple mechanisms are encoded to evade PKR activity (Fig. 1; Table 1). For most of these viruses it is unclear if these multiple PKR inhibitory mechanisms are redundant roles or are necessary functions to regulate PKR activity at different stages in the virus life cycle. Such viruses include vaccinia virus, herpes simplex virus, Epstein-Barr virus, influenza virus, and hepatitis C virus.

2. DsRNA binding proteins

DsRNA is the most well characterized danger signal that the cell uses to recognize the presence of viral infection. Therefore, it is not surprising that many viruses synthesize excessive amounts of dsRNA-binding proteins which function to bind to and sequester any free dsRNA molecules. Such well charac-

Table 1
Regulation of PKR by viral products

Mechanism	Virus	Gene product
I. dsRNA binding proteins	Vaccinia vims	E3L
	Reovirus	σ3
	Influenza virus	NS1
	Rotavirus group C	NSP3
	Rotavirus group A	NSP5?
	Herpes simplex virus	Us11
	Epstein-Barr virus	SM
II. RNA inhibitors	Epstein-Barr virus	EBER RNA
	Adenovirus	VAI RNA, VAII RNA?
	Hepatitis C virus	IRES
III. PKR interaction	Hepatitis C virus	NS5A, E2
	Influenza virus	p58
	Vaccinia virus	E3L
	Baculovirus	PK2
	Herpes simplex virus-1	Us11
	Epstein-Barr virus	SM
	Human herpes virus-8	vIRF-2
IV. Competitive inhibitor	Vaccinia virus	K3L
	Ambystoma tigrinum virus	ReIF2H
	HIV	Tat
V. PKR degradation	Polio virus	Protease
VI. eIF2α phosphatase	Herpes virus	γ34.5
	Papilloma virus	E6 (GADD34/PP1α)
	SV-40	Large-T antigen