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Antiviral activity of type I interferons and interleukins 29 and 28a (type III interferons) against Apeu virus

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ABSTRACT

Interferons (IFNs) are cytokines with important immunomodulatory activity in vertebrates. Although type I IFNs and interleukins (IL) 29 and 28a (type III IFNs) bind to different cellular receptors and have distinct structures, most of their biological activities are redundant. Apeu virus (APEUV) is a member of the Bunyaviridae family isolated from the Brazilian rain forest. In this paper we evaluated the antiviral activity of type I and type III IFNs against APEUV. All tested IFNs were able to induce an antiviral state against the virus in a dose-dependent way. The activity of type III IFNs did not need the presence of type I IFNs. Mixing both types of IFNs did not improve the biological activity of each type alone. The tested IFNs were also able to protect human peripheral blood mononuclear cells from infection. IFN alpha2, IFN beta, IL-29 and IL-28a induced the expression of 2′,5′-oligoadenylate synthetase (2′5′OAS) and 6–16 genes. Although MxA gene was related to antiviral activity against Bunyaviruses, there was no induction of MxA in our model. We were able to show activity of type I and type III IFNs against a RNA virus, and that this activity is not dependent on MxA gene.

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1. Introduction

Interferons (IFNs) were first described as molecules capable of interfering with the multiplication of Influenza virus in vitro (Isaacs and Lindenmann, 1957). Now it is known that besides their antiviral activity, IFNs also possess important immunomodulatory and physiologic activities. The first IFN gene probably evolved from an interleukin gene around 600–500 million years ago in chordates. IFNs belong to the class 2 cytokine receptor family, and are divided into three groups (Krause and Pestka, 2005).

Type I IFNs are divided into nine subtypes in mammals, and each order contains at least one IFN alpha and one IFN beta. All type I IFNs binds to a common cellular receptor formed by two chains. The binding of a type I IFN to the receptor initiates a signaling pathway that culminates in the activation of transcriptional factors that regulate the expression of interferon-stimulated genes (ISGs). Virtually all cell types are able to produce and respond to type I IFNs. These IFNs are important in the antiviral response and act as a link between innate and adaptive immune responses (Pestka et al., 2004).

IFN gamma is the only type II IFN known. It binds to a distinct receptor and its main function is immunomodulatory. It is produced mainly by immune cells and is important in modulating the adaptive immune response (Kontsek et al., 2003; Alcami and Smith, 2002).

The type III IFNs were described through in silico analysis of the human genome, and are represented by three genes with introns in the human chromosome 19. They were named interleukins 29, 28a and 28b (also noted as IFNs lambda1, lambda2 and lambda3, respectively). Similar to type I IFNs, type III IFNs are able to phosphorylate signal transducers and activators of transcription (STATs) 1 and 2, activate transcriptional factors gamma activated sequence (GAS) and IFN stimulated response element (ISRE), induce classical ISGs such as 2′,5′-oligoadenylate synthetase (2′5′OAS) and 6–16, upregulate class I major histocompatibility complex (MHC) and are produced after poly I:C stimulation or in response to viral infections. Type III IFNs binds to a distinct receptor complex, composed of one exclusive chain and a second chain that is shared with the receptors for IL10, 22 and 26 (Sheppard et al., 2003; Kotenko et al., 2003).

The biological activity of type III IFNs is redundant with the biological activity of type I IFNs, but is generally less intense and more restricted (Meager et al., 2005). Dendritic cells infected with Influenza virus or Sendai virus or treated with poly I:C, lipopolysaccharide or CpG produce type I and type III IFNs (Coccia et al., 2004).

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Similar to type I IFNs, type III IFNs also shows antiproliferative activity (Dumoutier et al., 2004; Zitzmann et al., 2006; Sato et al., 2006) and their activated ISGs are inhibited by suppressor of cytokine signaling (SOCS) 1 and 3 activity (Brand et al., 2005b; Zitzmann et al., 2007).

Type III IFNs also have immunomodulatory activities. Treatment of immature dendritic cells with human IL-29 results in a distinct maturation process, which results in mature dendritic cells with high levels of class I and class II MHC that are able to migrate but retain phagocytic capacity (Mennechet and Uzé, 2006). IL-29 also modulates human cytokine response (Jordan et al., 2007a,b).

Type III IFNs are capable of interfering with the multiplication of several human and murine viruses in vitro, such as encephalomyocarditis virus, Sinbdis virus (Sheppard et al., 2003; Kotenko et al., 2003), hepatitis B and C viruses (Robek et al., 2005), human and murine cytomegalovirus (Brand et al., 2005a) and murine herpes simplex virus 2 (Ank et al., 2006). It was also shown that type III IFNs can interfere with the multiplication of murine herpes simplex virus 2 in vivo (Ank et al., 2006). Recombinant vaccinia virus expressing murine IL-28a is attenuated when used to infect BALB/c mice (Bartlett et al., 2005). Recently, a viral evasion mechanism that directly targets type III IFNs was described, suggesting that these IFNs are important during viral infections (Huang et al., 2007).

The Bunyaviridae family is composed of a large group of more than 300 viruses distributed into five genera: Orthobunyavirus, Hantavirus, Nairovirus, Phlebovirus and Tospovirus. Mainly transmitted by arthropods, they are maintained in nature by an alternative cycle involving blood-feeding arthropods and susceptible small mammals (Calisher, 1996; Schmaljohn and Hooper, 2001). Members of the Bunyaviridae family are involved in producing mild to severe conditions varying from non-specific fever and encephalitis to hemorrhagic fever in humans (e.g. Hantaan, Rift Valley fever, La Crosse, and Crimean-Congo hemorrhagic fever viruses) and are recognized as posing an increasing threat to human health, an example of the so-called "emerging infections" (Elliott, 1997; Gerrard et al., 2004).

Earlier studies have demonstrated that type I IFNs have an antiviral effect against members of the Bunyaviridae family (Tamura et al., 1987; Morrill et al., 1989; Pinto et al., 1990; Weber and Elliott, 2002; Livonesi et al., 2007). Anti-bunyaviral activity has been investigated for the Mx proteins which are large GTPases (Frese et al., 1996). Growth of several members of the family, including La Crosse, Crimean-Congo hemorrhagic fever, Hantavirus and Dugbe viruses, is strongly inhibited if human MxA protein is expressed in cells (Kochs et al., 2002; Andersson et al., 2004; Kanerva et al., 1996; Bridgen et al., 2004).

Apeu virus (APEUV) (BeAn 848) is a member of group C from the genus Orthobunyavirus, family Bunyaviridae and was isolated in 1955 from a sentinel female monkey (Cebus apella) in the region of Apeu, Belém, Brazilian Amazon (Causey et al., 1961). In humans, the APEUV infection causes an illness characterized by high fever, myalgia and photophobia, usually with a favorable outcome (Gibbs et al., 1964). In other vertebrates, the APEUV can cause encephalitis and hepatitis post-infection (De Mucha Macias et al., 1969; Vasconcelos et al., 1991). Previous studies showed that members of group C, including APEUV, were sensitive to a mixture of IFNs produced in human amnioniotic membrane cells and their sensitivity was dependent on the type of assay used (Petrillo-Peixoto et al., 1980).

However, to date, the antiviral activity of type III IFNs against viruses from the Bunyaviridae family remains unknown. In this paper, we compared the antiviral activity of type I and type III IFNs against APEUV.

2. Materials and methods

2.1. Viruses

APEUV (BeAn 848) was obtained from the American Type Culture Collection (ATCC) and propagated in Vero cells at a multiplicity of infection (MOI) of 0.1. Viruses present in the supernatant were harvested 3 days after infection, titrated and kept frozen at −70 °C.

2.2. Cells

Vero cells (African green monkey kidney cell line) were obtained from the ATCC and grown at 37 °C in Dulbecco's modified Eagle's medium (DMEM) supplemented with 2 mM glutamine, 5% fetal calf serum (Cultilab, Campinas, SP, Brazil) and antibiotics.

Peripheral blood mononuclear cells (PBMCs) from healthy donors were purified using the Ficoll Hypaque purification technique (Böyum, 1968). Fresh blood collected in vacuum tubes containing heparin was diluted in an equal volume of 1× phosphate buffered saline (PBS). Twenty mililiters of the diluted blood were carefully added over 10 ml of Ficoll, and centrifuged at 400 × g for 40 min. The PBMC layer was collected, washed in 1× PBS and cultured in RPMI media supplemented with 1% fetal calf serum (Cultilab, Campinas, Sao Paulo, Brazil) and antibiotics.

2.3. Interferons

Recombinant human IFN alpha2A, produced in *Escherichia coli*, was purchased from Bergamo, Sao Paulo, Brazil. Human IFN beta, purified from human fibroblasts, was purchased from Rentschier Arzneimittel GmbH & Co, Germany. Recombinant IL-29 and IL-28a were produced in 293T cells. Plasmids pSPXIIneo containing cloned human IL-29 and IL-28a were kindly donated by Dr. Gilles Uzé (Université de Montpellier II, France) and used to transfect 293T cells. The supernatant was collected and titrated, using an IFN alpha2 sample as reference (Ferreira et al., 1979). Supernatants from mock-transfected cells were used as control.

2.4. Titration

Viral titer was determined by plaque assay (Dulbecco and Vogt, 1953). Frozen infected cells were submitted to two freeze–thaw cycles, resuspended and serially diluted in DMEM. The 10-fold dilutions were used to infect Vero cells seeded in six-well plates. After 1 h of adsorption at 37 °C, the cells were covered with 3 ml of carboxymethylcellulose diluted in DMEM supplemented with 2% fetal calf serum (Cultilab, Campinas, Sao Paulo, Brazil) and antibiotics. The cells were monitored daily to determine the formation of viral plaques. Five days after the infection the cells were fixed with 3.7% formaldehyde and stained with 1% crystal violet. Plaque forming units were counted and the viral titer was determined as plaque forming units per ml (pfu/ml).

2.5. Antiviral activity

Vero cells treated with IFNs for 18 h were infected with APEUV to evaluate the induction of an antiviral state (Ferreira et al., 1979). To evaluate the antiviral activity of type I and type III IFNs against APEUV, Vero cells were seeded in 96 wells plates for 24 h and then treated with 1000 U/ml of human IFNs alpha2, beta, IL-29, IL-28a diluted in DMEM or left untreated. Eighteen hours after treatment the cells were infected with APEUV (MOI 1). Then, at 18, 24 or 48 h after infection, the plates were frozen at −70 °C. The plates were submitted to two freeze–thaw cycles and titrated as described above.

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