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Comparison of transcriptional profiles of interferons, CXCL10 and RIG-1 in influenza infected A549 cells stimulated with exogenous interferons

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Summary. – Type I and type III interferons (IFNs) are induced by viral infection. It was concluded that these IFN species are identical in regulation and biological functions. However, these two systems differ in the tissue expression of their receptors and their transcriptional regulation is fundamentally different as well as cellular signaling pathways that drive expression of each IFN. Here, we have investigated the transcriptional profile of endogenous IFNs after stimulation of cells with exogenous IFNs and subsequent infection of A549 cells with A/chicken/Germany/27 [H7N7] influenza virus. Both type I and type III IFNs exhibit high degree of the cross-induction. Our results show that type III IFNs (IFN-λ1, IFN-λ2 and IFN-λ3) are better inducers of CXCL10 than type I IFNs. The IFN-β1a and IFN-λ2 were the most potent IFNs and they highly increased the level of IFN-α, IFN-β, IFN-λ, and CXCL10 mRNAs. Since type I IFNs up regulated expression of retinoic acid-inducible gene 1 (RIG-1) mRNA, type III IFNs-λ down regulated expression of RIG-1 mRNA in influenza infected cells. IFN-α and IFN-ω induced similar amount of IFN-α, IFN-β and IFN-λ mRNA but differ in induction of CXCL10 and RIG-1 mRNA.

Keywords: influenza virus; interferon; CXCL10; RIG-1; mRNA

Introduction

The interferon system represents one of the first line defences against influenza virus infection. IFNs represent a family of cytokines that are involved in several cellular functions. Type I interferon family consists of 13 IFN-α subtypes, IFN-β, IFN-ω, and IFN-ε (Cohen and Parker, 2016). Type II family is represented by IFN-γ and type III IFN family consists of IFN-λ1, IFN-λ2, IFN-λ3, and IFN-λ4 (Sheppard *et al*., 2003; Kotenko *et al*., 2003; Uzé *et al*., 2007; Prokunina-Olsson *et al*., 2013). Single nucleotide polymorphism in the majority of the human population results in a frameshift mutation inhibiting IFN-λ4 production (Hamming *et al*., 2013). There is 96% sequence identity between IFN-λ2 and IFN-λ3 and approximately 81% sequence homology between IFN-λ1 and IFN-λ2/3 (Sheppard *et al*., 2003; Kotenko *et al*., 2003).

IFNs are associated with innate immunity and induce anti-proliferative and anti-inflammatory responses and are involved also in adaptive immune responses (Alexopoulou *et al*., 2001; Au *et al*., 2001; Pestka *et al*., 2004; Lopušná *et al*., 2013). Type I IFNs receptor complex consists of two chains, IFN-αR1 and IFN-αR2 (Uze *et al*., 1990; Cleary *et al*., 1994). Type III IFNs are structurally different from type I IFNs and bind to a distinct heterodimeric receptor containing unique IFN-λR1 and IL10R2 chains. The IL10R2 chain is also the second subunit of the receptor complexes for IL-10, IL-22, and IL-26 (Kotenko *et al*., 2003; Sheppard *et al*., 2003; Kotenko and Langer, 2004). Type III IFNs are induced in response to viral and bacterial stimuli, with almost complete overlap with the type I IFN pathway (Ank *et al*., 2008; Durbin *et al*., 2013). Binding of IFN-λ to its receptor dimer induces JAK-STAT signaling similar to type I IFN signaling, result-

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Abbreviations: IFN(s) = interferon(s); RIG-1 = retinoic acid-inducible gene 1

ing in expression of over 300 interferon responsible genes (Dumoutier *et al*., 2004; Doyle *et al*., 2006; Cohen and Prince, 2013). While the type I and type III pathways activate a very similar gene set, there are significant differences between the pathways (Cohen and Parker, 2016). The expression of IFNλ-R is restricted to a subset of cells, primarily epithelial cells, keratinocytes, some dendritic cells and neutrophil population (Sommereyns *et al*., 2008; Cohen and Prince, 2013; Blazek *et al*., 2015; Lukacikova *et al*., 2015; Mahlakõiv *et al*., 2015). Type I IFNs induce a more rapid and higher magnitude response compared to type III IFN, while type III IFNs induce a more sustained response of gene induction (Zhou *et al*., 2007; Bolen *et al*., 2014; Jilg *et al*., 2014).

The type I IFNs are usually represented by IFN-α in most studies concerning immune response against influenza virus. Here, we have compared anti-influenza activities of individual type I (IFN-α, IFN-β, and IFN-ω) and type III (IFN-λ1, IFN-λ2, and IFN-λ3) IFNs and their abilities to induce IFN-α, IFN-β, IFN-λ, CXCL10, and RIG-1 mRNAs. Our data show that final inhibitory effect cannot be assigned only to interferon which was used for induction of A549 cells prior infection. Both type I and type III IFNs exhibit high degree of the cross-induction and several fold increase in the level of CXCL10 transcript. Amount of RIG-1 mRNA was elevated by the type I IFN and downregulated by the type III IFNs. Despite the use of different receptor for type I and type III IFNs, both types of interferon resulted in predominant activation of IFN-β.

Materials and Methods

Cells and viruses. A549 (ATCC CCL 185) cells were grown in Dulbecco modified Eagle medium (DMEM) containing 10% fetal calf serum (FCS). Influenza virus A/chicken/Germany/27 [H7N7] (kindly provided by Dr. AJ Hay, NIMR, London, UK) was cultured in 10 days old fertile hen's eggs.

Antiviral activity assay. Confluent monolayer of A549 cells (in 24-well plates) was pre-incubated for 24 h with 0, 10, 20, and 40 ng/ml of recombinant human IL-29/IFN-lambda 1, recombinant human IL-28A/IFN-lambda 2, recombinant human IL-28B/IFN-lambda 3, recombinant human IFN-ω (R&D System, USA) or 0 U, 50 U, 100 U, 200 U, 400 U, and 800U of recombinant human IFN-α 2b, recombinant human IFN-β 1a (R&D System). The cells were washed once with phosphate buffered saline (PBS) and then infected with influenza A/chicken/Germany/27 [H7N7] virus at a multiplicity of infection (MOI) of 0.5 plaque forming units per cell for 1 h at room temperature. After adsorption, cells were washed three times with PBS and then cultured in serum-free MEM at 37°C. At 16 h post-infection, cells were scraped and centrifuged at 500 × g for 2 min. The viral titers in supernatants were determined on MDCK cells by plaque assay as described by Svetlikova *et al.* (2010).

Quantitative RT-PCR. Interferons, CXCL10, and RIG-1 mRNAs were quantified by semi-quanitative RT-PCR as previously described (Svancarova *et al*., 2015b). Briefly, RNA from IFN pre-incubated and infected cells were extracted using the SV Total RNA isolation system (Promega, USA). RNA yields were evaluated by spectrophotometer at 260 nm. Four hundred ng of RNA were reverse transcribed using random hexa-nucleotide primers and murine leukemia virus (MuLV) reverse transcriptase (Thermo Fisher Scientific, USA). To determine mRNA levels of IFN-α, IFN-β, CXCL10, IFN-λ, RIG-1, and β-actin, RT-PCR was performed. The primers targeting β-actin, IFN-β and IP 10 (precursor IFN-γ) were described previously (Varga *et al*., 2011; Zhang *et al*., 2014). The sequences of the primers were as follows: 5'-CTT GGG ATG AGA CCC TCC TAG AC-3' (forward) and 5'-GCA CAA GGG CTG TAT TTC TTC TC-3' (reverse) for IFN-α universal for subtypes 1 and 2; 5'-CTG ACG CTG AAG GTT CTG GAG-3' (forward) and 5'-AAT TCA GGT CTC GCG TGA GGA GGC-3' (reverse) for IFN-λ2 and 3; 5'-TGC AGT CAC GTC TTA TGT GAT AG-3' (forward) and 5'-CTC CCA CTG CTC GAA CCA GAA AC-3' (reverse) for RIG-1. The intensity of the obtained PCR bands was determined by using Gene Tools image analysis software.

Statistical evaluation. Each sample was analyzed in duplicate and repeated twice or more if the variation was more than 10%. Significant differences in the virus titer between the control group (untreated cells) and IFNs pre-incubated cells were calculated using the unpaired Student's *t*-test. P values <0.05 were considered significant. The fold change ratios between control and experimental samples for each gene were calculated and normalized against β-actin. Statistical analysis was performed using Graph-Pad Prism software (http://www.graphpad.com/quickcalcs/ttest1.cfm).

Results

Virus A/chicken/Germany/27 [H7N7] is most inhibited in the cells pre-incubated with IFN-β1a and IFN-ω

Inhibition activity of IFNs was tested with avian strain [H7N7]. A549 cells were stimulated with different concentration of IFNs as described in material and methods. Subsequently, cells were infected with A/chicken/Gemany/27 [H7N7] virus and infected cells were scraped 24 h later and virus titer was determined. The concentration of IFN-α2b, IFN-β1a, IFN-ω, or IFNs-λ with highest inhibitory effect was consider as an optimal concentration and all further experiments were performed with 400U of IFN-α2b or IFN-β1a, 10 ng/ml of IFN-ω or IFN-λ1, and 20 ng/ml of IFN-λ2 or IFN-λ3. The best inhibitory activity was observed with IFN-ω and IFN-β1a. The virus titer was reduced to 17% (Fig.1). IFN-α2b decreased the virus titer to 58% and IFN-λs inhibited virus replication up to 63%.

IFN-α mRNA was induced only by IFN-β

To investigate the transcriptional profile of endogenous IFNs after stimulation of cells with exogenous type I and

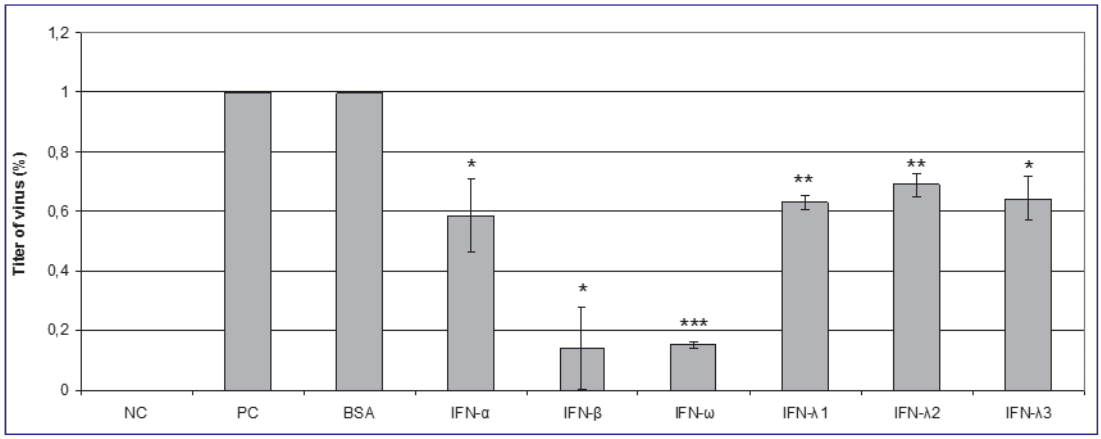

Fig. 1

Antiviral activity of IFN-α2, IFN-β1a, IFN-ω, IFN-λ1, IFN-λ2, and IFN-λ3 in induced A549 cells infected with A/chicken/Germany/27 [H7N7]
The column bars represent the average results with standard deviation from three experiments performed on different occasions. 100% represents infected cells without IFN. 400U of IFN-α2 and IFN-β1a were used. IFN-ω and IFN-λ1 were used in concentration 10 ng/ml and IFN-λ2 and IFN-λ3 were used in concentration 20 ng/ml. *Statistical significance (*P <0.05; **P <0.02; ***P <0.01 by unpaired Student's *t*-test).

type III IFNs and subsequent infection of cells with influenza virus, we performed semi-quantitative RT-PCR. The level of IFN-α mRNA was insignificantly increased in the A549 cells after infection with influenza H7N7 virus. We assumed, that IFN-α will be the most potent to induce expression of IFN-α mRNA. However, induction of A549 cells with IFN-α and as well as with IFN-ω and IFNs-λ did not result in the alteration of IFN-α mRNA expression in infected cells (Fig. 2). The level of IFN-α mRNA was significantly increased only in the A549 cells preincubated with IFN-β.

Induction of IFN-β and IFN-λ mRNA by type I and type III IFNs

In order to examine the induction capacity of individual IFNs, we analyzed the transcription level of mRNA IFN-β and IFN-λ. Among all tested IFNs, IFN-β1a appeared to be the most potent and IFN-λ2 induced expression of IFN-β mRNA to comparable level, approximately 1.5 times (Fig. 3). While IFN-β duplicated the production of IFN- λ mRNA, IFNs-λ significantly increased expression of its own

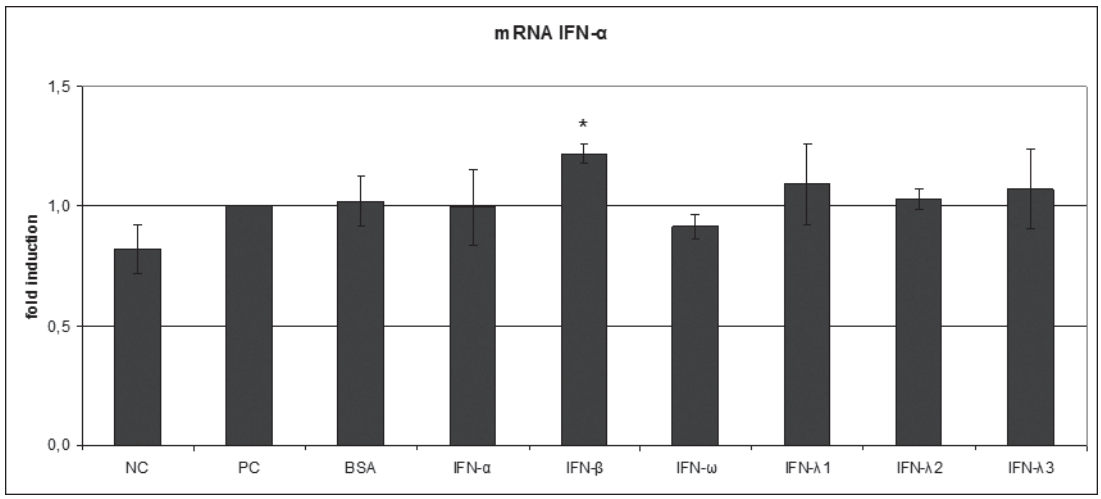

Fig. 2

Quantitative RT-PCR analysis of IFN-α mRNA in A549 cells
A549 cells were induced with IFNs and infected with influenza virus. NC-A549 cells, PC-A549 cells infected with influenza virus, BSA-A549 cells pre-incubated with 20 ng/ml BSA and then infected with influenza virus. The column bars represent the average results with standard deviation from three experiments performed on different occasions. *Statistical significance (*P <0.05; **P <0.02; ***P <0.01 by unpaired Student's *t*-test).

mRNA, but only 1.3 times (Fig. 4). The activity of IFN-α and IFN-ω was very similar and both IFNs induced expression of either IFN-β mRNA or IFN-λ mRNA approximately 1.2 time (Fig. 3 and 4). In conclusion, both type I and type III IFNs exhibit high degree of the cross-induction of IFN-β and IFN-λ mRNAs.

Type I and type III IFNs stimulate expression of CXCL10 mRNA

The binding of type I and type II IFNs to their receptors induces signaling cascades that result in the activation of STAT1 and STAT2. We wanted to examine the induction of CXCL10

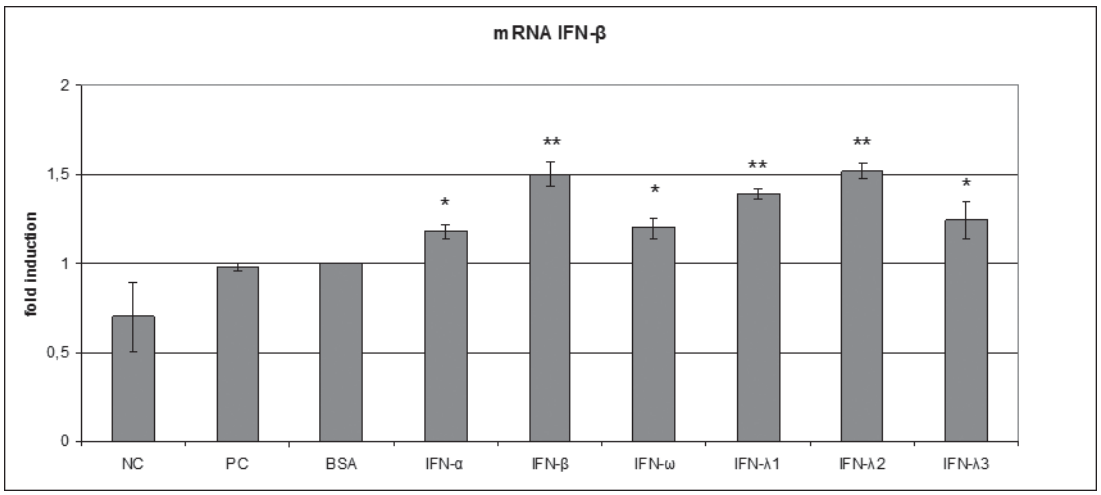

Fig. 3

Quantitative RT-PCR analysis of IFN-β mRNA in A549 cells

A549 cells were induced with IFNs and infected with influenza virus. NC-A549 cells, PC-A549 cells infected with influenza virus, BSA-A549 cells pre-incubated with 20 ng/ml BSA and then infected with influenza virus. The column bars represent the average results with standard deviation from three experiments performed on different occasions. *Statistical significance (*P <0.05; **P <0.02; ***P <0.01 by unpaired Student's *t*-test).

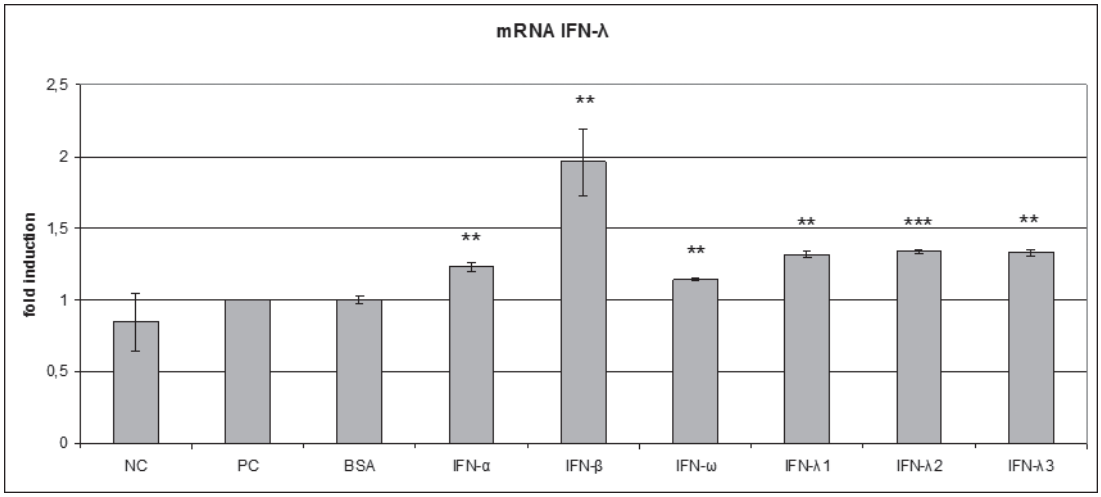

Fig. 4

Quantitative RT-PCR analysis of IFN-λ mRNA in A549 cells

A549 cells were induced with IFNs and infected with influenza. NC-A549 cells, PC-A549 cells infected with influenza virus, BSA- A549 cells pre-incubated with 20 ng/ml BSA and then infected with influenza virus. The column bars represent the average results with standard deviation from three experiments performed on different occasions. *Statistical significance (*P <0.05; **P <0.02; ***P <0.01 by unpaired Student's *t*-test).

and see whether type I and type III IFNs can cross-induce also the type II IFN pathway. Influenza virus induced expression of CXCL10 mRNA in infected cells. The expression of CXCL10 mRNA was several folds more upregulated in the A549 cells induced with IFNs. The type I IFNs, especially IFN-β increased expression of CXCL10 mRNA more than 6 times, while IFN-ω and IFN-α increased its expression 4 or 2.4 times, respectively (Fig. 5). The IFN-λ1 was lower than that of IFNs-λ2/3, which was comparable to activity of IFN-β.

The type I IFNs upregulated and the type III IFNs down-regulated expression of RIG-1 mRNA in influenza infected cells

Gene expressions of RIG-1 in induced A549 cells were also studied. Infection of A549 cells with H7N7 virus did not influence the level of RIG-1 mRNA (Fig. 6). While, the IFNs-α/β induced the level of RIG-1 mRNA 1.7 times, the IFN-ω exhibited lesser activity and induced RIG-1 mRNA

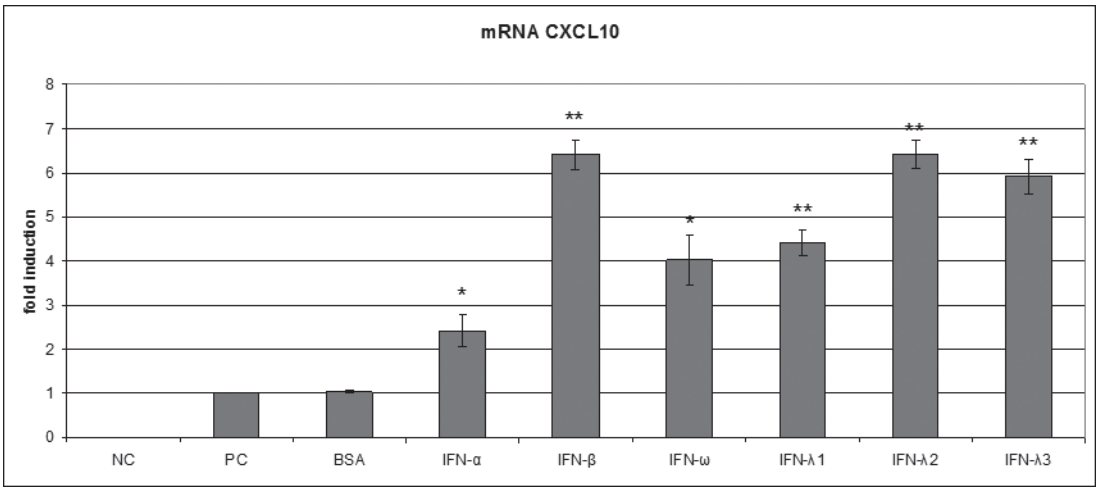

Fig. 5

Quantitative RT-PCR analysis of CXCL10 mRNA in A549 cells

A549 cells were induced with IFNs and infected with influenza virus. NC-A549 cells, PC-A549 cells infected with influenza virus, BSA-A549 cells pre-incubated with 20 ng/ml BSA and then infected with influenza virus. The column bars represent the average results with standard deviation from three experiments performed on different occasions. *Statistical significance (*P <0.05; **P <0.02; ***P <0.01 by unpaired Student's *t*-test).

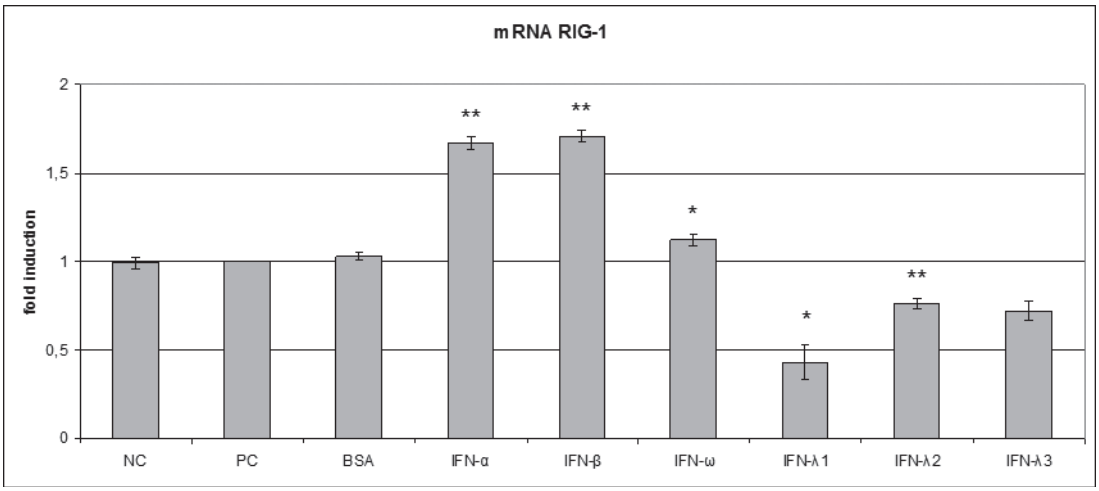

Fig. 6

Quantitative RT-PCR analysis of RIG-1 mRNA in A549 cells

A549 cells were induced with IFNs and infected with influenza virus. NC-A549 cells, PC-A549 cells infected with influenza virus, BSA-A549 cells pre-incubated with 20 ng/ml BSA and then infected with influenza virus. The column bars represent the average results with standard deviation from three experiments performed on different occasions. *Statistical significance (*P <0.05; **P <0.02; ***P <0.01 by unpaired Student's *t*-test).

only 1.12 times. On the other hand, the activity of IFN-λ2 and IFN-λ3 was indistinguishable and both IFNs reduced the production of RIG-1 mRNA 0.72 times. Induction of A549 cells with IFN-λ1 resulted in more than half decrease in RIG-1 mRNA production. In conclusion, the type I IFNs upregulated and the type III IFNs downregulated expression of RIG-1 mRNA in infected cells.

Discussion

Most viruses are able to induce production of IFNs (Biron, 1999; Kotenko *et al.*, 2003; Coccia *et al.*, 2004; Mihm *et al.*, 2004; Svetlikova *et al.*, 2010). It was already proved, that the type I IFN can stimulate production of the type III IFN and vice versa. They differ in receptor composition but they stimulate the same JAK/STAT pathways and induce a similar repertoire of genes (Zhou *et al.*, 2007; Cohen and Parker, 2016). Type I and type III IFNs are differentially regulated at the transcription level.

Anti-virus activity of IFN is generally assigned to the interferon which was used for induction of cells or for treatment of experimental animals. We were interested in comparing the activity of IFN-α2b with activity of IFN-β1a or IFN-ω. Primary sequence comparison between the IFN α and β subtypes reveal an approximately 50% amino acid homology (Pestka *et al.*, 1987). Human IFN-ω is antigenetically different from human IFN-α and IFN-β and has 65% amino acid sequence homology and similar function as IFN-α (Adolf, 1987). IFN-β, but not IFN-α, induces the association of tyrosine-phosphorylated receptor components IFNαR1 and IFNαR2, and has activity in cells lacking the IFN receptor-associated, Janus kinase TYK2 (Runkel *et al.*, 1998). Previous studies have shown the protective potential of human exogenous IFN-ω against influenza viruses (Xu *et al.*, 2011; Skorvanova *et al.*, 2015). The activities of individual type I IFNs differ from each other. The IFN-β1a was the only interferon which induced level of IFN-α mRNA. The IFN-α2b and IFN-ω activate similar amount of IFN-β and IFN-λ mRNA but they differ in activation of CXCL10 and RIG-1 mRNA. Thus IFN-ω may be a useful and alternative antiviral agent, in addition to IFN-α and IFN-β. The highest potency for induction of IFN-α, IFN-β, IFN-λ, CXCL10 and RIG-1 mRNA was manifested by the IFN-β1a. All IFN-λ stimulated the expression of IFN-β, IFN-λ and CXCL10 mRNA but did not influence level of IFN-α mRNA and downregulated RIG-1 mRNA.

RIG-1 can be induced by influenza virus infection (Gao *et al.*, 2012). However, the influenza virus NS1 protein can antagonize RIG-1 signaling and suppress its function (Pichlmair *et al.*, 2006; Mibayashi *et al.*, 2007). Previous studies show, that type III IFNs are produced at significantly higher level than type I IFNs in response to influenza virus without inducing expression of RIG-1 (Jewell *et al.*, 2010; Svancarova *et al.*, 2015a). Avian influenza virus did not induce expression of RIG-1 in A549 cells. The level of RIG-1 mRNA was significantly increased only in the infected cells pre-incubated with type I IFNs. This finding just proves that type I and type III IFNs are differentially regulated. Type I IFNs are induced by the combined action of the transcription factor AP-1, interferon regulatory factor (IRF) 3, IRF7, and NFκB (Thanos and Maniatis, 1995). However, only IRF3, IRF7, and NFκB are required for type III IFN production (Odendall *et al.*, 2014). The IFNs induction is dependent on the JNK1/2 signaling pathway and induction of the RIG-1 is dependent on the ERK1/2 or JNK1/2 pathways (Ludwig *et al.*, 2001; Gao *et al.*, 2012).

All tested IFNs highly increased level of CXCL10 mRNA. CXCL10 cytokine, formerly known as IFN-γ-inducible protein 10 (IP-10) plays critical roles in enhancing the recruitment and activation of Th1 and Tc cells (Padovan *et al.*, 2002; Villarroel *et al.*, 2014). Expression of CXCL10 can be highly induced in a variety of cells by stimulation with type I and type II IFNs (Luster and Ravetch, 1987; Padovan *et al.*, 2002). Our results show that type III IFNs induce expression of the CXCL10 and their induction ability is better than type I IFNs. Binding of IFN-γ to its receptor (IFN-γR) activates the JAK-STAT pathway and leads to CXCL10 secretion. Positive regulator for CXCL10 transcription is NF-κB (Helbig *et al.*, 2009; Brownell *et al.*, 2013; Liu *et al.*, 2016). Since the type I and type III IFNs induce JAK-STAT pathways as well as expression of NF-κB, it is not surprising that overexpression of CXCL10 mRNA occurs.

It is obvious that the transcriptional regulation of type I and type III IFNs are fundamentally different as well as cellular signaling pathways that drive expression of each IFN. It is not possible to study type I IFNs pathway and ignore the type II and type III IFNs pathway. Due to the parallel nature of these pathways, action of individual IFNs could be enhanced or reduced. Better understanding of IFNs signaling is essential for understanding the biological activities of individual IFNs, avoiding the toxicities associated with IFNs and/or designing of novel therapeutics.

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