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Type I Interferons and Their Efficacy in Treating Feline Retroviral Diseases: A Review

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Abstract

Interferon is one of the molecules that the organism has ready for fighting viral infections, as it forms part of the innate immune system. In this review we briefly describe why and how the different types of type I interferon (IFN-I) prevent viral infection, some of the mechanisms that viruses have for evading these actions, and their action on cells, both healthy and tumoral. The second part of the review focuses on the effect of IFN-I on retroviral infections, specifically on their use for treating feline immunodeficiency and feline leukemia viral infections.

Interferons were the first molecules identified shown to interfere with viral replication in mammalian cells [1]. They are cytokines produced by diverse cells and with pleiotropic functions, including a powerful antiviral ability, immunoregulatory functions, antiproliferative capacity and antiinflammatory potential [2,3]. The present classification considers three types: I, II and III [1,4].

• Type I or viral interferons (IFN-I). It includes IFN-α (or leukocyte IFN), IFN-β (or fibroblast IFN), IFN-ω, IFN-τ (produced by the trophoblasts of ruminants with an important role in gestation, [5], IFN-δ (produced by trophoblasts of pigs and with high antiviral activity), IFN-κ, IFN-ε, and IFN-ζ. Multiple cells can secrete IFN-α/-β, but mature dendritic cells are the main producers of IFN-α, producing up to 100 times more than other cellular types [4,6]. They induce anti-proliferative and antiviral responses, and they play an important role, not only in the innate response, but also in the adaptive immune response, as they activate the maturation of dendritic cells, triggering T-lymphocytes stimulation [6]. In addition, IFN-I increase the expression of type I molecules of the major histocompatibility complex (MHC), which contributes to the destruction of infected cells [7].

• Type II or immune interferon (IFN-II), which only includes IFN-γ. It is synthesized by both T-helper (Th) and T-cytotoxic (Tc) lymphocytes and by natural killer cells (NK). It initiates a signal that plays a key role in the establishment of cellular immunity and improves the response of IFN-I[4]. It contributes to antigen presentation, favoring the cytotoxic response, and activates macrophages. It also modulates the immune response and participates in the differentiation of Th1 and Th2 lymphocytes [4].

• Type III interferon (IFN-III), also known as IFN-λ [1-4]. It has high affinity for the receptor IFNLR1, which is synthesized only by epithelial cells [8].

In this review we are going to focus on IFN-I and their possible use as treatment in animal retroviral infections.

1. How do type I interferons work?

Type I IFN act through a series of stages: 1) a specific stimulus, such as viral infection, induces the synthesis of IFN-I, 2) IFN secreted by infected cells binds receptors in neighboring cells, activating an enzyme pathway which ultimately originates the expression of certain antiviral proteins, and 3) these antiviral proteins act directly on the viruses, inhibiting their replication cycle. In addition, IFN-I may affect the cell

itself, inducing apoptosis, which contributes to its anti-proliferative role.

1.1. Type I interferon is synthesized by many cellular types in response to a viral infection

Interferon is an inducible protein, i.e., it needs to be triggered by stimulus such as viruses, dsRNA, polypeptides, cytokines, mitogens, etc.) [9]. This induction is regulated by two signal transduction pathways: the classical pathway and the Toll-like receptors or TLR pathway [10,11]

• Most cells, including fibroblasts, hepatocytes and conventional dendritic cells, use the classical pathway. These cells have cytosolic receptors (CR) that are able to recognize internal viral nucleic acids. The presence of viral dsRNA and its reaction with the CR activates the routes of NF-κB and IRF-3, regulators of the IFN transcription factors. Alternatively, cytosolic dsDNA is sensed by cyclic GMP-AMP synthase (cGAS), which binds to the Stimulator of Interferon Genes (STING), triggering the phosphorylation of IRF3 [12]. NF-κB and IRF-3 translocate to the nucleus and bind the promoter of the gene for IFN-β, enabling IFN-β transcription, the first IFN to be secreted (Figure 1).

In the next phase of amplification, IFN-β is recognized by IFNAR, the receptor of IFN-I at the cell membrane, consisting of two subunits: IFNAR-1 and -2, which heterodimerize when they bind IFN. This activates molecules which, upon traslocation to the nucleus, bind DNA sequences known as Interferon-Stimulated Response Elements or ISRE. These ISRE are present in many genes, the transcription of which is triggered, followed by the synthesis of the corresponding proteins, some of which have anti-viral properties [4]. The expression of IRF-7, the main regulator of the expression of IFN-I genes, is also triggered. IRF-7 together with IRF-3 activate the synthesis of IFN-α, along with IFN-β [1,3,4] (Figure 1).

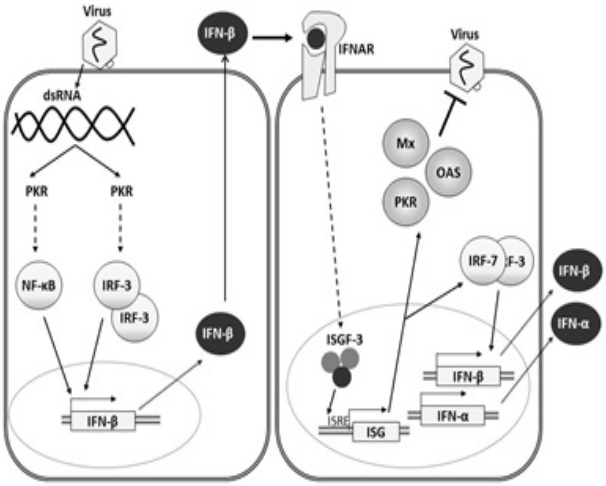

Figure 1. Mechanism of induction of IFN genes.

• Plasmocytic dendritic cells use the TLR pathway, expressed on the cell surface or in endosomes (which are sensitive to DNA and viral RNA). The TLR signal activates IRF-7, which is constitutively expressed in these cells), resulting in the secretion of high levels of IFN-α [4].

1.2. Proteins induced by type I interferon mainly block the viral infection

The signal produced by IFN is remarkably fast, because all the components of the cellular pathway are already present [4]. Antiviral proteins induced by IFN-I can act through three major routes: PKR (protein kinase-R), OAS (2', 5' - oligoadenylate synthetase) and Mx proteins [10] (Figure 1). PKR inhibits the translation of viral proteins and activates the transcription of cytokines and antigen presentation by type I-MHC, increasing the effectiveness of the immune response. OAS activates latent endoribonuclease (RNase L), destroying the viral RNA and thus inhibiting protein synthesis. Mx proteins, with GTPase function, interfere with viral replication by inhibiting the vesicular traffic (preventing the transport of the nucleocapsid) and the synthesis of viral RNA [10,13].

The overall effect of these antiviral proteins is that IFN-I decrease viral titers in vitro, and they reduce the viremia in vivo. Interferons do not block a specific step of the viral cycle but they act at various points: at the entrance of the virus, in the transcription of mRNA, in the synthesis of viral proteins, the replication of the viral genome, the assembly and formation of new virions, or at their exit from host cell. The step of action will depend on both the virus and the cell type infected, usually affecting several phases of viral replication [4].

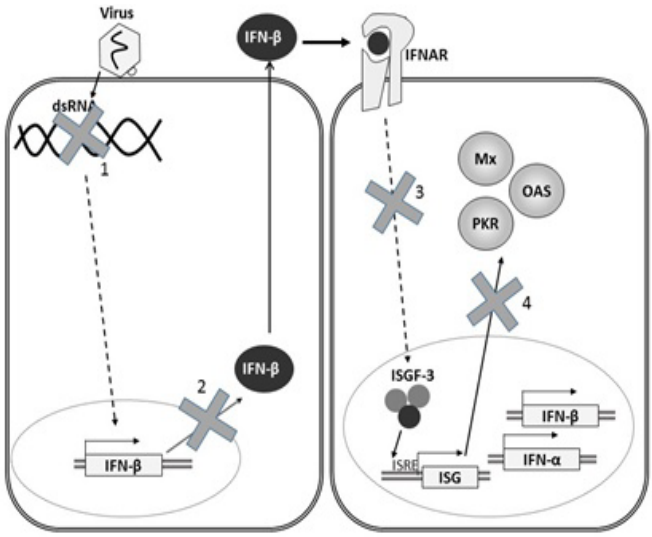

Figure 2. Mechanisms of evasion of viruses to IFN: 1) avoiding being recognized; 2) deactivating transcription factors; 3) blocking the signal of IFN-β at different levels; and 4) preventing or inhibiting the expression or action of antiviral proteins induced by IFN, mainly PKR.

Although the sensitivity of the different viruses to the action of the IFN varies depending on the host cell, RNA viruses generally are more sensitive to IFN than DNA viruses [2]. It seems that, in the case of the DNA viruses, interferons inhibit morphogenesis and maturation, while in RNA viruses interferons act on the replication of the viral RNA [14]. In addition, IFN can activate the expression of genes that induce apoptosis of infected cells, limiting the spread of the virus from one cell to another [15,16].

Viruses have developed different systems that allow them to escape the antiviral response induced by IFN. Some viral proteins inhibit the transcription of many cellular genes [10], while some viruses block the specific synthesis of IFN at different levels [2,16,17] (Figure 2).

1.3. Type I interferons also have an antitumoral activity

Interferons may control abnormal growth by either acting directly on tumor cells, or indirectly on other cells involved in tumor growth. This is particularly important in retroviruses, since some of them induce tumors, either dramatically fast or deceptively slow. Mechanisms used are the following (Figure 3):

a) Direct mechanisms. IFN-α and -β block the G1 phase of the cell cycle, and may lengthen all phases of the cycle (G1, G2 and S) through other proteins of the p200 family. In addition, IFN may induce apoptosis through different mechanisms, 15 of which have been identified by microarrays [16].

b) Indirect mechanisms. IFN may stimulate CD8+ T-cells (Tc), NK and dendritic cells (DCs) to fight the abnormal growth [1,3], or they may inhibit the organization of new vascular systems to nourish the tumor [13].

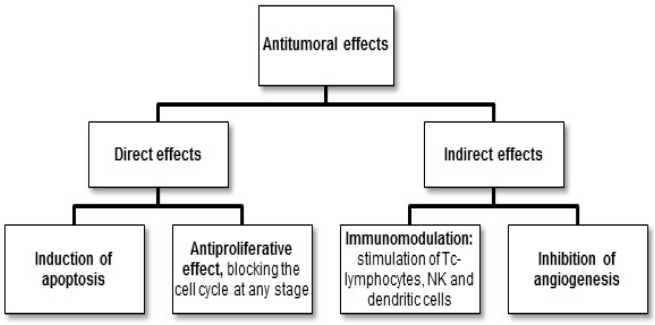

Figure 3: Antitumor effects of IFN-I.

1.4. Interferon may also be detrimental for cells

Some studies have suggested that high concentrations of IFN-α may have adverse effects, such as inhibition of the proliferation of T lymphocytes and of cytokines production. Even though the increased expression of type I MHC molecules (MHC-I) induced by IFN-I in all cells contributes to the removal of the infected cells [7], this increased expression may give rise to the dysfunctional selection of CD8+ T-lymphocytes, as observed in human immunodeficiency virus-infected (HIV^+) patients. Also, in HIV infection it has been observed that interferon produced by dendritic cells can induce the expression of TNF-related apoptosis induced ligand (TRAIL) by infected and non-infected $CD4^+$ T-lymphocytes [18]. Other mechanisms triggering apoptosis may include the activation by lentiviruses of the cGAS-STING pathway [19]. These observations agree with the high degree of apoptosis of non-infected $CD4^+$ T-lymphocytes in $HIV\text{-}1^+$ patients.

In addition, the local presence in the central nervous system of high concentrations of IFN has been associated with the onset of dementia. In animals with retroviral infections associated with disorders of the central nervous system and dementia, it has been observed that the increase in IFN-α levels in the cerebrospinal fluid correlates with cognitive deficits), and the use of neutralizing antibodies against IFN-α may revert the clinical signs.

2. Role of type I interferons in retroviral infections

In the case of feline leukemia virus (FeLV), IFN-α inhibits viral replication in feline cell cultures [15]. The effect is probably at the stage of virion assembly and maturation, as the synthesis of viral p27(SU) is not affected but the number of infective viral particles is decreased by increasing the concentration of IFN or the time of exposure [15]. Several studies with different retroviruses support this hypothesis [17,20]. However, in in vitro infections with simian immunodeficiency virus (SIV) it appears that IFN may block the binding of the virus to the cell and reverse transcription [21].

Other mechanisms involving genes and proteins induced by IFN may be also responsible for the effect of IFN on retroviruses: the OAS and Mx inhibit the formation of viral particles, reducing RT activity and the synthesis of p24 in HIV infected cells [22]; the intracellular factor that inhibits retroviral replication, APOBEC3G/F, is stimulated by IFN-α in infected cells, resulting in a greater antiviral activity against murine leukemia virus (MuLV), HIV or SIV [23]; recently it has been shown that even endogenous retroviruses may collaborate with the cGAS-STING pathway (Figure 1) to induce a B-cell response [24].

Most data regarding the role in vivo of IFN-I in retroviral infections come from studies in HIV. The increase in IFN-α concentration in the serum of patients with Kaposi's sarcoma and hemophilia was one of the first immunological abnormalities discovered in patients with HIV-AIDS, and the data seem to point out the important role of IFN-α in the pathogenesis of the disease. In the early stages of HIV infection the synthesis of IFN-I is normal. In asymptomatic and non-progressor HIV^+ patients the concentration of IFN-α is increased, associated with high counts of $CD4^+$ T-lymphocytes, low viral load and absence

of opportunistic infections [25]. However, as the patient starts to deteriorate, the synthesis of IFN-α is reduced, accompanied by the decrease in $CD4^+$ T-lymphocytes counts. Thus, the concentration of interferon may be used as an additional marker to establish the stage and evolution of the disease. Results of studies with Friend murine leukemia virus (F-MuLV) and human T-cell leukemia virus (HTLV-I) also seem to suggest that IFN is able to control to a certain degree infections by both viruses [6,26].

3. Are type I interferons an effective therapy for animal retroviral infections? Feline retroviroses as examples

Due to its antiviral and immunomodulatory effect, type I interferons have been used for some time for treating viral and tumor processes. IFN-α is licensed for treating leukemia, papillomatosis and infection by HIV in humans, applied by topical, nasal, eye, or intralesional routes. The administration of IFN-I to individuals infected with HIV [18] FeLV [27-29], feline immunodeficiency virus (FIV) [30,31], HTLV-I [20], bovine leukemia virus (BLV) [32] or MuLV [6] improves the clinical signs. IFN inhibits the infection of T-lymphocytes and monocytes when administered at the time of HIV infection, rendering p24 antigen, RT activity, and viral DNA and RNA undetectable [33].

Initially the use of IFN-α in veterinary medicine was intuitive, by extrapolation of the good results obtained in human medicine. However, at present there are several published studies showing its usefulness in feline medicine. IFN-α is used in cats to treat various viral processes, such as infections by Herpesvirus, Papillomavirus, Coronavirus, Feline Panleukopenia, or Feline Infectious Peritonitis [34]. IFN-I act as immunomodulators but they also have direct antiviral effects.

Different protocols and routes of administration (oral and subcutaneous) have been studied. Initial trials in feline medicine used recombinant human IFN-α (rHuIFN-α). Nowadays recombinant feline IFN-ω, commercialized by Virbac as Virbagen®, is also available, and most recent studies in feline medicine focus on its application.

Some studies reported that the parenteral administration of rHuIFN-α in cats results in the development of anti-IFN antibodies that decrease the efficacy of treatment after 3-7 weeks [34]. However, rHuIFN-α can be administered orally during a longer period because it is not recognized as foreign and these antibodies do not develop when this route is used (personal observation). IFN-α is inactivated by stomach acid pH and by trypsin and other enzymes in the duodenum, so it is not detected in blood after oral treatment. Nevertheless, it probably acts locally, stimulating the oral and pharyngeal lymphoid tissue and triggering an immune cascade that would finally have a systemic effect [34]. Likewise, interferon induces local cytokine response, increasing the expression of IFN-α and reducing that of IL-4 [35]. With respect to the dose, no significant differences between high or low IFN-α dose have been noted [36].

It has been observed that rHuIFN-α treatment decreased the mortality of cats with natural [37] or experimental [38] FeLV infection, though in the latter case there was no reduction of viremia. Treatment with rHuIFN-α was associated with an improvement in the clinical signs and laboratory alterations of the $FeLV^+$ cats [37, personal observation)].

Positive results have also been achieved by combining IFN-α with other antiviral drugs, such as the 3'-azido-2',3'-dideoxytimidina (AZT) which reduces the antigenemia [39,40]. However, other studies have not observed evidence of improvement in the clinical signs, laboratory parameters or viremia [41,42]. There are very few published studies with cats infected with FIV and treated with rHuIFN-α. In 2006 in a trial with a group of clinically sick FIV-infected cats it was observed that interferon (a) improved their general condition, (b) $CD4^+$ T-lymphocytes counts did not decrease, and (c) there was a slow but progressive increase of $CD8^+$ T-lymphocytes. However, no significant differences were observed throughout treatment regarding viral and proviral loads [31].

Recombinant feline interferon Omega (rFeIFN-ω) is obtained by infecting silkworms with a baculovirus containing the sequence for feline IFN-ω. rFeIFN-ω, unlike rHuIFN-α, does not stimulate the production of antibodies when administered parenterally to cats, and thus the antiviral, antitumor and anti-proliferative features are not diminished with treatment.

Few studies have been conducted to evaluate the effectiveness of this feline IFN. In a study involving FIV-infected cats, the survival of cats treated with rFeIFN-ω did not seem to increase, although improvements were observed in the clinical condition when compared to untreated cats [30]. In cats infected with FeLV or co-infected with FeLV+FIV and treated with rFeIFN-ω, the mortality rate decreased and the alterations of the leukogram improved when compared to non-treated cats. However, there was no positive evolution of the erythrogram [30]. Another study found no significant differences between the groups of treated and non-treated animals in parameters such as blood concentration of provirus, $CD4^+$ T cells, or leukocytes [43].

More recent studies with rFeIFN-ω have reported a non-specific general improvement of the clinical condition of cats infected by FIV or FeLV. However, as in the previous studies the positive evolution was not paralleled with that of the viral load or biochemical or immunological parameters in treated cats [28,29,39,44].

In summary, IFN-I is an interesting drug in veterinary practice,

and more specifically in feline medicine for treating retroviral infections. Its effect is both immunomodulatory and directly on the virus. Though viruses have developed different strategies to evade the effect of IFN, it appears that feline retroviruses are susceptible to these molecules and good results have been reported, especially as respects clinical and leukogram evolution.

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