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Mini Review

## Interferon: Role in health, current trends and therapeutic potentials

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### ABSTRACT

This mini review presents the current trends and topical issues on interferon. This article illustrates the theoretical background and details about interferon, its mechanism of action or roles in the prevention of microbial- or pathogenic disease progression, types and classes, and their therapeutic potentials. All the reported applications have shown that interferon has found its application in gene manipulation and expression of gene products; immunological techniques, viral disease treatment and in the treatment of cancers.

**Keywords:** Interferon, cancers, cancer therapy, viral infection, viral disease treatment.

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### INTRODUCTION

When host cells are invaded by several pathogens, which are majorly viruses, bacteria, parasites, and tumour cells inclusive; host cells respond by releasing a group of signaling proteins, known as interferons (IFNs) <sup>1-4</sup>. IFNs are considered to be cytokines which are protein molecules that induce cell-to-cell communication to trigger immunity against invading pathogens. Because of their ability to "interfere" with the process of viral replication and ultimately protecting cells from virus infections, they are named interferon. IFNs also act by: activating cells involved in immunity, such as macrophages and NK cells (natural killer cells); increasing host defenses via inducing foreign antigen uptake and increasing the expression of major histocompatibility complex (MHC) antigens<sup>5</sup>. The production of IFNs and other cytokines cause certain symptoms associated with infections, such as muscle pain, fatigue, fever and flu-like "symptoms" <sup>6</sup>. In humans and animals, over 20 distinct interferon genes and proteins have been identified<sup>7</sup>.

Currently, interferons are categorized as cytokines under the group of interleukins and there are three known types of IFNs namely: alpha ( $\alpha$ ), beta ( $\beta$ ), gamma ( $\gamma$ ) and Lambda ( $\lambda$ ) interferon. The IFN- $\alpha$  and IFN- $\beta$  are classified under type I sub-class, whereas IFN- $\gamma$  is classified under type II sub-class<sup>8</sup>. The IFN- $\lambda$  subtype is poorly understood at this time. After cells have been exposed to foreign antigens or agents, the cells are stimulated to release these IFNs, which then act as functionally modulating proteins, leading to events that protect against the invading agents. In order to obtain a complete antiviral effect, however, other proteins known as

'effector' proteins must be synthesized and released. Therefore, interferons are generally known as "inducer" molecules because they act on other proteins which trigger an antiviral and/or antiproliferative mechanism<sup>9,10</sup>. To date interferons are characterized by three key features: antiviral action, immunomodulatory action and an antiproliferative action which have been recently reported <sup>11, 12</sup>. Under certain conditions, because of the ability of some IFNs to block cells at a given phase of the cell cycle, investigation of their antitumour activity has become crucial<sup>12</sup>.

### TYPES OF INTERFERON

#### Alpha interferon

Alpha interferon, because it is produced by leukocytes, it is also named 'leukocyte interferon'. It is coded for by 15 genes and 9 pseudogenes found on human chromosome 9 and murine chromosome 4<sup>13</sup>. Each of these genes does not contain any intron (non coding region) but only exons (DNA-coding region) <sup>13</sup>. The production of IFN- $\alpha$  is influenced by the action of external agents such as tumour or eukaryotic cells, or by virus-infected cells; and one crucial point to note is that all these inducers trigger the production of IFN- $\alpha$  by lymphocytes and macrophages.

#### Beta Interferon

The beta type (IFN- $\beta$ ) was the first interferon to be discovered in 1957 by Isaacs and Lindenmann<sup>14</sup>. Isaacs and Lindenmann observed that the cells exposed to the dead viruses secreted a previously unknown substance which blocked future viral attack. IFN- $\beta$  is also named 'fibroblast

interferon' because it is produced by fibroblasts and epithelial cells under the action of foreign nucleic acids like viruses or other types. Also, IFN- $\beta$  is coded by a gene docked on human chromosome 9<sup>15</sup>. In this case, only one gene exists and again there are no introns, therefore the whole gene codes for the protein.

### Gamma interferon

The gamma interferon (IFN- $\gamma$ ) belongs to a separate subclass, called type II interferon that is named 'immune interferon'. The IFN- $\gamma$  is produced especially by lymphocytes (activated T cells); and it can promote macrophage activation, mediate antiviral and antibacterial immunity, enhance antigen presentation, orchestrate activation of the innate immune system, coordinate lymphocyte-endothelium interaction etc.<sup>16,17</sup>. IFN- $\gamma$ , like IFN- $\beta$ , is also coded by a single gene which, however, is not docked on chromosome 9, but on chromosome 12<sup>18,19</sup>. In addition, it contains 3 introns, which was not the case with The IFN- $\alpha$  and IFN- $\beta$ <sup>19</sup>. These and other features resulted to allocating IFN- $\gamma$  to a separate class which has different characteristics with respect to IFN- $\alpha$  and IFN- $\beta$ . Interestingly, another unique trait of IFN- $\gamma$  is that it has unstable nature at an acidic pH and these are very important characteristics, especially as far as interferon-based therapy is concerned.

### Lambda interferon

The lambda interferon (IFN- $\lambda$ ) is classified under the type III IFN. It is induced by viruses and other IFNs and displays

potent antiviral activity against some virus infections *in vivo*<sup>20</sup>. Acceptance of this classification is less universal than that of type I and type II, and unlike the other two, little is known of this class and lots of investigations are currently ongoing to properly understand it. The type III interferon group consists of four IFN- $\lambda$  (lambda) molecules called IFN- $\lambda$ 1, IFN- $\lambda$ 2, IFN- $\lambda$ 3 (also known as IL29, IL28A and IL28B respectively), and IFN- $\lambda$ 4<sup>21</sup>.

### CLASSIFICATION

**Type I interferon:** Are produced in direct response to viral infection and comprise the products of the IFN- $\alpha$  multigene family, which are predominantly synthesized by leucocytes, and the product of the IFN- $\beta$  gene, which is synthesized by most cell types but particularly by fibroblasts.

**Type II Interferon:** Consists of the product of the IFN- $\gamma$  gene and, rather than being induced directly by virus infection, is synthesized in response to the recognition of infected cells by activated T lymphocytes and natural killer (NK) cells

**Type III interferon:** The type III interferons are structurally more closely related to the IL-10 family of proteins than either of the other IFN subtypes, but contribute to antiviral responses and induce activation of many of the same genes as the type I and II IFN molecules. This subtype is poorly understood at this time and has not been studied in graft-versus-host disease (GVHD) or graft-versus-leukemia (GVL) responses. Both type I interferons and IFN- $\gamma$  play critical roles in GVHD and GVL<sup>22</sup>.

### MECHANISM OF ACTION OF INTERFERON

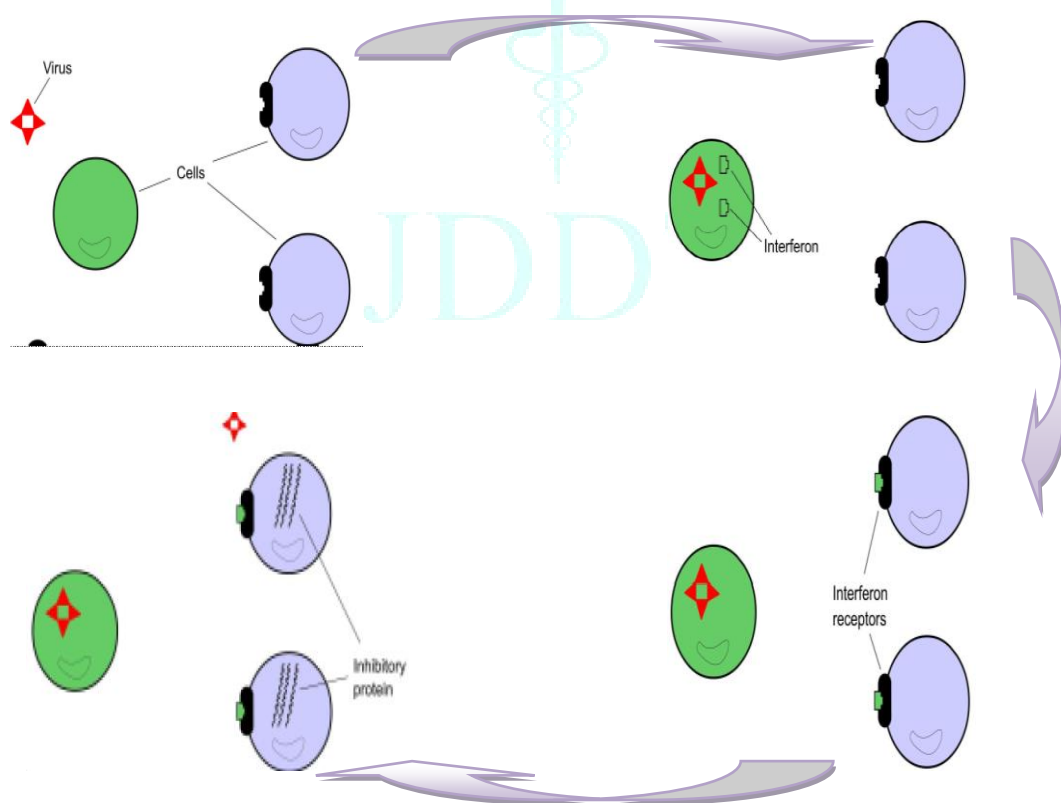


Figure1: **Mechanism of action of interferon:** Role of interferon starts after an initial viral attack on target cells. Several cell types when infected with virus secrete interferon. The secreted interferon enters the interstitial fluid and blood and binds to interferon receptors. This induces synthesis of inhibitory proteins that inhibit progressive or subsequent viral attack and possible viral replication

## THERAPEUTIC APPLICATIONS AND FUNCTIONS OF INTERFERON

### Antiviral activity

Significant successes have been achieved in the wide use of recombinant IFN- $\alpha$  forms in the treatment of chronic hepatitis B virus (HBV) and hepatitis C virus (HVC) infections and some forms of cancer<sup>23-25</sup>. IFN- $\beta$  treatment for multiple sclerosis is regularly used to limit exacerbations of the disease<sup>26-28</sup>. IFN- $\gamma$  has been approved for clinical use only in a rare congenital disorder and in chronic granulomatous disease<sup>29,30</sup>.

### Antiproliferative and antitumour activities

Currently, the antiproliferative action, together with its antitumour activity, is one major breakthrough concerning interferon function<sup>31-35</sup>. It is known that IFN- $\alpha$  can act on T-cells causing the differentiation of the T-helper 1 cells, while at the same time inhibiting the growth of other lymphocytes<sup>34</sup>. Similarly, IFN- $\alpha$  can act on NK cells and macrophages, thus enhancing their production of interferon and especially their production of interleukin 1 and their proliferation, thus increasing the number of circulating cells<sup>36</sup>.

Because of their cell differentiation and growth regulatory properties, interferons have been used in attempts to treat neoplasms<sup>37,38</sup>. Several forms of haematological cancers and solid tumours have been treated with interferons with some success<sup>33,34</sup>.

### Treatment of multiple sclerosis

Treatment of multiple sclerosis with IFN- $\beta$  was initiated based on the immunomodulatory properties of the interferon<sup>39,40</sup>. Well-controlled studies have demonstrated that intramuscular treatment with IFN- $\beta$  results in a reduction in the annual rate of relapses of multiple sclerosis<sup>41</sup>.

### Signal transduction

To exert their first messenger activities, IFNs bind to specific membrane receptors. These receptors enable cells sense the external signal of IFN and then transfer it in the interior, so that the cell can produce what is known as interferon-inducible proteins<sup>42</sup>. Just like the interferons, receptors are classified into two, namely the receptor for IFN- $\alpha$  and IFN- $\beta$  on the one side and the receptor of IFN- $\gamma$  on the other side<sup>43</sup>. The interferon receptors consist of two sub-units. These are transmembrane proteins with an extra-cytoplasmic domain and an intra-cytoplasmic domain displaying particular motifs that bind to proteins which make it possible for this external signal to be sensed within the cell<sup>44</sup>. These receptors are grouped under the JAK proteins, which mainly comprise the tyrosine kinase proteins that can phosphorylate tyrosine residues<sup>44</sup>. The STAT proteins are other important proteins, and they too have dual role; i.e. they act as signal transducers and also as transcription activators<sup>45</sup>. Finally, another group of proteins playing a pivotal role in the interferon signal transduction is composed by the Interferon Regulatory Factors (IRFs), known to act as transcription factors but are still being studied to fully understand their functional roles or mechanisms<sup>46,47</sup>.

### SIDE EFFECTS OF INTERFERONS

Common side effects of Interferons are:

- Fever
- Fatigue

- Malaise
- muscle pains
- Cardiorenal toxicity, bone marrow and liver toxicities.  
48-50

### CONCLUSION

Interferon is gaining significance based on clinical and laboratory results and the availability of improved molecular technology. Therapeutic application of interferon applications can be envisaged in all areas of biomedical sciences, including molecular biology techniques. Hence the usefulness of interferon continues to expand into the field of medicine, molecular biology, pharmaceutical medicine and biotechnology.

### COMPETING INTERESTS STATEMENT

The authors declare no conflicts of interest.

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