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Review on: The role of type-I interferon (inf-1) in infectious disease

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Abstract
Interferon (INF) is one of the important cytokines groups, an essential component of the immune system. It is produced in response to microbes and other antigens that mediate and regulate immune and inflammatory reactions. They are classified into two types: type-I (IFN-α, β) and type-II (IFN-γ). Type-I IFNs consist of two distinct groups of proteins called IFN-α and IFN-β. Mononuclear phagocytes are the major source of IFN-α, whereas IFN-β is produced by many cells, such as fibroblasts. The most potent stimulus for type-I IFN synthesis is viral infection; antigen-activated T-cells also stimulate mononuclear phagocytes to synthesize type-I IFNs. The biological action of Type-I IFNs have been associated with antiviral immunity for several decades. More recently studies have been shown its role in non-viral infections, bacterial and protozoan infections. The several antiviral functions of the IFN-I include direct suppression of viral replication and activation of the immune response against viruses. In addition to their antiviral effects, IFN-I are also protective against several extracellular bacterial infections, in part, by promoting the induction of TNF-α and nitric oxide. Even though there is a subsequent loss of host resistance later in infection, type-I IFNs play a role in early resistance to protozoan parasites like trypanosome. In contrast, there is a negative effect of IFN-I on host resistance during chronic viral infection and acute infections with intracellular bacteria. Due to chronic IFN-I signaling induce adaptive immune system suppression and during acute intracellular bacterial infection, IFN-I suppress innate immunity respectively. Despite its limitations, interferons have been prepared in biotechnology industry for the treatment of diseases like hepatitis, sclerosis and cancer. Hence, further studies should be done to determine biological outcomes of IFN-I for many classes of bacterial, protozoa and other non-viral pathogens and also to determine the applicability of IFN-I modulation as a therapeutic to important chronic human viral infections.

Keywords: Immune system, Infectious diseases, Type-I IFNs

1. Introduction
Molecules that communicate among cells of the immune system are referred to as cytokines. Cytokines are polypeptides, an essential component of the immune system, produced in response to microbes and other antigens that mediate and regulate immune and inflammatory reactions. Cytokine signal an immune cell to increase or decrease the activity of particular enzymes or to change its transcriptional program, thereby altering and enhancing its effector functions. Even they can instruct a cell when to survive and when to die [1, 2].
In recent years, immunologists have enjoyed an explosion of information about new cytokines and cytokine receptors as a result of advances in genomic and proteomic analysis. Cytokines characterized so far belong to one of six groups: the Interleukin 1 (IL-1) family, the Hematopoietin (Class I cytokine) family, the Interferon (Class II cytokine) family, the Tumor Necrosis Factor (TNF) family, the Interleukin 17 (IL-17) family, and the Chemokine family [3].
The interferon (IFNs) is perhaps the most important cytokines in the initial innate response to viral infection. The term interferon derives from the ability of these cytokines to interfere with viral infection. They are classified into two types: IFN-α (a family of related proteins) and the single protein IFN-β together form type I; IFN-γ is the sole and unrelated type-II IFN [1].
Type-I IFNs (IFN-α and IFN-β) mediate the early innate immune response mainly to viral infections. They are secreted by cells in response to viral infection and promote an antiviral response in otherwise susceptible cells. Interferon α and β are secreted by activated macrophages and dendritic cells, as well as by virus-infected cells [2].
Type-II IFNs called IFN-γ is produced by activated T-cells (T_H1 cells, $CD8^+$) and NK cells

that activates macrophages; increases expression MHC Class-I and Class-II molecules and increases antigen presentation [3]. It is the principal macrophage-activating cytokine and serves as critical functions in innate immunity and in adaptive cell-mediated immunity. In addition, it has some antiviral activity, but it is not a potent antiviral interferon, and it functions mainly as an effector cytokine of immune responses [1].

The biological action of Type-I IFNs have been associated with antiviral immunity for several decades. Recently they have been shown to affect the course of a variety of protozoan and bacterial infections. Moreover, the immune-modulatory activities of interferon could also contribute to the mediation of resistance to non-viral infections [4]. However, a few researchers have been indicated that they can also cause decreased host resistance to some acute intracellular bacteria and chronic viral infections. Thus, despite some of its negative role in immune system, Type-I IFNs could play a crucial role in natural host defenses to a wide variety of microbial infections [5]. Moreover, Type-I Interferon has been prepared in biotechnology industry for the treatment of diseases like hepatitis, sclerosis and cancer [1]. Hence, this seminar paper is aimed to review on the role of type-I interferon in infectious diseases. Therefore, the objective of this seminar paper is: Review on the role of type-I interferon in infectious diseases

2. Overview of induction and function of cytokines/INFs

Cytokines including interferon regulate the intensity and duration of the immune response by stimulating or inhibiting the activation, proliferation, and/or differentiation of various cells, by regulating the secretion of other cytokines or of antibodies, or in some cases by actually inducing programmed cell death in the target cell. In addition, cytokines can modulate the expression of various cell-surface receptors for chemokine, other cytokines, or even for themselves (fig. 1). Thus, the cytokines secreted by even a small number of antigen-activated lymphocytes can influence the activity of many different types of cells involved in the immune response [2].

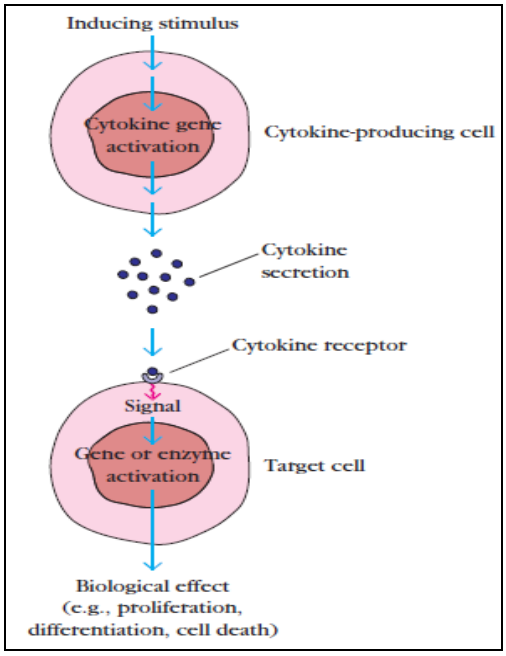


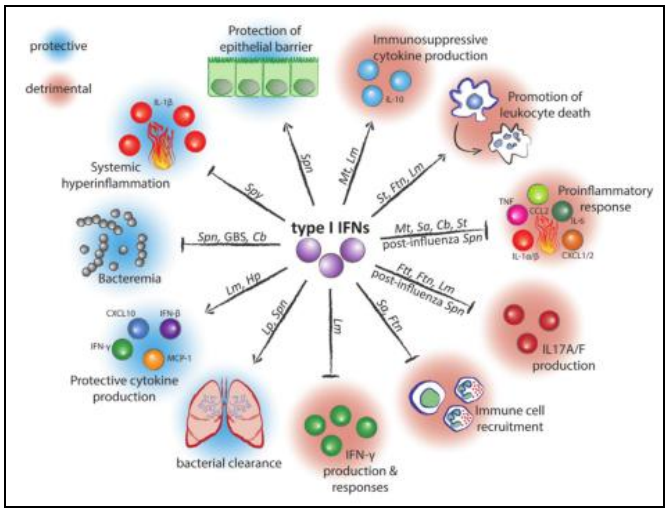
Fig 1: Overview of induction and function of cytokines

3. Structure, production and receptors of type-I INFs

Type-I IFNs consist of two distinct groups of proteins called IFN-α and IFN-β. IFN-α is actually a family of about 20 structurally related polypeptides, each encoded by a separate gene. Mononuclear phagocytes are the major source of IFN-α, and IFN-α is sometimes called leukocyte interferon. Whereas IFN-β is a single protein produced by many cells, such as fibroblasts, and it is sometimes called fibroblast interferon [1].

The most potent stimulus for type-I IFN synthesis is viral infection, specifically double stranded RNA that is produced by viruses during their replication in infected cells. Experimentally, production of type-I IFN is commonly elicited by synthetic double-stranded RNA, which mimics the signal produced during viral infection. Antigen-activated T cells also stimulate mononuclear phagocytes to synthesize type-I IFNs [1].

Although IFN-α and IFN-β are structurally different, they bind to the same cell surface receptor and induce similar biologic responses. The type-I IFN receptor is a hetero-dimer of two structurally related polypeptides; one binds the cytokine, and the other transduces signals through a JAK/STAT pathway. Both chains are members of the type-II cytokine receptor family [1].



4. Biologic actions of INF type-I

Host effectors mechanisms are essential for the survival of all multi-cellular organisms. To cope with an enormous microbial challenge, vertebrates have evolved additional levels of cell-autonomous control beyond the pre-existing repertoire of constitutive host defense factors. These additional factors include hundreds of gene products that are transcribed in response to signals originating from several cytokines including the interferon [6, 7]. Many of the induced proteins confer direct microbcidal immunity in all nucleated cells [8].

IFNs are among the most potent vertebrate-derived signals for mobilizing antimicrobial effector functions against intracellular pathogens in all nucleated cells, a process termed cell autonomous immunity [9]. Nearly 2,000 human and mouse IFN-stimulated genes (ISGs) have been identified to date, most of which remain uncharacterized [10]. The recent large-scale examination of newly described ISGs reveals a highly diverse but integrated host defense programme dedicated to protecting the interior of a vertebrate cell [11, 12-13].

Recently, genomic and sub-genomic analyses have begun to assign functional properties to novel IFN-inducible effector proteins that restrict bacteria, protozoa and viruses in different sub-cellular compartments and at different stages of the pathogen life cycle [14].

4.1. The role of Type-I IFN against Viral Infection

The actions of type-I IFNs protect against viral infections and promote cell-mediated immunity against intracellular microbes (Fig. 2).

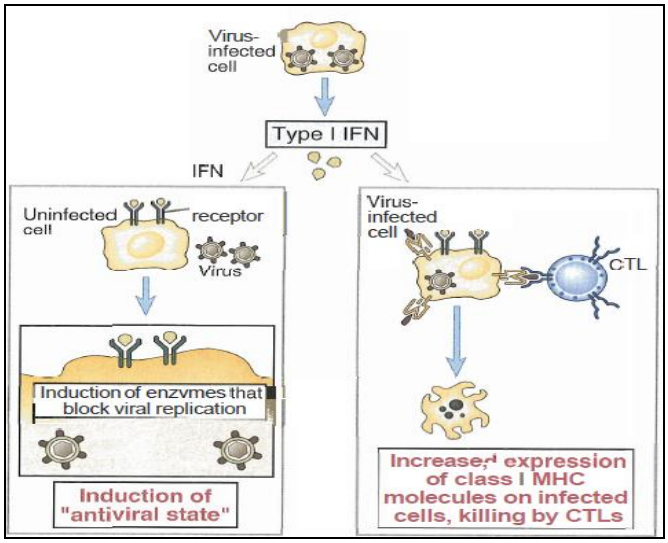


Fig 2: Biological action of type-I Interferon against viral infection

4.1.1. Inhibition of viral replication

Interferon α and β are also secreted by viral infected cells after recognition of viral components by pattern recognition receptors (PRRs) located either at the cell surface, or inside the cell. Intracellular PRRs may interact with virally derived nucleic acids or with endocytosed viral particles [2].

The secreted Type-I interferon then interact in turn with membrane-bound interferon receptors on the surfaces of many different cell types. The interaction of INF with their receptor causes cells to synthesize a number of enzymes, such as 2', 5' oligoadenylate synthetase, which when polymerized activate the latent ribonuclease that interfere with the transcription of viral RNA or DNA, and the cessation of cellular protein synthesis. Thus, interferon prevents virally infected cells from replicating and from making new viral particles. The effects of IFN-I that limit viral infection are extensive, but several aspects are important to consider. IFN-I signaling enhances the susceptibility of virally infected cells to undergo programmed cell death (destroy virally infected cells), thereby limiting viral replication and infection cannot be spread [7, 2 15].

The antiviral action of type-I IFN is primarily a paracrine action, in that a virally infected cell secretes IFN to protect neighboring cells that are not yet infected. A cell that has responded to IFN and is resistant to viral infection is said to be in an "antiviral state." IFN secreted by an infected cell may also act in an autocrine fashion (receive signal via its own membrane receptor from its cytokine) to inhibit viral replication in that cell [1].

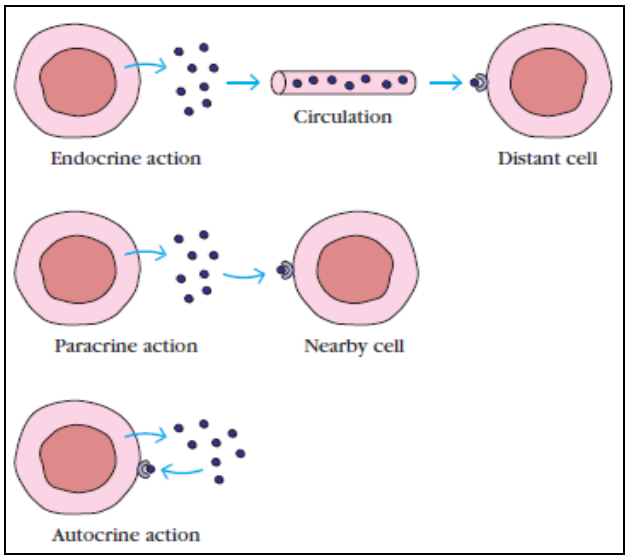


Fig 3: Endocrine, paracrine and autocrine action of cytokines

4.1.2. Activation of the adaptive immune response

Because $CD8^+$ CTLs recognize foreign antigens bound to class-I MHC molecules, type-I IFN enhances the recognition of class-I associated viral antigens on infected cells and therefore the efficiency of CTL mediated killing of these cells. Moreover, type-I IFN stimulates the development of T_H1 cells in humans. This effect is mainly due to the ability of type-I IFN to promote in T cells the expression of functional receptors for the major T_H1-inducing cytokine IL12. Type-I IFN may also increase the cytolytic activity of NK cells [16].

Dendritic cells (DCs) exposed to IFN-I become activated and secrete pro-inflammatory cytokines that lead to activation of the adaptive immune response. NK cells become potent killers of virally infected cells after exposure to IFN-I [16, 17].

IFN-I has direct effects on adaptive αβ T-cells and sensitizes them to activation via the TCR [18]. IFN-I production by plasma cystoids DCs promotes B-cell activation and production of antiviral antibody In general, these effects of IFN-I signaling are beneficial to the host, as they lead to control of viral replication and spread [19].

The importance of host IFN-I signaling is further reinforced by viral evolution. Viruses have evolved extensive immune-evasion strategies many of which center around inhibition of the host IFN-I response [20, 21]. However, the biological responses to IFN-I do not always lead to beneficial outcomes to the host. INF-I promotes suppression of adaptive immunity during chronic viral infection [5].

The best studied example of the negative role of IFN-I are chronic viral infections of mice with lymphocytic choriomeningitis virus (LCMV). Several factors have been implicated in the suppression of T-cell mediated clearance of chronic LCMV; most salient among them are IL-10 and PD-1 (programmed cell death 1). IL-10 is known to antagonize inflammatory activation on multiple immune cell types [22].

PD-1, a member of the CD28/CTLA4 family of T-cell regulators, is up-regulated on exhausted T cells found in chronically infected mice. Its ligands, PD-1L and PD-2L, are broadly expressed and inducible by interferon [23]. The interaction of PD-1 with PD-L1 acts to limit T-cell activity during chronic infection [24]. In two recent publications, the effects of IL-10 and PD-1 in limiting the response to LCMV infection have been causally linked to IFN-I signaling [25, 26].

4.2. The role of Type-I IFN against bacterial Infection

Type-I IFNs have been associated with antiviral immunity for several decades. Only recently have they been additionally attributed to bacterial infections [4].

Recently, an in vivo study in mice has been indicated that the response of type-I INF to bacterial infections varies depending on the species and route of infection. Based the initial studies, the simplest conclusion is that INF type-I signaling is beneficial during extracellular bacterial infection and detrimental during intracellular bacterial infection [5].

IFN-I are protective against several extracellular bacterial infections, in part, by promoting the induction of TNF-α and nitric oxide. During acute intracellular bacterial infection, IFN-I suppress innate immunity by at least two defined mechanisms. During *Francisella* infection, IFN-I prevent IL-17 up-regulation on γδ T cells and neutrophil recruitment. Following *Listeria* infection, IFN-I promote the cell death of macrophages and lymphocytes, which leads to innate immune suppression [5].

Type-I IFN signaling provides increased protection during *Streptococcus* infection by promoting up-regulation of TNF-α, IFN-γ and nitric oxide [27]. This is associated with restriction of bacterial growth. Moreover, *Helicobacter pylori* infected mice have higher titers, but the mechanism of IFN-I action in this infection remains unresolved [28]. Further work needs to be done on the extracellular bacterial infections to determine how IFN-I is protective and what distinguishes IFN-I from IFN-II in these types of infections.

Following *Brucella* infection (intracellular bacteria), there is IFNAR-dependent Up-regulation of TNF-related apoptosis-inducing ligand (TRAIL) and spleenic apoptosis that is associated with increased susceptibility to infection [29]. IFNAR- mice also express more IFN-γ and nitric oxide. In addition, in the case of *Salmonella enterica* and *Chlamydia muridarum*, IFN-I signaling sensitizes the infected macrophage to undergo cell death [30, 31]. Prevention of macrophage cell death during *S. enterica* infection led to decreased bacterial titer. IFNAR- mice infected with *Francisella* have decreased titers and lethality compared with controls. This is attributed to the inhibitory effect of IFN-I signaling on IL-17A/F expression [32]. IFNAR- mice express more IL-17A/F, have an expansion of IL-17+ γδ T cells and increased neutrophils at the site of infection. [32].

Furthermore, treatment with IFN-I agonists such as poly (I: C) also promotes negative outcomes during bacterial infection. In the case of *Mycobacterium tuberculosis*, intranasal delivery of poly (I: C) throughout the course of infection led to increased inflammatory infiltrates and necrosis of lung tissue that was dependent of IFN-I signaling [33]. Similar detrimental effects of poly (I: C) treatment are also seen following *Streptococcus pneumoniae*, *Staphylococcus aureus* and L. monocytogenes infections [34].

IFN-I signaling is a negative regulator of the innate immune response to L. monocytogenes. Biological outcomes of IFN-I signaling during L. monocytogenes infection Listeria monocytogenes causes apoptotic cell death of macrophages that is enhanced by IFNAR signaling. Within 2 h of infection, bone marrow-derived macrophages up-regulate IFN-β and phosphorylate STAT1 [5].

4.3. The role of Type-I IFN against protozoa Infection

More recently, few works have been done on the role of INF-I in protozoan infections [35, 36-37].

Research on mice model showed that type-I IFNs play a role in early control of parasites in infected mice but may contribute to down-regulation of IFN-*γ* production and subsequent loss of host resistance later in infection [16]. It is presumed that macrophage activation by IFN-*γ* results in the production of factors such as TNF-*α*, reactive nitrogen intermediates, and reactive oxygen intermediates into the extra-vascular tissues that are known to be cytolytic for trypanosomes [16].

Moreover, [39] D Amin *et al*, (2012) [15] indicated that innate immune (Toll- Like Receptor) TLR signals stimulate the expression of tumor necrosis factor α (TNF α) and IFN-β that initiate brain invasion of T cells and trypanosomes, and control T. brucei brucei load in the brain by molecules distinct from these. The penetration of T cells and trypanosomes into the brain parenchyma is a major pathogenneticve event in African trypanosomiasis [39].

5. Interferone therapy

Despite much progress in treating many bacterial and fungal infections, only a few clinically useful antiviral drugs are available today. Interferon is one of the few antiviral drugs candidates. IFN-α is in clinical use as an antiviral agent in certain forms of viral hepatitis. IFN-β is used as a therapy for multiple sclerosis, but the mechanism of its beneficial effect in this disease is not known [2].

Cloning of the genes that encode IFN-α, IFN-β, and IFN-γ has made it possible for the biotechnology industry to produce large amounts of each of these interferon's at costs that make their clinical use practical [2].

IFN-α (also known by its trade names Roferon and Intron A) has been used for the treatment of hepatitis C and hepatitis B. It has also been found useful in a number of different applications in cancer therapy. A type of B-cell leukemia known as hairy-cell leukemia (because the cells are covered with fine, hair like cytoplasmic projections) responds well to IFN-α. Chronic myelogenous leukemia, a disease characterized by increased numbers of granulocytes, begins with a slowly developing chronic phase that changes to an accelerated phase and terminates in a blast phase, which is usually resistant to treatment. IFN-α is an effective treatment for this leukemia in the chronic phase (70% response rates have been reported), and some patients (as many as 20% in some studies) undergo complete remission.

Moreover, Kaposi's sarcoma, the cancer most often seen in AIDS patients in the United States, also responds to treatment with IFN-α, and there are reports of a trend toward longer survival and fewer opportunistic infections in patients treated with this agent [2].

Most of the effects mentioned above have been obtained in clinical studies that used IFN-α alone, but certain applications such as hepatitis C therapy commonly use it with an antiviral drug such as ribavirin. The clearance time of IFN-α is lengthened by using it in a form complexed with polyethylene glycol (PEG) called pegylated interferon [2].

IFN-β has emerged as the first drug capable of producing clinical improvement in multiple sclerosis (MS). Young adults are the primary target of this autoimmune neurologic

disease, in which nerves in the central nervous system (CNS) undergo demyelination. This results in progressive neurologic dysfunction, leading to significant and, in many cases, severe disability. This disease is often characterized by periods of non-progression and remission alternating with periods of relapse. Treatment with IFN-β provides longer periods of remission and reduces the severity of relapses. Furthermore, magnetic resonance imaging (MRI) studies of CNS damage in treated and untreated patients revealed that MS induced damage was less severe in a group of IFN-β treated patients than in untreated ones [2].

6. Conclusion and Recommendations

Interferon is an extraordinary group of proteins with important effects on the immune system. The several antiviral functions of the IFN-I include direct suppression of viral replication and activation of the immune response against viruses. In addition to their antiviral effects, IFN-I are also protective against several extracellular bacterial infections, in part, by promoting the induction of TNF-α and nitric oxide. Even though there is a subsequent loss of host resistance later in infection, type-I IFNs play a role in early resistance to protozoan parasites like Trypanosomiasis. In contrast, there is a negative effect of IFN-I on host resistance during chronic viral infection and acute infections with intracellular bacteria. Due to chronic IFN-I signaling induce adaptive immune system suppression and during acute intracellular bacterial infection, IFN-I suppress innate immunity respectively. Despite its limitations, Interferon has been prepared in biotechnology industry for the treatment of diseases like hepatitis, sclerosis and cancer.

Therefore, in line with the above conclusion, the following recommendations are forwarded:

- Further studies should be done to determine biological outcomes of IFN-I for many classes of bacterial, Protozoa and other non-viral pathogens.
- Further work should be done to determine the applicability of IFN-I modulation as a therapeutic to important chronic human viral infections.

Abbreviations

DCs: Dendritic Cells, IL: Interleukin, INF-α: Interferon Alpha, INF-β: Interferon Beta

INF-γ: Interferon Gamma, ISG: Interferon Stimulating Gene, NK-cell: Natural Killer Cells, PRR: Pattern Recognition Receptor, TNF: Tumor Necrosis Factor, TRAIL: TNF-Related Apoptosis-Inducing Ligand

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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