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INDUCION, MODE OF ACTION AND APPLICATIONS OF INTERFERON FOR TREATMENT OF VARIOUS HUMAN DISEASES: A REVIEW

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ABSTRACT

Interferons are member of cytokines family that alter a broad range of cellular activities. These are low molecular weight, host encoded proteins or glycoproteins that induce a series of interferon stimulated genes that code for anti-viral proteins. There are three classes of interferons that can induce interferon stimulated genes, type 1 with alpha and beta, type 2 includes only gamma and type 3 with only lambda interferons. At first interferon was isolated from animals for therapeutic uses but now it is produced either by genetic engineering or by natural methods its production is induced in cell cultures. In host cells Viruses, Polymers, Small molecules, Bacteria, Immunogens and many others act as inducers for IFNs production. INFAR are the receptors for interferon binding. Type-1 interferons exert diverse biological effects. Most important among these effects is anti-viral activity that controls virus replication and pathogenesis. Interferons promote antiviral and antibacterial innate immunity and on the other hand they also suppress immune response by anti-inflammatory cytokines. Type-III interferons are the components of innate immune response against HCV. This review focuses on brief introduction of interferon, what are the inducers of interferon production, its mode of action and different applications of interferons by which it is used to enhance public health standards.

KEYWORDS: Cytokines, INFAR, alpha Interferon, beta Interferon, gamma and lambda Interferon.

INTRODUCTION

IFNs are members of cytokine family and cytokines are cell active molecules formed by a wide range of cells, perform their function by interacting with cells and altering their behavior. IFNs are secreted molecules that represent one of the cell's first lines of defense against pathogens. These are low molecular weight proteins or glycoproteins depending upon species of origin and whether they are produced naturally or recombinally. These interferons are produced by all vertebrate cells (Wilson *et al.*, 1983) and perform many functions in cells including interfering viral replication, cell growth and immune response stimulation.

Interferon was the first cytokine to be discovered. Viral interference, a phenomenon in which replication of one type of virus in a cell prevents replication of other types of viruses in same cell. This phenomenon was first described in 1935 (Hoskins, 1935). Study of this phenomenon lead to discovery of interferons. Vial interference was first reported by Jenner in 1804 when vaccination remained unsuccessful in patients that suffered from herpetic affections. And second time it was more properly reported by experiments of Isaacs and Lindenmann in 1957, it was found that if cells were treated with heat killed viruses that cells were able to resist infection by live virus. Experiment included release of soluble anti-viral factors by treating cells of chick chorioallantoic membrane with heat inactivated influenza virus A. They showed that factor which is involved is not specific for virus type and this factor induces anti-viral state. The factor was named "Interferon". They were named so because they interfere with replication of live viruses, establishment of interference was due to release of interferon (Isaacs and Lindenmann, 1957). Fig 1 shows experiment performed by Isaacs and Lindenmann that lead to discovery of interferons. And stepwise research related to interferon is summarized in table number 1.

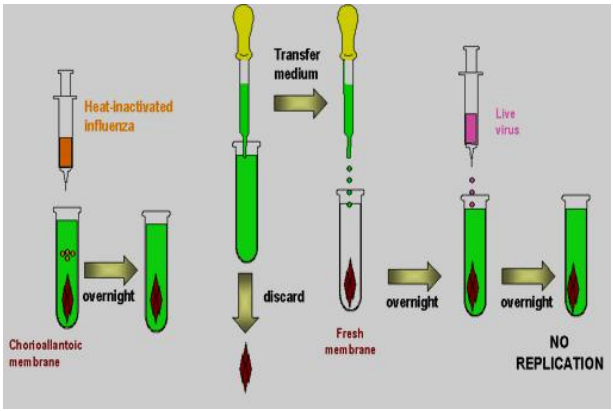


Fig 1: Experiment by Isaacs and Lindenmann that lead to discovery of interferon.

Three species of interferons are alpha **α** (leucocyte), beta **β** (fibroblast) and gamma **γ** (immune). Other than these there are lambda interferons. These species differ from each other in cellular origins, biological, antigenic and physicochemical properties. Alpha and beta interferons are called type I interferons and gamma interferons are type II interferons, lambda interferons are type III interferons. Generally type I interferons are acid stable and type II interferons are acid labile (Langford *et al.*, 1979). Type I interferons are produced by all nucleated cells. In in vitro experiments alpha interferons are released by stimulated leukocyte or Lympho-blastoid cultures and beta interferons are produced by fibroblasts or epithelial cells. Production of alpha and beta interferons is stimulated by bacteria, bacterial product, viruses, antigens, polymeric chemicals and foreign nucleic acids (Epstein, 1979). Whereas gamma interferons are true lymphokines as these type II interferons are released from T-lymphocytes after stimulation by IL-2, mitogens and antigens (Epstein, 1981). There are 15-17 genes in humans for alpha interferons, two or more beta interferon genes and only two gamma interferon genes (Allen *et al.*, 1980).

Table 1: History of research on interferon.

Date	Event
1957	Type I IFNs were discovered.
1964	Type II IFNs were discovered.
Mid-1960s	Human IFNs in treatment of viral infection was used as first trial.
Early 1970s	Human IFNs in treatment of malignant disease was used for the first time.
Mid- 1970s	Type I IFNs were purified.
1979 to early 1980s	IFN genes were cloned and expression was studied.
1982	It was demonstrated that IFNy is a T cell lymphokine.
1980s	It was demonstrated that IFNs play wide biological effects in immune system.
1980s	Extensive clinical trials show that IFNs have little therapeutic efficacy
Early 1990s	IFN signal transduction mechanisms were defined.
Early 1990s	Gene knockout experiments confirm importance of IFNs in resistance to infectious diseases
1997	Worldwide sales of IFNs exceed US$2 billion dollars annually

Production of Interferon

Interferons can be produced on large scale by recombinant DNA technology and it can be obtained by natural sources (Cantell and Hirvonen, 1978). Natural sources for production of interferons are cells. Cells in culture are stimulated for production of natural interferons (native interferon) and then interferon is purified from supernatant. This stimulus can be any virus, when cells are infected they produce interferon. In a series of activities interferons are produced by recombinant DNA technology. This type is of pure quality as compared to natural sources. Because in natural method when interferon is collected from cell culture this is in form of mixture of different types of interferons and other lymphokines (Vilchek *et al.*, 1983). Commonly viruses are used to induce production of IFNs in cell culture. Although single stranded RNA are good inducers for production of IFNs but double stranded RNA are best inducer for production (Cantell and Hirvonen, 1978). When culture of cells are infected these cells retain RNA of virus as transcriptive intermediates. And induce production of interferon. Viruses irradiated with UV light are also used to induce interferon release from cell (Portner and Kingsbury, 1972).

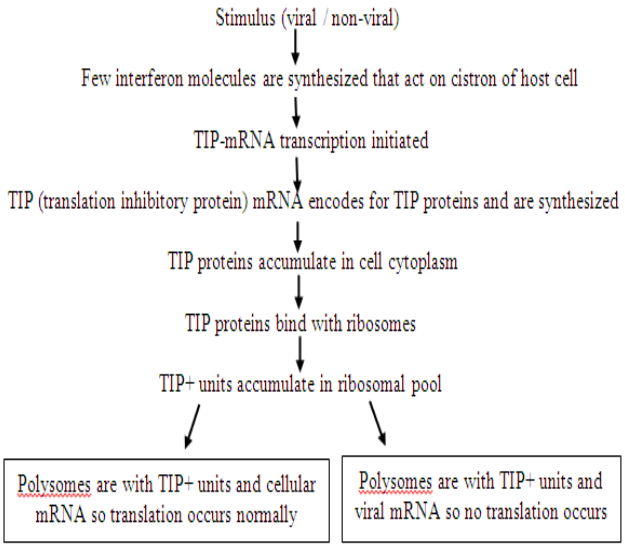
Induction

There are many substances that can induce interferon production these substances include both living and non-living agents: Viruses, polymers, small molecules, bacteria, immunogens plant phyto-hemagglutinin, a fungal cell wall carbohydrate, bacterial endotoxin and mitogens. Most active inducer of interferon is double stranded RNA. It triggers induction of interferon and it is analog of a viral replicative intermediate. Some factors control inductive property of double stranded RNA which are temperature, molecular weight and nuclease resistance (Pitha and Hutchinson, 1977). Different viruses have variable interferon inducing capacity and this capacity varies with virulence of virus. Synthetic anionic plastic copolymers, bacteriophage, double stranded synthetic ribonucleotide homopolymers and double stranded RNA isolated from Helanine (a fungal virus) all these can stimulate interferon (Ruiz-Gomez and Isaacs, 1973).

Induction of interferon is a regulated process in which maximum induction can be easily achieved even after a minor and short time duration exposure. Together with this now cell becomes hyporesponsive for induction. 'Priming' is pretreatment of cell with release of interferon after induction. If inhibitors of RNA or protein synthesis are used an effect opposite to hypo - responsivity can be achieved. This effect is called super-induction. Once interferon production is started now metabolically labile repressors are required to suppress its release. After the cell interferes with inducers, mRNA of interferon is translated. The mRNA of interferon is the only protein in eukaryotic cell that has ability to be translated in cell free system (Pestka *et al.*, 1975). Super-induction is a phenomenon in which synthesis of interferon is increased and metabolic stability of interferon mRNA is also increased. It is found that catabolic pathway of RNA which is usually present in interferon activated cells is not correlated with decay of interferon mRNA. It was noticed that during priming although this catabolic pathway has also started but this pathway has no effect on stability of interferon (Sehgal and Gupta, 1980). But opposite to this in priming a large increase in translatable interferon mRNA occurs. This interferon mRNA translation is not effected by reticulocyte lysates. This enzyme that inhibits translation of double stranded RNA (Lebleu *et al.*, 1978).

Mode of Action

If inhibitors of RNA and Protein synthesis are added to interferon producing cell then effect of interferon can be blocked on target cell. Interferon when produced it stimulates production of another protein which is 'anti-viral protein' because this protein protects from viral infection. This protein inhibits synthesis of viral proteins on ribosomal level. So viral proteins are not formed. Although target cell may be destroyed but replication of virus and further spread of virus to others cells is stopped now. A new protein appears in interferon treated cells on ribosomes (Marcus and Salb, 1966). 'Stimulon' or 'enhancers' are virus induced proteins these proteins inhibit interferon action thus promoting replication of viruses. On the other hand 'Blockers' are those proteins by which action of interferon remains unaffected but it blocks further production of interferon. And these proteins are not sensitive to proteolytic enzymes (Isaacs *et al.*, 1966). Activity of interferon can be inhibited by using different substances for example 40 percent fetal calf serum or 5 to 10 percent dimethyl-sulfoxide (DMSO) (Ilcek and Lowy, 1967).



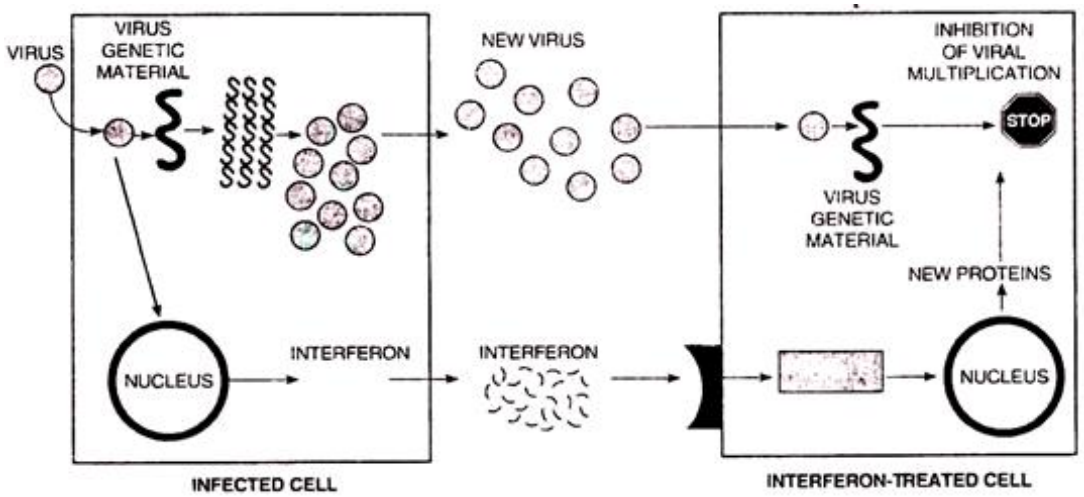


Fig 2: mode of action of interferon.

On the other hand there are some materials that enhance activity of interferon one example is 'Coferon' this is a protein extract from *E.coli* and it is active in *vitro* to promote activity of interferon. Another example is poly L-ornithine, poly-cationic nature of poly L-ornithine allows greater penetration of interferon into treated cells (Tilles, 1967). Fig number 2 illustrates how interferon works. All viruses are sensitive to interferon but their sensitivity varied from one another. Most resistive viruses that are inhibited by interferon but to lesser extent are Adenovirus and Cytomegalovirus. Reason behind this resistivity is perhaps similarity in RNAs of

cell and these viruses. Therefor these are translated by ribosomes as they are detected as cellular RNA (Oxman *et al.*, 1967). Trachoma conjunctivitis group which are more like bacteria than viruses in their replicative cycle, they also have their own ribosomes they are also inhibited by interferon (Hanna *et al.*, 1966). *Toxoplasma gondii*, a protozoan is also inhibited in tissue culture by purified interferon. *P. Berghei malariae* is also inhibited. It was noticed that once anti-viral activity of interferon is started then if interferon is separated from tissue culture then this anti-viral activity is retained for 28 hours and then started to decline. And after interferon is added increase in protection is checked after seen hours. This protection is maintained only when transcription and translation of interferon gene is continued. But if mRNA synthesis and protein synthesis is blocked then this activity is stopped (Baron *et al.*, 1967).

Temperature required for activation of interferon function in chick cells is 37°C (98.6 °F). Effect of interferon was also checked against DNA virus. It was found that interferon reduces concentration of DNA polymerase and viral DNA (Levine *et al.*, 1967). Replication of mature virus in host cell requires many enzymes, all these enzymes are inactivated by interferon, for example vaccinia virus requires alkaline DNAse, and this enzyme is also inhibited (Bodo and Jungwirth, 1967). Interferon also effects oncogenic virus, e. g; in newborn hamsters interferon inhibited tumor formation by polyoma virus and in chick cells by Rous sarcoma virus (Bader, 1962). If ribosomes are isolated from interferon treated cells these ribosomes contain different proteins than normal cells. These ribosomes also have ability to distinguish between viral and cellular genetic material. And this ability by which they distinguish can be inhibited by trypsin.

Applications of Interferons

Antiviral activity

Interferon acts in different ways. It activates series of enzymes by which viral replication is stopped. These enzymes effect transcription, translation, protein synthesis and viral assembly. Some of these inhibitory enzymes and their actions are given in following figure No. 3.

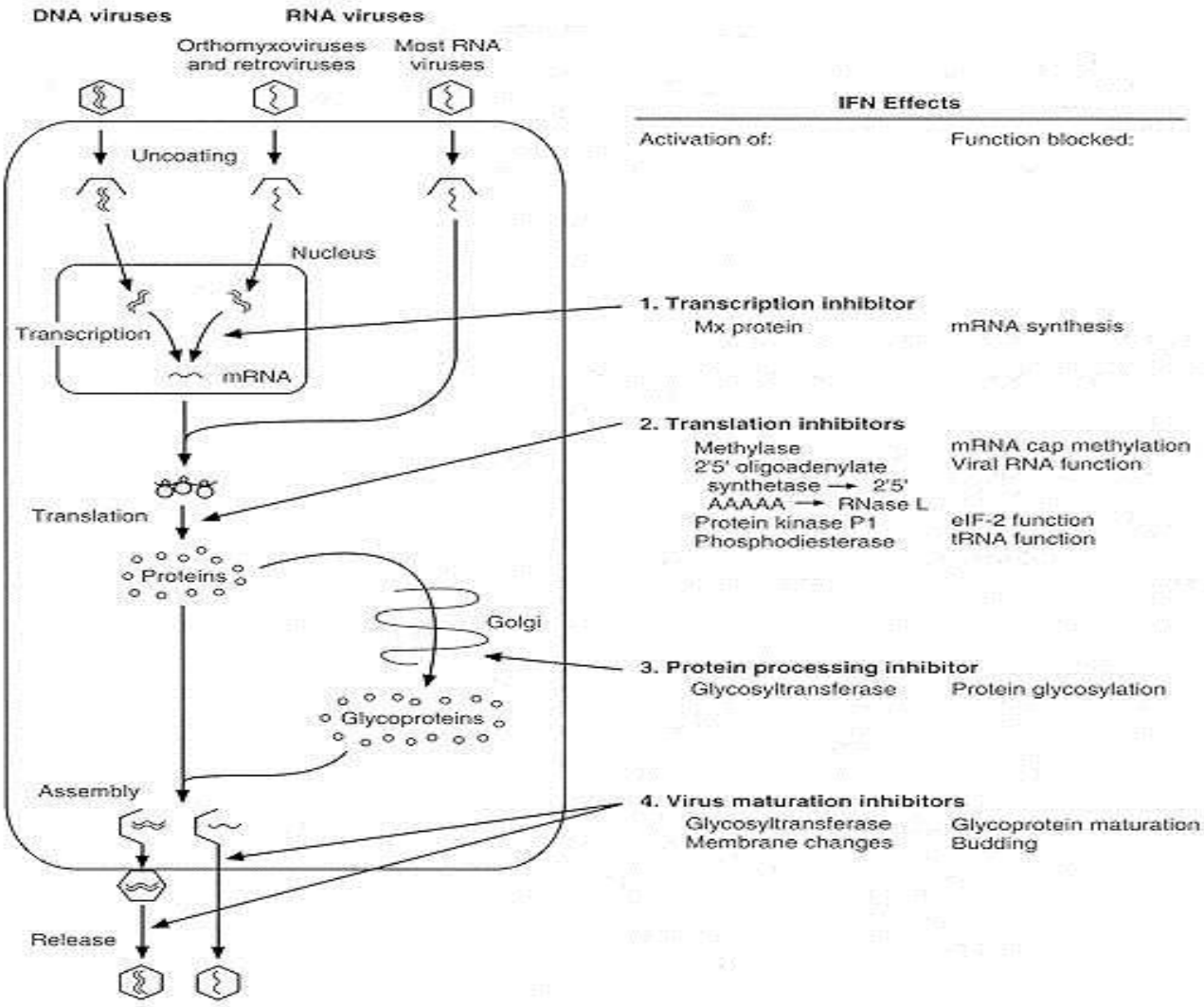


Fig 3: Effect of Interferon on viral replication.

Different families of mammalian viruses use different ways and strategies for replication, and IFNs also effect different viruses in different way. It is dependent on type of virus that which step of virus replication will be effected. Interferons are released from cell after glycosylation and this addition of carbohydrate occurs in membranous structures before they are released (Ng *et al.*, 1972). IFNs are released from cell prior to formation of antibodies so that against a specific virus interferons are present prior to antibodies (Gerber *et al.*, 1978). Interferons do not directly interfere with virus particles but they exert their effect on infected cell make a cell able to stop viral replication in different ways. Several enzymes are changed some are activated and some are stopped so that a cell retains anti-viral state (White, 1984). For example enzymes that are activated are oligo A synthetase (2-5A synthetase), endoribonuclease (RNase L), and protein kinase. When oligo A synthetase is activated it activates endoribonuclease that results in destruction of cellular mRNA and rRNA. Protein kinase inactivates eIF-2 by phosphorylation, eIF-2 is the peptide chain initiation factor so viral and cellular protein synthesis is inhibited (Besancon and Ankel, 1974). Elongation of viral protein is stopped due to action of phosphodiesterase and post-translational modification of viral proteins is stopped due to action of Glycosyltransferase. So IFNs induce a series of enzymes and all these enzymes exert their effect in different way. Interferon interact with cell by receptors after attachment fluidity of cell membrane decreases this electrophoretic mobility change then lead to effect viral attachment maturation and release (Castiglia *et al.*, 2016).

Antibacterial activity

INFs also play a protective role as anti-bacterial molecules e. g; Alpha type of interferon play a role as critical resilience-promoting cytokines in infection with different streptococcal species (Besancon and Ankel, 1974). Several bacterial, fungal and viral infections induce production of IFN-alpha. Gram negative bacterial cell wall has LPS lipopolysaccharides that stimulate IFNs and bacterial nucleic acid also induce IFNs (Carrero *et al.*, 2006). This type of interferon induce hundreds of different Interferon Stimulated Genes (ISG) by activating transcription factors e. g; the homodimeric STAT1 and the heterotrimeric STAT1–STAT2–IRF9 (i.e., ISGF3) transcription factors. Bacterial DNA induces production of beta type of interferons. There are different pathways for its induction, most common of which is cytosolic DNA sensor cyclic GMP-AMP synthase. This pathway is described for *Francisella novicida*, group B *streptococcus* (GBS) (*Streptococcus agalactiae*), *Legionella pneumophila*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, and *Neisseria gonorrhoeae* (Andrade *et al.*, 2016).

Three types of IFNs (alpha, beta and gamma) effect division of both normal and tumor cells. Rate of division is reduced by IFNs (Czarniecki *et al.*, 1984). But it is found that the growth rate of rapidly dividing cells is more effected as compared to rate of normally dividing cells. So interferon can be used as antineoplastic agent. But this inhibition of cell growth is more by natural IFNs than that of recombinant IFNs (Stebbing *et al.*, 1981). Anti-proliferative effect differs among different species of interferon. Natural gamma interferons have more anti-proliferative effect than natural alpha and beta interferons. Anti-proliferative effects of IFNs is due to elongation and extension of phases of growth G_1, S and G_2 phase. IFNs have more effect on early events of G_1 than S and G_2 phases. For example interferon induces an enzyme, 2-5 A synthetase that in turn activates 2-5 oligoadenylate, this enxyme causes delay in entry to S phase of cell division (Kimchi *et al.*, 1979).

IFNs and immune response

Interferons and their preparations stimulate process of phagocytosis and also induce antibody production. Interferons induce antibody production, gamma interferons are more potent in this aspect than other types. Exposure time and doses of interferons are factors that control antibody production. If interferons are added to cells prior to antigen exposure they suppress antibody production and stimulate production if added in cells after antigen exposure. If interferons are added to patients, low doses induce more antibodies than do high doses. Interferons can regulate differentiation of macrophages (Vogel and Friedman, 1984). Non-specific and receptor mediated macrophages, both are stimulated by interferons. Gamma interferons and macrophage activating factor that are lymphokines derived from T-cells are identical molecules. Antibody dependent cell mediated cytotoxicity a process in which macrophages, neutrophils and killer cells cause lysis of antibody coated cells (viral infected cells and tumor cells). And on the other hand Natural Killer cells lyse tumor cells and other viral infected cells in absence of antibodies. This process of Antibody dependent cell mediated cytotoxicity increased by alpha and beta interferons. And three types of interferon increase cytotoxicity by natural killer cells (Droller *et al.*, 1979).

Cross species activity of interferon

Interferons are generally thought to be species specific but in cross species activity interferons have defined host range. Alpha, beta and gamma all have cross species activities. But their host range differs. There is a little effect of phylogenetic relations on IFNs cross species reactivity. Interferons are more effective on cells of distantly related species than similar species. For example human's leukocyte interferon if injected in monkey, bovine or feline cells there will be more effect on bovine and feline than on monkey (Ahl and Ramp, 1976).

Type I Interferons

Type-1 interferons that include alpha and beta type of interferons provide a sophisticated system that governs early defense mechanisms to provide protection from microbial functions and provide assistance in adaptive

immune response. INFAR are the receptors of INF-1. 13 are the sub species of interferon alpha in humans. IFN-1 also performs potent immune modulatory functions together with inhibiting viral propagation. IFN-1 regulates MHC-1 expression in various cells (Lindahl *et al.*, 1976). This expression is required for optimal stimulation, differentiation and expansion of T-cells. Dendritic cells are activated by autocrine functions of IFN-1 and their T-cell stimulating capacity is enhanced. IFN-1 also has stimulatory effect on CD8 T-cells, enhancing their proliferation. Time for which IFN-1 exposes with CD8 t-cells determines magnitude of response (T-cell activation). As IFN-1 effects T-cells it also effects B-cells. INF-1 signaling inhibits survival and maturation of immature B-cells. And it promotes B-cell activation and antibody production (Lin *et al.*, 1998). IFN-1 has both protective and pathogenic control in viral acute infection. Some viral proteins prevent IFN-1 production and signaling or one of both, despite these proteins an elevated level of type 1 interferon is seen after acute viral infection. Thus interferon-1 influence virus control. Despite viral proteins that inhibit interferon production, a robust increase in concentration is seen after viral infection. For curbing viral replication and inhibiting viral pathogenesis type 1 interferons are necessary. Experiments in which anti-IFN-β and anti-IFN-α neutralizing antibodies were used against West Nile Virus their results reveal that IFN-α is necessary for controlling virus replication and pathogenesis. In pathogenic control, many pro-inflammatory cytokines and chemokines are produced due to INFAR1 signaling. And these control viral infection and pathogenesis (Davidson *et al.*, 2014).

Some events characterize chronic infection. Chronic immune activation, negative immune regulator expression, an elevated interferon concentration and lymohid tissue destruction are the events that occur in persistent or chronic infection of virus. A highly increase concentration of IFN-1 is seen HIV and HCV infection in humans and non-human primates also in Lymphocytic Choriomeningitis Virus in mice (Hahm *et al.*, 2005). So IFN-1 therapy is beneficial in persistent viral infection. IFN-1 therapy can be used in both acute and chronic viral infection.

Type II Interferons

IFN-γ is the only member of type II interferon. In contrast to type I interferons that are secreted by all infected and damaged cells, IFN-γ is secreted by activated T-cells, NK cells and other activated immune cells in neurodegenerative and neuro-inflammatory conditions and in return they activate other immune cells and enhance MHC-I and MHC-II expression and add up in net immunity (Steimle *et al.*, 1994). It clears neurotropic viruses such as measles viruses from neurons. In neural diseases it helps in neurodegeneration. It acts to modifies activity of Neural Stem or Progenitor Cells.

When IFN-γ is secreted it binds with its receptors IFNGR (IFN-γ receptors). There are two subunits for this receptors IFNGR1 and IFNGR2. If IFN-γ binds with IFNGR it will hetrotetramerize this receptor and activate kinases. For example Janus Associated Kinases JAK that will phosphorylate STAT1 (among STATs family, IFN-γ effects STAT1). It will translocate to nucleus and then will activate IFN-γ stimulated genes. There are 500 different such genes. Viral clearance, inflammatory control and cell growth control are different functions of these genes (Ramana *et al.*, 2002).

IFN-γ when overexpressed it cause pro-inflammation and damaging effects but when expressed in lower concentration it has protective and regulatory role in neuronal inflammation. There are two types of glial cells (that provide functional support to neurons) in CNS: microglia and macroglia (including astrocytes, ependymal cells and oligodendrocytes). Oligodendrocytes are myelin producing cells and IFN-γ play critical role in determining survival of oligodendrocytes. Low level of IFN-γ is helpful for oligodendrocytes in oxidative stress and also enhance proteasome activity. These two factors cause apoptosis of oligodendrocytes (Balabanov *et al.*, 2007). Microglia control inflammation, neural modulation and repair. Their phagocytic activity is enhanced by IFN-γ. Which also enhances MHC-II expression and as a result these behave as antigen presenting cells, leading to inflammation and demyelination (Merson *et al.*, 2010). Astrocytes control brain homeostasis. And maintain structure and function of brain blood barrier. If astrocytes are exposed to IFN-γ these cells will induce myelin specific T-cells and Th1 differentiation. IFN-γ effects innate immune cells and effector memory cells. Normal conc. of interferon gamma re important for optimal functions of innate immune cells. And it is also critical for survival and functioning of memory cells. Innate immune cells mechanisms are enhanced by IFN-γ priming. These are the multipotent populations of cells in brain. NSPCs proliferation and differentiation is controlled by JAK-STAT family. That is controlled by IFN-γ. Interferon gamma controls NSPCs function by activating STAT family of proteins. That will inhibit NSPCs proliferation because G1 phase of cell cycle is stopped. So interferon gamma has anti-proliferative effects on NSPCs (Avalle *et al.*, 2012).

Type III Interferons

This type of interferon includes only lambda (λ) interferons also called IL-28 or IL-29 for which there are four ligands from IFNL-1 to IFNL-4. IFNL-1 is also called IL-29, IFNL-2 is IL-28A, IFNL-3 is IL-28B and IFNL-4. First three ligands from IFNL 1-3 are more similar to each other and IFNL4 is different from these only share 40.8% similarity in amino acid sequence with IFNL3. Type 2 myeloid dendritic cells are the main source of IFN-λ (Zhang *et al.*, 2013). Anti-viral *in vivo* activity of type III interferon is more apparent against those viruses that infect epithelial cells of respiratory,

gastrointestinal and urogenital tract. If we see mode of action of type three interferons, after its secretion IFN-λ binds to its receptor IFNLR (having two subunits one is α and other is β-subunit) binding affinities for these subunits differ from IFNL 1-4. Janus kinase 1 and Tyrosine kinase 2 become activated after binding. These kinases phosphorylates STAT-1 and STAT-2. And many IFN stimulated genes are activated (Egli *et al.*, 2014).

In respiratory epithelial cells, IFN- λ receptors are expressed in high amount. Mice exhibited decreased inflammatory response and lowered viral titre when human meta-pneumovirus (HMPV) was injected in mice cells treated with IFN-λ (Banos-Lara Mdel *et al.*, 2015). When human myeloid and bronchial cells are treated with rhinoviruses these cells produce a high amount of IFN-λ and this interferon lambda will inhibit replication of rhinovirus in bronchial epithelial cells. When humans were inoculated with rhinovirus, it was found that there is an inverse relation in conc. of interferon lambda and virus load and also with severity of disease (Contoli *et al*., 2006). Type I and type III interferons are produced by respiratory epithelial cells (Mahlakoiv *et al.*, 2015) whereas epical and basolateral surfaces cultured cells respond to type III interferons (Fox *et al*., 2015; Hamming *et al*., 2013).

Due to HCV and HBV infection there is great concern with role of type III interferon in liver. These two viruses stimulate production of IFN-λ rather than that of type I interferons. And INFLR (receptors for interferon lambda) are present in high amount in liver (Sato *et al*., 2015). Different protective alleles of interferon lambda pose different effect against HCV. For example one allele from promotor of type III interferon lambda gene, controls infection of HCV by promoting Interferon Stimulated Genes (Tanaka *et al*., 2009). And an unfavorable allele is formed as a result of elevated levels of interferon stimulated genes that allele will code for protein that in result will render antiviral activity (Sheahan *et al*., 2014). GIT is a main site were microbes attack, and in mice stomach and intestine there is great amount of IFNLR1 (Sommereyns *et al.*, 2008). Gastrointestinal tract epithelial cells are the main effectors after production of IFN-λ (Pott *et al.*, 2011).

CONCLUSION

Interferons play crucial role in body as they maintain anti-viral state in body. IFNs have broad spectrum of effects on different cells including neurons, immune cells and other normal cells of body. There are many inducers for interferon production either by using these inducers interferon can be produced naturally or it can be produced by using genetic engineering. IFNs have numerous applications in body and use of synthetic interferon can be helpful in combating a no. of viral diseases.

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