Interferons

By the 1950s, (Blocking of virus infection by a competing virus) was a well-known phenomenon in virology. The mechanism responsible is envelope glycoprotein of an endogenous provirus present in the cells which sequesters the cellular receptor needed by the exogenous virus for infection.

In 1957, Alick Issacs and Jean lindemann were studying this phenomenon and performed the following experiment. Pieces of chick chorioallantoic membrane were exposed to ultraviolet inactivated influenza virus (noninfectious) and this virus in tissue culture. The medium form this experiment was found to inhibit the infection of chick chorioallantoic membrane by (infectious) influenza virus in separate cultures. Their conclusion was that a soluble factor, which they called interferon was produced by cells as a result of virus infection and that this factor could prevent the infection of other cells.

The three types of interferon are α, β, and δ.

Interferon- α: There are at least 15 molecular species of interferon- α, all of which are closely related; some species differ by only one amino acid. They are synthesized predominantly by lymphocytes. The mature protein s contains 134 amino acids, with minimum homology of 77% between the different types. The entire gene encoding interferon- α are located one human chromosome 9.

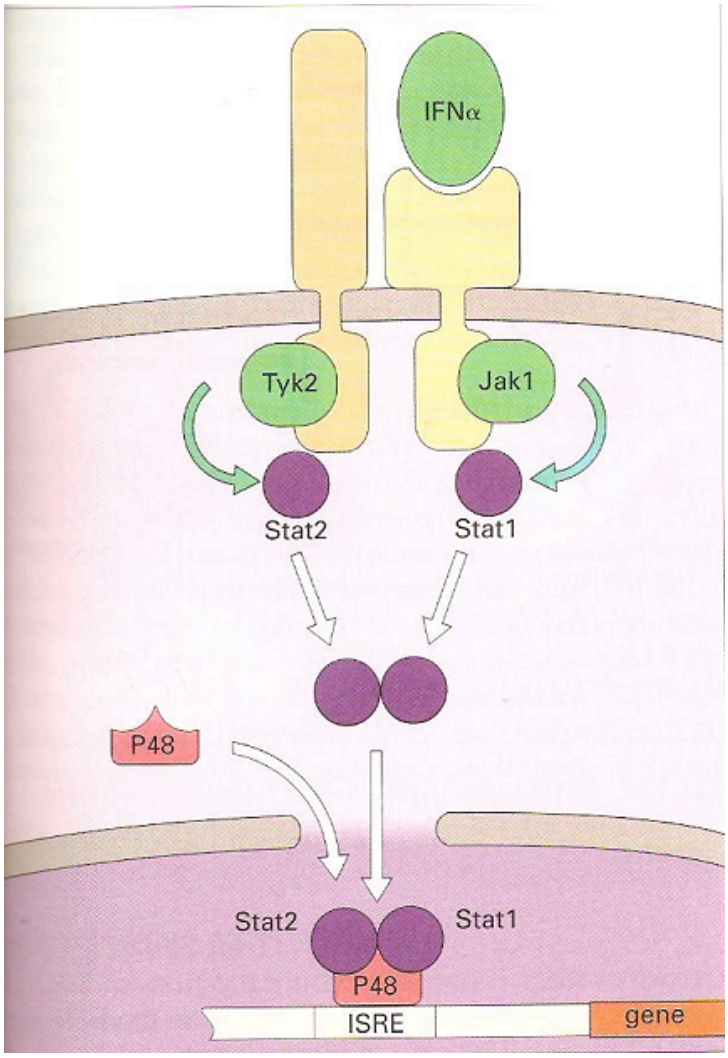
Interferon- β: The single gene for interferon- β is also located on human chromosome 9. The mature protein contains 145 amino acids with approximately 30% homology to other interferons. It is synthesized predominately by fibroblast.

Interferon- δ: The single gene for interferon- δ is located on human chromosome 12. The mature protein contains 146 amino acids, is glycosylated, and has very low sequence homology to other interferons. It is synthesized predominately by lymphocytes.

Type of IFNs	Homology to other IFNs	Number of A.A in protein	Cell Secreted	Location on Chromosome
IFN-alpha	**77% (15 types)**	**134**	**Lymphocyte**	**9**
IFN-beta	**30%**	**145**	**Fibroblast**	**9**
IFN-gamma	**Very low**	**146**	**Lymphocyte**	**12**

Mechanism of Action: Intracellular signaling pathways activation by Interferon.

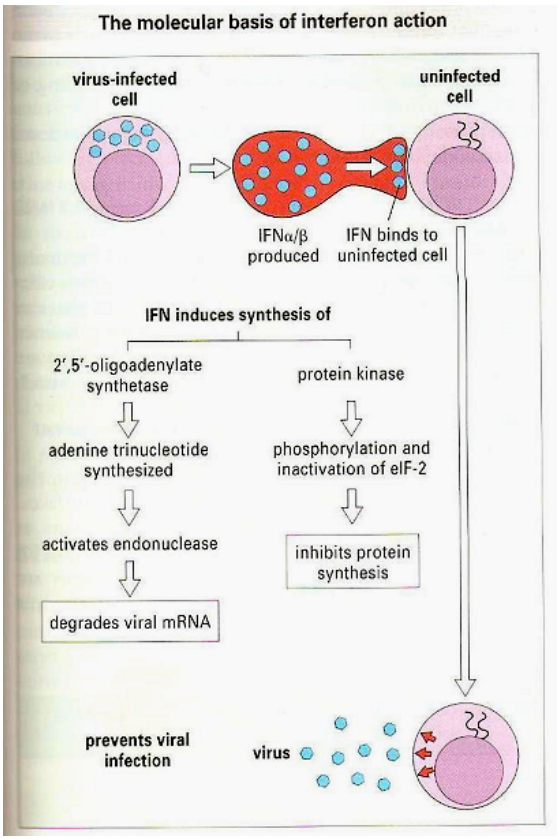
IFN α binding aggregates the tow sub units of receptor. This leads to activation and phosphorylation of two jak kinase, jak1 and Tyk2, which then phosphrelate stat1 and stat2. The tow transcription factors form a complex with DNA binding protein called p48. The complex moves to the nucleus and includes transcription of genes bearing an interferon response element (ISRE).



IFN stimulates inhibition of viral replication.

Virus infection of a cell lead to the production of IFN α/β which activates antiviral mechanism in neighboring cells enabling them to resist virus infection.

- IFN activate a number of genus, including 2 direct antiviral activity:
  - A- 67 KDa protein kinase which inhibit phosphorelation of elf-2 and blocks translation of protein.
  - B- 2, 5 olgoadenylate synthetase which activate endonuclease (RNase L) involve in degradation of viral RNA.
- IFN δ and IFN α/β enhance efficiency of adaptive immune response by stimulating increased expression of MHC class I and II.
- Both IFNs serve to activate microphage and NK cells.



Evasion of Immune Responses by Viruses

Innate and adaptive components of the immune system present a powerful barrier to virus replication on the other hand virus have effective mechanisms aginst immune system.

1- Inhibition of MHC-I restricted antigen presentation

CTLs can only respond to forigen Ag presented by MHC-I complexes on the target cell. Anumber of viruses interfer with MHC-I expression or function to disrupt this procss and evad the CTL response.

Adenoviruses downregulate MHC I expression

Herpesviruses interfe with Ag processing required to form an MHC-I Ag complex.

2- Inhibition of MHC-II restricted antigen presentation

MHC-II Ags are essential in the adaptive immune response in order to stimulate the development of immune response.

Herpesviruses and **papillomaviruses** interfere with the processing and surface expression of MHC-II –Ag complexes, inhibiting the CTL response.

3- Inhibition of natural killer cell lysis

Poxvirus encodes homolog of MHC-I that expressed on the surface of infected cells but unable to bind an antigenic peptide, thus avoiding killing by NK cells that would be

triggered by the absence of MHC-I on the cell surface. Similar protein made by other viruses such as **HHV-5**, **CMV,** and **herpesviruses.**

4- Inhibition of cytokine action

Cytokine are secreted polypeptides that coordinate important aspects of the immune response, including inflammation, cellular activation, proliferation, differentiation, and chemotaxis.

Some viruses are able to inhibit the expression of certain chemokines directly. Alternatively, **herpesviruses** and **poxviruses** encode "viroceptor" virus homologs of host cytokine receptors that compete with cellular receptors for cytokine binding but fail to give transmembrane signals.

5- Interferon inhibitors

The general effect of viral infection is inhibition of protein synthesis in virus infected cell other mechanisms of virus resistance to interferons include:

- **Epstein-Barr virus** synthesis EBNA-2 protein which blocks interferon-induced signal transduction.

- **Vaccinia virus** encoded a protein that homologous to eIF-2α, which inhibits the action of PKR.

- **Poliovirus** infection activates a cellular inhibitor of PKR in virus infected cells.

- **Reovirus** capsid protein σ3 is believed to sequester dsRNA and therefore prevent activation of PKR.

6- Evasion of Humoral Immunity

High frequency genetic variation of the B-cell epitopes on antigens to which antibody bind. This is for viruses that are genetically variable (**Influenza virus** and **HIV**). **Herpesvirus** encodes Fc receptors to prevent Fc-dependent immune activation.

7- Evasion of complement cascade

Poxviruses, herpesvruses, and **retroviruses** secreted protein that block C3 convertase assembly and accelerate its decay.

Poxviruses can inhibit C9 polymerization, preventing membrane permeabilization.

Evasion Mechanism	Mode of Action	Example
Inhibition of MHC-I restricted antigen presentation	Interfere with MHC-I expression and disrupt this process and evade CTL response	**Adeno virus**/Down regulate MHC **Herpes virus**/Interfere with Ag processing
Inhibition of MHC-II restricted antigen presentation	Interfere with the processing and surface expression of MHCII-Ag	**Papillomavirus** **Herpesvirus**
Inhibition of natural killer cell lysis	Encoded homolog MHC-I bind to Ag and activate inhibitory receptor thus avoid killing by NK	**Pox Virus** **HHV-5, CMV** **Herpes virus**
Inhibition of cytokine action	Encode "Viroceptor" homologus to cytokine receptor but fail to give transmembran signal	**Pox virus** **Herpes virus**
Interferon Inhibition	Synthesis ,EBNA-2 block IFN signal transduction, homologus protein eIF-2a inhibits PKR, activate cellular inhibitor for protein kinase	**EPV** **Viccenia virus** **Poliovirus**
Evasion of humoral immunty	Genetic variation and epitop change	**Influenza virus** **HIV virus**
Evasion of complement cascade	Screted protein that block C3 convertase Inhibit C9 polymerazation	**Pox, Herpes,HIV** **Pox**