Viral Interference and Interferon
Interference is...

...a phenomenon in which infection by a first virus results in resistance of cells or tissues to infection by a second virus.
Interference can occur:

- On receptors
- On the level of transcription and translation
- By induction of interferon synthesis
The discovery of interferon
Types of interferon

**Type I (viral type)**
- synthesis induced by virus or ds RNA
- class INF- and class INF-

**Type II (immune type)**
- synthesis induced by mitogenes and specific Ag
- class INF -
Chemical composition of interferon

- All classes of interferon are glycoproteins
- They are cleaved from the precursor polypeptide made of 166 amino acids
Classes of interferon

INF- (leukocyte interferon)

- 10-16 subtypes, length 143 amino acids
- cell source: mononuclear phagocytes
- 24 genes, chromosome 9
Classes of interferon

INF- (fibroblast interferon)

1 type, length 145 amino acids

cell source: fibroblasts

1 gene, chromosome 9
Classes of interferon

INF - (immune interferon)

- length 146 amino acids
- cell source: T lymphocytes
- chromosome 12
Inductors of interferon genes

1. Viruses
   - viral replication is not necessary for induction of interferon synthesis
   - RNA viruses are stronger inducers of INF syntheses than DNA viruses
Inductors of interferon genes

2. Double-stranded RNA (ds RNA)
   - Reoviruses
     - replicative forms of single-stranded RNA
     - double-stranded synthetic polyribonucleotides
Inductors of interferon genes

3. Metabolic activators and inhibitors

- mitogenes and specific Ag (INF - )
- inhibitors of mRNA transcription
- inhibitors of protein synthesis
Inductors of interferon genes

4. Other microorganisms

(Chlamydia, Rickettsia, Mycoplasma, Protozoa, bacterial endotoxin - LPS, L. monocytogenes, B. abortus)
Specificity of interferon

- Interferon is **species-specific**: protects only cells of the same species.
- Interferon is **not virus-specific**: not specific for the virus that induced its' synthesis.
To perform its antiviral and other biological actions, INF must be secreted from the cell that synthesized it and must attach to the receptors on other, neighboring cells (paracrine action).
Activity of interferon

1. Formation of INF - receptor complex
2. Receptor-mediated endocytosis
3. Transportation to nuclear membrane
4. Induction of transcription of many genes that are normally never or seldom transcribed
5. Biological action of interferon: antiviral, anti-proliferative, immuno-regulatory and antioncogenic
Activity of interferon

- INF acts in minimal amounts: 3 pg INF can protect 1 million cells from 10 million infective viral particles

- Clinical manifestations of interferon activity ("influenza-like" syndrome): pain in muscles and joints, severe headache, malaise, fever...
Antiviral action of interferon

PROTEIN KINASE SYSTEM

INF

inactive PK (nonphosphorylated)

dsRNA

active PK (phosphorylated)

nonphosphorylated elongation factor
elF2-

phosphorylated elongation factor
elF2--P

phosphatase

inhibition of translation
Antiviral action of interferon

2’5’- OligoA SYSTEM

INF
inactive 2’5’-OAS

dsRNA
active 2’5’-OAS

ATP
2’5’-oligo-adenilat

AMP
2’5’-phosphodiesterase

latent RNase
active RNase
destruction of mRNA
Antiviral action of interferon

1. Virus infects the cell.
3. IFN binds to its receptor on a neighboring cell.
4. IFN receptor.
5. Gene expression.
   - 2'5' oligoadenylate synthase
   - Protein kinase
   - Other enzymes made
7. Viral mRNA broken down.
8. Viral protein synthesis inhibited.
10. MHC I expressed.
Can viruses evade interferon activity?

- Inhibition of PK activity - reoviruses, adenoviruses, EBV, HCV, HIV
- Inhibition of eIF2- phosphorylation - HSV, vaccinia virus
- Inhibition of 2’5’ OAS - HIV, HSV, reoviruses, vaccinia virus, influenza virus
Therapeutic use of interferon

- Viral infections (HBV, HCV, VZV, HPV...)
- Tumors
- Multiple sclerosis