Virology Lecture Series

Interferon and Interference

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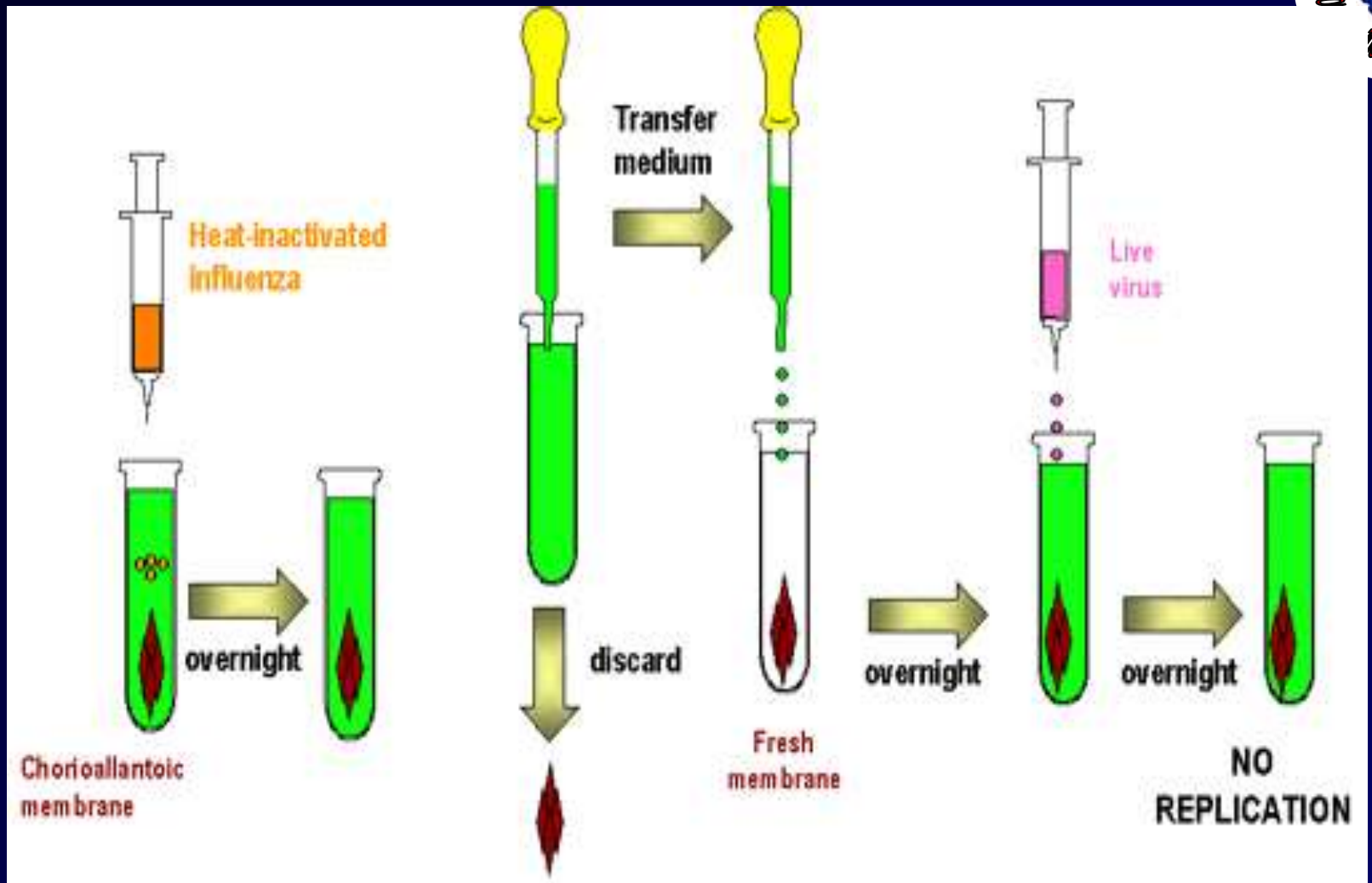


The Discovery of Interferon

From Isaacs and Lindenmann, Proc. Roy Soc B, 1957

INTERFERENCE

1. The condition in which infection of a cell by one virus prevents superinfection by another virus.

2. The condition in which infection of a cell by one virus prevents subsequent infection of neighboring cells by the same or another virus.

Mechanisms of interference

1. Prevent attachment or adsorption of the superinfecting virus by destroying cell surface receptors (Newcastle disease virus).

2. Inhibit an essential biosynthetic step during viral eclipse (Certain leukemia viruses).

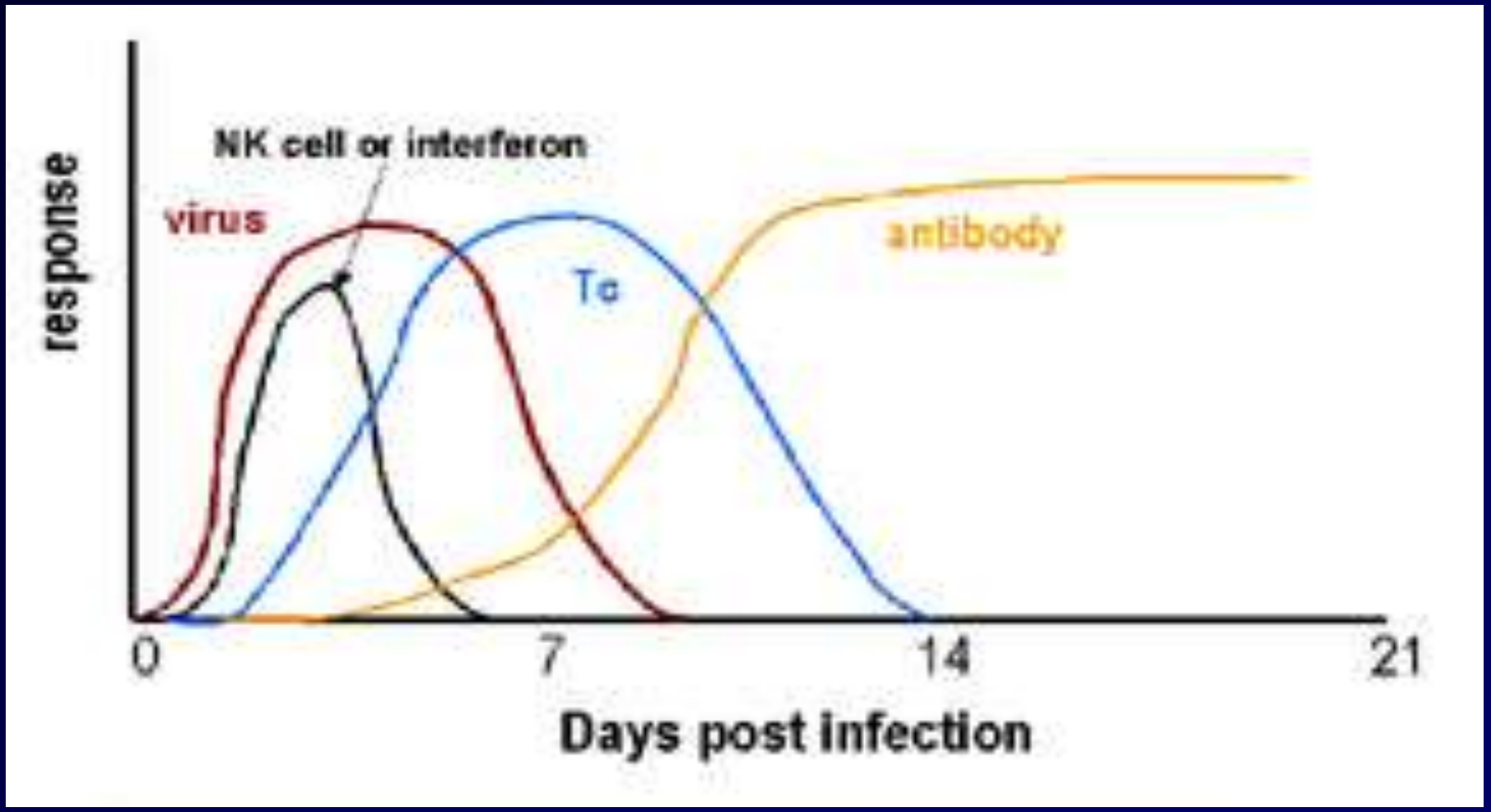
3. Competition between the coinfecting viruses for biological building blocks from the cell (some polioviruses).

4. The production of interferons (soluble inhibitors released from infected cells to trigger resistance in neighboring cells).

This is what we will be discussing next.

- Small interfering RNA (siRNA). We will not discuss this topic.

Typical Response to an Acute Viral Infection

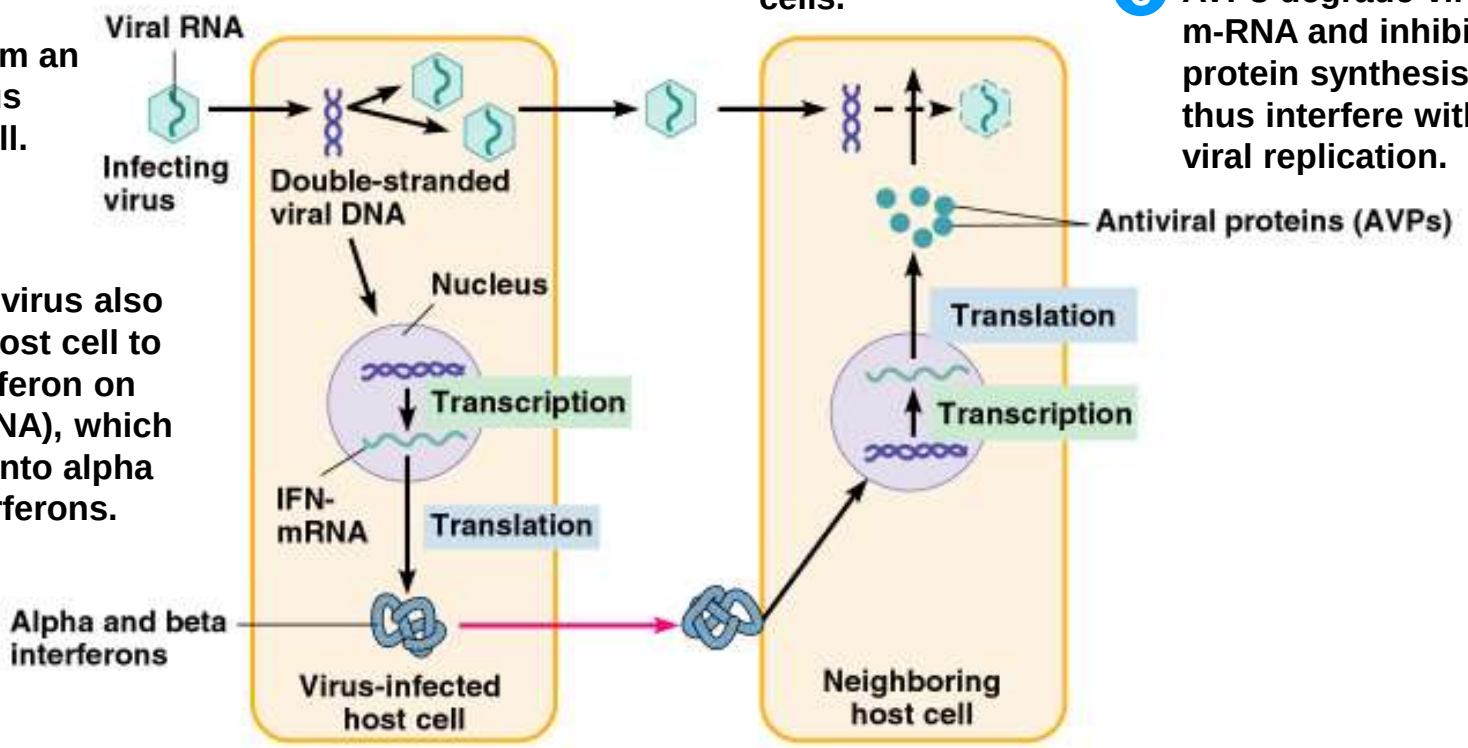


General Steps of Interferon Induction and Effect

1 Viral RNA from an infecting virus enters the cell.

2 The infecting virus replicates into new viruses.

3 The infecting virus also induces the host cell to produce interferon on RNA (IFN-mRNA), which is translated into alpha and beta interferons.



4 Interferons released by the virus-infected host cell bind to plasma membrane or nuclear membrane receptors on uninfected neighboring host cells, inducing them to synthesize antiviral proteins (AVPs). These include oligoadenylate synthetase, and protein kinase.

5 New viruses released by the virus-infected host cell infect neighboring host cells.

6 AVPs degrade viral m-RNA and inhibit protein synthesis and thus interfere with viral replication.

TYPES OF INTERFERON

- TYPE I (alpha, -beta, -tau, and –omega)
  - **Interferon-alpha** (leukocyte interferon, about 20 related proteins)
  - **Interferon-beta** (Fibroblasts, epithelial cells, etc).

- TYPE II
  - **Interferon-gamma** (Immune interferon)
    - Certain activated T-cells, NK cells, etc.

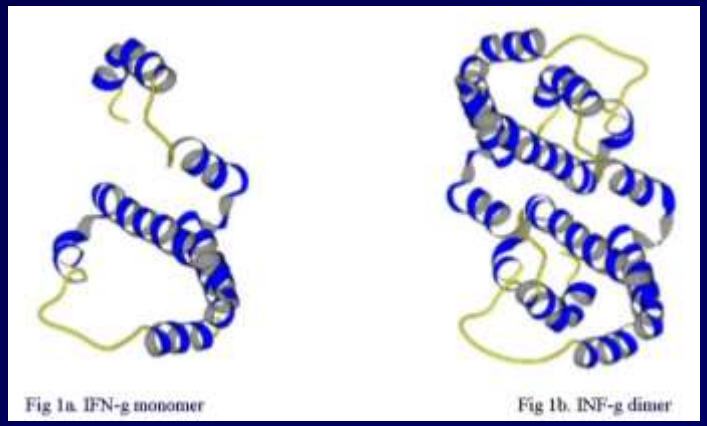


Fig 1a. IFN-g monomer

Fig 1b. INF-g dimer

INDUCTION OF INTERFERON

- **Interferon-alpha and interferon-beta**

  -Viral infection (especially RNA viruses), double stranded RNA, certain bacterial components, certain parasites.

- **Interferon-gamma**

  - Antigens, mitogenic stimulation of lymphocytes.

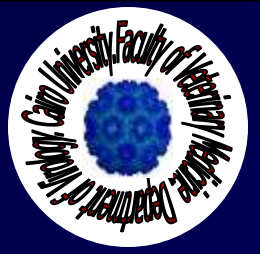
Factors affecting production and potency of interferons

1. Type of virus (RNA viruses produce more interferon than DNA viruses but interferon itself is not virus specific).

2. Type of cells (species specific).

3. Age of cells (6-day-old chick embryos less).

4. Physiological status (stress).



INTERFERON-ALPHA, INTERFERON-BETA

INTERFERON RECEPTOR

Induction of 2’5’oligo A synthetase

ds RNA

Activated 2’5’oligo A synthetase

ATP

2’5’oligo A

Induction of ribonuclease L

2’5’oligo A

Activated Ribonuclease L

mRNA degraded

Induction of a protein kinase

ds RNA

Activated protein kinase

ATP

Phosphorylated Initiation Factor (eIF-2)

Inhibition of Protein synthesis

Viral Evasion of The Host Interferon Responses

1. Block interferon binding.
2. Inhibit function of interferon-induced proteins.
3. Inhibit NK function.
4. Interfere with MHC I or MHC II expression.
5. Block complement activation.
6. Inhibit apoptosis.

etc!

THERAPEUTIC USES OF INTERFERONS

- **ANTI-VIRAL**
  - Interferon-alpha is currently approved for certain cases of acute and chronic HCV and chronic HBV.
- **MACROPHAGE ACTIVATION**
  - Interferon-gamma has been tried for lepromatous leprosy, leishmaniasis, toxoplasmosis.

SIDE EFFECTS OF INTERFERONS

- FEVER
- MALAISE
- FATIGUE
- MUSCLE PAINS

CORE IDEAS DISCUSSED

- Interferon production is just one mechanism of interference, there are other mechanisms.
- Interferon production is a quick defense mechanisms, but it is not just that.
- The presence of an interferon response does not necessitate the mounting of an effective defense.