Interferons

Interferons (IFNs) are **natural proteins** produced by the cells of the immune system of most vertebrates in response to challenges by foreign agents such as **viruses, parasites esp. protozoa** and **tumor cells**.

- Interferons belong to the large class of **glycoproteins** known as **cytokines**.

- Generally, interferons are produced by a wide variety of cells **in response to the presence of double-stranded RNA**, a key indicator of viral infection.

- However, **single-stranded viral RNA trapped within endosomes** may also act as a stimulus.

- They can also recognize **viral double stranded DNA.**

Role in immune response

Interferons are part of the **"first-wave"** immune response of the **innate** immune system, acting **within hours**, whereas **antibody production takes several days.**

Interferons **assist** the immune response by:

-- **inhibiting viral replication** within host cells

-- **activating** natural killer cells and macrophages

-- **increasing antigen presentation** to lymphocytes

-- inducing the **resistance** of host cells to viral infection.

Types of interferons

There are **three major classes** of interferons that have been described for humans **according to the type of their receptor.**

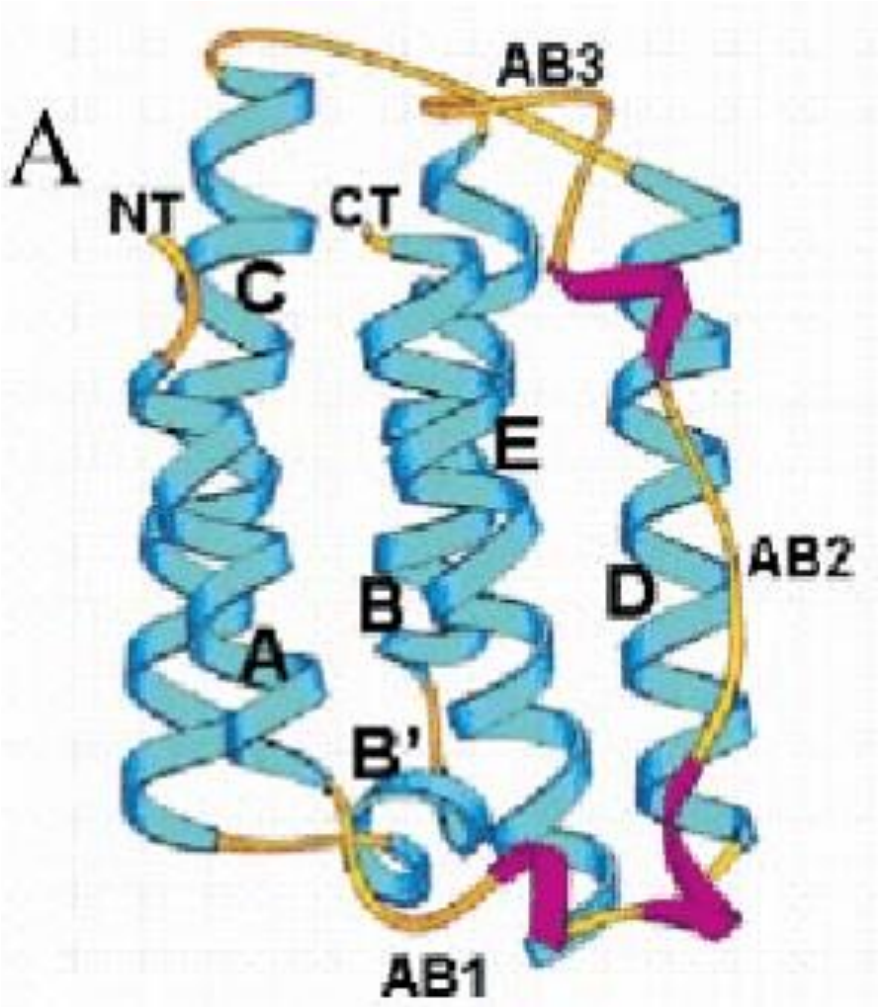
Interferon type I:

- All **type I IFNs** bind to a specific cell surface receptor complex known as the **IFN-α receptor (IFNAR)** that consists of **IFNAR 1** and **IFNAR 2** chains.

- The type I interferons present in humans are **IFN-α** (leukocyte or alpha family), **IFN-β** (fibroblast or beta family) and **IFN-ω** (leukocytes).

Structure:

The **Type I IFNs** consist of **five α-helices** (labeled A–E) which are linked by **three larger loops** (**AB** loops) and **three shorter segments** (**BC, CD,** and **DE** loops).



The α helix is a common structural motif of proteins, consists of a right-handed helix with a repeat length of 3.6 amino acid residues per helical turn

Interferon type II:

Binds to **IFNGR**. In humans this is **IFN-γ.**

Its role is similar to prototype IFN-α .

Interferon type III:

Acts through a receptor complex consisting of **IL10R2** (Interleukin 10 receptor, beta) and **IFNLR1** (Interferon Lambda Receptor 1).

This is active in gastrointestinal tract against viruses.

Interferon is species-specific:

For example

The interferon prepared from infected egg protects **only chicken cells** from virus infection, while that prepared from mice protects **only mouse cells.**

Viral induction of interferons

- All classes of interferon are very important in fighting **RNA virus infections.**
- However, their presence also accounts for some of the host symptoms, such as **sore muscles** and **fever** due to secretion of some substances.
- They are secreted when abnormally large amounts of **ds RNA** are found in a cell.
- Normally **dsRNA** is present in very low quantities.

The **dsRNA** acts like a trigger for the production of interferon via **TLR receptor 3.**

Interferon productions leads to:

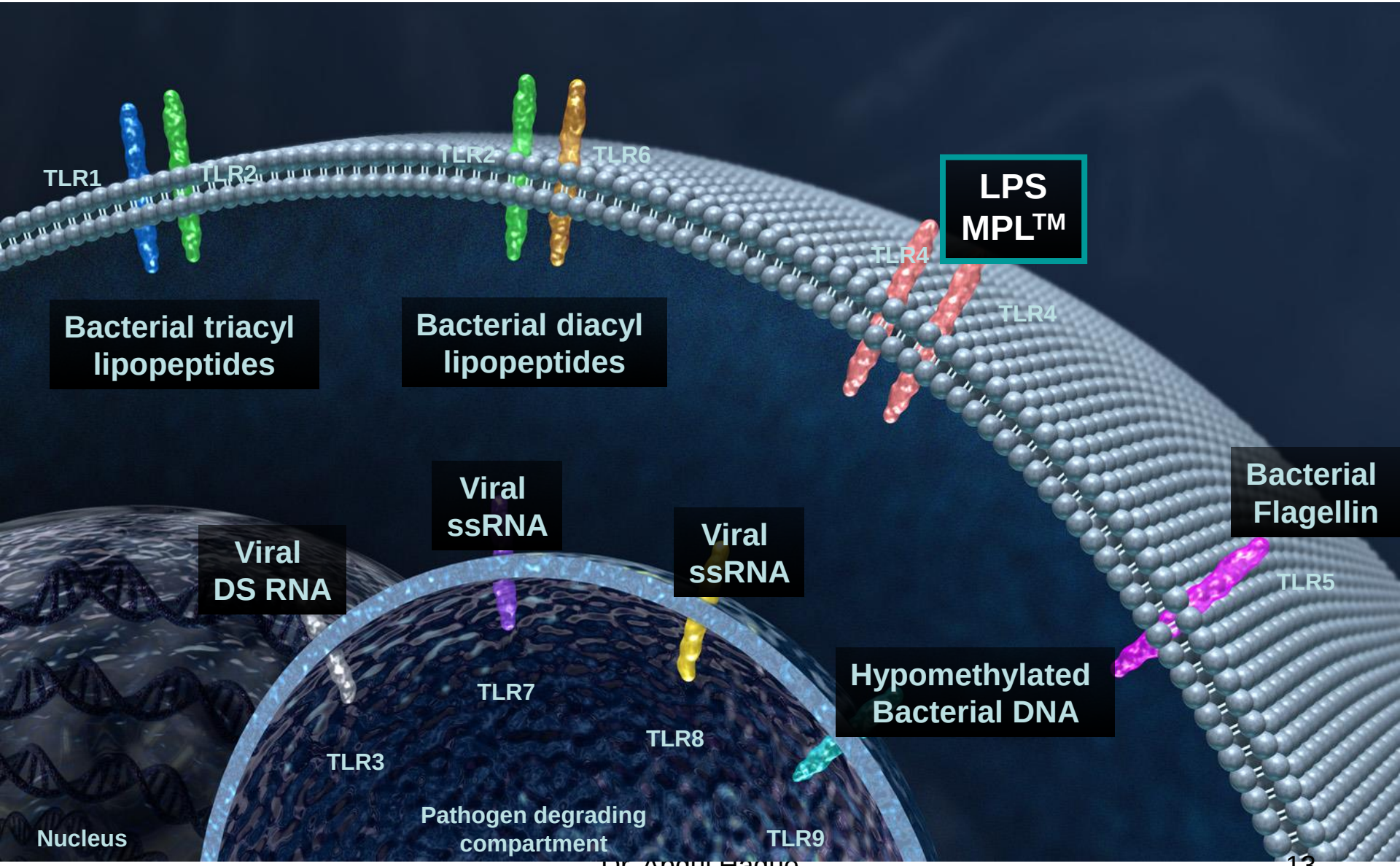
- activation of the transcription factor **IRF3** (interferon regulatory transcription factor 3).

- Induction of late phase **NF κB** (nuclear factor kappa-light-chain-enhancer of activated B cells).

The gene that codes for this cytokine is **switched on in an infected cell**, and more interferon is synthesized and secreted to surrounding cells.

Single-stranded viral RNA **trapped within endosomes** attaches to **TLR 7**. Rest of the mechanism is similar.

Toll-like receptors and their natural ligands



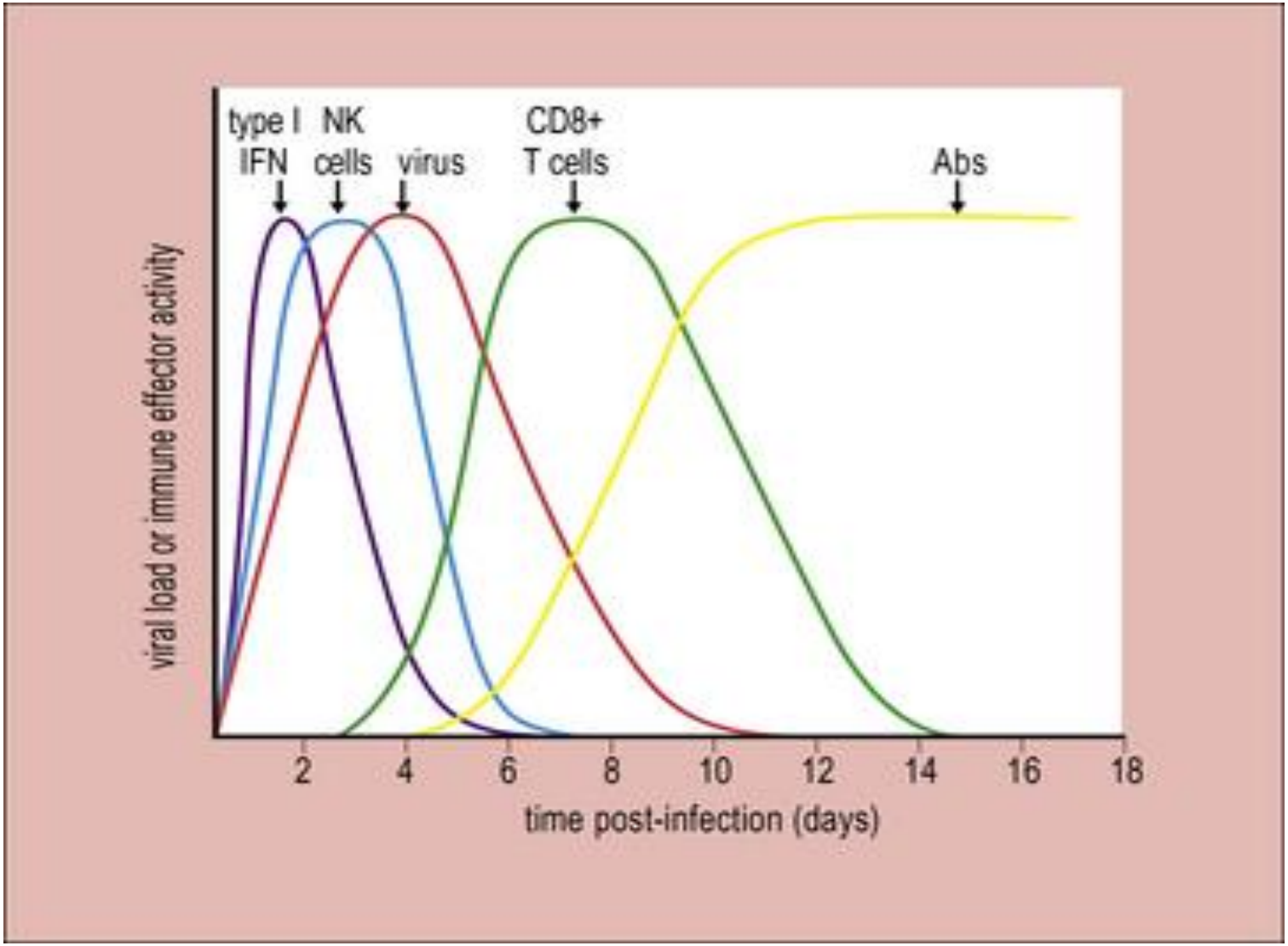
- The interferon activated cells start producing large amounts of a protein known as **protein kinase R** (or PKR).

  This protein **prevents viral replication** and **inhibits normal cell ribosome function**, killing both the virus and the host cell if the response is active for a sufficient amount of time.

- Furthermore, presence of interferon leads to **upregulation of MHC I** and therefore to increased presentation of viral peptides to **cytotoxic CD8 T cells.**

- Presence of interferon also **alters the proteasome** which leads to increased production of MHC I compatible peptides.

The proteasome is a highly sophisticated protease complex designed to carry out selective, efficient and processive hydrolysis of proteins.



Timeline of immune responses to infection

Virus resistance to interferons

- Some viruses have found methods that give them a way around the **IFN-α/β response**.

- These include the **inhibition** of **interferon signaling**, and **production**, and the **blocking** of the functions of **IFN-induced proteins.**

- Some viruses can encode proteins that **bind to dsRNA** so that interferon mechanism **cannot sense it.**

- The **H5N1 influenza** virus, also known as **bird flu**, has been shown to have resistance to interferon and other anti-viral cytokines.

  This is part of the reason for its **high mortality rates** in humans.

  It becomes resistant due to a single amino acid mutation in **Non-structural protein 1 (NS1)**.

Therapeutic effect against cancer

- Just as their natural function, interferons have **antiviral, antiseptic** and **antioncogenic** properties when administered as drugs.

- **Interferon therapy** is used (in combination with chemotherapy and radiation) as a treatment for many **cancers,** e.g., hairy cell leukemia.

- One mechanism of this effect is **p53** induction.
- p53 is one of the most important **suppressor genes** in **human cancers.**
- Interferon can cause **increased p53 activity** in virus infected cells.
- Interferon acts as an inducer and causes increased production of the **p53** gene product.
- This promotes **apoptosis**, limiting the ability of the virus to spread.

- One of the genes that is blocked is **p21**, which can **promote cell survival.**

- Leaving this gene inactive would help **promote the apoptotic effect.**

Therapeutic effect against hepatitis

- Interferon is a major component of therapy for **Hepatitis B (HBV)** and **Hepatitis C (HCV).**

- More than half of the **patients** treated with interferon respond with **viral elimination** (sustained virological response), **better blood test results** and **better liver histology results**.

Therapeutic effect against autoimmune diseases

- **Interferons** are also used in the treatment and control of **multiple sclerosis**, an autoimmune disorder.

Therapeutic effect against respiratory diseases

- Administered **intranasally** in very low doses, interferon is extensively used in Eastern Europe and Russia as a method to prevent and treat viral respiratory diseases such as **cold** and **flu**.

Adverse effects

- The most frequent adverse effects are **flu-like symptoms**: increased body temperature, feeling ill, fatigue, headache, muscle pain, convulsion, dizziness, hair thinning, and depression.

- **Erythema, pain** and **hardness** on the spot of injection are also frequently observed.

- **Interferon therapy** causes **immunosuppression**, in particular through **neutropenia** and can result in some infections manifesting in unusual ways.

- All known adverse effects are **usually reversible** and disappear a few days after the therapy has been finished.


Are you sure about this.?
Hmmm,
Damn sure ! The moment you start walking on 2 legs, they'll send you to School. That's why I never started walking on 2 legs.

Work smart not hard


Thank You!