Host defenses in viral infections

- Infective virus
- Interferons
- NK activity
- Cytotoxic T-cells
- Antibodies

Time post infection

Innate (constitutive) defenses

Acquired (immune) defenses
Interferon induction

**Inducer**
- Foreign nucleic acids
  - Viral
  - Other
- Foreign cells
  - Eukaryotic, xenogenic, tumor, virus-infected
  - Prokaryotic
  - Some mitogens
- Foreign antigens
  - T cell mitogens

**Responding cell**
- Epithelial cells
- Fibroblasts

**Interferon**
- IFNβ
- IFNα
- IFNγ
- Sensitized T lymphocytes + macrophages
Interferon α/β inducer molecules of viruses

- double stranded RNA (RNA viruses are stronger inductors than DNA viruses)
  - RNA replication complex,
  - mRNA secondary duplex structure

- certain viral proteins
  - e.g. envelope glycoproteins of paramyxoviruses
  - penton (capsid) of adenoviruses
Viral interference

- Infection by an interferon inductor virus renders the tissue resistant to other virus infections
- *only until the initial infection lasts*
  *(thereafter the tissue becomes susceptible to other viral infections)*
- medical importance:
  *e.g. oral (live) poliovirus vaccine can be ineffective in other viral infections*
Effect of interferon $\alpha/\beta$ on target cells

Activated cells gain resistance before infection – spreading infection is inhibited
Intracellular changes mediated by interferon α/β receptor

- **2’-5’A synthetase**
  - synthesis of antiviral proteins
  - activation of antiviral proteins by dsRNA i.e. viral infection

- **proteinkinase R**
  - eIF-2 + ATP
  - P-eIF-2
  - peptide chain initiation is inhibited

- ATP → 2’-5’ oligoadenilate
- RNAse L endonuclease
- activated RNAse L
- mRNA hydrolysis

**viral replication is blocked**
Immune modulatory effects of interferons

- Activation of NK cells
- Upregulation of MHC I expression on the cell surface

- Th1 induction
- Activation of macrophages
- Upregulation of MHC II expression on certain cells

α/β and γ interferons

Only γ interferon (immune interferon)
**NK cells**

**A**

Activating receptor bound to KAR. Without enough MHC, KIR can’t bind. NK cell only receives activating stimulus, which results in target cell death.

**B**

Activating receptor bound to KAR. When MHC is present in adequate amounts, NK cell receives BOTH activating and inhibiting stimuli. Thus, target cell death is averted.
Humoral immunity I

Infection at level of cell (antibody absent)
- Adsorption
- Penetration
- Uncoating
- Expression of viral antigens

Antibody neutralization at level of cell
- Inhibition of adsorption
- Inhibition of penetration
- Inhibition of uncoating
- Antibody plus complement-mediated lysis of cell
  or ADCC
Humoral immunity II

1. Aggregation

Virions  Antibody  Effect

2. Complement-enhanced neutralization

Fewer infectious particles

Inactivation

Complement
Cell mediated immunity - CMI (MHC restriction)

- Virus infected cells
- Antigen presenting cells
- Th0 (CD4+)
- MHC II + peptide epitope
- Th1 (CD4+)
- IL-12
- MHC I + peptide epitope
- CTL (CD8+)
- IL-2
- IFN-γ
- MHC I + epitope
- Recognition and cytolysis

Activation of CMI
Viral escape from immune surveillance

- Immunosuppression
- Escape from antibodies
- Escape from cell mediated immunity
Immunosuppression by viruses

- Destroying lymphocytes (*HIV, measles virus*)
- vIL-10 of EBV
- Inhibiting the antigen presenting function of dendritic cells and macrophages (*HIV, measles*)
- Inhibiting the replication & differentiation of progenitor cells in bone marrow (*hCMV*)
Escape from antibodies

- High mutation rate of RNA viruses (HIV, HCV)
  - immune selection of escape variants
- Antigen drift of influenza viruses
- Antigen shift of influenza A virus
  - genome segmented for the viral proteins
    recombination of genomic segments
Escape from cell mediated immunity

- Hiding from immune responses
  - renal tubules (hCMV), salivary gland (EBV)
  - non replicating host cell, no viral expression
    (HSV, VZV in sensory neurons)

- MHC I downregulation on the target cell surface
  (adenoviruses, hCMV, HIV, HTLV)

- Inhibiting MHC II expression
  (HIV, measles virus, hCMV)
ANTI-VIRAL CHEMOTHERAPY

• Antiviral drugs are available to treat only a few viral diseases.
Stages in virus replication which are possible targets for chemotherapeutic agents

• Attachment to host cell
• Uncoating - (Amantadine)
• Synthesis of viral mRNA - (Interferon)
• Translation of mRNA - (Interferon)
• Replication of viral RNA or DNA - (Nucleoside analogues)
• Maturation of new virus proteins (Protease inhibitors)
• Budding, release (neuraminidase inhibitors)
Replication of viral nucleic acid

1. **compétitive inhibition**

2. alternative substrate

physiological nucleoside (N)

1. phosphorylation

- NMP → NMP
- Np* → Np*

2. phosphorylation

- NDP → NTP
- Np*P → Np*PP

3. phosphorylation

- NTP

Non nucleoside inhibitor

viral nucleic acid

- Pol

- cell membrane
ACYCLOVIR
(acycloguanosine)

GANCYCLOVIR

IDOXURIDINE

RIBAVIRIN

DIDEOXYinosine

DIDEOXYCYTIDINE

ZIDOVUDINE
(azidothymidine)
"Normal" Immune globulin
This is a pooled product, prepared from the serum of normal blood donors. It contains low titres of antibody to a wide range of human viruses. It is mainly used as prophylaxis against:

- hepatitis A virus infection,
- parvovirus infection, and
- enterovirus infections (in neonates).
Immunoglobulin Therapy

Hyper-immune globulin
Immunoglobulin may be prepared from the serum of selected individuals who have high titres of antibody to particular viruses. Examples include:

- **Zoster** immune globulin
  Prevention of Varicella in immunocompromised children and neonates.

- **Human Rabies** immunoglobulin
  Post-exposure prophylaxis in an individual who has been bitten by a rabid animal.

- **Hepatitis B** Immune globulin
  Non-immune individual who has been exposed to HBV.

- **RSV** Immune globulin
  Treatment of respiratory syncitial virus infections in the very young.
Vaccines are available for:

- **Hepatitis B virus** recombinant protein
- **Hepatitis A virus** inactivated virus
- **Influenza** inactivated virus
- **Measles**
- **Mumps**
- **Polio**
- **Rubella**
- **Rabies** inactivated virus
- **Yellow Fever**
- **Varicella Zoster**
Attributes - live vaccines
(Measles, Mumps, Polio, Rubella, Zoster, Yellow fever)

• **Good immune response**
  – Both Cell Mediated Immunity and antibody responses.
  – Immunity is long lived
  – Single dose

• **Safety**
  – Danger of reversion to virulence, or
  – Severe disease in immunocomprised

• **Stability**
  – Organisms in the vaccine must remain viable in order to infect and replicate in the host
  – Vaccine preparations are therefore very sensitive to adverse storage conditions
  – Maintenance of the cold chain is very important.
• Attributes – Non live vaccines

• Immune response
  • poor; only antibody - no cell immedidated immune response.
  • response is short-lived and multiple doses are needed.
  • may be enhanced by the incorporation of adjuvants into the vaccine preparation (see below)

• 1. Safety
  – Inactivated, therefore cannot replicate in the host and cause disease.
  – Local reactions at the site of injection may occur.

• 2. Stability
  – Efficacy of the vaccine does not rely on the viability of the organisms.
  – These vaccines tend to be able to withstand more adverse storage conditions.