Immunity to Infection

Marie Lipoldová

Institute of Molecular Genetics
Academy of Sciences of the Czech Republic

www.img.cas.cz/mci/

tel: 2243 10 195, 220183 462
Recommended literature I.

Roitt I., Brostoff J., Male D.: *Immunology*,

Immunity to viruses: pp. 235-243
Immunity to bacteria: pp. 245-258
Immunity to parasites: pp. 259-273
Vaccination: pp. 277-287
Recommended literature II.

Gerald B. Pier, Jeffrey B. Lyczak, Lee M. Wetzler:  
*Immunology, Infections, and Immunity*  
ASM Press, 2004

Chapter 18 – Immunity to Bacterial Infections  pp. 425 - 452  
Chapter 19 – Immunity to Viruses  pp. 453 - 467  
Chapter 20 – Immunity to Parasitic and Fungal Infections  pp. 469 - 496  
Chapter 21 – Vaccines and Vaccination  pp. 497 - 528
Recommended literature III.

Cedric Mims, Anthony Nash, and John Stephen:  
*Mims’ pathogenesis of infectious disease*  

Roderic Nairn, Matthew Helbert:  
*Immunology for Medical Students*, Mosby 2002

Chapter 22: Infections and vaccines pp. 207 - 213
<table>
<thead>
<tr>
<th>Disease</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>chronic hepatitis (hepatitis B)</td>
<td>300x10^6 infectious carriers (200 x greater risk of developing liver cancer)</td>
</tr>
<tr>
<td>diarrhoeal disease</td>
<td>750x10^6 children annually infected</td>
</tr>
<tr>
<td>acute respiratory disease</td>
<td>4x10^6 children die annually</td>
</tr>
<tr>
<td>HIV</td>
<td>36x10^6 infected, 2.3x10^6 die annually</td>
</tr>
<tr>
<td>tuberculosis</td>
<td>1600x10^6 infected, 3x10^6 die</td>
</tr>
<tr>
<td>malaria</td>
<td>300-500x10^6 infected, 3x10^6 die</td>
</tr>
<tr>
<td>schistosomiasis</td>
<td>200x10^6 cases annually</td>
</tr>
</tbody>
</table>
Unexpected outbreaks

Examples of emerging and re-emerging infectious diseases 1994-1999

- Anthrax
- Brucellosis
- Cholera
- Crimean-Congo haemorrhagic fever
- Cryptosporidiosis
- Dengue haemorrhagic fever
- Diphtheria
- Ebola haemorrhagic fever
- E.coli O157
- Echinococcosis
- Enterovirus 71
- Epidemic meningitis
- Hendra
- Human monkeypox
- Influenza A (H5N1)
- Influenza A (H9N2)
- Lassa fever
- Leptospirosis
- Lyme borreliosis
- Malaria
- New variant CJD
- Nipah
- Omsk haemorrhagic fever
- O’nyong-nyong fever
- Plague
- Poliomyelitis
- Reston virus
- Rift Valley fever
- Ross River virus
- Typhoid
- Venezuelan equine encephalitis
- West Nile fever
- Yellow fever

SOURCE:WHO
We are continuously exposed to microorganisms that can cause disease.
Host-Pathogen interaction
One of the most important factors in evolution
Pathogen versus multicellular organism

a never ending story.

smallpox

leprosis

Leishmaniásis visceral form

Cancer of hepar induced by hepatitis B virus

© Harcourt Publishers Limited 2001
Influence on development of infection:

- **environment** (hygiene conditions, presence of vector)
- **pathogen** (virulence and titer)
- **host** (age, nutritional and immune status, stress, genotype)
Immune system

Functional rather than anatomical system

Functions

- Protection against pathogens
- Elimination of tissues and cells that have been damaged, infected or killed

Distinguishes between self and non-self.
Two types of resistance cooperate

- **Innate = nonspecific**
  general defence against wide range of pathogens
  rapid response
  in place at birth
  **mechanisms** – intact membranes, phagocytes, antimicrobial chemicals, inflammation

- **Adaptive = specific**
  specific response to pathogens
  slower than innate system
  acquired after exposure
  **mechanisms** – T lymfocytes, antibodies
Nonspecific (Innate) Resistance

- Mechanical barriers
  - skin (cutaneous membrane)
  - mucous membranes
- Inflammation
  - chemical and cellular barriers
  - phagocytes and killer T cells
  - complement and other antimicrobial proteins
- Fever
THREE STRATEGIES
OF INNATE IMMUNE RECOGNITION

of vertebrate animals:

- recognition of microbial nonself
- recognition of missig self
- recognition of induced or altered self

Detection of conserved molecular patterns, that are essential products of microbial physiology

PAMPs = pathogen-associated molecular patterns (they are not unique to pathogens and are produced by all microorganisms and are invariant among microorganisms of a given class.)
RECOGNITION OF MISSING SELF
molecular passwords of self identity

- **MHC I** – recognized by various inhibitory receptors, often down regulated as a result of viral infection or cellular transformation

- **CD46, CD55** – expressed by all self cells, inhibit formation of the active C3 convertase and formation of an active protease complex of the alternative pathway

- **sialic acid** – on normal self-tissues – recognized by Siglecs (on macrophages, dendritic cells, Neutrophils)
RECOGNITION OF INDUCED OR ALTERED SELF

lead to induction of apoptosis or cell killing

- **viral infection** triggers **apoptosis** through **PKR/RnaseL** pathway

- **infection, transformation** or **stress** induces the expression of molecular markers that flag affected cells for killing (e.g. **MICA** – [MHC class I-related chain A] and **ULBP** [UL16 binding protein]. They serve as signals for **assisted suicide** by triggering an activating receptor **NKG2D** on NK cells, CD8+ cells and myeloid cells)
COMPONENTS OF INNATE IMMUNITY

cellular:
- phagocytes (neutrophils, eosinophils, monocytes/macrophages)
- NK cells
- mast cells, basophils

humoral:
- complement
- antimicrobial proteins
- interferons, TNF, other cytokines
COMPONENTS OF ADAPTIVE (SPECIFIC) IMMUNITY

**cellular:**
- **T lymfocytes**
  - cytotoxic – CD8⁺
  - helper - CD4⁺
- **B lymfocytes**

**humoral:**
- **antibodies**

**Important:** amplification, immunological memory
Effector and memory T cells

Fig 10.27 © 2001 Garland Science
IMMUNITY TO VIRUSES

- HIV
- SARS- Severe Acute Respiratory Syndrome
  Human Coronavirus - SARS
- parvovirus
  (DNA)
- herpesvirus
- variola
- Hepatitis B virus
WHAT IS A VIRUS

- A small segment of nucleic acid (RNA or DNA) wrapped in a protein or lipoprotein shell

- An obligate intracellular parasite always completely dependent on cells on
  provision of energy
  the provision of raw materials (amino acids, lipids, sugars)
  protein synthesis
VIRUS ENTRY

- mucosal surfaces
- puncturing skin (insect bites, needles)
Viruses bind to host cells via specific receptors. This specificity identifies in part tropism of a virus for a particular host or cell.
## VIRUS RECEPTORS ON HOST CELLS

<table>
<thead>
<tr>
<th>virus</th>
<th>receptor</th>
<th>cell type infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>CD4</td>
<td>Th cells</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>CR2</td>
<td>B cells</td>
</tr>
<tr>
<td></td>
<td>(complement rec.type2)</td>
<td></td>
</tr>
<tr>
<td>influenza A virus</td>
<td>glycophorin A</td>
<td>many cell types</td>
</tr>
<tr>
<td>polio virus</td>
<td>polio virus receptor</td>
<td>neurons</td>
</tr>
<tr>
<td></td>
<td>(immunoglobulin superfamily)</td>
<td></td>
</tr>
<tr>
<td>measles virus</td>
<td>CD46</td>
<td>many cell types</td>
</tr>
<tr>
<td>human herpes virus 6</td>
<td>CD46</td>
<td>many cell types</td>
</tr>
</tbody>
</table>
Both cell and virus play an important role in interaction.

Example: an acutely cytopathogenic infection in one cell and latency in another.
VIRUS-CELL INTERACTION

- cytopathogenic
- persistent
- latent
- transforming
- abortive
- null
DEFENCE AGAINST VIRUSES

Innate immune mechanisms:
  - type I interferon
  - natural killer cells
  - macrophages

Specific response:
  - T cells
  - B cells
ANTIVIRAL IMMUNITY

<table>
<thead>
<tr>
<th>IFNα/β</th>
<th>NK cells</th>
<th>CD8+ T cells</th>
<th>B cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>IFNγ</td>
</tr>
</tbody>
</table>

**Innate response:** 3-5 first days

**T cells:** influenza – after four or five days

HIV – three weeks
INNATE IMMUNE MECHANISMS

- first line defence against virus infections
- does not require prior exposure or amplification to be effective

restrict early stages of infection and delay spread of virus

Principle components:
• type I interferons
• natural killer cells
• inflammatory mediators (cytokines)
Viral infection stimulates the production of type I interferons.

**Type I Interferons**

Viral infection stimulates the production of type I interferons.

- $\text{IFN}^\alpha$ - leukocyte interferon
- $\text{INF}^\beta$ - fibroblast interferon
- $\text{IFN}_\omega$, $\text{IFN}_\kappa$, limitin

bind to the same receptor $\text{IFN}^\alpha\beta R$
Type I IFNs induce an "anti-viral state"

- Virus infected cell
  - Release of Type I IFN
  - Induction of enzymes-block viral replication
    - ANTI-VIRAL STATE
FUNCTION OF TYPE I INTERFERONS

stimulate transcription of more than 100 cellular genes

1) INHIBITION OF VIRAL INFECTION AND REPLICATION BY INDUCING AN "ANTIVIRAL STATE"
   - block of translation of viral proteins
   - degradation of viral RNA

2) ENHANCEMENT OF CYTOTOXIC T CELL ACTIVITY AGAINST VIRALLY INFECTED CELLS
   - stimulation of increased expression of MHC I
Type I IFNs enhance CTL activity against virally infected cells

- Virus infected cell
- Release of Type I IFN
- MHC class I expression
- Infected cell lysis by CTLs
NATURAL KILLER CELLS

- cytotoxic for virally infected cells
  active NK cells detected within 2 days of a viral infection

Major effector cells against herpes viruses, in particular cytomegalovirus (CMV)

- an inverse correlation between MHC I expression and NK killing – majority of viruses downregulate MHC I expression to evade T cell recognition

- NK cells are also one of the main mediators of antibody-dependent cellular cytotoxicity (ADCC)
NK cell-mediated killing of virally infected cells

Virus infected cell → NK cell → Infected cell lysis
Cytotoxic T cells recognize virus-infected cells. They are able to destroy infected cells early in the virus replication cycle before new viral progeny appear.

B cells=> Antibodies restrict the spread of virus to neighbouring cells and tissues by neutralizing. Prevent reinfection.

ADCC antibody dependent cell killing
Cytotoxic T lymphocyte kills virus infected cell

Virus infects cells

Protein synthesis

Peptide fragments generated and associate with MHC I

Peptide+MHC I displayed on cell surface

Kills

Tc Cell

MHC Class I

CD8
ANTIBODIES

a major barrier to virus spread between cells and tissues
particularly important in restricting virus spread in the blood stream

Antibodies block:
- binding to cell
- entry into cell
- uncoating of virus

IgA – on mucosal surface – prevents binding
IgG, IgM – neutralizing
**ADCC**
(antibody dependent cell cytotoxicity)

antibodies IgG cover infected cell and interact with Fc receptors (CD16) on NK cell ⇒ perforin, granzymes
Defense against viruses

Mechanical barriers
- skin
- mucosal membranes

Innate immunity
- IFN
- NK- cells
- Macrophages

Acquired immunity
- CD8+ T cells
- CD4+ T cells
- B-cells - Antibody
IMMUNITY TO BACTERIA

Mycobacterium tuberculosis
Mycobacterium leprae
Salmonella typhi
Vibrio cholerae
Treponema pallidum
MAN AND BACTERIA

Man – cca $10^{13}$ cells in the body

skin - cca $10^{12}$ bacteria

mouth - cca $10^{10}$ bacteria

digestive tract - cca $10^{14}$ bacteria
Mechanism of protection from a bacterial species can be deduced from the structure of the organism.
Important:

**cell wall**

Mechanisms of immunity are related to bacterial surface structure.
FOUR MAIN TYPES OF CELL WALL

Gram⁺ peptidoglycan

Gram⁻ lipopolysaccharide

Mycobacteria

Spirochetes
Mechanisms of immunity are related to bacterial surface structure.

- **PHAGOCYTES** – most bacteria are killed by phagocytes (innate mechanisms or cooperation with adaptive response)

- **COMPLEMENT** – a few, mostly Gram-negative bacteria - outer lipid bilayer often susceptible to mechanisms that can lyse membranes = complement and certain CYTOTOXIC CELLS

- **ANTIBODY** - outer surface of bacterium – fimbriae or flagellae, or may be covered by a protective capsule ⇒ impede functions of phagocytes or complement, but acts as target for the **ANTIBODY** response

- **CELL-MEDIATED ADAPTIVE IMMUNITY** (against intracellular bacteria)
INNATE SYSTEM

1) BARRIERS OF ENTRY - first line defence

2) RECOGNITION OF COMMON BACTERIAL COMPONENTS - the second line of defence

PAMPs (pathogen-associated molecular patterns)
BARRIERS OF ENTRY - first line defence
DO NOT DEPENDS ON ANTIGEN RECOGNITION

- intact skin impenetrable to most bacteria
- fatty acids toxic to most bacteria
- epithelial surfaces – cleansed by ciliary action in the trachea or by flushing of the urea
- pH changes in the stomach and vagina (acid)
- commensals in the vagina, the epithelium secretes glycogen, which is metabolized by particular species of commensal bacteria, producing lactic acid

Generally – commensals can limit pathogen invasion through production of antibacterial proteins – colicins
Commensals may occupy an ecological niche – compete for nutrients
INNATE IMMUNITY TO EXTRACELLULAR BACTERIA

- Activation of complement (killing of Gram−)
- Phagocytosis
  opsonisation by complement as a result of C3 convertase stabilisation by cell wall components including LPS
- Endotoxins directly stimulate pro-inflammatory cytokines (IL-1, IL-6, TNFα) ⇒ extravasation, migration and activation of macrophages and neutrophils, fever, acute phase proteins
MOST BACTERIA ARE KILLED BY PHAGOCYTES

a) a few, mostly Gram-negative bacteria are directly killed by complement

b) some Gram-negative can be killed by NK cells or even Tc cells
INNATE IMMUNITY

STEPS OF PHAGOCYTE–PATHOGEN INTERACTION

• chemotaxis

• attachment of the phagocyte to bacteria

• triggering the uptake

• triggering of microbicidal activity
DEFENCE TO BACTERIA

PHAGOCYTOSIS

CHEMOTAXIS

• bacterial components as f-Met-Leu-Phe

• complement products e.g. C5a

• locally released chemokines and cytokines

⇒ attract the phagocytes
ATTACHMENT OF THE PHAGOCYTE TO THE ORGANISM

important interaction, which may determine, whether uptake occurs, and whether killing mechanisms are triggered

microbe: **PAMPs** (pathogen-associated molecular patterns)
- lipopolysaccharide
- peptidoglycan

phagocyte: **PRRs** (pattern recognition receptors)
- scavenger receptors
- the Toll-like receptors (TLR)
- receptors for polysaccharides (CD36)
- complement receptors CR3

**IMPORTANT**: recognition of microbe may involve more than one receptor, e.g. LPS binds to CD14 and TLR-4
TRIGGERING OF UPTAKE

the binding of an organism to a receptor on the macrophage membrane does not always lead to uptake

⇒ OPSONIZATION

• Fc receptors
• complement receptors

they promote by several thousand-fold the uptake of microbes containing bound Ab and/or C proteins
DEFENCE TO BACTERIA

PHAGOCYTOSIS

TRIGGERING OF MICROBICIDAL ACTIVITY

phagosome (acid environment) + lysosome (enzymes hydrolases) \(\Rightarrow\) phagolysosome

LIMITATION OF NUTRIENTS (e.g. iron)

RESPIRATORY BURST:

Production of reactive oxygen intermediates:

\[
\begin{align*}
H_2O_2 \\
O^{2-} & \\
iNOS \Rightarrow NO \text{ (arachidonic acid metabolite)}
\end{align*}
\]

killing of pathogen.
How pathogens resist killing

*Mycobacterium* – arrest maturation
(fusion phagosome + lysosome)

*Leishmania, Coxiella* – live in low pH

*Shigella, Listeria* – escape into cytoplasm

*Legionella* – converts phagosome to vacuole
Killing of microbe by phagocyte

- **a** attachment by non-specific receptors
- **b** pseudopodia forming a phagosome
- **c** lysosome fusion and killing
- **d** release of microbial products
ANTIBODY PROVIDES AN ANTIGEN-SPECIFIC PROTECTIVE MECHANISMS

- toxin neutralization
- preventing bacterial adherence
- facilitates phagocytosis
- ADCC – antibody dependent cell-mediated cytotoxicity
Toxin Neutralization

1. Toxins bind to cellular receptor
2. Endocytosis of toxin:receptor complex
3. Dissociation of toxin to release active chain, which poisons cell
4. Antibody protects cell by blocking binding of toxin
Colonization of cell surface by bacteria via bacterial adhesins

Some bacteria become internalized and propagate in internal vesicles

Preventing Bacterial Adherence

Antibodies to adhesins block colonization and uptake

STIMULATION OF PHAGOCYTOSIS MORE THAN 1000 X

Antibody-coated bacterium binds to Fc receptors on cell surface

Macrophage membrane surrounds bacterium

Macrophage membranes fuse, creating a membrane-bounded vesicle, the phagosome

Lysosomes fuse with the phagosome creating a new vesicle, the phagolysosome

Natural Killer Cells and Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)
T LYMFOCYTES

T helper lymfocytes CD4⁺
production of proinflammatory cytokines

Th1 type – activation of macrophages leads to microorganisms killing

Th2 type – stimulation of B cells ⇒ production of antibodies

Cytotoxic T lymfocytes CD8⁺
Mechanisms of protection are related to bacterial surface structure

- **Phagocytosis** – most bacteria
- **Complement, cytotoxic cells**
  - a few mostly Gram negative bacteria
- **Antibodies** – neutralizing toxins, block toxins interfere with mobility stops binding to epithelial cells
- **Cell-mediated adaptive immunity** – against intracellular bacteria
IMMUNITY TO PROTOZOA AND WORMS

- *Ascaris lumbricoides*
- *Trichinella spiralis* (by P.W. Poppas and S.M. Wardrop)
- *Plasmodium falciparum*
- *Trypanosoma cruzi*
Features of parasitic infections:

EPIDEMIOLOGY

• infect very large number of people

PARASITOLOGY

• often complicated life cycles

IMMUNOLOGY

• parasites are large ⇒ many antigens ⇒ stimulate a number of defence mechanisms
Parasites infect very large numbers of people—a major medical problem, especially in tropical countries.

Malaria kills $1-3 \times 10^6$ people every year.

Schistosoma kills $0.5 – 1 \times 10^6$ people every year.

Intestinal worms infect $1/3$ of the world’s population:

- *Ancylostoma, Necator* - $800 \times 10^6$
- *Ascaris lumbricoides* - $700 \times 10^6$
- *Trichuris trichura* - $500 \times 10^6$
• **direct invasion** by penetrating the skin – hookworms and schistosome larvae
• **ingested** – tapeworms, pineworms, roundworms, few Protozoa (*Toxoplasma, Giardia*)
• **depend on** intermediate insect host or vector to transmit them from person to person:
  - filarial worms, Protozoa
  - malarial parasites – mosquites
  - trypanosomes – tse-tse flies
  - *Trypanosoma cruzi* – Triatomid bugs
  - *Leishmania* – sandflies
Parasitic protozoa may live:
- in blood (e.g. African trypanosomes)
- within erythrocytes (e.g. *Plasmodium* spp.)
- in macrophages (*Leishmania, Toxoplasma gondii*)

Parasitic worms:
- trematodes or flukes (e.g. schistosomes)
- cestodes (e.g. tapeworms)
- nematodes or round worms (e.g. *Trichinella spiralis*, hookworms, pinworms, *Ascaris* spp., and the filarial worms)

- Tapeworms and adult hookworms inhabit the **gut**
- adult schistosomes live in **blood vessels**
- some filarial worms live in the **lymphatics**

⇒ widespread potential for damaging pathological reactions
COMMON FEATURES OF PARASITIC INFECTIONS

- a greater variety of antigens than bacteria and viruses
- antigen variations - some species can change their surface antigens
- a stage specific response
- a special mode of entry – bind to certain receptors
- host specific – most of parasites
- chronic – many parasitic infections
- host defence complex – a number of immunological effector mechanisms
COMMON FEATURES OF PARASITIC INFECTIONS

A GREAT VARIETY OF ANTIGENS

Protozoan parasites – considerably larger than bacteria and viruses

⇒ contain greater variety and a greater quantity of antigens

Girardia lamblia

Trypanosoma cruzi

Ascaris lumbricoides

(by P.W. Peppas and S.M. Wardrop; original by P. Barbesi)
COMMON FEATURES OF PARASITIC INFECTIONS

ANTIGEN VARIATIONS

some species can change their surface antigens

example: Trypanosoma
COMMON FEATURES OF PARASITIC INFECTIONS

A STAGE SPECIFIC RESPONSE

parasites with complicated life histories may express certain antigens only at a particular stage of development
A STAGE SPECIFIC RESPONSE

example

Malaria

the protein coat of the sporozoite (the infective stage of the malarial parasite transmitted by the mosquito) induces the production of antibodies that do not react with the erythrocytic stage

*Trichinella spiralis*

different stages of worm *Trichinella spiralis* also display different surface antigens
A SPECIAL MODE OF ENTRY

bind to certain receptors

• the merozoite (the invasive form of the blood stage of the malarial parasite) binds to certain receptors on erythrocyte and uses a specialized organelle – the rhoptry – to enter the cell

• *Leishmania* – use complement receptor, mannose-fucose receptor
COMMON FEATURES OF PARASITIC INFECTIONS

HOST SPECIFIC

most of parasites million years of evolution ⇒ parasites become well adapted to their hosts

e.g. malarial parasites of birds, rodents or man can each multiply only in their own particular kind of host

exception – *Toxoplasma gondii* – able to invade and multiply in all nucleated mammalian cells, can infect immature mammalian erythrocytes, insect cell cultures, and the nucleated erythrocytes of birds and fish

tapeworm of the pig can also infect humans
Many parasitic infections are chronic. It is not in the interest of a parasite to kill its host – transmission necessary.

During the course of chronic infection the type of immune response may change. Common:

- immunosuppression
- immunopathological effects
COMMON FEATURES OF PARASITIC INFECTIONS

HOST DEFENCE IS COMPLEX

- interaction of many **different** kinds of cells
- effects often local – **many cell types** secreting several **different mediators** may be present at sites of infection
- the processes involved in controlling the multiplication a parasite – **differ in different individuals**
First – parasite must overcome innate immunity

a) humoral mechanisms

b) cellular mechanisms
**HUMORAL RESPONSES**

humoral responses are necessary to eliminate extracellular parasites living in:

- blood
- body fluids
- the gut

**IMPORTANT** – the type of response conferring most protection varies with the parasite
HUMORAL MECHANISMS OF INNATE IMMUNITY

preexisting soluble factors that can recognize and destroy invading parasites

1) COMPLEMENT
2) ALTERNATIVE MEDIATORS
3) CYTOKINES
COMPLEMENT

• the alternative pathway

• a lectin-mediated pathway
Innate immunity

ALTERNATIVE MEDIATORS

A primate specific, innate cytolytic defence mechanisms resistance of humans to African trypanosomes and probably also to *Plasmodium* ssp.

- **trypanosome lysis factor 1 (TLF1)** – composed of several common apolipoproteins (high density lipoproteins) and a haptoglobin-related protein (Hrp)
- **TLF2** – shares many of the components of TLF1, but contains a unique immunoglobulin M (IgM) component and has a lower lipid content
cytokines are normally associated with regulation and activation of cells of the immune system, but TNFα is directly involved in innate immunity to *T. brucei*

**TNFα binds and is internalized to *T. brucei***

**cytolysis**

the susceptibility of parasites to this mechanisms is specific:

- insect stages are resistant to lysis
- only parasites isolated during the peak of parasitemia are lysed by TNFα

?! – mechanisms unknown
CELLULAR MECHANISMS OF INNATE IMMUNITY

- macrophages
- neutrophils
- eosinophils
- mast cells
- platelets
- NK cell
- NK T cells
- γδ T cells
- B1 cells
Antiparasitic response

[Diagram showing specific T-cell-dependent processes involving TH2 cytokines (IL-4, IL-5, IL-10) and nonspecific inflammatory processes (e.g., TNF, IL-1) leading to stimulation of goblet cell proliferation. Key steps include parasite antigens stimulating B cells to produce IgE, attracting mast cells with Fe receptor, and leading to increased mucus secretion and expulsion of damaged nematode.]
Idealized patterns of general pathways

Innate

- Bacteria
  - Intracellular
  - Protozoan Parasites
- Viruses
- Extracellular Parasites

Adaptive

- TNF/IL-12
- NK cells
- IFNγ
- CD4 T cells
- IFNγ
- B cells
- IgGs
- CD8 T cells
- IFNγ/CTL
- CD4 T cells
- IL-4/IL-5
- B cells
- IgE

Biron and Sen, Fields Virology, 2001
VACCINATION

Edward Jenner 1798
KEY MECHANISM OF VACCINATION

induction of clonal expansion in specific T and/or B cells – population of memory cells

⇒ encounter with the same antigen(s) will induce secondary response

• more rapid and
• more effective

than the normal primary response
Principle of vaccination

- Vaccination
  - Toxoid
- Primary antibody response
- Natural infection
  - Toxin
- Secondary antibody response
  - Acquired immunity

Antibody response over time:
- Memory cells formed
Effector and memory T cells

Naive T cell encounters antigen

Most activated T cells become effector cells

Some activated and/or effector cells become long-lived memory cells

Target cell

Many effector cells are short-lived and die by apoptosis

Cytokines may be required for survival

Cytokines

Fig 10.27 © 2001 Garland Science
ANTIGENS USED AS VACCINES

• living organisms ← not changed
  attenuated
• intact but non living organisms
• subcellular fragments
• toxoids
• recombinant DNA-based
ATTENUATED LIVE VACCINES

strategy: to attenuate a human pathogen by series of passages

aim: • to diminish the virulence
     • to retain the desired antigens

(example – BCG – bacille Calmette-Guérin – obtained after 13 years 1908-1921)
ANTIGEN USED AS VACCINES

ATTENUATED LIVE VACCINES

**bacteria** – *Mycobacterium tuberculosis* ⇒ BCG

**viruses** – polio – Sabin (types 2,3 may revert)
  - measles
  - mumps
  - yellow fever
EFFECTS OF ATTENUATION

a purely random set of mutations induced by adverse monitoring of growth

sequencing of genome ⇒ different mutations responsible for “attenuation”

polio (Sabin) – type 1 – 57 mutations – almost never revert
type 2, type 3 – only two key mutations – frequent reversions
KILLED VACCINES

intact but non-living organisms

highly effective: rabies
Salk polio vaccine

moderately effective: typhoid
cholera
influenza
ANTIGEN USED AS VACCINES

INACTIVATED TOXINS AND TOXOIDS

<table>
<thead>
<tr>
<th>Disease</th>
<th>Organisms</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>tetanus</td>
<td><em>Clostridium tetani</em> (formalin)</td>
<td>inactivated toxin</td>
</tr>
<tr>
<td>cholera</td>
<td><em>Vibrio cholerae</em></td>
<td>toxin, B subunit</td>
</tr>
</tbody>
</table>

*Clostridium tetani*

*Vibrio cholerae*
antigens either purified from microorganisms or produced by recombinant DNA technology

example: influenza
hepatitis B
*Neisseria meningitidis*
*Streptococcus pneumoniae*
*Haemophilus influenzae B*
The immune system can respond to more than one antigen at a time ⇒ a vaccine “coctail”

EXAMPLES
- the live poliovirus vaccine – three serotypes
- a triple live vaccine of measles, mumps and rubella viruses (MMR)
FEATURES OF GOOD VACCINE

- safe to administer
- induce the right sort of immunity
- affordable by the population
- Suitable for certain population (genetics)
SAFETY OF VACCINES

when poliovirus was endemic

1:100 chance of contracting paralytic poliomyelitis

1: 1 000 000 the risk of poliomyelitis from the live vaccine (reversion)
EFFECTIVENES OF VACCINES

an effective vaccine must:

• Induce the right sort of immunity
• be stable at storage
  (particularly important for living vaccines)
• have sufficient immunogenicity
  (sometimes adjuvant necessary)
Induction of appropriate immunity

• **Living vaccines** – the great advantage
  - providing an increasing antigenic challenge (day or week)
  - in the right site
  - likely to contain the greatest number of microbial antigens

• **Killed vaccines** - + inconveniences
  T – cell independence
  MHC restriction
  (must be coupled with a carrier)
Antibody responses to live and killed polio vaccine
INDUCTION OF APPROPRIATE IMMUNITY

- **ANTIBODIES** – toxins and extracellular organisms (e.g. *Streptococcus pneumoniae*)

- **CELL-MEDIATED IMMUNITY** – intracellular organisms (e.g. *Mycobacterium tuberculosis*)

Ignorance of effective immunity ⇒ difficult to prepare
### Major diseases for which no vaccines are available

<table>
<thead>
<tr>
<th>disease</th>
<th>problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>antigenic variation; immunosuppression?</td>
</tr>
<tr>
<td>herpes viruses</td>
<td>risk of reactivation? (but varicella-zoster appears safe)</td>
</tr>
<tr>
<td>adenoviruses, rhinoviruses</td>
<td>multiple serotypes</td>
</tr>
<tr>
<td>staphylococci</td>
<td>early vaccines ineffective (antibiotics originally better)</td>
</tr>
<tr>
<td>group A streptococci</td>
<td>(BCG gives some protection)</td>
</tr>
<tr>
<td><em>Mycobacterium leprae</em></td>
<td>ignorance of effective immunity</td>
</tr>
<tr>
<td><em>Treponema pallidum</em> (syphilis)</td>
<td></td>
</tr>
<tr>
<td><em>Chlamydia</em></td>
<td>early vaccines ineffective</td>
</tr>
<tr>
<td>fungi</td>
<td></td>
</tr>
<tr>
<td><em>Candida</em></td>
<td>ignorance of effective immunity</td>
</tr>
<tr>
<td><em>Pneumocystis</em></td>
<td></td>
</tr>
<tr>
<td>malaria</td>
<td>antigenic variation</td>
</tr>
<tr>
<td>trypanosomiasis: sleeping sickness</td>
<td>extreme antigenic variation immunopathology; autoimmunity trials encouraging</td>
</tr>
<tr>
<td>Chagas’ disease</td>
<td></td>
</tr>
<tr>
<td>leishmaniasis</td>
<td></td>
</tr>
<tr>
<td>worms</td>
<td></td>
</tr>
<tr>
<td>schistosomiasis</td>
<td>(trials in animals encouraging)</td>
</tr>
<tr>
<td>onchocerciasis</td>
<td>ignorance of effective immunity</td>
</tr>
</tbody>
</table>
100% immunity is not usually need for elimination of a virus from the population

**REQUIRED** - a sufficient percentage of immune individuals to break the chain of transmission
PASSIVE IMMUNIZATION
injecting of preformed antibodies to treat infection

<table>
<thead>
<tr>
<th>disease</th>
<th>source of antibody</th>
<th>indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>diphtheria</td>
<td>human, horse</td>
<td>prophylaxis, treatment</td>
</tr>
<tr>
<td>tetanus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>varicella-zoster</td>
<td>human</td>
<td>treatment in immunodeficiencies</td>
</tr>
<tr>
<td>gas gangrene</td>
<td>horse</td>
<td>post-exposure</td>
</tr>
<tr>
<td>botulism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>snake bite scorpion sting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>rabies</td>
<td>human</td>
<td>post-exposure (plus vaccine)</td>
</tr>
<tr>
<td>hepatitis B</td>
<td>human</td>
<td>post-exposure</td>
</tr>
<tr>
<td>hepatitis A</td>
<td>pooled human immunoglobulin</td>
<td>prophylaxis (travel)</td>
</tr>
<tr>
<td>measles</td>
<td></td>
<td>post-exposure</td>
</tr>
</tbody>
</table>