Immune Mechanisms against Pathogens

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PATHOGENS

The major pathogens to human beings, animals and birds include:

1. Bacteria
2. Extracellular
3. Intracellular
4. Viruses
5. Fungi
6. Yeast
7. Moulds
8. Parasites
9. Protozoa
10. Helminths

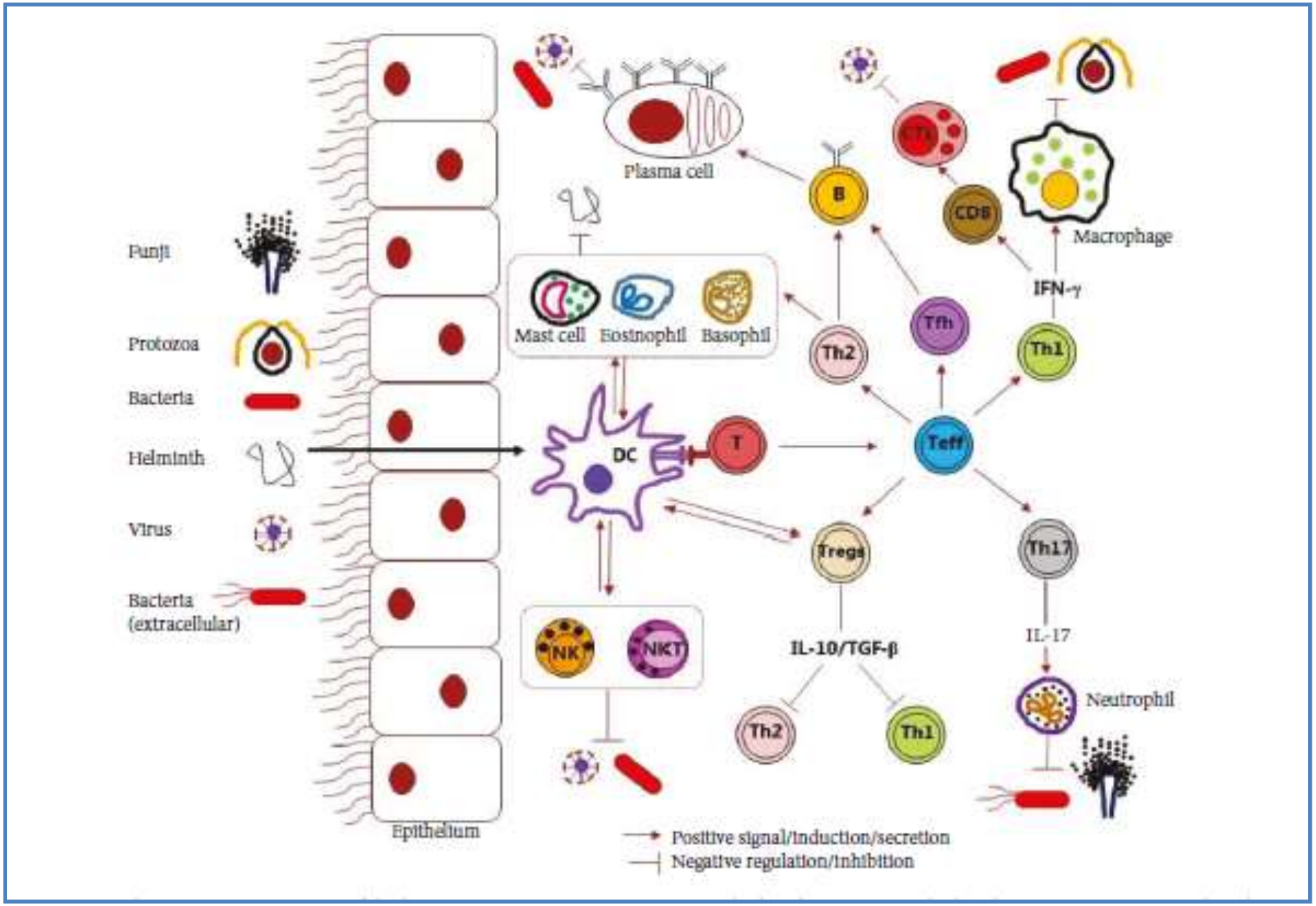
Immune Responses against pathogens

- Anti-pathogen immunity comprises of an early innate response followed by, if required, a more sustained adaptive response.
- For all types of pathogens, the mechanisms of innate immunity offer an immediate response that either prevents the establishment of infection or slows the infection down until adaptive immune mechanisms are induced.
- The components of innate immunity include various physical, chemical, and cellular factors, such as epithelial layers, mucus, lysozyme, anti-microbial peptides, interferons, complement, neutrophils, macrophages, ILCs, etc.
- Recognition of pathogens or their components (PAMPs) by membrane bound or soluble pattern recognition receptors (TLR, NLR, etc.) induces inflammation, cytokine release and complement activation.
- If above innate responses are insufficient to eliminate the invaders, adaptive immunity take over.
- The APCs (DCs and macrophages) are key cells which act as bridge between innate and adaptive immunity and initiate the latter by secreting cytokines.
- The cytokines, thus produced, directs the induction of acquired immunity by triggering appropriate T and/or B cell responses

Immune Responses against pathogens

- The type of adaptive immune response induced depend on whether the pathogen is extracellular or intracellular.
- Humoral immune response, characterized by production of antigen-specific antibodies, eliminates extracellular pathogens that are relatively small, such as extracellular bacteria, virus particles, protozoan parasites, and some fungi, by antibody-and complement-mediated mechanisms that involve either direct lysis or phagocytic destruction.
- Large helminth parasites are also subject to antibody mediated destruction, which occurs extracellularly without phogocytosis, by IgE antibodies.
- Intracellular pathogens cannot be targeted by antibody and require induction of cell mediated immunity characterized by secretion of various cytokines and cytolytic mechanisms by CTLs, NK cells, NKT cells, and γδ T cells.
- The cytokines of the innate immune response creates a mileu that differentiates Th0 cells to the appropriate subtype - Th1 for CMI against internal threats, and Th2 responses for AMI against external threats or Tregs to suppress/control immune response

Schematic representation of the host immune response against microbial pathogens



Immune responses against bacteria

- There are five basic mechanisms of adaptive immunity against bacterial infections. These are:
  - the neutralization of toxins or enzymes by antibodies,
  - the killing of bacteria by antibody mediated (classical) complement activation,
  - the opsonization of bacteria by antibodies or antibodies and complement components followed by their phagocytosis and destruction,
  - the destruction of intracellular bacteria by activated macrophages, and
  - direct destruction of cells infected by intracellular bacteria by CTLs and NK cells
- The relative importance of each of these processes depends on the species of bacteria and their location (intra- versus extra-cellular) and mechanism(s) of pathogenesis in the body of host

Immune responses against extracellular bacteria

- Extracellular bacteria inhabitate and replicate outside the host cells in interstitial spaces in tissues/organs, blood or lumen of body cavities.
- These bacteria cause disease either by producing toxins or enzymes or by inducing immunopathologies.
- **Major Mechanisms of Immune Defense against Extracellular Bacteria are:**
  1. Polysaccharides on bacteria can act as Ti antigens and activate B cells that produce anti-bacterial IgM antibodies.
  2. Other bacterial components can act as Td antigens and activate additional B cells that produce anti-bacterial IgM and IgG antibodies.
  3. Neutralizing antibodies recognizing bacterial pili and block access of these bacteria to host cell glycoproteins, thus preventing adhesion.

Immune responses against extracellular bacteria (contd.....)

4. Neutralizing antibodies bound to bacterial surface antigens act as opsonin and promote phogocytosis and destruction of bacteria by macrophages and neutrophils and production of pro-inflammatory cytokines.
5. B cell recognizing a bacterial toxin produces neutralizing anti-toxin antibodies that prevent the toxin molecules from damaging the cell surfaces.
6. Bacteria that have been bound by antibody plus C1, C3b, or MBL activate complement via all three pathways.
7. Mast cells activated by an encounter with a FimH-expressing bacterium release histamine and pro-inflammatory cytokines that lead to the recruitment of neutrophils.
8. Bacterial components captured by DCs are processed and presented to $CD4^+$ Th2 cells, which supports antibody production.
9. Evidences have shown that antibodies not only mark bacteria for destruction, but they can also be directly bacteriostatic (e.g. anti-*E.coli* Abs interfere with the secretion of iron chelator) or bactericidal (produce oxidants)
10. An anti- heat shock protein (HSPs) response against bacterial HSPs by some γ/δ T cells

Immune responses against intracellular bacteria

- Intracellular bacteria evade host innate and adaptive defence mechanisms and enter and replicate inside the host cells.
- These may infect variety of cells including macrophages, RBCs, endothelial and epithelial cells.
- Some bacteria may be obligatory intracellular while for others it may be an optional phase
- **Major Mechanisms of Immune Defense against Extracellular Bacteria are:**
  1. Phagocytosis of bacteria by neutrophils triggers phagosomal killing and cytokine secretion.
  2. Phagocytosis of bacteria by macrophages initiates phagosomal killing and secretion of cytokines that maintain inflammation, activate NK cells, and promote Th1 differentiation.
  3. NK cells activated by IL-12 kill infected host cells by natural cytotoxicity and secrete IFNγ which activates macrophages and supports Th1 differentiation.

Immune responses against intracellular bacteria (contd.....)

4. Phosphorylated metabolites released by a bacterium activate γδ T cells that generate Teff cell.
5. Infected DCs present bacterial components on CD1 to γδ T cells and NKT cells. Once activated, these cells generate cytotoxic- and Th-like effectors.
6. CTLs recognizing bacterial peptides presented on MHC class I by an infected host cell kill the cell by perforin- and granzyme-mediated cytotoxicity.
7. Unconventional (Uncon) CTL subsets are activated by bacterial components presented on CD1 by infected DCs. One subset kills infected host cells by Fas killing, while another relies on perforin-mediated cytotoxicity.
8. Infected macrophages present bacterial peptides on MHC class II to $CD4^+$ Th1 cells that both support the CTL response and hyperactivate macrophages thru IFN-γ. Hyperactivated M1 macrophages produce increased levels of pro-inflammatory cytokines and ROIs that increase killing.
9. Bacterial components released from a dying infected cell can activate B cells to produce neutralizing antibodies.
10. Autophagy is a key mechanism by which IFN-γ control intracellular bacteria. IFN-γ in association with TNFα also increase RNOs.

Immune responses against fungi

- Fungi are either unicellular (yeasts) or multicellular (moulds). Majority of fungi are saprophytes and act as an oppprtunistic pathogens, particularly in immunocompromised hosts.
- Fungal infections could be restricted to skin epithelial (dermatomycosis), subcutaneous tissues or in internal organs.
- **Major Mechanisms of Immune Defense against Fungi are:**
  1. Neutrophils activated by PRR-mediated (TLR2 or Dectin-1) recognition of fungal PAMPs carry out phagocytosis and secrete cytokines (PAMP-PRR → IL-23 → Th17 → activate neutrophils)
  2. Macrophages also carry out these functions plus can undergo hyperactivation and form granulomas to contain resistant fungi.
  3. Activated NK cells kill fungi by secreting cytotoxic cytokines rather than by natural cytotoxicity.

     (Neutrophils cannot totally ingest the fungal hyphae, but damage them by releasing enzymes into the tissue fluid. Macrophages and NK cells can ingest and destroy fungal spores and very small fungal elements)

Immune Responses against fungi (contd…..)

4. Fungal TLR ligands such as GXM (glucuronooxylomannan) activate DCs that in turn initiate T cell activation and Th1 effector differentiation. Th1 cells produce cytokines that stimulate macrophage hyperactivation and NK cell activation. Th1 cells also promote epidermal growth and keratinization.
5. Infected macrophages that establish CD40-CD40L contacts with activated Th1 cells produce copious amounts of IL-1 and TNF that are directly toxic to fungal cells.
6. Mucosal γδ T cells activated by fungal products generate effectors that secrete additional cytokines supporting B cells.
7. Fungi coated in either anti-fungal antibody or C3b undergo opsonized phagocytosis by macrophages and neutrophils; the structure of the fungal cell wall allows them to resist MAC lysis.

Immune responses against viruses

- Viruses are acellular obligate intracellular parasites having either DNA or RNA as genetic material surrounded by a protein capsid. An additional envelope is present in some viruses.
- **Major Mechanisms of Immune Defense against viruses are:**
  1. Type-I IFN (IFN-α/β) secreted by infected host cells induces an antiviral state in neighbouring uninfected host cells. They also activates macrophage killing and production of pro-inflammatory cytokines and NO.
  2. IFNγ induce production of anti-viral enzymes, such as PKR. It also sensitize virus-infected cells to destruction by Tc cells and help them in killing viruses (along with TNF-α) without cytolysis
  3. IL-12 produced by macrophages activates NK cells that secrete additional cytokines and kill infected host cells that fail to express MHC class I.
  4. Infected APCs present viral peptides to $CD4^+$ T cells that supply cytokine help to Tc cells and B cells. Antiviral neutralizing antibodies block further spread of the virus, and antiviral CTLs secrete cytotoxic molecules and kill virus-infected host cells by Fas killing or perforin/granzyme-mediated cytotoxicity **(major mechanism)**

Immune responses against viruses (contd…..)

5. DCs infected by a “strong” virus upregulate their co-stimulatory molecules even in the absence of CD40 ligation, and activate Tc cells in absence of Th help.
6. Antibodies bound to a viral antigen on the surface of an infected host cell may trigger ADCC, promote phagocytosis through opsonization, activate classical complement pathway leading to MAC-mediated destruction of the infected cell (cytolysis, e.g.) or viruses (virolysis) or cause virus clumping (Ab-mediated destruction of infected cells occurs with NDV, rabies, BVDV, IBV, FeLV, etc.)
7. Complement may also be activated by the binding of conglutinin, C1, C3b, or MBL to the virus and inducing virolysis via alternate / mannose pathways.
8. Lysozymes, gastric acidic pH, intestinal enzymes and bile salts can also destroy several viruses.
9. Defensins can inactivate enveloped viruses (e.g. influenza viruses) and/or interfere with viral RNA transcription.
10. Premature apoptosis of virus infected cells may occur thus preventing viral replication and dissemination.
11. Activated macrophages (by IFN-γ) can endocytose and destroy some viruses

Immune responses against protozoans

- Protozoans are unicellular parasites which replicate intra-cellularly in host with an extra-cellular phase. In general, Ab-mediated immune responses are effective against extra-cellular phase of protozoans, whereas CMI control intracellular protozoas.
- **Major Mechanisms of Immune Defense against protozoans are:**
  1. The antigen specific antibodies are effective in opsonization, ADCC, activation of classical complement pathway and neutralization for elimination of pathogens.
  2. The major role in immunity against protozoans is played by INF-γ produced by activated Th1 cells, CTLs, NK, and NKT cells:
     a) hyperactivation of macrophages and granuloma formation that control resistant protozoans;
     b) direct toxicity to many protozoan species;
     c) stimulation of IL-12 production by infected DCs to sustain a feedback loop of Th1 differentiation;
     d) induction of iNOS and increased NO production as well as increased p47GTPase activity in infected macrophages; and
     e) induction of Fas expression on infected macrophages.

Immune responses against protozoans (contd…..)

- APCs, such as DCs play an important role in inducing Th1 response. DCs on contact with parasites secrete large amount of IL-12, which drives activated anti-parasite Th0 cells along the Th1 path.
- Parasite antigens may enter the endogenous antigen processing system and be presented on MHC class I to $CD8^+$ T cells, which are then activated and initiate cytolysis of target cells.
- Although CTL-mediated cytolysis is not actually very effective against acute protozoan infections, but perforin-mediated cytotoxicity may be important for controlling the chronic stages of protozoal infections.
- Antibodies may opsonize, agglutinate, immobilizen and/or induce complement or ADCC mediated destruction of protozoa (e.g. in *Babesia*). 'Ablstins' are antibodies that inhibit division of protozoa.
- Activated macrophages are important in many protozoan diseases where the organisms are resistant to intracellular destruction. RNOs are lethal to many protozoans, such as *Leshmania, Toxoplasma a*nd *T.cruzi*

Immune responses against helminths

- Th2 responses are vital for defense against large, multicellular helminth worms. The anti-helminth Th2 response involves IgE, eosinophils, and mast cells, a combination that does not contribute significantly to defense against other types of pathogens
- **Major Mechanisms of Immune Defense against helminths are:**
  1. DCs that have captured a worm antigen activate $CD4^+$ T cells that are induced to undergo Th2 differentiation. Th2 effectors produce cytokines (IL-4) that induce isotype switching to IgE.
  2. IL-5 produced by Th2 cells activates eosinophils that bind to worm-bound antibodies via their FcεRIs (CD23). Eosinophil cytotoxic granules contain molecules that directly damage the worm surface and stimulate mast cells to degranulate.
  3. Mast cells pre-armed with anti-parasite IgE are activated by worm antigens and release histamine, which induces gut and airway spasms to eject the worm. Mast cells also release proteins that are directly toxic to the worm.
  4. IL-5 produced by Th2 cells also induces isotype switching to IgA in mucosal anti-worm B cells. Secretory IgA (SIgA) blocks the worm from gaining a foothold on the mucosal surface.

Immune responses against helminths (contd….)

5. IL-13 produced by Th2 cells promotes expulsion of parasites by stimulating epithelial cell proliferation (‘epithelial elevator’).
6. Chitinases are enzymes which degrade chitin found in cuticles of helminths. They are produced by macrophages, mast cells, and neutrophils and are important in innate defense against helminths.
7. The detachment of worms from the intestinal walls by self-curing phenomenon is an outcome of an IgE-mediated allergic response (Type-1 hypersensitivity) to salivary antigens of worms. This response causes severe spasms of smooth muscles of intestines which result in detachment of worms. Subsequently an efflux of fluid in lumen (leaky gut) due to increased vascular permeability wash out parasites in faeces.
8. CMI has a little role to play in immunity against worms, but Tc cells have been found to be effective against parasites that are deeply embedded in the intestinal mucosa (induce delayed type hypersensitivity promoting infiltration of mononuclear cells and granuloma formation to restrict spread) or undergoing tissue migration (causing larvae destruction).