IMMUNE RESPONSE TO INFECTIONS

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Introduction

- Defense against microbes is mediated by both innate and adaptive immunity
- The innate response plays a role in determining the nature of specific response
- Immune system responds in specialized ways to specific types of microbes

Introduction

- Survival and pathogencity of microbes influenced by their ability to evade or resist protective defenses
- Tissue injury and disease result when microbes overcome host defense

Introduction

Infection and immunity

- Pathogens
  - Extracellular and intracellular bacteria
  - Viruses
  - Parasites
  - Fungi

- Host immune responses
  - Innate immunity
  - Adaptive immunity

- Pathogen/host interactions
  - Mechanisms of survival and evasion

Introduction

- Distinct effector responses elicited are dependent on
  - site of entry,
  - route of spread,
  - tissue specificity, and
  - transmission
- Pathogenicity and survival of the microbes depend on ability to evade or resist host immune responses
- Disease or tissue injury can be the consequence of the
  - Pathogenicity of microbe as well as
  - The host immune response itself

Immune response to Viral Infections

- A number of specific immune effector mechanisms, together with nonspecific defense mechanisms, are called into play to eliminate an infecting virus.

1. Innate immune response to viral infection

- **Interferon**
  - A group of proteins produced in response to virus infection which stimulates cells to make proteins that block viral transcription, and thus protects them from infection.

Immune response to Viral Infections

- dsRNA produced during viral replication induce the expression of interferons by the infected cells.
- Monocytes , macrophages & fibroblasts also synthesize interferons .
- Anti-viral activity of interferons (IFNs)
  - Virus infected cells produce INF-α;
  - INF-α inhibit intracellular replication of viruses

Immune response to Viral Infections

- IFN-α activate NK-cells to kill virus infected cells
- IFNs have no direct effect on extracellular virus
- IFNs act early in viral diseases before antibody
- INFs activity is not specific

- **NK cells**
  - Destroy some virus-infected cells, and are not MHC restricted.
  - Natural killer cells lyse virally infected cells

Immune response to Viral Infections

2. Specific immune response

- **Humoral immunity**
  - Anti-viral antibodies :
    - prevent spread during acute infection.
    - protect against reinfection .
    - Virus neutralization:- In viraemic infections, antibodies neutralize virus, preventing its attachment to receptor sites on susceptible. cells e.g. Poliovirus, mumps, measles, rubella

Immune response to Viral Infections

- In superficial non-viraemic infections (infleunza) Secretory IgA neutralizes virus infectivity at the mucous surfaces.

- Antibodies destroy free virus particles directly by:
  - i- Aggregation of virus and opsonization
  - ii- Complement mediated lysis

Both mechanisms also act on virus infected cells

Immune response to Viral Infections

- **Cell mediated immunity(CMI)**
  - Cell – mediated immunity is important for control & clearance of viral infections.
  - CMI acts on virus infected cells through:
    - Cytotoxic T-cells (CTLs)
    - NK cells
    - Activated macrophages
  - CTLs kill virus infected cells directly after recognition of viral antigens on cell surface in association with MHC I

Immune response to Viral Infections

- TH-cells stimulated by viral antigens release cytokines. Cytokines attract and activate macrophages to kill virus infected cells
- Nk-cells destroy virus infected cells early in infection before appearance of antibodies
- Antibody-dependent cell mediated cytotoxicity (ADCC):
  - Antibody binds to virus infected cells such cells are lysed by NK cells, macrophages and polymorphs

Immune response to Viral Infections

Immune evasion by viruses

- Viruses can evade host defenses

1. Overcome anti - viral effect of INFs blocking the action of protein kinase example Hepatitis C virus .
2. Reduce surface expression of MHC-I example Adenoviruses & CMV.
3. Reduce MHC -II levels example Measles ,CMV & HIV
4. A large no. of viruses cause generalized immnoduppression. example mumps , measles, EBV., CMV.,& HIV.
5. Antigenic variation example influenza virus

Immune response to Bacterial Infections

Immunity to extracellular bacteria

1- The innate immunity:

a- Complement activation

b- Phagocytosis

c- The inflammatory response

2- The acquired immune responses:

a- The humoral mechanisms (antibodies) “main role”

b- Cell mediated immune response “less role”

Immune response to Bacterial Infections

Immunity to extracellular bacteria

i- Antibodies induce immunity through:

a- Neutralization of bacterial toxins

b- Antibodies attach to the surface of bacteria and;

- Act as opsonins, enhance phagocytosis (Opsonization)
- Prevent adherence of bacteria to their target cells

  e.g. IgA on mucosal surfaces

Immune response to Bacterial Infections

- Activation the complement leading to bacterial lysis
- Agglutinate bacteria, preventing their spread and facilitating phagocytosis

ii- Cell mediated immune mechanisms:

- Microbes are internalized by APCs and presented to TH
- TH cells are activated and release cytokines which;
  - Activate phagocytosis their microbicidal functions
  - Stimulate antibody production
  - Induce local inflammation

Immune response to Bacterial Infections

Immunity to intracellular bacteria

- Innate immunity is not very effective against intracellular bacterial pathogens.
- Intracellular bacteria can activate NK cells, which, in turn, provide an early defense against these bacteria.
- Intracellular bacterial infections tend to induce a cell-mediated immune response, specifically, delayed type hypersensitivity.

Immune response to Bacterial Infections

- In this response, cytokines secreted by CD4+ T cells are important—notably IFNγ, which activates macrophages to kill ingested pathogens more effectively.
- Killing of phagocytosed bacteria as result of macrophage activation by T cell derived cytokines and by direct lysis of infected cells by CD8+ cytotoxic T lymphocytes.
- A pathogenic outcome of chronic T cell and macrophage stimulation to intracellular bacteria can be the formation of granulomas.

Immune response to Bacterial Infections

Mechanisms of escape of bacteria from immune response

- Existence of polysaccharide capsules
- Excretion of toxins (eg.streptolysins toxic for neutrophils)
- Pathogen variability
- Persistence in cells
- Induction of cell apoptosis (*shigella flexneri)*

Immune response to Bacterial Infections

- Blockage of cell lysosome action (*mycobacterium*)
- Inactivation of complement components
- Induction of synthesis of actin fibres (*Listeria*, *Shigella*)
- Enzymatic inhibition of active oxygen radicals (*S.aureus*)
- „Hiding” from immune cells in other, such as epithelia
- Ability to interfere with the immune reactions

Immune response to fungal infections

- Fungal infections are normally only a superficial nuisance (e.g. ringworm: top), but a few fungi can cause serious systemic disease, usually entering via the lung in the form of spores

- The outcome depends on the degree and type of immune response, and may range from an unnoticed respiratory episode to rapid fatal dissemination or a violent hypersensitivity reaction

Immune response to fungal infections

- Predominant defense mechanisms differ depending on the specific causative agent
- Immune response to fungi consist mainly of :

1) Innate immunity is mediated by
   - Neutrophils and macrophages
   - Fungi are readily eliminated by phagocytes
   - Activated neutrophils are critical in the defense against disseminated candidiasis and aspergillosis

2) Acquired immunity (cell mediated immunity)
   - CMI acts in a manner similar to its action against intracellular bacteria

Immune response to fungal infections

- Cell-mediated immunity predominates in protection against cryptococcosis, histoplasmosis and mucosal *C. albicans* infection
- In general, the survival mechanisms of successful fungi are similar to those of bacteria: antiphagocytic capsules (e.g. Cryptococcus), resistance to digestion within macrophages (e.g. Histoplasma, etc.), and destruction of polymorphs (e.g. Coccidioides).
- Some yeasts activate complement via the alternative pathway, but it is not known if this has any effect on survival.

Immune response to Protozoan Diseases

- Both humoral and cell-mediated immune responses have been implicated in immunity to protozoan infections.

- Ingeneral, humoral antibody is effective against blood-borne stages of the protozoan life-cycle, but once protozoans have infected host cells, cell-mediated immunity is necessary.

Immune response to Protozoan Diseases

- Similar process to that of bacteria
  - Macrophages must be activated by T cells to enhance killing mechanism
- Intercellular protozoa like malaria also CMI
- Large protozoa utilize antibody mediated response

Immune response to Protozoan Diseases

- Protozoans escape the immune response through several mechanisms.
- *Trypanosoma brucei—are covered* by a glycoprotein coat that is constantly changed by a geneticswitch mechanism.
- Others (including *Plasmodium, slough off their* glycoprotein coat after antibody has bound to it.

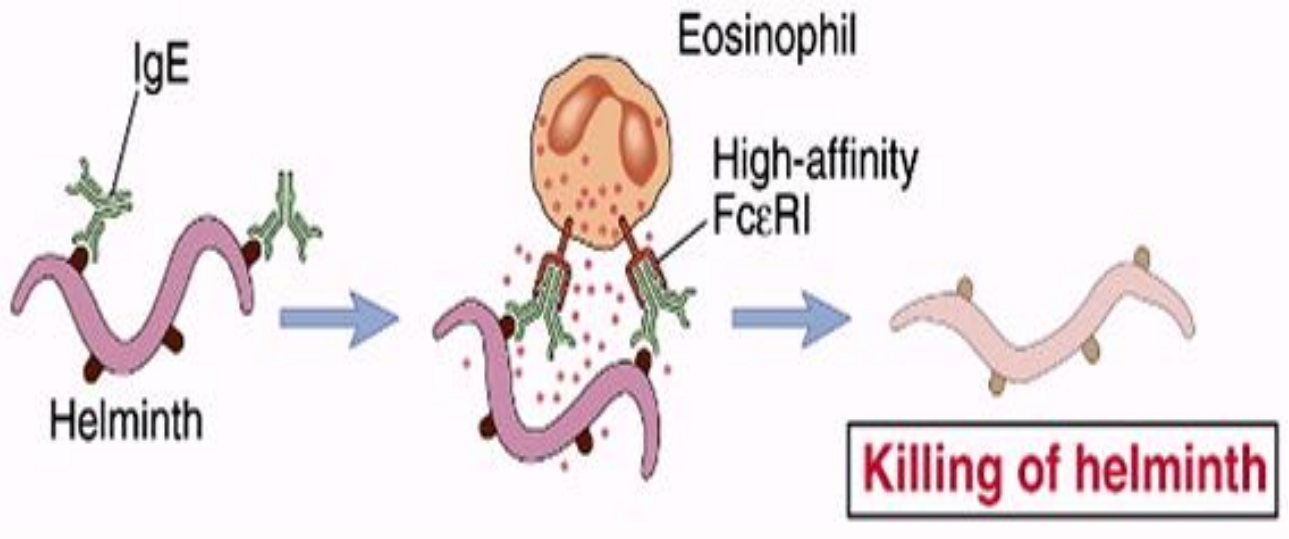
Immune response to Diseases Caused by Helminths

- Helminths are large parasites that normally do not multiply within cells.

- Because few of these organisms are carried by an affected individual, immune-system exposure to helminths is limited; consequently, only a low level of immunity is induced.

- Although helminths generally are attacked by antibody-mediated defenses, these may be ineffective.

- A cell-mediated response by CD4+ T cells plays a critical role in the response to *Schistosoma*
- CMI in response to helminthic parasites is mediated by TH2 cells that stimulate the production of IgE and activation of eosinophils.



Helminth evasion of immune responses

- **Antigenic disguise** – parasites synthetise host-like antigens to mask their own foreigness. Alternatively they absorb host molecules to their surfaces (Schistosomes)

Reference

1. Kuby; Goldsby et. al. Immunology. 2007 (5th ed)
2. Abul K. Abbas and Andrew H. Lichtman. Cellular And Molecular Immunology 2008, 5th edition
3. Mary T. Keogan, Eleanor M. Wallace and Paula O'Leary Concise clinical immunology for health professionals , 2006