Abbas Chapter 11: Immunological Tolerance

Christina Ciaccio, MD
Children’s Mercy Hospitals and Clinics
February 1, 2010

Objectives
- To introduce the concept of immunologic tolerance
- To understand what factors lead to immunologic tolerance
- To review apoptosis and the 2 pathways by which apoptosis is initiated

Question 1
- Immunologic Tolerance is defined as
  A. The removal of an antigen, or the microbes expressing the antigen, by the immune system, so that the host can tolerate the infection
  B. Activation of only B cells, and not T cells, on exposure to an antigen
  C. Unresponsiveness of the immune system to an antigen, which is induced by previous exposure to that antigen
  D. The production of memory B cells and T cells on primary exposure to an antigen, which allows the host to tolerate a secondary exposure to the antigen
  E. Vaccination of individuals against particular pathogens to prevent subsequent infections

Question 2
- Failure of self-tolerance is the cause of which of the following types of disease?
  A. Allograft rejection
  B. Autoimmunity
  C. Atopy
  D. Anergy
  E. Acne

Question 3
- Which one of the following factors favors tolerance to an antigen and not stimulation of an immune response?
  A. High doses of antigen
  B. Short-lived persistence of antigen
  C. Cutaneous portal of entry
  D. Presence of adjuvant
  E. Costimulator expression on antigen-presenting cells

Definitions
- Immunologic tolerance:
  Unresponsiveness to an antigen (Ag) that is induced by previous exposure to that Ag
- Tolerogens
  Ag that induce tolerance
- Self tolerance
- Tolerance to self Ag
Introduction

- Normal individuals are tolerant of their own Ag because self-reactive lymphocytes are killed or change specificity.
- Foreign Ag may be administered in ways that inhibit immune responses by inducing tolerance.
- Induction of tolerance may be exploited as a therapeutic approach for preventing harmful immune responses (e.g., IT).

General Features

- Central tolerance occurs because all lymphocytes encounter self antigen which leads to cell death or the expression of new antigen receptors or a change in functional capabilities if recognition occurs.

General Features

- Peripheral tolerance occurs when mature lymphocytes that recognize self antigens become incapable of responding to that antigen, or lose their viability and become short-lived cells, or are induced to die by apoptosis.

T Cell Tolerance: Central

- In the thymus, T cells that recognize Ag with high avidity are deleted.
- AIRE: transcription factor to promote the expression of selected tissue Ag in the thymus.
- Deletion of AIRE leads to autoimmune polyendocrinopathy.

Some self-reactive CD4+ T cells that recognize self Ag differentiate into Treg.

T Cell Tolerance: Peripheral

- Mechanism by which mature self reactive T cells (periphery) become incapable of subsequently responding to these Ags.
- Exposure to Ag in absence of costimulation leads to tolerance.
- Anergy results from biochemical or genetic alterations that reduce the ability of lymphocytes to respond to self Ags.
- CTLA-4
- PD-1
**T Cell Tolerance: Peripheral**

- Treg are a subset of CD4+ whose function is to suppress immune responses and maintain self-tolerance
- IL-2Rα=CD25
- FoxP3 transcription factor
- Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)
- IL-10 and TGF-β

---

**Apoptosis**

- Apoptosis is a form of cell death in which a cell initiates a suicide program and characteristic morphologic alterations are observed in dying and dead cells
  - Chromatic condensation
  - Nucleolar disruption
  - Cytoplasmic contraction
  - Membrane blebbing

---

**Apoptosis**

- Cells are systematically dismantled into “bite-size” packages, called apoptotic bodies, that are recognized and disposed of by macrophages without concomitant inflammation

---

**Apoptosis**

- “Mitochondrial” or “Intrinsic” pathway involves the induction of proteins that induced mitochondrial leakiness
- “Death receptor” or “Extrinsic” pathway, triggering of cell surface receptors activate that common death pathway
**Apoptosis**
- The induction of death is linked to proteolytic enzymes called caspases
- Caspases are cysteine proteases that cleave proteins immediately after aspartic acid residues

**Apoptosis: Intrinsic**
- Regulated by Bcl-2 family
- Bcl-2 and Bcl-X<sub>L</sub> contribute to mitochondrial stability
- Bax and Bak disrupt the integrity of the outer mitochondrial membrane

**Apoptosis: Death Receptor**
- Fas: Death Receptor
- FasL is induced in Th

**B Cell Tolerance: Central**
- B cells that recognize self Ag with high affinity change their specificity or are deleted
- Receptor editing
- RAG1/RAG2 are reactivated to express new Ig light chain
**Immunological tolerance** is unresponsiveness to an Ag induced by the exposure of specific lymphocytes to that Ag

**Tolerance to self Ag** is a fundamental property of the normal immune system and the failure of self tolerance leads to autoimmune diseases.
Summary

- Ag may be administered in ways that induce tolerance rather than immunity
- This may be exploited for the prevention and treatment of transplant rejection and autoimmune and allergic disease

Summary

- Central tolerance is induced in the generative lymphoid organs (thymus and bone marrow) when immature lymphocytes encounter self Ag present in these organs
- Peripheral tolerance occurs when mature lymphocytes recognize self Ag in peripheral tissues under particular conditions

Summary

- In T cells, central tolerance occurs when immature thymocytes with high-affinity receptors for self Ag recognize these Ag in the thymus
- Some immature T cells that encounter self Ag in the thymus die and others develop into CD4+CD25+ Treg, which function to control responses to self Ag in peripheral tissues

Summary

- Several mechanisms account for peripheral tolerance in mature T cells
- In CD4+ anergy is induced by Ag recognition without adequate costimulation or with engagement of inhibitory receptors like CTLA-4 and PD-1

Summary

- Treg inhibit immune responses in part by producing immunosuppressive cytokines
- T cells that encounter self Ag without other stimuli or that are repeatedly stimulated die by apoptosis

Summary

- In B cells, central tolerance is induced when immature B cells recognize multivalent self Ag in the bone marrow
- The usual result is apoptotic death of the B cells or the acquisition of a new specificity, called receptor editing
Summary

Mature B cells that recognize self Ag in the periphery in the absence of T cell help may be rendered anergic or are excluded from lymphoid follicles, cannot be activated by antigen, and ultimately die by apoptosis.

Summary

Immune responses to foreign Ag decline with time after immunization. This is mainly because of apoptotic death of activated lymphocytes that are deprived of survival stimuli as the Ag is eliminated and innate immunity wanes. Various active mechanisms of lymphocyte inhibition may also function to terminate immune responses.

Question 1

Immunologic Tolerance is defined as

A. The removal of an antigen, or the microbes expressing the antigen, by the immune system, so that the host can tolerate the infection
B. Activation of only B cells, and not T cells, on exposure to an antigen
C. Unresponsiveness of the immune system to an antigen, which is induced by previous exposure to that antigen
D. The production of memory B cells and T cells on primary exposure to an antigen, which allows the host to tolerate a secondary exposure to the antigen
E. Vaccination of individuals against particular pathogens to prevent subsequent infections

Question 1

Immunologic Tolerance is defined as

A. The removal of an antigen, or the microbes expressing the antigen, by the immune system, so that the host can tolerate the infection
B. Activation of only B cells, and not T cells, on exposure to an antigen
C. Unresponsiveness of the immune system to an antigen, which is induced by previous exposure to that antigen
D. The production of memory B cells and T cells on primary exposure to an antigen, which allows the host to tolerate a secondary exposure to the antigen
E. Vaccination of individuals against particular pathogens to prevent subsequent infections

Explanation

Immunologic tolerance refers to the unresponsiveness of the immune system to particular antigens and develops on previous exposure to the antigen. Although the exact requirements for inducing tolerance have not been clearly defined, factors that do influence tolerance include the concentration of antigen, the mode of administration of the antigen, and the presence of costimulatory molecules on antigen-presenting cells for peptide antigens.

Question 2

Failure of self-tolerance is the cause of which of the following types of disease?

A. Allograft rejection
B. Autoimmunity
C. Atopy
D. Anergy
E. Acne
Question 2

Failure of self-tolerance is the cause of which of the following types of disease?
A. Allograft rejection
B. Autoimmunity
C. Atopy
D. Anergy
E. Acne

Explanation

Autoimmunity is an immune reaction against self (autologous) antigens. For this reaction to occur, normal mechanisms of tolerance must fail. Allograft rejection is an immune reaction against allogeic, not autologous, antigens. Atopy is the name for allergic diseases, which are caused by IgE and mast cell-mediated immune responses to foreign antigens. Acne is an infection of hair follicles in the skin and was included as a choice because it begins with the letter A; it is not an autoimmune disease.

Question 3

Which one of the following factors favors tolerance to an antigen and not stimulation of an immune response?
A. High doses of antigen
B. Short-lived persistence of antigen
C. Cutaneous portal of entry
D. Presence of adjuvant
E. Costimulator expression on antigen-presenting cells

Explanation

High doses of antigens favor thymic deletion (if the antigen is a self-antigen) or peripheral deletion by activation-induced cell death. Antigens that induce immune responses are often present for short durations, enter through skin, and are associated with adjuvants that enhance antigen presentation and costimulatory molecule expression.