



Allergy and Immunology Board Review Corner: 2016

Table of Contents

Cellular and Molecular Immunology, 8th Edition, by Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD

January

[Chapter 15 Set 1: Immunological Tolerance and Autoimmunity](#)
[Chapter 15 Set 2: Immunological Tolerance and Autoimmunity](#)

February

[Chapter 16: Immunity to Microbes](#)

March

[Chapter 17 Set 1: Transplantation Immunology](#)
[Chapter 17 Set 2: Transplantation Immunology](#)

April

[Chapter 18: Immunity to Tumors](#)

May

[Chapter 19: Hypersensitivity Disorders](#)

June

[Chapter 20: Allergy](#)

July

[Chapter 21 Set 1: Congenital and Acquired Immunodeficiencies](#)

August

[Chapter 21 Set 2: Congenital and Acquired Immunodeficiencies](#)

Middleton's Allergy Principles and Practice, 7th Edition, edited by N. Franklin Adkinson, et al.

September

[Chapter 27: Aerobiology of Outdoor Allergens](#)

October

Chapter 28: Indoor Allergens

November

Chapter 30 Set 1: Air Pollution

December

Chapter 30 Set 2: Air Pollution



FIT Board Review Corner – January 2016

Welcome to the FIT Board Review Corner, prepared by Sarah Spiet, DO, and Tammy Peng, MD, senior and junior representatives of ACAAI's Fellows-In-Training (FITs) to the Board of Regents. The FIT Board Review Corner is an opportunity to help hone your Board preparedness.

Review Questions

Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition
By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 15 (pages 316-326): Immunological Tolerance and Autoimmunity
Prepared by Tara Shankar, MD, Children's Hospital of Pittsburgh (Ohio)

1. Which of the following is an end pathway of central tolerance?
 - a. Anergy
 - b. Suppression
 - c. Change in receptors
 - d. Enucleation
2. The process by which self-reactive T cells stay living but become unresponsive to an antigen is called which of the following?
 - a. Apoptosis
 - b. Anergy
 - c. Regulatory suppression
 - d. Change in receptors (receptor editing)
3. The absence/mutation of the AIRE protein within medullary thymic epithelial cells leads to an absence of _____ and can cause _____.
 - a. CD4, HIV
 - b. AIRP, APS1
 - c. TRAs, APS1
 - d. TRAs, APS2
4. Which receptor does the regulatory receptor CTLA-4 bind with?
 - a. CD28
 - b. B7
 - c. PD-L2
 - d. FOXP3
5. Signaling block, initiated by engagement of CTLA4 by B7 activates a _____ which terminates response associated with TCR and CD28-associated signaling molecules.
 - a. Kinase
 - b. DNA polymerase
 - c. Lipase

- d. Phosphorylase
6. The differences in the functions of CTLA-4 and PD-1 can be summarized in which of the below statements:
- PD-1 may be more important in controlling the initial activation of CD4+ T cells and serving as a mediator in the suppressive function of regulatory T cells. CTLA-4 serves a role in terminating the peripheral responses of effector T cells.
 - CTLA-4 may be more important in controlling the initial activation of CD4+ T cells and serving as a mediator in the suppressive function of regulatory T cells. PD-1 serves a role in terminating the peripheral responses of effector T cells.
 - CTLA-4 may be more important in controlling the initial activation of CD4+ T cells and serves in terminating the peripheral responses of effector T cells. PD-1 serves a role in the mediatory response of regulatory T cells.
 - CTLA-4 may be more important in controlling the initial activation of CD4+ T cells and serving as a mediator in the suppressive function of regulatory T cells. PD-1 serves a role in terminating the peripheral responses of regulatory T cells.
7. A three-month-old male with atopic dermatitis presents for evaluation of failure to thrive. For several weeks he has had profound watery diarrhea and GI evaluation with enteroscopy and biopsies has revealed villous atrophy. Immunologic evaluation demonstrates peripheral eosinophilia, elevated IgE, and absence of Treg cells. Mutation in which gene is responsible for this clinical picture?
- IPEX
 - FOXP3
 - AIRE
 - XIAP
8. What cytokine is necessary for the survival and functional competence of Tregs?
- IL-2
 - IL-10
 - TGF-beta
 - IL-12
9. Which of the following describes a role of TGF-beta in the immune system?
- Inhibits the production of IL-12 by activated dendritic cells
 - Activates the transcription factor STAT5
 - Binds to B7 molecules to mediate inhibitory activity
 - Stimulates the production of IgA antibodies by inducing B cells to switch to this isotype
10. A three-year-old female presents for evaluation of autoimmune anemia. She is additionally found to have marked cervical and axillary lymphadenopathy on exam. Immunology evaluation demonstrates elevated soluble Fas-L. What disease is suspected?
- APECED
 - IPEX
 - ALPS
 - APS1

Answers

1. C, page 316.

"Central tolerance...may lead to cell death or replacement of a self-reactive antigen receptor with one that is not self-reactive."

2. B, page 318.

"Exposure of mature CD4+ T cells to an antigen in the absence of costimulation or innate immunity may make the cells incapable of responding to that antigen. In this process, which is called anergy, the self-reactive cells do not die but become unresponsive to the antigen."

3. C, page 318.

"Mutations in the AIRE gene are the cause of a multi organ autoimmune disease called autoimmune polyendocrine syndrome type I (APS1)...AIRE protein may function as a transcriptional regulator to promote the expression of selected tissue-restricted antigens (TRAs) in the thymus."

4. B, page 320.

"CTLA-4 is a member of the cD28 receptor family, and like the activating receptor CD28, it binds to B7 molecules."

5. D, page 320.

"Engagement of CTLA-4 by B7 activates a phosphatase which removes phosphates from TCR and CD28 associated signaling molecules and thus terminates responses."

6. B, page 321.

7. B, page 322, FoxP3.

"A rare autoimmune disease in humans called IPEX syndrome is caused by mutations in the FOXP3 gene and is associated with deficiency of regulatory T cells."

8. A, page 323.

"The survival and functional competence of regulatory T cells are dependent on the cytokine IL-2."

9. D, page 324.

"TGF-beta stimulates production of IgA antibodies by inducing B cells to switch to this isotype."

10. C, page 326.

"The gld strain produces FASL with a point mutation that interferes with its signaling function... Children with...mutations in the gene encoding Fas or in genes encoding proteins in the Fas-mediated death pathway [have a] disease called autoimmune lymphoproliferative syndrome (ALPS)."

Review Questions

Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition
By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 15 (pages 317-333): Immunological Tolerance and Autoimmunity
Prepared by Erin E. Kempe, DO, Nationwide Children's Hospital (Ohio)

1. Which of the following is an inhibitory receptor on T cells that binds B7, leading to T cell anergy?
 - a. CD28
 - b. CTLA-4
 - c. ICOS
 - d. PD-1
2. Which of the following phenotypic markers would be consistent with T regulatory cells?
 - a. CD4+ CD25^{high} CD127^{high}
 - b. CD4+ CD25^{high} FOXP3+
 - c. CD4+ CD25^{low} FOXP3+
 - d. CD8+ CD25^{high} CD127^{low}
3. A young male patient is admitted to your service with eczematous dermatitis, chronic diarrhea, failure to thrive, and hypoglycemia. You correctly make the diagnosis of IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) based on genetic testing for mutation in what gene?
 - a. AIRE
 - b. FOXP3
 - c. IFNGR1
 - d. WAS
4. Development and survival of T regulatory cells are dependent on which of the following cytokines:
 - a. IL-2
 - b. IL-7
 - c. IL-12
 - d. IL-17
5. Which of the following proteins serves as an inhibitor of apoptosis in the mitochondrial pathway for cell death?
 - a. Bax
 - b. Bcl-2
 - c. Bim
 - d. Caspase-9
6. Which of the following is upregulated on the surface of mature self-reactive T cells?
 - a. Bcl-2
 - b. CD28
 - c. CD127

- d. Fas
7. Which property of self-reactive lymphocytes occurs only in B cells?
- a. Anergy
 - b. Apoptosis
 - c. Deletion
 - d. Receptor editing
8. Which of the following genetic polymorphisms is associated with Crohn's disease?
- a. CTLA-4
 - b. IL2RA
 - c. NOD2
 - d. PTPN22
9. Which of the following cytokines released by Tregs is involved in suppression of immune response?
- a. BAFF
 - b. INF- γ
 - c. TGF- β
 - d. TNF
10. Which of the following is true regarding negative selection of T cells in the thymus:
- a. Expression of the AIRE gene by T cells leads to negative selection
 - b. Low-affinity binding to self-antigens leads to negative selection of T cells
 - c. Negative selection occurs in double negative T cells
 - d. T cells that recognize antigens with high affinity undergo negative selection

Answers

1. B, page 320.

CTLA-4 is an inhibitory receptor in the same family as CD28. Both CD28 and CTLA-4 on T cells bind B7 molecules on antigen-presenting cells, but CTLA-4 has a higher affinity for B7. Engagement of CTLA-4 by B7 inhibits the activation of naïve T cells.

2. B, page 323.

T regulatory cells are members of the T helper cell lineage, and are thus CD4+. Tregs depend on IL-2 for development and survival, and therefore express high levels of CD25, which is the IL-2 receptor alpha chain. Tregs express the FOXP3 transcription factor, which is necessary for their function. CD127 is the IL-7 receptor, and this is expressed only in low levels on Tregs, which do not use IL-7 as a growth factor.

3. B, page 322.

Mutations in the FOXP3 gene lead to development of IPEX and deficient Treg cells. AIRE mutations lead to autoimmune polyendocrine syndrome type I (APS1), and the IFNGR1 gene leads to susceptibility to mycobacterial and salmonella infections. The WAS gene is mutated in Wiskott Aldrich Syndrome, which is also X-linked and can present with eczematous dermatitis.

4. A, page 323.

IL-2 is the major growth factor for regulatory T cells, while IL-7 is the major growth factor for naïve and memory T cells. IL-12 is involved in T_H1 differentiation, among other things. IL-17 is a product of T_H17 cells that contributes to mucosal immunity and defense against fungal and bacterial organisms.

5. B, page 325.

When T lymphocytes recognize self-antigens, apoptosis pathways may be triggered via the intrinsic mitochondrial pathway or by the extrinsic death receptor pathway. Bcl-2 serves as a regulator or inhibitor of this pathway, but the pathway is activated when cell stress activates Bim, which binds Bax and Bak. The resulting oligomer inserts into the mitochondrial membrane, allowing mitochondrial proteins to leak into the cytoplasm, triggering caspase-9 and other caspases that lead to cell death.

6. D, page 326.

Fas and FasL are involved in the death receptor pathway of apoptosis, and are upregulated when mature self-reactive T cells are repeatedly stimulated by antigen binding. Bcl-2 is involved in the mitochondrial pathway of apoptosis. CD28 is a costimulatory molecule on T cells that binds B7 on APCs, leading to T cell activation. CD127 is the IL-7 receptor.

7. D, page 327.

Unlike T cells, recognition of self-antigen by B cells can trigger the reactivation of RAG1 and RAG2, allowing for receptor editing. Self-reactive B and T cells are capable of anergy or deletion by apoptosis with self-antigen recognition.

8. C, pages 332-333, Table 15-3.

Polymorphisms in NOD2 can lead to ineffective defense against intestinal microbes, and are associated with Crohn's disease. CTLA-4 polymorphisms can be seen in Type 1 diabetes and rheumatoid arthritis, among other autoimmune diseases. IL2RA polymorphisms can be associated with multiple sclerosis and Type 1 diabetes, while PTPN22 is associated with rheumatoid arthritis, Type 1 diabetes, and others.

9. C, pages 323-324.

TGF- β , as well as IL-10, is produced by Tregs and acts on many different immune cells to suppress immune responses. BAFF is a B cell growth factor. IFN- γ has many roles in the immune response, including macrophage activation and T_H1 differentiation. TNF is produced by activated macrophages and lymphocytes and is a major mediator of septic shock.

10. D, pages 317-318.

Negative selection in the thymus occurs for double positive T cells in the cortex, and single positive T cells in the medulla. AIRE is expressed by thymic medullary cells (TMECs), and controls expression of peripheral tissue antigens in the thymus. T cell receptor binding to self-antigen with high affinity results in deletion, or negative selection, while binding with low affinity may lead to development of T regulatory cells.



FIT Board Review Corner – February 2016

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Review Questions

Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition

By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 16 (pages 343-354): Immunity to Microbes

Prepared by Lorraine Anderson, MD, VA Greater Los Angeles Healthcare System (California)

1. The principal cytokine mediators of septic shock are:
 - a. TNF, IL6, IL1
 - b. IFN γ , IL12, IL4
 - c. TNF, IL12, IL3
 - d. IL6, IL4, IL1

2. _____ is a sequel to _____ infection with some serologic types of β hemolytic streptococci. This is due to production of antibodies against the bacterial cell wall protein (_____), which cross reacts with _____ and cause inflammation.
 - a. Scarlet fever, skin/throat, S protein, skin proteins
 - b. Rheumatic fever, skin/throat, M protein, myocardial proteins
 - c. Scarlet fever, pharyngeal, S protein, myocardial proteins
 - d. Rheumatic fever, pharyngeal, M protein, myocardial proteins

3. Capsules of many pathogenic gram-positive and gram-negative bacteria contain _____ residues that inhibit complement activation by the alternative pathway.
 - a. LPS
 - b. Mannose
 - c. Sialic acid
 - d. Peptidoglycan

4. IL2 and IFNy are important in immunity. Individuals with inherited mutations in receptors for IFNy or IL12 are highly susceptible to what kinds of infections?
 - a. Fungi
 - b. Atypical mycobacteria
 - c. Viruses
 - d. Protozoa

5. The principal mechanism of innate immunity against viruses are:
 - a. Inhibition of infection by type 1 interferons and CTLs
 - b. Inhibition of infection by type 1 interferons and NK cell mediated killing of infected cells

- c. CTLs and NK cell mediated killing of infected cells
 - d. NK cell mediated killing of infected cells and neutralizing antibodies
6. What is the signal for NK cells to kill a virally infected cell?
- a. MHC I expression
 - b. Lack of MHC I expression
 - c. Recognition of viral RNA and DNA by endosomal TLRs
 - d. Activation of cytoplasmic RIG like receptors by viral RNA
7. In the adaptive immune response the elimination of viruses that live within cells is mediated by:
- a. CTLs that recognize cytosolic viral peptides presented on MHC I molecules
 - b. High affinity antibodies produced in T -dependent germinal center reactions
 - c. Complement activation and phagocytosis
 - d. Neutralizing antibodies
8. Which virus evades the immune system by blockade of TAP transporter?
- a. HSV
 - b. CMV
 - c. HIV
 - d. EBV
9. The adaptive immune response to protozoa that survive within macrophages is:
- a. Antibody dependent cytotoxicity
 - b. Phagocytosis
 - c. Cytotoxic T cells
 - d. Cell mediated immunity
10. The adaptive immune response to helminthic infection is mediated by:
- a. Macrophage activation by Th1 cell derived cytokines
 - b. Activation of Th2 cells ,production of IgE antibodies and activation of eosinophils
 - c. CTLs
 - d. Complement
11. The most effective vaccines:
- a. Stimulate the production of high affinity antibodies and memory B cells
 - b. Utilize a killed form of an infectious agent
 - c. Utilize an attenuated form of an infectious agent
 - d. Are DNA vaccines

Answers

1. A, page 343.

TNF, IL6 and IL1 are the principal cytokine mediators of septic shock but IFNy and IL12 may also contribute.

2. D, page 343.

Rheumatic fever is a sequel to pharyngeal infection with some serologic types of β hemolytic streptococci. This is due to production of antibodies against the bacterial cell wall protein (M protein), which cross reacts with myocardial proteins and are deposited in the heart and subsequently cause inflammation (carditis). Post streptococcal glomerulonephritis is a sequel to infection of skin or throat with other serotypes of β hemolytic streptococci.

3. Page 344.

Capsules of many pathogenic gram-positive and gram-negative bacteria contain sialic acid residues that inhibit complement activation by the alternative pathway.

4. Page 345.

Individuals with inherited mutations in receptors for IFN γ or IL12 are highly susceptible to infections with atypical mycobacteria. Proper IFN γ and IL12 signaling is required to activate phagocytes (macrophages) to clear intracellular pathogens such as mycobacteria.

5. Page 348.

The principal mechanism of innate immunity against viruses are inhibition of infection by type 1 interferons and NK cell mediated killing of infected cells.

6. B, page 348.

Lack of MHC1 expression. Virally infected cells shut off class I MHC expression as an escape mechanism from CTLs. This enables NK cells to kill the infected cell because the absence of class 1 releases NK cells from a normal state of inhibition.

7. A, page 349, Figure 16-7.

In the adaptive immune response the elimination of viruses that live within cells is mediated by CTLs which kill the infected cell. Antibodies and complement lead to opsonization, phagocytosis, direct lysis of the viruses with lipid envelopes; all of which is effective only during the extracellular stage.

8. A

- a. HSV- blockade of TAP transporter
- b. CMV- removal of class 1 molecule from ER, production of cytokine receptor homologues
- c. HIV- recruitment of factor H, inhibition of complement, incorporation of CD59 in viral envelope, inhibition of RIG1 RNA sensor, inhibition of PKR (signaling by INF receptor), antigenic variation
- d. EBV-production of immunosuppressive cytokine IL10

9. Page 353.

The principal defense mechanism against protozoa that survive within macrophages is cell mediated immunity, particularly macrophage activation by TH1 cell derived cytokines.

10. Page 353.

Defense in helminthic infections is mediated by activation of Th2 cells, production of IgE antibodies and activation of eosinophils.

11. Page 354

The most effective vaccines are those that stimulate the development of long-lived plasma cells that produce high affinity antibodies as well as memory B cells.



FIT Board Review Corner – March 2016

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Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition
By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 17 (pages 359-369): Transplantation Immunology

Prepared by Kristen Dazy, MD, Scripps Clinic Medical Group, San Diego (California)

1. Which term best describes the type of graft which is transplanted between individuals of different species?
 - a. Autologous graft
 - b. Syngeneic graft
 - c. Allogenic graft
 - d. Xenogeneic graft

2. What is the primary molecule responsible for the strong rejection reaction seen in allogenic transplants?
 - a. Major histocompatibility complex (MHC)
 - b. Minor histocompatibility antigens
 - c. Natural killer cells
 - d. Host T cell receptor

3. Allogenic MHC molecules of a graft can be presented for recognition by the recipient's T cells in two fundamentally different ways. Which of the following terms describes the process in which T cells of a graft recipient recognize intact, unprocessed MHC molecules in the graft?
 - a. Transferred recognition
 - b. Direct recognition
 - c. Indirect recognition
 - d. Uptake recognition

4. Indirect presentation of an alloantigen largely results in recognition by CD4+ T cells because the antigen is acquired by host APCs primarily through the endosomal vesicular pathway and is therefore presented by class II MHC molecules. Some antigens of phagocytosed graft cells appear to enter the class I MHC pathway of antigen presentation and are indirectly recognized by CD8+ T cells. Which of the following terms best describes this phenomenon of activation of CD8+ T lymphocytes?
 - a. Autophagy
 - b. Cross-trafficking
 - c. Cross-presentation

- d. Cross-immunity
5. Where does the majority of the activation of alloreactive T lymphocytes take place?
- a. Donor graft
 - b. Donor lymphatic vessels
 - c. Recipient lymph nodes
 - d. Spleen
6. Which of the following molecules is found on APCs and serves as a costimulator of alloreactive T cells?
- a. B5
 - b. B6
 - c. B7
 - d. B8
7. What is the name of the test that has been used clinically in the past to predict T cell-mediated graft rejection?
- a. Mixed lymphocyte reaction
 - b. Graft versus host reaction
 - c. Transplantation test
 - d. Agglutination test
8. What is the primary mechanism of graft rejection once alloreactive T cells are stimulated via the indirect pathway?
- a. Cytotoxic T lymphocyte-mediated killing of graft cells
 - b. Cytokine-mediated inflammation
 - c. Antibody-mediated inflammation
 - d. Immune complex-mediated inflammation
9. Hyperacute rejection begins within minutes to hours after transplantation and is mediated by which of the following mechanisms?
- a. T lymphocyte-mediated killing of graft parenchymal cells
 - b. Fibroblast occlusion of blood vessels
 - c. Immune complex deposition
 - d. Preexisting antibodies to donor endothelial antigens
10. Which of the following is an example of hyperacute rejection?
- a. ABO blood group incompatibility
 - b. HLA mismatch
 - c. Graft vs. host disease
 - d. Transfusion-related acute lung injury

Answers

1. D, page 360.

A graft transplanted between individuals of different species is called a *xenogeneic* graft (or *xenograft*) and the molecules that are recognized as foreign on *xenografts* are called *xenoantigens*. The other answers described other types of transplanted grafts between the same individual (*autologous*), between two genetically identical individuals (*syngeneic*), and between two genetically different individuals of the same species (*allogenic*).

2. A, pages 362-363.

Transplants of most tissues between any pair of individuals, except identical twins, will be rejected because MHC molecules are so polymorphic that no two individuals inherit the same ones. The role of MHC molecules as the antigens that cause graft rejection is a consequence of the nature of T cell antigen recognition. Minor histocompatibility antigens typically induce weaker or slower rejection reactions than do MHC molecules but their relevance in clinical solid organ transplantation is uncertain.

3. B, pages 363-364.

In the case of direct recognition, intact MHC molecules displayed by cells in the graft are recognized by recipient T cells without a need for processing by host antigen presenting cells (APCs). A likely explanation is that T cell receptors (TCRs) have an inherent specificity for MHC molecules regardless of whether they are self or foreign. In the case of indirect recognition, allogenic MHC molecules from graft cells are taken up and processed by recipient APCs and peptide fragments of these allogenic MHC molecules are bound and presented by self MHC molecules.

4. C, page 365.

This phenomenon is an example of cross-presentation or cross priming (see also Fig. 6-20), in which dendritic cells ingest antigens of another cell (i.e. the graft), and present these antigens on class I MHC molecules to activate (prime) CD8+ T lymphocytes.

5. C, page 365.

It is believed that donor APCs migrate to regional recipient lymph nodes and present unprocessed allogenic MHC molecules to the recipient's T cells (direct pathway). Host dendritic cells may also migrate into the graft, pick up graft alloantigens, and transport these back to the draining lymph nodes where they are displayed (indirect pathway). The connection between lymphatic vessel in allografts and the recipient's lymph nodes is not made surgically and is likely established by growth of new lymphatic channels in response to inflammatory stimuli produced during grafting.

6. C, page 365.

In addition to recognition of alloantigen, costimulation of T cells primary by B7 molecules on APCs is important for activation alloreactive T cells. Blocking this costimulation may therefore serve as a therapeutic strategy to inhibit graft rejection.

7. A, pages 366-367.

The response to alloreactive T cells to foreign MHC molecules can be analyzed in an *in vitro* reaction called the mixed lymphocyte reaction (MLR). The MLR was previously used clinically as a predictive test of T cell-mediated graft rejection, and as an *in vitro* model of graft rejection. Studies of the MLR were among the first to establish the role of class I and class II MHC molecules in activating distinct populations of T cells.

8. B, pages 367-368

Only CTLs that are generated by direct allorecognition can kill graft cells, whereas both CTLs and helper T cells generated by either direct or indirect alloantigen recognition can cause cytokine-mediated damage to grafts. CLTs that are generated by the indirect pathway are self MHC restricted and will not be able to kill the foreign graft cells because these cells do not express self MHC allogenic peptides. Therefore, when T cells are stimulated by the indirect pathway, the principle mechanism of rejection is not CTL-mediated killing of graft cells but inflammation caused by the cytokines produced by the effector T cells.

9. D, pages 368-369.

Hyperacute rejection is characterized by thrombotic occlusion of the graft vasculature and is mediated by preformed antibodies in the host circulation that binds to donor endothelial antigens and activates complement which then promotes a number of changes within the graft endothelium to promote intravascular thrombosis.

10. A, pages 368-369.

The best known example of hyperacute rejection due to preexisting alloantibodies are those directed against the ABO blood group antigens expressed on red blood cells. This is seen in hemolytic disease of the newborn when the fetus has type A or B blood and is born to a mother with type O blood. Maternal alloantibodies directed against A and B antigens cross the placenta and result in direct hemolysis of the newborn's red blood cells.

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Chapter 17 (pages 370-380): Transplantation Immunology

Prepared by Erin Kempe, MD, Nationwide Children's Hospital, Columbus (Ohio), and Kara Wada, MD, Nationwide Children's Hospital, Columbus (Ohio)

1. Histologic examination of a kidney allograft undergoing acute rejection would exhibit which of the following:
 - a. CD4+ T cells
 - b. Neutrophil infiltration
 - c. Smooth muscle cell proliferation in blood vessels
 - d. Thrombotic occlusion of graft vasculature
2. Matching which HLA type is most important for predicting the survival of kidney allografts?
 - a. HLA-A
 - b. HLA-C
 - c. HLA- DP
 - d. HLA- DQ
3. Hyperacute rejection of allografts is mediated by incompatibility of which antigen class?
 - a. ABO blood group antigens
 - b. HLA-A alleles
 - c. HLA-DQ alleles
 - d. RH antigens
4. Calcineurin inhibitors can be effective immunosuppressive medications for the prevention of graft rejection through which of the following mechanisms:
 - a. Accumulation of metabolic toxins that kill lymphocytes
 - b. Inhibition of mTOR
 - c. Inhibition of NFAT activation
 - d. Upregulation of IL-2 transcription
5. Individuals with the Bombay blood group lack which of the following antigens?
 - a. H antigen
 - b. O antigen
 - c. Rh antigen
 - d. Sialyl Lewis X
6. Acute transplant rejection can be treated by various modalities. Which treatment and mechanism are paired correctly?
 - a. Anti-thymocyte globulin – depletes circulating T cells by activating complement or opsonizing for phagocytosis
 - b. Anti-CD25 antibodies – bind to the IL-2 receptor and stimulate IL-2 signaling
 - c. Anti-CD52 antibodies – deletes central B cell populations
 - d. CTLA4-Ig – binds to CD28 on T cells preventing their interaction with APCs.

7. Which statement is most true about allograft rejection?
 - a. Chronic rejection is always preceded by episodes of acute rejection.
 - b. Arterial occlusion due to smooth muscle cell proliferation is dominant lesion in acute rejection.
 - c. Acute rejection is managed by rapidly intensifying the immunosuppressive regimen and is more reversible than chronic rejection.
 - d. Chronic rejection is characterized by Cd deposition in the vessels.
8. Which immunosuppressant drug inhibits growth factor mediated T cell proliferation by binding to FKBP and inhibits mTOR?
 - a. Tacrolimus
 - b. Sirolimus
 - c. Mycophenolate mofetil
 - d. Azathioprine
9. Graft versus host disease a serious and known complication of hematopoietic stem cell transplant and characterized by:
 - a. Grafted T cells recognizing host alloantigens.
 - b. A lack of involvement by NK cells
 - c. A reaction against major histocompatibility antigens
 - d. A minor cause of mortality among bone marrow transplant recipients
10. A first-time mother comes into your practice. She is worried because she is Rhesus antigen negative and read about erythroblastosis fetalis. What should you tell her?
 - a. If the baby's father is Rhesus antigen negative she will still need an anti-RhD antibody injection.
 - b. She should be concerned about the development of erythroblastosis fetalis with her current pregnancy.
 - c. Erythroblastosis fetalis is mediated by IgM antibodies.
 - d. Erythroblastosis fetalis can be prevented by administration of an anti-RhD antibody injection within 72 hours of birth for the first Rh positive baby.

Answers

1. A, page 370, Figure 17.9.

Acute rejection can be cell-mediated through alloreactive CD4+ T cells, or antibody-mediated through the effects of alloantibodies binding to alloantigens on vascular endothelial cells. Hyperacute rejection is mediated by pre-formed alloantibodies binding to endothelial antigens resulting in thrombotic occlusion of the vasculature. Neutrophilic infiltration can sometimes be seen. Chronic rejection is mediated by intimal smooth muscle cell proliferation and fibrosis.

2. A, page 371.

Matching HLA-A, HLA-B, and HLA-DR are most important for kidney allograft survival.

3. A, page 371.

Hyperacute rejection occurs due to incompatible ABO blood group antigens, and is performed for most types of transplantation. HLA typing is done for grafts that can survive outside the donor for longer periods of time, such as in renal transplantation, and can help improve graft survival. Rh typing is important in prevention of erythroblastosis fetalis.

4. C, pages 372-373, Figure 17.11.

Calcineurin inhibitors such as cyclosporine and tacrolimus, block IL-2 dependent proliferation of T cells by preventing calcineurin activation of NFAT. Rapamycin exerts a similar effect by inhibiting mTOR which is required for transcription of other proteins important for cell survival and proliferation. Immunosuppressants like mycophenolate mofetil and azathioprine exert their effects through production of toxic antimetabolites.

5. A, pages 377-378.

The Bombay blood group occurs in patients who are unable to produce A, B, and H blood group antigens. This phenotype is seen in patients with LAD type 2.

6. A, page 374.

ATG depletes circulating T cells, anti-CD25 binds to the IL-2R and blocks IL-2 signaling, anti-CD52 depletes peripheral T and B cells. CTLA4 antibody binds to B7 on APCs preventing them from interacting with CD28 on T cells.

7. C, pages 370-375.

Chronic rejection develops insidiously during months or years and may or may not be preceded by episodes of acute rejection. Arterial occlusion due to smooth muscle cell proliferation is dominant lesion in chronic rejection. Acute antibody mediated rejection is characterized by C4d deposition.

8. B, Figure 17-11.

Sirolimus (rapamycin) inhibits growth factor mediated T cell proliferation by binding to FKBP. FKBP then binds to and inhibits mTOR thus blocking proliferation.

9. A, pages 379-380.

GVHD is characterized by grafted T cells recognizing and damaging host alloantigens. NK cells are thought to play an important role in acute GVHD. The reactions occur against the minor histocompatibility antigens and GVHD is the principal cause of mortality among BMT recipients.

10. D, page 379.

Erythroblastosis fetalis is a potentially lethal condition that occurs when Rh negative mothers become sensitized to Rhesus factor by an Rh positive baby typically at that time of delivery. Subsequent Rh positive babies can then develop RBC destruction via anti-Rh antigen IgG antibodies that cross the placenta. This is prevented by administration of an anti-RhD antibody injection within 72 hours of birth for the first Rh positive baby.



FIT Board Review Corner – April 2016

Welcome to the FIT Board Review Corner, prepared by Sarah Spiet, DO, and Tammy Peng, MD, senior and junior representatives of ACAAI's Fellows-In-Training (FITs) to the Board of Regents. The FIT Board Review Corner is an opportunity to help hone your Board preparedness.

Review Questions

Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition
By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 18 (pages 383-3697): Immunity to Tumors

Prepared by Kate Ruda Wessell, MD, HealthSpan, Cleveland Heights (Ohio)

1. As confirmed by transplantation experiments where mice that have been resected of a tumor are re-transplanted with the tumor cells and no tumor growth occurs, the most effective response against naturally arising tumors appears to be mediated mainly by:
 - a. T lymphocytes
 - b. B lymphocytes
 - c. NK cells
 - d. Macrophages
2. Tumor antigens that are expressed on both tumor cells and normal cells are called:
 - a. Tumor-specific antigens
 - b. Tumor-associated antigens
 - c. Tumor-regulator antigens
 - d. Primary Tumor-specific antigens
3. The products of oncogenic viruses function as tumor antigens and elicit specific T cell responses that may serve to eradicate tumors. This knowledge led to the development of vaccines against oncogenic viruses. The classic example of a commercially available vaccine against a DNA virus with this purpose is:
 - a. Vaccine against EBV associated B cell lymphoma
 - b. Vaccine against HHV-8 associated with Kaposi sarcoma
 - c. Vaccine against HPV associated carcinomas of the uterine cervix and oropharynx
 - d. Vaccine against HTLV-1 associated with adult T cell leukemia/lymphoma
4. Helper T cells specific for tumor antigens secrete cytokines that are important for mediating immune response to tumors. _____ is a cytokine secreted by Helper T cells that can increase tumor cell class I MHC expression and sensitivity to lysis by CTLs, and may also activate macrophages to kill tumor cells.
 - a. IFN-gamma
 - b. TNF-alpha
 - c. TNF-beta
 - d. GM-CSF

5. The main mechanisms by which tumor cells escape immune defenses is by failure to produce tumor antigen, mutations in MHC genes or genes needed for antigen processing, and by:
 - a. Secretion of immunosuppressive proteins
 - b. Expression of inhibitory cell surface proteins
 - c. Both a and b
 - d. None of the above
6. Myeloid-derived suppressor cells (MDSCs) are immature myeloid precursors that are recruited from the bone marrow that suppress anti-tumor innate and T cell responses. They do so by secreting:
 - a. IL-10
 - b. IL-4
 - c. IL-13
 - d. IL-35
7. Blocking inhibitory pathways to promote tumor immunity has emerged as method of effective enhancement of the patients' immune response to their tumor. The approach of stimulating immune responses by removing inhibition is called:
 - a. Checkpoint activation
 - b. Checkpoint regression
 - c. Checkpoint signaling
 - d. Checkpoint blockade
8. The largest clinical experience with augmenting host immunity to tumors using cytokines to boost host responses to tumors is with:
 - a. IFN-alpha
 - b. TNF
 - c. IL-2
 - d. IFN-gamma
9. Adoptive therapy using T cells expressing chimeric antigen receptors (CARs) has been successful in treatment of hematologic malignancies. The steps of the procedure to create CAR-expressing T cells therapy in order are:
 - a. Expanding T cell transfected with the CAR gene with TNF-alpha, then isolating lymphocytes from the blood or tumor for ex-vivo killing then transfer back T cells to the patient
 - b. Expanding T cell transfected with the CAR gene with IL-2, then isolating lymphocytes from blood or tumor for ex-vivo killing, then transfer back T cells to the patient
 - c. Isolating lymphocytes from blood or tumor infiltrate, then expanding the cells in culture with TNF-alpha and transfecting with the CAR gene, then transfer back the T cells to the patient
 - d. Isolating lymphocytes from blood or tumor infiltrate, then expanding the cells in culture with IL-2 and transfecting with the CAR gene, then transfer back the T cells to the patient

10. Many variations of anti-tumor antibodies have been created to improve their effectiveness.

Tumor-specific antibodies may be coupled to toxic molecules, radioisotopes, and anti-tumor drugs to promote the delivery of the cytotoxic agents to the tumor. Toxins that are carried to tumors attached to anti-tumor antibodies are called:

- a. Immunotoxins
- b. Anti-toxins
- c. Immuno-regulators
- d. Immuno-variant toxins

Answers

1. A, page 385.

The most effective response against naturally arising tumors appears to be mediated mainly by T lymphocytes. The tumor is also rejected in normal mice that are given adoptive transfer of T lymphocytes from the original tumor-bearing animal.

2. B, page 385.

Antigens that are expressed on tumor cells but not on normal cells are called tumor-specific antigens. Antigens that are expressed on both tumor cells and normal cells are called tumor-associated antigens.

3. C, page 387.

The HPV vaccine is the only commercially available vaccine among the answers. Answers A and B are both correct DNA viruses associated with corresponding tumors, but without vaccine availability. Answer D is the correct RNA virus associated with the corresponding tumor. HTLV-1 is the only well-defined human retrovirus that is known to cause tumors.

4. A, page 389.

IFN-gamma and TNF can increase tumor cell class I MHC expression and sensitivity to lysis by CTLs. IFN-gamma may also activate macrophages to kill tumor cells. There is an increased incidence of tumors in knockout mice lacking the IFN-gamma cytokine, its receptor, or components of its signaling cascade.

5. C, page 390, Figure 18-3.

Tumor cells may evade immune responses by losing expression of antigens or MHC molecules or by producing ligands for T cell inhibitory receptors and immunosuppressive cytokines.

6. A, page 391.

All of the above are examples of anti-inflammatory cytokines, but MDSCs specifically suppress innate immune response by secreting IL-10, which inhibits various inflammatory functions of activated macrophages and dendritic cells.

7. D, page 392.

Tumor cells exploit various normal pathways of immune regulation or tolerance to evade host immune response. Because the inhibitors establish checkpoints in immune responses, the approach of stimulating host immune response by removing inhibition is called checkpoint blockade.

8. C, page 393.

Cell-mediated immunity to tumors can theoretically be enhanced by treating tumor-bearing patients with cytokines that stimulate the proliferation and differentiation of T lymphocytes and NK cells. The largest clinical experience with this technique is with high dose IL-2 administered IV. IFN-alpha is approved for malignant melanoma and carcinoid tumors. TNF and IFN-gamma are effective in animal models.

9. D, page 394 Figure 18-6.

Lymphocytes isolated from the blood or tumor infiltrate of a patient may be expanded by culture in IL-2 and infused back into the patient.

10. A, page 395.

Toxins such as ricin and diphtheria toxin are potent inhibitors of protein synthesis and can be effective at extremely low doses if they are carried to tumors attached to anti-tumor antibodies; such conjugates are called immunotoxins.



FIT Board Review Corner – May 2016

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Review Questions

Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition
By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 19 (pages 399-415): Hypersensitivity Disorders

Prepared by Malika Gupta, MD, Children's Hospital of Philadelphia, (Philadelphia)

1. What determines the pathological features of immune complex disease?
 - a. Source of the antigen
 - b. Type of antibody
 - c. Site of deposition of the immune complex
 - d. Age of the patient
2. The amount of immune complex deposition in the tissues is determined by all of the following except?
 - a. Nature of the complexes
 - b. Characteristics of the blood vessels
 - c. Size of the immune complex
 - d. Age of the patient
3. What is the target antigen in Goodpasture's Syndrome?
 - a. Streptococcal cell wall antigen
 - b. Non collagenous NC1 protein of the basement membrane in glomeruli
 - c. Acetylcholine receptor
 - d. Intrinsic factor of gastric parietal cells
4. Multiple sclerosis is a T cell mediated disease. The pathogenic T cells in this disease are specific for which of the following?
 - a. Collagen
 - b. Protein antigens in myelin
 - c. Unknown skin antigens
 - d. Antigens of pancreatic islet β cells
5. Which is true about delayed type hypersensitivity (DTH) reactions?
 - a. About 4 hours after the antigen is injected in a sensitized individual, there is an accumulation of eosinophils at the injection site
 - b. By 12 hours, the injection site becomes infiltrated by Both a and b
 - c. Induration is first noticed about 48 hours later

- d. Loss of DTH responses to universally encountered antigens is an indication of deficient T cell function

6. Antagonist of which of the following cytokines reduces survival of B lymphocytes with treatment potential in SLE?
 - a. IL-4
 - b. IL-6
 - c. IL-17
 - d. BAFF

7. Genetic deficiencies of which complement members are most frequently associated with SLE?
 - a. C1q, C2, and C4
 - b. C3, C5, C6
 - c. C6, C7
 - d. C7, C9

8. Susceptibility to rheumatoid arthritis is linked to which HLA haplotype?
 - a. HLA-A
 - b. HLA-B
 - c. HLA-DP
 - d. HLA-DR4

9. Which are the most frequent haplotypes associated with diabetes mellitus 1 in Caucasians?
 - a. HLA DR3 and HLA DR4
 - b. HLA-A and HLA-B
 - c. HLA-DP and HLA-DQ
 - d. HLA-A and HLA-DP

10. What is the target antigen in pemphigus vulgaris?
 - a. IgG basement membrane zone
 - b. Proteins in intercellular junctions of epidermal cells
 - c. Type VII collagen
 - d. Endomysial IgA

Answers

1. C, page 403.

“The pathologic features of diseases caused by immune complexes reflect the site of immune complex deposition and are not determined by the cellular source of the antigen. Therefore, immune complex–mediated diseases tend to be systemic and affect multiple tissues and organs, although some are particularly susceptible, such as kidneys and joints.”

2. D, page 405.

“Antigen-antibody complexes are produced during normal immune responses, but they cause disease only when they are produced in excessive amounts, are not efficiently cleared, and become

deposited in tissues. Small complexes are often not phagocytosed and tend to be deposited in vessels more than large complexes, which are usually cleared by phagocytes. Complexes containing cationic antigens bind avidly to negatively charged components of the basement membranes of blood vessels and kidney glomeruli. Such complexes typically produce severe and long-lasting tissue injury. Capillaries in the renal glomeruli and synovia are sites where plasma is ultrafiltered (to form urine and synovial fluid, respectively) by passing through specialized basement membranes, and these locations are among the most common sites of immune complex deposition. However, immune complexes may be deposited in small vessels in virtually any tissue.”

3. B, page 403, Table 19-2.

The target antigen in Goodpasture’s Syndrome is non collagenous NC1 protein of the basement membrane in glomeruli and lung. Streptococcal cell wall antigen is the target antigen for acute rheumatic fever, acetylcholine receptor for myasthenia gravis, and intrinsic factor of gastric parietal cells is the target antigen for pernicious anemia.

4. B, page 407, Table 19-4.

In multiple sclerosis, the specificity of the pathogenic T cells is towards protein antigens in myelin (myelin basic protein). Collagen is targeted by T cells in rheumatoid arthritis, unknown skin antigens in psoriasis and pancreatic islet β cells in type 1 diabetes mellitus

5. D, page 407.

“About 4 hours after the antigen is injected in a sensitized individual, there is an accumulation of neutrophils around the post-capillary venules at the injection site. By about 12 hours, the injection site becomes infiltrated by T cells and blood monocytes. The endothelial cells lining these venules become plump, and become leaky to plasma macromolecules. Fibrinogen escapes from the blood vessels into the surrounding tissues, where it is converted into fibrin. The deposition of fibrin, edema, and the accumulation of T cells and monocytes within the extracellular tissue space around the injection site cause the tissue to swell and become firm (indurated). Induration is detected by about 18 hours after the injection of antigen and is maximal by 24 to 48 hours. In clinical practice, loss of DTH responses to universally encountered antigens (e.g., Candida antigens) is an indication of deficient T cell function, a condition known as anergy.”

6. D, page 410 & 412, Table 19-5.

“An antibody that blocks the B cell growth factor BAFF is now approved for the treatment of SLE.”

7. A, page 411.

“Genetic deficiencies of classical pathway complement proteins, especially C1q, C2, or C4, are seen in about 5% of patients with SLE.”

8. D, page 413.

“Susceptibility to RA is linked to the HLA-DR4 haplotype.”

9. A, page 415

“Between 90% and 95% of Caucasians with type 1 diabetes have HLA-DR3, or DR4, or both, in contrast to about 40% of normal subjects, and 40% to 50% of patients are DR3/DR4 heterozygotes, in contrast to 5% of normal subjects.”

10. B, page 403, Table 19-2.

Proteins in intercellular junctions of epidermal cells (desmoglein) are the target antigens for pemphigus vulgaris. IgG basement membrane zone is the target antigen for bullous pemphigoid. Type VII collagen is the antigen for epidermolysis bullosa acquisita, and endomysial IgA is the target in dermatitis herpetiformis.



FIT Board Review Corner – June 2016

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Review Questions

Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition
By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 20 (pages 417-430): Allergy

Prepared by Sarah Spiet, DO, Walter Reed National Military Medical Center, (Maryland)

1. The late-phase reaction is characterized by the accumulation of macrophages, eosinophils and what other type of cell?
 - a. Neutrophils
 - b. Basophils
 - c. B cells
 - d. CD8+ T cells
2. The Fc ϵ R1 molecule on mast cells is composed of:
 - a. one α chain, one β chain, one γ chain
 - b. one α chain, two β chains, one γ chain
 - c. one α chain, one β chain, two γ chains
 - d. one α chain, two β chains, two γ chains
3. Signaling in eosinophils is mediated by which of the following?
 - a. α chain
 - b. β chain
 - c. γ chain
 - d. ζ chain
4. Which of the following receptors contains an immunoreceptor tyrosine-based inhibition motif (ITIM)?
 - a. Fc γ RI
 - b. Fc γ RIIA
 - c. Fc γ RIIB
 - d. FcRN
5. What is the major arachidonic acid-derived mediator produced by the cyclooxygenase pathway in mast cells?
 - a. PGD₂
 - b. SRS-A

- c. LTB₄
 - d. PAF
6. Which of the following cytokines may be pre-formed in mast cells and stored in granules for rapid release upon FcεRI cross-linking?
- a. IL-3
 - b. IL-5
 - c. GM-CSF
 - d. TNF
7. Which of the following is the correct chemokine and chemokine receptor pair involved in eosinophil recruitment?
- a. CCL9 : CCR3
 - b. CCL11 : CCR3
 - c. CCL17 : CCR4
 - d. CCL26 : CC4
8. Which of the following cytokines produced by mast cells and basophils promotes IgE production?
- a. TGF-β
 - b. IL-7
 - c. IL-13
 - d. RANTES
9. Which Mutations in which of the following genes have been associated with mastocytosis in humans?
- a. c-kit
 - b. ORMDL
 - c. PHF11
 - d. FcεI β chain
10. Which of the following are required for mast cell activation?
- a. Fyn, Lyn, Syk, LAT
 - b. Lck, Fyn, Zap-70, LAT
 - c. Fyn, Lyn, Syk, Igα
 - d. Fyn, Lyn, Zap-70, Igα

Answers

1. A, page 417.

The term immediate hypersensitivity is commonly used to describe the combined immediate and late-phase reactions. The late-phase reaction is the slowly developing inflammatory component characterized by the accumulation of neutrophils, eosinophils and macrophages.

2. C, page 422.

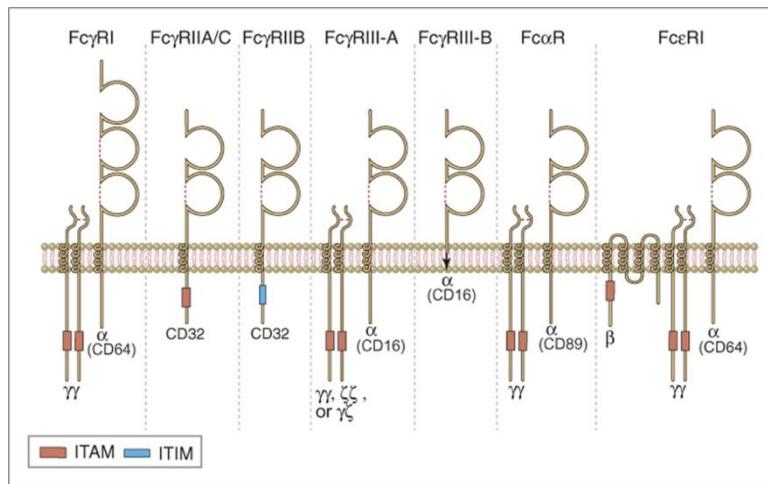
Mast cells and basophils express a high-affinity Fc receptor specific for ε heavy chains, called FcεR1, which binds IgE. Each FcεR1, molecule is composed of a n α chain that binds the Fc region of IgE and a β chain and two γ chains that are responsible for signaling.

3. C, page 422.

The FcεR1 on eosinophils and several other cell types lack the β chain, so signaling is mediated only by the γ chain in these cells.

4. C, page 425.

Mast cell activation through the FcεRI pathway is regulated by various inhibitory receptors which contain an ITIM within their cytoplasmic tails. One such inhibitory receptor is FcγRIIB, which coaggregates with FcεRI during mast cell activation. FcγRI and FcγRIIA contain ITAMS. The neonatal Fc receptor (FcRN) contains neither. See page 270 to review the structure of these receptors further.



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5. A, page 427.

Mast cell activation results in rapid de novo synthesis and release of lipid mediators that have a variety of effects on blood vessels, bronchial smooth muscle and leukocytes. The most important of these mediators are derived from arachidonic acid. Arachidonic acid is metabolized by either the cyclooxygenase (COX) or lipoxygenase (LO) pathways to produce mediators of allergic reactions.

Prostaglandin D₂ (PGD₂) is the major arachidonic acid-derived mediator produced by the COX pathway in mast cells.

Leukotrienes are produced by the LO pathway. Collectively, LTC4, LTD4, and LTE4 constitute what was once called the slow-reacting substance of anaphylaxis (SRS-A). Leukotriene B4 is a pro-inflammatory mediator synthesized in myeloid cells from arachidonic acid. Synthesis is catalyzed by 5-lipoxygenase and leukotriene A4 hydrolase and is increased by inflammatory mediators. Platelet activating factor (PAF) is synthesized by acylation of a derivative of PLA2-mediated hydrolysis of membrane phospholipids.

6. D, page 427.

Mast cells produce many different cytokines that contribute to allergic inflammation (the late-phase reaction). These cytokines include TNF, IL-1, IL-4, IL-5, IL-6, IL-1, CCL3, CCL4, and various colony-stimulating factors such as IL-3 and GM-CSF. Mast cell activation induces transcription and synthesis of these cytokines, but preformed TNF may also be stored in granules and rapidly released on Fc ϵ RI cross-linking.

7. B, page 428.

Eosinophil recruitment and infiltration into tissues also depend on the chemokine eotaxin (CCL11) which is produced by epithelial cells at sites of allergic reactions and binds to the chemokine receptor CCR3, which is expressed constitutively by eosinophils. See Table 3-2 on page 40 for further review of chemokine and chemokine receptor pairings.

8. C, page 419.

Atopic individuals produce high levels of IgE in response to environmental allergens, whereas normal individuals generally produce other Ig isotypes, such as IgM and IgG and only small amounts of IgE. The quantity of IgE synthesized depends on the propensity of an individual to generate allergen-specific helper T cells that produce IL-4 and IL-13, because these cytokines stimulate B cell antibody class switching to IgE.

9. A, pages 420, 430 and ACAAI Review book page 399.

All mast cells are derived from progenitors in the bone marrow. Progenitors migrate to the peripheral tissues as immature cells and undergo differentiation in response to local microenvironmental biochemical cues, including stem-cell factor released by tissue cells which binds to the c-Kit receptor on the mast cell progenitor. Activating mutations in c-kit (e.g., KIT D816V) can lead to increased number of mast cells due to constitutive activation of KIT tyrosine kinase signaling and aberrant expression of anti-apoptotic proteins (e.g., Bcl-XL & Bcl-2).

The other answer choices listed are examples of candidate genes or encoded proteins associated with asthma.

10. A, pages 423-424 and Chapter 7.

The signaling cascades initiated by allergen-mediated Fc ϵ RI cross-linking are similar to the proximal signaling events initiated by antigen binding to lymphocytes. The correct combination of tyrosine kinases and adaptor protein for mast cell activation is Fyn, Lyn, Syk and LAT (see figure 20-5).

Answer choice B refers to T-cell signaling. Answer choice C refers to B-cell signaling.

FIT Board Review Corner – July 2016

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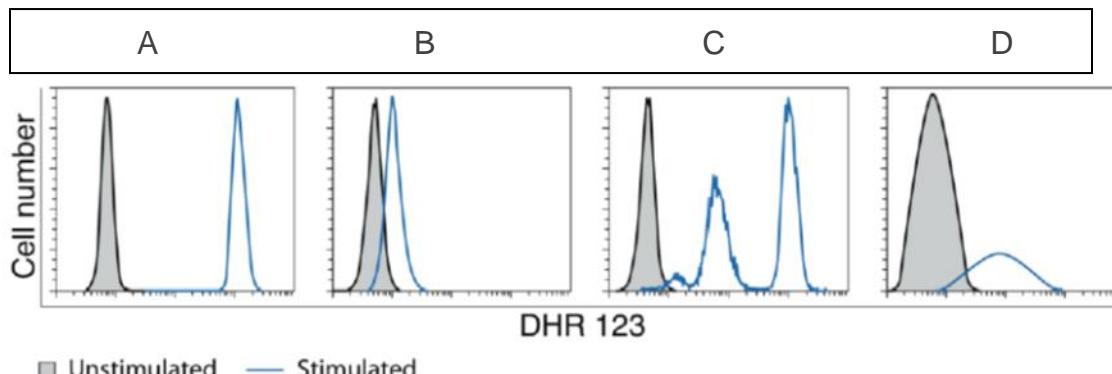
Review Questions

Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition
By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 21 (pages 437-445): Congenital and Acquired Immunodeficiencies

Prepared by Priscilla Wong, MD, Wilford Hall Ambulatory Surgical Center

1. Chronic granulomatous disease is characterized by defective production of reactive oxygen species by phagocytes as evidenced by recurrent intracellular bacterial and fungal infections and development of granulomas. Mutations in which of the following genes characterize the XL form?
 - a. phox-67
 - b. phox-40
 - c. phox-91
 - d. phox-47
2. In the diagnosis of chronic granulomatous disease (CGD), the dihydrorhodamine (DHR) test detects the generation of superoxide free radicals and leads to a change in flow cytometry-detected fluorescence. Which pattern represents the **mother of a male child with XL CGD?**



- a. A
- b. B
- c. C
- d. D

3. A patient with leukocyte adhesion deficiency type 2 (LAD-2) is characterized by which defect?
 - a. Absent of deficient expression of the $\beta 2$ integrins (heterodimer CD18 and CD11) due to various mutation in the CD18 gene
 - b. Defect in gene encoding KINDLIN-3, a protein that binds to the cytoplasmic tail of some integrins and is involved in signaling
 - c. Mutation in RAC2, a protein involved in the regulation of actin cytoskeleton
 - d. Defect in the GDP fucose transporter responsible for responsible for the transport of fucose into the Golgi, resulting in inability to synthesize sialyl Lewis X (CD15)
4. A homozygous mutation in which of the following results in reduced type I interferon generation and susceptibility to herpes simplex encephalitis?
 - a. IRAK4
 - b. UNC93B
 - c. MyD88
 - d. TLR4
5. The classical form of the inherited isolated NK cell deficiency characterized by recurrent, severe herpesviruses and papillomaviruses is associated with which genetic defect and inheritance pattern?
 - a. GATA-2 – Autosomal dominant
 - b. Fc γ RIIA (CD16) – Autosomal recessive
 - c. GATA-3 – Autosomal dominant
 - d. MCM4 – Autosomal recessive
6. Describe the T cell, B cell, and NK cell pattern typically seen with X-linked Severe Combined Immunodeficiency (SCID):
 - a. Marked decreased in T cells, B cells, and NK cells
 - b. Marked decrease in T cells, normal or increased B cells, and decreased NK cells
 - c. Marked decrease in T cells and B cells, and normal or increased NK cells
 - d. Marked decreased in T cells, and normal B cells and NK cells
7. Which autosomal recessive form of SCID is linked to a mutation involved in defective pre-TCR signaling a block in $\alpha\beta$ T cell development with normal B cells and NK cells?
 - a. AID (activation-induced cytidine deaminase)
 - b. WASP
 - c. Itk
 - d. CD 45 phosphatase
8. Autosomal recessive class I MHC deficiencies involving mutations in TAP-1 or TAP-2 genes are characterized primarily by which of the following infections?
 - a. Necrotizing granulomatous skin lesions
 - b. Urinary tract infections
 - c. Urinary tract infections

- c. Aspergillus infections
- 9. A rare form of SCID in which patients have proper T cell development but impaired T cell activation results from a mutation in:
 - a. CIITA
 - b. ORAI1
 - c. PI3K
 - d. RFX5
- 10. Recurrent mycobacterial infections may be characterized by defects in which of the following:
 - a. IL-15p40
 - b. IL-1p38
 - c. STAT 1
 - d. STAT 4

Answers

1. C, page 439.

"In the most common XL form of the disease, there is a mutation in the gene encoding the 91-kD subunit of cytochrome b558, an integral membrane protein also known as phox-91."

2. C, see page 317 from the 2013 ACAAI Board Review book.

A is normal. B is XL CGD. D is AR CGD.

3. D, page 440.

"LAD-2...this defect is caused by a mutation in the GDP-fucose transporter responsible for the transport of fucose into the Golgi, resulting in the inability to synthesize sialyl Lewis X."

4. B, page 441.

"Heterozygous mutations in TLR3 and homozygous mutations in UNC93B result in reduced type I interferon generation and susceptibility to herpes simplex encephalitis."

5. A, page 440.

"Autosomal dominant mutations in the gene encoding GATA-2 results in diminished precursor populations in the bone marrow and a resulting loss of NK cells as well decreases in monocytes, DCs, and B cells...Patients present with severe infections with viruses mainly of the herpesvirus and papillomavirus families."

6. B, page 442, Table 21-3, 444.

"X-linked SCID functional deficiencies characterized by marked decrease in T-cells, normal or increased B cells, and deficiency of NK cells." The SCID subtypes that characterize answer A are ADA deficiency, reticular dysgenesis, and PNP deficiency. Examples of the SCID subtypes that characterize answer C are RAG1/2, Artemis defects, DNA-PKcs, CERUNNOS). Examples of the SCID subtypes that characterize answer D are IL-7Ra.

7. D, page 444 and 155.

“Other forms of autosomal recessive SCID are caused by mutations encoding the CD45 phosphatase, that is a positive regulator of the Src family kinases such Fyn, Lck, and Lyn and mutations in the CD3 δ or ε or the CD3-associated ζ chain.” (Recall also that CD45 is a phosphatase that dephosphorylates the inhibitory tyrosine kinase residues.)

8. A, page 445.

Autosomal recessive class I MHC deficiencies are characterized by decreased CD8+T cell numbers and function. In some cases, the failure to express class I MHC molecules is due to mutations in TAP-1 or TAP-2 genes...such patients suffer mainly from necrotizing granulomatous skin lesions and respiratory tract bacterial infections, but not virus infections, which is surprising considering that a principal function of CD8+ T cells is defense against viruses.

9. B, page 446.

“Another rare form of SCID is caused by a mutation in the gene encoding Orai1, a component of the CRAC channel...this process is crucial for lymphocyte activation, and it is defective in cells with mutation ORAI1. A similar phenotype is observed in patients with mutations in STIM1, which encodes in endoplasmic reticulum protein that senses the depletion of Ca⁺ stores and contributes to the opening of the CRAC channel. Patients with ORAI1 and STIM1 mutations do not exhibit a defect in T cell development, but their T cells cannot be properly activated.”

10. C, page 441.

“Mutations in the genes encoding IL-12p40, the IL-12Rβ1 chain, and both chains of the IFN-γR as well as some mutations in STAT 1 and IKK γ /NEMO result in susceptibility to environmental Mycobacterium species.”



FIT Board Review Corner – August 2016

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Review Questions

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By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 21 (pages 445-462): Congenital and Acquired Immunodeficiencies

Prepared by Tara Shankar, MD, Children's Hospital of Pittsburgh of UPMC.

1. What retrovirus affects CD4+ T cells but instead of killing helper T cells transforms them to produce adult T cell lymphoma?
 - a. EBV
 - b. Measles
 - c. HIV
 - d. HTLV
2. Which is an example of acquired immunodeficiency?
 - a. ataxia-teleangiectasia
 - b. bruton's agammaglobulinemia
 - c. HIV
 - d. Wiskott-Aldrich syndrome
3. What proteins are required for HIV infection of cells?
 - a. p17 and p24
 - b. gp 120 and p24
 - c. gp 120 and gp41
 - d. p17 and gp41
4. Which of the following is true about CXCR4 in HIV infection?
 - a. Overcomes the inhibitory effect of host cell enzyme APOBEC3G.
 - b. Binds to gp120 to induce a conformational change in gp41 to enable the viral membrane to fuse with the target cell membrane.
 - c. Is expressed primarily on macrophages.
 - d. Promotes the nuclear export of incompletely spliced viral RNAs Promotes the nuclear export of incompletely spliced viral RNAs.
5. The product of which gene produces reverse transcriptase, protease, ribonuclease, and integrate enzymes?

- a. Tat
 - b. pol
 - c. env
 - d. gag
6. Which of the following is an example of a host restriction factor to inhibit viral infection in HIV?
- a. Tetherin inhibits the HIV budding process.
 - b. TRIM5 alpha is a cytidine deaminase that interferes with viral replication.
 - c. APOBEC3 targets Vif proteins for ubiquination and proteasomal degradation.
 - d. Vpu causes premature uncoating of the virus and proteasomal degradation of the viral reverse transcriptase complex.
7. During which clinical stage of HIV infection is viremia at the highest point?
- a. Primary infection
 - b. Acute HIV syndrome
 - c. Acute latency
 - d. Clinical latency
8. Which of the following is a direct toxic effect of HIV on infected CD4+ cells?
- a. Budding of viral particles may lead to increased plasma membrane permeability and the influx of lethal amounts of calcium.
 - b. Viral production over activates cellular protein synthesis.
 - c. The inflammasome pathway is activated and leads to cell phagocytosis.
 - d. Antibodies against HIV envelope proteins may bind to HIV-infected CD4 cells and target them for antibody-dependent cell-mediated cytotoxicity.
9. AIDS is defined as a CD4 count below ____.
- a. 500
 - b. 400
 - c. 300
 - d. 200
10. How many weeks after HIV infection can antibody responses to HIV antigens be detected?
- a. 2-3 weeks
 - b. 4-6 weeks
 - c. 6-9 weeks
 - d. 9-12 weeks

Answers

1. D, page 451.

"Like HIV, HTLV-1 is a retrovirus with tropism for CD4+ cells; however, instead of killing helper T cells, it transforms them and produces an aggressive malignant neoplasm called adult T cell leukemia/lymphoma (ATL)."

2. C, page 450.

"Immunodeficiency may be acquired by an infection that target cells of the immune system. The most prominent of these is HIV infection."

3. C, page 452.

"The envelope glycoproteins gp120 and gp41...noncovalently associate with each other and are required for infection of cells."

4. B, page 452.

"Coreceptor binding [to gp 120] induces a conformational change in gp41 that exposes a hydrophobic region, called the fusion peptide, which inserts into the cell membranes and enables the viral membranes to fuse with the target cell membrane."

5. B, page 454.

"The pol gene product is a precursor protein that is sequentially cleaved to form reverse transcriptase, protease, ribonuclease, and integrate enzymes."

6. A, page 455.

"Tetherin prevents the pinching off of certain viruses including HIV, and its inhibition of the budding process can be antagonized by an HIV protein Vpu."

7. B, page 456.

"This replication leads to viremia, during which large numbers of HIV particles are present in the patient's blood, accompanied by an acute HIV syndrome..."

8. A, page 457.

"The process of virus production with the expression of gp41 in the plasma membrane and budding of viral particles may lead to increased plasma membrane permeability and the influx of lethal amounts of calcium."

9. D, page 459.

"HIV disease progresses to the final and once almost invariably lethal phase, called AIDS, when the blood CD4 T cell count drops below 200."

10. C, page 460.

"Antibody responses to a variety of HIV antigens are detectable within 6 to 9 weeks after infection."



FIT Board Review Corner – September 2016

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Review Questions

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Chapter 27 (pages 431-448): Aerobiology of Outdoor Allergens

Prepared by Kristen Walters, MD, Scripps Clinic Medical Group, San Diego, California.

1. Which of the following is a characteristic of wind-pollinated (anemophilous) plants?
 - a. Plants have complete flowers (i.e. male and female functions are found on the same structure).
 - b. The female flower (pistil) needs to be exposed to the wind.
 - c. Petals and sepals are visible and present.
 - d. Vector attractants such as color, aroma or nectar are present.
 - e. Pollen grains are small, dry, with reduced surface ornamentation.
2. In 1930, August Thommen created 5 necessary principles for a plant to be considered an important inducer of hay fever, referred to as “Thommen’s Postulates”. Which of the following is NOT correct?
 - a. The pollen must be wind-borne.
 - b. The pollen does not need to be produced in large quantities.
 - c. The pollen needs to be buoyant to be carried long distances.
 - d. The pollen must be widely distributed.
 - e. The pollen must contain an excitant of hay fever.
3. In North America, the National Allergy Bureau is the American Academy of Allergy, Asthma & Immunology (AAAAI)-sponsored pollen and mold counting network. What form of aeroallergen sampling is used to monitor the type and intensity of aeroallergen exposure in the environment?
 - a. Gravimetric samplers
 - b. Intermittent rotary samplers
 - c. Automatic counters
 - d. High-volume filtration devices
 - e. Suction drums

4. The grass family, Poaceae, is a large botanical group with several subfamilies and numerous tribes. Which subfamily includes temperate-climate pasture grasses and most cereal grains, and is considered the most prominent in pollinosis?
 - a. Pooideae
 - b. Bambusoideae
 - c. Panicoideae
 - d. Arundinoideae
 - e. Chloridoideae
5. Which of the following is a native grass of Africa that is generally found south of the 38th parallel (with extension northward along the coasts) and is considered the most important southern grass?
 - a. Johnson grass
 - b. Bermuda grass
 - c. Timothy grass
 - d. Buffalo grass
 - e. Salt grass
6. What is the major allergen of birch pollen?
 - a. Bet v 1
 - b. Bet v 2
 - c. Bet v 3
 - d. Bet v 4
 - e. Bet v 5
7. During The majority (90-95%) of patients with ragweed hypersensitivity will react to which of the following allergens?
 - a. Amb a 1, Amb a 2
 - b. Amb a 1, Amb a 3
 - c. Amb a 1, Amb a 4
 - d. Amb a 2, Amb a 3
 - e. Amb a 3, Amb a 4
8. Ragweed, as well as other pollen members of the Heliantheae tribe, is characterized by which of the following surface features?
 - a. Square or pentagonal shape
 - b. Multiple pores
 - c. Single pore
 - d. Broad-based spikes

9. Which of the following best describes the appearance of an *Alternaria* spore?
- Cigar-shaped
 - Paintbrush
 - Club-shaped
 - Spheroidal with spines
 - Yeast-like
10. Based on sampling surveys from around the world, what mold is the most common airborne allergenic fungus?
- Alternaria*
 - Penicillium*
 - Helminthosporium*
 - Aspergillus*
 - Cladosporium*

Answers

1. E, page 431 (Box 2701).

Anemophilous characteristics include: 1) plants with incomplete flowers – spatially separate male (staminate) and female (pistillate); 2) male flowers (stamens) are exposed to the wind; 3) petals and sepals are inconspicuous or absent rather than “showy”; 4) vector attractants (color, aroma or nectar) are absent; 5) pollen grains are small, dry with reduced surface ornamentation to minimize turbulence in the air.

2. B, page 432 (Box 27-2).

All of the above are true statements, except answer B. The pollen must be produced in sufficiently large quantities in order to ensure successful reproduction and be considered an important inducer of pollinosis. Today, these postulates continue to be generally correct. The “excitant of hay fever” appears to be a protein or glycoprotein that is easily eluted on contact with water, or coated on respirable cytoplasmic particles. Although most pollinosis-inducing plants are wind pollinated, entomophilous plants can also release sufficient airborne pollen to cause sensitization.

3. C, pages 434-436. Refer to Table 27-3 for a complete list of the different types of aeroallergen samplers.

4. A, pages 437-438 (Table 27-5).

This subfamily of grasses have a wide range throughout the U.S. and western Europe. With only minor exceptions, members of this subfamily have strongly cross-reactive major allergens and include Kentucky bluegrass, timothy, and perennial ryegrass.

5. B, pages 437-438.

Bermuda grass is part of the subfamily Chloridoideae and is generally considered to have little cross-reactivity with northern pasture grasses (such as Timothy grass). Johnson grass is primarily a southern grass but also found throughout the Eastern Agricultural zone and across the Arid

Southwest. Buffalo, salt and grama grasses are native prairie grasses related to Bermuda grass (and are cross-reactive) but less potent than Bermuda.

6. A, page 443.

Bet v 1 is the major pollen allergen and belongs to the pathogenesis-related protein group-10 (PR-10) family and shows strong homology with the group 1 allergens of both Betulaceae and Fagaceae members (Table 27-6). This is also the allergen that shows cross-reactivity to various fruit and vegetable proteins and is therefore responsible for a large number of cases of pollen-food allergy syndrome.

7. A, page 445.

Short ragweed allergens Amb a 1 to 10 have been characterized; the most important in clinical terms is Amb a 1. Approximately 90-95% of ragweed sufferers will react to Amb a 1 and Amb a 2; the other allergens are minor.

8. D, page 445.

Ragweed pollen is characterized by short furrows and a surface studded which broad-based spikes which range in length depending upon the specific pollen (ex: shorter in ragweed and marshelder, longer in sunflower and goldenrod, Figure 27-36). A = Alder pollen; B = burning bush (*Kochia scoparia*); C = grass pollen.

9. C, pages 446-448.

Alternaria spores are club-shaped (clavate), pale tan to medium brown, and segmented with both transverse and longitudinal septa, with a smooth or microverrucate surface (Figure 27-39). A = *Cladosporium* (Fig 27-41); B = *Penicillium* (Fig 27-43); D = Ragweed (Fig 27-36); E = *Aureobasidium* (Fig 27-45).

10. E, pages 447-448.

Sampling surveys from around the world reveal *Penicillium* to be the third most common airborne allergenic fungus, after *Cladosporium* and *Alternaria*. *Cladosporium* is most common in temperate and artic climates and frequently accounts for the largest number of spores collected on samplers.



FIT Board Review Corner – October 2016

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Chapter 28 (pages 456-465): Indoor Allergens

Prepared by Ashmi Doshi, MD, UCSD Allergy & Immunology

1. The major dust mite allergen Der p 1 is homologous to:
 - a. The Homocysteine
 - b. Cysteine protease
 - c. Serine protease
 - d. Serine bridge
2. Which of the following is true regarding activation of innate immune system in response to allergens?
 - a. Endotoxin activates TLR-4, unmethylated DNA activates TLR-9, Chitin activates TLR-2
 - b. Chitin activates TLR-4, Endotoxin activates TLR-9, and unmethylated DNA activates TLR-2
 - c. Umethylated DNA activates TLR-4, Chitin activates TLR-9, and Endotoxin activates TLR-2
 - d. Endotoxin activates TLR-4, methylated DNA activates TLR-9, and Chitin activates TLR-2
3. How long after a cat is removed from a home does the allergen level reduce?
 - a. 12-16 days
 - b. 120-160 days
 - c. 12-16 weeks
 - d. 12-16 months
4. What is the perfect environment for dust mites?
 - a. Temperature between 40-60F, low humidity
 - b. Temperature between 40-60F, high humidity
 - c. Temperature between 65-80F, low humidity
 - d. Temperature between 65-80F, high humidity

5. What is true regarding the major dust mite allergen, Der p 1?
 - a. Monoclonal antibodies to Der p 1 were reported in 1974 and protein was sequenced in 1992.
 - b. It is a 24 KD glycoprotein with homology to cysteine proteases and enzymatic activity
 - c. It is a 32 kD glycoprotein with homology to serine proteases and enzymatic activity
 - d. Buffalo grass
 - e. Monoclonal antibodies to Der p 1 were reported in 1964 and protein was sequenced in 1994.
6. Where is the major cat allergen, Fel d 1, is secreted?
 - a. In the urine
 - b. In the saliva
 - c. In the skin
 - d. On the fur
7. The term dust mites refers to:
 - a. Pyroglyphid mites
 - b. Pyroglyphid and sarcoptid mites
 - c. Pyroglyphid and storage mites
 - d. Any mites in the order astigmata
8. What is the approximate size of a dust mite?
 - b. 3µm
 - c. 30 µm
 - d. .3mm
 - e. 3mm
9. Which one of the following is true regarding *B. tropicalis*?
 - a. It does not cross-react with any other dust mites
 - b. It is mostly present in South East Asia
 - c. The first allergen identified and cloned is called Ber t 1
 - d. The first allergen identified and cloned is called Blot t 5
10. Cockroach sensitization is most common in people who live in which place?
 - a. Inner city apartments
 - b. Suburban homes
 - c. Lakeside villas
 - d. Mountain cabin basements

Answers

1. B, page 456-457.

Der p 1 has sequence homology with cysteine proteases.

2. A, page 460.

Endotoxin is potent TLR-4 agonist, unmethylated DNA can activated TLR-9, and chitin and its breakdown products can act on TLR-2 and dectin-1.

3. C, pages 465 (Box 28-3).

Refer to Table 27-3 for a complete list of the different types of aeroallergen samplers.

4. D, pages 456.

Optimal growth temperature is 65-80F for dust mites, and they are dependent on the humidity of their environment for their moisture balance. They are not able to drink liquids or search for moisture, and they absorb water through their bodies only.

5. C, pages 456-457.

Der p 1 was the first major mite allergen purified. It is a 24 kD glycoprotein with sequence homology with cysteine proteases and functional enzymatic activity. The monoclonal antibodies to Der p 1 were first reported in 1984, and the protein was sequenced in 1988.

6. C, page 458.

Fel d 1 still accumulated on shaved skin, even when cats were restrained from licking themselves, thus it became clear that it was excreted from the skin itself.

7. A, page 456.

The term dust mites is best reserved for pyroglyphid mites, with broader designation of domestic mites for any species of mites found in homes.

8. C, page 456.

Dust mites are approximately 0.3mm in length, and difficult to see with naked eye.

9. D, pages 457-458.

B. tropicalis, the tropical dust mite, is present in florida, Puerto rico, Venezuela, and brazil. Antibodies to B. tropicalis partially cross-react with other dust mites. The first allergen identified and cloned from B. tropicalis is called Blot t 5 because it has sequence homology with Der p 5.

10. A, pages 459.

Positive testing was found in clinic populations in various cities, but suburban clinics found few or no positive test responses to cockroach extracts.



FIT Board Review Corner – November 2016

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Chapter 30 (pages 482-497): Air Pollution

Prepared by Jackie Eastman, MD

1. What is the mechanism by which tobacco smoke may promote development of allergy and asthma?
 - a. Promotion of Th2 response to allergen at time of sensitization.
 - b. Direct chemotactic effect on eosinophils and mast cells.
 - c. Toxic effect on Th1 cells leading to increased apoptosis of this cell type.
 - d. Inhibition of CD8+ T-cell mediated cytotoxicity.
2. Which molecule is found in both tobacco smoke and diesel exhaust that may be responsible for Th2-promoting effect?
 - a. Lead
 - b. Carbon monoxide
 - c. Polyarmoatic hydrocarbons
 - d. Ozone
3. What is the effect of diesel exhaust particles on immune response to allergens?
 - a. Increase number of eosinophils
 - b. Enhance production of allergen-specific IgE
 - c. Increase number and activity of cytotoxic T cells
 - d. Increase production of IFN γ
4. Nitrogen dioxide affects the airway of asthmatics by:
 - a. Augmenting acute response to allergen
 - b. Direct bronchospastic effect
 - c. Causing recruitment of eosinophils
 - d. Enhancing production of allergen-specific IgE

5. Ozone causes inflammatory and bronchospastic responses through hyaluronic acid and which receptor?
 - a. TLR7
 - b. TLR4
 - c. Dectin 1
 - d. B-cell receptor
6. Asthmatics are more susceptible to ozone-induced bronchospasm due to:
 - a. Increased IgE production
 - b. Increased activation of Th17 cells
 - c. Increased activation of the innate immune system
 - d. Increased activation of the Th2 pathway
7. Decreases in air pollution directly lead to decreases in which of the following:
 - a. Cardiovascular deaths
 - b. Respiratory deaths
 - c. Asthma exacerbations
 - d. All of the above
8. Genetic polymorphisms in which gene have shown to mitigate effects of air pollution?
 - a. Anti-oxidant enzymes, such as glutathione S-transferases
 - b. Type I cytokines such as IFN α
 - c. Integrins such as ICAM-1
 - d. Transcription factors such as AP-1
9. Diesel exhaust particles affect allergic volunteers by:
 - a. Direct bronchospastic effect
 - b. Increasing sinus mucus production
 - c. Increasing development of IgE to new antigens, increasing local IgE and eosinophilic response to allergen challenge
 - d. Increasing susceptibility to infection
10. Biomass, and burning it for cooking, is an important cause of COPD and asthma. Which air pollutants are responsible for this effect?
 - a. PAHs and endotoxins
 - b. Ozone
 - c. Nitrogen dioxide
 - d. Carbon monoxide

Answers

1. D, page 486.

In mouse model, found that sensitization to ovalbumin was skewed more towards Th2 if done in presence of tobacco smoke than if done without tobacco smoke exposure. In humans, have found that allergen challenges had enhanced IgE and IgG4 production, increased IL-4, IL-5, and IL-13, and increased histamine if done in presence of tobacco smoke.

2. C, page 486.

PAH has been found to likely be responsible for Th2-promoting actions of diesel exhaust. It is also found in tobacco smoke and may be the molecule responsible for tobacco-induced allergy.\

3. B, page 488.

In presence of DEP, more allergen-specific IgE is made. In addition, DEPs induce B cell isotype switching to IgE.

4. A, page 489.

Nitric oxide may induce neutrophilic inflammation. At low levels, it does not have effect on reactivity. In controlled studies, patients exposed to nitric oxide and then exposed to an allergen had increased reactivity, meaning they were primed to react. It also increased allergen-induced eosinophil cationic protein levels (ECP).

5. B, page 490.

Ozone can cause immediate decrease in FVC and FEV1 and chest discomfort. Neutrophilic, and in asthmatics eosinophilic, infiltrate may happen later. Response to ozone and lipopolysaccharide appears to be similar. TLR4 knockout mice decreased the levels of this hyperreactivity. Hyaluronic acid appears to be part of this pathway and increases during ozone exposure.

6. C, page 490.

Asthmatics have increased immune signaling involving the NF- κ B network and increased proinflammatory cytokine production (IL-1B, IL-6 and IL-8) upon exposure to ozone than healthy controls.

7. D, page 493.

Bans for various reasons (such as the Olympics) have allowed a natural experiment in an urban setting with effect of air pollution on public health. Mortality and asthma all improved during these bans.

8. A, page 491.

Polymorphisms in many enzymes associated with oxidative stress have shown to increase the risk of wheezing and allergen development after exposure to air pollution.

9. C, pages 483 Table 30-1.

10. A, pages 485.

Biomass includes wood, crop residues, animal dung, twigs, grass and coal. Burning of it releases PAHs that are metabolized to quinones and other oxidant species. It also releases endotoxins. Both are implicated in driving towards Th2 responses.



FIT Board Review Corner – December 2016

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Chapter 30 (pages 497-508): Particulate and Pollen Interactions

Prepared by Lisa Fu, MD

1. What is Allergotoxicology?
 - a. The study of how toxic compounds cause allergic diseases.
 - b. The study of how toxic food additives cause allergic diseases.
 - c. The study of how medication accumulation cause allergic diseases.
 - d. The study of the influence of environmental pollutants on the development of allergic diseases.
2. Which criteria in the Classification of Air Pollutants describes the pollutant as gaseous or particulate air pollutants?
 - a. Compartment
 - b. Aggregate state
 - c. Origin
 - d. Source
3. What percentage of atmospheric aerosols are biogenic in origin?
 - a. 5%
 - b. 25%
 - c. 50%
 - d. 75%
4. What airborne particulate matter has been found to be associated with allergic disease?
 - a. Coal smoke
 - b. Diesel exhaust
 - c. Asbestosis
 - d. Forest fires

5. Pollen grains are a carrier of:
 - a. Male genetic material
 - b. Female genetic material
 - c. Nutrients
 - d. Chlorophylls
6. What structure on the pollen do airborne particle attach to?
 - a. Pollen granules
 - b. Intine
 - c. Extine
 - d. Cytoplasm
7. Which gaseous pollutant has been shown to have an inhibitory effect on allergen release?
 - a. SO₂
 - b. CO
 - c. NO
 - d. Ozone
8. What is a low molecular weight substance release by pollen grains that cause an allergic response?
 - a. Lipoprotein pollus
 - b. Pollen associated lipid mediators
 - c. Prostanphillans
 - d. Pollen leukotriene induction proteins
9. Which of the following statements accurately describes the ‘farmer hypothesis?’
 - a. People who consume farm cow’s milk have lower incidence of lactose intolerance.
 - b. Farmers have a higher incidence of allergic asthma.
 - c. Children’s growing up in a farm experience less respiratory allergic disease than age matched children from urban areas.
 - d. Eczema is less common in children growing up in farms compared to children growing up in urban environments.
10. What is the mechanism by which airborne particles affect the alveolar epithelium?
 - a. Cytokine response
 - b. Macrophage activation
 - c. Cell apoptosis
 - d. Oxidative stress

Answers

1. D, page 497.

Allergotoxicology is the study of the influence of environmental pollutants on the development of allergic reactions and diseases.

2. B, page 498.

Aggregate state: Air pollutants can be classified as gaseous or particulate matter. Particulate matter can be further classified according to size. Large or coarse particulate matter (PM) is 2.5 to 10 μm in diameter (PM10); fine particles are 0.1 to 2.5 μm in diameter (PM2.5); and UFPs are less than 0.1 μm in diameter.

3. B, page 498.

Approximately 25% of atmospheric aerosols are biogenic in origin, and they consist of pollen, plant fragments, mold spores, bacteria, algae, crystalline proteins, animal epithelia, and other particles. Unlike inorganic particles, bioaerosols are characterized by their aerodynamic diameters, which are different from crude physical diameters.

4. B, page 500.

Among the fine particles and UFPs (Ultrafine particles), diesel exhaust in particular has been shown to exert allergy-enhancing effects in a variety of in vitro and in vivo studies.

5. A, page 501.

Pollen grains are the carriers of male genetic material. They are the male gametophytes in angiosperms and gymnosperms.

6. C, page 504.

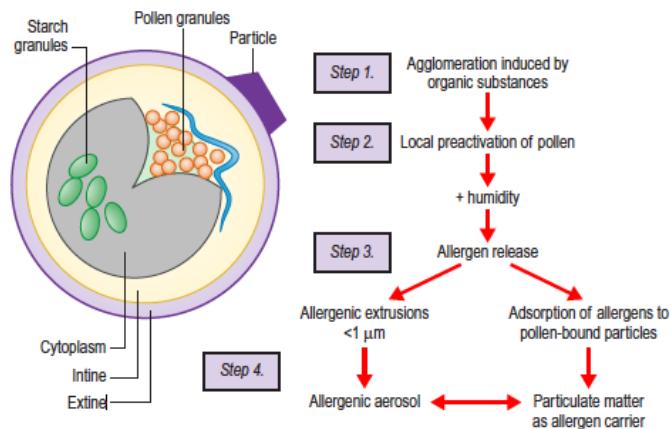


Figure 31-8 Airborne particles and pollen interact in the ambient air to produce allergen-containing aerosols via different steps. (From Behrendt H, Becker WM. Localization release and bioavailability of pollen allergens: the influence of environmental factors. *Curr Opin Immunol* 2001;13: 709-15.)

7. A, page 505.

Among the gaseous pollutants, SO₂ has been shown to have a clear-cut inhibitory effect on allergen release, which may help to explain the decreased allergy prevalence in regions with high SO₂ pollution levels, such as in Eastern Europe.

8. B, pages 502-503.

Pollen grains are allergen carriers. They also release a variety of low-molecular-weight substances on reaching a humid environment or coming into contact with a moist mucosal surface or skin. Powerful biologic activities are exhibited by components of these low-molecular-weight substances, such as pollen-associated lipid mediators (PALMs), which have leukotriene B4 (LTB4)-like proinflammatory activity in attracting and activating neutrophil and eosinophil granulocytes.

9. C, page 500.

The farmer hypothesis states that children growing up on a farm experience less respiratory allergic disease than age-matched children growing up in the nearby village with an absence of livestock.

10. D, pages 500.

Airborne particles are deposited at a higher rate in the peripheral airways and can cross the alveolar epithelium where they exert an oxidative stress effect.