Allergy and Immunology Review Corner: Chapter 17 of Immunology IV: Clinical Applications in Health and Disease, by Joseph A. Bellanti, MD.

Chapter 17: Mechanisms of Immunologic Injury

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1. The Type I hypersensitivity reaction is mediated by which antibody?
   A. IgA
   B. IgG
   C. IgM
   D. IgE

2. Which of the following reactions is characterized by cell death which begins with the binding of antigen-specific antibody with a target cell?
   A. Type I hypersensitivity
   B. Type IIA hypersensitivity
   C. Type IIB hypersensitivity
   D. Type IIC hypersensitivity

3. Which of the following is an example of a Type IIA hypersensitivity reaction?
   A. Myasthenia gravis
   B. Graves’ disease
   C. Autoimmune urticaria
   D. Hemolytic anemia

4. Which of the following describes a Type IIC hypersensitivity reaction?
   A. Anaphylactic
   B. Antibody-mediated cytotoxic
   C. Antibody-mediated neutralizing
   D. Antibody-mediated stimulatory

5. Which of the following types of reactions characterizes an Arthus reaction?
   A. Type IIIA hypersensitivity
   B. Type IIIB hypersensitivity
   C. Type IVA hypersensitivity
   D. Type IVB hypersensitivity

6. Which of the following types of hypersensitivity reaction does not involve humoral immunity but is largely mediated by T lymphocytes?
   A. Type I hypersensitivity
   B. Type II hypersensitivity
   C. Type III hypersensitivity
   D. Type IV hypersensitivity
7. Type IVC hypersensitivity reactions are mediated by which of the following subtypes of T cells?
   A. Th1 cells
   B. Th2 cells
   C. Th17 cells
   D. CD8+ cytotoxic cells

8. Which of the following types of reactions has granulomas as a prominent clinical feature?
   A. Type IVA hypersensitivity
   B. Type IVB hypersensitivity
   C. Type IVC hypersensitivity
   D. Type IVD hypersensitivity

9. Which of the following states describes optimum binding of antibody with antigen and allows for extensive lattice formation of antigen-antibody complexes?
   A. Zone of antibody excess
   B. Zone of equivalence
   C. Zone of antigen excess
   D. Zone of lattice formation

10. Which of the following types of reaction is responsible for the late reaction observed in allergic patients after immediate skin-prick testing?
    A. Type IVA hypersensitivity
    B. Type IVB hypersensitivity
    C. Type IVC hypersensitivity
    D. Type IVD hypersensitivity

Answers
1. D, page 664
   “The Type I reaction in the human is mediated by IgE antibodies (formerly referred to as “reaginic” antibodies).”

2. B, page 666
   “In the cytotoxic subtype of Type II hypersensitivity (Type IIA), the consequences of cell death begin with the binding of antigen-specific antibody with a target cell.”

3. D, page 664, Table 17-1
   Hemolytic anemia is an example of a Type IIA hypersensitivity reaction.

4. D, page 668
   “Type IIC hypersensitivity reactions are characterized by cytostimulation as a result of the enhancing effect of an autoantibody directed to a normal cell receptor, resulting in the pathologic stimulation of the target cell with a pathologic overproduction of a cell product, e.g., a hormone.”
5. A, page 670
“With immune complex deposition, two manifestations of the mechanisms of tissue injury have been described: (1) a localized (Arthus reaction; Type IIIA) and (2) a systemic (serum sickness; Type IIIB) reaction.”

6. D, page 673
“The fourth major mechanism of immunologic injury is the cell-mediated (delayed hypersensitivity) or Type IV reaction. Unlike the previous three mechanisms [Types I, II, and III], this response does not involve humoral antibody but is mediated primarily by the action of T lymphocytes.”

7. C, page 676
“Following uptake and processing of antigen by dendritic cells, naïve Th0 cells not only undergo maturation to Th17 cells under the influence of the combined actions of IL-1β, IL-6, and TGF-β, but also the stabilization and further expansion of these cells is indirectly provided by the dendritic cell/macrophages derived IL-23.”

8. A, page 674
“The chronic persistence of antigen incapable of elimination promotes the development of a prominent Type IVA reaction and subsequent formation of granuloma, a collection of organized cells, mainly macrophages with an infiltrate of lymphocytes of other leukocytes.”

9. B, page 670, Box 17-1
“In the...zone of equivalence, the binding of antigen with antibody is optimal and extensive lattices are formed by the cross-linking of large antibody-antibody complexes that precipitate in the bottom of the tube with neither antigen nor antibody detected in the supernatant fluid.”

10. B, pages 674-675
“The type of injury [Type IVB hypersensitivity] is seen in many clinical conditions such as the late reaction observed in allergic patients after immediate skin-prick testing. This late reaction is part of the late component of the dual “early” and “late” IgE-mediated skin reaction that waxes and wanes during the several-hour course of a Type I-mediated reaction.”

**Allergy and Immunology Review Corner:** Chapter 18 of *Immunology IV: Clinical Applications in Health and Disease*, by Joseph A. Bellanti, MD.

**Chapter 18:** Allergic Diseases and Asthma

*Prepared by Monica Bhagat, MD, University of Pennsylvania, and David Scott, MD, Scripps Clinic/Scripps Green Hospital Program*

1. Which of the following statements is **FALSE** regarding the IgE antibody?
A. IgE antibody is made up of two light chains and two isotype-specific heavy chains.
B. IgE crosses the placenta.
C. About half of the total IgE resides in the intravascular compartment, with the other half found in tissues (primarily bound to mast cells).
D. The half-life of IgE in peripheral blood is about 1-5 days but may persist in tissues for months when bound to its receptor on mast cells.

2. IgE production requires the coordinated interaction of APCs, T cells, and B cells. The reciprocal T/B cell activation cascade requires three stimulatory signals. Which of the following is NOT one of these signals?
A. Interaction of co-stimulatory interactions between upregulated molecules on B cells with those on CD4+ T cells (CD80/CD86 with CD28).
B. Peptides are presented to a naïve Th0 cell through its TCR in the context of MHC-II with the participation of the CD4 co-receptor.
C. The stimulation of macrophages by IFN-γ and TNF-β allows more efficient antigen presentation.
D. This signal is a cytokine-induced phase brought about by the activation of naïve T cells by IL-2, IL-4-mediated Th2 differentiation, and the production of IL-4, IL-5, IL-9, and IL-13 that provide additional signals to B cells required to drive IgE synthesis.

3. During which phase of the allergic response do mast cells undergo degranulation?
A. Elicitation
B. Challenge
C. Sensitization
D. Priming

4. Which of the following agents results in IgE-independent antibody-mediated anaphylaxis?
A. Latex
B. Opioids
C. IVIG infusion
D. Dialysis membranes

5. Celiac disease is an example of a non-IgE mediated food disorder. Which of the following statements is NOT true?
A. The pathogenesis of this disease is caused by the generation of autoreactive T cells.
B. In this disease, autoantibodies are generated against human tissue transglutaminase.
C. In celiac disease, genetically susceptible individuals include those expressing MHC-II-associated HLA-DR2 or DR8.
D. On a pathological level, this disease affects all layers of the gastrointestinal wall, but particularly leads to a damaged submucosal layer.

6. Which of the following protein allergens is an enzyme protease from egg white?
A. Trypsin
B. Lysozyme
C. Papain
D. Vicilins
E. 2S albumins

7. Which of the following statements is true?
A. Proteins with linear IgE-binding epitopes generally constitute more effective allergens than those with conformational variations in three-dimensional structures.
B. All antigens are allergens but not all allergens are antigens.
C. Of the five immunoglobulin isotypes, IgA displays the lowest serum concentration, with a peak concentration at 10 to 15 years of age in nonatopic individual
D. IL-4 is strong chemoattractant for eosinophils.
E. Allergens are named using the first three letters of the Phylum.

8. Which of the following is true regarding mast cells and basophils.
A. MC\textsubscript{T} mast cells contain both tryptase and chymase and are found predominantly in the skin.
B. Basophils are typically found in tissue and migrate to the blood upon activation.
C. Upon activation, mast cells, unlike basophils, are capable of producing prostaglandins.
D. Mast cells and basophils utilize the Fc\textgreek{R}1 for IgE-dependent activation.
E. Both c and d

9. The following would not be expected to be secreted in high levels by Th2 cells:
A. IL-4
B. IL-5
C. IL-9
D. IL-12
E. IL-13

10. Aspirin-induced asthma is an example of what category of drug reaction?
A. Primary side effect
B. Secondary side effect
C. Idiosyncrasy
D. Allergic hypersensitivity
E. Non-allergic hypersensitivity

Answers
1. B, page 690
IgE neither crosses the placenta nor activates complement.

2. C, page 690, Figure 18-4
Signal 1 is outlined in choice (b), followed by signal 2 outlined in choice (a), followed by signal 3 outlined in choice (d). Choice (c) is not part of the signal cascade.

The allergic response occurs in a cascade of sequential events known as sensitization, challenge, and elicitation. In sensitization, a person is exposed to the allergen, and in a Th2 cytokine-rich environment, this leads to allergen-specific IgE production. These specific IgE antibodies can now bind the high-affinity IgE receptors on the surface of mast cells and basophils. These cells are now considered “primed”. Upon re-exposure to the allergen, the person enters the second phase known as the challenge phase. In this phase, the allergen interacts with specific IgE molecules bound to the high-affinity FcERI receptors on mediator cells. Cross-linking of two adjacent FcERI leads to degranulation of these cells with release of mediators that cause allergic reactions. Degranulation occurs in the challenge phase. The release of inflammatory mediators and subsequent allergic reactions is the third phase and is called the elicitation phase.

4. C, pages 716-717, Table 18-18
IgE-independent mediator release is presumably triggered by interactions between antigen-specific IgG antibodies or immune complexes and Fc receptors on the surface of mast cells. Remember, Opioids, along with muscle relaxants and vancomycin can result in non-specific degranulation of mast cells and basophils in a non-allergic nonantibody-mediated reaction.

5. D, pages 729-730
Celiac disease is a food allergic disorder directed to dietary glutens from wheat, barley, rye, and sometimes oats. It is due to the generation of autoreactive T cells. Disease is confined to the mucosa of the small intestine and is characterized by T lymphocyte-mediated injury and eventual destruction of fingerlike projections, called villi, where absorption of key nutrients normally takes place.

6. B, pages 689, Table 18-1. In Summary, all of the proteins listed are various allergens. Lysozyme is an enzyme protease from egg whites. Other major allergens in egg white include ovalbumin, conalbumin, and ovomucoid, which is the most clinically relevant. Trypsin is an enzyme protease from dust mite. Papain is an enzyme protease found in papaya, pineapple and kiwi. Vicilins are a type of seed storage protein from peanuts, sesame seeds, tree nuts and legumes. 2S albumins are seed storage proteins found in mustard, brazil nut and walnut.

7. A, pages 687-688
- Statement B should read, “All allergens are antigens but not all antigens are allergens.”
- Statement C should read, “Of the five immunoglobulin isotypes, IgE displays the lowest serum concentration, with a peak concentration at 10 to 15 years of age in nonatopic individuals.”
- Statement D should read, “IL-5 is a strong chemoattractant for eosinophils.”
Statement E should read, “Allergens are named using the first three letters of the Genus.”

8. E, pages 692 and 703-704?
Upon activation, mast cells, unlike basophils, are capable of producing prostaglandins. Also, mast cells and basophils utilize the FcεR1 for IgE-dependent activation. MC\textsubscript{T} mast cells demonstrate predominantly tryptase activity and are found mostly in the airways and small bowel mucosa. Basophils are typically found in the blood and migrate to the tissue upon activation.

9. D, page 698
IL12 is released from TH1 cells. All of the others are released from Th2 cells.

10. E, page 718, Table 18-9
Aspirin-induced asthma is an example of a nonallergic hypersensitivity reaction, similar to radiocontrast allergy. Allergic hypersensitivity reactions involve IgE, which aspirin-induced asthma does not. Primary side effects are a result of a drug’s primary mechanism of action, such as drowsiness with antihistamine. Secondary side-effects are due to an additional effect of a drug, such as candidiasis following an antibiotic. Idiosyncratic reactions are not immunologically mediated (ie – not hypersensitivity reactions) and are independent of pharmacologic properties of the drug, such as G6PD deficiency associated hemolytic anemia.