FIT Board Review Corner – October 2015

Welcome to the FIT Board Review Corner, prepared by Andrew Nickels, MD, and Sarah Spriet, DO, 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. Questions? Contact your national FIT representative.

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 12 (pages 239-250): B Cell Activation and Antibody Production
Prepared by Kathryn R. Wessell, DO, University Hospitals Richmond

1. Antibody responses to protein antigens that require the antigen to be internalized by specific B cells, processed, and then the peptides to be presented to CD4+ helper T lymphocytes which then activate the B cells are called:
    a. T-independent antigens
    b. T-dependent antigens
    c. Non-protein antigen response
    d. Non-polysaccharide antigen response

2. Antigen and other stimuli stimulate the proliferation and differentiation of the specific B cell clone. B cell proliferation results in a B cell progeny of the clone that undergoes 4 primary endpoints: antibody secretion, Isotype switching, affinity maturation and _____.
    a. Recruiter B cells
    b. Mature B cells
    c. Memory B cells
    d. Secondary B cells

3. The primary antibody immune response is different from the secondary antibody in many ways. The primary response peak is smaller, the antibody affinity is lower, and the antibody isotype is usually IgM > than IgG, compared to the antibody isotype of the secondary response being typically a relative increase in IgG and _____ in certain situations.
    a. IgA or IgE
    b. IgM or IgA
    c. IgM or IgD
    d. IgA or IgD

4. One of the major distinctions between the forms of antigens recognized by B lymphocytes compared to T lymphocytes is that the antigen that is presented to B cells is generally:
    a. Processed by antigen presenting cells
    b. Presented in its intact, native conformation
    c. Small antigens are taken up by macrophage in the subcapsular sinus

   d. Large antigens are delivered to follicles via conduits

5. B cell activation is facilitated by the _____ co-receptor on B cells, which recognize complement fragments covalently attached to the antigen or that are part of the immune complexes containing the antigen.
   a. CR4/CD 19
   b. CR4/CD 21
   c. CR2/CD 21
   d. CR2/CD 19

6. There are 4 major functional responses induced by antigen-mediated cross-linking of the BCR (B cell receptor) complex. These include expression of proteins that promote survival and cell cycling, antigen presentation increased B7 expression that aides in the interaction with helper T cells, increased expression of cytokine receptors that results in responsiveness to cytokines, and increased expression of _____ that leads to migration of the B cell from the follicle to T cell areas.
   a. CCR7
   b. CCR8
   c. CCR9
   d. CCR10

7. Antigen activated helper T cells and B cells move toward one another in response to chemokine signals and make contact with one another adjacent to the edge of:
   a. Germinal centers
   b. T cell zone
   c. Primary follicles (B cell zone)
   d. Capsule of the lymph node

8. The interaction of _____ in T-Dependent B cell activation stimulates B cell proliferation and differentiation.
   a. CD40 on T cells and CD40 Ligand on B cells
   b. CD 40 Ligand on T cells and CD40 on B cells
   c. CD 40 on Both T cells and B cells
   d. CD40 Ligand on Both T cells and B cells

9. The germinal center consists of a light zone and dark zone. Proliferating B cells accumulate in the dark zone of the germinal center. The small non-dividing progeny of the B cells migrate to the adjacent light zone where they contact _____.
   a. Reticular dendritic cells
   b. Follicular dendritic cells
   c. Mantle zone dendritic cells
   d. Antigen presenting dendritic cells

10. Differentiation of T_{FH} cells from naïve CD4+ T cells requires two steps:
   a. Initial activation by B Cells and subsequent activation by antigen-presenting dendritic cells

b. Initial activation by the follicular dendritic cell and subsequent activation by the antigen-presenting dendritic cell
c. Initial activation by the antigen-presenting dendritic cells and subsequent activation by B cells
d. Initial activation by B cells and subsequent activation by follicular dendritic cells.

Answers

1. B, page 240.
Antibody responses to protein antigens that require that the antigen be internalized by specific B cells, processed, and then that the peptides be presented to CD4+ helper T lymphocytes, which then activate the B cells are called T-dependent antigens. T-independent antigens do not require antigen-specific helper T lymphocytes. Examples are non-protein antigens with repeating determinants such as polysaccharides, some lipids, and nucleic acids.

2. C, page 240, Figure 12-1.
Memory B cells survive in a resting state without secreting antibodies for many years, but they mount rapid responses on subsequent encounters with the antigen.

3. A, page 241, Figure 12-2.
The secondary response has an antibody isotype with a relative increase in IgG and under certain situations an increase in IgA or IgE, compared to IgM, the antibody isotype that predominates in the primary antibody response.

4. B, pages 242-243.
Antigens that are presented to B cells are generally presented in their intact, native conformation and not processed by antigen presenting cells. Small antigens are delivered to naïve B cells in follicles via conduits and larger antigens are delivered to naïve B cells by macrophages in the subcapsular sinus and by dendritic cells in the medulla.

5. C, page 244, Figure 12-5.
The CR2/CD21 coreceptor on B cells facilitates B cell activation. CR2/CD21 enhances BCR (Bell Cell Receptor) signaling.

6. A, page 245, Figure 12-6.
The functional response of migration of B cells toward T cells is a result of the expression of CCR7.

7. C, page 246, Figure 12-8.
T cells and B cells make contact adjacent to the edge of primary follicles.

8. B, page 248.
On activation, helper T cells express CD40 ligand (CD40L) which engages its receptor, CD40, on antigen-stimulated B cells and induces B cell proliferation and differentiation. Cytokines produced by the helper T cells also contribute to B cell responses.

9. B, page 250.
Follicular dendritic cells (FDCs) are found only in lymphoid follicles. Proliferating B cells accumulate in the dark zone of the germinal center, which contains neither FDCs nor T cells. The small non-dividing progeny of the B cells migrate to the adjacent light zone, where they come into close contact with the processes of FDCs and T_{FH} cells, and this is where subsequent selection events occur.

10. C, pages 250 and 251, Figure 12-3.
Differentiation of T_{FH} cells from naïve CD4+ T cells requires initial activation by antigen presenting dendritic cells, then activated T cells express high levels of CXCR5, subsequently the interaction of ICOS with ICOS ligand on activated B cells promotes the differentiation of T cells into T_{FH} cells.

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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 13 (pages 276-287): Regional Immunity: Specialized Immune Responses in Epithelial and Immune Privileged Tissues

Prepared by Shalia E. Smith, DO, Larkin Comm Hosp/Nova Southeastern Univ

1. Which of the below explanations accurately describe why free IgM cannot bind C1q?
    a. Free IgM is a pentameric and are in a configuration that is inaccessible to C1q
    b. IgG molecules bind the Fc portion of IgM making C1q inaccessible to bind
    c. IgM is most efficient in complement binding
    d. IgG is most efficient in complement activation

2. Classical complement activation is essential for ridding the host of various microbes. Which statement best describes the components in C3 convertase?
    a. Binding of C3b to antigen surface thus cleaving C5
    b. Cleavage of C4 to C4b, then binding of C2, then cleavage of C2 leaving C4bC2a
    c. Cleavage of C4 to Ig-associated C1q allowing formation of C3 convertase
    d. C3 binds to C1q and cleaves C5 making C3 convertase

3. How is the lectin pathway activated?
    a. Microbial polysaccharide antigen binds to IgG and this complex binds to free lectins in serum, thus activating lectin pathway
    b. C1q binds antigen (polysaccharide) bound to mannose and other lectins
    c. C3b binds to circulating lectin molecules and then bind to microbial polysaccharides
    d. Activation is triggered in the absence of antibody. Instead microbial activation is triggered in the absence of antibody. Instead microbial

4. Which of the following describes how the host is safe from enzymatic activity in the alternative pathway?
    a. Microbial surfaces degrade C3 convertase thus allowing rapid expansion of microbes
    b. Mammalian cells contain markers which inhibit C3bBb from binding
    c. If the C3bBb complex if bound to mammalian cells, it's rapidly degraded and the activation is inhibited by regulatory proteins
    d. C3 convertase does not bind mammalian cells due to configuration of active sites

5. Which of the below complement components is the most integral to formation of the membrane attack complex?
    a. C5 convertase
    b. C6
    c. C9 convertase
    d. C8
    e. C7 inhibitors

6. Complement receptor 2 (CR2 or CD21) functions to….
    a. Stimulate humoral immune responses by enhancing B cell activation by antigen and by promoting the trapping of antigen-antibody complexes in germinal centers
    b. Promotes phagocytosis of C3b- and C4b- coated particles and clearance of immune complexes from circulation
    c. Function as a receptor for the iC3b fragment generated by proteolysis of C3b
    d. Be expressed on Kupffer cells in the liver

7. A family is seen by you for recurrent swelling in arms, abdomen and face. These episodes are not ameliorated by histamine blockade and last for 1-2 days. One family member had to be intubated due to laryngeal edema and respiratory failure.
   Laboratory values:
    - C1 INH <20% of normal
    - C4 markedly decreased

   You start the family on C1 INH replacement therapy. They ask you about the pathophysiology of this regulatory protein. You tell them….
    a. This autosomal dominant disease causes deficient C1 INH which causes excessive degradation and consumption of C4 and C2 leading to increased fluid in tissues causing pain and swelling
    b. Sun exposure causes mutations in C1 INH and increased degradation of C4 thus making bradykinin induced swelling
    c. Increases in C4 causes C1 INH malfunction thus leading to swelling
    d. This autosomal recessive disease causes deficiency in Ci INH, C4 and C2 which leads to clinical manifestations

8. You are asked to give a lecture to medical students on the functions of complement in humoral immunity and innate immunity. They inform you that they know complement is responsible for opsonization and phagocytosis. You then tell them how complement also causes inflammation. Which statement best describes this?
    a. Complement mediated lysis of foreign organisms is mediated by membrane attack complex
    b. The proteolytic fragments C5a, C4a, and C3a induce inflammation by activating mast cells, neutrophils and endothelial cells
    c. Immune complexes are NOT made more soluble by complement and does not aid in clearance
    d. C3b binds to CR4 on B cells and facilitates B cell activation and the initiation of humoral responses

9. A 20 year old male is admitted to the ICU with sepsis due to meningitis. This is his fourth episode of meningitis in one year. He is sexually active and his CD4+ counts are normal. Infectious Disease staff ask you if there is any immune deficiency that could explain these recurrent severe infections. You tell them…
    a. No. This patient is just unlucky or you all have not given him the right antibiotics
    b. Yes, deficiencies in the terminal complement components including C5, C6, C7, C8 and C9 predispose patients to disseminated infections with Neisseria meningitidis and Neisseria gonorrhoeae
    c. Yes, deficiency in factor H will cause this

d. Yes, deficiency in the terminal complement components can cause lupus

10. A 27 year old female plans to breastfeed her newborn. She says she read on the internet that babies have a weak immune system and that breast feeding protects them. She wants to know how this works. Which of the following describes how this works?
    a. IgA and IgG in breast milk. Transepithelial transport of maternal IgA is dependent on poly Ig receptor and transport of maternal Ig is mediated by neonatal Fc receptor.
    b. Maternal IgE in breast milk provided passive immunity to bacterial microbes
    c. Ingested maternal IgA and IgM colonize the gut and stop opportunistic infections
    d. Maternal IgA is the only type of antibody a mother can provide her infant after birth

Answers

1. A, page 276.
Free IgM is not accessible to C1q, but once IgM binds to antigen, the conformational shape is altered and exposes the sites of Fc portions so that C1q can bind.

2. B, pages 276-278, Figure 13-9.
C4 first binds to Ig-associated C1q and then is cleaved by C1r2S2 enzyme; covalent attachment of C4b to antigenic surface and antibodies. Then C2 binds to C4 and is cleaved into C2a and C2b. C4b and C2a make C3 convertase or C4b2a.

3. D, page 278.
Lectin pathway is antibody independent process. Microbial polysaccharides are bound by circulating lectins. MASPs act at enzymatic proteins cleaving C4 and the rest of the pathway is akin to classic pathway.

4. C, page 276.
Alternative pathway activation readily occurs on microbial cell surfaces and not on mammalian cells page.

5. A, page 279.
C5 convertase from any pathway initiates the last stages of complement pathway which leads to formation of membrane attack complex.

6. A, pages 280-81.

7. A, page 282.

8. B, pages 284-85.

9. B, page 285-86

10. A, page 287.

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Chapter 13 (pages 294-316): Regional Immunity: Specialized Immune Responses in Epithelial and Immune Privileged Tissues

Prepared by Niti S. Agarwal, MD, New York And Presbyterian Hospital (Columbia Campus)

1. Which of the following pairs are correct regarding immunity in the gastrointestinal tract?
    a. M cells: luminal antigen processing
    b. Paneth cells: neutralization of microbes in the lumen
    c. Secretory IgA/IgM: defensin production
    d. Intestinal epithelial cells: luminal antigen sampling

2. DC subsets in the GI tract have which of the following important functions?
    a. Mesenteric antigen sampling
    b. T cell tolerance induction and effector T cell activation
    c. Induction of B cell IgG class switching
    d. Imprinting gut homing phenotypes of strictly B cells

3. Which of the following tissues encompasses the greatest number of lymphocytes?
    a. Bone Marrow
    b. Spleen
    c. Skin
    d. GI tract

4. Which of the following statements is accurate in regards to IGA class switching in the gut?
    a. IgA class switching can occur by only T cell dependent mechanisms
    b. DCs in the subepithelial dome of Peyers patches capture bacterial antigens delivered by M cells and migrate to interfollicular zone where they present antigen to CD8+ T cells
    c. TLR ligand activated DCs induce IgA class switch through factors such as BAFF, APRIL, and TGF-B
    d. B cell class switching to IgA is stimulated primarily through TGF-beta

5. IBD is thought to be related to which of the following immune mechanisms?
    a. Defects in innate immunity to gut commensals such as defensins and NOD2 cytoplasmic innate immune sensors
    b. Abnormalities primarily in the TH2 and TH17 immune response
    c. Adequate T reg mediated suppression of immune responses to commensal organisms
    d. Mutations in select genes relating to cell apoptosis

6. Which of the following immunodeficiency is a result of FOXP3 mutations resulting in failure to develop proper T regulatory response leading to immune dysregulation, polyendocrinopathy, enteropathy, and autoimmunity?
    a. Complete DiGeorge
    b. Nethertons Disease
    c. Deficiency of Interleukin 1 receptor antagonist
    d. IPEX

7. Which of the following is considered an immune privileged site?
    a. Brain
    b. Conjunctiva
    c. Scrotum
    d. Skin

8. Which of the following pairs is correct regarding the cutaneous immune system?
    a. Epidermis: innate immune defense function/physical barrier protection to microbial invasion
    b. Keratinocytes: mixed population of mast cells, macrophages, and DCs mediating inflammatory response
    c. Dermis: secrete defensins as well as inflammatory cytokines to various PAMPs and DAMPs
    d. Keratinocytes: IL-18 and IL-22 induce expression of defensins in keratinocytes

9. Which describes the function of alveolar macrophages best?
    a. Maintaining an anti-inflammatory phenotype
    b. Activate T cell responses as well as antigen presentation of airway Dendritic cells
    c. Expression of IL-5, nitric oxide, and TGF-beta
    d. Highly phagocytic compared with resident macrophages

10. Skin homing molecules include which of the following?
    a. CCR3
    b. CC10
    c. CLA
    d. CCL26

Answers

1. A, page 294.

M cells involved with luminal antigen processing is correct. Paneth cells are involved with defensing production, Secretory IgA/IgM involved with neutralization of microbes in the lumen. Intestinal epithelial cells are involved with mucus secretion, and finally, DC subsets are involved with luminal antigen sampling amongst other functions.

2. B, page 294.
DC subsets in the GI tract are involved with lamina propria antigen sampling, T cell tolerance induction and effector T cell activation, induction of B cell IgA class switching, and imprinting gut homing phenotypes of both B and T cells.

3. B, page 294, Figure 13-2.
The spleen has greatest numbers of lymphocytes, followed by bone marrow and GI tract which have similar numbers, followed by skin.

4. C, page 303, Figure 13-7.
IgA class switching occurs through both T cell dependent and independent mechanisms. DCs in the subepithelial dome of Peyers patches capture bacterial antigens delivered by M cells and migrate to interfollicular zone where they present antigen to CD4+ T cells. TLR ligand activated DCs induce IgA class switch through factors such as BAFF, APRIL, and TGF-B. B cell class switching to IgA is stimulated through action of both TGF-beta and through T cell CD40L binding to B cell CD40.

5. A, pages 307.
IBD is thought to be due to many different immune mechanisms including the following: Defects in innate immunity to gut commensals such as defensins and NOD2 cytoplasmic innate immune sensors, abnormalities primarily in the TH1 and TH17 immune response, inadequate T reg mediated suppression of immune responses to commensal organisms, and mutations in select genes relating to cell autophagy.

6. D, page 307.
IPEX also known as immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX), including severe gut inflammation as well as autoimmunity, is due to FOXP3 mutations leading in failure of Tregs to develop.

7. A, page 316.
Immune privileged sites are tissues where immune responses are not readily initiated, including the brain, anterior chamber of the eye, and testis. Mechanisms include tight junctions of endothelial cells in blood vessels at these sites, local production of immunosuppressive cytokines, and expression of cell surface molecules that inactivate or kill lymphocytes.

8. A, page 315.
Epidermis is involved wtih innate immune defense function/physical barrier protection to microbial invasion. Keratinocytes secrete defensins as well as inflammatory cytokines to various PAMPs and DAMPs, and the dermis has a mixed population of mast cells, macrophages, and DCs mediating inflammatory response. Additionally, IL-17 and IL-22 induce expression of defensins in keratinocytes.

9. A, page 309.
Alveolar macrophages represent the majority of free cells within the alveolar spaces. These cells are functionally distinct from macrophages in most other tissues in that they maintain an anti-inflammatory phenotype. They express IL-10, NO, and TGF-beta, and are poorly phagocytic compared with resident macrophages. Aloveolar macrophages inhibit T cell responses as well as the antigen presentation function of CD103+ airway DCs.

10. C, page 311.
CLA, CCR4, and CCR 10 are all examples of skin-homing molecules. In addition, T cell expression of CCR4 and CCR10 which bind to chemokines CCL17 and CCL27 are also required for T cell trafficking to the skin.