Abbas: Basic Immunology, 5th Edition

Chapter 07: Humoral Immune Responses

Test Bank

MULTIPLE CHOICE

1. Which one of the following statements about primary and secondary antibody responses is NOT true?
   A. Antibodies in primary responses generally have lower affinity for antigen than those produced in secondary responses.
   B. Secondary responses reach peak levels more quickly than primary responses.
   C. Primary responses require higher concentrations of antigen for initiation than secondary responses.
   D. Primary responses occur to all types of antigens, but secondary responses mostly occur only to protein antigens.
   E. Primary responses are characterized by IgG antibodies, whereas secondary responses are dominated by IgM antibodies.

ANS: E
In a primary immune response, IgM antibodies are initially produced against antigens. IgG production requires T cell–dependent isotype switching and is seen predominantly in secondary responses. Primary antibody responses can be mounted to any type of antigen, but secondary responses usually require $CD4^+$ T cell help, and therefore the antigen must be a protein. Primary responses do require higher concentrations of antigen for initiation. The affinity of membrane Ig for antigen is lower on naive B cells, which are responsible for primary responses, compared with memory B cells, which are responsible for secondary responses. Secondary responses develop more quickly and produce higher peak levels of antibody as compared with primary responses.

2. Which one of the following statements about humoral immune responses is true?
   A. Naive B cells are required for initiation of primary responses and memory B cells are required for initiation of secondary responses.
   B. Antibody responses to bacterial polysaccharide antigens require $CD4^+$ helper T cells.
   C. Heavy chain isotype switching typically occurs in response to bacterial polysaccharide antigens.
   D. Affinity maturation does not require helper T cells.
   E. Antibody-secreting cells generated during a humoral immune response live for only a few hours.

ANS: A
Humoral responses require antigen-dependent activation of B cells through binding of the antigen to membrane Ig on naive B cells or on memory B cells, for primary or secondary responses, respectively. In most cases, nonprotein antigens do not stimulate isotype switching or affinity maturation because these changes require T cell help, and only protein antigens can

stimulate T cells. For both nonprotein and protein antigens, antibody-secreting cells that are generated may live for months, often in the bone marrow.

3. All of the following assays are used to detect antibody production EXCEPT:
   A. BrdU (bromodeoxyuridine) assay
   B. Enzyme-linked immunosorbent assay (ELISA)
   C. ELISPOT assay
   D. Hemolytic plaque assay
   E. Radioimmunoassay (RIA)

ANS: A
BrdU (bromodeoxyuridine) is a thymidine analogue that is used to measure cellular proliferation in vivo. BrdU is injected into the organism, and tissues are subsequently stained with anti-BrdU antibody to quantify the extent of BrdU incorporation into cellular DNA. The other assays listed all can be used to detect antibody production.

4. A 5-year-old boy has a history of recurrent pneumococcal pneumonia, *Pneumocystis carinii* pneumonia (PCP), and bacterial ear infections. His maternal uncle and an older brother experienced the same symptoms, but he has an older sister who is healthy. Laboratory studies indicate normal numbers of B cells and T cells, and the serum contains mostly IgM and very little IgG. Which of the following abnormalities would NOT be likely in this patient?
   A. The IgG antibodies that are present are of lower affinity for antigen than of those of a healthy individual.
   B. Lymph nodes are without well-developed follicles containing germinal centers.
   C. Macrophage killing of intracellular microbes is impaired.
   D. There is limited diversity in the repertoire of IgM antibodies produced.
   E. There is no evidence of somatic mutation of IgM variable regions.

ANS: D
This is a common presentation of hyper-IgM syndrome. Patients with this disease have B cells that are unable to undergo isotype switching, and therefore contain only IgM in the serum but very low levels of IgG, IgA, and IgE. Clinically, these patients are susceptible to bacterial infections and often present with a history of recurrent pneumonia, otitis media, and gastrointestinal infections. Mutations in genes coding for CD40L, CD40, and activation-induced deaminase (AID) have been identified in these patients. During an immune response, T cell interactions with B cells via CD40L-CD40, as well as active AID, are both essential for numerous processes, including isotype switching, somatic mutation, and germinal center formation. Thus, patients with hyper-IgM syndrome produce antibodies that typically have a lower affinity for antigen (due to the lack of somatic mutation) and do not develop large follicles containing a light zone and dark zone (germinal center) within lymph nodes. Mechanisms of generation of diversity of the Ig repertoire should not be impaired in this patient. Although somatic mutation of variable regions will be impaired, this will not be manifest in IgM antibodies. In addition, patients with either CD40L or CD40 mutations, but not AID mutations, will have an increased susceptibility to certain intracellular infections (such as *Pneumocystic carinii* pneumonia), because the microbicidal activity of macrophages is partially dependent on CD40-mediated signals.

5. A 5-year-old boy has a history of recurrent pneumococcal pneumonia, *Pneumocystis carinii* pneumonia (PCP), and bacterial ear infections. His maternal uncle and an older brother experienced the same symptoms, but he has an older sister who is healthy. Laboratory studies indicate normal numbers of B cells and T cells, and the serum contains mostly IgM and very little IgG. Which of the following genes most likely contains a mutation in this patient?

A. *AID* (activation-induced deaminase)
B. *CD40*
C. *CD40L*
D. *CD28*
E. *CTLA-4*

ANS: C
Because both a maternal uncle and an older brother, but not the patient's sister, are affected, the inheritance pattern is most likely X-linked recessive. The *CD40L* gene is located on the X-chromosome.

6. A 5-year-old boy has a history of recurrent pneumococcal pneumonia, *Pneumocystis carinii* pneumonia (PCP), and bacterial ear infections. His maternal uncle and an older brother experienced the same symptoms, but he has an older sister who is healthy. Laboratory studies indicate normal numbers of B cells and T cells, and the serum contains mostly IgM and very little IgG. If this patient did have a sister affected with the same condition, which of the following genes would most likely contain a mutation?

A. *AID* (activation-induced deaminase)
B. *CD40*
C. *CD40L*
D. *CD28*
E. *CTLA-4*

ANS: B
If the patient's sister is also affected with hyper-IgM syndrome, then the inheritance pattern is autosomal recessive. Both the *AID* and *CD40* genes are located on autosomal chromosomes, and mutations in both have been identified as causes of hyper-IgM syndrome. However, only a mutation in *CD40* will result in reduced macrophage function and susceptibility to *Pneumocystis carinii* pneumonia, as is observed in this patient.

7. The B cell receptor (BCR) complex and the signaling cascades to which it is linked share many similarities with the T cell receptor (TCR) complex and its linked signaling cascades. Which of the following comparisons between BCR and TCR signaling is NOT true?

A. There are ITAMs in the cytoplasmic tails of CD3 in the TCR complex and in the cytoplasmic tails of Igα and Igβ in the BCR complex.
B. The cytoplasmic tails of membrane Ig and TCR $\alpha\beta$ antigen receptors are very short and lack intrinsic signaling functionality.
C. Early signaling events induced by antigen binding to both BCR and TCR involve both Src family and Zap-70 family protein tyrosine kinases.
D. Phospholipase C–mediated generation of IP_3 and DAG occurs downstream of both BCR and TCR signaling.

E. CD4/CD8 coreceptors in T cells and the CR2 coreceptor in B cells both enhance responses to antigen by a PI3 kinase–dependent mechanism.

ANS: E
The CR2 coreceptor, in association with CD19 and CD81, activates PI3-kinase. CD4 and CD8 do not activate PI3-kinase but, rather, bring the Src family tyrosine kinase Lck into proximity of the TCR complex.

8. The initial cellular events that are induced by antigen-mediated cross-linking of the B cell receptor (BCR) complex include all of the following EXCEPT:
A. Increased percentage of time spent in mitosis, resulting in rapid proliferation
B. Increased expression of B7, resulting in enhanced APC function
C. Increased expression of bcl-2, resulting in improved survival
D. Increased expression of CCR7, promoting migration into lymph node follicles
E. Increased expression of the interleukin-2 receptor, resulting in enhanced proliferation and response to T cell signals

ANS: D
In the initial events after antigen binding to the B cell receptor, B cells migrate out of, not into, the lymph node follicles and toward the T cell zones by increasing expression of CCR7, a chemokine receptor that responds to chemokines produced in the T cell zone. Helper T cells play an important role in the activation of B cells, inducing proliferation, isotype switching, and somatic mutation both by the release of cytokines as well as through direct interactions with the B cell via CD40L. T cell–mediated activation of B cells can only occur in the presence of protein antigens. Other early events that occur in B cell activation include increased proliferation and time spent in mitosis, increased expression of B7 to enhance the B cell's ability to activate T cells, increased expression of the anti-apoptotic protein bcl-2 to promote survival, and increased expression of cytokine receptors to enhance survival and proliferative signals coming from T cells.

9. Which one of the following statements accurately describes antigen recognition events in a lymph node during a helper T cell–dependent antibody response to a protein antigen?
A. Naive B cells and naive T cells simultaneously recognize the intact protein antigen.
B. Naive B cells recognize intact proteins, generate peptide fragments of these proteins, and present them in complexes with major histocompatibility complex (MHC) molecules to naive helper T cells.
C. Naive B cells recognize intact proteins, generate peptide fragments of these proteins, and present them in complexes with MHC molecules to differentiated helper T cells.
D. Naive T cells recognize peptides bound to MHC molecules presented by dendritic cells, and naive B cells recognize the intact protein antigen bound to the surface of follicular dendritic cells.
E. Differentiated helper T cells recognize peptides bound to MHC molecules on dendritic cells, and the T cells secrete cytokines that promote antibody production by any nearby B cells that have recognized different protein antigens.

ANS: C

T cells and B cells cannot recognize the same protein antigen molecule simultaneously because T cells only recognize peptide-MHC complexes. B cells bind intact proteins, internalize them via surface Ig, and then present peptide-MHC complexes to helper T cells, not to naive T cells. The helper T cells specific for the peptide-MHC complexes have been differentiated from naive T cells that recognized the same peptide-MHC complexes presented by dendritic cells. Follicular dendritic cells display intact protein antigens to previously activated (but not naive) B cells during the germinal center reaction. Collaboration of T cells and B cells requires direct contact of T cells and B cells specific for the same antigen, even though the antigen recognition events are not simultaneous, because the bidirectional activation requires membrane-bound molecules (i.e., CD40 ligand on the T cells and CD40 on the B cells).

10. Which one of the following B cell responses is NOT stimulated by CD40 ligand?
    A. Association of TRAFs with the cytoplasmic tails of CD40 molecules
    B. Activation of NF-κB
    C. Enhanced expression of B7-1 and B7-2
    D. Enhanced Ig isotype switch recombinase activity
    E. Enhanced production of membrane Ig

ANS: E
CD40 ligand binding to B cell CD40 enhances production of secreted, not membrane, Ig. CD40 signaling involves recruitment of signaling intermediates, called tumor necrosis factor–receptor associated factors (TRAFs), to the cytoplasmic tails of CD40 and the downstream activation of NF-κB, as well as other transcription factors. The signaling cascades result in increased expression of various genes, including B7 costimulators, and increased Ig isotype switching, which is mediated by switch recombinases.

11. Which of the following mechanisms contributes to the change from B cell production of membrane Ig to secreted Ig?
    A. V(D)J recombinase-mediated deletion of the exon encoding the transmembrane domain
    B. Alternative processing of primary RNA transcripts to remove the transmembrane domain and include a secretory tail piece
    C. Increased vesicular exocytosis of intracellular stores of the secretory form of Ig
    D. Switch recombinase-mediated recombination of the heavy chain locus to juxtapose the V(D)J segment with the exon encoding a secretory tail piece
    E. Up-regulation of ectoenzymes that proteolytically cleave membrane Ig heavy chains just proximal to the membrane

ANS: B
Primary transcripts of Ig genes include sequences encoding both transmembrane and secretory tail piece domains. Alternative splicing of these transcripts determines which form of Ig is ultimately made. V(D)J recombinases are not involved in modifications of Ig heavy chain expression, and switch recombinases are only involved in changes in DNA related to isotype switching. Membrane Ig is not cleaved to form secretory Ig.

12. Which of the following statements about Ig isotype switching is NOT true?
    A. Interleukin-4 promotes switching to the IgE isotype by increasing germline transcription of the Cε exon.

B. Isotype switching involves recombination of a V(D)J complex with downstream C region genes and the deletion of intervening DNA including other C region genes.
C. Activation-induced deaminase (AID) is required for switch recombination.
D. The enzymes that mediate isotype switching recognize conserved heptamer and nonamer DNA sequences adjacent to the constant region exons.
E. The same recombined V(D)J gene complex is used to encode the antigen-binding region of the antibodies produced by a B cell before and after isotype switching.

ANS: D
Heptamer and nonamer sequences are part of the recombination signal sequences recognized by V(D)J recombinases, and not by the enzymes that mediate switch recombination. I exons and S (switch) regions are the DNA "landmarks" just upstream of each constant region gene that dictates where switch recombination will occur. Switch recombination is incompletely understood, but requires AID as well as other enzymes that gain access to the S regions when germline transcription through the I, S, and C exons is induced by cytokines. The same V(D)J unit is used to encode the antigen-binding site after switch recombination, and this preserves antigen specificity of the antibodies produced while effector functions of the antibodies change.

13. Which one of the following molecules is important for the production of IgE antibodies?
A. CD28
B. CD40
C. IFN-γ
D. IL-2
E. TGF-β

ANS: B
Cytokines play essential roles in regulating the switch to particular heavy chain isotypes. IFN-γ is important in switching to the IgG isotype (specifically IgG3), whereas TGF-β is a stimulator of IgA production. The cytokine that promotes IgE production is IL-4, but this is not an answer choice. However, the process of isotype switching in general is known to depend on signaling through CD40L-CD40, and is also dependent on the activity of the enzyme activation-induced deaminase (AID). CD28 is a costimulatory molecule that is important for T cell activation and CD40L up-regulation. However, other costimulatory molecules are also present on T cells that can cause up-regulation of CD40L. IL-2 is a growth factor cytokine for T cells.

14. Which of the following events does NOT occur within germinal centers?
A. Somatic mutation of Ig V genes
B. Generation of memory B cells
C. B cell proliferation
D. Affinity maturation
E. Ig gene V(D)J recombination

ANS: E
V(D)J recombination to form functional Ig genes occurs only in developing B cells, mostly in the bone marrow. Germinal centers are sites of differentiation of mature B cells, in response to T cell–dependent protein antigens. The germinal center "reaction" begins with helper T cell signals delivered to B cells via CD40 ligand and cytokines. This results in B cell movement back into

the follicle and brisk B cell proliferation of one or a few clones of B cells specific for an inciting antigen. The proliferating B cells undergo somatic mutation of the variable genes, at which point mutations are introduced that may alter the affinity of the encoded antibodies for their antigens. Antigens are displayed in limited concentrations on the surfaces of follicular dendritic cells in the germinal center, and only B cells whose high-affinity Ig receptors can bind these antigens are selected to survive. Some of these cells become antibody-secreting cells, and others become memory B cells.

15. Which of the following descriptions about affinity maturation is correct?
    A. Depends on somatic mutation of V genes
    B. Depends on negative selection of B cells that can bind antigen in the germinal center
    C. Depends on antigen processing and presentation by dendritic cells within the germinal center
    D. Depends on the autoimmune regulator (AIRE) gene
    E. Depends on somatic recombination of Ig V genes

ANS; A
Somatic mutation of V genes is the basis for production of immunoglobulins with different affinities, which are then positively selected in the germinal center; B cells that cannot bind antigen with high affinity die through a default pathway of apoptosis. Antigen processing and presentation by dendritic cells are required to generate helper T cells outside the follicle, but not to activate B cells in the follicle. Autoimmune regulator (AIRE) is involved in thymic expression of tissue antigens but is not involved in affinity maturation. Somatic recombination of V genes is involved in producing functional Ig genes during B cell development, but it is not involved in germinal center reactions.

16. Which of the following antigenic structures might activate B cell antibody production without the aid of T cells?
    A. Lysozyme
    B. Benzene
    C. Glucose-6-phosphate
    D. ABO blood group antigen
    E. Rh factor antigen

ANS: D
T cell–independent antigens consist of polysaccharides, glycolipids, and nucleic acids with multiple repeated epitopes, so that maximal cross-linking of the B cell receptor is induced, thus bypassing the need for T cell help. Of the answer choices, the best choice is the ABO blood group antigen, because of its polyvalent glycolipid structure. Lysozyme and the Rh factor are protein antigens. Benzene and glucose-6-phosphate are not polyvalent.

17. Antibody feedback is mediated by which of the following molecules?
    A. Ig FcγRIIB
    B. Ig Fcε
    C. Ig FcγRI
    D. CR1
    E. IgM

ANS: A
Antibody feedback is the mechanism of regulation of humoral immune responses and is mediated by the Ig FcγRIIB receptor, which delivers inhibitory signals into the B cells on binding the Fc portion of IgG.