ANSWERS TO END-OF-CHAPTER QUESTIONS

Chapter 1 Answers

1.1 **A.**

1.2 **C.**

1.3 **False.**

1.4 A, myeloid; B, lymphoid; C, myeloid; D, lymphoid; E, myeloid; F, myeloid.

1.5 **B.**

1.6 **False.**

1.7 **A, 2; B, 3; C, 4; D, 1.**

1.8 **C.**

1.9 A, central; B, peripheral; C, peripheral; D, central; E, peripheral.

1.10 **A, 3; B, 1; C, 2.**

1.11 **D.**

1.12 Cytotoxic, helper.

1.13 **False.**

1.14 **False.**

1.15 **A.**

1.16 **B.**

1.17 **False.**

Chapter 2 Answers

2.1 **B.** Even though β-lactams disrupt the cell wall through a different mechanism, lysozyme also disrupts the bacterial cell wall structure via enzymatic digestion, specifically, cleavage of the β-(1,4) linkage between *N*-acetylglucosamine and *N*-acetylmuramic acid.

2.2 A single carbohydrate-recognition domain of an MBL has low affinity for mannose, fucose, and *N*-acetylglucosamine (GlcNAc) residues. Therefore, its capacity to oligomerize is important because it increases the total binding strength, or avidity, of MBL.

2.3 **D.** Ficolins have a fibrinogen-like domain that provides them with a general specificity for oligosaccharides containing acetylated sugars. Ficolins can be synthetized by the liver, lungs, and blood cells. In contrast, mannose-binding lectins contain C-type lectin domains that recognize mannose, fucose, and *N*-acetylglucosamine (GlcNAc) residues and are synthesized only in the liver.

2.4 **MASP-1; MASP-2; C4; C2; C4b2a; C3.**

2.5 Despite the fact that the initiating C3 convertase is soluble, the membrane-attack complex can develop because part of the C3b produced by the alternative C3 convertase becomes membrane-bound, allowing the formation of a membrane-bound C3 and C5 convertase.

2.6 **CD59; DAF; alternative.** Paroxysmal nocturnal hemoglobinuria is caused by a somatic mutation in an enzyme that normally synthesizes glycophosphatidylinositol tails that are necessary for anchoring and expressing proteins such as CD59 and DAF at the cell surface. Failure to express these complement-regulatory proteins in red blood cells leaves them susceptible to lysis by the complement system, particularly by the alternative pathway given the baseline spontaneous cleavage of C3 that occurs.

2.7 **A, 2; B, 1; C, 3.** The classical complement pathway can be regulated at multiple steps, and malfunction of regulatory proteins can result in multiple pathologies. For example, the activation of C1 is controlled by the plasma serine protease C1INH, and deficiency in this regulatory protein leads to episodic activation of the complement system and can cause hereditary angioedema. The critical balance between regulation and activation can also be exemplified by heterozygous mutations in factor H, factor I, or MCP. The resulting haploinsufficiency tips the balance toward complement activation and leads to a predisposition to atypical hemolytic uremic syndrome. Dysfunction of membrane-bound regulatory proteins can also result in pathology. For example, mutations in the enzyme involved in the synthesis of the glycosylphosphatidylinositol (GPI) tail that anchors DAF (and CD59) to the membrane causes paroxysmal nocturnal hemoglobinuria.

2.8 **A.** Cryoglobulinemia or systemic lupus erythematosus patients have low C4 and C3 because these autoimmune diseases activate the classical pathway. In contrast, dense deposit disease and C3 glomerulonephritis activate the alternative pathway, which does not use C2 or C4 to form the C3 convertase; therefore, the levels of C2 and C4 are usually normal.

2.9 **False.** Mucins only prevent adherence of microorganisms to the cell surface; they do not directly display microbicidal activities.

2.10 *Neisseria meningitidis* produces (1) factor H-binding protein to recruit factor H and inactivate C3b, and (2) PorA to recruit C4b-binding protein (C4BP) and inactivate C4b. *Staphylococcus aureus* bears (1) protein A, which binds to the Fc regions of Ig and interferes with C2 recruitment; (2) staphylokinase, which cleaves immunoglobulins bound to the surface; and (3) staphylococcal complement inhibitor (SCIN) to inhibit the activity of the C3 convertase.

2.11 **False.** Neutrophils produce antimicrobial peptides constitutively and store them in granules, but release them only upon stimulation or activation. Paneth cells produce and secrete antimicrobial peptides constitutively.

2.12 All complement pathways lead to the formation of the C3 convertase, which cleaves C3 to form C3a and C3b. C3b formation leads to opsonization, MAC formation/lysis, and potentiation of antibody responses (when its breakdown product C3dg is formed). C3a causes local inflammation (cell recruitment).

2.13 **True.**

Chapter 3 Answers

3.1 **A, iii; B, iv; C, ii; D, v; E, i; F, vi.**

3.2 **A, iv; B, ii; C, i; D, vi; E, iii; F, v.**

3.3 **D.** During an inflammatory response, vascular permeability increases in order to allow influx of serum factors and extravasation of immune cells into the inflamed tissue.

3.4 Conventional dendritic cells are antigen-presenting cells that bridge the innate and adaptive immune systems by integrating danger signals via PRRs and translating them into co-stimulatory signals for adequate T-cell priming, while plasmacytoid dendritic cells are dedicated high-level type I interferon producers.

3.5 **A.**

3.6 **False.** As discussed in this chapter, certain ubiquitin lysine linkages (e.g., K63) activate cellular signaling rather than target substrates for proteasomal degradation.

3.7 **A, IL-1R; B, JAK, STATs; C, TLR-4.**

3.8 **True.**

3.9 **D.** The inflammasome is composed of NLRP3, ASC, and caspase 1 oligomers. Caspase 1 is responsible for processing pro-IL-1β into IL-1β. Caspase 8 is involved in the initiation of the extrinsic pathway of apoptosis.

3.10 **False.** NK cells do not have antigen receptors, and although KIRs bind MHC class I, they are not bona fide antigen receptors, because of their broad reactivity to various MHC class I alleles.

3.11 **A, ii; B, v; C, iii; D, i; E, iv.**

3.12 B7.1 (CD80) and B7.2 (CD86) are expressed on macrophages and dendritic cells upon pathogen recognition via PRRs in order to ligate CD28 on T cells and provide a co-stimulatory signal.

Chapter 4 Answers

4.1 **False.** An antibody proteolytically cleaved by papain yields a fragment with *lower* avidity to the cognate antigen than an antibody cleaved with pepsin because it yields a single monomeric Fab fragment, while pepsin digestion will yield an $F(ab')_2$ dimer, which will have higher avidity.

4.2 CD4 and CD8 co-receptor binding to MHC is important for TCR signaling because CD4 and CD8 bind Lck on their cytoplasmic tails and brings the kinase into proximity with the T-cell receptor complex and helps to activate the signaling cascade induced by the T-cell receptor after antigen recognition.

4.3 It is advantageous to have heterozygosity of the MHC locus because having different alleles increases the diversity of the set of peptides that can be presented by each allele for a specific pathogen, thus increasing the chance of efficiently targeting a pathogen-derived epitope.

4.4 **A, i; B, iv; C, iii; D, ii.**

4.5 heavy, light, V (variable), C (constant), heavy chain only IgGs (hcIgGs), immunoglobulin new antigen receptor (IgNAR)

4.6 **A.** TCRα-chain recombination deletes the TCRδ-chain locus, thus eliminating the possibility of co-expression of an αβ and a γδ TCR during T-cell development.

4.7 **D.**

4.8 **E.**

4.9 **C.** Affinity is determined by the antigen-recognition site only.

4.10 **F.**

Chapter 5 Answers

5.1 **False.** TCRα chain recombination deletes the TCRδ chain locus, thus eliminating the possibility of co-expression of an αβ and a γδ TCR during T-cell development.

5.2 **B.** TdT adds N-nucleotides and is necessary to create the massive amount of diversity seen in CDR3, but is not necessary for recombination. The recombinases RAG-1 and RAG-2 and all DNA repair enzymes are, however, necessary for proper recombination and antigen-receptor formation.

5.3 **False.** B cells undergo somatic hypermutation and affinity maturation even after B-cell development and maturation, but T cells do not.

5.4 The four processes that contribute to the vast diversity of antibodies and BCRs are combinatorial diversity from different V(D)J segment joining; junctional diversity engendered by the actions of Artemis, exonucleases, and TdT; different heavy- and light-chain pairings; and somatic hypermutation during an immune response.

5.5 **A, iii; B, ii; C, i; D, iv; E, v.**

5.6 The 12/23 rule states that an RSS that has a 12-bp spacer can recombine with and be joined to only an RSS with a 23-bp spacer. This ensures that in the heavy-chain, TCRβ, and TCRδ loci, D segments will join only to J segments and V segments will only join to D segments, while in the light-chain, TCRα, and TCRγ loci, V segments will join only to J segments.

5.7 **A, ii; B, iii; C, i.**

5.8 **A, iii; B, v; C, iv; D, i; E, ii.**

5.9 IgA, IgM, J chain, IgD, splicing, ZFP318, CstF-64, ELL2, IgG1, IgG3, IgE, FcRn.

5.10 **E.** MHC class I and class II genes arose at the same time as T cells and immunoglobulin in cartilaginous fish.

Chapter 6 Answers

6.1 Presentation of exogenous antigens on MHC class I molecules is called cross-presentaion. This capability is important because it allows dendritic cells to mount a CD8 T-cell response against bacteria or viruses without having been infected themselves. All nucleated cells can present antigens via MHC class I molecules; however, all cells other than dendritic cells can present only cytosolic antigens that have been transported into the endoplasmic reticulum for direct MHC class I loading.

6.2 **A, ii; B, iii; C, i; D, v; E, iv.**

6.3 **False.** An *in vitro* study of mutant cells deficient in the supply of peptides to the endoplasmic reticulum found that MHC class I surface expression is affected by this ability. This defect could be corrected by adding synthetic peptides to the culture medium.

6.4 **Cytosol, TAP1/2, endoplasmic reticulum, 8–16, hydrophobic, proline, three.**

6.5 **D.** CD8 dendritic cells require BATF3 for their development and can be uniquely identified using XCR1.

6.6 **A, ii; B, iv; C, i; D, v; E, iii.**

6.7 **False.** The most likely way in which cytosolic proteins are processed for MHC class II presentation is through a natural process called autophagy, in which damaged organelles or proteins are delivered to lysosomes.

6.8 **4, 1, 5, 2, 6, 3.**

6.9 **C. Tap1/2.**

6.10 **A. IRGM3.**

6.11 **True.** Superantigens promote an uncontrolled and unspecific T-cell expansion that results in immunosuppression and systemic toxicity. The activity of superantigens depends on binding as an intact protein, as fragmentation ablates their function.

6.12 **C.** Some pathogens have been shown to exert evolutionary pressure to select for specific alleles. For example, people from West Africa, where malaria is endemic, have a high allelic frequency for HLA-B53, which is associated with recovery from a potentially lethal form of malaria. However, in regions in which malaria is rare, the allelic frequency of HLA-B53 is low.

6.13 **True.**

6.14 **A, iv; B, iii; C, i; D, ii.**

Chapter 7 Answers

7.1 **False.** Antigen receptors have no intrinsic enzymatic activity; instead, they rely on co-receptors and adaptor proteins that recruit and activate cytoplasmic tyrosine kinases upon antigen receptor engagement by its ligand.

7.2 **A: RTK; B: null; C: RTK; D: RSTK.**

7.3 Scaffolds can themselves specifically recruit signaling proteins as well as their protein substrates to a particular site, such as the cell membrane, which can change the efficiency and specificity of the protein enzymes, as well as cause conformation changes that alter activity or expose certain domains. Adaptors work similarly by specifically linking two or more proteins, thus allowing them to act on each other or work in conjunction.

7.4 **B and E**. Any alteration that results in prolongation of the GTP-bound state of Ras will result in enhanced activity. GEFs will enhance Ras activity by catalyzing the exchange of GDP for GTP. GAPs, however, will decrease Ras activity by enhancing the GTPase activity of Ras, which leads to the hydrolysis of GTP to GDP.

7.5 **3; 2; 5; 4; 1.**

7.6 **LAT:Gads:SLP-76; PI 3-kinase; SH2; PH/PX; PLC-γ; Akt; ADAP; Vav.**

7.7 **A: iv; B: i; C: iii; D: ii.**

7.8 **D**. Mono- and di-ubiquitination of surface receptors leads to recognition by ubiquitin-binding proteins that target the receptor for degradation in lysosomes.

7.9 **A: iii; B: iv; C: i; D: ii.**

7.10 **A: Igα:Igβ; B: CD4 or CD8; C: CD40; D: Lck; E: ZAP-70, F: SLP-65 (BLNK).**

7.11 **False.** PD-1 contains ITIMs that recruit and activate the protein tyrosine phosphatase SHP and the inositol phosphatase SHIP upon ligand binding, but CTLA-4 does not bear an ITIM or any known canonical inhibitory motif. It is believed that CTLA-4 interferes with co-stimulatory signaling pathways—namely, CD28—by binding CD28 ligands B7.1 (CD80) and B7.2 (CD86) with much higher affinity and sequestering them away from CD28.

7.12 **B.** CD22 is an inhibitory receptor on B cells that binds sialic acid-containing glycoproteins, which are commonly found on mammalian cells. Antibodies themselves are highly sialylated glycoproteins, and thus can exert an inhibitory effect on B cells when produced at high levels. This serves as a negative-feedback mechanism to antibody production, although negative feedback through other inhibitory receptors (for example FcγRIIB) can also occur in this and other contexts.

Chapter 8 Answers

8.1 **False.** The IL-7 receptor forms from the dimerization of the IL-7 receptor α and the common γ chain. Due to the importance of IL-7 for murine B-cell development, mice with a genetic deficiency in IL-7, IL-7 receptor α, or γ-c all exhibit a severe block in B-cell development.

8.2 **Early pro-B-cell; E2A and EBF; pre-B-cell receptor; allelic exclusion.**

8.3 **False.** The pre-B-cell receptor contains a protein called VpreB, which mediates the cross-linking with adjacent pre-B-cell receptors and does not depend on self-antigen recognition.

8.4 **A: ii; B: iv; C: v; D: i; E: iii.** Early pro-B cells start to rearrange their D–J segments in both of the heavy-chain alleles. As the early pro-B cell transitions into the late pro-B cell, only one allele of the heavy-chain locus rearranges V–DJ; if such rearrangement results in a functional pre-B-cell receptor, signaling during the large pre-B-cell stage induces the process of allelic exclusion and the heavy-chain allele that has not rearranged V–DJ is inhibited from doing so. After several rounds of division the small pre-B cell rearranges the V–J segments of the light-chain locus. Successful rearrangement of both light and heavy chain allows the expression of IgM, at which point the cell becomes an immature B cell.

8.5 Signaling from the pre-B-cell receptor promotes allelic exclusion by the following mechanisms: (1) reduces RAG-1 and RAG-2 expression, (2) targets RAG-2 for degradation, and (3) reduces access to the incompletely rearranged heavy-chain locus to the rearrangement machinery. This process is important because successful allelic exclusion prevents a B cell from having multiple receptors with different antigen specificities.

8.6 A B-cell progenitor that has successfully rearranged its heavy-chain locus can expand from 30- to 60-fold before it starts to rearrange the light-chain locus. This process allows each of the small pro-B cells to produce receptors with different antigen specificities, by each rearranging and expressing a different light chain, thereby increasing the overall B-cell receptor diversity.

8.7 **A: iv; B: ii; C: i; D: v; E: iii.**

8.8 **False.** This population also includes γ:δ T cells and iNKT cells.

8.9 **A: ii; B: i; C: iii; D: iv.**

8.10 TCR β chain, DN3, pre-Tα, cell proliferation, β-chain, CD8 and CD4, TCR α chain.

8.11 **A: iv; B: iii; C: ii; D: i; E: v.**

8.12 **C.** A difference in the development of T-cell receptors and B-cell receptors is the ability to suppress further rearrangements once the mature antigen receptor is expressed. This process does not occur in T cells, because RAG proteins are not downregulated upon successful formation of a T-cell receptor, and signaling upon peptide:MHC binding is needed in order to suppress further rearrangements. This allows T cells to possess multiple TCR α chains.

8.13 **C.** T_{reg} cells belong to the $CD4^+$ branch of T cells, and their main function is to maintain self-tolerance. They can be identified by expression of FoxP3. As opposed to conventional T cells, T_{reg} cells have a high affinity for MHC:self peptide complexes.

8.14 **A.** Cathepsin L is involved in processing of peptides for loading onto MHC class II molecules, and thus its deletion would not affect $CD8^+$ T-cell development, which depends on MHC class I molecules. Runx3 is a transcription factor necessary for $CD8^+$ T-cell development, and ThPOK, a transcription factor necessary for $CD4^+$ T-cell development, represses its expression. The proteasomal subunit β5T in cortical thymic epithelial cells is important for presentation of self peptides on MHC class I molecules that mediate positive selection to developing thymocytes.

8.15 **C.** Because CD4 and CD8 bind up intracellular Lck, it is necessary that the ligand the T-cell receptor binds is an MHC protein, as MHC proteins also bind to CD4 or to CD8 and bring Lck close to the T-cell receptor complex and lead to phosphorylation of ITAM-containing tails and downstream cellular signaling. Thus, MHC restriction is ensured given that non-MHC ligands would not recruit the CD4 or CD8 co-receptors, an event that would result in inefficient downstream signaling and, ultimately, death by neglect of the non-MHC-restricted thymocyte.

8.16 The affinity hypothesis is the theory that positive and negative selection of thymocytes is determined by the strength of binding of self peptide MHC to T-cell receptor. Under this hypothesis, low-affinity interactions result in positive selection of thymocytes that would have undergone death by neglect if not slightly stimulated, whereas high-affinity interactions lead to apoptosis.

Chapter 9 Answers

9.1 **D.**

9.2 Stromal cells, HEVs, CCL19, CXCL13, folicular dendritic cells, follicles, CXCR5.

9.3 **C.**

9.4 Peripherally infected antigen-presenting cells that migrate to the lymph node can die due to the infection. Resident dendritic cells, in particular, $CD8^+$ or BDCA-3^+, can take up the dying dendritic cells and present the viral antigens through cross-presentaion.

9.5 **False.** CCR7 induction promotes migration of the dendritic cell through the lymphatic system.

9.6 **cDC, pDC, cDC, cDC, pDC.** cDC activation causes important physiological changes that enhance cDC T-cell priming abilities. For example, cDCs produce CCL18 to attract T cells, express CD80 and CD86 co-stimulatory molecules, and increase expression of adhesion molecules such as DC-SIGN. In contrast, upon activation, pDCs continue recycling the MHC molecules and express CD40L upon TLR-9 stimulation, which can help cDCs express more IL-12.

9.7 Dendritic cells continuously survey tissues for invading pathogens and can activate naive T cells to the extent that their migratory capacity, co-stimulatory molecule expression, and anatomical position allow them to. In contrast, macrophages cannot migrate to the lymph node and present antigens that have been encountered in the periphery, and those that reside within the lymph node are largely sequestered from the T-cell zone, diminishing their ability to activate naive T cells. Nevertheless, antigen presentation and co-stimulation in the periphery are likely important to locally amplify T-cell responses. On the other hand, presentation of antigens by B cells recruits help from T cells to stimulate antibody production and class switching.

9.8 **A.** Both CCR7 and TCR signaling induce activation of LFA-1, which stabilizes the antigen-presenting cell and the antigen-specific T cell and in the context of migration promotes diapedesis by increasing the strength of the interaction.

9.9 **A.** CD28 signaling induces expression of proteins that block activity of the instability sequence AUUUAUUUA in the 3′ untranslated region of IL-2 mRNA.

9.10 **True.** Activated CD4 T cells induce CD40L expression, which in turn increases B7 and 4-1BBL expression in the antigen-presenting cell, which in turn provides more co-stimulation for the naive CD8 T cell.

9.11 **A, ii; B, iii; C, i; D, iv.**

9.12 **A, iii; B, iv; C, i; D, ii.**

9.13 **A.** T-cell receptor (TCR) signaling is weakest at the cSMAC because TCRs are being endocytosed and actively degraded.

9.14 Apoptotic, FasL, TNF-α, LT-α, extrinsic, perforins, caspase 3, ICAD, CAD, BID, cytochrome *c*, apoptosome.

Chapter 10 Answers

10.1 **D.** Linked recognition is the property whereby B cells and T cells recognize the same antigen even though they recognize different epitopes.

10.2 The current Hib vaccine exploits the immunological phenomenon of linked recognition. By conjugating the Hib capsule-derived polysaccharide with a toxoid, Hib polysaccharide-specific B cells will endocytose and process the toxoid and present toxoid-derived peptides on MHC class II molecules, which will be recognized by toxoid-specific helper T cells that will stimulate a potent TD response.

10.3 **A, T; B, B; C, T; D, T; E, B; F, N; G, TB.**

10.4 **A, iii; B, iv; C, i; D, ii.**

10.5 **A, IgM; B, IgG, IgD, IgE; C, IgA; D, IgM; E, IgA, IgM; F, IgM, IgG; G, IgA; H, IgM; I, IgE; J, IgA, IgM; K, IgG.**

10.6 TRIM21 is a cytosolic Fc receptor that is also an E3 ubiquitin ligase. When it recognizes antibody-coated viruses in the cytosol, it ubiquitinates proteins on the virus to target it to proteasomal degradation.

10.7 **C.** Mast-cell degranulation depends on IgE binding to the high-affinity FcεRI.

10.8 **D.** Plasma cells express low levels of MHC class II, B7, and B-cell receptor, as they are specialized for long-lasting antibody secretion and not T-cell priming, unlike plasmablasts.

10.9 **False.** The descriptions of the light and dark zones are reversed.

10.10 **C.** R-loops are thought to induce stalling of the polymerase through the switch region, but not to directly promote accessibility of the V region to AID. It is the enzyme UNG, not APE1, that removes the deaminated cytosine base to create an abasic residue. APE1 excises this abasic residue to create a single-strand nick in the DNA. C is correct, in that class switch recombination occurs within the switch regions, which are introns, so that no frameshift mutations are produced.

10.11 Low, high, FcεRI, prostaglandin D_2, leukotriene C4, histamine, vascular permeability.

Chapter 11 Answers

11.1 **False.** The immune system develops integrated innate and adaptive modules that are pathogen type-specific, and no single response can effectively control all types of pathogens.

11.2 **B.** TSLP acts on ILC2 cells to induce IL-13 production; this stimulates mucus production by goblet cells and mucosal smooth muscle contraction.

11.3 **A, ii; B, i; C, iv; D, iii.**

11.4 $\alpha_4\beta_7$, MAdCAM-1, CCR9, CCL25, CLA, E-selectin.

11.5 **C.** As a result of macrophage activation by T_H1 cells, macrophages produce TNF-α, which signals through TNFR-I and maintains the viability of these cells.

11.6 M1 and M2 macrophages metabolize arginine differently. For example, M1 macrophages express iNOS, which produces NO, as opposed to M2 macrophages, which express arginase-1, used to produce ornithine and proline. Proline can then stimulate collagen production, formation of which requires this amino acid.

11.7 **E.** IL-23 does not initiate the commitment of naive $CD4^+$ T cells to T_H17 cells, but instead stimulates their expansion and maintenance. TGF-β in combination with IL-6 and/or IL-1 is responsible for induction of T_H17 cells.

11.8 **C.** Although $CD4^+$ T cells are essential for 'licensing' of dendritic cells that subsequently induce $CD8^+$ T-cell responses, certain pathogens, particularly *Listeria monocytogenes* and *Burkholderia pseudomallei*, are able to directly license dendritic cells to induce primary $CD8^+$ T-cell responses.

11.9 CD25, CD127, CD45, β1 and β2 integrins, CCR7, IL-7, IL-15.

11.10 **False.** CD27, a TNF receptor family member that binds CD70 expressed on dendritic cells, is expressed on memory B cells as well as naive T cells.

11.11 The inflammasome is responsible for cleaving IL-1β and IL-18 into their active forms, which induce differentiation and effector functions of type 3 and type 1 responses, respectively. The inflammasome, however, also cleaves and inactivates IL-33, which is important for type 2 responses.

11.12 **A, iv; B, ii; C, i; D, iii.**

Chapter 12 Answers

12.1 **A.** Microfold cells possess low amounts of mucus, allowing for better interaction with pathogens.

12.2 **False.** Intraepithelial lymphocytes are mostly CD8 T cells and can express either CD8α:β or α:α, as opposed to the lamina propria, in which CD4 T cells predominate.

12.3 **A, iv; B, ii; C, i; D, iii.**

12.4 **B.**

12.5 Lectin receptors such as Dectin-1 and DC-SIGN expressed on dendritic cells and microfold cells enhance antigen uptake through binding of the carbohydrate residues on IgA. Targeted uptake of pathogenic antigens in turn allows dendritic cells to process and present any pathogenic antigen to T cells for the development of an adaptive immune response.

12.6 IgA deficiency in humans does not usually lead to susceptibility to infections because IgM can compensate for the roles of IgA and be secreted into the gut lumen through the pIgR and target commensals and pathogens.

12.7 **G.** IELs are unique in their composition, being mostly T cells that express CD8 either as an α:α homodimer or an α:β heterodimer. These T cells express the $\gamma\delta$ or the $\alpha\beta$ TCR, and express the gut-homing receptors CCR9 and $\alpha_E\beta_7$ integrin (CD103), which binds to E-cadherin expressed on epithelial cells.

12.8 **A.** Type b intraepithelial lymphocytes (IELs), also known as 'natural' IELs, as well as ILC3 cells, require the aryl hydrocarbon receptor for proper development.

12.9 **A, ii; B, iv; C, i; D, iii.**

12.10 **False.** Lamina propria $CD4^+$ T cells secrete large amounts of cytokines at baseline during homeostasis. This is sometimes referred to as 'physiological inflammation' and is believed to be a normal physiological response to the commensal flora.

12.11 **True.** Most T_{reg}s in the small intestine do not express FoxP3, while most in the colon do.

Chapter 13 Answers

13.1 **A, iii; B, i; C, vi; D, ii; E, v; F, iv.**

13.2 **True.** The IL-12 p40 subunit is shared by IL-23, which is a key cytokine in the differentiation of T_H17 cells and activation of ILC3 cells.

13.3 ZAP-70 deficiency and MHC class I deficiency result in $CD8^+$ T-cell absence while sparing $CD4^+$ T cells, and MHC class II deficiency results in $CD4^+$ T-cell absence while sparing $CD8^+$ T cells. It is not well understood why ZAP-70 deficiency spares $CD4^+$ T-cell development. MHC class I deficiency results in lack of $CD8^+$ T-cell development in the thymus, while MHC class II deficiency results in lack of $CD4^+$ T-cell development in the thymus.

13.4 CD40L–CD40 interactions are necessary not only for T-cell–B-cell interactions and class switching, but also for T-cell interactions with monocytes, macrophages, and dendritic cells; thus, in CD40L deficiency, there are also defects associated with T-cell responses and the control of intracellular pathogens. AID is a cytidine deaminase involved in somatic hypermutation and class switching in germinal center B cells, but does not play a prominent role in other immune-cell functions, thus making AID deficiency an isolated B-cell class-switching defect.

13.5 **False.** Common variable immunodeficiency (CVID) impairs antibody responses, and is characterized by hypogammaglobulinemia and the presence of nonfunctioning B cells. T-cell responses are preserved. This disorder comprises a heterogeneous group of genetic defects leading to similar outcomes, but the genetic causes of only a minority of the cases is currently understood.

13.6 **F.** Chronic granulomatous disease leads to defective microbial killing by phagocytic cells, making patients vulnerable to bacterial infections. There is no associated autoimmune or autoinflammatory phenotype.

13.7 **D.** Activation of the complement component C3 leads to its covalent bonding to pathogen surfaces, where it acts as an opsonin. Defects in the activation of C3 will directly affect the organism's capacity to prevent pyogenic infections.

13.8 **A.** Mutations in *GFI1* can cause severe congenital neutropenias. GFI1 is a transcriptional repressor, a deficiency of which leads to lower expression of *ELA2*, resulting in apoptosis of the developing myelocytes.

13.9 **A, ii; B, i; C, iv; D, iii.** Kindlin-3 deficiency results in leukocyte adhesion deficiency type 3 (LAD-3). Neutrophil elastase deficiency results in apoptosis of developing myelocytes, thus impairing myeloid cell production. Myeloperoxidase is involved in reactive oxygen species production and microbial killing. MyD88 is a downstream adaptor of TLR and IL-1 receptor family members and thus is critical for pathogen recognition and response to inflammatory cytokines.

13.10 **A, D, E.** Influenza A virus undergoes antigen shift and antigenic drift, *Trypanosoma brucei* has variable surface glycoproteins (VSGs) and a capability of interchanging them, and *Plasmodium* also varies its surface antigens and has various stages in its life cycle.

13.11 **A.** Vpr is responsible for inhibiting the restriction factor SAMHD1.

13.12 Reverse transcriptase; CD4; CCR5; CXCR4; seroconversion; escape mutations.

13.13 **B.** No known polymorphisms in CXCR4 that influence HIV infection have been found.

Chapter 14 Answers

14.1 **False.** In addition to T_H2 cells, mast cells and basophils can express CD40 ligand and secrete IL-4 upon IgE cross-linking, which also drives IgE production by B cells.

14.2 **E.** IFN-γ is a T_H1 cytokine not involved in the genetic susceptibility to allergic asthma and atopic eczema, which is associated with T_H2 responses.

14.3 **A.** Environmental factors and genetic variation each account for about 50% of the risk of developing atopy.

14.4 **False.** Most IgE in the human body is fixed on cells carrying FcεRI, specifically, mast cells and basophils.

14.5 **A, iii; B, i; C, iv; D, v; E, ii.**

14.6 **D**. Penicillin allergies occur as the result of a T_H2-predominant immune response to penicillin bound to altered self proteins.

14.7 **A, C,** and **D.** Immune complexes can be pathogenic because they can activate leukocytes via Fc receptors, activate complement and lead to the production of the anaphylatoxin C5a, and also can deposit in blood vessel walls and even the alveoli of the lung.

14.8 sensitization; elicitation; Langerhans cells; memory T cells.

14.9 **A, i; B, iii; C, ii; D, iv.**

14.10 **B.** T_H1 and CD8 T cells can cause hypersensitivity reactions. For example, the tuberculin test induces a T_H1-mediated delayed-type hypersensitivity. After exposure to antigen, in patients who have been infected with *M. tuberculosis* or vaccinated with BCG, T_H1 cells recognize peptide:MHC complexes and release inflammatory cytokines such as IFN-γ and TNF-α.

14.11 Endotype classification of asthma appears to be needed because asthma does not behave as a single disease. Asthma phenotypes vary greatly on the basis of the responsiveness of asthmatics to therapies, the inflammatory cell infiltrates that are present in patients' airways, and the inflammatory mediators that are found in the airways. While there are some endotypes that are more common than others, such as allergic asthma or exercise-induced asthma, the immune response is different for each type.

14.12 **True.** Asthmatics can have chronic inflammation even without apparent ongoing exposure to the initial allergen trigger.

Chapter 15 Answers

15.1 **False.** In inflammatory bowel disease, the target antigen is derived from the intestinal microbiota rather than self.

15.2 **A, iii; B, ii; C, i.**

15.3 **C.** Blau syndrome appears to result from a gain-of-function mutation of *NOD2*, unlike Crohn's disease.

15.4 **C.** The Y chromosome contains a set of proteins that can be recognized as minor histocompatibility antigens. Therefore a graft from a male mouse can be rejected by a female host due to H-Y responses.

15.5 Leukemia patients receiving HSC transplants can benefit from GVHD because of the associated graft-versus-leukemia effect, which leads the donor T cells to kill the leukemic host cells.

15.6 **C.** The trophoblast expresses low levels of MHC class I and so is vulnerable to NK cell attack. To compensate, the trophoblast expresses HLA-G, which has been shown to inhibit NK cell-mediated killing.

15.7 **A.** Immune privileged sites do allow influx of effector T cells during infection.

15.8 **B.** Negative selection is a mechanism of central tolerance that occurs in the thymus for T cells or in the bone marrow or periphery for B cells.

15.9 Autoreactive B cells specific for DNA pick up DNA:histone complexes (chromatin) and present histone-derived peptides on MHC molecules and thus recruit histone-specific autoreactive T cells. Those autoreactive T cells that recognize histones will help the original DNA-specific B cells but also help other B cells specific for the histone proteins, resulting in the production of anti-DNA and anti-histone antibodies.

15.10 The delayed and varied disease onset of APECED reflects the importance of peripheral tolerance, which is able to slow or prevent autoimmune attack of endocrine organs in some cases. The sporadic nature reflects the intersection of the genetics of autoimmune disease with the breakdown of natural tolerance mechanisms and environmental triggers.

15.11 Myasthenia gravis; acetylcholine; Graves' disease; thyroid-stimulating hormone (TSH).

15.12 **A, iii; B, vi; C, ii; D, viii; E, v; F, iv; G, vii; H, i.**

Chapter 16 Answers

16.1 **A.** Mycophenolate and azathioprine have similar mechanisms since both of these can block the *de novo* synthesis of guanosine monophosphate.

16.2 **A, iii; B, iv; C, i; D, ii.**

16.3 **False.** Rather than using a T-cell receptor, CAR T cells are transduced with another receptor that allows the T cell to target molecules other than peptide:MHC complexes.

16.4 **C.** Cell-based cancer vaccines can use the patient's tumor as a source of antigen. However when CpG is used as an adjuvant, it is used to activate TLR-9.

16.5 **A** and **D**. CTLA-4 is highly expressed on T_{reg}s, and ipilimumab depletes these, thus reducing regulatory cells. PD-1 is an inhibitory receptor that checks T-cell activation, and when its function is blocked, T cells regain effector functions.

16.6 **True.** CAR T cells are T cells engineered to express a chimeric antigen receptor that is a fusion of the intracellular domains of the T-cell receptor CD3ζ chain and the 4-1BB/CD137 co-receptor chains with an extracellular domain consisting of the antigen-binding site of an antibody, such as anti-CD19. Thus, there is no MHC restriction.

16.7 **A, T; B, P; C, A; D, A; E, K; F, A.**

16.8 linked recognition; heterosubtypic; herd.

16.9 First, a single peptide may not bind all MHC alleles in a given population. Second, given that processing is not required, the peptide may load onto many cell types and may lead to tolerance. Third, presentation onto MHC class I requires cross-presentation, which occurs only in specialized dendritic cell types.

16.10 **False.** While the commonly used intramuscular vaccination results in potent immunity, mucosal vaccination results in more robust mucosal immunity, while oral immunization may induce oral tolerance.

16.11 **A, iii; B, iv; C, ii; D, i; E, v.**