**Allergy and Immunology Board Review Corner: 2019**

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Welcome to the FIT Board Review Corner, prepared by Christin Deal, MD, and Miriam Samstein, MD, PhD, senior and junior representatives of the College'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:** Middleton's Allergy Principles and Practice, 8th Edition N. Franklin Adkinson Jr., MD, Bruce S Bochner, MD, A Wesley Burks, MD, William W Busse, MD, Stephen T Holgate, MD, DSc, FMedSci, Robert F Lemanske, Jr., MD and Robyn E O'Hehir, FRACP, PhD, FRCPath

**Chapter 80:** Hypersensitivity to Aspirin and Other Nonsteroidal Anti-Inflammatory Drugs
Prepared by: Rebecca Koransky, MD

1. Aspirin Exacerbated Respiratory Disease (AERD) describes a clinical syndrome with three features - the "ASA triad." Which of the following choices below is not included in this triad?
    a. Chronic rhinosinusitis with polyps
    b. Asthma
    c. Increased pulmonary infections
    d. Hypersensitivity reactions to aspirin and other cross-reacting NSAIDs

2. Large amounts of infiltrates of what cell are most often found in the upper and lower airway mucosa of patients with AERD?
    a. Neutrophils
    b. Lymphocytes
    c. Macrophages
    d. Eosinophils

3. Patients with AERD have abnormal arachidonic acid metabolism. Which of the following is seen in patients with AERD?
    a. Decreased production of Prostaglandin E2
    b. Decreased production of leukotrienes
    c. Decreased production of lipoxin A4
    d. Increased production of all anti-inflammatory prostaglandins

4. What allele has been identified as a genetic marker for AERD in Polish and Korean populations?
    a. HLA DQB1*0301
    b. HLA DPB1*0301
    c. HLA DRB1*0301
    d. HLA AB1*0301

5. AERD develops in a distinctive pattern. What is the usual order of symptom development?
    a. Rhinosinusitis with polyps, asthma, aspirin hypersensitivity
    b. Aspirin allergy, rhinosinusitis with polyps, asthma
    c. Asthma, aspirin allergy, rhinosinusitis with polyps
    d. Aspirin allergy, asthma, rhinosinusitis with polyps

6. How do you definitively diagnosis AERD?
    a. Clear history of adverse reaction to aspirin
    b. Improvement of asthma when stopping aspirin
    c. Identifying nasal polyps in at risk patients on exam
    d. Aspirin provocation challenges

7. Aspirin desensitization can be used a treatment option for some patients. Desensitization to which dose of aspirin is recommended to maintain cross-desensitization to any dose of all NSAIDs?
    a. 81mg
    b. 162mg
    c. 325mg
    d. 650mg

8. Which NSAID hypersensitivity likely involves COX-1 inhibition?
    a. Fixed drug eruption
    b. Multiple NSAID induced urticaria
    c. Single drug induced urticaria
    d. Single drug induced anaphylaxis

9. A patient presents with urticaria to multiple NSAIDs. What is the next step in management?
    a. Oral challenge with non-COX-1 inhibitor
    b. Confirmatory oral challenge with COX-1 inhibitor
    c. Desensitization to preferred NSAID
    d. Avoid all NSAIDs

10. A patient presents with angioedema to a single NSAID. What is the next step in management?
    a. Oral challenge test with chemically unrelated NSAID
    b. Confirmatory oral challenge with same NSAID
    c. Oral challenge with non-COX-1 inhibitor
    d. Desensitization

**Answers:**

1. **C**. Page 1296. Patients with AERD, or Samter disease, usually present with chronic rhinosinusitis with polyps, moderate to severe asthma, and hypersensitivity reactions to aspirin and other cross-reacting NSAIDs.

2. **D.** Page 1298, 1301. The pathogenesis of AERD includes development of chronic inflammation of the upper and lower airway mucosa. Abundant amounts of eosinophils are found in mucosa of patients with AERD.

3. **A.** Page 1298. Abnormalities of arachidonic acid in patients with AERD include decreased prostaglandin E2 (PGE2 is anti-inflammatory), overproduction of leukotrienes, and increased production of lipoxin A4.

4. **B.** Page 1299. This allele was identified in studies of a Polish and Korean population. Patients with this allele showed lower FEV1 and high prevalence of rhinosinusitis with nasal polyps.

5. **A.** Page 1301. Nasal symptoms usually start by middle age and asthma develops a few years later. Aspirin hypersensitivity develops last - usually manifested as bronchospasm, rhinitis, and ocular injection.

6. **D.** Page 1301. “The diagnosis of AERD can be definitively established only through aspirin-provocation challenges”. Challenges can be oral, inhaled, nasal, or IV. Controlled oral challenge with aspirin is the gold standard.

7. **C.** Page 1304. The target dose of desensitization depends on the diseases underlying the aspirin desensitization. The target dose for cardiovascular disease prevention is 81mg, the target dose to maintain cross-desensitization to all NSAIDs is 325mg, and the target dose for AERD patients is 650mg twice daily.

8. **B.** p. 1297, Table 80-1. Cox-1 inhibition is the likely mechanism in urticaria/angioedema induced by multiple NSAIDs. Single drug induced urticaria and anaphylaxis are IgE mediated. A fixed drug eruption is a form of delayed type hypersensitivity.

9. **B.** p. 1306, Figure 80-3. The first step is a confirmatory oral challenge with a COX-1 inhibitor. If positive, then an oral challenge with a non-COX-1 inhibitor should be done next.

10. **A.** p. 1306, Figure 80-3. The first step is an oral challenge test with a chemically unrelated NSAID. If positive, patient should be treated as a reactor to multiple NSAIDs.

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**Chapter 83:** Oral Food Challenge Testing
**Prepared by:** Evelyn Lomasney, MD

1. What is considered the gold-standard test for the diagnosis of IgE-mediated food allergy?
    a. Double-blinded, placebo-controlled oral food challenge
    b. Single-blinded, placebo-controlled oral food challenge
    c. Open oral food challenge
    d. In-vitro IgE testing

2. Oral food challenges (OFC) are NOT indicated in the following clinical situations:
    a. Chronic allergic eczema without clear reaction history and sIgE testing positive but below predictive level.
    b. Known history of food allergy and sIgE testing below predictive level.
    c. History of acute reaction with positive sIgE testing.
    d. History of acute reaction with equivocal sIgE testing.

3. In the research setting, OFC are utilized to determine the following except:
    a. The accuracy of other diagnostic methods such as patch testing, skin tests and allergen-specific IgE levels.
    b. To determine the threshold doses for different food allergens.
    c. To assess the efficacy of potential food allergy treatments.
    d. To determine the role of packaging on the allergenicity of different foods

4. Open food challenges are limited by the potential for bias on part of the patient and the observer most often resulting in false positive results. Some suggest the false positive rate is as high as:
    a. 15%
    b. 20%
    c. 25%
    d. 30%

5. Open food challenges are characterized by:
    a. Low negative predicative value
    b. Lower false positive rate in infants and toddlers compared to older patients
    c. Complicated multiday protocols
    d. Higher false positive rate in infants and toddlers compared to older patients

6. Which of the following is true about double-blinded, placebo-controlled food challenges (DBPCFC)?
    a. DBPCFC are not recommend for patients with chronic symptoms, delayed reactions or subjective symptoms.
    b. DBPCFC protocols can be completed in one visit.
    c. Open challenges should be completed after a negative DBPCFC for full evaluation of food allergy.
    d. Although used regularly in research, DBPCFC are not the gold standard for diagnosis of food allergy.

7. What is the estimated false positive rate in double blinded placebo-controlled food challenges (DBPCFC)?
    a. 1%
    b. 5%
    c. 10%
    d. 30%

8. What would preclude proceeding with OFC?
    a. Recent asthma exacerbation over one week ago
    b. 1-2 isolated hives
    c. Subjective symptoms such as abdominal pain
    d. Atopic dermatitis flare on challenge day

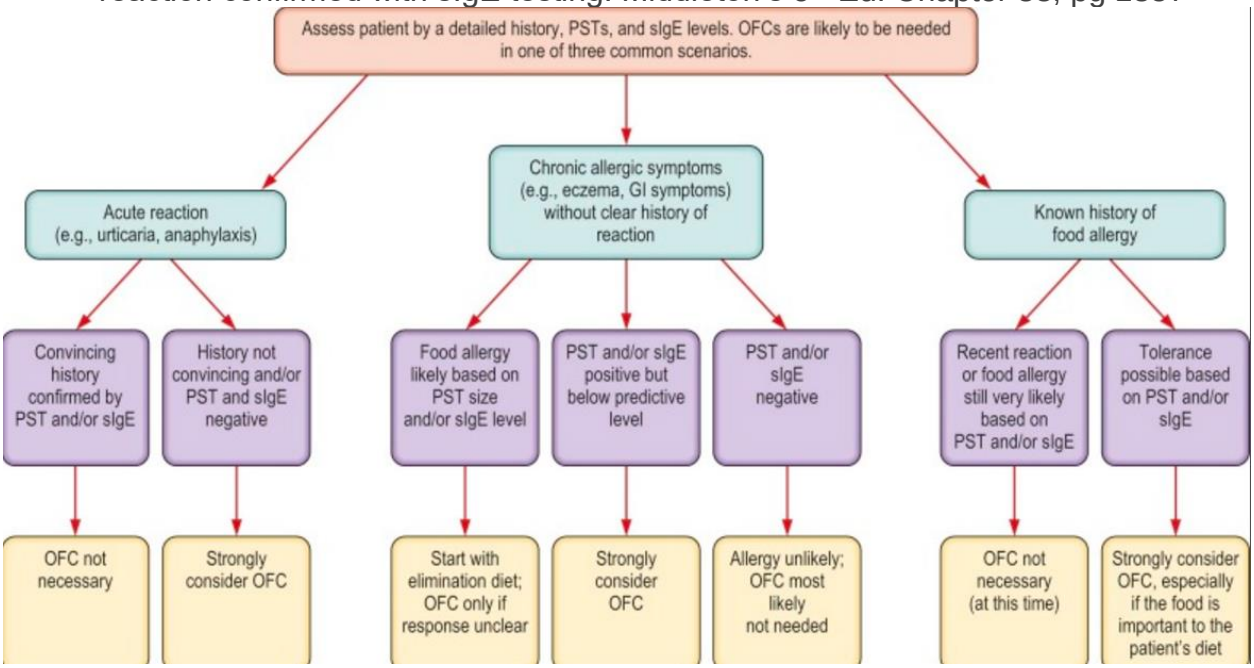
9. What is the recommended time interval between doses during an OFC?
    a. 0-5 minutes
    b. 5-10 minutes
    c. 10-20 minutes
    d. 20-30 minutes

10. What are the most common reactions elicited during a positive OFC?
    a. Skin and gastrointestinal reactions
    b. Respiratory and gastrointestinal reactions
    c. Respiratory and skin reactions
    d. Skin and cardiovascular reactions

Answers

1. A. In vivo and in vitro IgE mediated testing for food allergy has improved over time. However methods are still significantly limited that oral food challenge testing, specifically double blinded placebo controlled oral food challenges remain the gold standard for diagnosis. Middleton's 8th Ed. Chapter 83, pg 1357

2. C. Page 1357. OFC are not necessary in the setting of a convincing history of an acute reaction confirmed with sIgE testing. Middleton's 8th Ed. Chapter 83, pg 1357




3. D. In the research setting OFC are utilized for many indications. First to determine the accuracy of other diagnostic methods such as patch testing, skin tests and allergen specific IgE levels. Second to determine the threshold doses for different food allergens. Third to determine the effects of processing on the allergenicity of different foods. Fourth, to assess the efficacy of potential food allergy treatments. Middleton's 8th ed. Chapter 83, pg 1358

4. D. The limitations of OFC include the chance of bias on the part of the patient and the observer. This bias most often results in false-positive challenge results, with some authorities suggesting a false-positive rate of up to 30%. This common problem occurs most often when the patient has significant anxiety about the challenge or when the patient's prior symptoms have been more subjective in nature. Middleton's 8th ed. Ch. 83, pg 1358

5. B. Despite limitations of bias open OFC's have significant clinical utility due to high negative predictive value. Negative open challenges often serve as the first line test when the risk of true IgE mediated food allergy based on SPT of sIgE testing is low. A negative challenge may obviate the risk for DBPCFC. in infants and toddlers, for whom the impact of anxiety and other psychological factors is likely to be minimal thus minimizing the risk of bias, open challenges may be appropriate as a first-line challenge procedure. Open challenges are significantly

easier to perform because food preparation is far simpler than for a blinded challenge, and the entire challenge can be performed with a single visit. Middletons 8th Ed Ch 83 pg 1358-59

6. C. Because of the limited observer and patient bias, DBPCFC remain the gold standard is diagnosis of food allergy. It is the recommend test in patients with chronic symptoms, delayed reactions or subjective symptoms. DBPCFC require 2 visits to complete the protocols. Open challenges should be completed after a successful negative DBPCFC. Middleton's 8th ed, CH 83 1359-1360

7. A. Although it is the best available test to diagnose food allergy, even the DBPCFC is not perfect, and estimated false-positive and false-negative rates are between 1% and 3%. Middleton's 8th ed, CH 83, pg 1360

8. D. OFC may be given if the patient is at their clinical baseline prior to starting the challenge. It should be postponed if the patient has been treated for an asthma exacerbation within 1 week of the challenge. If there are 1-2 isolated hives during the challenge, particularly in area where food may have touched, the provider may continue the challenge. The same is true for subjective complaints such as abdominal pain. Middleton's 8th ed, CH 83, pg 1360

9. C. The challenge food should be provided gradually at 10- to 20-minute intervals and should begin with a dose unlikely to trigger a reaction. The challenge should progress stepwise with escalating doses, with an option to repeat doses or delay doses longer should symptoms develop. Middleton's 8th ed CH 83 pg 1360-1362

10. A. Positive OFC elicit some combination of cutaneous, gastrointestinal, respiratory, and cardiovascular reactions. Skin and gastrointestinal reactions are most common, and severe or life-threatening reactions are rare. Middleton's 8th ed. CH 83, pg 1360-1361

TABLE 83-3

System Involvement in Positive Food Challenges

| System | Milk ( *n* = 90) | Egg ( *n* = 56) | Peanut ( *n* = 71) | Soy ( *n* = 21) | Wheat ( *n* = 15) | Total ( *n* = 253) |
|---|---|---|---|---|---|---|
| Skin | 68 (75%) | 43 (77%) | 55 (77%) | 16 (76%) | 15 (100%) * | 197 (78%) |
| Oral | 23 (26%) | 12 (21%) | 27 (38%) † | 3 (14%) | 1 (7%) | 66 (26%) |
| Upper respiratory | 16 (18%) | 15 (27%) | 25 (35%) † | 4 (19%) | 2 (13%) | 62 (25%) |
| Lower respiratory | 24 (27%) | 19 (34%) | 15 (21%) | 4 (19%) | 5 (33%) | 67 (26%) |
| Gastrointestinal | 37 (41%) | 31 (55%) | 28 (39%) | 9 (43%) | 3 (20%) | 108 (43%) |
| Cardiovascular | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

From Perry TT, Matsui EC, Conover-Walker MK, Wood RA. The risk of oral food challenges. J Allergy Clin Immunol 2004:114:1164-8.

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**Chapter 84:** Food Allergy Management
Prepared by: Tammy Peng, MD

1. Which of the following describes the United States Food Allergen Labeling and Consumer Protection Act of 2004?
    a. Requires the listing of rye, barley, oats, celery, mustard and sesame seeds on ingredient labels
    b. Regulates the use of advisory labeling, including statements about potential presence of unintentional ingredients
    c. Requires milk, egg, peanut, tree nuts, fish, crustacean shellfish, wheat and soy be declared on ingredient labels
    d. Applies to agricultural products and alcoholic beverages

2. What is the Acceptable Macronutrient Distribution Range (AMDR) for carbohydrates?
    a. 5-20%
    b. 10-35%
    c. 30-40%
    d. 45-65%

3. Which of the following is an immunomodulatory effect of probiotics?
    a. Increased IgA and IL-10 synthesis
    b. Activation of allergen-induced T cell activation
    c. Inhibition of regulatory T cells (Tregs)
    d. Decreased Toll-like receptor 4 (TLR4) signaling

4. Which of the following is a risk factor associated with fatal food anaphylaxis?
    a. Dairy or egg allergy
    b. Young child
    c. Presence of skin symptoms
    d. Asthma

5. Food allergy treatments modulate the food allergic response through activation of which of the following cells?
    a. Basophils
    b. Mast cells
    c. Regulatory T cells
    d. B cells

6. Which one of the following immune parameters is decreased in IgE-mediated food allergy?
    a. Mast cell reactivity
    b. Helper T cell (Th2) cytokines
    c. Basophil activation
    d. Regulatory T cell activation

7. Which one of the following immune parameters is increased in effective immunotherapy?
    a. Serum IgE
    b. Serum IgG4
    c. Mast cell reactivity
    d. Helper T cell (Th2) cytokines

8. Which of the following examples of food allergens in unexpected and/or non-food items likely pose low risk for adverse reaction in patients with food allergies?
    a. Almond or milk in shampoos and ointments
    b. Milk, egg, fish or soy in pet food
    c. Lactose in dry powder inhaler
    d. Shrimp or crustacean shell derivatives found in glucosamine-chondroitin supplements or chitosan or chitin products

9. Which of the following foods is one of several identified to account for most episodes of fatal anaphylaxis?
    a. Egg
    b. Soy
    c. Milk
    d. Wheat

10. Which of the following describes the dual-allergen-exposure hypothesis for pathogenesis of food allergy?
    a. Lack of early childhood exposure to infectious agents, gut flora and parasites increases susceptibility to allergic diseases by modulating immune system development
    b. Decrease in consumption of antioxidants accounting for increase in allergies
    c. Excessive vitamin D or vitamin deficiency leads to increased allergies
    d. Allergic sensitization occurs via cutaneous exposure whereas tolerance occurs as a result of oral exposure to food.

**Answers:**

1. **C.** Requires milk, egg, peanut, tree nuts, fish, crustacean shellfish, wheat and soy be declared on ingredient labels, p. 1366 “Labeling of Manufactured Products.” In the United States, the Food Allergen Labeling and Consumer Protection Act (FALCPA) of 2004 requires that milk, egg, peanut, tree nuts, fish, crustacean shellfish, wheat and soy be listed on ingredient labels, using plain English words. The law also requires that the specific type of allergen within a category be named (i.e. “walnut” or “shrimp”). FALCPA applies only to foods manufactured in or imported into the United States and does not apply to agricultural products of alcoholic beverages that may use food proteins as ingredients or processing agents. The European Union enacted legislation in 2005 requiring six allergens that are not cover in FALCPA to be declared (rye, barley, oats, celery, mustard and sesame seed). FALCPA of 2004 does not regulate the use of advisory labeling, including statements about potential presence of unintentional ingredients—these declarations are done so voluntarily in the United States.
2. **D**. 45-65%, p. 1368. AMDR for carbohydrates is 45-65% of total caloric intake. AMDR for protein varies by age—5-20% for children ages 1-3, 10-30% children 4-18 years of age and 10-35% for adults. AMDR for fat is 25-35% for older children and adults, 30-40% for children age 1-3.
3. **A**. Increased IgA and IL-10 synthesis, p.1376 “Probiotics and Prebiotics” Probiotics are ingested, live, health-promoting microbes that modify intestinal microbial populations to benefit the host. Pro biotic dietary supplements have been used in clinical trials to evaluate preventative impact on atopic disease. Immunomodulatory effects of probiotics may include increased synthesis of IgA and IL-10, with reciprocal suppression of tumor necrosis factor alpha (TNF- α) and other inflammatory cytokines, inhibition of allergen-induced T-cell activation, activation of regulatory T cells and enhanced toll-like receptor 4 signaling.
4. **D.** Asthma, p. 1369, Box 84-1 Risks for Fatal Food Anaphylaxis and Comorbid Conditions. Risk factors associated with fatal food anaphylaxis include delayed treatment with epinephrine, allergy to peanut, tree nuts, fish or shellfish, an adolescent or young adult, asthma, cardiovascular disease in a middle-aged or older patient and lack of skin symptoms.
5. **C**. Regulatory T Cells, p. 1375 Figure 84-2. Food allergy treatments modulate the food allergic response through activation of regulatory T cells and suppression of a variety of effector cell types.
6. **D**. Regulatory T cell Activation p. 1376 Table 84-7 “Immunologic Changes in IgE-mediated Food Allergy Compared with Effective Immunotherapy” Regulatory T cell activation is decreased in food allergy whereas other immune parameters including serum IgE, mast cell reactivity, basophil activation and helper T cell cytokines are increased.
7. **B**. Serum IgG4, p. 1376 Table 84-7 “Immunologic Changes in IgE-mediated Food Allergy Compared with Effective Immunotherapy” With effective immunotherapy, increases in both serum IgG4 and regulatory T cell activation are seen. Immune parameters including serum IgE, mast cell reactivity, basophil activation and helper T cell cytokines are decreased in effective immunotherapy.
8. **D**. Shrimp or crustacean shell derivatives found in glucosamine-chondroitin supplements or chitosan or chitin products, p. 1367, Table 84-2 “Examples of Food Allergens in Unexpected and Nonfood Items” Relevance of shrimp or crustacean shell derivatives found in glucosamine-chondroitin supplements or chitosan or chitin products is uncertain and risk is likely low. It is possible for patients with food allergies to develop contact urticaria or dermatitis with exposure to almond or milk in shampoos or ointments. Although some derivatives such as shea nut

butter may have negligible protein. In regards to pet foods, fish food on fingers may result in transfer of protein to the eyes or mouth resulting in symptoms. Additionally, animal lick may cause contact urticaria. For food allergens in medications such as lactose in dry powder inhalers, there have been case reports of reactions to casein identified in dry powder inhalers. The relevance to milk in pills or pharmaceutical grade lactose is unclear.

9. **C.** Milk, p. 1368-1369 “Emergency Management” Although any food has the potential to trigger anaphylaxis, peanut, tree nuts, fish, shellfish and milk account for most episodes leading to fatalities.
10. **D.** Allergic sensitization occurs via cutaneous exposure whereas tolerance occurs as a result of oral exposure to food. P. 1371-1373. The dual-allergen exposure hypothesis proposes that allergic sensitization to food can occur through low-dose cutaneous exposure and that early consumption of food protein induces tolerance. The balance of cutaneous and oral exposures as well as timing is thought to determine whether a child develops allergy or tolerance. The hygiene hypothesis suggests that the lack of early childhood exposure to infectious agents, gut flora and parasites increases susceptibility to allergic diseases by modulating immune system development. There are four hypotheses related to changes in diet that could have led to increase in allergies, including hypotheses regarding obesity, dietary fat antioxidant and vitamin D.

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**Chapter 93:** Cytokine-Specific Therapy in Asthma.
Prepared by: Aba Al-Kaabi, MD, Baylor College of Medicine at Texas Children's Hospital.

1. Airway inflammation in asthma is a multicellular process. What cells are involved in this process?
   A. Eosinophils and neutrophils.
   B. Monocytes and basophils.
   C. Eosinophils and monocytes.
   D. Basophils and lymphocytes.

2. The growth factor TGF-beta is important in the allergic airway for mucin hypersercretion, smooth muscle hypertrophy, extracellular matrix collagen deposition and subepithelial fibrosis. Which cells are involved in upregulation of TGF-beta to increase smooth muscle contractility?

A. Eosinophils
   B. Basophils
   C. Mast cells
   D. Lymphocytes

3. Which important cytokine is involved in the proliferation and function of natural killer cells and T regulatory lymphocytes?
   A. Interleukin 1.
   B. Interleukin 2.
   C. Interleukin 3.
   D. Interleukin 4.

4. Which cytokines are considered the "Th2 defining" cytokines and regarded as being the most important cytokines in asthma pathogenesis?
   A. IL-2 and IL-13.
   B. IL-4 and IL-2.
   C. IL-4 and IL-13
   D. IL-4 and IL-6.

5. Which cytokine modulates eosinophilic production, maturation, activation, and survival in blood?
   A. IL-9.
   B. IL-4.
   C. IL-13.
   D. IL-5.

6. Which cytokine uniquely promotes airway mastocytosis and mast cell progenitor development and localization to the airway?
   A. IL-9.
   B. IL-13.
   C. IL-2.
   D. IL-1.

7. Which pleiotropic cytokine is considered the principle Th1 effector cytokine that plays an important role in Th1 differentiation?
   A. IL-2.
   B. IL-9.
   C. TNF-α.
   D. IFN-γ.

8. Which family of cytokines are linked to autoimmune diseases including rheumatoid arthritis, inflammatory bowel diseases and multiple sclerosis, in addition to increased expression in asthmatic patients?
   A. IL-16 family cytokines.
   B. IL-17 family cytokines.
   C. TNF-α.
   D. IFN-γ.

9. IL-18 is a proinflammatory cytokine related to the IL-1 family that induces IFN-γ in activated NK cells, Th1, and CD8+ cytotoxic T cells. What is the source of this cytokine?
   A. CD4+CD8+ cells, macrophages, and airway epithelium.
   B. CD4+CD8- cells, macrophages, and airway epithelium.
   C. CD4-CD8+ cells, macrophages, and airway epithelium.
   D. CD4-CD8- cells, macrophages, and airway epithelium.

10. Which anti-IL5 allows for successful oral corticosteroid withdrawal in prednisone-dependent patients with asthma?
    A. Mepolizumab
    B. Tralokinumab
    C. Lebrikizumab
    D. Malzumab.

**Answers**:
1. **A**. Eosinophils and neutrophils page 1492
Airway inflammation in asthma is a multicellular process involving eosinophils, CD4+ T cells, mast cells, and neutrophils.

2. **C**. Mast cells. page 1492-1493 and table 93-2.
Mast cells are in an activated state in asthma and are an important source of cytokines, chemokines, autocoid mediators, proteases and histamine. They affect airway smooth muscle contractility directly and indirectly by upregulation of airway smooth muscle transforming growth factor beta which transforms smooth muscle into a more contractile phemotype.

3. **B**. Interleukin 2. page 1492.
IL-2 is a potent activator of the proliferation and function of T lymphocytes and natural killer cells. IL-2 functions as a T cell growth factor, can augment natural killer (NK) cell cytolytic activity, contributes to the development of regulatory T (Treg) cells and promotes immunoglobulin production by B cells, as well as regulating the expansion and apoptosis of activated T cells.

4. **C**. IL-4 and IL-13 page 1495.
IL-4 and IL-13 are the “Th2 defining” cytokines and arguably are the most important cytokines in asthma pathogenesis. Owing to structural homogeneity, their actions are broadly similar, and they are therefore considered together.

5. **D**. IL-5. page 1496.
IL-5 modulates eosinophil progenitor production, maturation, activation, and survival in blood and can induce airway eosinophilia.

6. **A**. IL-9 page 1498.
IL-9 is derived from CD4+ (Th9) cells, eosinophils, and mast cells. It causes T cell proliferation, increases IgE production by B cells, and increases expression of the α-subunit of IgE receptors. It uniquely promotes airway mastocytosis and mast cell progenitor development and localization to the airway.

7. **D**. IFN-γ. page 1500.
IFN-γ is a pleiotropic cytokine that induces and modulates an array of immune responses, but most important, it is the principal Th1 effector cytokine, with a crucial role in Th1 differentiation. IFN-γ mainly inhibits eosinophils, which are a crucial cell type in the allergic Th2 model of asthma, as evidenced when targeted disruption of the IFNγR receptor gene resulted in a prolonged airway eosinophilia in response to allergen.

8. **B**. IL-17 family cytokines. page 1500.
The IL-17 family cytokines, IL-17A to IL-17F, are linked with several autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis; in particular, IL-17E and IL-17F are of interest in asthma because their expression is increased in the airways of asthmatic patients, and levels have been correlated with disease severity.

9. **A**.  CD4+CD8+ cells. page 1500.
IL-18 is a proinflammatory cytokine related to the IL-1 family that induces IFN-γ in activated NK cells, Th1, and CD8+ cytotoxic T cells and hence was formerly called IFN-γ–inducing factor. The sources of IL-18 are CD4+CD8+ cells, macrophages, and more recently, airway epithelium.

10. **A**. Mepolizumab. pages 1497-1498.
Mepolizumab therapy allowed for successful oral corticosteroid withdrawal in prednisone-dependent patients with asthma compared with placebo. The median time to exacerbation was 20 weeks in the mepolizumab group and 12 weeks in the placebo group (P = .003).

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**Chapter 99:** Glucocorticoids

1. In the absence of a spacer device, what percentage of inhaled corticosteroid delivered by a metered-dose inhaler (MDI) or dry powder inhaler (DPI) is delivered to the lungs?
    a. 10-20%
    b. 30-40%
    c. 60-75%
    d. 90-100%
2. What is a feature of an inhaled drug (such as an inhaled corticosteroid) with a good therapeutic index?
    a. High oral bioavailability
    b. Large particle size
    c. Slow metabolism
    d. Low (or short) systemic half-life

3. Glucocorticoids have which of the following effects on eosinophils?
    a. Decrease eosinophil chemotaxis
    b. Decrease eosinophil degranulation
    c. Prevent an increase in blood eosinophil progenitors after antigen challenge
    d. Acutely increase circulating eosinophil numbers

4. In the airway epithelial cells, glucocorticoids suppress the expression and release of a number of inflammatory cytokines, chemokines, and growth factors likely by affecting which transcription factor?
    a. NOTCH1
    b. GATA3
    c. FoxP3
    d. NF-κB

5. A pregnant woman at 31 weeks gestational age presents to the ER with signs of early labor. Measures to stop labor are begun. She is also given Betamethasone which she is told will protect her baby's lungs. Expression of what protein is enhanced by glucocorticoids, a factor that may be important in preventing neonatal respiratory distress syndrome?

a. ICAM-1
b. Surfactant protein B
c. Monocyte chemoattractant protein 4
d. Zonula occludens-1

6. Inhibitors targeted at which enzyme have been able to restore glucocorticoid sensitivity in patients with steroid refractory asthma?
    a. P38 MAPK (MAPK14)
    b. DNase I
    c. HDAC6
    d. IκB kinase

7. Which interleukin, associated with neutrophilic asthma, is elevated in sputum and serum samples from patients with severe asthma and has been shown experimentally to inhibit corticosteroid responsiveness in human bronchial epithelial cells?
    a. IL-2
    b. IL-12
    c. IL-10
    d. IL-17

8. Supplementation of which vitamin may augment responsiveness to glucocorticoids in patients with steroid-refractory asthma by increasing steroid-induced T cell secretion of IL-10?
    a. Vitamin A
    b. Vitamin $B_2$ (Riboflavin)
    c. Vitamin $D_3$ (calcitriol)
    d. Vitamin $B_{12}$ (cobalamin)

9. A patient with asthma-COPD overlap syndrome presents to your clinic. He is unwilling to stop smoking, and his lung disease has been difficult to control with ICS/LABA therapy and inhaled tiotropium. He asks what other medications he might try. The bronchodilator theophylline has been used to restore the activity of which enzyme (and thus glucocorticoid sensitivity) in COPD patients and in smoking asthmatic patients in whom the activity of this enzyme is reduced?
    a. Histone deacetylase 2 (HDAC2)
    b. Interferon-regulatory factor-1 (IRF)
    c. Mitogen-activated protein kinase (MAPK)
    d. NF-κB

10. The glucocorticoid receptor is which type of receptor?
    a. Cell surface receptor
    b. Nuclear receptor
    c. G-protein coupled receptor
    d. Tyrosine kinase receptor

**Answers:**

1. **A**. Page 1580-1581. In the absence of a spacer, 10-20% of topical inhaled corticosteroids is delivered to the lungs by an MDI or DPI with greater than 50% (and up to 90%) of the drug being deposited in the mouth and pharynx before being swallowed. Use of a spacer and mouth rinsing after inhaler use can reduce oral deposition by 90%.
2. **D**. Page 1581. In using inhaled therapies, the goal is to exert effects on local tissue while minimizing systemic effects and thus side effects. An inhaled drug with a good therapeutic index has low oral bioavailability, small particle size, rapid metabolism, high clearance, high plasma protein binding, and low systemic half-life. When designing inhaled corticosteroids, increasing lipophilicity increases pulmonary tissue retention as well.
3. **C**. Page 1583. Glucocorticosteroids (GCs) given orally or intravenously cause an acute reduction in circulating basophils, eosinophils, and monocytes with numbers returning to baseline 24-48 hours after a single dose. GCs have been shown to prevent eosinophil migration to the lung and prevent the increase in blood eosinophil progenitors after antigen challenge. In vitro studies have shown that GCs also induce eosinophil apoptosis although that has been difficult to corroborate in vivo. GCs do not modulate eosinophil chemotaxis, adhesion, or degranulation.
4. **D**. Page 1584-1585. Glucocorticoids suppress the expression and release of a host of inflammatory cytokines (e.g. IL-1, IL-6, IL-11, GM-CSF, TNF-α,), chemokines (e.g. CXCL8, CXCL12, CXCL10, growth-regulated oncogene-α, GRO-γ, CCL2, CCL13, CCL11, 24, 26; CCL17, CCL22, CCL5), and growth factors (e.g. TGF-β, PDGF, bFGF, IGF-1) from epithelial cells in vitro and in vivo. This suppression is thought to be through an effect on NF-κB, which is reduced in vivo by ICS in some studies. GC do enhance expression of Foxp3 inducing formation and activation of Tregs but not in airway epithelium.
5. **B**. Page 1585. Glucocorticoids enhance the expression of surfactant protein B (SP-B) and SP-C to reduce airway surface tension which may be important in preventing neonatal respiratory distress syndrome. Glucocorticoids also induce the expression of SP-A and SP-D, important host defense collectins.
6. **A**. Page 1593-4. IL-2, IL-4, and IL-13 can induce glucocorticoid receptor (GR) phosphorylation under the MAPK14 pathway although the precise mechanisms that result in enhanced activation or increased expression of MAPK14 in the airways of refractory asthma are unclear. Phosphorylation of GR in a specific location induced by pro-inflammatory insults and mediated by the MAPK14 pathway leads to a conformational change in GR which downregulates GR responses. Patients with severe asthma have inappropriate overexpression of MAPK14 compared to patients with non-severe asthma, and MAPK inhibitors have been shown to restore glucocorticoid sensitivity in some of these patients.
7. **D**. Page 1594. Neutrophilic asthma, a subset of corticosteroid-refractory asthma, is associated with the presence of IL-17 and Th17 cells. Many chemokines and neutrophil survival factors are elevated in response to IL-17, and this chemokine also enhances the production of profibrotic cytokines and extracellular matrix proteins. In one study, IL-17A pretreatment of cells attenuated the ability of budesonide to inhibit TNF-α-induced CXCL8 production. IL-17 levels are elevated in sputum and serum from patient with severe asthma, and sputum IL-17 levels correlate with sputum neutrophilia.

8. **C**. Page 1595. Glucocorticosteroids induce the anti-inflammatory gene IL-10 (particularly in Treg cells), thus inhibiting secretion of cytokines by Th2 cells. Vitamin $D_3$ has been shown to increase the secretion of IL-10 from Treg cells isolated from patients with steroid-refractory asthma to comparable levels in patients with non-severe asthma who were treated with Dexamethasone alone. Pediatric patients with severe therapy-resistant asthma have lower levels of Vitamin D than children with mild or no asthma, and Vitamin D level is inversely correlated with exacerbations, ICS use, ASM mass, and bronchodilator response, so supplementation may be beneficial in pediatric patients.
9. **A**. Page 1596. Reactive oxygen species have been shown to increase glucocorticoid resistance, both directly and indirectly. In patients who smoke, increased formation of peroxynitrite (another ROS) leads to enzymatic inactivation of HDAC2 which is usually enhanced by GR-α activity. HDAC2 is important in the GR-mediated repression of inflammatory genes including GM-CSF and CXCL8. Theophylline has been shown to increase HDAC2 activity in cells and thus restore glucocorticoid effects.
10. **B**. Page 1588. The glucocorticoid receptor (GR) is a nuclear hormone receptor and is divided into distinct functional modules including a ligand-binding domain, a nuclear translocation domain, and transactivation domains, the latter of which enables GR to associate with transcriptional coactivators or repressors.

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**Review Questions**
**Allergy and Immunology Review Corner:** Middleton's Allergy Principles and Practice, 8th Edition N. Franklin Adkinson Jr., MD, Bruce S Bochner, MD, A Wesley Burks, MD, William W Busse, MD, Stephen T Holgate, MD, DSc, FMedSci, Robert F Lemanske, Jr., MD and Robyn E O'Hehir, FRACP, PhD, FRCPath

**Chapter 100:** Antileukotriene Therapy in Asthma
Prepared by: Jackie Eastman

1. The 5-lipoxygenase pathway is most abundant in which cell type:
    a. Epithelial
    b. Myeloid
    c. Smooth muscle
    d. Lymphoid

2. The function of 5-lipoxygenase (5-LO) activating protein (FLAP) is:
    a. Ubiquitination of 5-LO
    b. Transport of 5-LO to the endoplasmic reticulum
    c. Channeling of arachidonic acid to the enzyme 5-LO
    d. Production of arachidonic acid

3. Which of the following statements is true about the two cysteinyl leukotriene receptors, CysLT1 and CysLT2?
    a. Leukotriene receptor antagonists block both receptors equally.
    b. CysLT1 and CysLT2 have been mapped to airway smooth muscle cells.
    c. Only CysLT1 is found on mast cells.
    d. Both are receptors for leukotriene $B_4$.

4. 5-lipoxygenase inhibitor zileuton may be more effective in inhibiting the effect of leukotrienes because:
    a. It promotes the degradation of cysteinyl leukotrienes
    b. It completely prevents all cysteinyl leukotriene production
    c. It is able to block the production of $LTB_4$ as well as $LTC_4$
    d. It is not more effective than the leukotriene receptor antagonists.

5. In humans, which of the following is not a proposed function of $LTB_4$?
    a. Chemoattractant for neutrophils and eosinophils.
    b. Activation of neutrophils
    c. Sensitization to allergen
    d. Bronchoconstriction

6. Leukotriene receptor antagonists are able to prevent which of the following after allergen challenge:
    a. Immediate and late response
    b. Immediate response only
    c. Eosinophil number in the late response
    d. Mucus production

7. What effect do antileukotriene drugs have on FEV1?
    a. No effect
    b. Small effect but not until 24 hours after ingestion
    c. Small but immediate effect
    d. Same effect as beta agonists and should be used in acute asthma exacerbations

8. In general, when a school age child requires an asthma controller medication for mild persistent asthma, what is the appropriate order for trial of medications?
    a. Trial of low-dose ICS and, if no improvement, trial of LTRA, either as add on or replacement
    b. Trial of LTRA and, if no improvement, trial of low-dose ICS
    c. Concurrent trial of LTRA and low-dose ICS
    d. Trial of low-dose ICS and increase to medium-dose ICS if no improvement, no role for trial of LTRA

9. Montelukast is approved for use in which of the following atopic conditions:
    a. Allergic rhinitis
    b. Atopic dermatitis
    c. Food allergy
    d. EoE

10. The primary toxicity with antileukotriene drugs include which of the following:
    a. Liver
    b. Kidney
    c. Cardiac
    d. GI

**Answers:**

1. **B**. (page 1602). Arachidonic acid can be metabolized via various lipoxygenase pathways, depending on the cell type. 5-LO, the one most relevant to asthma, is most abundant in myeloid cells.

2. **C.** (page 1603). 5-LO activating protein is thought to be required due to its function of channeling arachidonic acid to the enzyme 5-LO. It has no role in 5-LO transport or ubiquitination. Arachidonic acid is metabolized from membrane phospholipids by phospholipase A2.

3. **B.** (page 1603). Both CysLT2 and CysLT1 have been mapped to airway smooth muscle. LTRAs only antagonize CysLT1. Both receptors are found on mast cells. $LTB_4$ has its own receptors (BLT1 and BLT2).

4. **C**. (Page 1604). Since it blocks 5-LO, it also decreases production of $LTB_4$ and this may contribute to the anti-inflammatory effect. It is only 80% effective in vitro and less than that in vivo in abolishing cysteinyl leukotriene production. It is not involved in degradation.

5. **D**. (page 1604). The first three have been proposed as functions of $LTB_4$.

6. **A**. (page 1605). Zafirlukast given prior to allergen challenge inhibited the immediate response by 80% and the late response by 50%. It has no effect on eosinophil number after challenge or mucus production. It does decrease the cellular influx of basophils and lymphocytes.

7. **C**. (page 1606). Oral and IV preparations have an immediate bronchodilator effect of 10-30% improvement in FEV1. IV is more potent and rapid than oral. Antileukotrienes are synergistic with beta agonists but are not sufficient to treat acute asthma attacks and not recommended in that setting.

8. **A**. (page 1608). More patients will have good response to ICS than to LTRA. In one trial of children ages 6-17, 40% responded well to ICS, but 22% had good response to LTRA meaning this may be the most effective therapy for that small group. In other studies it has been as high as 30% of mild persistent asthmatics have better control with LTRA (page 1610). Due to greater adherence to LTRAs, one pragmatic study from the UK found no difference in outcomes between the two groups at two months, although this has not been shown in other studies. There appear to be some patients that benefit from LTRA alone and therefore, a trial with this medication only may be reasonable, especially if ICS was not effective or the patient would like to avoid steroids.

9. **A**. (page 1610). Although less efficacious than intranasal steroids, montelukast is approved for both seasonal and perennial rhinitis in the US. It is also approved for asthma. It has no role in atopic dermatitis, food allergy or EoE.

10. **A.** (page 1610). Elevated liver enzymes have been seen with zileuton and zafirlukast. Montelukast does not have this effect. These agents have also been associated with neuropsychiatric changes.

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**Review Questions**
**Allergy & Immunology Review Corner:** Cellular and Molecular Immunology, 9th edition
Abdul K. Abbas, MBBS, Andrew H. Lichtman, MD, PhD, and Shiv Pillai, MBBS, PhD
**Chapter 3:** Leukocyte circulation and migration into tissues
Prepared by: Amar Dixit

1. Which of the following is NOT a correct integrin-ligand pairing?
a. LFA-1:ICAM-1
b. VLA-4:ICAM-2
c. MAC-1:ICAM-1
d. LFA-1:ICAM-2

2. Which of the following selectins is located on leukocytes?
a. P-selectin
b. E-selectin
c. L-selectin
d. Z-selectin

3. Which of the following is NOT a correct pairing of the chemokine with its original name?
a. CCL5: Rantes
b. CCL11: Eotaxin
c. CCL21: TARC
d. XCL1: Lymphotactin

4. What is the defect in type 1 leukocyte adhesion deficiency?
a. Inability to encode the beta subunit of LFA-1 and MAC-1
b. Error in encoding ICAM-1, ICAM-2, and ICAM-3
c. Lack of the Golgi GDP-fructose transporter needed to express the carbohydrate ligands for E-selectin and P-selectin
d. Mutation in the signaling pathways linking chemokine receptors to integrin activation

5. What is the defect in type 2 leukocyte adhesion deficiency?
a. Inability to encode the beta subunit of LFA-1 and MAC-1
b. Error in encoding ICAM-1, ICAM-2, and ICAM-3
c. Lack of the Golgi GDP-fructose transporter needed to express the carbohydrate ligands for E-selectin and P-selectin
d. Mutation in the signaling pathways linking chemokine receptors to integrin activation

6. How does the sphingosine 1-phosphate (S1P) gradient drive T-cells from the blood into the lymph nodes?
a. High levels of S1P in the lymph nodes compared to the blood drive naïve T-cells into the lymph node, where the naïve T-cells down regulate S1PR1 to remain in the lymph node
b. S1P binds to S1PR1 in blood causing a cascade that leads naïve T-cells to migrate into the lymph node
c. High levels of S1P in the lymph nodes compared to the blood drive naïve T-cells into the lymph node, where the naive T-cells upregulate S1PR1 to remain in the lymph node
d. High levels of S1P in the blood cause internalization of S1PR1, thus allowing naïve T-cells in the lymph node to remain until externalization of S1PR1 increases due to the gradient

7. If a naïve T cell is activated by antigen in the lymph node, which of the following proteins helps the activated naïve T-cell to remain in the lymph node?
a. CD31
b. CD69
c. Albumin
d. Ficolin

8. Which of the following chemokine receptors is important for B cells to migrate into the white pulp of the spleen?
a. CXCR4
b. CXCR5
c. CCXR7
d. CXCR8

9. What do bone marrow-homing IgG-secreting plasma cells express?
a. LFA-1 and VLA-4
b. VLA-4 and CCR9
c. CXCR4 and CCR9
d. VLA-4 and CXR4.

10. Which chemokine receptor plays a critical role in dendritic cell migration into the lymph nodes and is expressed at high levels on naïve T-cells to promote their interaction?
a. CXCR5
b. CCR5
c. CXCR7
d. CCR7

**Answers**:
1. b. Page 42. LFA-1 binds to ICAM-1, ICAM-2, and ICAM-3. MAC-1 binds to ICAM-1. VLA-4 DOES NOT bind to ICAM-2. VLA-4 binds to VCAM-1.
2. c. Page 41 and 42. L-selectin is located on leukocytes. P-selectin and E-selectin are located on endothelial cells. Z-selectin is a fictitious selectin.
3. c. Pages 44. CCL21 is SLC. CCL17 is TARC. It is important to know that CCL11 is eotaxin. CCL5 is rantes. XCL1 is lymphotactin.
4. a. Page 45-46. Type 1 leukocyte adhesion disorder is due to an inability to encode the beta subunit of LFA-1 and MAC-1. It is an autosomal recessive inherited deficiency in the CD18 gene.

5. c. Page 46. Type 2 leukocyte adhesion deficiency is due to the lack of the Golgi GDP-fructose transporter needed to express the carbohydrate ligands for E-selectin and P-selectin.
6. d. Page 51. S1PR1 stimulates migration of cells towards a gradient of S1P. Circulating naïve T cells have very little surface S1PR1 because the high blood concentration of S1P causes internalization of the receptor. After a naïve T cell enters a lymph node, where S1P concentrations are low, S1PR1 reappears on the cell surface over a period of several days.
7. b. Page 52. CD69 is a protein that binds S1PR1 and reduces its cell surface expression. This prevents the naïve T cell from migrating from the low concentration of S1P in the lymph node to the high concentration of S1P in the blood.
8. b. Page 53. CXCR5 promotes the movement of B cells into the white pulp in response to a chemokine called CXCL13.
9. d. Page 55. VLA-4 and CXCR5, which bind respectively to VCAM-1 and CXCL12 expressed on bone marrow sinusoidal endothelial cells.
10. d. Page 49. CCR7. CCR7 is expressed at high levels on naïve T cells. Chemokines CCL19 and CCL21 interaction with CCR7 ensures that naïve T cells increase integrin avidity and are able to adhere firmly to HEVs. Shared expression of CCR7 between naïve T cells and dendritic cells maximizes chances of the two cells interacting.

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**Review Questions**

**Allergy & Immunology Review Corner:** Cellular and Molecular Immunology, 9th edition
Abdul K. Abbas, MBBS, Andrew H. Lichtman, MD, PhD, and Shiv Pillai, MBBS, PhD
**Chapter 4:** (pages 57-95) Innate Immunity

Prepared by: Christin Deal, MD

Questions:

1. Which of the following is *FALSE* regarding innate versus adaptive immune systems?
    a. Receptors of innate immune system are inherited by germline genes, whereas receptors of adaptive immune system are generated by somatic recombination.
    b. Innate immune system recognizes molecular structures produced by microbial pathogens called PAMPs (Pathogen-Associated Molecular Patterns).
    c. Innate immune system has increased magnitude of response with repeated exposure to microbes
    d. Damage Associated Molecular Patterns (DAMPs) are released by infections, chemical toxins, burns, trauma, loss of blood supply but not by cells dying of apoptosis.
2. Which of the following Toll Like Receptors (TLRs) is located on the cellular membrane?
    a. TLR3
    b. TLR2
    c. TLR8
    d. TLR7
3. Genetic deficiency in UNC-93B results in susceptibility to which of the following?
    a. HSV encephalitis
    b. Staphylococcal infections
    c. Candidal infections
    d. Streptococcal pneumonia
4. Which of the following membrane TLRs does not exclusively signal via myD88 to the transcription factor NF-kB?
    a. TLR1
    b. TLR2
    c. TLR4
    d. TLR5
5. Muckle-Wells, NOMID, FCAS are all CAPS (cryopyrin associated periodic syndromes). CAPS are autoinflammitory syndromes resulting in spontaneous inflammation without an inciting trigger due to dysregulation of the inflammasome. Which of the following can be used to treat CAPS?
    a. IFNγ
    b. IL-5 antagonist
    c. Rituximab
    d. IL-1R antagonist

6. Which of the following cytokines is necessary for Th1 differentiation?
    a. IL-10
    b. IL-15
    c. IL-12
    d. IL-23
7. Activated neutrophils and macrophages kill phagocytosed microbes using all of the following *EXCEPT*:
    a. Nitric oxide
    b. Elastase
    c. Reactive oxygen species
    d. Granzymes
8. TNF can cause all of the following EXCEPT:
    a. Inhibit myocardial contractility
    b. Intravascular thrombosis
    c. Cachexia
    d. Elevated CRP
9. Type 1 interferons (IFN-α and IFN-β) are important for protection against viral infections, they act through which of the following mechanisms?
    a. Sequestration of lymphocytes in lymph nodes
    b. Upregulating class II MHC molecules
    c. Promote naïve T cell differentiation to Th17 cells
    d. Stimulating adaptive immune response via two-signal hypothesis
10. Which of the following is true regarding ILC2 cells?
    a. They are important for defense against helminthic parasites
    b. They resemble Th1 cells
    c. They are activated by IL-15 and IL-7
    d. They are important for defense against extracellular fungi

Answers:

1. C. p. 59-62. Adaptive immune system has significantly higher diversity as a result of somatic recombination, whereas innate immune recognition is mediated by only about 100 different receptors. The innate immune system recognizes both PAMPs and DAMPS using pattern recognition receptors located in different parts of the various cell types (phagocytic vesicles, cytosol, surface). PAMPs are structures not present on normal host cells suck as double stranded RNA, unmethylated CpG DNA, LPS, lipoteichoic acid. DAMPs are produced from damaged and dying cells due to infections, chemical toxins, burns, trauma, loss of blood supply but not by cells dying of apoptosis. The innate immune system does NOT have an appreciable change in the quality or magnitude of response with repeated exposure showing evidence of little or no memory – whereas the adaptive immune response demonstrates both increase in quality and magnitude of response upon repeat exposure.
2. B. p 63. Toll Like Receptors are a family of pattern recognition receptors expressed on many cell types that recognize products of a wide variety of microbes. TLR2 is located on the cell membrane and recognizes bacterial peptidoglycan and lipopeptides. The cellular membrane TLRs are 1, 2, 4, 5, 6.
3. A. p 64. HSV infections. UNC-93B is a protein on the endoplasmic reticulum required for endosomal localization and proper function of TLR 3, 7, 8 and 9. Endosomal TLRs recognize dsRNA (TLR3), ssRNA (TLR7) and unmethylated CpG motifs in DNA (TLR9). The endosomal

location of ssRNA and dsRNA reflects microbial origin. The mutation in UNC-93B reflects the importance of the endosomal location of TLRs for innate defense against viruses.

4. C. p 65. TLR4 can signal via myD88 to NF-kB or via the adaptor protein TRIF to activate IRF3 and IRF7 transcription factors. IRF3 and IRF7 promote induction of type 1 interferons (IFN-α and IFN-β) which are important for antiviral responses. The NF-kB pathway encodes molecules required for inflammatory response including TNF and IL-1 as well as chemokines (CCL2 and CXCL8) as well as endothelial adhesion molecules (E-selectin).
5. D. p 69-71. Muckle-Wells, NOMID, FCAS are due to a mutation in NLRP3 (aka cryopyrin) and results in a cryopyrin-associated periodic syndrome (CAPS). IL-1 and IL-1R antagonists can be used to treat these disorders as IL-1 is converted from pro-IL-1β in the NLRP3 inlammasome (anakinra and canakinumab).
6. C. p 83-86. IL-12 is secreted by dendritic cells and macrophages. It is produced in response to TLR signaling from bacterial LPS or lipoteichoic acid and virus infections.
7. D. p 75-88. Granzymes are used by NK cells, not macrophages or neutrophils, and are injected into the cytosol of affected cells to induce cell death. Elastases are proteolytic enzymes like granzymes but are used by macrophages and neutrophils.
8. D. p87-89. TNF may be produced in large quantities in severe infections and can inhibit myocardial contractility and smooth muscle tone resulting in shock. It can also cause intravascular thrombosis by stimulating endothelial cell expression of tissue factor. Prolonged exposure to TNF can result in wasting of muscle and fat cells from TNF-induced appetite suppression. Elevation in acute phase reactants such as CRP, SAP and fibrinogen are due to IL-1 and IL-6, not TNF.
9. A. p 90-92. Type 1 interferons protect against viral infections by sequestering lymphocytes in lymph nodes, increasing cytotoxicity of NK cells, upregulating class I MHC molecules (increasing probability that virally infected cells will be killed by CD8 cells). Promote differentiation of naïve T cells to Th1 cells. The two-signal hypothesis states that lymphocytes require activation from both an antigen as well as additional stimuli such as cytokines. This prevents adaptive immune cells from attacking normal cells and tissues.
10. A. p 74-75. ILC2 cells resemble Th2 cells. Their development is dependent on IL-7 (ILC1 cells require IL-7 and IL-15). They are important for defense against helminthic parasites and may contribute to allergic diseases. ILC3 cells participate in defense against extracellular fungi.

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**Review Questions**
**Allergy & Immunology Review Corner:** Cellular and Molecular Immunology, 9th edition
Abdul K. Abbas, MBBS, Andrew H. Lichtman, MD, PhD, and Shiv Pillai, MBBS, PhD
Chapter 5 (pages 97-115) Antibodies and Antigens
Prepared by: Eliane Abou Jaoude

1. Which of the following is true about the $V_L$ and $V_H$ domains of antibodies?
    a. Located at the carboxy terminus
    b. Are located in the Fab portion of the antibody
    c. Are located in the Fc portion of the antibody
    d. Do not participate in antigen binding

2. Which of the following is true about Papain digestion of an antibody?
    a. Generates a single bivalent antigen-binding fragment, $F(ab')_2$
    b. Cleaves between the $V_L$ and $C_L$ region of the antibody
    c. Cleaves between the $V_H$ and the $C_H1$ region of the antibody
    d. Allows the separation of 2 Fab fragments from the Fc fragment

3. Which of the following is true about IgG?
    a. Binds to the neonatal FcRn receptor
    b. Forms a pentamer
    c. Has a half-life of 5 days
    d. Has 2 subtypes

4. Which of the following is true about complementary determining regions?
    a. They are confined of 2 stretches in the V region of the heavy chain and 2 stretches in the variable region of the light chain.
    b. They have only 2 types, CDR1 and CDR2.
    c. CDR2 is the most diverse of all the complementary determining regions.
    d. Are segments of greatest diversity known as the hypervariable regions

5. What is the strength of the binding between a single combining site of an antibody and epitope of an antigen called?
    a. Avidity
    b. Affinity
    c. Diversity
    d. Affinity maturation

6. Which of the following is true about antibodies?
    a. IgA has 4 subtypes
    b. IgG is a pentamer
    c. IgE has a half life of 2 days
    d. IgM is a monomer

7. The hinge region
    a. Is located between the $C_H2$ and $C_H3$ domains
    b. Is located between the $C_H1$ and $C_H2$ domains
    c. Allows for rigidity in the antibody structure
    d. Allows for rotation between the $C_H2$ and $C_H3$ domains

8. TNF is associated with which disease states?
    a. Rheumatoid arthritis, Crohn's disease, Psoriasis
    b. Multiple sclerosis
    c. Cardiovascular disease
    d. Allergy Related Asthma

9. Immature B cell produces
    a. Membrane IgD
    b. IgG secretion
    c. Membrane IgA
    d. Membrane IgM

10. Membrane forms of Ig heavy chains
    a. Contain transmembrane regions made up of hydrophobic amino acid residues
    b. Contain transmembrane regions made up of hydrophilic amino acid residues
    c. Have similar cytoplasmic domains that are identical between isotypes
    d. Ends in C terminal tail pieces.

Answers:

1. Answer: B

Page 99. $V_L$ and $V_H$ domains of an antibody are located in the Fab portion of the antibody. They are located at the amino- terminus of the antibody. $V_L$ and $V_H$ domains of an antibody participate in antigen recognition.

2. Answer: D.

Page 101. If rabbit IgG is treated with the enzyme papain, the enzyme acts on the hinge region and cleaves the IgG into three separate pieces. Two of the pieces are identical and consist of the light chain $V_L$ and $C_L$ associated with the $V_H$ and $C_H1$ fragment of the heavy chain. The third piece is composed of two identical disulfide linked peptides each containing $C_H2$ and $C_H3$.

3. Answer: A.

Page 104. IgG binds to the neonatal Fc receptor which allows for the long half life of IgG (23 days). The FcRn is involved in the transport of IgG from maternal circulation across the placental barrier. IgG is a monomer. IgG has 4 subtypes, y1, y2, y3, y4. The half life of IgG is 23 days.

4. Answer: D
Page 101-102. Complementary determining regions are made of CDR1, CDR2, CDR3. CDR3 generates the most sequence diversity. The area is composed of three short stretches in the V region of the heavy chain and to three stretches in the V region of the light chain.

5. Answer: B.
Page 111-112. The strength of the binding between a single combining site of an antibody and an epitope of an antigen is the affinity of the antibody. The affinity is represented by the dissociation constant ($k_D$), which indicated how easy it is to separate an antigen-antibody complex into its constituents. A smaller $k_D$ indicates a stronger or higher affinity interaction because a lower concentration of an antigen and of antibody is required for complex formation. Avidity is the overall strength of an attachment that takes into account binding of all sites to all available epitopes.

6. Answer: C
Page 104. IgA has 2 subtypes, a1 or a2. IgM is a pentamer in the secreted form. IgD, IgG, and IgE are monomers. IgE has a half life of 2 days. IgG has a half life of 23 days. IgG has 4 subtypes, y1, y2, y3, y4.

7. Answer: B
Page 104. The flexibility of the antibody is mainly due to the hinge regions located between the $C_H1$ and $C_H2$ domains, which permit independent movement of antigen binding sites relative to the rest of the molecule.

8. Answer: A
Page 108. TNF is associated with rheumatoid arthritis, Crohn's disease, psoriasis. A4 integrins are associated with multiple sclerosis and Crohn's disease. IgE is associated with allergy related asthma. Glycoprotein IIb/IIIa is associated with cardiovascular disease.

9. Answer: D
Page 108-109. Immature B cells produce membrane IgM. Mature B cells produce membrane IgM and IgD. Antibody secreting cells produce high rates of IgM, IgG, IgA, or IgE secretion.

10. Answer: B
Page 105. The membrane forms of the Ig heavy chains have hydrophilic amino acid residues, but not the secreted forms contain transmembrane regions made up of hydrophobic amino acid residues. The cytoplasmic domains differ between the different isotypes.

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**Review Questions**
**Allergy & Immunology Review Corner:** Cellular and Molecular Immunology, 9th edition
Abdul K. Abbass, MBBS, Andrew H. Lichtman, MD, PhD, and Shiv Pillai, MBBS, PhD
**Chapter 6:** (pages 118-142) Immune Receptors and Signal Transduction
Prepared by: Ohn Chow, MD

1. Which of the following can be recognized by the T-Cell receptor using MHC to bind them?
    a. Carbohydrates
    b. Short peptides
    c. Long peptides
    d. Lipids
    e. Small chemicals

2. Which of the following is not thought to be an APC for CD4+ T-lymphocytes?
    a. Dendritic cells
    b. Macrophages
    c. CD8+ T-cells
    d. B-cells

3. Which chromosome contains the MCH locus?
    a. Chromosome 2
    b. Chromosome 4
    c. Chromosome 6
    d. Chromosome 8

4. Which of the following is NOT an MHC II locus?
    a. HLA-DO
    b. HLA-DP
    c. HLA-DQ
    d. HLA-DR

5. Which of the following increases cellular expression of MHC I complex?
    a. Interferons
    b. IL-4
    c. IL-1
    d. IL-2

6. Which of the following statements about MHC is true?
   a. MHC I can bind a longer peptide than MHCII
   b. Each MHC molecule can only bind one type of peptide
   c. Very small numbers of peptide-MHC complexes are capable of activating specific T lymphocytes
   d. The MHC molecules of an individual can only bind foreign peptides.

7. Mutations in which of the following genes results in X-linked hyper IgM syndrome?
   a. CD40L
   b. AID
   c. CD40
   d. UNG

8. Which of the following is true about class I MHC pathway?
   a. Digestion of protein occurs in endosomes/lysosomes
   b. Endocytosis of extracellular protein is required
   c. Digestion of protein occurs via proteasome
   d. Protein is expressed on cell surface to CD4+ T cells.

9. What effect does successful presentation of an antigen on MHC I to T cells have on surrounding cells and tissues?
   a. It activates surrounding macrophages to kill microbes
   b. It triggers release of cytokines
   c. It stimulates B cells to secrete antibodies
   d. It stimulates CD8+ T cells to kill antigen-expressing target cell

10. Where does affinity maturation occur in the lymph node?
   a. Parafollicular area
   b. Marginal zone
   c. Germinal center
   d. Subcapsular sinus

**Answers:**

1. **B**. Short peptides. p 117. B cells can recognize larger folded proteins, lipids, carbohydrates, and small molecules. T-cells can recognize certain chemical (i.e. urushiol, penicillin), although it is thought that these substances bind to and modify self proteins, which are then recognized by T-cells.

2. **C**: CD8+ T-cells. p 118. The others have APC functions, although dendritic cells are thought to be the most effective, particularly for activation of naïve T-cells. Essentially all nucleated cells can present antigen to CD4+ cells.

3. **C**: Chromosome 6. P.125. There are three class I MHC genes called HLA-A, HLA-B, HLA-C and three class II HLA gene loci called HLA-DP, HLA-DQ, and HLA-DR.

4. **A**. HLA-DO. P. 127.

5. **A**. Type 1 interferons. P 127. IFN-alpha and IFN-beta are produced during the innate immune response to viruses. MHC I presents antigens to virus specific T cells (CD8+ T cells). IFNγ also increases MHC I as well as MHC II.

6. **C**. p 130-132. Very small numbers of peptide-MHC complexes are capable of activating specific T lymphocytes. Because APCs continuously present peptides derived from all proteins, only a very small fraction of surface peptide-MHC complexes will activate a specific T cell response. Unlike MHC I, the MHC II peptide binding groove is open on each end, which allows a longer peptide to bind (up to 10-30 amino acids). Each MHC molecule (I or II) can only bind one peptide at a time, but can bind many different peptides. MHC molecules from an individual can bind and display foreign or self antigens.

7. **A**. CD40L. AID, CD40 and UNG mutations are associated with hyper IgM syndromes type 2, 3 and 5, respectively. These are all autosomal recessive.

8. **C**. Digestion of protein in proteasome. Class I MHC molecules are typically intracellular molecules and are presented on cell surface to CD8+ T cells.

9. **D**. It stimulates CD8+ T cells to kill antigen-expressing target cell. The other effects are class II MHC presentation.

10. **C**. Affinity maturation occurs in the germinal center of the lymph node.

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**Review Questions**
**Allergy & Immunology Review Corner:** Cellular and Molecular Immunology, 9th edition
Abul K. Abbas, MBBS, Andrew H. Lichtman, MD, PhD, and Shiv Pillai, MBBS, PhD
**Chapter 13:** (pages 275-298) Effector Mechanisms of Humoral Immunity
Prepared by: Neelam Phadke, MD

1. Which of the following statements accurately describes humoral and cell-mediated immunity?
   a. Humoral immunity is mediated by antibodies and defends against intracellular microbes while cellular immunity is mediated by T lymphocytes and defends against extracellular microbes
   b. Humoral immunity is mediated by antibodies and defends against extracellular microbes while cellular immunity is mediated by T lymphocytes and defends against intracellular microbes
   c. Humoral immunity is mediated by T lymphocytes and defends against intracellular microbes while cellular immunity is mediated by antibodies and defends against extracellular microbes
   d. Humoral immunity is mediated by T lymphocytes and defends against extracellular microbes while cellular immunity is mediated by antibodies and defends against intracellular microbes

2. What is one mechanism used by humoral immunity to protect against microbes?

   a. Antibodies block the binding of microbes to their receptors
   b. Antibodies phagocytose microbes and microbial toxins
   c. Antibodies release mediators to lyse microbes
   d. Antibodies release mediators to cause local inflammation

3. What is the main antibody isotype found in the blood? What is the main antibody isotype found on mucosal surfaces?

   a. IgA is the main antibody isotype found in the blood, IgG the main antibody isotype found in the mucosal surfaces
   b. IgM is the main antibody isotype found in the blood, IgA is the main antibody isotype found in the mucosal surfaces
   c. IgG is the main antibody isotype found in the blood, IgA highest is the main antibody isotype found in the mucosal surfaces
   d. IgG is the main antibody isotype found in the blood, IgM is the main antibody isotype found in the blood

4. Which of the following is an accurate description of one of the effector mechanism of adaptive immunity?
   a. Mononuclear phagocytes and neutrophils directly bind and ingest microbes
   b. Neutrophils bind microbial surface receptors to cause self-destruction
   c. Complement proteins actively phagocytose microbes
   d. Antibodies coat microbial surfaces to promote phagocytosis

5. What opsonins are the most efficient for promoting phagocytosis?

a. IgG2 and IgG3
b. C3b
c. IgG 1 and IgG 3
d. IgG 4

6. What is one mechanism for the therapeutic benefit of IVIG therapy in autoimmune disorders?
a. IVIG delivers inhibitory signals to B lymphocytes and activating signals to myeloid cells
b. IVIG binds to the FcγRIIB receptor
c. IVIG increases antibody production
d. IVIG antagonizes the FcγRIIB receptor

7. Which cell type functions to destroy cells coated by antibody?
a. Natural Killer Cells
b. Plasmacytoid DC's
c. CD4+ T cells
d. Neutrophils

8. What is the most common human complement deficiency?
a. C1q deficiency
b. C1 inhibitor deficiency
c. C2 deficiency
d. C3 deficiency

9. Deficiencies in the terminal complement proteins (C5-9) predispose to infection by which of the following organisms?

a. Streptococcus
b. Staphylococcus
c. Neisseria
d. Pseudomonas

10. Which of the following is an important component of neonatal immunity in the first days to weeks of life?
a. Maternal neutrophils
b. Vaccines
c. Maternal IgM transported through breastmilk
d. Maternal IgA and IgG transported through breast milk

**Answers:**

1. **B**. Humoral immunity is mediated by antibodies and defends against extracellular microbes while cellular immunity is mediated by T lymphocytes and defends against intracellular microbes p 275. B cells can recognize larger folded proteins, lipids, carbohydrates, and small molecules. T-cells can recognize certain chemical (i.e. urushiol, penicillin), although it is thought that these substances bind to and modify self proteins, which are then recognized by T-cells.

2. **A**: Antibodies block the binding of microbes to their receptors p 276-277. Antibodies block the binding of microbes and microbial toxins to cellular receptors, thus neutralizing or inhibiting the infectivity of microbes and minimizing the injurious effects of microbial toxins. Antibodies neutralize microbes and toxins, opsonize them for phagocytosis, sensitize them for antibody-dependent cellular cytotoxicity, and activate the complement system. Different antibody types mediate various effector functions .

3. **C**: P. 277 IgG is the main antibody isotype found in the blood, IgA highest is the main antibody isotype found in the mucosal surfaces

4. **D**. Antibodies coat microbial surfaces to promote phagocytosis P 275
IgG antibodies coat (opsonize) microbes and promote their phagocytosis by binding to Fc receptors on phagocytes. Choice A describes a function of the innate immune system in protection against microbes. Neutrophils can ingest microbes, but do not cause microbial self-destruction. Complement can play a role in active immunity as C3b coats microbes and leads to phagocytosis, but complement proteins themselves do not phagocytose microbes.

5. **C**. IgG1 and IgG3 P 280. Antibody-coated particles bind Fc receptors on phagocytes to cause engulfment of the particles and phagocytic activation. IgG1 and IgG3 are the IgG subtypes that best bind these receptors and hence the most efficient opsonins to promote phagocytosis.

6. **B**. IVIG binds to the FcγRIIB receptor P. 281. IVIG increases expression of FcγRIIB and binds to this receptor. It delivers inhibitory signals to B lymphocytes and myeloid cells leading to decreased antibody production and dampened inflammation.

7. **A**. Natural killer Cells. P 281 : Natural Killer cells and other leukocytes bind to antibody-coated cells by Fc receptors and destroy these cells through the process of antibody-dependent cell-mediated cytotoxicity (ADCC). ADCC only occurs if the target cell is coated with antibody molecules, as free plasma IgG cannot activate NK cells or compete with cell-bound IgG for binding to FcγRIII.

8. **C**. C2 deficiency P 296. While deficiencies in C1q, C1r, C2, C3, and C4 have all been described, C2 deficiency is the most commonly described complement deficiency in humans.

9. **C**. Neisseria P 296 Terminal complement protein deficiency leads to increased infection with *N. meningitidis* and *N. gonorrhoeae*. Because of the rarity of some of these infections, some clinicians feel that a single episode of *Neisseria* meningitis is reason to evaluate for terminal complement deficiency

10. **D** Maternal IgA and IgG transported through breast milk P297. Maternal antibodies transported across the placenta and in ingested milk protect neonates from infection. IgG is transported across the placenta and maternal IgA and IgG are shared via breast milk ingestion. While the infant has mechanisms of innate immunity that are active at birth, these are not directly shared from the mother.

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**Review Questions**

**Allergy & Immunology Review Corner:** Cellular and Molecular Immunology, 9th edition
Abul K. Abbas, MBBS, Andrew H. Lichtman, MD, PhD, and Shiv Pillai, MBBS, PhD
**Chapter 7:** (pages 145-177) Immune Receptors and Signal Transduction
Prepared by: Catherina Cranford, MD

1. Which type of cellular receptor is an integral membrane protein with intrinsic catalytic enzyme domain(s) in the cytoplasmic tail?
    a. Non-receptor tyrosine kinase
    b. Receptor tyrosine kinase
    c. Nuclear receptor
    d. G-protein coupled receptor

2. The T cell receptor (TCR) complex consists of a TCR αβ heterodimer and these proteins which have ITAMs in their tails that contribute to signal transduction.
    a. CD3 and ζ proteins
    b. CD4 and β polypeptide chain
    c. CD2 and ζ proteins
    d. CD3 and α polypeptide chain

3. Which Syk family tyrosine kinase phosphorylates adaptor proteins such as LAT, an event which is an important part of early T cell activation?
    a. Lck
    b. PI3-kinase
    c. SLP-76
    d. ZAP-70

4. A 45-year-old, poorly controlled diabetic patient develops progressive renal failure and requires a renal transplant. He is placed on Tacrolimus as part of his immunosuppressive regimen. Tacrolimus complexes with FKBP and inhibits what molecule, thus blocking NFAT translocation into the nucleus?
    a. Cyclophilin
    b. FK506
    c. Calcineurin
    d. NF-kB

5. A 65-year-old woman presents with weight loss and bone pain. She has noticed several large, dark moles which have not been previously evaluated. She is diagnosed with metastatic melanoma and started on a monoclonal antibody which targets and blocks which inhibitory receptor with high affinity for B7-1 (CD80) and B7-2 (CD86), thus leading to increased T cell activation?
    a. CTLA-4 (CD152)
    b. PD-1
    c. CD28
    d. CD2

6. C3d binds this cell surface molecule which forms part of the B cell coreceptor complex.
    a. CD16 (FcyRIII)
    b. CD20
    c. CD86
    d. CD21 (CR2)

7. Mutations in *SH2D1A*, the gene which encodes which of the following, are the cause of X-linked lymphoproliferative syndrome (XLP)?
    a. SLAM
    b. ICOS
    *c.* SAP
    d. CD28

8. Type II cytokine receptors (interferon receptor family) utilize which signaling pathway?
    a. Ras-MAP kinase
    b. JAK-STAT
    c. PKC-β
    d. NF-κB

9. Which of the following is a ligand for the IL-1 receptor family?
    a. IL-18
    b. IL-10
    c. IFN-γ
    d. IL-2

10. Gain-of-function mutations in which of the following cause myelodysplastic syndrome?
    a. STAT1
    b. STAT3
    c. JAK2
    d. JAK3

**Answers:**

1. B. Page 147. Receptor tyrosine kinases are integral membrane proteins that activate an intrinsic tyrosine kinase domain (or domains) located in the cytoplasmic tails of the receptors when they are cross-linked by multivalent extracellular ligands. Non-receptor tyrosine kinases do not have intrinsic

catalytic activity in their cytoplasmic tails. Nuclear receptors are intracellular, and G protein-coupled receptors are associated with GTP-binding proteins which then interact with enzymes downstream.

2. A. Page 153-154. The CD3 and ζ proteins are noncovalently associated with the TCR αβ heterodimer to form the TCR complex. When the TCR recognizes antigens, these proteins transduce the signals that lead to T cell activation. CD4 is a coreceptor on helper T cells which binds to class II MHC molecules. CD2 (LFA-2) is an adhesion molecule which binds CD58. The α and β polypeptide chains make up the TCR heterodimer.

3. D. Page 157-158. ζ-associated protein of 70 kD (ZAP-70) is a Syk family tyrosine kinase. Activated ZAP-70 phosphorylates several adaptor proteins which then can bind signaling molecules. Phosphorylation of such proteins as SLP-76 and LAT form a key early event in T cell activation. Lck phosphorylates tyrosine residues of ZAP-70, allowing it to acquire its own tyrosine kinase activity. PI3-kinase is activated in another signaling pathway in T cells but is not a tyrosine kinase of the Syk family.

4. C. Page 163. Tacrolimus binds to a protein called FK506-binding protein (FKBP), and the complex inhibits calcineurin. Cyclosporine binds to cyclophilin, also inhibiting calcineurin. Inhibition of calcineurin blocks translocation of NFAT into the nucleus. FK506 is another name for Tacrolimus, and NF-kB is not directly affected by either Tacrolimus or Cyclosporine.

5. A. Page 169. CTLA-4 (CD152) has a higher affinity than CD28 for B7 proteins and is a competitive inhibitor of B7-CD28 interactions. This receptor inhibits immune responses by out-competing the activating receptor CD28 and thus blockade of CTLA-4 by a monoclonal antibody leads to increased costimulatory signals in T cells, leading to their increased activation. PD-1 does not bind B7-1 and B7-2. CD28 is an activating receptor, and CD2 is an adhesion molecule.

6. D. Page 167. The B cell coreceptor complex is composed of CD21 (CR2), CD19, and CD81. CD21 (CR2) is also known as the type 2 complement receptor and binds C3d when it is complexed with antigen or to an antigen-antibody complex. When C3d complexed to antigen binds CD21 (CR2), several steps occur which lead to enhanced B cell activation. CD20 is found on B cells but is not part of the B cell coreceptor complex. CD86 is also known as B7-2 and is important in T cell costimulation. CD16 is present on NK cells and plays a role in antibody-dependent cellular cytotoxicity.

7. C. Page 165. Mutations in *SH2D1A* lead to X-linked lymphoproliferative syndrome. *SH2D1A* encodes SLAM-associated protein (SAP) which is an adaptor protein which can associate with proteins which contain immunoreceptor tyrosine-based switch motif (ITSM) which can mediate inhibitory or activating functions. One such protein is 2B4, and defective 2B4 signaling contributes to the immune deficits in patients with XLP. The other mentioned proteins are not encoded by *SH2D1A*.

8. B. Page 171. All of the type II receptors engage JAK-STAT signaling pathways. Type I cytokine receptors also use the JAK-STAT pathway. The other listed proteins are involved in signaling, but type II cytokine receptors do not use these pathways

9. A. Page 172. IL-18 and IL-1 are both ligands of the IL-1 receptor family, and both of these cytokines are involved in activity of the inflammasome. The receptors of this family share a conserved cytosolic sequence called the Toll/IL-1 receptor (TIR) doman and engage similar signal transduction pathways. IL-10 and IFN-γ are ligands of type II cytokine receptors, and IL-2 engages a type I cytokine receptor.

10. C. Page 175. Gain-of-function mutations in JAK2 can cause of myelodysplastic syndrome with varying phenotypes of aplastic anemia and polycythemia vera. Type I cytokine receptors of the IL-6 family use JAK2 to activate STAT3, but STAT3 can also be activated by several other cytokines. Mutations affecting JAK3 can lead to a form of SCID similar to common γ chain deficiency. Negative mutations in STAT3 can lead to problems with Th17 responses, leading to an immunodeficiency disease while activating mutations are seen in large granular lymphocytic leukemias.