FIT Board Review Corner – July 2015

Welcome to the FIT Board Review Corner, prepared by Andrew Nickels, MD, and Sarah Spriet, DO, senior and junior representatives of ACAAI’s Fellows-In-Training (FITs) to the Board of Regents. The FIT Board Review Corner is an opportunity to help hone your Board preparedness.

Review Questions

Allergy and Immunology Review Corner: Cellular and Molecular Immunology, 8th Edition
By Abul K. Abbas, MBBS, Andrew H. H. Lichtman, MD, PhD and Shiv Pillai, MBBS, PhD.

Chapter 6 (pages 119-133): Major Histocompatibility Complex Molecules and Antigen Presentation to T Lymphocytes

Prepared by Tara Shankar, MD, Children’s Hospital of Pittsburgh of UPMC

1. What is the principal cytokine involved in stimulating expression of class II molecules in APCs?
   a. IFN-alpha
   b. IFN-beta
   c. IFN-gamma
   d. IL-1

2. What is the binding site for CD8 on the Class I MHC molecule?
   a. a1
   b. a2
   c. a3
   d. b2

3. MHC Class I molecules accommodate peptides of what length?
   a. 4-9
   b. 8-11
   c. 10-20
   d. 12-30

4. What type of interaction does a peptide and MHC molecule have?
   a. Saturable, slow off
   b. Saturable, fast off
   c. Non saturable, slow off
   d. Non saturable, fast off
5. Listeria monocytogenes can resist microbiocidal mechanisms by producing listeriolysin which allows the bacteria to escape from vesicles into the cytosol. What type of molecule would then present the listeria microbial protein?
   a. Class I MHC
   b. Class II MHC
   c. HLA DM
   d. CIITA

6. HSV has evolved to block the TAP transporter. How does this evolutionary change allow HSV to evade the host immune response?
   a. The invariant chain peptide cannot be removed to make the peptide binding cleft of class II molecules available.
   b. Cytosolic peptides cannot be transported into the ER where they can associate with a class II MHC molecule.
   c. The invariant chain peptide cannot be removed to make the peptide binding cleft of class I molecules available.
   d. Cytosolic peptides cannot be transported into the ER where they can associate with a class I MHC molecule.

7. Where do processed peptides associate with class II MHC molecules?
   a. Endoplasmic reticulum
   b. Endosomal vesicle
   c. Surface of the APC
   d. Endocytic vesicle

8. What is the function of HLA-DM?
   a. Transports cytosolic peptides to the ER.
   b. Brings the TAP transporter into a complex with the class I MHC molecules awaiting arrival of peptides.
   c. Chaperones the folding and assembly of class II MHC dimers.
   d. Removes CLIP to make the peptide cleft available.

9. Though most ingested proteins do not enter the class I pathway, in cross-presentation, ingested antigens are transported from vesicles to the cytosol where peptides enter the class I pathway. This process is unique to which cell?
   a. Macrophages
   b. NK cells
   c. Dendritic cells
   d. Gamma delta T cells

10. What molecule is structurally homologous to the class I MHC molecule and displays lipid antigens for recognition by NKT cells?
    a. CD1
    b. CD2
    c. CD3
    d. CD4
Answers
"IFN-gamma is the principal cytokine involved in stimulating expression of class II molecules."

2. C, page 121.
"The alpha3 segment of the alpha chain...contains most of the binding site for CD8."

"Class I molecules can accommodate peptides that are 8-11 residues long."

"The association of peptides and MHC molecules is a saturable interaction with a very slow off rate...This extraordinarily slow off rate of peptide dissociation from MHC molecules ensures that after an MHC molecule has acquired a peptide, it will display the peptide long enough to maximize the chance that a particular T cell will find the peptide it can recognize and initiate a response."

5. A, page 125.
"Protein antigens that are present in the cytosol...generate class I associated peptides that are recognized by CD8+ T cells."

"Because antigenic peptides for the class I pathway are generated by proteases in the cytosol...but class I MHC molecules are synthesized in the ER, a mechanism is needed to deliver cytosolic peptides into the ER. This delivery is mediated by a dimeric protein called transporter associated with antigen processing (TAP)."

7. B, page 130
"Within the endosomal vesicle, the invariant chain dissociates from class II MHC molecules...and antigenic peptides are then able to bind to the available peptide binding clefts of the class II molecules."

"CLIP must be removed so that the cleft becomes accessible to antigenic peptides produced from extracellular proteins. This removal is accomplished by the action of a molecule called HLA-DM."

"Ingested antigens are transported from vesicles to the cytosol for where peptides enter the class I pathway. This permissiveness for protein traffic from endosomal vesicles to the cytosol is unique to dendritic cells."

10. A, page 133.
"NKT cells recognize lipids and glycolipids displayed by the class I-like non-classical MHC molecule called CD1."
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Chapter 7 (pages 137-150): Immune Receptors and Signal Transduction

Prepared by Erin Kemp, DO, Ohio State University Hospital

1. Btk is a tyrosine kinase of the Tec family that recognizes which of the following molecules:
   a. Leucine
   b. PIP3
   c. Proline
   d. Ubiquitin

2. Which of the following receptors contains an immunoreceptor tyrosine-based inhibitory motif (ITIM) in its cytoplasmic tail?
   a. CD3ζ
   b. FcεRI
   c. FcγRIIB
   d. Igα

3. Which of the following components of the T cell receptor complex serve as the binding site for a peptide-MHC complex?
   a. αβ
   b. εδ
   c. εγ
   d. ζζ

4. Signal transduction for the T cell receptor complex is mediated by which component?
   a. α
   b. β
   c. β2m
   d. ζ

5. Which portion of the TCR complex serves as a binding site for microbial superantigens?
   a. α
   b. β
   c. δ
   d. ζ

6. After recognition of MHC-peptide complexes by the TCR, phosphorylation of ITAMs on the CD3 and ζ chains is initiated by which kinase on the CD4/CD8 coreceptor?
7. Which of the following MAP kinases is activated through the Ras G protein pathway?
   a. ERK  
   b. JAK  
   c. JNK  
   d. STAT

8. Which of the following G protein pathways leads to activation of the AP-1 transcription factor through the MAP kinase JNK?
   a. DAG  
   b. PLCγ1  
   c. Rac  
   d. Ras

9. Which of the following is the initial step leading to an increase in cytosolic free calcium as a result of TCR activation?
   a. DAG activates PKC  
   b. Grb-2 docks to phosphorylated LAT  
   c. PLCγ is phosphorylated and hydrolyzes PIP2 into IP3  
   d. STIM1 activates opening of the CRAC channel

10. Which of the following transcription factors is activated by calcineurin and results in expression of genes for IL-2, IL-4, and TNF?
    a. AP-1  
    b. c-Fos  
    c. NFAT  
    d. NF-κB

Answers
1. B, page 140, figure 7.3.
   Btk is a member of the TEC family of tyrosine kinases, which recognizes PIP3 on the inner leaflet of the plasma membrane via a pleckstrin-homology (PH) domain. Proline is recognized by SH3 homology domains.

2. C, page 142, figure 7.5.
   FcγRIIB is an inhibitory B cell receptor that contains an ITIM. CD3ζ exists as a homodimer in the T cell receptor complex, and each of the z chains contain 3 ITAMs each. FcεRI is an ITAM-
containing B cell receptor, and Igα is associated with membrane-bound Ig molecules which also contains an ITAM.

The T cell receptor complex consists of a collection of homodimers and heterodimers. The αβ heterodimer serves as the binding site for a peptide-MHC complex. Each TCR complex also contains one CD3γε heterodimer and one δε heterodimer, as well as a ζζ homodimer, all of which contain ITAMs on their cytoplasmic tails.

The TCR complex is made up of multiple polypeptide chains. The TCR α and β chains bind antigen, but have short cytoplasmic tails without signal transduction capability. Signal transduction is mediated through the cytoplasmic tails of the ζζ homodimer, or through one of the CD3 heterodimers (γε or δε).

The α and β chain each contain 3 complementarity-determining regions (CDRs) that contribute to the variability of the TCR. The β chain contains a fourth CDR that serves as the binding site for superantigens.

6. C, page 147, figure 7.11.
The cytoplasmic tails of CD4/CD8 contain the Src family kinase Lck. After the TCR binds an MHC-peptide complex, the CD4/CD8 coreceptor brings Lck close to the ITAMs on the cytoplasmic tails of the CD3 and ζ chains, allowing the ITAMs on these chains to be phosphorylated. Once phosphorylated, the ITAMs on the ζ chain serves as a docking site for ZAP-70. LAT is an adaptor protein phosphorylated by ZAP-70. Btk is a kinase involved in B cell signaling.

During TCR activation, ZAP-70 phosphorylates LAT, allowing Grb-2 to dock. SOS is then recruited to a site on Grb-2, which exchanges GTP for GDP on the Rac molecule, resulting in Rac-GTP. Rac-GTP activates Raf, which activates MEK-1, which activates the MAP kinase ERK.

8. C, pages 151-52, figure 7.14
Ras and Rac are both G proteins. The Ras pathway activates AP-1 through the ERK MAP kinase, while the Rac pathway activates AP-1 via JNK. DAG and PLCγ1 are not G proteins, and are involved in activation of PKC.

LAT recruits PLCγ1 to the plasma membrane where it is phosphorylated and hydrolyzes PIP2 into IP3 and DAG. IP3 stimulates the release of membrane-sequestered calcium stores, which is sensed by STIM1 and leads to opening of the CRAC channel. DAG activates PKC.

10. C, pages 152-54, figure 7.16.
NFAT is involved in expression of IL-2, IL-4, and TNF. c-Fos is a component of the AP-1 transcription factor, and NF-κB is a transcription factor important in innate immune cell signaling.