

FAQs 9/17/03

Q1: Do B-cells and T-cells respond to the same antigen?

This is an excellent question. The following is an attempt to answer it: The TCR recognizes the primary amino acid sequence of an antigen. The BCR, which is a membrane immunoglobulin, recognizes higher order structure, such as secondary and tertiary structure (circulating antibodies recognize Ag in a similar fashion). Therefore, T- and B-cells recognize their targets differently and seldom recognize the same epitopes on any given molecule.

The tricky question is whether specific T helper cells and a particular clone of B-cells (with which they interact) recognize epitopes present on the same protein. The answer is probably yes. B-cells have a dual function: they act as effectors in the immune system and produce antibodies; they also serve as “professional” antigen presenting cells (along with dendritic cells and macrophages). Unlike dendritic cells and macrophages, which are very non-discerning in the antigens that they capture, B-cells possess specific surface membrane immunoglobulins (aka “BCR”) that efficiently trap specific antigens. This is followed by endocytosis, degradation, and presentation of peptides derived from this antigenic protein via Class II MHC molecules on the surface of the B-cell. The B-cell then presents Ag to particular T helper cells that recognize these peptides. Thus, the likelihood is high that the responding T-cells recognize a sequence within the antigen that was recognized by the B-cell’s specific BCR; hence, T- and B-cells often recognize the same antigen.

Q2: What is cross-priming and why is it necessary for viral immunity?

Fig. 5-7 in the Abbas text is a little confusing on this point. First, the MHC molecules that are doing the presenting are derived from newly-synthesized MHC Class I molecules in the DC, not the dead/dying virally infected cell. Second, although CD4+ T-cells provide help to CD8 cells, cross-priming (aka cross-presentation or the “exogenous pathway” refers only to the phenomenon of MHC Class I presentation, not Class II presentation. It is likely that both processes are going on at the same time, even via the same DC, but the CD8+ T-cell is participating only in the former. DCs can simultaneously engage many different clones of T-cells which can either be of the CD8 or CD4 phenotype.

The next question, which was asked in class, is an excellent one. Because it is a teleological one, there is no definitive answer, but I can think of at least two potential explanations. First, although MHC Class I-bearing virally-infected cells have the potential to present Ag directly to T-cells, they may well lack the full array of co-stimulatory molecules otherwise present on DCs. So the efficiency of Ag presentation by cells other than DCs may be much less efficient, if not tolerogenic. Co-stimulation is critical for the primary immune response, whereas the requirement for co-stimulation is less stringent in a recall response. Second,

the primary immune response occurs only in secondary lymphoid organs. DCs bearing Ag utilize CCR7 to sense chemokines elaborated in the T-cell zones of lymph nodes and the spleen and migrate toward the source of chemokines. Other cells (e.g., a virally-infected epithelial cell) probably lack this chemokine receptor and unless viral proteins leak out of the dying cell and are transported by bulk flow to the lymph node, the relevant Ag would have no way of getting there. In addition, cross-priming is apparently much more efficient when the Ag is delivered via phagocytosis, rather than endocytosis or pinocytosis.

Q4: What is a “lipid raft?”

Lipid rafts (aka detergent-insoluble glycolipid-rich domains (DIGs) or glycolipid-enriched membranes (GEMs)) are discrete regions within the plasma membrane (microdomains) that are enriched in cholesterol, glycolipids, and a subset of proteins that participate in transmembrane signaling. Upon activation, many components of the TCR and the BCR accumulate in these microdomains. It is thought that these structures contribute to the enrichment of signaling proteins in a spatially localized area. This contributes to the overall efficiency of signaling.

Q5: Help!!! what is the TCR? What is the BCR? And am I responsible for these for the exam?

Let’s answer the last part first. You are responsible for learning immunology and retaining what you learn. You will be tested only on important aspects of immunology, not minutiae. Important aspects of immunology will be repeated again and again in multiple different contexts, so pay attention to these points. They tend to be discussed in the lectures and Small Group Sessions. The test is a means to an end.

Table I may help you better understand how these receptors function. It emphasizes the conservation in signaling pathways but also illustrates important functional differences. **It is more detailed than you need to know. The pathways that are not important to commit to memory are indicated in light blue.** They are provided for the sake of completeness as they are essential for signaling.

It is easiest to read this Table across each row:

Table I. Comparison of BCR and TCR Signaling Pathways (Simplified)¹

	BCR			TCR		
Triggering cell	T helper cell ²			Professional APCs (DCs, M, B-cells)		
Triggering ligand (Signal 1)	Soluble antigen			MHC II/peptide		
Epitopes recognized	1°, 2° and 3° structure			1° structure; 8-9-mer peptide		
Relevant sites of interaction	Lymph nodes, spleen			Thymus, lymph nodes, spleen		
Major co-stimulatory molecules (Signal 2)	B-cell	Th cell		T-cell	APC	
	CD40	CD40L		CD4 CD28 LFA-1	MHC II CD80/86 ICAM-1, 2	
	CD19, CD21 CD81			ICAM-3 CD2	DC-SIGN LFA-3	
Major signaling ITAM ³	Ig, Ig			subunit of CD3		
Major initiating Src family tyrosine kinase (TK) that phosphorylates ITAMs ⁵	Blk, Fyn, Lyn			Lck		
Major initiating tyrosine phosphatase	CD45			CD45		
ITAM-binding TK	Syk			ZAP-70		
Key pathways downstream of Syk/ZAP-70	Enzymes	Adaptor Proteins ⁴		Enzymes	Adaptor Proteins	
	Btk, Tec	BLNK		Itk, Txk	Lad/RIBP	
	PI 3-kinase ³	Cbl, CD19 BCAP, Gab1		PI 3-kinase	LAT, TRIM	
Key substrate of Btk family	PLC-	BLNK		PLC-	LAT, Gads, SLP-76	
Products of PIP ₂ hydrolysis	IP ₃	DAG		IP ₃	DAG	
Outcome of PLC- activation	Ca ²⁺	PKC activ.	Ras ⁷	Ca ²⁺	PKC activ.	Ras
Target of former	Calcineurin	?	MAPK	Calcineurin	?	MAPK
Major transcription factors activated ⁶	NF-AT	NF- B AP-1	SRE	NF-AT	NF- B AP-1	SRE
Primary outcomes	Proliferation Differentiation into memory B-cells or plasma cells Ig class switching			IL-2, IL-2R induction Proliferation Differentiation into T helper cell		

Notes:

1. For simplicity, the pathway depicted for the TCR comprises the MHC Class II pathway, only. The MHC Class I pathway is similar, except that in addition to APCs, all nucleated cells express MHC Class I, and CD8, rather than CD4, is the major co-receptor of the TCR. Instead of a T helper cell, the primary outcome of the MHC Class I pathway is the production of a T cytotoxic cell.

Not depicted are soluble factors, especially cytokines, that are required for signaling. For example, IL-4 is required for Ig class switching in B-cells and IL-2 is required for proliferation in T-cells.

2. The T-cell provides help to the B-cell by ligating co-stimulatory molecules, such as CD40 on the B-cell. T-cells also provide help by secreting cytokines, such as IL-4, in the small cleft between the cells. The antigen triggering the B-cell, however, is not provided by the T-cell, but is present in soluble form.

3. ITAM is an acronym for “immunoreceptor tyrosine-based activation motif.” Once phosphorylated by a member of the Src family of tyrosine kinases (e.g., Lck), it binds Syk or ZAP-70 with high-affinity.

4. Adaptor proteins have no recognized enzymatic activity. They serve to couple one signaling element to another. For example, BLNK is a substrate of Syk. Upon BCR activation, Syk is recruited to the ITAMs of Ig- and Ig- . Syk then phosphorylates BLNK, which triggers its binding to both Btk and PLC- . The close proximity of Btk and PLC- favor phosphorylation and activation of PLC- by Btk.

5. Extensive signaling cross-talk exists. For example, PI 3-kinase generates phosphatidylinositol 3,4,5 trisphosphate (PIP₃) from PIP₂. PIP₃ (not IP₃) binds to PLC- and activates it.

6. Many transcription factors are activated following BCR or TCR activation. Three major ones are depicted.

7. Not depicted are the elements that lead to activation of Ras and other GTPases.