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DEPARTMENT OF BIOTECHNOLOGY
FACULTY OFENGINEERING & TECHNOLOGY

B & T- cell Activation

Content Outline

1. B-Cell lymphocyte activation
2. Signal Transduction in B-Cell
3. T-Cell lymphocyte activation

B-cell activation

B cell activation

B cells are activated when their B cell receptor (BCR) binds to either soluble or membrane bound antigen. This activates the BCR to form microclusters and trigger downstream signalling cascades. The microcluster eventually undergoes a contraction phase and forms an immunological synapse, this allows for a stable interaction between B and T cells to provide bidirectional activation signals. Once activated B cells may undergo class switch recombination. In their inactivated state B cells express IgM/IgD but once activated they may express IgA, IgE, IgG or retain IgM expression. They do this by excision of the unwanted isotypes (Figure 1). Cytokines produced by T cells and other cells are important in determining what isotype the B cells express.

Signal Transduction in the B Cell

Unlike T, B-lymphocyte activation (in germinal centers) starts with the first signal via BCR (antigen binding), the second signal being the help of CD4 T lymphocytes. The T–B interactions include a number of molecular bonds of which the most important are: (1) TCR–peptide/MHC ligand; (2) CD4–MHC; (3) CD28–CD80/86; (4) CD40L (CD154)–CD40; and (5) Secretion of cytokines in the immune synapse between T and B cells.

Molecular factors in B cells during BCR signal transduction are products of the genes similar or identical to those during the T-cell activation

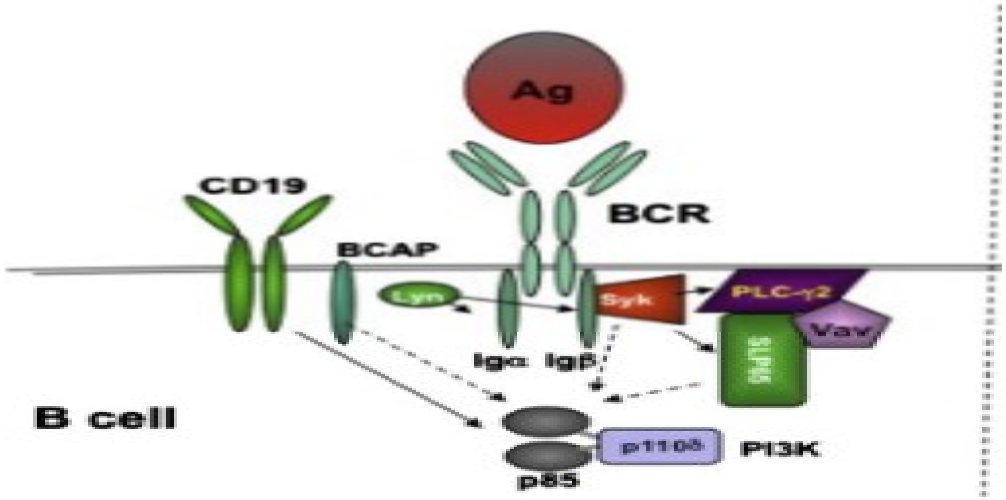
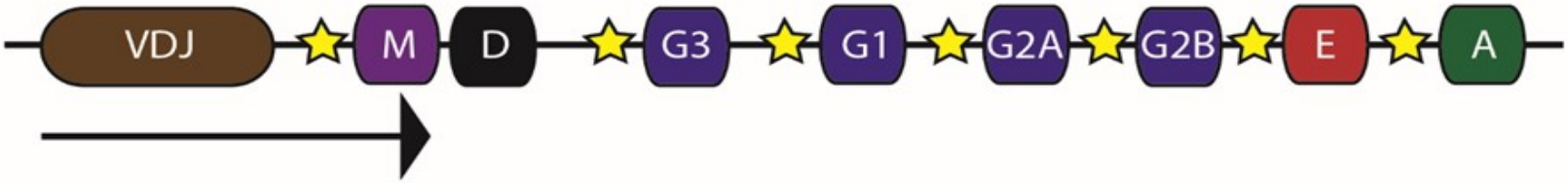
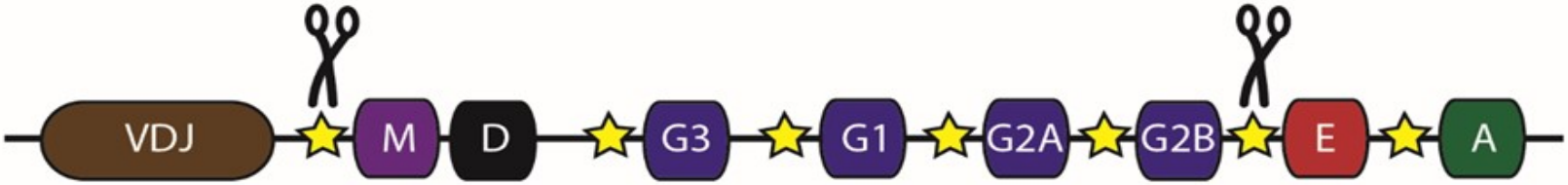


Figure Signal transduction during activation of B lymphocytes. BCR (B-cell receptor)is the antibody ”anchored” in cell membrane with help of Igα i Igβ chains; Ag (antigen); Lyn: tyrosine kinase of Src family; Syk (spleen tyrosine kinase); PLC-γ2 (phospholipase C-γ2); SLP-65 (*SH2 domain containing leukocyte specific phosphoprotein of 65 kDa*); Vav (exchange factors for Rho-family of GTP-ases); PI3K (*phosphatidylinositol-6-kinase); p110δ*: catalytic subunit PI3K; p85: regulatory subunit PI3K; BCAP (*B cell adapter for PI3K*).

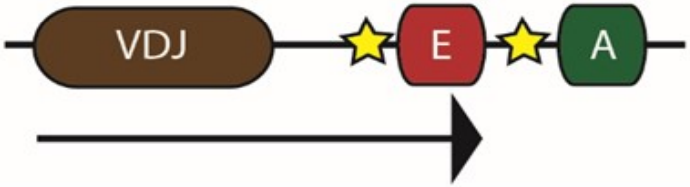
Mature B cells express IgM and IgD as they are the first heavy chain segments in the Ig locus.



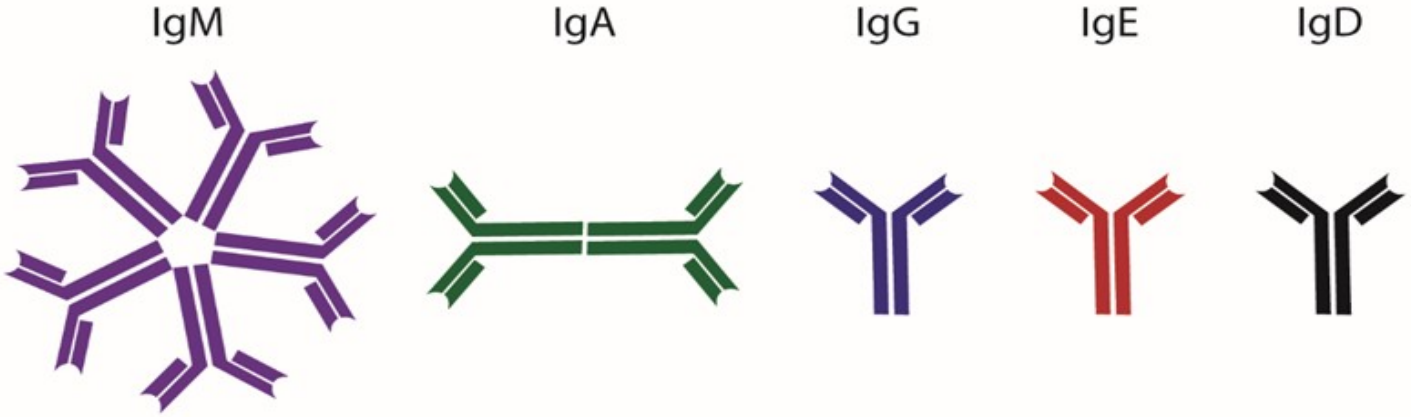
After a B cell is activated segements of the locus are cut out and the locus is joined back together.



Now another heavy chain segment, IgE, is first on the Ig locus and it is expressed.



There are five different types of Immunoglobulin antibodies.



Class switch recombination. After VDJ recombination class switch recombination may occur. In this process unwanted Immunoglobulin (Ig) genes are excised so that the desired gene can be expressed. In this depiction excision occurs and IgE is expressed. There are five isotypes which can be found in difference circumstances. For example, IgE is common in allergic responses such as asthma.(Figure on previous slide)

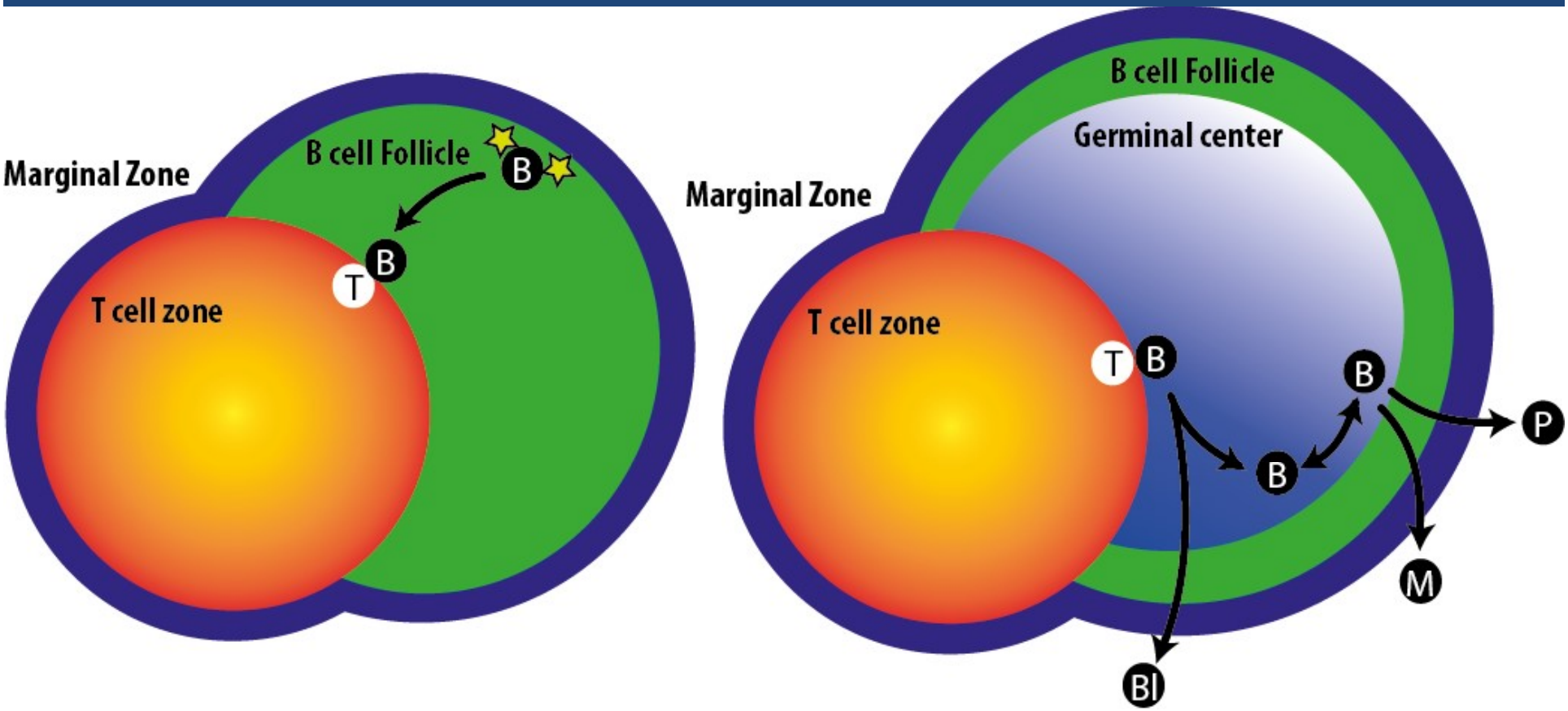
The germinal centre

B cells have two main types of immune responses. In a T-Independent immune response B cells can respond directly to the antigen. In a T-dependent immune response the B cells need assistance from T cells in order to respond.

In this situation activated B cells move to the border of the T cell zone to interact with T cells (Figure 2). CD40 ligand is found on these T helper cells and interacts with CD40 on the B cells to form a stable attraction. Cytokines secreted by T cells encourage proliferation and isotype switching and maintain germinal centre size and longevity. Without these signals the germinal centre response will quickly collapse.

B cells that have encountered antigen and begun proliferating may exit the follicle and differentiate into short-lived plasma cells called plasmablasts (Figure 2). They secrete antibody as an early attempt to neutralize the foreign antigen. They do not survive more than three days but the antibody produced can provide important assistance to stop fast-dividing pathogens such as viruses.

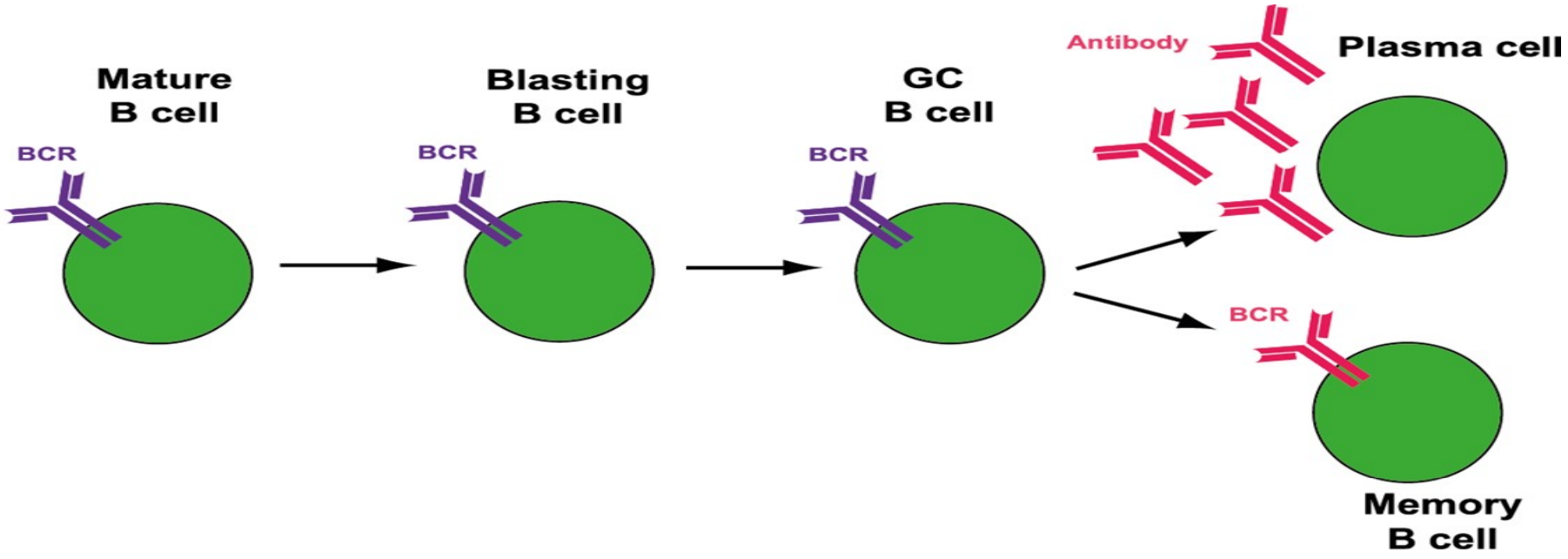
The germinal centre has a light zone and a dark zone. The germinal centre response begins in the dark zone where the B cells rapidly proliferate and undergo somatic hypermutation. During somatic hypermutation, random mutations are generated in the variable domains of the BCR by the enzyme activation-induced cytidine deaminase (AID). B cells then enter the light zone and compete with each other for antigen. If the mutation resulted in a BCR with an improved affinity to the antigen the B cell clone can out-compete other clones and survive. The light zone is also thought to be where B cells undergo class switch recombination, although a germinal centre is not crucial for this process. The B cells may migrate between both zones to undergo several rounds of somatic hypermutation and class switch recombination. The ultimate goal of the germinal centre is to produce B cells with a BCR which has high affinity for the initial antigen.



The migration of B cells in an immune response. When B cells (B) first encounter antigen (★) they migrate to the T-B border to receive survival signals from T cells (T). If they receive survival signals they will begin to proliferate and either become plasmablasts (BI) or form a germinal centre (Blue). B cells can migrate between the light zone and dark zone of the germinal centre to undergo somatic hypermutation and class switch recombination. Eventually they may leave the GC as high-affinity memory cells (M) or plasma cells (P).

Plasma and memory cells

B cells leave the germinal centre response as high-affinity plasma cells and memory B cells (Figure 3). Plasma cells secrete antigen-binding antibodies for weeks after activation. They migrate to the bone marrow soon after formation where they can reside indefinitely, ready to encounter the antigen again and respond. Memory B cells circulate throughout the body on the lookout for antigen with a high-affinity for their BCR and then quickly respond to the antigen, stopping infection. This is how vaccination works. As your body has been previously exposed to the antigen the immune cells can quickly respond to remove the antigen if it is encountered again, stopping you getting sick.



B cell differentiation after activation. When a mature B cell encounters antigen that binds to its B cell receptor it becomes activated. It then proliferates and becomes a blasting B cell. These B cells form germinal centres. The germinal centre B cells undergo somatic hypermutation and class switch recombination. Plasma cells and memory B cells with a high-affinity for the original antigen stimuli are produced. These cells are long lived and plasma cells may secrete antibody for weeks after the initial infection.

T-cell activation

Activation of T-cel involves three types of signal in concert. These are

Signal one: initial binding between a T cell specific for one antigen and the antigen-MHC. This normally takes place in the secondary lymphoid organs.

Signal two: helper T cells, the first of these is provided by **CD28**. This molecule on the T cell binds to one of two molecules on the APC – **B7.1 (CD80)** or **B7.2 (CD86)** – and initiates T-cell proliferation. Cytotoxic T cells are less reliant on CD28 for activation but do require signals from other co-stimulatory molecules such as **CD70** and 4-1BB (**CD137**).

Signal 3: Once the T cell has received a specific antigen signal and a general signal two, it receives more instructions in the form of cytokines. These determine which type of responder the cell will become – in the case of helper T cells, it will push them into **Th1 type** (cells exposed to the cytokine IL-12), **Th2** (IL-4), or **IL-17** (IL-6, IL-23). Each one of these cells performs a specific task in the tissue and in developing further immune responses.

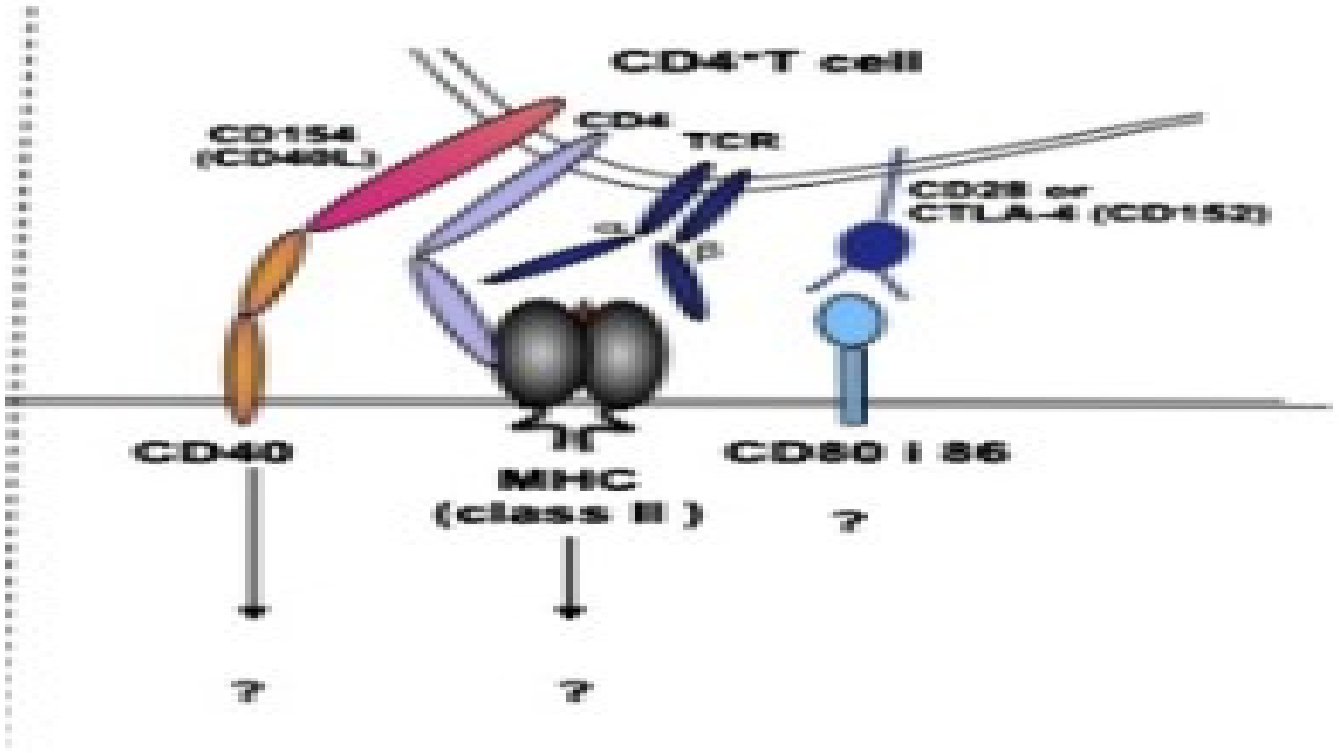
T-cell activation process

➢Initial recognition of processed antigen by T cells is via molecules the T-cell antigen receptor. Accessory molecules further link the APC and the T cell, leading to a stronger cell interaction. For example, CD4 binds to the constant-region domain of class II MHC molecules while CD8 binds to class I MHC molecules. Other ligand–receptor pairs such as LFA-1 and ICAM-1 are also important.

➢Full activation of antigen-specific T cells requires **two**molecules: two **signals**—one signal coming via the TCR and the other signal signals required through engagement of co-stimulatory molecules. T cells for T-cell receiving one signal via their TCR are turned off (become activation anergic), while those also receiving the second signal, that is, via T-cell CD28 binding to CD80/86 on the APC, induce T-cell lymphokine production and T-cell proliferation.

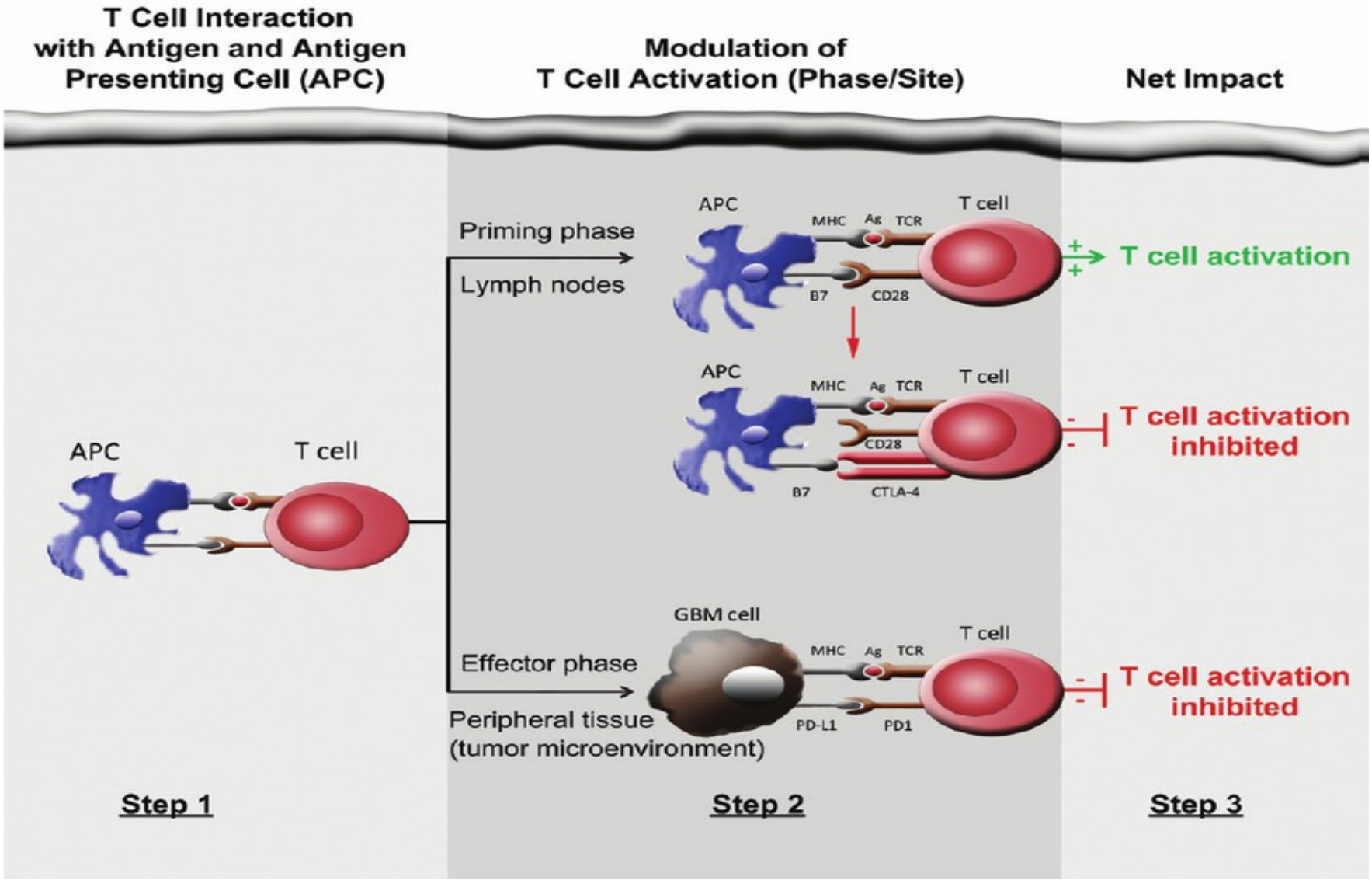
➢Contact between TCR, accessory, and co-receptor molecules events through with antigen-presenting molecules and ligands on the APC is the TCR called the “immunological synapse.” This specialized co-receptors signaling domain conveys a signal to the nucleus resulting in specific gene transcription. *Signal transduction* is brought about by phosphorylation and dephosphorylation of particular amino acids, thus activating them in a sequential fashion leading eventually to activation of specific transcription factors in the nucleus and production of functional proteins.

CD45 (a phosphatase) on the APC initiates this process by activation of a CD4-associated kinase (lck), which together with Fyn then phosphorylates ITAMs on the ζ chain of the signaling complex. Binding of ZAP70 to the phosphorylated ITAMs initiates two biochemical pathways.



Signal Transduction in T-cell

Visualizing T-cell activation



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References & Further reading

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Further reading

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