T-Cell Receptor

i. The domain structures of αβ and γδ TCR heterodimers are strikingly similar to that of the immunoglobulins; thus, they are classified as members of the immunoglobulin superfamily.

ii. Each chain in a TCR has two domains containing an intrachain disulfide bond that spans 60–75 amino acids.

iii. The amino-terminal domain in both chains exhibits marked sequence variation, but the sequences of the remainder of each chain are conserved. Thus the TCR domains–one variable(V) and one constant (C)–are structurally homologous to the V and C domains of immunoglobulins, and the TCR molecule resembles an Fab fragment.

iv. The TCR variable domains have three hypervariable regions, which appear to be equivalent to the complementarity determining regions (CDRs) in immunoglobulin light and heavy chains.

v. There is an additional area of hypervariability (HV4) in the β chain that does not normally contact antigen and therefore is not considered a CDR.

vi. In addition to the constant domain, each TCR chain contains a short connecting sequence, in which a cysteine residue forms a disulfide link with the other chain of the heterodimer.

vii. Following the connecting region is a transmembrane region of 21 or 22 amino acids, which anchors each chain in the plasma membrane.

viii. The transmembrane domains of both chains are unusual in that they contain positively charged amino acid residues. These residues enable the chains of the TCR heterodimer to interact with chains of the signal-transducing CD3 complex.

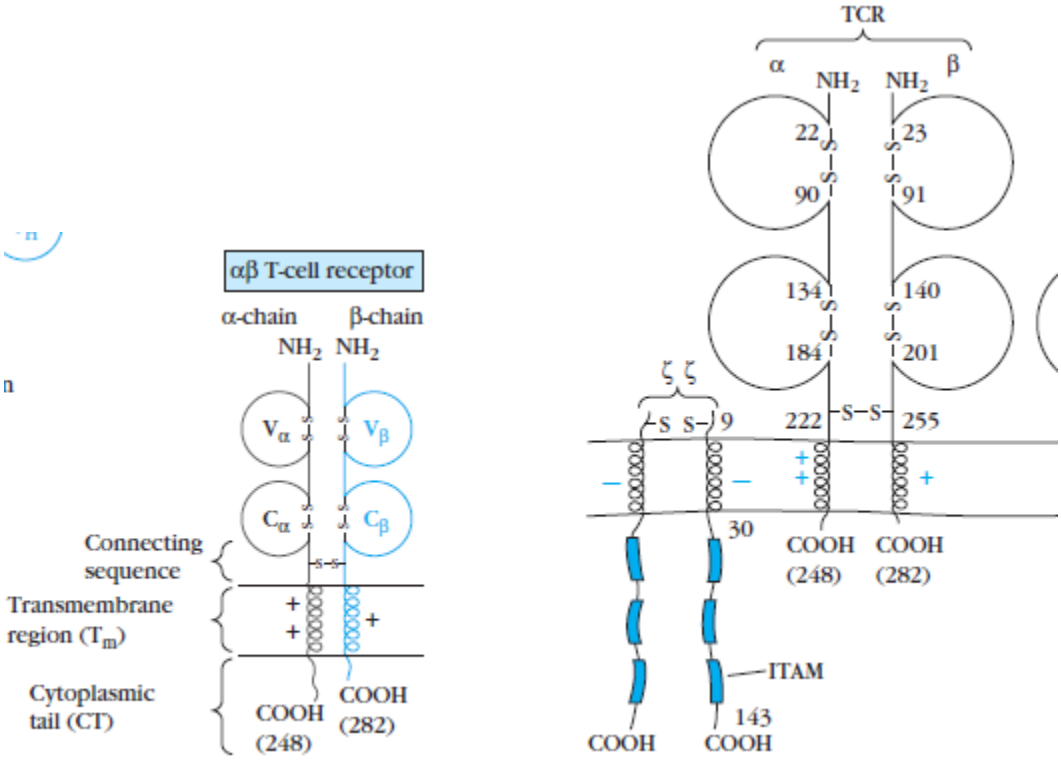
ix. Finally, each TCR chain T-Cell Receptor contains a short cytoplasmic tail of 5–12 amino acids at the carboxyl-terminal end.

x. Majority of the T cells have αβ chains but a small fraction of T cells also contain γδ chains.

xi. These receptors interact with peptide antigens processed and presented on the surface of antigen-presenting cells.

xii. A deep cleft on the surface of the molecule accommodates the microbial phospholipid for which the γδ receptor is specific. This antigen is recognized without MHC presentation.

xiii. The most striking feature of the structure is how it differs from the αβ receptor in the orientation of its V and C regions. The so-called elbow angle between the long axes of the V and C regions of γδ TCR is 111°; in the TCR, the elbow angle is 149°, giving the molecules distinct shapes.



Signaling Pathways involved with TCR

The following two phases can be recognized in the antigen-mediated induction of T-cell responses:

1. **Initiation**.

i. The engagement of MHC-peptide by the TCR leads to clustering with CD4 or CD8 coreceptors as these coreceptors bind to invariant regions of the MHC molecule.
ii. Lck, a protein tyrosine kinase associated with the cytoplasmic tails of the coreceptors, is brought close to the cytoplasmic tails of the TCR complex and phosphorylates the immunoreceptor tyrosine-based activation motifs (ITAMs).
iii. The phosphorylated tyrosines in the ITAMs of the ζ chain provide docking sites to which a protein tyrosine kinase called ZAP-70 attaches and becomes active.
iv. ZAP-70 then catalyzes the phosphorylation of a number of membrane-associated adaptor molecules, which act as anchor points for the recruitment of several intracellular signal transduction pathways.
v. One set of pathways involves a form of the enzyme phospholipase C (PLC), which anchors to an adaptor molecule, is activated by phosphorylation and cleaves a membrane phospholipid to generate second messengers. Another set activates small G proteins.

2. **Generation of multiple intracellular signals**. Many signaling pathways are activated as a consequence of the steps that occur in the initiation phase, as described below:

a. Phospholipase C (PLC):

i. PLC is activated by phosphorylation and gains access to its substrate by binding to a membrane- associated adaptor protein.
ii. PLC hydrolyzes a phospholipid component of the membrane to generate inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG).
iii. IP3 causes a rapid release of Ca2from the endoplasmic reticulum and opens Ca^{2+} channels in the cell membrane.

iv. DAG activates protein kinase C, a multifunctional kinase that phosphorylates many different targets.

b. **$Ca2^{+}$**: It is an essential element in many T-cell responses, including a pathway that leads to the movement of a major transcription factor, NFAT, from the cytoplasm into the nucleus. In the nucleus, NFAT supports the transcription of genes required for the expression of the T-cell growth-promoting cytokines IL-2, IL-4, and others.

Protein kinase C (PKC): This enzyme, which affects many pathways, causes the release of an inhibitory molecule from the transcription factor NF- κB, allowing NF- κB to enter the nucleus, where it promotes the expression of genes required for T-cell activation. NF-κB is essential for a variety of T-cell responses and provides survival signals that protect T cells from apoptotic death.

The Ras/MAP kinase pathway:

i. Ras is a pivotal component of a signal-transduction pathway that is found in many cell types and is evolutionarily conserved across a spectrum of eukaryotes from yeasts to humans.
ii. Ras is a small G protein whose activation by GTP initiates a cascade of protein kinases known as the mitogen-activated protein kinase (MAP kinase) pathway.
iii. Phosphorylation of the end product of this cascade, MAP kinase (also called ERK), allows it to activate Elk,
iv. Elk is a transcription factor necessary for the expression of Fos.
v. Phosphorylation of Fos by MAP kinase allows it to associate with Jun to form AP-1.
vi. AP1 is an essential transcription factor for T-cell activation.

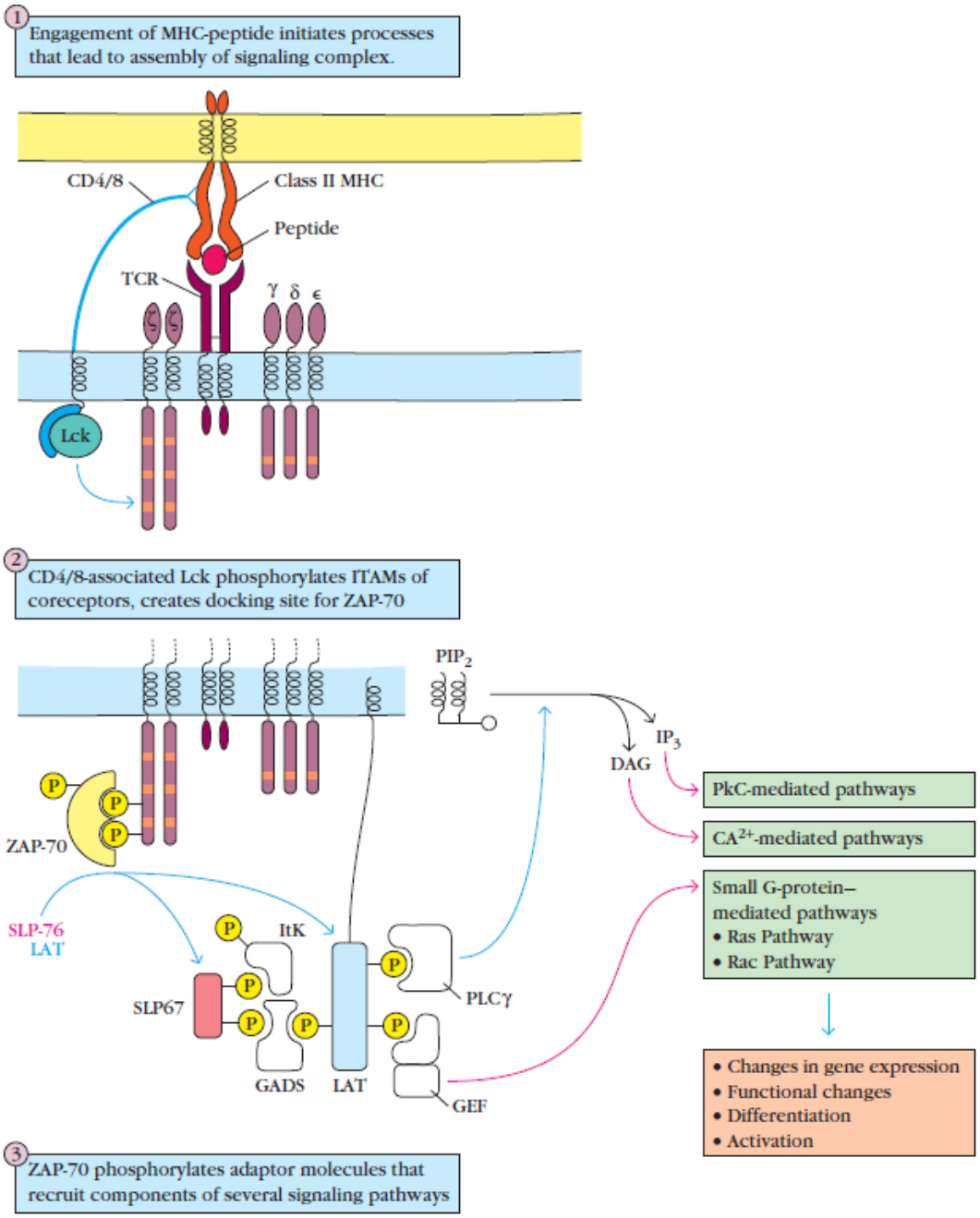
Co-Stimulation

T-cell activation requires the dynamic interaction of multiple membrane molecules described above, but this interaction, by itself, is not sufficient to fully activate naive T cells. Naive T cells require more than one signal for activation and subsequent

proliferation into effector cells:

Signal 1, the initial signal, is generated by interaction of an antigenic peptide with the TCR-CD3 complex.

Signal 2A subsequent antigen-nonspecific co-stimulatory signal, signal 2, is provided primarily by interactions between CD28 on the T cell and members of the B7 family on the APC.


1
Engagement of MHC-peptide initiates processes that lead to assembly of signaling complex.
CD4/8
Class II MHC
Peptide
TCR
γ δ ε
Lck
2
CD4/8-associated Lck phosphorylates ITAMs of coreceptors, creates docking site for ZAP-70
PIP2
IP3
DAG
PkC-mediated pathways
CA2+-mediated pathways
Small G-protein–mediated pathways
• Ras Pathway
• Rac Pathway
ZAP-70
SLP-76
LAT
ItK
SLP67
PLCγ
GADS
LAT
GEF
• Changes in gene expression
• Functional changes
• Differentiation
• Activation
3
ZAP-70 phosphorylates adaptor molecules that recruit components of several signaling pathways