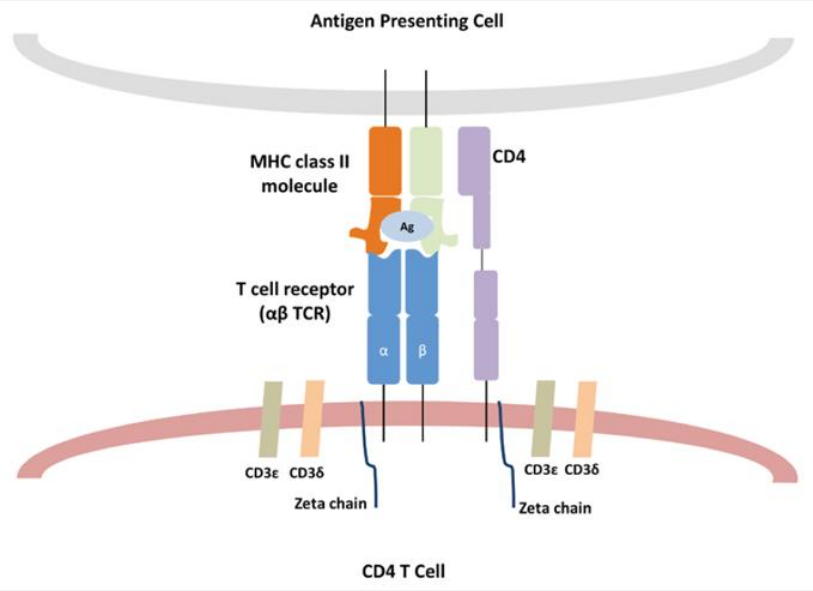
T CELL RECEPTOR

1. Introduction

- **The T-cell receptor is a protein complex, located on the surface of T cells.**
- **They are responsible for recognizing fragments of antigen as peptides bound to major histocompatibility complex molecules.**
- **The binding between TCR and antigen peptides is of relatively low affinity and is biologically degenerate.**
- The T-cell receptor (TCR)–CD3 complex is **composed of a diverse αβ TCR heterodimer noncovalently associated with the invariant CD3 dimers CD3єγ, CD3єδ, and CD3ζζ**.
- The TCR mediates recognition of antigenic peptides bound to MHC molecules (pMHC), whereas the CD3 molecules transduce activation signals to the T cell.
- The **T Cell Receptor (TCR)** is a **membrane-bound glycoprotein complex** found on the surface of **T lymphocytes (T cells)**.

- It allows T cells to **recognize antigens** that are **processed and presented** by **Major Histocompatibility Complex (MHC)** molecules on antigen-presenting cells (APCs).
- Unlike the B cell receptor (BCR), the TCR **cannot bind free (native) antigens** — it recognizes **peptide fragments** bound to MHC molecules.

2. Structure of the T Cell Receptor



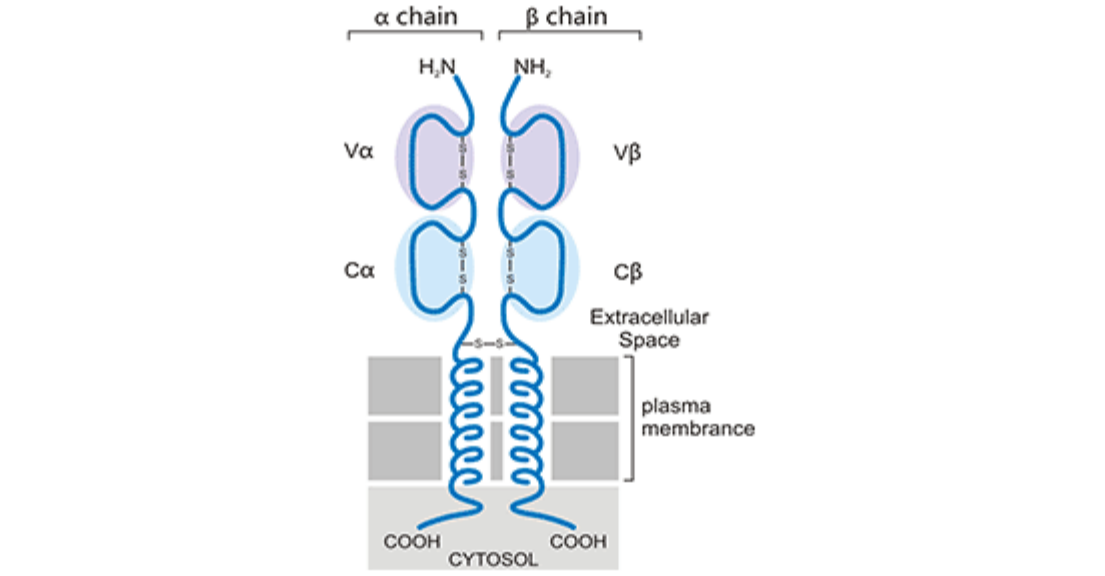
The TCR is a **heterodimer** composed of two polypeptide chains:

(i) α (alpha) and β (beta) chains — most common

- Found on **95%** of T cells (αβ T cells).
- Each chain has:
  - **Variable (V) region** – responsible for antigen recognition.
  - **Constant (C) region** – provides structural support.
  - **Transmembrane region** – anchors the receptor to the cell membrane.
  - **Short cytoplasmic tail** – too short for signaling (needs accessory molecules).

(ii) γ (gamma) and δ (delta) chains — less common

- Found on **5%** of T cells (γδ T cells).
- Often located in **epithelial tissues** (skin, gut, etc.).
- Recognize **non-peptide antigens** (e.g., lipids) and act as a bridge between innate and adaptive immunity.



3. Associated Signaling Complex (CD3 Complex)

The TCR cannot signal by itself — it's **non-covalently associated** with the **CD3 complex**, which transduces signals into the cell.

Components of the CD3 Complex

- **CD3γ (gamma), CD3δ (delta), and two CD3ε (epsilon)** chains
- **ζ (zeta) chain homodimer**
- Together, these form the **TCR–CD3 complex**.

Each CD3 chain contains **ITAMs (Immunoreceptor Tyrosine-based Activation Motifs)** in its cytoplasmic domain, which initiate signaling after antigen recognition.

4. Antigen Recognition

- The **TCR recognizes a peptide antigen only when it is presented by an MHC molecule** on an antigen-presenting cell (APC).
- This recognition is **MHC-restricted** — meaning:
  - **$CD4^+$ T cells** recognize antigen presented by **MHC class II** (on APCs).
  - **$CD8^+$ T cells** recognize antigen presented by **MHC class I** (on all nucleated cells).

TCR Binding Components

- The **variable regions (Vα and Vβ)** form the **antigen-binding site**.
- The **Complementarity Determining Regions (CDRs)** — especially **CDR3** — determine antigen specificity.

5. Signal Transduction

Steps in TCR Signaling

1. **Antigen recognition:**
   - TCR binds to peptide–MHC complex.
   - Co-receptors (CD4 or CD8) bind to MHC molecules simultaneously.
2. **Activation of Src-family kinases:**
   - **Lck (linked to CD4/CD8)** phosphorylates ITAMs on the CD3 and ζ chains.
3. **Recruitment of ZAP-70:**
   - **ZAP-70**, a tyrosine kinase, binds to phosphorylated ITAMs and becomes activated.
4. **Downstream signaling cascades:**
   - Activation of pathways leading to:
     - **PLCγ → IP_3 + DAG → Ca^{2+} signaling**
     - **MAPK pathway (Ras/Raf/Erk)**
     - **NFAT, NF-κB, and AP-1** transcription factor activation
5. **Cellular outcomes:**
   - Gene transcription for:
     - **IL-2 production**
     - **T cell proliferation**
     - **Differentiation into effector T cells**

Co-stimulatory Signals

- TCR signaling alone is **not sufficient** for full activation.
- A **second signal** is required:
  - **CD28 (on T cell)** binds to **B7-1 (CD80)** or **B7-2 (CD86)** on APC.
  - Ensures activation only during genuine immune responses.
- Absence of co-stimulation → **Anergy** (non-responsiveness).

6. TCR Diversity and Generation

Mechanisms creating diversity (similar to BCR):

1. **V(D)J recombination:**
   - Random recombination of V, D, and J gene segments during T cell development.
   - α chain → V and J gene segments
     β chain → V, D, and J gene segments
2. **Junctional diversity:**
   - Random addition/deletion of nucleotides at junctions.
3. **Combinatorial pairing:**
   - Random pairing of α and β chains.
4. **No somatic hypermutation:**
   - Unlike BCRs, TCRs **do not undergo affinity maturation**.

❖ This creates an **enormous TCR repertoire (~10^{18} possible specificities).**

7. T Cell Development and TCR Expression

Stage	Location	TCR Form	Function
Pro-T cell	Thymus cortex	No TCR	Gene rearrangement begins
Pre-T cell	Thymus cortex	Pre-TCR (β chain + surrogate α chain)	Signals α chain rearrangement
Immature T cell	Thymus	Complete TCR (αβ)	Positive/negative selection
Mature T cell	Peripheral tissues	Functional TCR	Antigen recognition ($CD4^+$ or $CD8^+$)

8. Types of T Cells Based on TCR and MHC Recognition

T Cell Type	MHC Restriction	Co-receptor	Function
$CD4^+$ Helper T cells (Th)	MHC Class II	CD4	Activate B cells, macrophages, cytokine secretion
$CD8^+$ Cytotoxic T cells (Tc)	MHC Class I	CD8	Kill infected or tumor cells
γδ T cells	Non-classical MHC or lipid antigens	None	Rapid response, innate-like defense

9. Co-receptors and Accessory Molecules

Molecule	Found on	Function
CD4	Helper T cells	Binds MHC II, recruits Lck kinase
CD8	Cytotoxic T cells	Binds MHC I, recruits Lck kinase
CD28	All T cells	Co-stimulation (binds B7)
CTLA-4 / PD-1	Activated T cells	Inhibitory checkpoints (downregulate response)

10. Comparison: BCR vs. TCR

Feature	B Cell Receptor (BCR)	T Cell Receptor (TCR)
Structure	2 heavy + 2 light chains	α and β (or γ and δ) chains
Recognizes	Native antigens	Peptide antigens + MHC
Soluble form	Yes (antibodies)	No
MHC restriction	No	Yes
Signaling molecules	Igα/Igβ (CD79)	CD3 complex
Diversity generation	V(D)J recombination, SHM	V(D)J recombination only
Function	Antigen binding + effector (antibody)	Antigen recognition + activation