

# T-Cell Receptors — Structure and Organization

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## Introduction

T cells are key players in the adaptive immune system. They help the body recognize and remove infected or abnormal cells.

To recognize antigens, T cells use a special molecule on their surface called the **T-cell receptor (TCR)**.

Unlike B-cell receptors, the TCR cannot bind free antigens. It only recognizes **peptides presented on MHC molecules** on the surface of antigen-presenting cells.

There are **two main types** of TCRs:

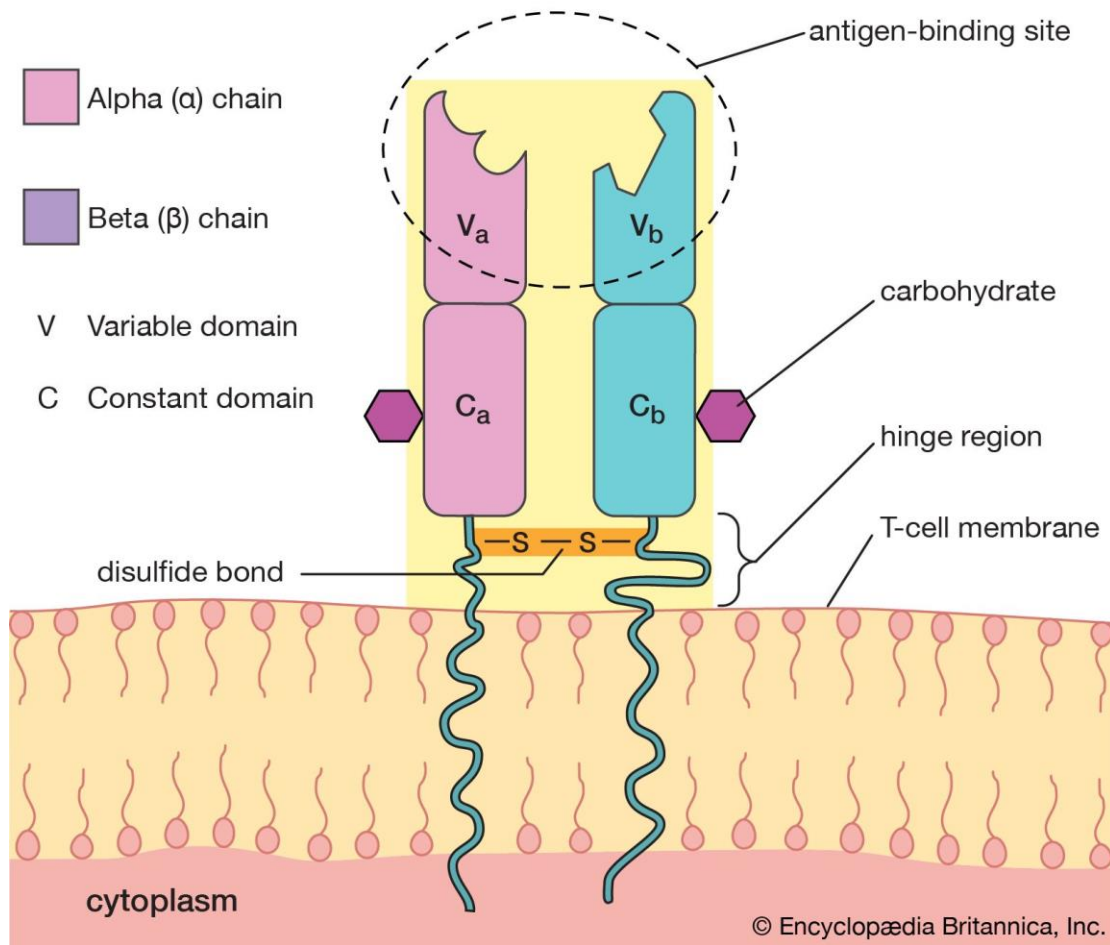
1.  **$\alpha\beta$  TCRs** — the most common type (about 95% of T cells).
2.  **$\gamma\delta$  TCRs** — found mostly in tissues like skin and gut.

In this lecture, we discuss the structure of TCRs, their gene organization, and how they help T cells recognize antigens.

## Structure of the $\alpha\beta$ T-Cell Receptor

The  $\alpha\beta$  TCR consists of **two protein chains**:

- Alpha ( $\alpha$ ) chain
- Beta ( $\beta$ ) chain



Fig(1) Structure of  $\alpha$  and  $\beta$  chains in the TCR receptor

These two chains form a **heterodimer**, connected by a disulfide bond.

### 1. Components of Each Chain

Each  $\alpha$  or  $\beta$  chain has:

- **Variable (V) region** → recognizes antigen
- **Constant (C) region** → provides support
- **Transmembrane part** → anchors receptor
- **Short cytoplasmic tail** → too short to signal alone

## 2. CDR Regions

The antigen-binding site is formed by **three regions** on each chain:

- **CDR1 and CDR2** → interact mainly with MHC
- **CDR3** → interacts mainly with the peptide antigen

CDR3 is the most variable and gives the TCR its unique specificity.

## 3. How $\alpha\beta$ TCRs Bind Antigen

The  $\alpha\beta$  TCR binds diagonally over the **peptide–MHC complex**.

This ensures:

- TCR recognizes the peptide
- TCR recognizes the MHC → called **MHC restriction**

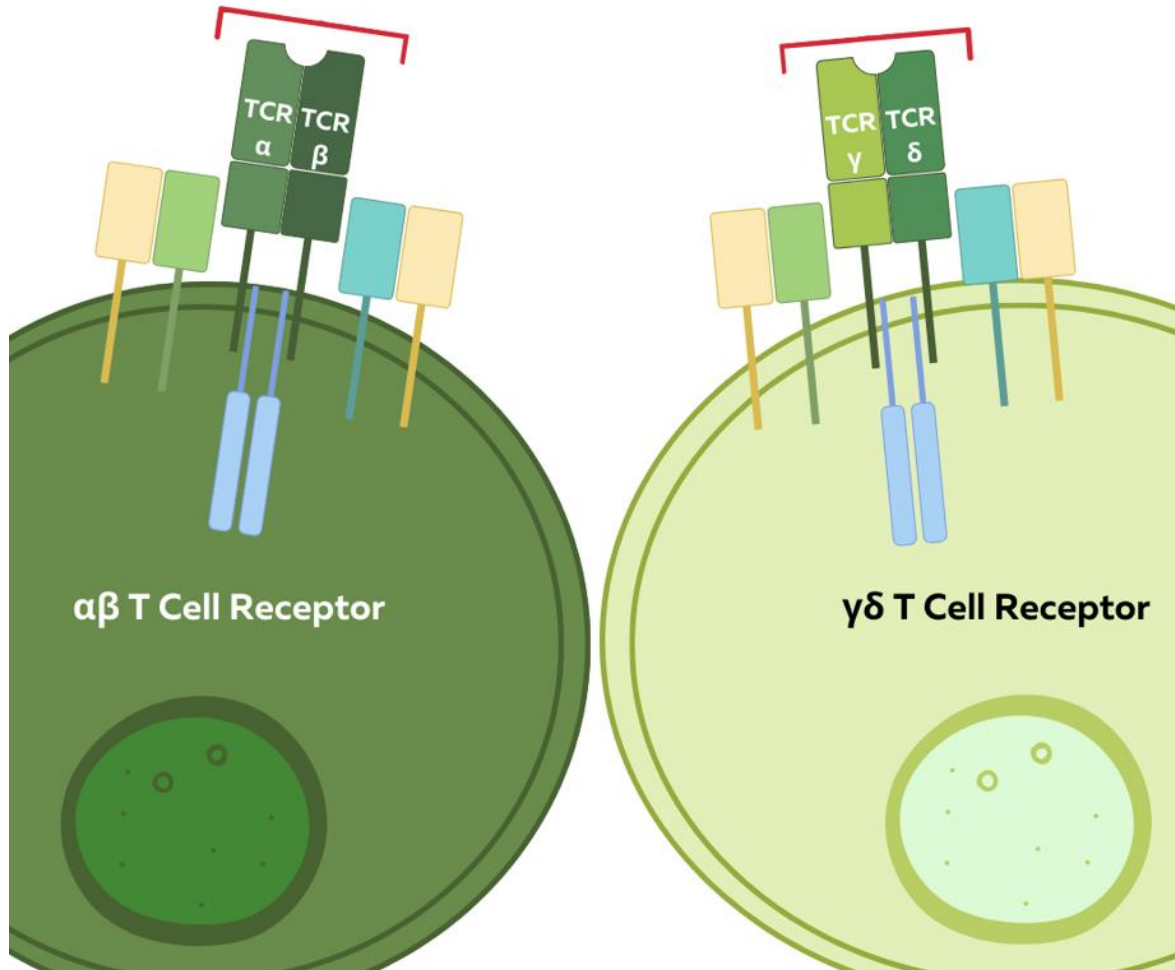
## Structure and Role of the $\gamma\delta$ T-Cell Receptor

$\gamma\delta$  TCRs look similar to  $\alpha\beta$  TCRs but behave differently.

### 1. $\gamma$ and $\delta$ Chains

Each  $\gamma$  and  $\delta$  chain has:

- Variable and constant regions
- Transmembrane region
- Very short cytoplasmic tail



Fig(2) Structure comparison between  $\alpha\beta$  and  $\gamma\delta$  T cell receptors (TCRs).  $\alpha\beta$  T cells constitute the majority of T cell

## 2. Antigen Recognition

Unlike  $\alpha\beta$  TCRs,  $\gamma\delta$  TCRs:

- Do **not** require classic MHC molecules
- Can recognize lipid antigens, stress molecules, and microbial products
- Respond quickly, like innate immune cells

### 3. Where They Are Found

They are common in:

- Skin
- Gut mucosa
- Reproductive tract

They help in early defense, tissue repair, and tumor surveillance.

## Genetic Organization of TCR Genes

The body must produce millions of different TCRs.

This diversity comes from special gene arrangements in T cells.

### 1. Gene Locations

In humans:

- **$\alpha$  chain** → chromosome 14
- **$\beta$  chain** → chromosome 7
- **$\gamma$  chain** → chromosome 7
- **$\delta$  chain** → inside the  $\alpha$  locus (chromosome 14)

### 2. Gene Segments

TCR genes are built from small DNA pieces:

- **V, D, J segments**  
 $\beta$  and  $\delta$  chains use **V–D–J**,  
 $\alpha$  and  $\gamma$  chains use **V–J** only.

### 3. V(D)J Recombination

T cells rearrange these gene segments to create unique receptors.

Enzymes involved:

- **RAG1/2** → cut and join DNA
- **TdT** → adds random nucleotides → increases variation

#### 4. Why So Much Diversity?

Because of:

- Many V/D/J segments
- Random joining
- Random nucleotide addition
- Pairing of alpha with beta chains

This creates enormous diversity — more than  $10^{15}$  possible TCRs.

### The TCR–CD3 Complex and How It Sends Signals

The TCR cannot send signals by itself.

It works together with other proteins called **CD3 molecules**.

#### 1. CD3 Components

The full complex includes:

- CD3 $\gamma$
- CD3 $\delta$
- CD3 $\epsilon$
- CD3 $\zeta$  (zeta)

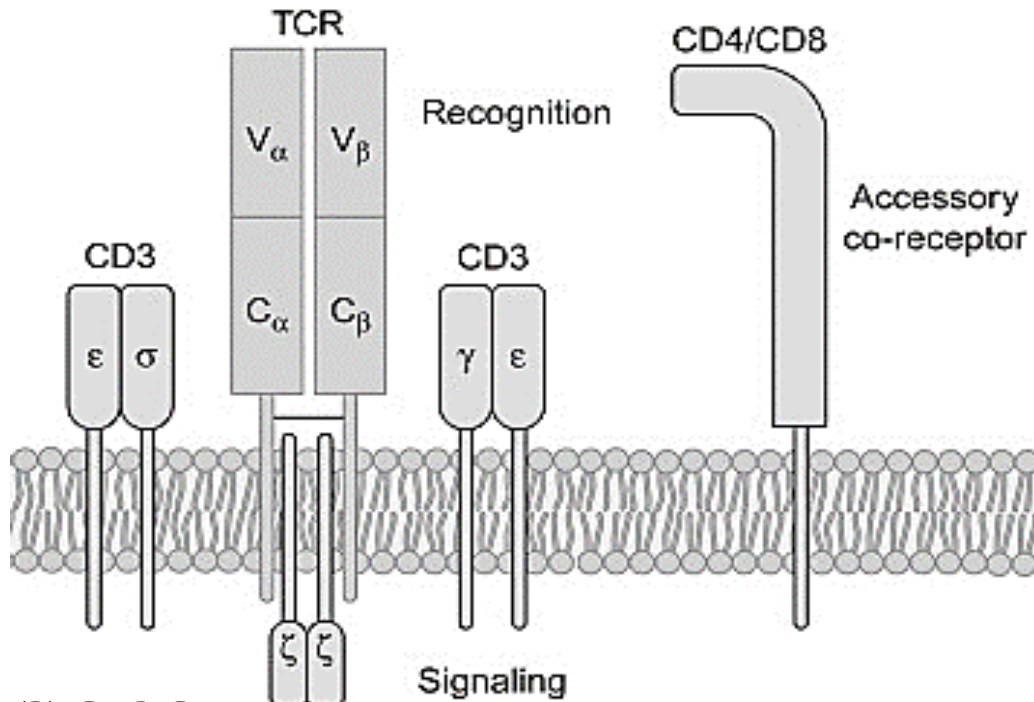


Fig (3) CD3 Components

Together, they form an **eight-chain complex**.

## 2. ITAM Motifs

CD3 molecules contain special sequences called **ITAMs**, which become phosphorylated when the TCR binds antigen.

## 3. Steps of T-Cell Activation

1. TCR binds peptide–MHC.
2. CD4 or CD8 co-receptor binds to MHC.
3. Lck kinase phosphorylates ITAMs.
4. ZAP-70 is activated.
5. Signaling pathways activate NFAT, AP-1, NF-κB.
6. T cell becomes activated and starts dividing.

## 4. Co-Stimulation

TCR signaling alone is **not enough**.

CD28 must bind B7 on the APC → otherwise the T cell becomes inactive (anergic).

# Importance and Medical Applications

## 1. Role in Immunity

TCRs allow T cells to:

- Recognize infected or cancerous cells
- Help other immune cells
- Form memory responses
- Maintain self-tolerance

## 2. Diseases Related to TCR Problems

- Severe combined immunodeficiency (SCID)
- Autoimmune diseases
- T-cell lymphomas

## 3. Summary

TCRs are essential for the adaptive immune system.

Their unique structure and genetic organization allow them to recognize a huge variety of antigens.

Understanding TCRs helps advance immunotherapy, vaccines, and clinical immunology.