T-Cell Receptors — Structure and Organization

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:

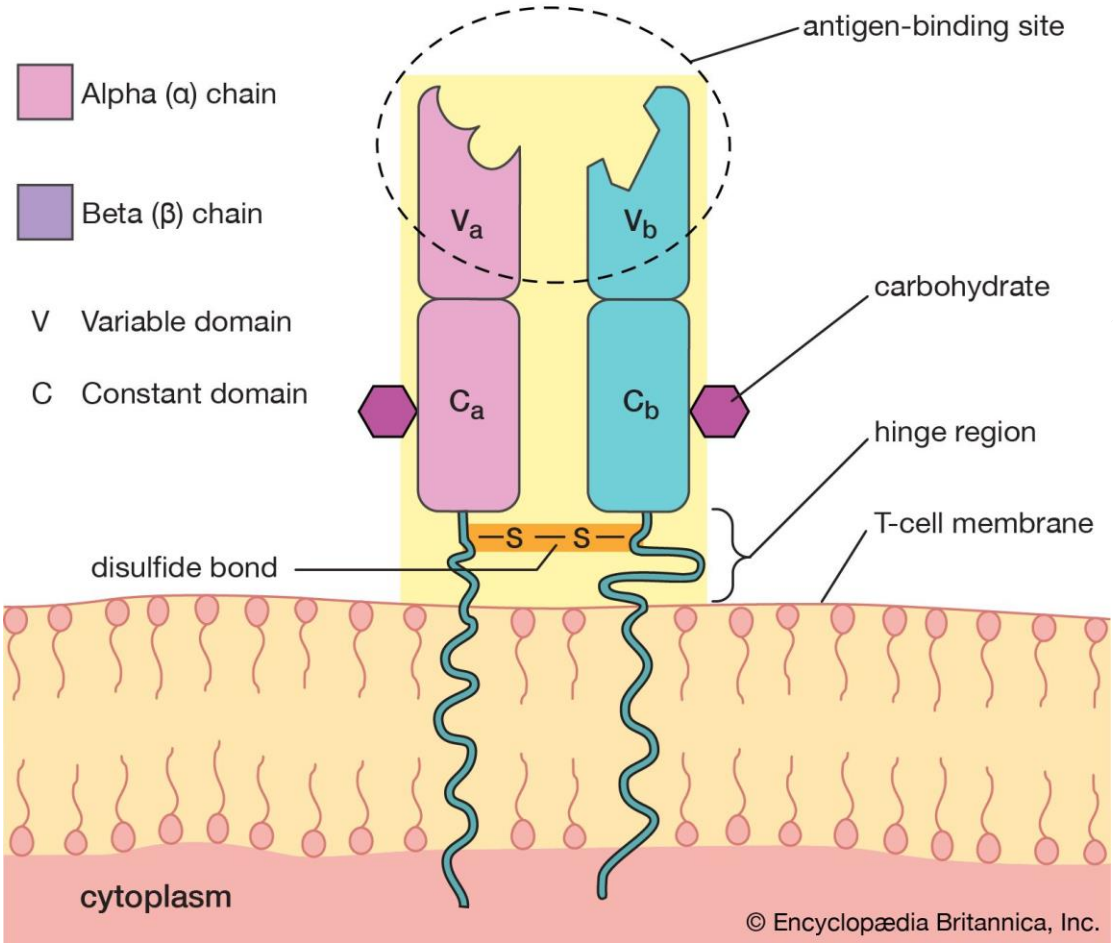
1. **αβ TCRs** — the most common type (about 95% of T cells).
2. **γδ TCRs** — found mostly in tissues like skin and gut.

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

Structure of the αβ T-Cell Receptor

The αβ TCR consists of **two protein chains**:

- Alpha (α) chain
- Beta (β) chain



Fig(1) Structure of α and β chains inthe TCR receptor

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

1. Components of Each Chain

Each α or β 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 αβ TCRs Bind Antigen

The αβ TCR binds diagonally over the **peptide–MHC complex**.
This ensures:

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

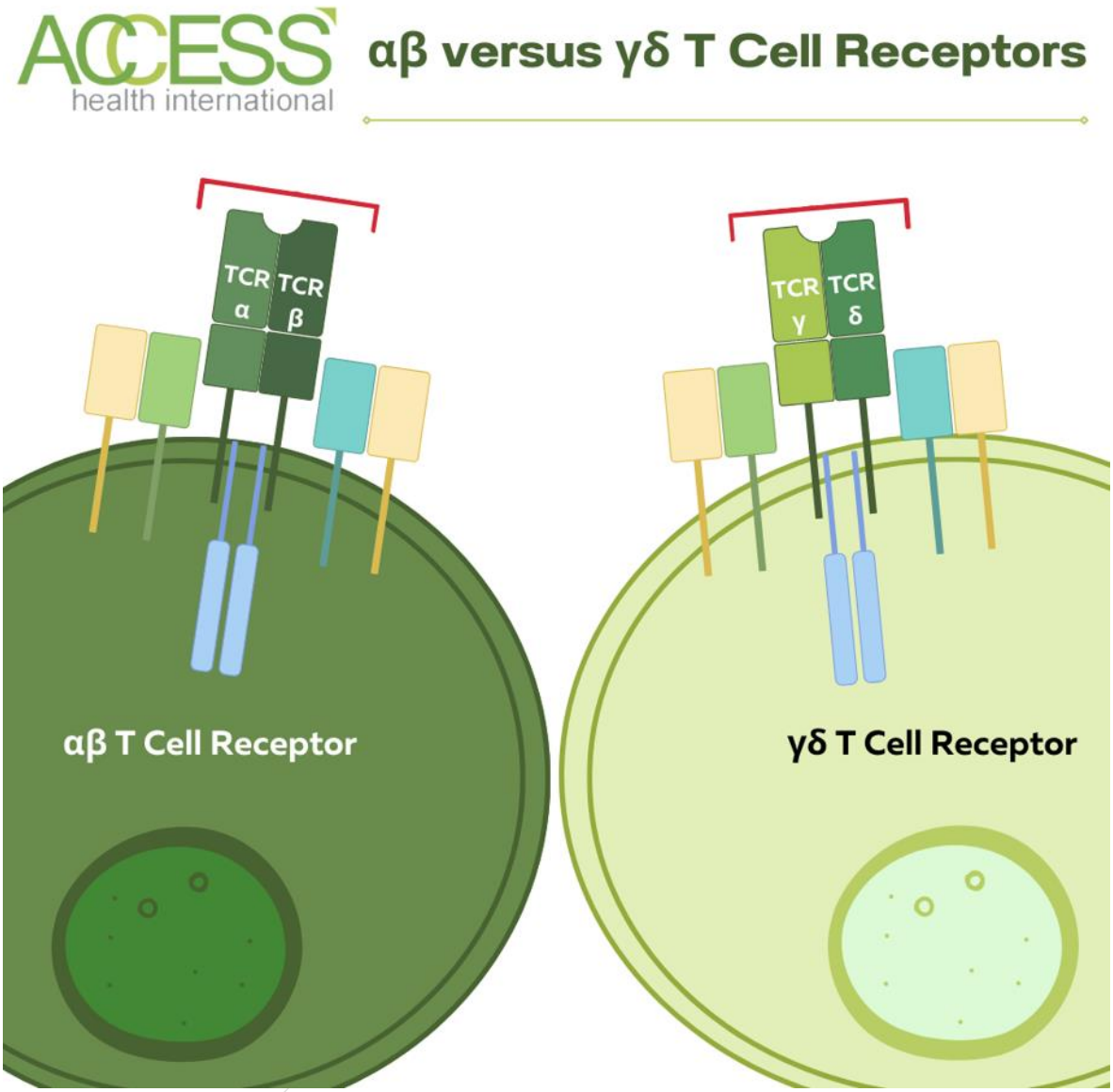
Structure and Role of the γδ T-Cell Receptor

γδ TCRs look similar to αβ TCRs but behave differently.

1. γ and δ Chains

Each γ and δ chain has:

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



Fig(2) Structure comparison between αβ and γδ T cell receptors (TCRs). αβ T cells constitute the majority of T cell

2. Antigen Recognition

Unlike αβ TCRs, γδ 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:

- **α chain** → chromosome 14
- **β chain** → chromosome 7
- **γ chain** → chromosome 7
- **δ chain** → inside the α locus (chromosome 14)

2. Gene Segments

TCR genes are built from small DNA pieces:

- **V**, **D**, **J** segments
  β and δ chains use **V–D–J**,
  α and γ 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:

- CD3γ
- CD3δ
- CD3ε
- CD3ζ (zeta)

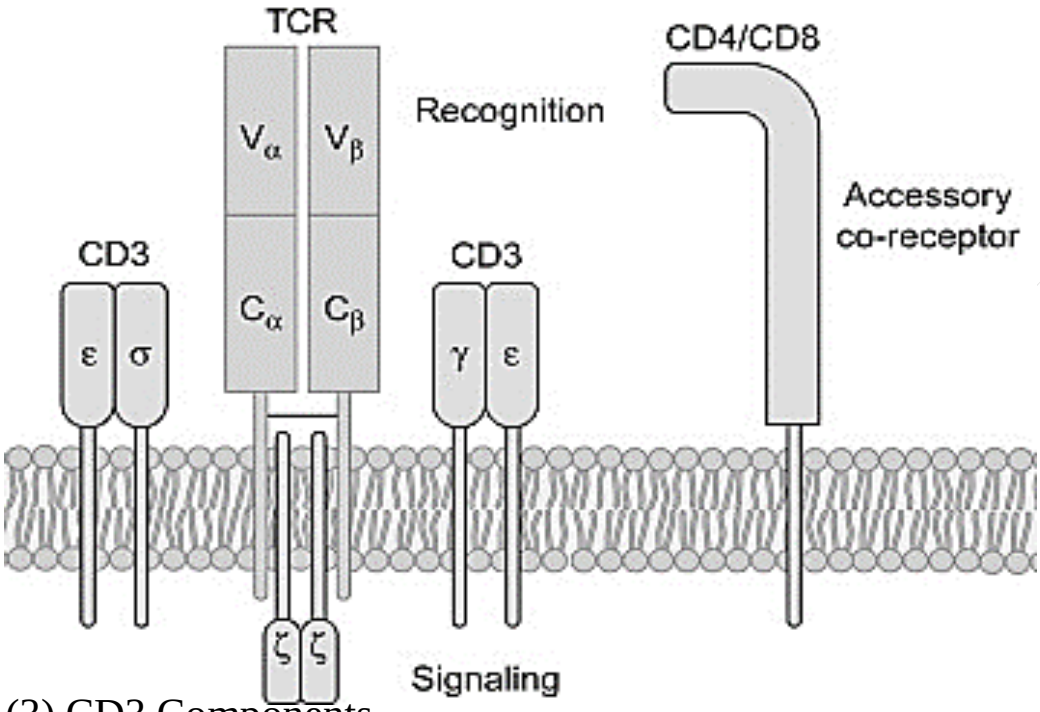


Fig (3) CD3 Components

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.