Chapter 5: Antigen Recognition by T Lymphocytes

- The sole function of B cells is to produce antibodies but the functions of T cells are more diverse and always involve interactions with other cells
- T cell receptors and B cell receptors share some similarities

Similarities	Differences
• Similar structure • Produced as a result of gene rearrangement • Highly variable and diverse in antigen specificity • Each clone expresses single kind of antigen receptor	• Binding sites o IGs bind intact molecules (proteins, carbohydrates, and lipids) that are present on bacteria, viruses, parasites, and soluble protein toxins o T cells receptors bind to peptide antigens that come from pathogen's proteins

T-cell receptor diversity

- Membrane-bound glycoprotein that looks like a single arm of IG molecule
- Made of 2 different polypeptide chains
- **One antigen-binding site**
- **No secreted form** of T-cell receptor as there is for IGs
- There is a variable region (where the antigen binds) and a constant region
- Same mechanisms used in B cells and T cells to make variable regions
- After T cell is activated (meets with antigen), **there is no more change** in the structure → no somatic hypermutation or isotype switching
    - This is because T cells are only antigen receptors while B cells are receptors (recognition) and effector molecules

5-1 The T-cell receptor resembles a membrane-associated Fab fragment of immunoglobulin

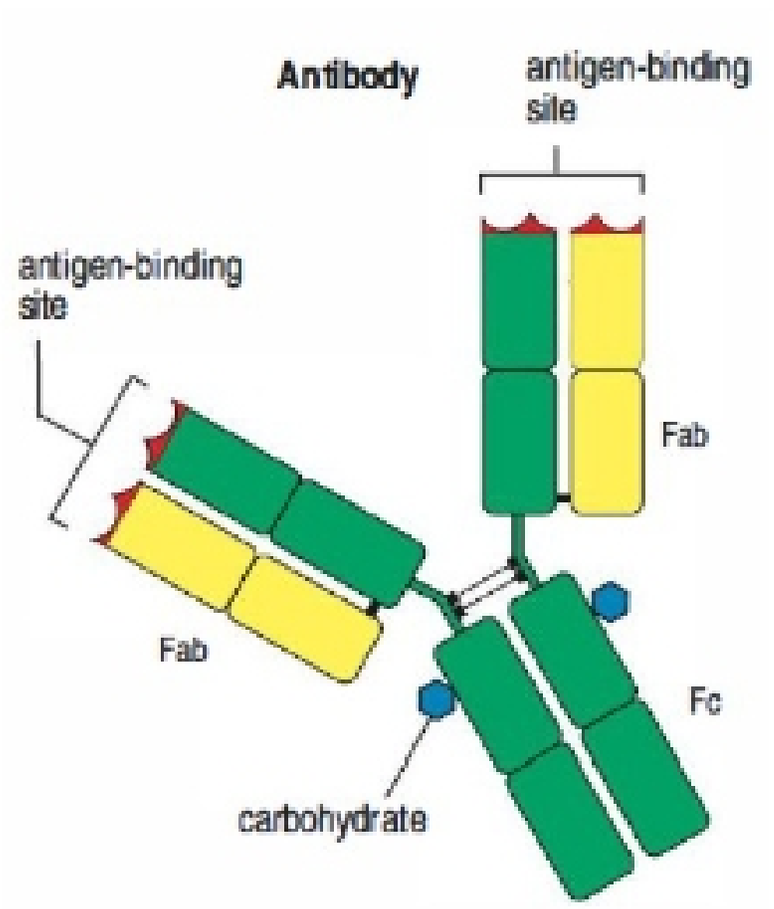
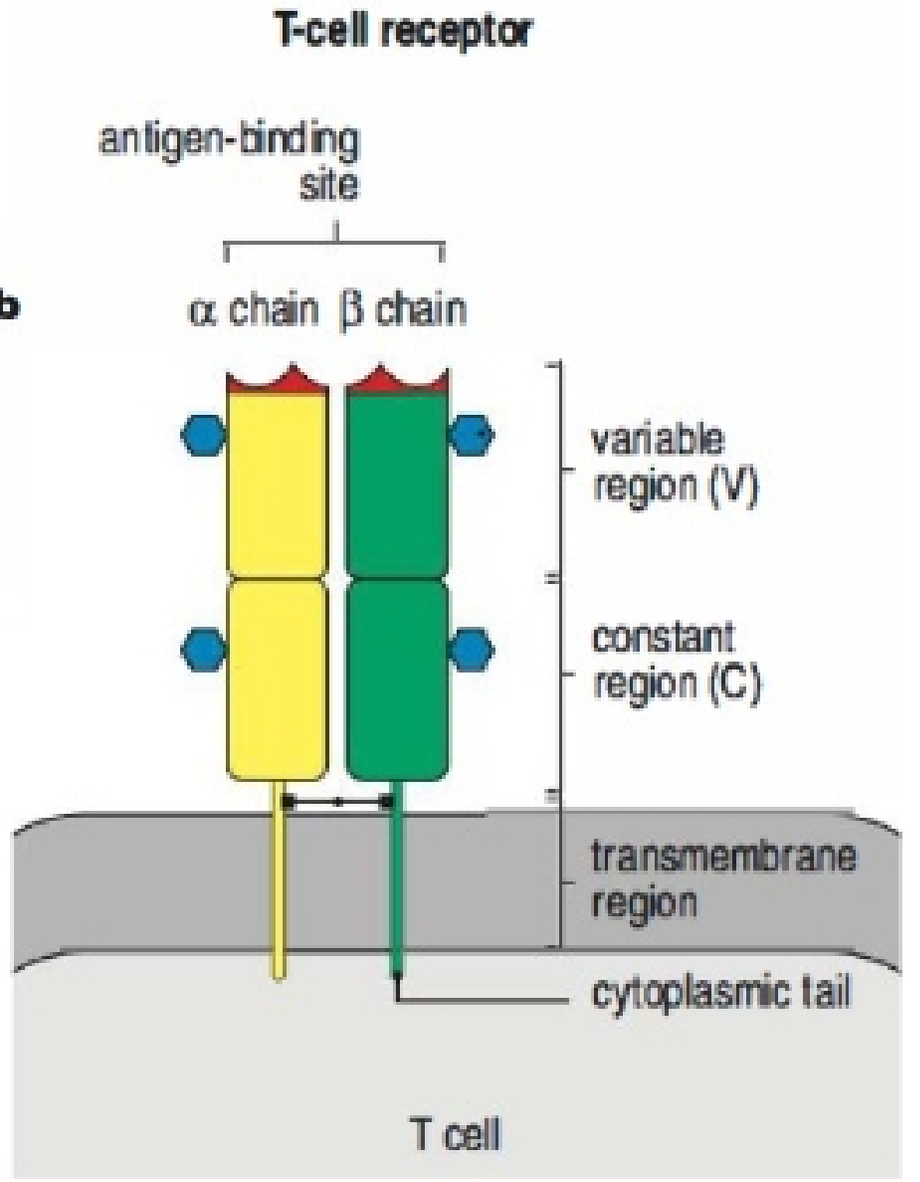


Figure 5.1 The T-cell receptor resembles a membrane-bound Fab fragment. Comparison of the T-cell receptor with an IgG antibody. The T-cell receptor is a membrane-bound heterodimer composed of an α chain of 40–50 kDa and a β chain of 35–46 kDa.



- T-cell receptors are made of 2 polypeptide chains: TCRα and TCRβ
- Genes encoding the 2 chains have similar germline organization to B cells' heavy and light chains
    - Segments have to be rearranged to form a functional gene
- α and β chains each have a variable region and constant region
- Each chain is folded into protein domains
    - Amino-terminal V domain, then C domain, then membrane-anchoring domain
    - Antigen-recognition site is in the V_α and V_β domains on the CDRs → most variable part of molecule
        - Each chain (a and B) has three CDR loops (CDR1, CDR2, and CDR3) which are the loops that are farthest from the membrane and are clustered regions of hypervariability
- While immunoglobulins have 2 or more binding sites for antigen, **T cell receptors only have one binding site** for antigen and are only used as cell-surface receptors (never soluble)

5-2 T-cell receptor diversity is generated by gene arrangement

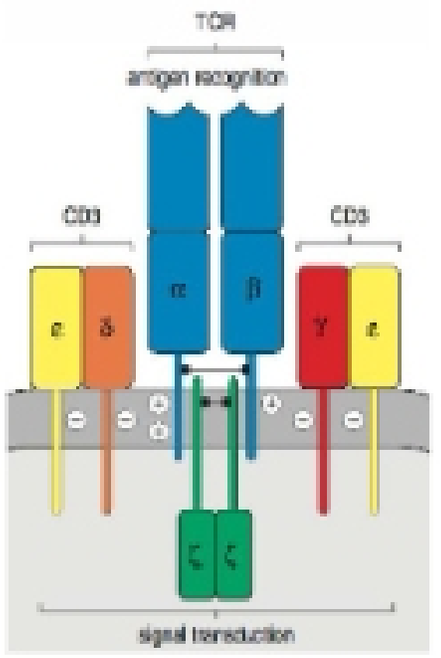
- **Remember:** In immunoglobulins, diversity is achieved through mechanisms before and after B cell activation
  - Before: gene rearrangements → V-region sequence diversity
  - After: changes in mRNA splicing → secreted immunolglobulin; C-region RNA rearrangements → switch heavy-chain isotype; somatic hypermutation of V-region gene → higher affinity (tight binding)
- In T cells, the mechanisms are same before; after activation, **genes remain unchanged** (no mechanisms)
  - This is because T cells are only for recognition, **not** for effector functions
- Human T cell alpha-chain locus is on **chromosome 14** and beta-chain locus is on **chromosome 7**
  - Only one C_α gene, two C_β genes but no functional difference
  - Alpha-chain locus only has V and J segments, beta-chain has V, D, and J segments
- Gene rearrangement occurs **during T cell development in the thymus**
  - Alpha-chain gene: V segment joined to J segment by somatic DNA recombination → V-region sequence
  - Beta-chain gene: D joined to J first, then V joins
  - Similar recombination signal sequences as IG genes and RAG complex, and same enzymes are involved
  - P and N nucleotides are added during recombination (don't code for anything) → junctional diversity
- Severe combined immunodeficiency disorder (**SCID**)
  - Occurs when genetic defects result in absence of RAG proteins
  - B and T lymphocytes are both missing
  - Bone marrow transplant or other medical intervention is needed
- **Omenn Syndrome**
  - RAG proteins with partial enzymatic activity are found
  - Different symptoms than SCID
- After gene rearrangement → alpha and beta chains have genes encoding leader peptide, V region, C region, and membrane-spanning region
  - Introns are still in there → RNA transcript is spliced during transcription → introns are removed → alpha and beta chains go to the ER → they pair to form the α:β T-cell receptor

5-3 The RAG genes were key elements in the origin of adaptive immunity

- Both T cells and B cells use V(D)J recombination for gene rearrangement
- The 2 subunits of RAG recombinase are essential (lacking them leads to SCID and Omenn)
- RAG is only made by lymphocytes → specific to adaptive immunity
- RAG genes are in common ancestor of vertebrates
- RAG genes don't resemble eukaryotic genes, they resemble **transposons**
  - Transposons are genetic elements that can make and move copies of itself to different locations on the chromosome
  - Because they're so similar, it's thought that T-cell receptor gene segments originated from insertion of transposon into some type of innate immune receptor gene in ancestor
    - Transposases (characteristic of transposons; enzyme that cuts double-stranded DNA) evolved to encode RAG proteins; terminal repeat sequences (characteristic of transposons; regions of repeating DNA) evolved to become recombination signal sequences
- Today, RAG genes are on **chromosome 11**

5-4 Expression of the T-cell receptor on the cell surface requires association with additional proteins

- Alpha and beta chains can't leave ER without help of four invariant membrane proteins
- Three of the four are encoded by closely linked genes on **chromosome 11** and together are called the **CD3 complex** (CD3γ, CD3δ, and CD3ε)
- Fourth one is encoded by gene on **chromosome 1** and is called ζ chain
- The CD3 proteins, the ζ chain, and the T-cell receptor form the **T-cell receptor complex**
  - Once an antigen has been recognized, the CD3 proteins and the ζ chain emit signals to the interior of the cell because the alpha and beta chains of the T-cell receptor have very short cytoplasmic tails that don't signal very well
  - People lacking CD3δ or CD3ε chains have low numbers of receptors that don't signal effectively → immunodeficiency



5-5 A distinct population of T cells expresses a second class of T-cell receptor with γ and δ chains

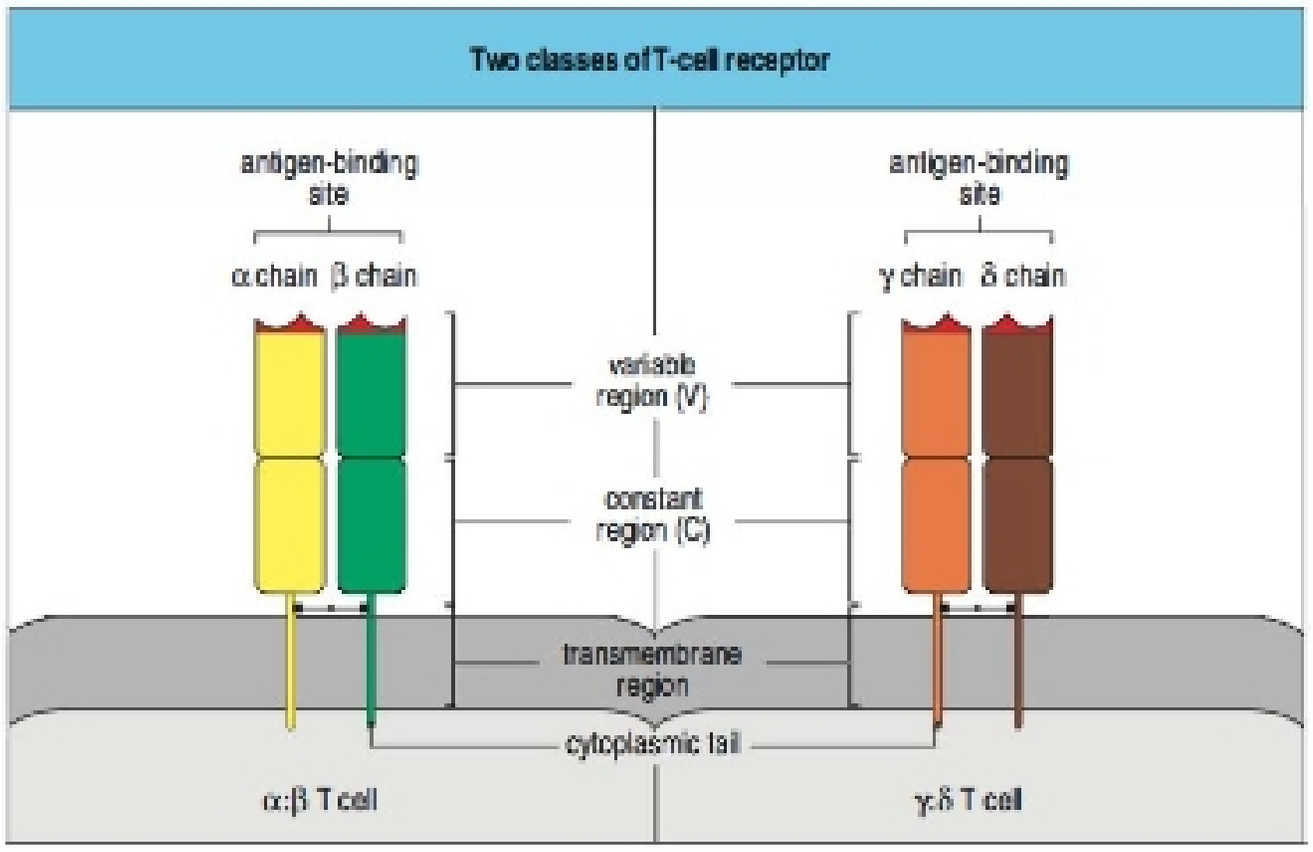
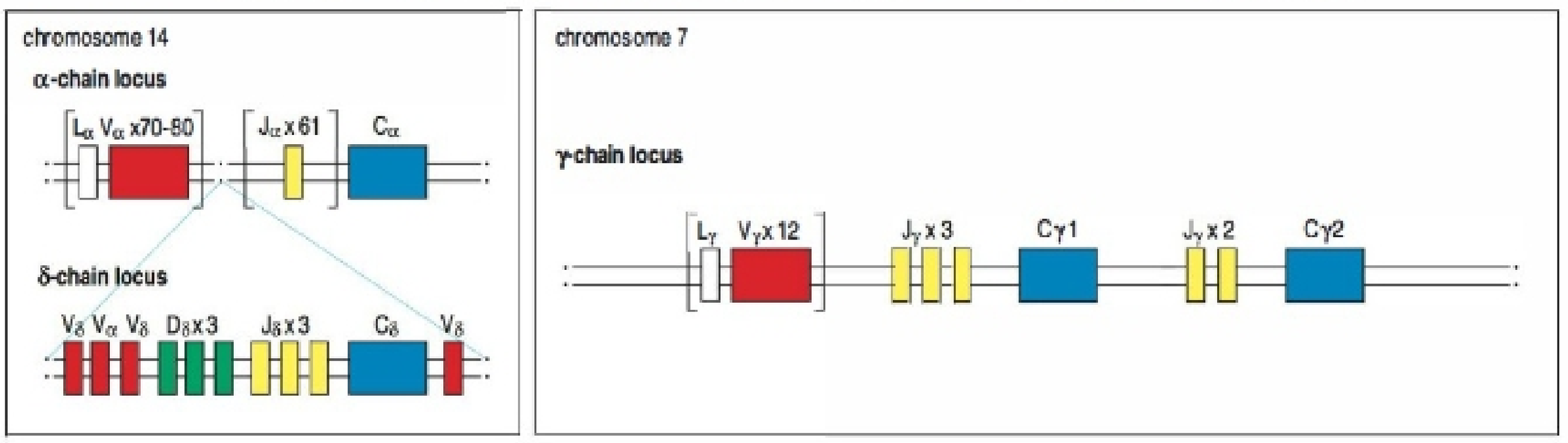


Figure 5.7 There are two classes of T-cell receptor. The α:β T-cell receptor (left panel) and the γδ T-cell receptor (right panel) have similar structures, but they are encoded by different sets of rearranging gene segments and have different functions.

- Another type of T-cell receptor has γ and δ chains instead of alpha and beta chains (1-5% of the T-cells found in circulation, but they can be the dominant T-cell in epithelial tissue)
- T cells express either alpha/beta or γ/ δ; **never both**
- More is known about alpha/beta because they are much more common and plentiful
- The two types are very similar but there are some differences
  - The δ gene segments lie **within** the alpha-chain locus on **chromosome 14** (between V and J segments)
    - This location means that rearrangement within the alpha-chain locus results in deletion and inactivation of δ-chain
  - γ chain locus is on **chromosome 7**
  - The weirdo chains have less V gene segments (which should lead to less diversity) but an increase in junctional diversity
    - Rearrangement for the weirdo chains is the same as for alpha/beta **except** during δ-chain rearrangement, **two D segments can be incorporated into final sequence**
      - Increases variability in two ways → potential number of combinations increases **and** more N nucleotides are added between the two D segments, the VD junction, and DJ junction



SECTION SUMMARY ON PAGE 131

Antigen processing and presentation

- **Antigen processing:** degradation of pathogen's proteins into peptides; occurs inside body's own cells
- **Antigen presentation:** binding of peptide antigen by an MHC molecule and its display at cell surface

5-6 The two classes of MHC molecule present antigen to CD8 and CD4 T cells, respectively

- CD8 T cells are **cytotoxic;** main function is to kill cells that are infected with virus or other **intracellular pathogen**
- CD4 T cells are **helper T cells** and their main function is to help other cells in immune system respond to **extracellular** infection
  - Stimulates B cells to make antibodies → antibodies bind to extracellular bacteria and virus particles