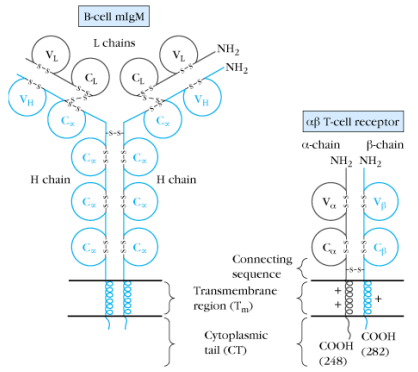
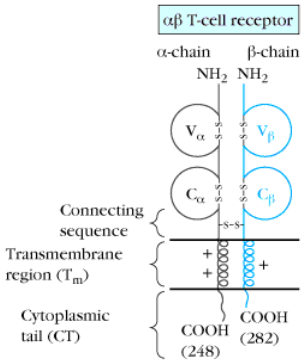
Chapter 9

T cell Receptor

The αβ TCR is similar in size and structure to an antibody Fab fragment



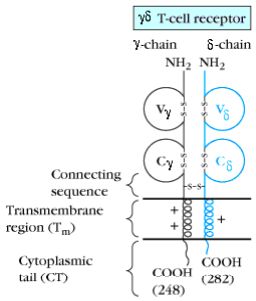
Kuby Figure 9-3



Kuby Figure 9-3

The αβ T cell receptor

- **Two chains - α and β**
- **Two domains per chain**
  - **constant (C) domain**
  - **variable (V) domain**
- **Chains held together by disulfide bonds**
- **Small cytoplasmic tails on each chain**



Kuby Figure 9-9 (modified)

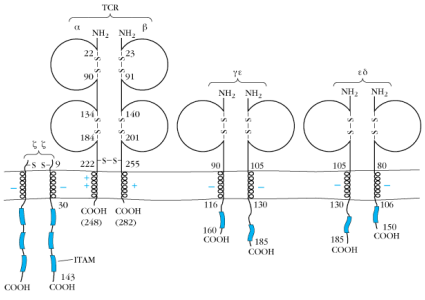
- **Some T cells express a TCR made of two alternate chains - γ and δ**
- **The γδ TCR is structurally similar to the αβ TCR.**
- **0.5-15% of peripheral blood T cells use the γδ TCR. A higher proportion of T cells in the skin and intestinal epithelium use the γδ TCR.**
  - **γδ T cells seem to be biased toward recognition of specific microbial antigens.**
  - **γδ T cells are thought to represent a different lineage of T cells with specialized functions.**

Comparison of TCR

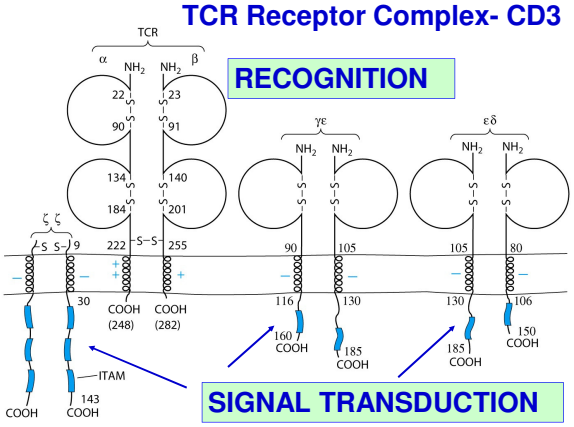
	αβ T cells	γδ T cells
• % CD3⁺	90-99%	1-10%
• TCR V gene in germline	Large	Small
• CD4/CD8		
CD4	60%	<1%
CD8	30%	30%
$CD4^-CD8^-$	<1%	60%
• MHC restriction	Yes	No
• Ligands	Peptide+ MHC	Phospholipid antigen Intact protein

The TCR complex includes CD3 - 3 heterodimers: γε, εδ and ζζ

- **1) TCR is not expressed without CD3. It is required to bring TCR to surface**
- **2) All chains of CD3 possess ITAM motifs. (Immunoreceptor tyrosine-based activation motif) → Signal Transduction**



TCR Receptor Complex- CD3

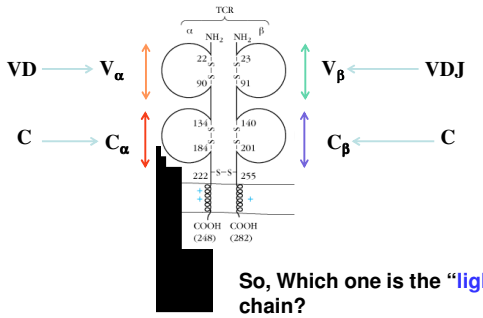


RECAP:

-The BCR consists of IgM or IgD plus Ig-α/Ig-β heterodimers. The Ig binds the antigen while the Ig-α/Ig-β heterodimers are involved in activation of the B cell.

- The TCR consists of either the α / β chains or the γ / δ chains plus CD3. The αβ or γδ chains bind the antigen while CD3 is involved in activation of the T cell.

The signaling components possess ITAM motifs.



So, Which one is the "light" chain?

Which one is the "heavy" chain?

Kuby Figure 9-9

TABLE 9-2 TCR Multigene families in humans

Gene	Chromosome location	NO. OF GENE SEGMENTS V	D	J	C
α Chain	14	50		70	1
δ Chain*	14	3	3	3	1
β Chain†	7	57	2	13	2
γ Chain‡	7	14		5	2

*The δ-chain gene segments are located between the V_α and J_α segments.

†There are two repeats, each containing 1 D_β, 6 or 7 J_β, and 1 C_β.

‡There are two repeats, each containing 2 or 3 J_γ and 1 C_γ.

SOURCE: Data from P. A. H. Moss et al., 1992, *Annu. Rev. Immunol.* **10**:71.

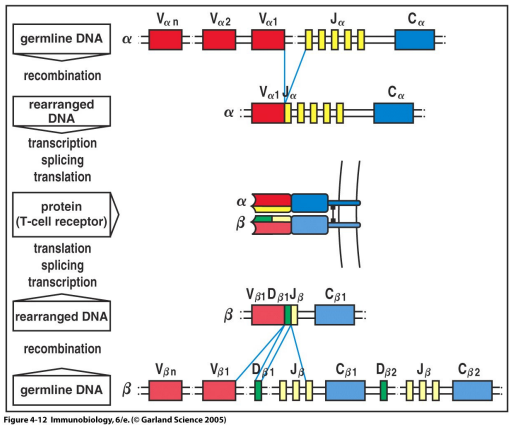
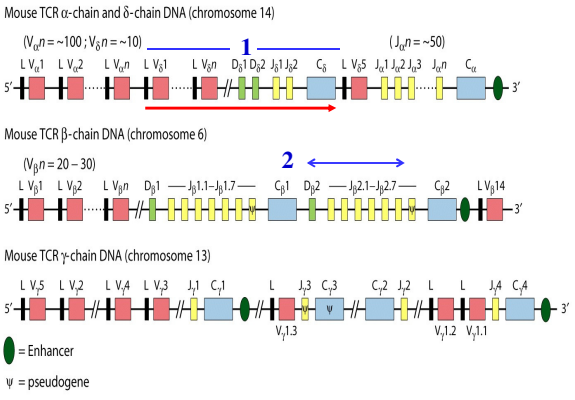


Figure 4-12 Immunobiology, 6/e. (© Garland Science 2005)



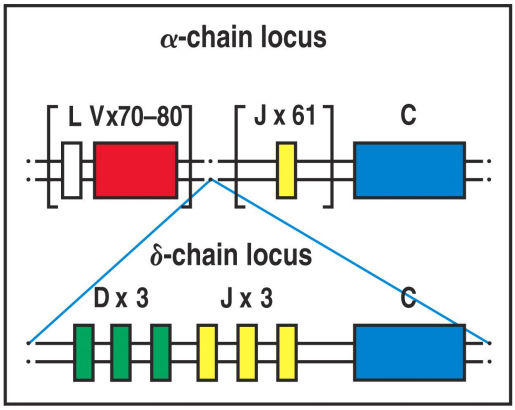
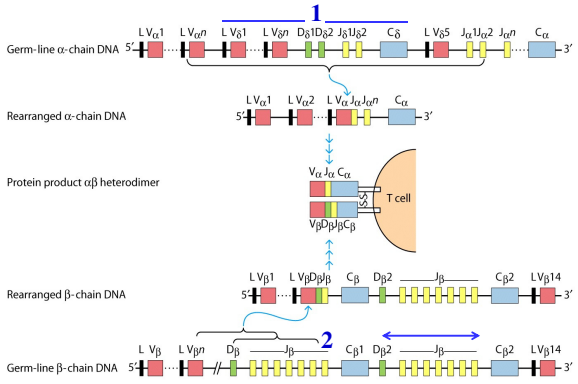
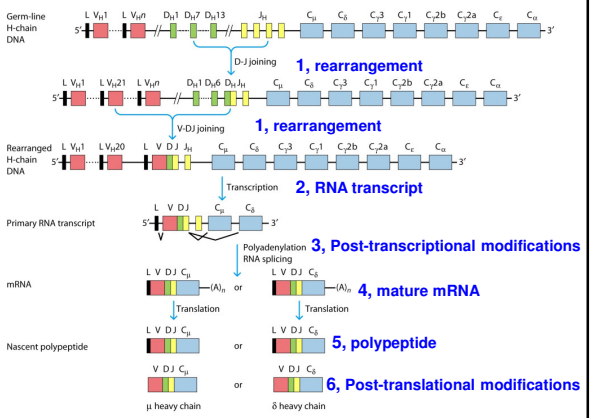


Figure 4-15 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

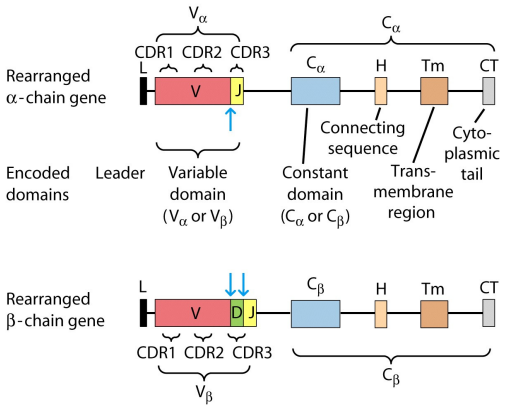




Rearrangement of TCR genes

- TCR Genes are also composed of V, D, J and C gene segments
- Genes are located in different chromosomes
- The β and δ chains contain D segments (like Ig Heavy chains!) while the α and γ chains do not.
- α and γ chains - VJ rearrangement only
- β and δ chains - V-DJ rearrangement
- Segments of the δ chain are embedded within the segments encoding the α chain
- When the α chain rearranges, δ segments are deleted
- T cells express only αβ or γδ TCR
- Rearrangement involves RAG-1 and RAG-2 and TdT
- Rearrangement is governed by the one turn-two turn rule

Variability in CDRs Regions



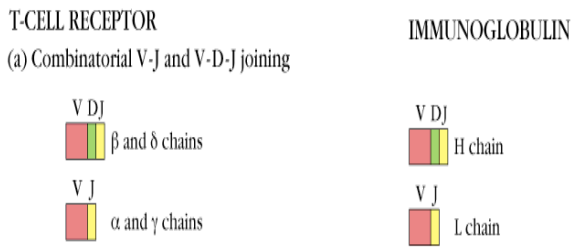
Generation of antibody diversity

1. Multiple germline V, D and J gene segments
2. Combinatorial V-J and V-D-J joining
3. Somatic hypermutation
4. Junctional flexibility
5. P-nucleotide addition
6. N-nucleotide addition
7. Combinatorial association of heavy and light chains

Generation of TCR diversity

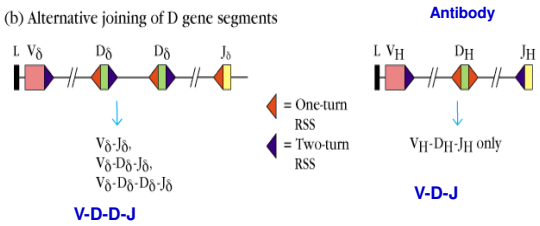
- **Combinatorial V-J and V-D-J joining**

- **Combination of two chains to make the antigen-binding site**



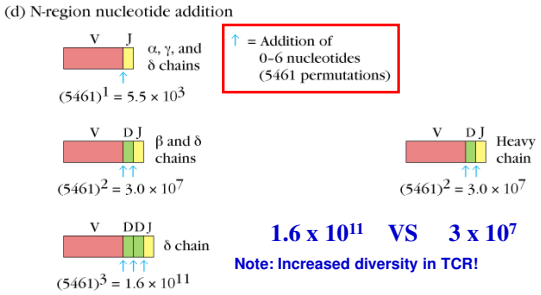
Generation of TCR diversity

-**Varying number of D segments in the delta (and beta) chain, why?**
(arrangement of RSS sequences differs from that in Ig loci to allow this)



Generation of TCR diversity

- **N-region nucleotide addition**
- **Occurs in all chains ---------- Antibodies ONLY in Heavy chain**



1.6×10^{11} VS 3×10^7

Note: Increased diversity in TCR!

MAJOR DIFFERENCES BETWEEN TCR AND Ig GENES

- **Somatic hyper-mutation (affinity maturation)**
  - During an antibody response, mutations accumulate at a rapid rate in the VDJ gene segments encoding the BCR.
  - Thus, as an immune response proceeds, the affinity of the antibody produced (i.e. its ability to bind to the antigen) increases.
- **Alternative joining of D segments (β, δ)**

TABLE 9-3 Sources of possible diversity in mouse immunoglobulin and TCR genes

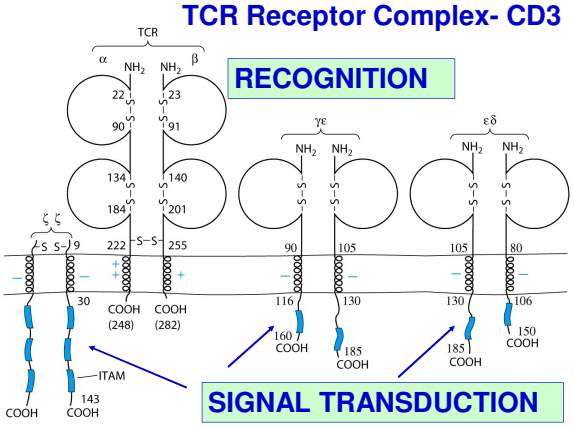
Mechanism of diversity	IMMUNOGLOBULINS H Chain	IMMUNOGLOBULINS κ Chain	αβ T-CELL RECEPTOR α Chain	αβ T-CELL RECEPTOR β Chain	γδ T-CELL RECEPTOR γ Chain	γδ T-CELL RECEPTOR δ Chain
ESTIMATED NUMBER OF SEGMENTS						
Multiple germ-line gene segments						
V	134	85	100	25	7	10
D	13	0	0	2	0	2
J	4	4	50	12	3	2
POSSIBLE NUMBER OF COMBINATIONS*						
Combinatorial V-J and V-D-J joining	134 × 13 × 4 = 7 × 10^3	85 × 4 = 3.4 × 10^2	100 × 50 = 5 × 10^3	25 × 2 × 12 = 6 × 10^2	7 × 3 = 21	10 × 2 × 2 = 40
★ Alternative joining of D gene segments	–	–	–	+ (some)	–	+ (often)
Junctional flexibility	+	+	+	+	+	+
N-region nucleotide addition†	+	–	+	+	+	+
P-region nucleotide addition	+	+	+	+	+	+
★ Somatic mutation	+	+	–	–	–	–
Combinatorial association of chains	+		+		+	

*A plus sign (+) indicates mechanism makes a significant contribution to diversity but to an unknown extent.
A minus sign (–) indicates mechanism does not operate.
†See Figure 9-8d for theoretical number of combinations generated by N-region addition.

Element	Immunoglobulin H	Immunoglobulin κ+λ	α:β T-cell receptors β	α:β T-cell receptors α
Variable segments (V)	40	70	52	~70
Diversity segments (D)	25	0	2	0
D segments read in three frames	rarely	–	often	–
Joining segments (J)	6	5(κ) 4(λ)	13	61
Joints with N- and P-nucleotides	2	50% of joints	2	1
Number of V gene pairs	1.9 x 10^6		5.8 x 10^6	
Junctional diversity	~3 x 10^7		~2 x 10^11	
Total diversity	~5 x 10^13		~10^18	

Figure 4-13 Immunobiology, 6/e. (© Garland Science 2005)

TCR Receptor Complex- CD3



WHY ACCESSORY MOLECULES?

1) Due to low affinity of TCR with peptide MHC complex

2) Provide:

- Adhesion, Activation and Co-stimulation
- Some show increased expression in response to cytokines

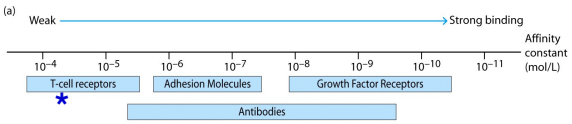


TABLE 9-4 Selected T-cell accessory molecules

T cell Name	APC Ligand	FUNCTION: Adhesion	FUNCTION: Signal transduction	Member of Ig superfamily
CD4	Class II MHC	+	+	+
CD8	Class I MHC	+	+	+
CD2 (LFA-2)	CD58 (LFA-3)	+	+	+
LFA-1 (CD11a/CD18)	ICAM-1 (CD54)	+	?	+/(−)
CD28	B7	?	+	+
CTLA-4	B7	?	+	−
CD45R	CD22	+	+	+
CD5	CD72	?	+	−

Accessory Molecules Involved in Cell-Cell Interactions

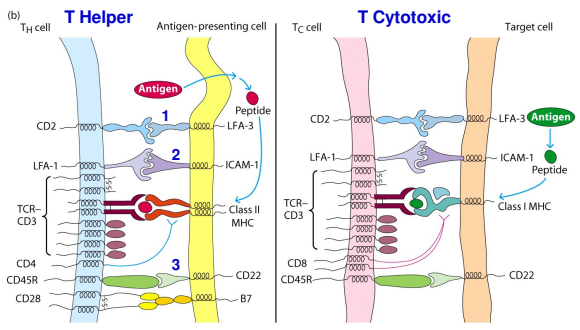
Cell Adhesion:

T Cell	Ligand on APC
CD2(LFA-2)	LFA-3
LFA-1	ICAM-1, ICAM-2

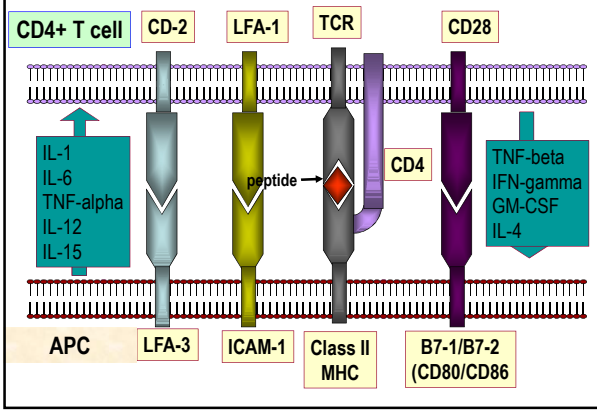
LFA = **L**eukocyte **F**unction-associated **A**ntigen

ICAM = **I**nter**C**ellular **A**dhesion **M**olecule

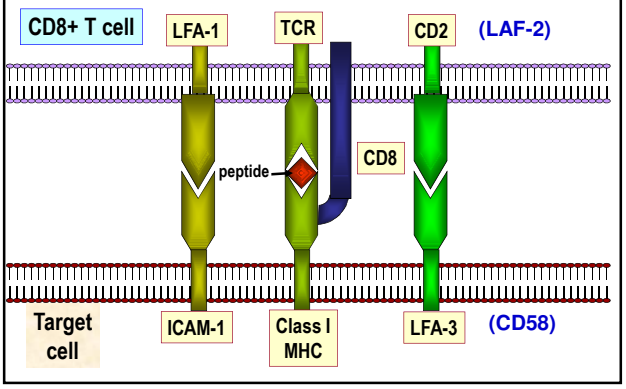
Accessory Molecules Involved in Cell-Cell Interactions

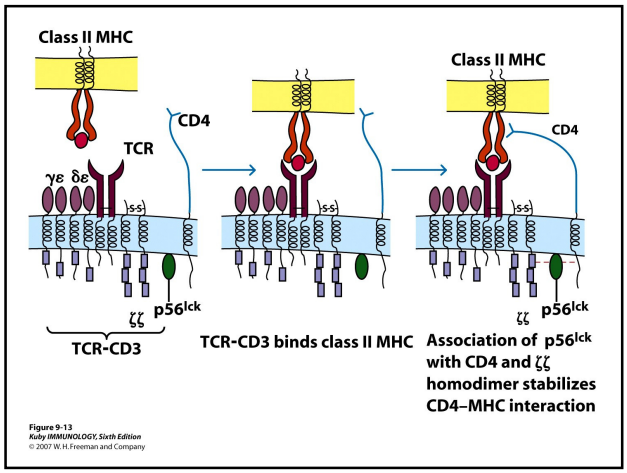


Interactions of Th Cell and APC



Interactions of Tc Cell and Target Cell





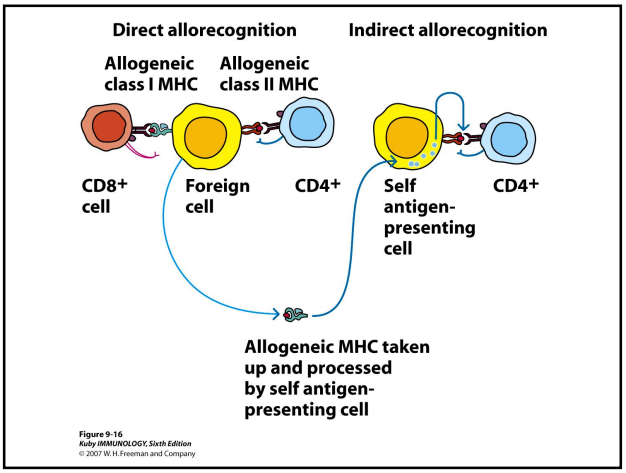
T-cell Accessory molecules

- CD4 and CD8 are co-receptors because they recognize the peptide-MHC complex
- CD8 recognizes the α3 MHC-I domain; while CD4 interacts with α2 MHC-II domain
- Both CD4 and CD8 act in signal transduction
- **OTHER**

Costimulatory Molecules

- Molecules on T cell and 2nd cell that engage to deliver 2nd signal required for activation of T cell
- Most important co-stimulatory molecules:

T cell	Ligand on 2nd cell
CD28	B7-1 (CD80), B7-2 (CD86)
CTLA-4	B7-1 (CD80), B7-2 (CD86)
CD45R	CD22
CD4/CD8	MHC-I/II



Self-MHC restriction of the T cell receptor (TCR)

- **Self restriction-** T cell can only be activated by a unique peptide associated with self-MHC.
- Two models:
  - A) **Dual receptor model:** two receptors, one for the antigen and one for the MHC molecule
  - B) **Altered self model**: One receptor that recognizes both antigen and MHC molecule