"The best way to have a good idea is to have lots of ideas"

Linus Pauling

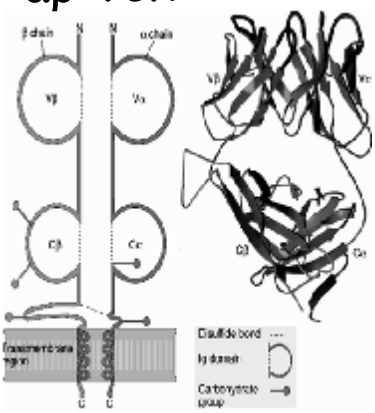
T cell

central role in the adaptive immune response

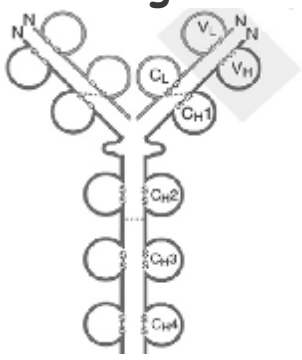
T cell receptors

TCRs are similar to Igs molecules

αβ TCR

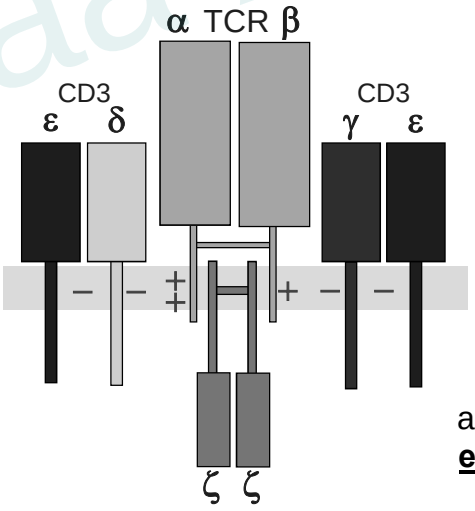


Ig



αβ chain (or γδ) consists of one 'Ig-like' N-terminal variable region (V), one Ig-like constant (C) domain, a hydrophobic transmembrane region, and a short cytoplasmic region. hinge regions

TCRs remain membrane-bound contain a single Ag-binding site



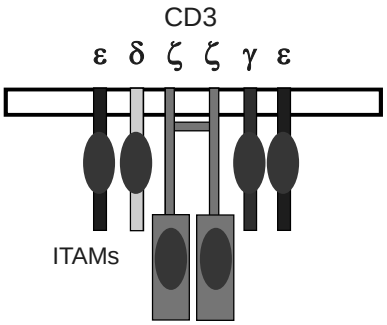
TCR-CD3 complex

The intracytoplasmic region of the TCR chain is too short to transduce a signal

The CD3γ, δ, ε or ζ chains are required **for cell surface expression** of the TCR-CD3 complex and **signalling through the TCR**

Signalling is initiated by **aggregation of TCR by MHC-peptide complexes on APC**

Transduction of signals by the TCR



The cytoplasmic domains of the CD3 complex contain **Immunoreceptor Tyrosine -based Activation Motifs (ITAMs)**

are essential for T cell activation, and mutational substitution of the tyrosines in the motif prevents activation

As with BCR ,ITAMs are involved in the transmission of the signals from the receptor
When the TCR is bound to its cognate antigen–MHC complex, the ITAM motifs become phosphorylated

The TCR γδ structurally resembles the TCR αβ but may function differently

Anatomic distribution

αβ TCRs : > 90% on peripheral blood T cells and on the majority of thymocytes

γδ TCRs : are rare in spleen, lymph nodes, and peripheral blood
predominate at **epithelial surfaces**:

skin/ the epithelial linings of the reproductive tract
in the intestine, where they are found as **intraepithelial lymphocytes (IELs)**.

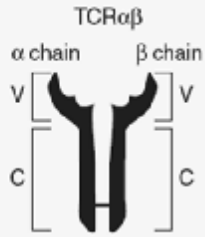
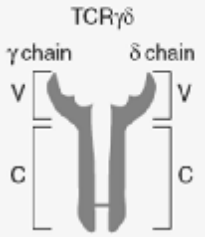
Antigen recognition by γδ T cells is unlike that of their αβ counterparts

•**γδ** T cells can recognize Ag in an MHC-independent fashion:

• **γδ** T cells found in normal numbers in MHC class I/class II-deficient mice.
• their antigens are not necessarily peptides, do not require classical processing

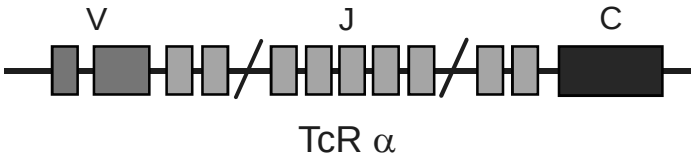
• some murine **γδ** T cells have been found to recognize proteins directly, including MHC molecules and viral proteins, in a manner that requires neither antigen processing nor presentation by MHC.

T cell receptors

	TCRαβ	TCRγδ
TCR icon		
% Mature T Cells	>90%	<10%
Tissue Distribution	Secondary lymphoid tissues	Intraepithelial tissues
Nature of Ligand	Peptide–MHC	Unprocessed ligand

Organisation of TcR genes

mouse TcR locus



TcR α

TcR β

TCR genes segmented into V, (D), J & C elements
(variable, diversity, joining & constant)
closely resemble Ig genes (α,γ~IgL and β,δ~IgH)

- ***The mechanism of V(D)J recombination is the same in both T cells and B cells***

✓ recombination signal sequences

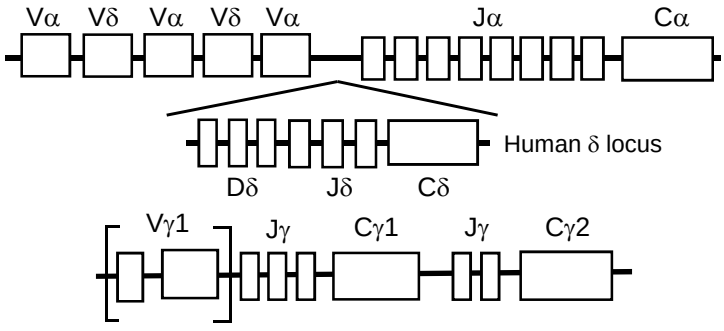
✓ the recombination machinery (the RAG proteins).

✓ addition of N regions (non-templated nucleotides added to the junctions by terminal deoxynucleotidyl transferase,TdT) is much more pronounced in TCRs,

However

- **no somatic hypermutation**
- **no class switching occur in TCRs**
- **are never secreted**

An alternative TcR: γδ



The δ locus is located between the Vα and Jα regions
Vα to Jα rearrangement deletes Dδ, Jδ and Cδ . TcRαβ cells can not express γδ TcR

Generation of diversity in the TcR

- **Multiple germline segments**

Human TcR

Variable (V) segments, diversity (D) segments, joining (J) segments

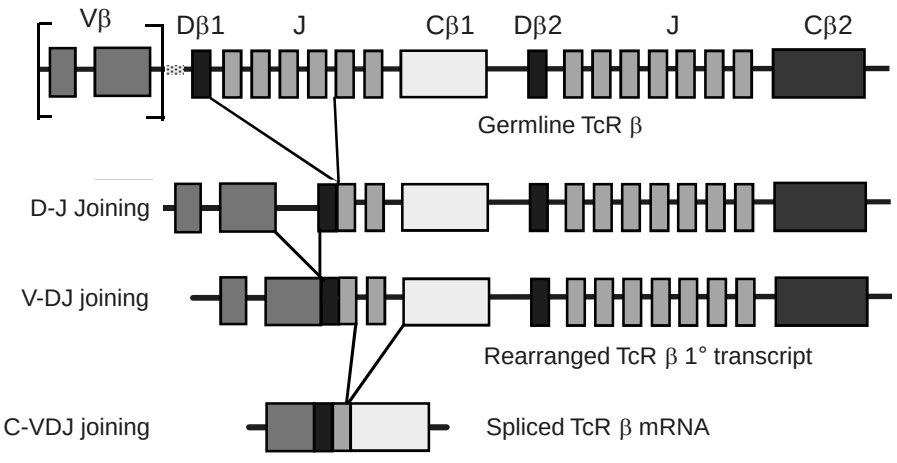
- **Recombination of genes**

- **The need to pair α and β chains to form a binding site**

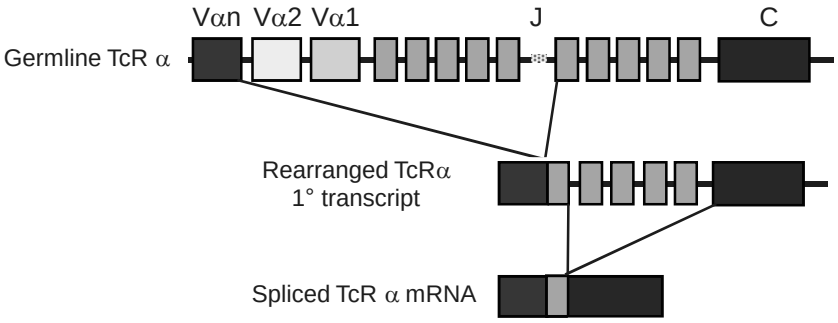
- **JUNCTIONAL DIVERSITY**

Addition of non-template encoded (N) and palindromic (P) nucleotides at imprecise joints made between V-D-J elements

TcR β gene rearrangement
SOMATIC RECOMBINATION



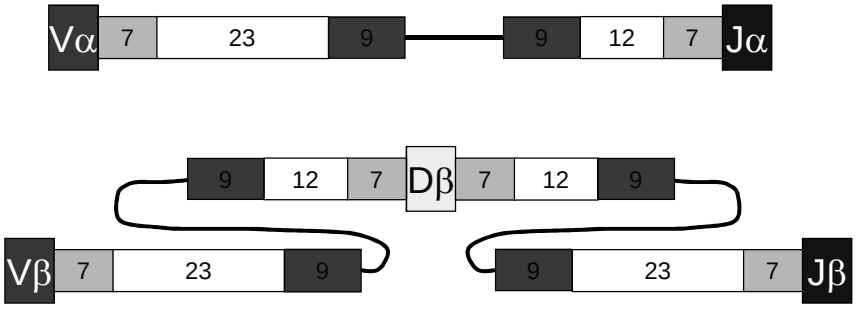
TcR α gene rearrangement by SOMATIC RECOMBINATION



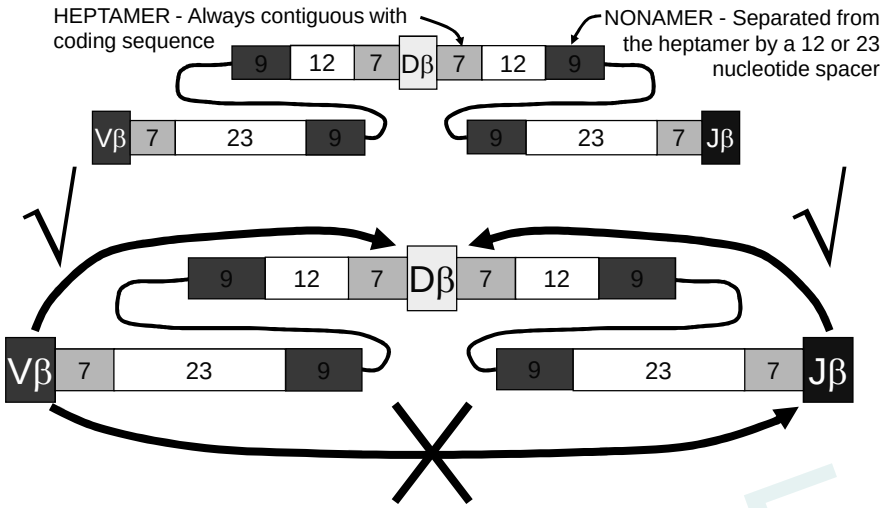
Rearrangement very similar to the IgL chains

V, D, J flanking sequences

Sequencing upstream and downstream of V, D and J elements revealed conserved sequences of 7, 23, 9 and 12 nucleotides.

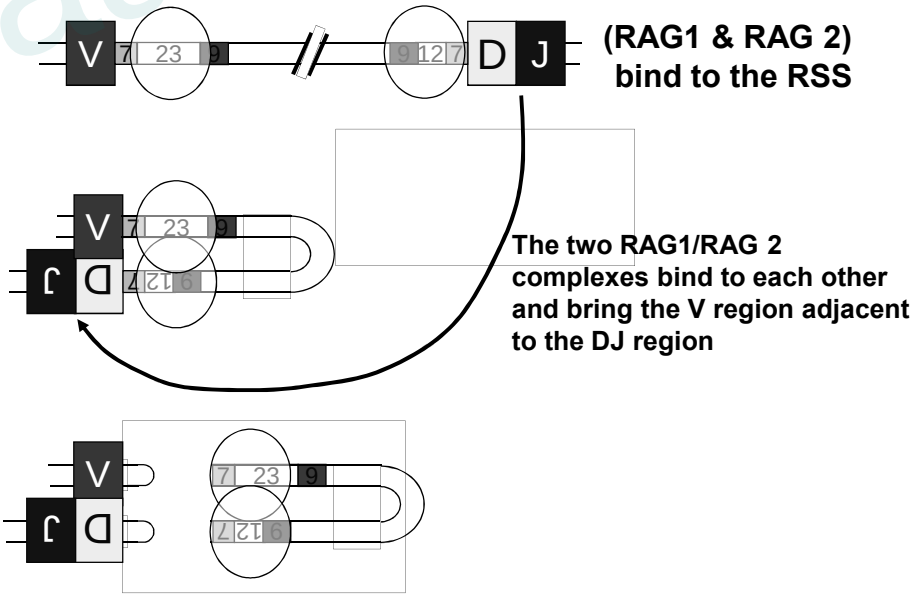


Recombination signal sequences (RSS)

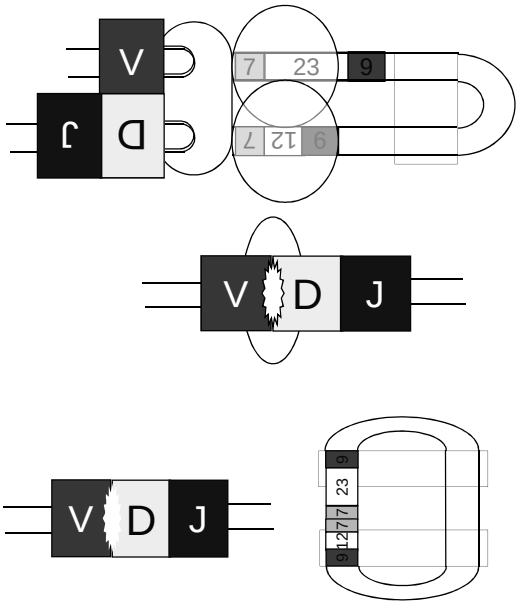


12-23 RULE – A gene segment flanked by a 23mer RSS can only be linked to a segment flanked by a 12mer RSS

Steps of TCR gene recombination



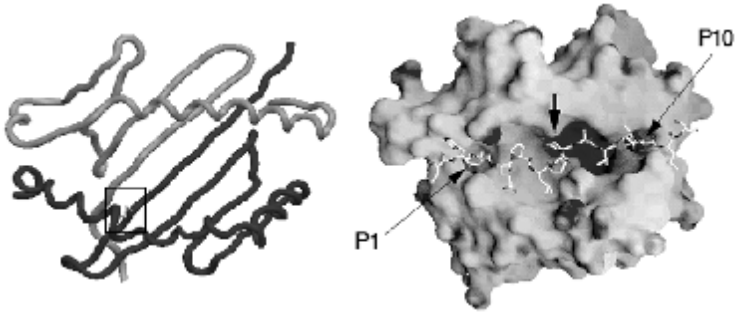
Steps of TcR gene recombination



The hairpins at the end of the V and D regions are opened, and **exonucleases and transferases remove or add random nucleotides to the gap between the V and D region**

DNA ligase joins the ends of the V and D region to form the coding joint and the two heptamers to form the signal joint.

If TCR *did* undergo somatic mutation:

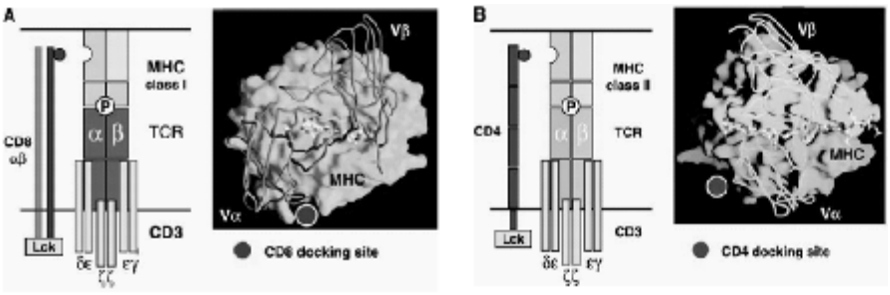


TCR interacts with *entire* top surface of MHC-peptide antigen complex
Somatic mutation in the TCR *could* mutate amino acids that interact with the MHC molecule causing a complete loss of peptide-MHC recognition

Summary

- Antibodies and TCR share many similarities, but there are significant differences in structure and function
- The structure and organisation of the TCR genes is similar to the Ig genes
- Somatic recombination in TCR genes is similar to that in Ig genes
- diversity of TCR include recombination and junctional diversity
- TCR do not somatically mutate

TCR/peptide-MHC Complex



the presence of CD4 or CD8 can help stabilize the interaction of the TCR and MHC–peptide.
kinases associated with these molecules are brought into proximity with CD3 so they can phosphorylate the ζζ dimer that initiates activation