PRESENTATION
on
T-CELL RECEPTOR

T-CELL RECEPTOR

- Antigen-specific nature of T-cell responses implies that T cells possess an antigen-specific and clonally restricted receptors.
- T-cell receptor is a membrane bound and does not appears in a soluble form
- Antigen-binding interaction of T-cell receptors is weaker than that of Abs
- Most T-cell receptors are specific not for Ag alone but for Ag combined with a molecule encoded by the MHC.

- The molecule responsible for T-cell specificity is a heterodimer composed of either α and β or γ and δ chains.
- The αβ TCR is characterized by its high degree of specificity & thus considered a signature molecule of the adaptive immune system.
- By contrast, certain receptors on γδ T cells appear to recognize classes of antigens present on group of pathogens & so function in a manner more consistent with innate immunity.

Classical Experiment demonstrating self- MHC restriction of the T-cell receptor

- When mice were infected with lymphocytic choriomeningitis (LCM) virus ⟹ CTLs produce that could lyse LCM infected target cells.
- But CTLs failed to bind free LCM virus (why)????
- R.M zinkernagel and P.C Doherty – experiment ⟹ nobel prize in 1966

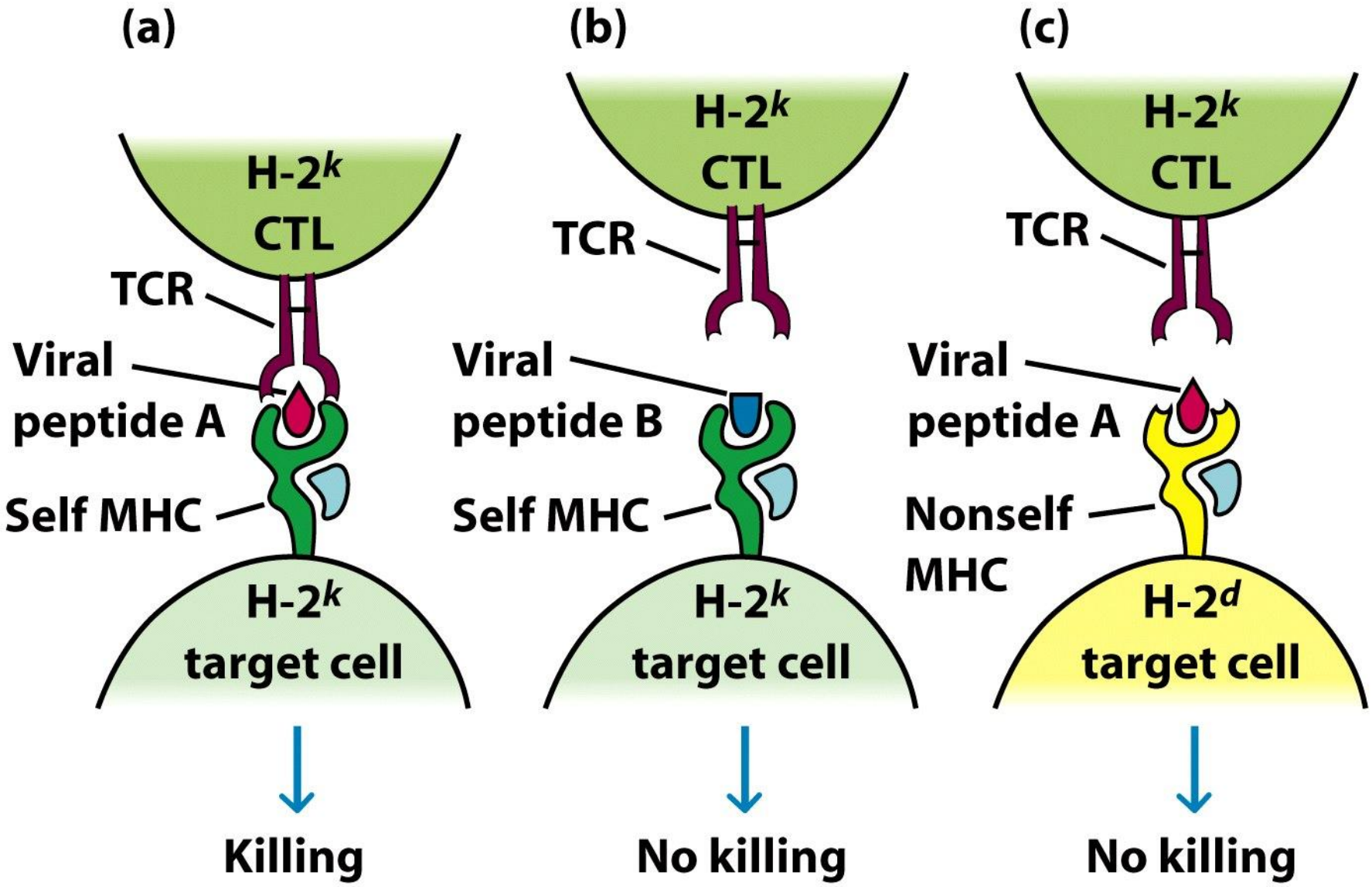

Figure 9-1
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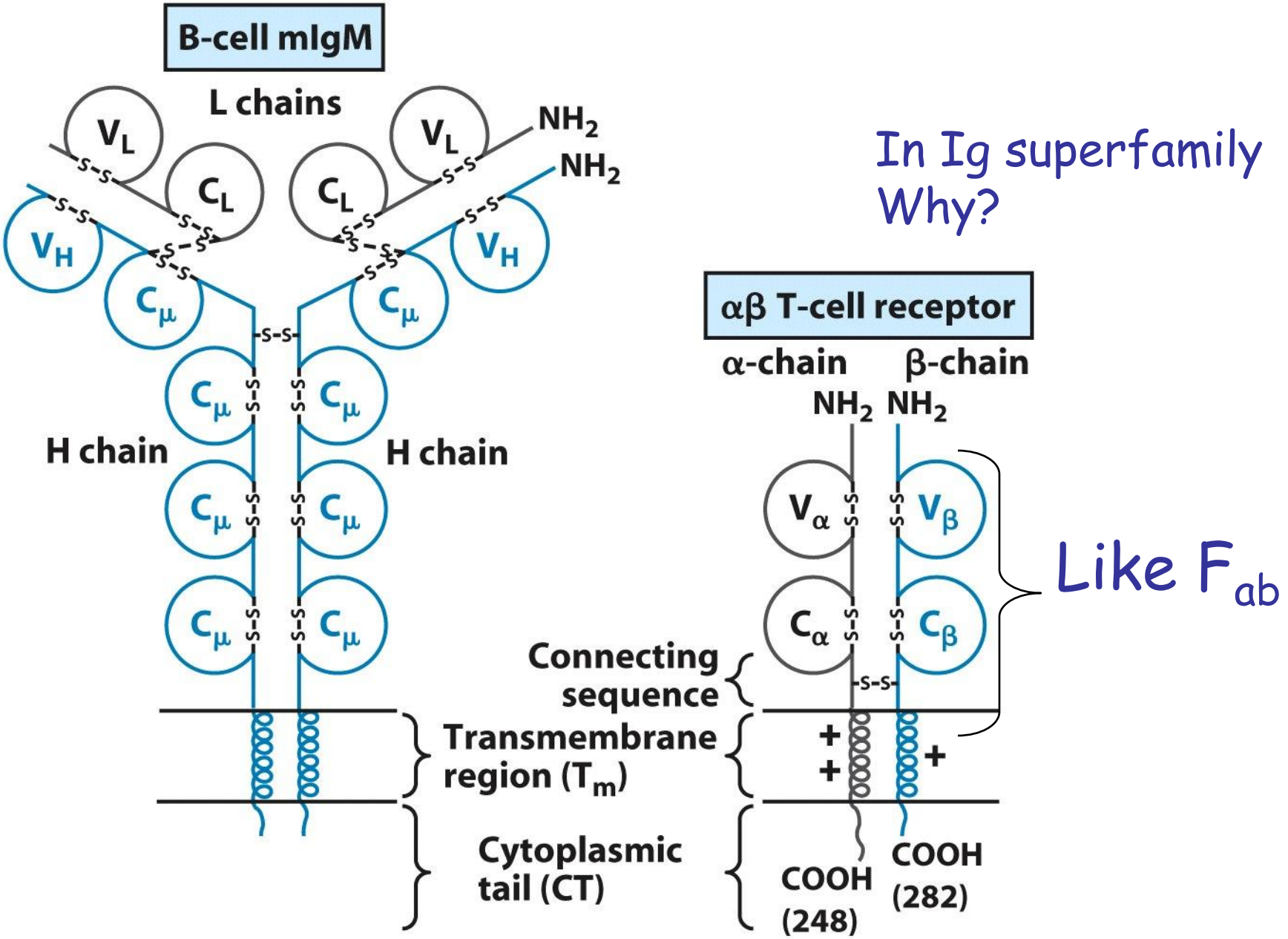

In Ig superfamily
Why?

Like F_{ab}

Other TCRs are γδ

Figure 9-3
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DIFFERENCES

αβ RECEPTOR

- Orientation of V & C regions so called elbow angle b/t the long axes of the V & C is 147 degree
- Contributes to adaptive immunity
- Recognize Ag processed & presented in the context of an MHC
- Present in circulating blood

γδ RECEPTOR

- Elbow angle is 111 degree
- Contributes to innate immunity
- Do not required either MHC processing or presentation for Ag recognition
- Mainly present in peripheral blood

In humans the predominant receptor expressed on circulating $\gamma\delta$ cells recognizes a microbial phospholipid Ag, 3-formyl-1-butyl pyrophoshate ,found on microbacterium tuberculosis & other bacteria & parasite

Germ Line Organisation of the Mouse TCR Gene Segments

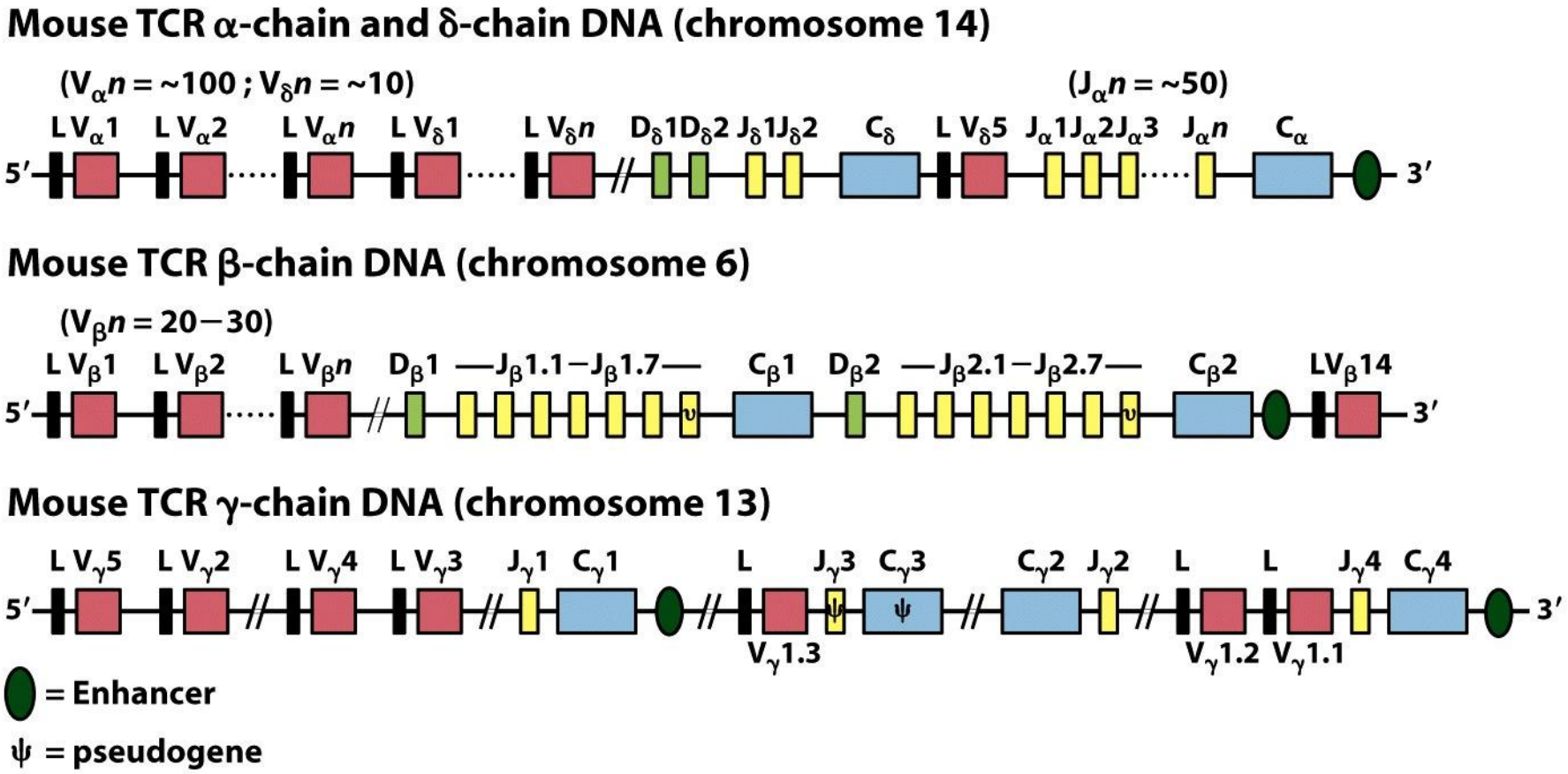

Figure 9-5
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TCR Multigene families in humans

- α chain – chromosome 14
- δ chain - chromosome 14
- β chain – chromosome 7
- γ chain - chromosome 7

GENE REARRANGEMENT- YIELDING A FUNCTIONAL GENE ENCODING THE αβ TCR

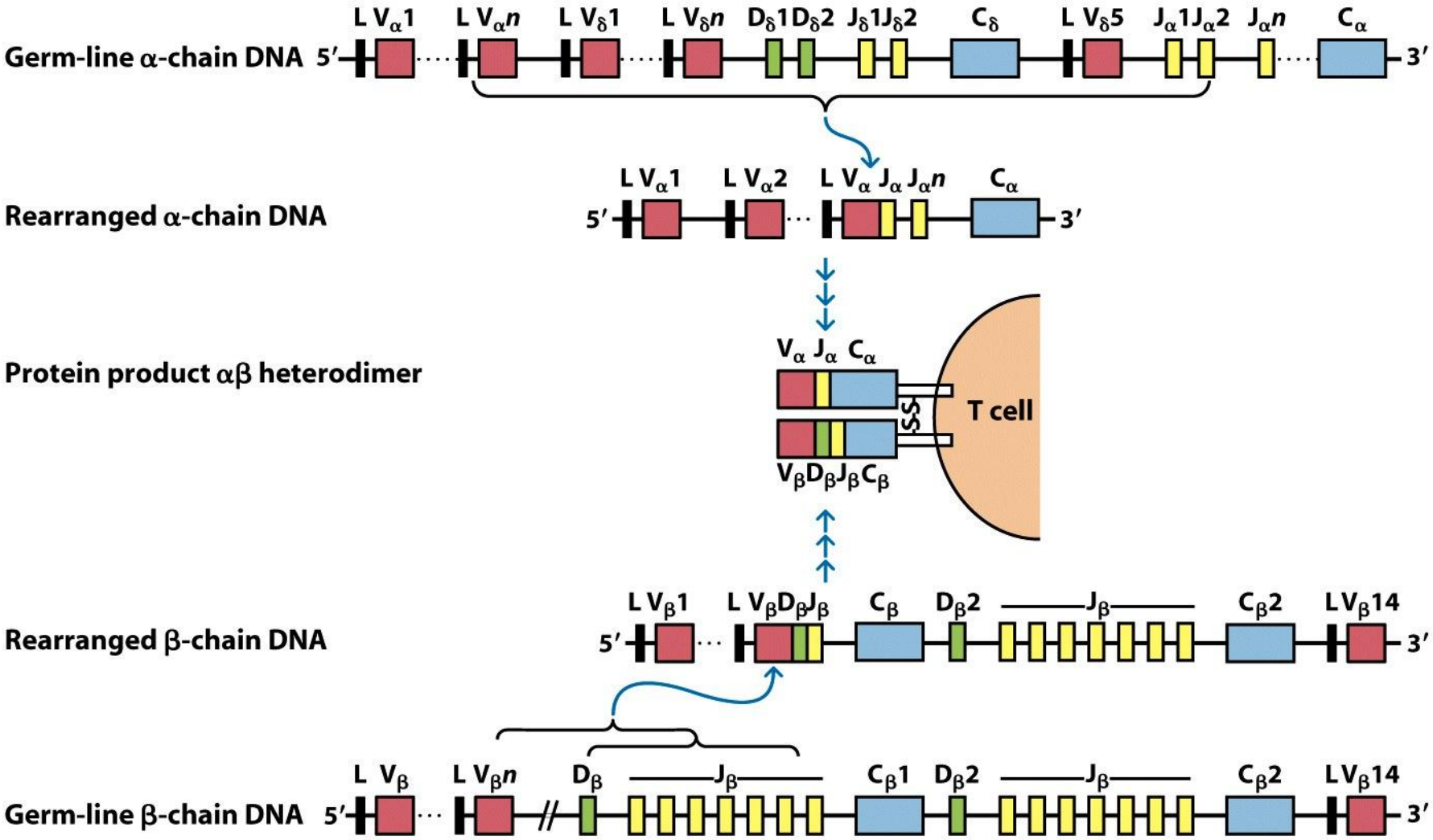

Figure 9-6
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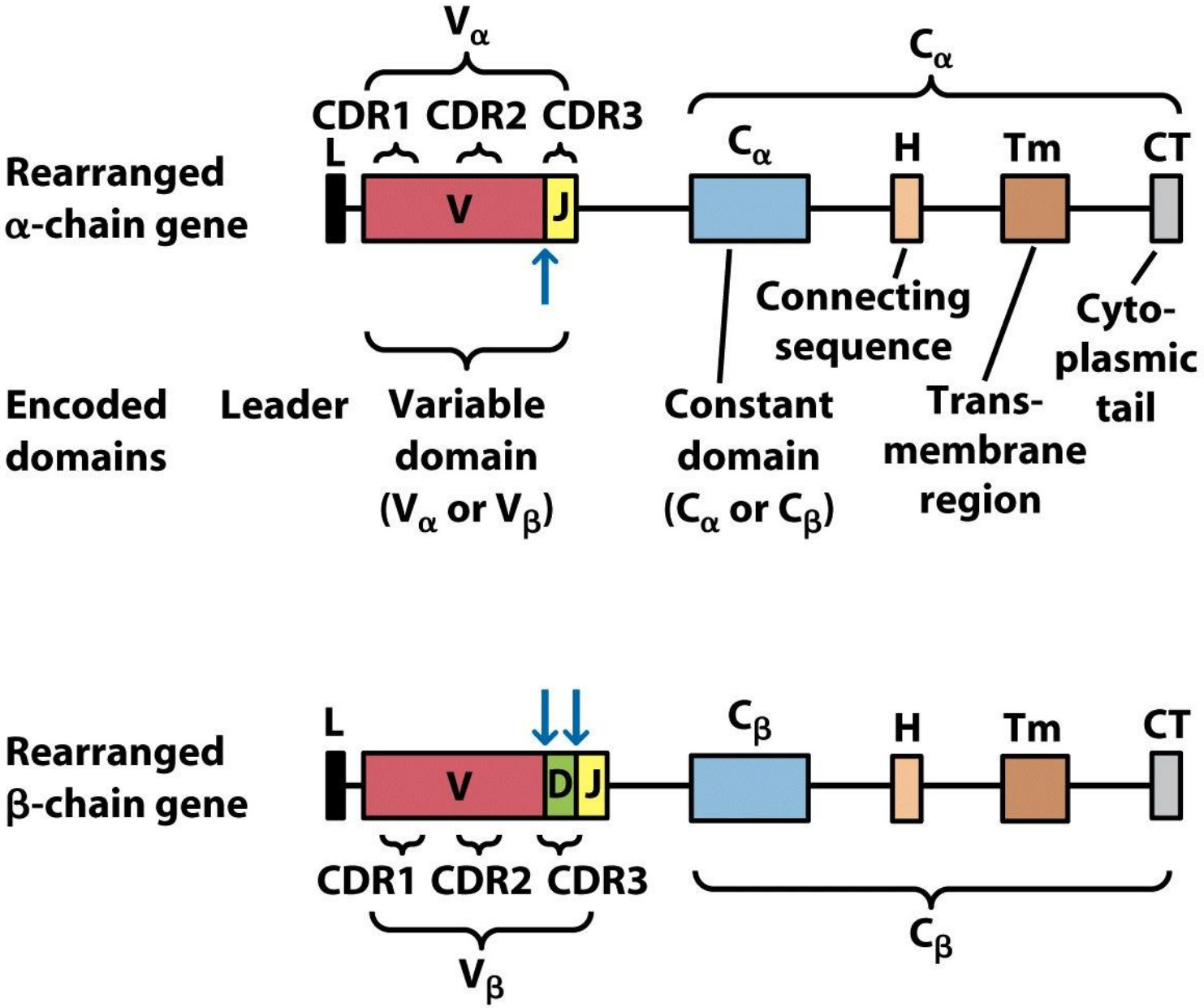
MECHANISM OF TCR DNA REARRANGEMENTS

Similar to the mechanism of Ig –gene rearrangement

Conserved heptamer & nonamer RSSs , containing 1/2 turn spacer sequences ,find flanking each V,D&J gene segment in TCR germ –line DNA

Follow 1/2 joining rule

RAG-1/2 recombinase by deletion al or inversional mech.



Rearranged αβ-TCR genes showing the exons encode the various domains of the αβ TCR

Generation of diversity in the TcR

COMBINATORIAL DIVERSITY
Multiple germline segments

In the human TcR

Variable (V) segments: ~70α, 52β

Diversity (D) segments: 0α, 2β

Joining (J) segments: 61α, 13β

The need to pair α and β chains to form a binding site doubles the potential for diversity

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

SOMATIC MUTATION IS NOT USED TO GENERATE DIVERSITY IN TcR

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

Mechanism of diversity	IMMUNOGLOBULINS		αβ T-CELL RECEPTOR		γδ T-CELL RECEPTOR	
	H Chain	κ Chain	α Chain	β Chain	γ Chain	δ Chain
ESTIMATED NUMBER OF FUNCTIONAL GENE SEGMENTS*						
V	101	85	79	21	7	6
D	13	0	0	2	0	2
J	4	4	38	11	3	2
POSSIBLE NUMBER OF COMBINATIONS†						
Combinatorial V-J and V-D-J joining	$101 \times 13 \times 4$ 5.3×10^3	85×4 3.4×10^2	79×38 3.0×10^3	$21 \times 2 \times 11$ 4.6×10^2	7×3 21	$6 \times 2 \times 2$ 24
Alternative joining of D gene segments	–	–	–	+ (some)	–	+ (often)
Junctional flexibility	+	+	+	+	+	+
N-region nucleotide addition‡	+	–	+	+	+	+
P-region nucleotide addition	+	+	+	+	+	+
Somatic mutation	+	+	–	–	–	–
Combinatorial association of chains	+		+		+	

*Immunoglobulin data from Table 5-2; TCR data from Baum et al., 2004, *Nucleic Acids Research* **32**:D51.
†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.

Table 9-3
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Combinatorial V-J and V-D-J joining

T-cell receptor

V DJ — β and δ chains

V J — α and γ chains

Immunoglobulin

V DJ — H chain

V J — L chain

Alternative joining of D gene segments

T-cell receptor

L V_δ D_δ D_δ J_δ

V_δ-J_δ,
V_δ-D_δ-J_δ,
V_δ-D_δ-D_δ-J_δ

Immunoglobulin

L V_H D_H J_H

V_H-D_H-J_H only

= One-turn RSS
= Two-turn RSS

Figure 9-8b
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N-region nucleotide addition

T-cell receptor

V J — α, γ, and δ chains
$(5461)^1 = 5.5 \times 10^3$

V D J — β and δ chains
$(5461)^2 = 3.0 \times 10^7$

V DD J — δ chain
$(5461)^3 = 1.6 \times 10^{11}$

↑ = Addition of 0–6 nucleotides (5461 permutations)

Immunoglobulin

V D J — Heavy chain
$(5461)^2 = 3.0 \times 10^7$

Figure 9-8d
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Junctional flexibility

T-cell receptor

One-turn RSS: CACTGTG
D_δ: GTGGACT
V_δ: GATGCTCC
Two-turn RSS: CACAGTG

V D J
V J

Immunoglobulin

One-turn RSS: CACTGTG
D_H: ATGGACT
V_H: TGGCCG
Two-turn RSS: CACAGTG

Figure 9-8c
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