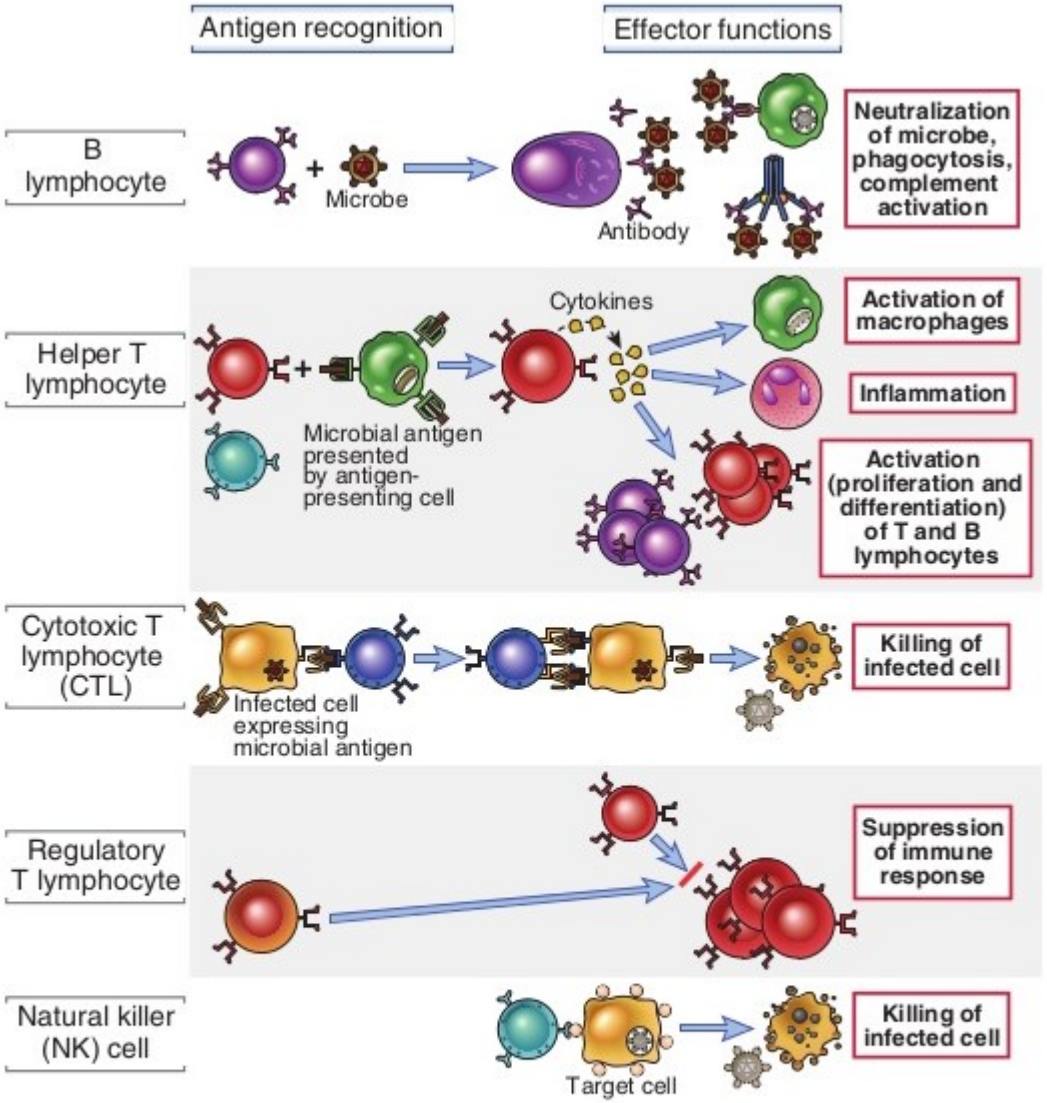


FIGURE 1–9 Classes of lymphocytes. Different classes of lymphocytes recognize distinct types of antigens and differentiate into effector cells whose function is to eliminate the antigens. B lymphocytes recognize soluble or cell surface antigens and differentiate into antibody-secreting cells. Helper T lymphocytes recognize antigens on the surfaces of antigen-presenting cells and secrete cytokines, which stimulate different mechanisms of immunity and inflammation. Cytotoxic T lymphocytes recognize antigens in infected cells and kill these cells. (Note that T lymphocytes recognize peptides that are displayed by MHC molecules, discussed in Chapter 3.) Regulatory T cells limit the activation of other lymphocytes, especially of T cells, and prevent autoimmunity. Natural killer cells recognize changes on the surface of infected cells and kill these cells. NK cells are cells of innate immunity, and all the other lymphocytes are cells of the adaptive immune system.

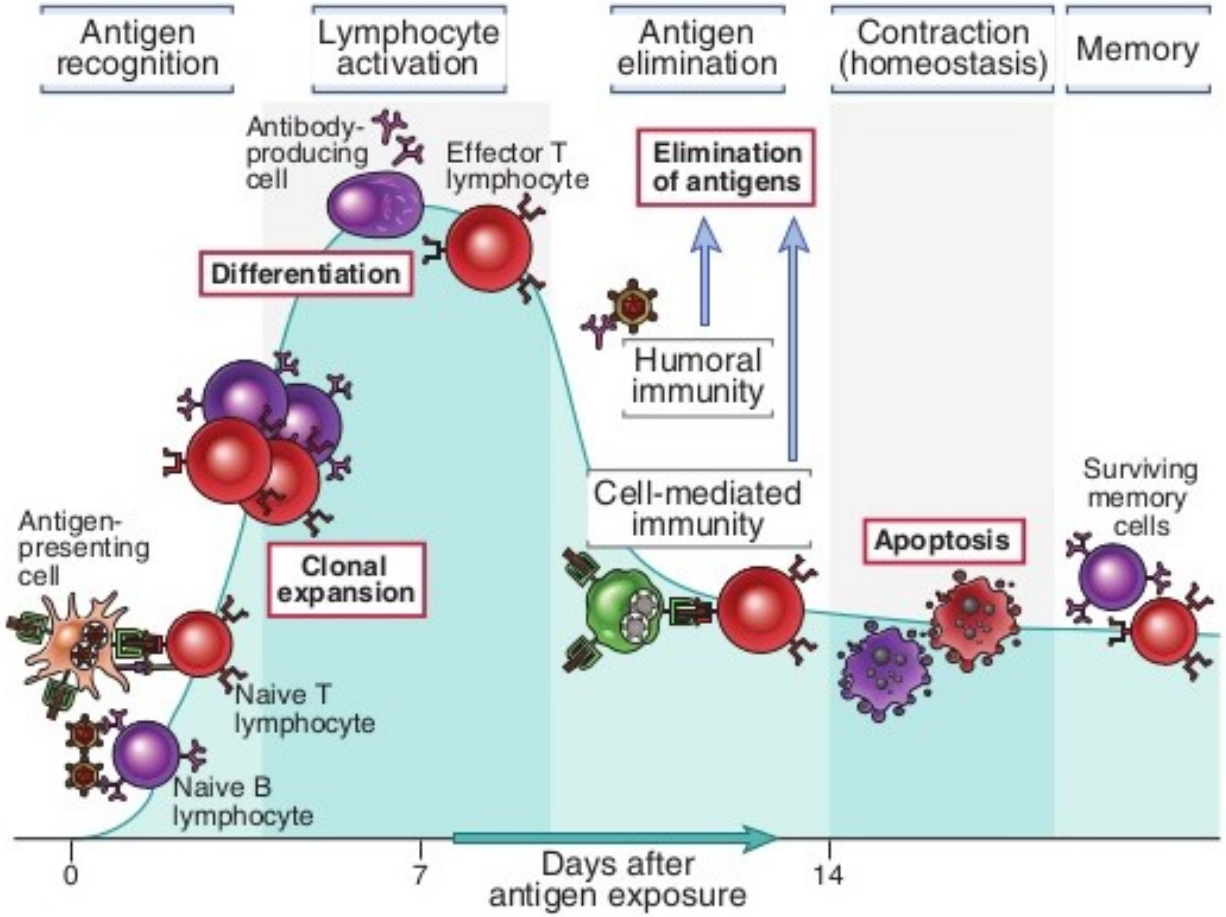


FIGURE 1–17 Phases of adaptive immune response. An adaptive immune response consists of distinct phases; the first three are recognition of antigen, activation of lymphocytes, and elimination of antigen (effector phase). The response declines as antigen-stimulated lymphocytes die by apoptosis, restoring the baseline steady state called homeostasis, and the antigen-specific cells that survive are responsible for memory. The duration of each phase may vary in different immune responses. These principles apply to both humoral immunity (mediated by B lymphocytes) and cell-mediated immunity (mediated by T lymphocytes).

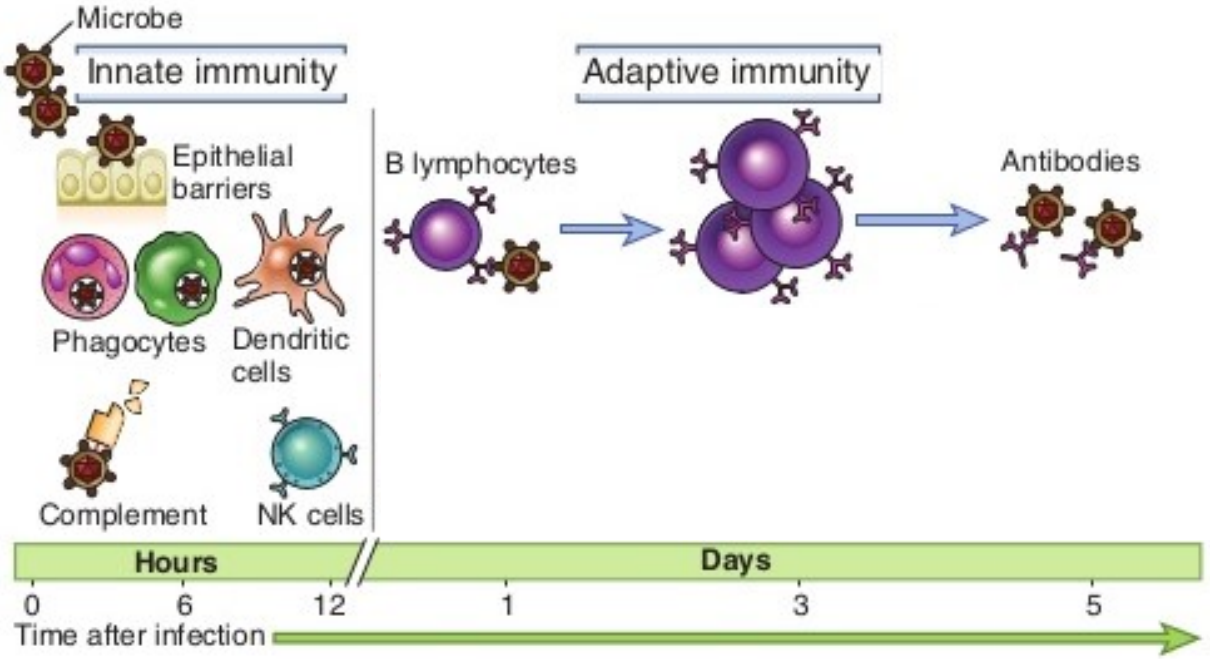


FIGURE 1–3 Principal mechanisms of innate and adaptive immunity. The m
the inital defense against infections. Some mechanisms (e.g., epithelial barriers) prevent inf
phagocytes, natural killer (NK) cells, the complement system) eliminate microbes. Adaptive
are mediated by lymphocytes and their products. Antibodies block infections and eliminate m
intracellular microbes. The kinetics of the innate and adaptive immune responses are appr
infections.

Selezione clonale

I cloni di linfociti si sviluppano prima ed in modo indipendente dall'esposizione all'antigene

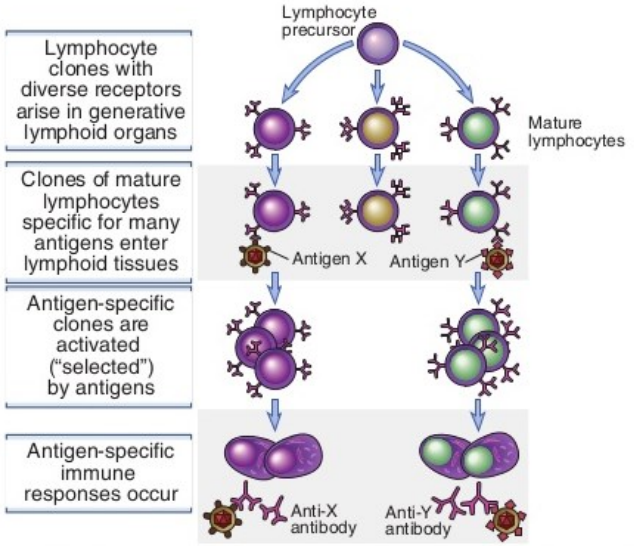


FIGURE 1–6 Clonal selection. Mature lymphocytes with receptors for many antigens develop before encountering these antigens. A clone refers to a population of lymphocytes with identical antigen receptors and therefore specificities; all these cells are presumably derived from one precursor cell. Each antigen (e.g., X and Y) selects a preexisting clone of specific lymphocytes and stimulates the proliferation and differentiation of that clone. The diagram shows only B lymphocytes giving rise to antibody-secreting cells, but the same principle applies to T lymphocytes. The antigens shown are surface molecules of microbes, but clonal selection also is true for extracellular soluble and intracellular antigens.

Repertorio anticorpale individuale: 10^11

Il repertorio anticorpale è generato da:

RICOMBINAZIONE SOMATICA del DNA durante lo sviluppo delle cellule B

Presenza di più SEGMENTI GENICI codificanti

IPERMUTAZIONE SOMATICA

MATURAZIONE LINFOCITI

RIARRANGIAMENTO GENI PER RECETTORI-ANTIGENE (Immunoglobuline/TCR)

CAMBIAMENTO NELL'ESPRESSIONE DI PROTEINE DI SUPERFICIE E DI MEMBRANA

SEGNALI DAL MICROAMBIENTE: CELLULE STROMALI

MOLECOLE DI SUPERFICIE (ADESIONE)

FATTORI SOLUBILI

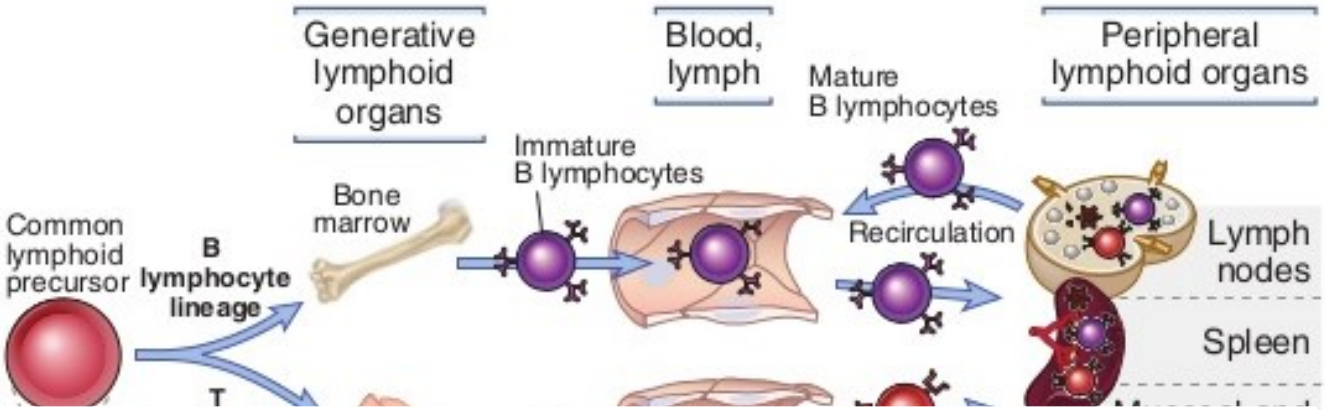
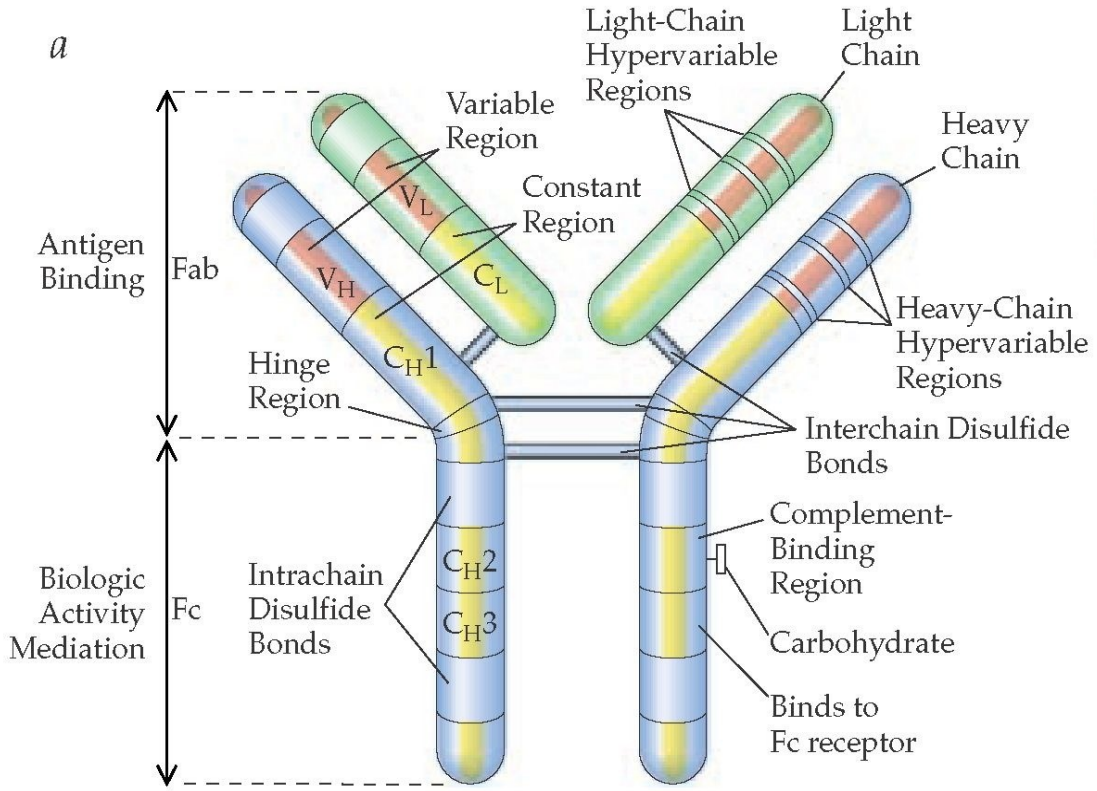
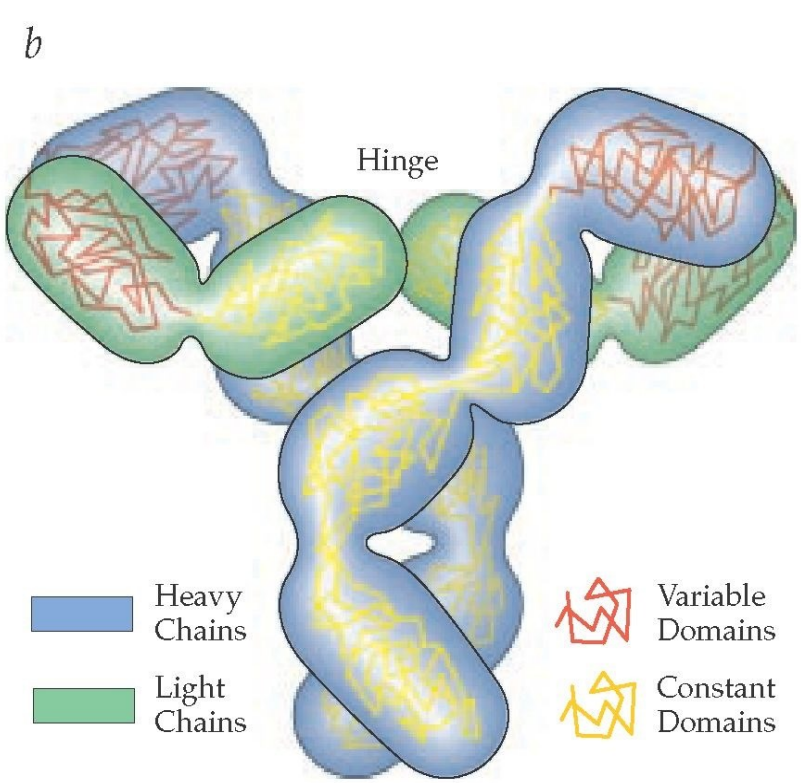


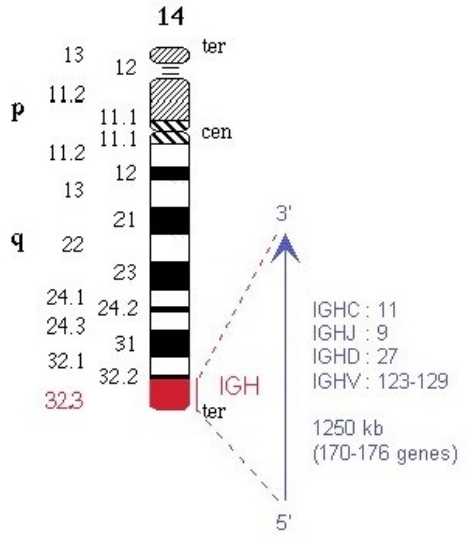
FIGURE 1–10 Maturation of lymphocytes. Lymphocytes develop from precursors in the generative lymphoid organs (bone marrow and thymus). Mature lymphocytes enter the peripheral lymphoid organs, where they respond to foreign antigens and recirculate in the blood and lymph.



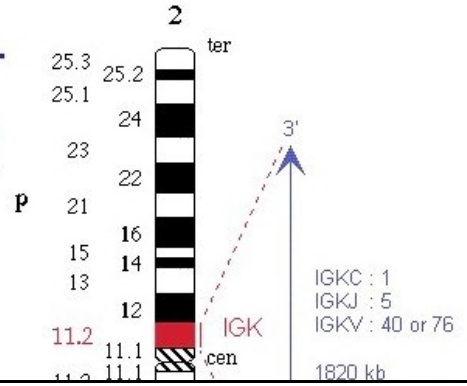


Regioni ipervariabili: CDR (regioni che determinano la complementarietà) – capacità dell'anticorpo di legare l'antigene

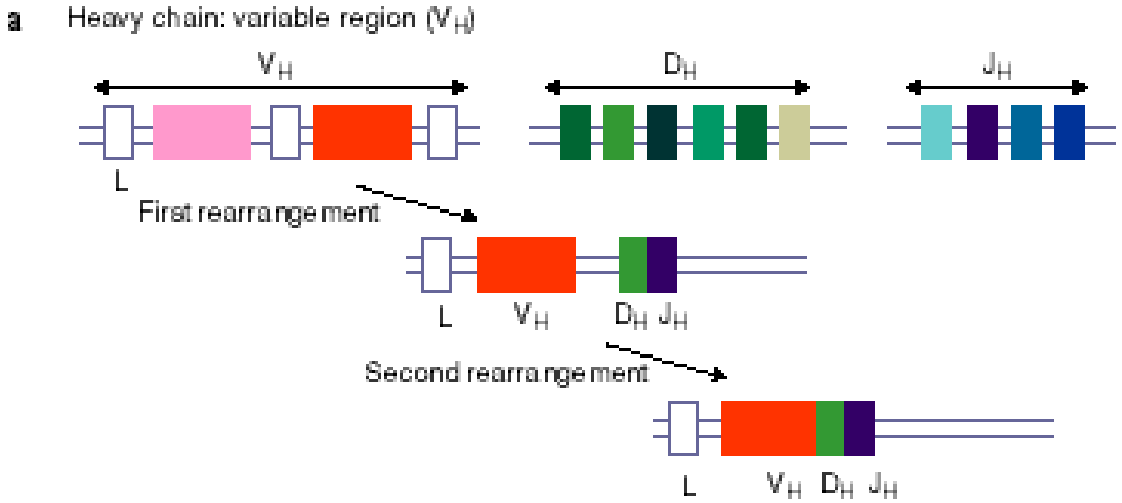
Chromosomal location of the antibody H, λ and κ chain loci in man



locus representations from the Internation
Information System (IMGT) server (http://v



22 5'



Rearrangement of the variable regions of an immunoglobulin molecule

Piú segmenti per ogni dominio V, D, J

3 loci genici:

2 catene leggere

1 catena pesante

Number of functional gene segments in human immunoglobulin loci

Segment	Light chains		Heavy chain
	κ	λ	H
Variable (V)	40	30	40
Diversity (D)	0	0	25
Joining (J)	5	4	6

Figure 4-3 Immunobiology, 6/e. (© Garland Science 2005)

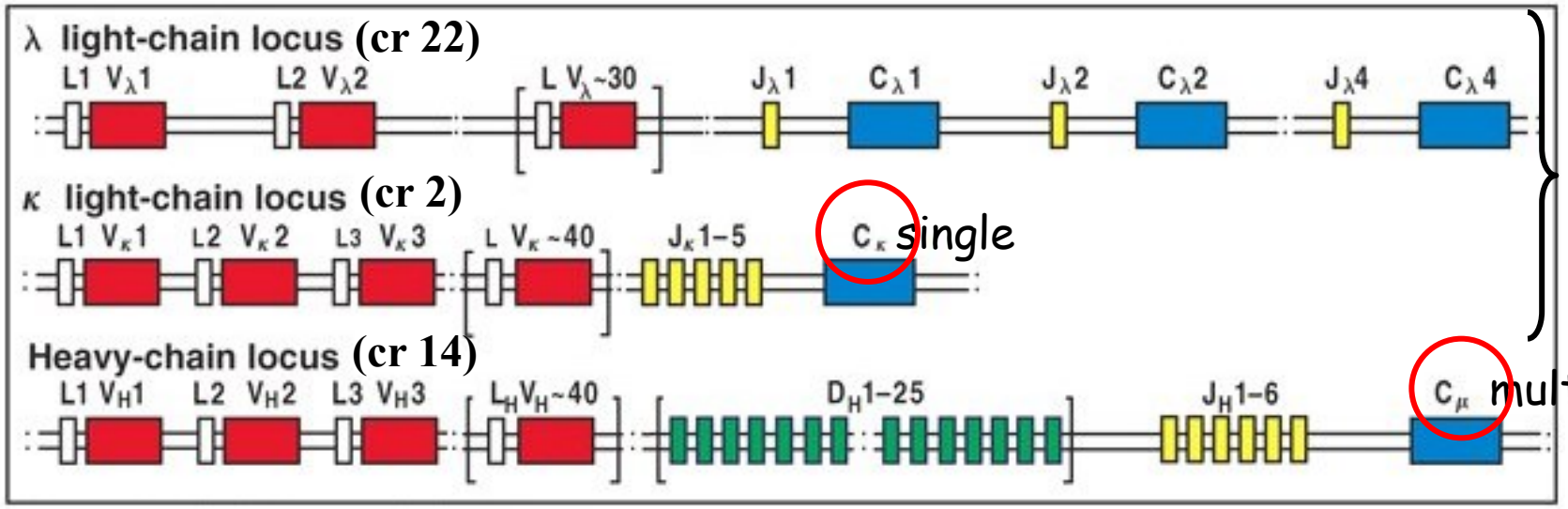


Figure 4-4 Immunobiology, 6/e. (© Garland Science 2005)

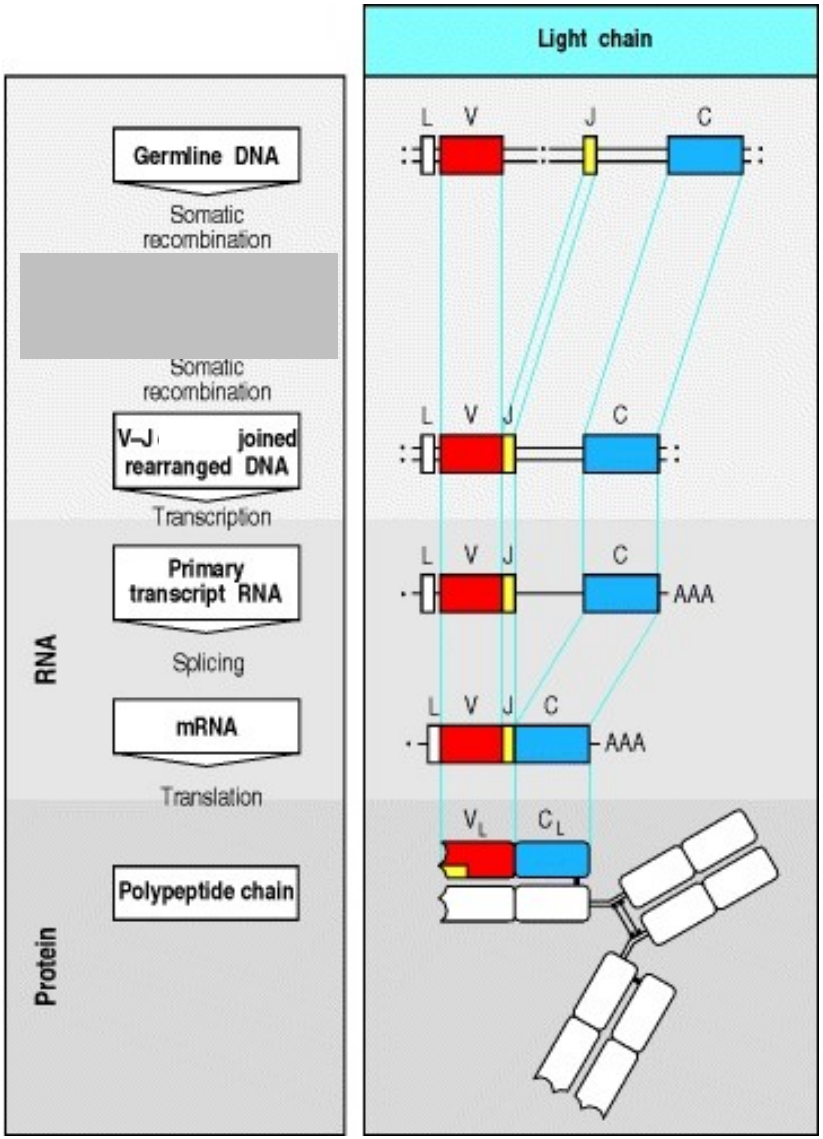
RIARRANGIAMENTO REGIONE VARIABILE CATENA LEGGERA

Dominio V catene leggere: codificato da 2 segmenti separati di DNA

Primi 95–101 aminoacidi: **segmento V**

Successivi aminoacidi (96-108): **joining o segmento J** d'unione

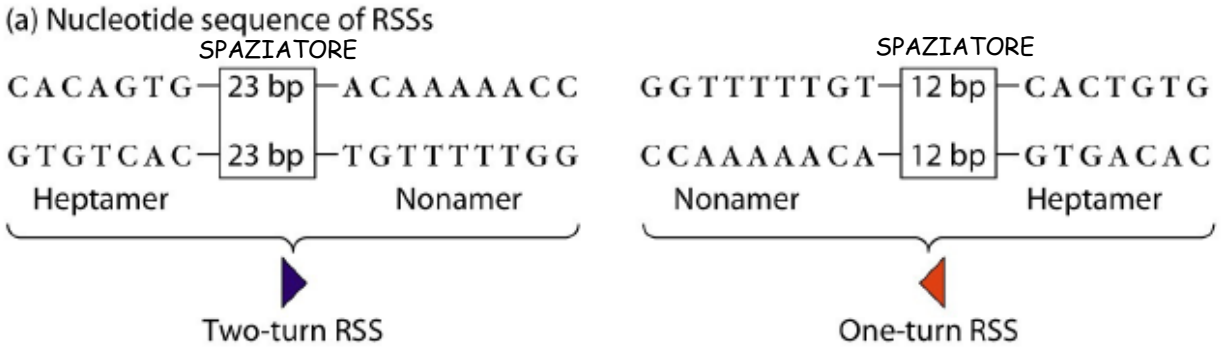
A valle vi è l'unico esone codificante per la parte **costante (C)**

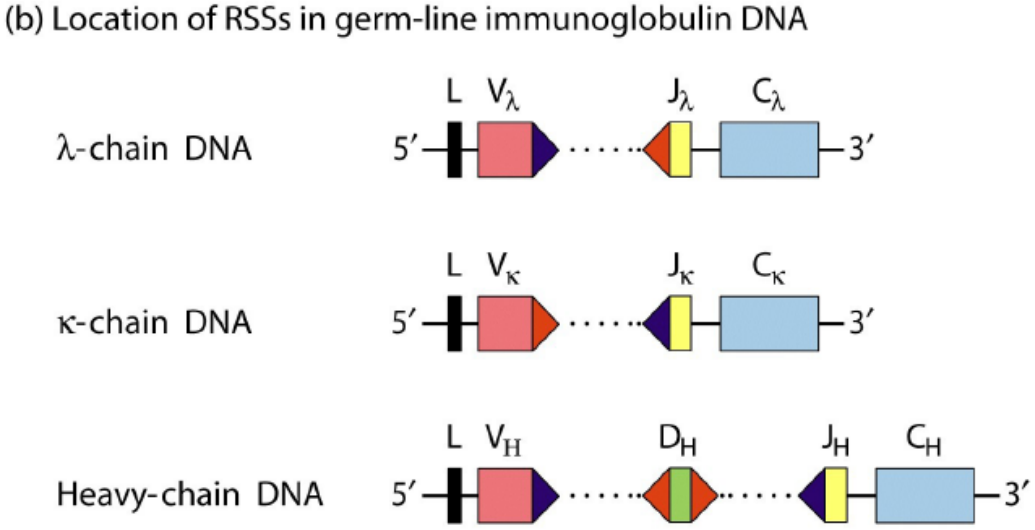


SEQUENZA SEGNALE RICOMBINATORIO (RSS)

Eptamero e nonamero: sequenze segnale conservate

Spaziatore: sequenza variabile





Regola 12/23: ricombinazione tra eptamero-12-nonamero ed eptamero-23-nonamero

V(D)J RICOMBINASI

Linfocita specifici:

RAG (ricombination activatin gene) **1** e **RAG2** : riconoscimento RSS adiacenti, attivitá endonucleasica

Ubiquitari:

HMG (high-mobility group): si associa con RAG1 e 2 per riconoscere RSS

Ku70-Ku80 e DNA-PK (DNA-dipendente protein kinasi) : stabilizzano chromosomal looping

ARTEMIS: apertura hairpin

TdT (terminal deossinucleotidil transferasi): rimozione ed aggiunta nucleotidi (diversità giunzionale)

DNA ligasi IV: unione hairpins

Sinapsi

Taglio

Attivitá endonucleasica RAG

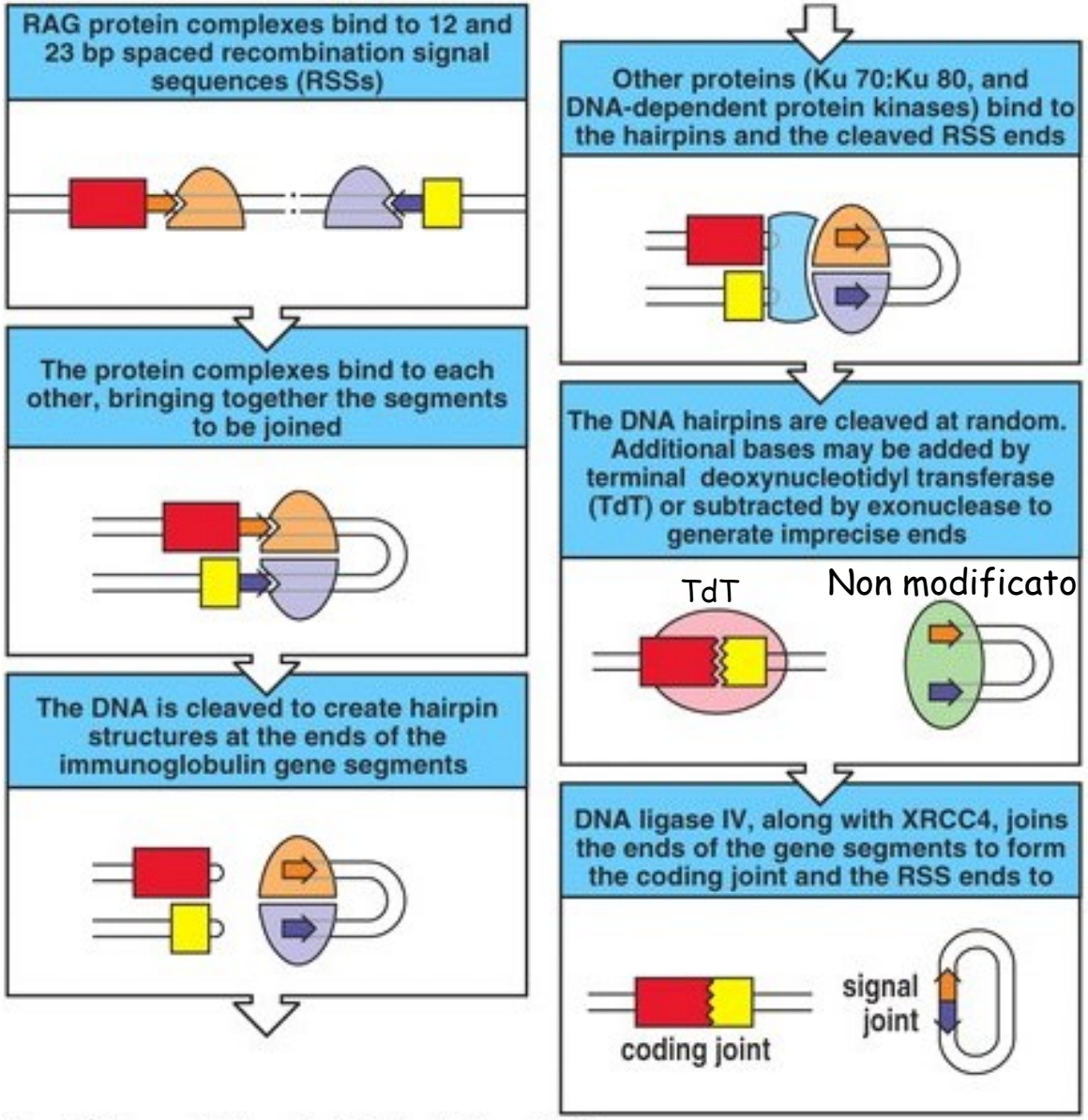
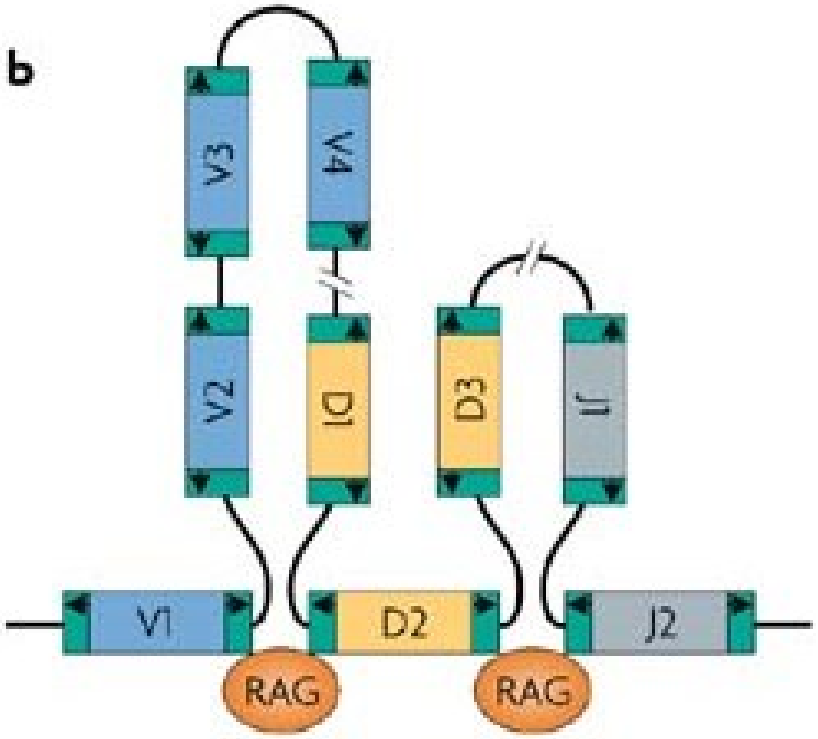


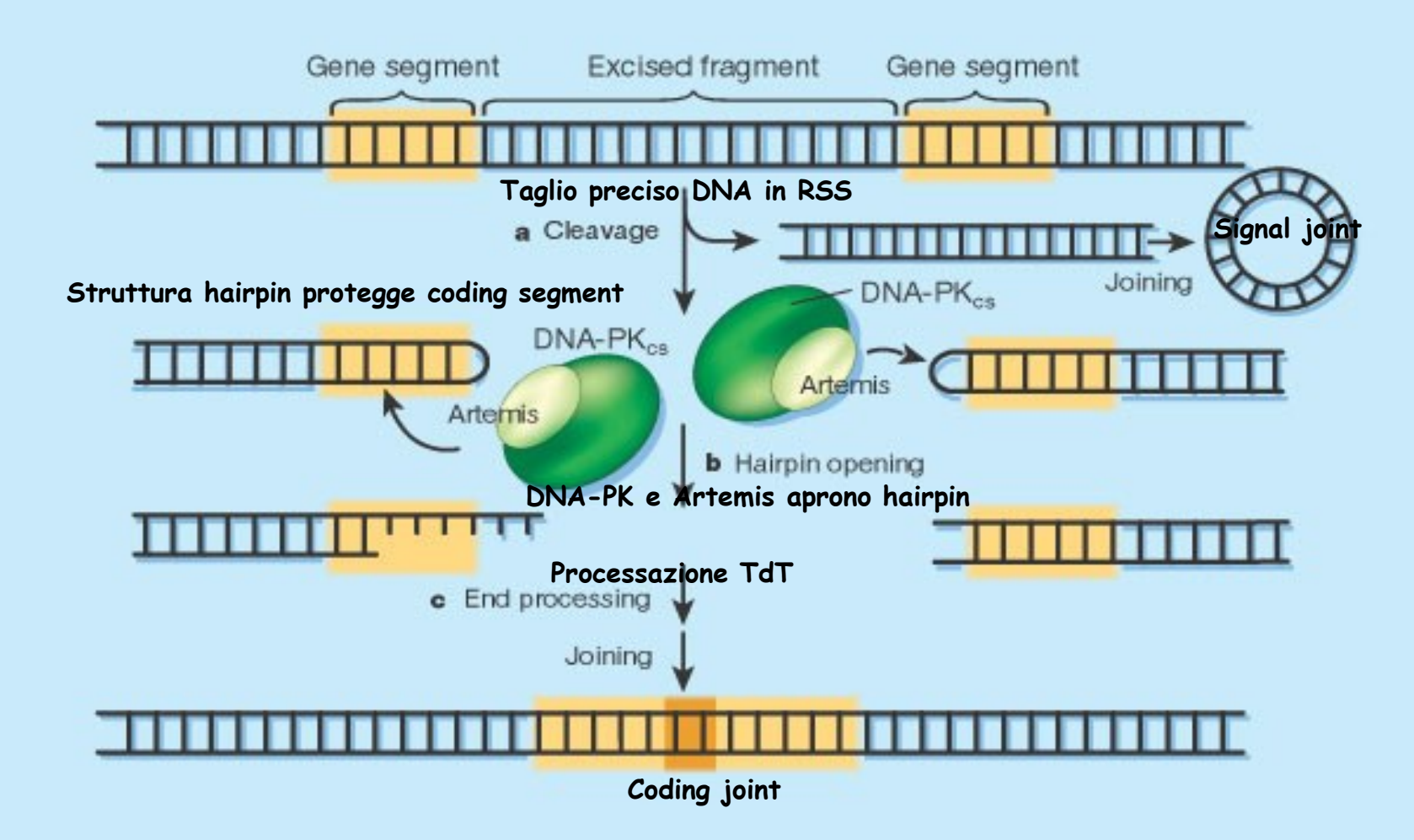
Figure 4-7 Immunobiology, 6/e. (© Garland Science 2005)

Processazione

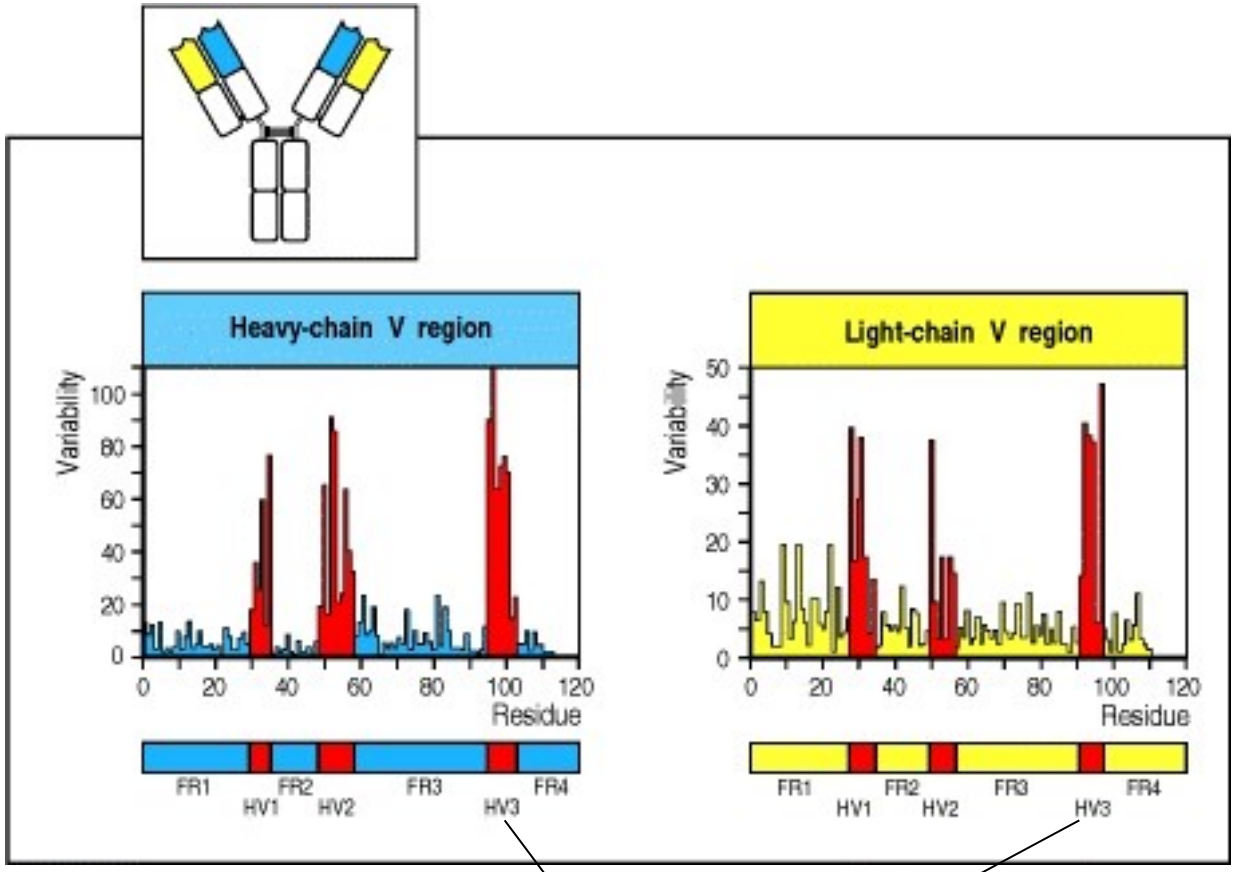
Unione


b
V3
V4
V2
D1
D3
J1
V1
D2
J2
RAG
RAG

DNA-repair machinery



Unione imprecisa coding joint: aumento variabilitá



Zona giunzione V-J

Ottenuto durante ricombinazione per aggiunta nucleotidi

CDR

RIARRANGIAMENTO REGIONE VARIABILE CATENA PESANTE

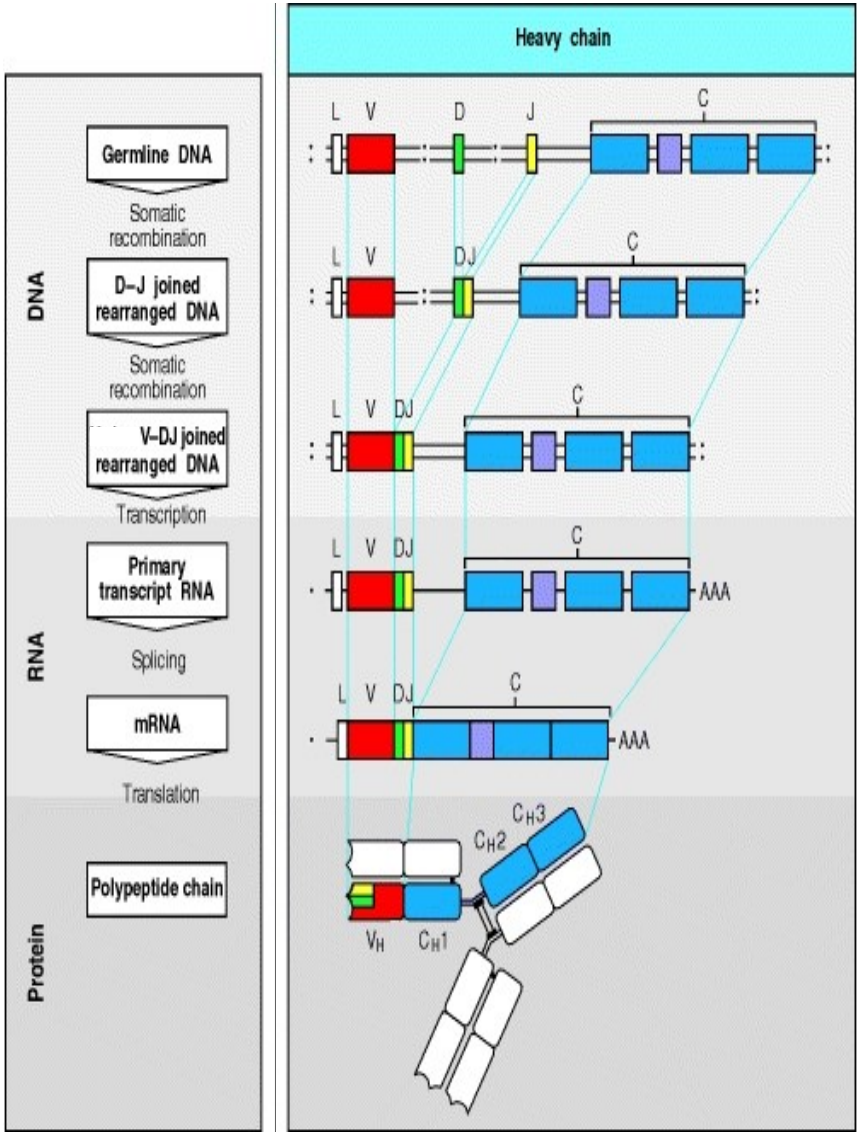
Dominio V catene pesanti: codificato da 3 segmenti separati di DNA

Primi 95–101 aminoacidi: **segmento V**

Successivi aminoacidi (96-108): **joining o segmento J d'unione**

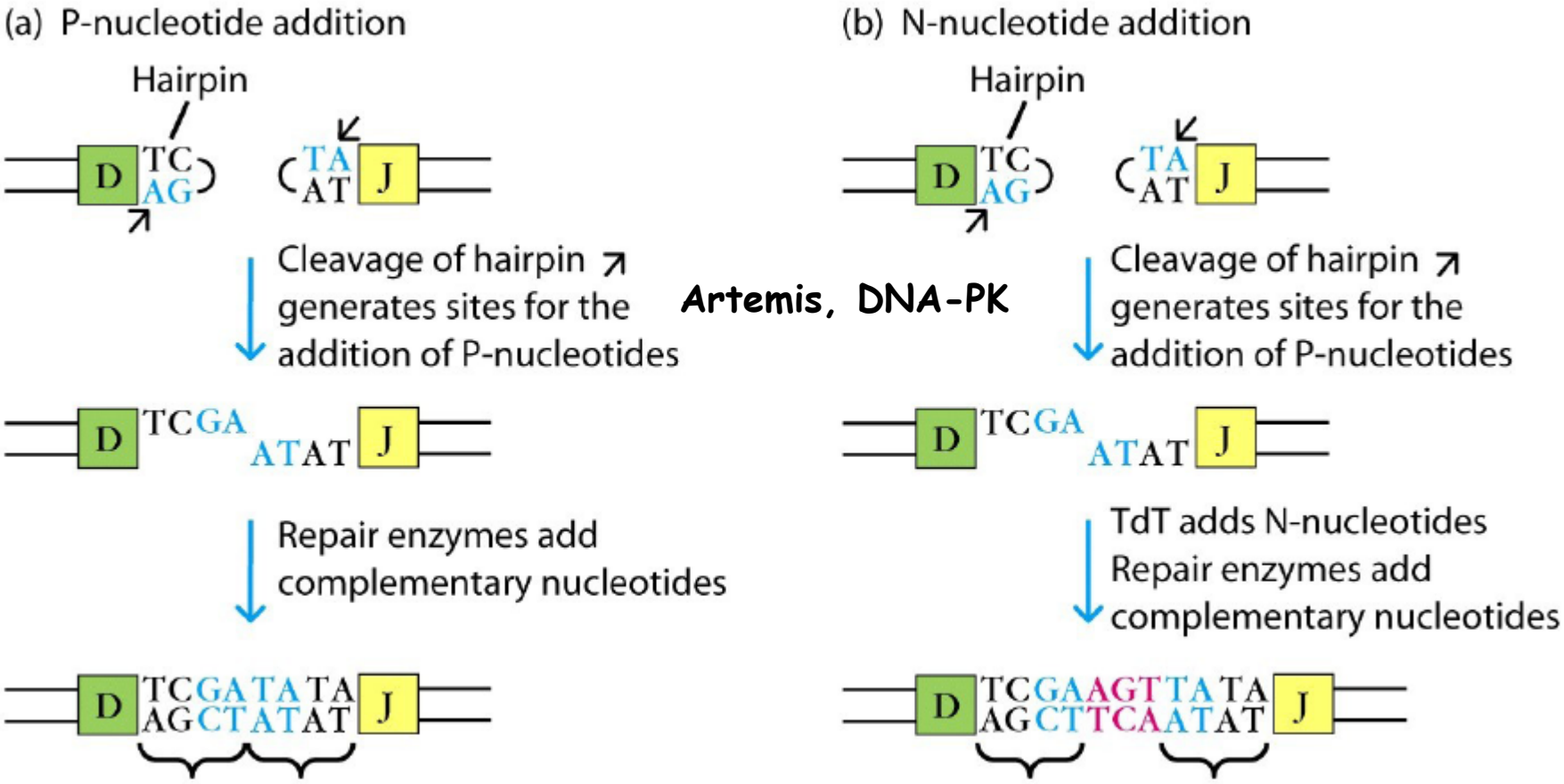
Segmento D di diversitá

A valle vi sono 3 esoni codificanti per i tre domini **costanti (C1-3)**



Catena leggera

Catena pesante

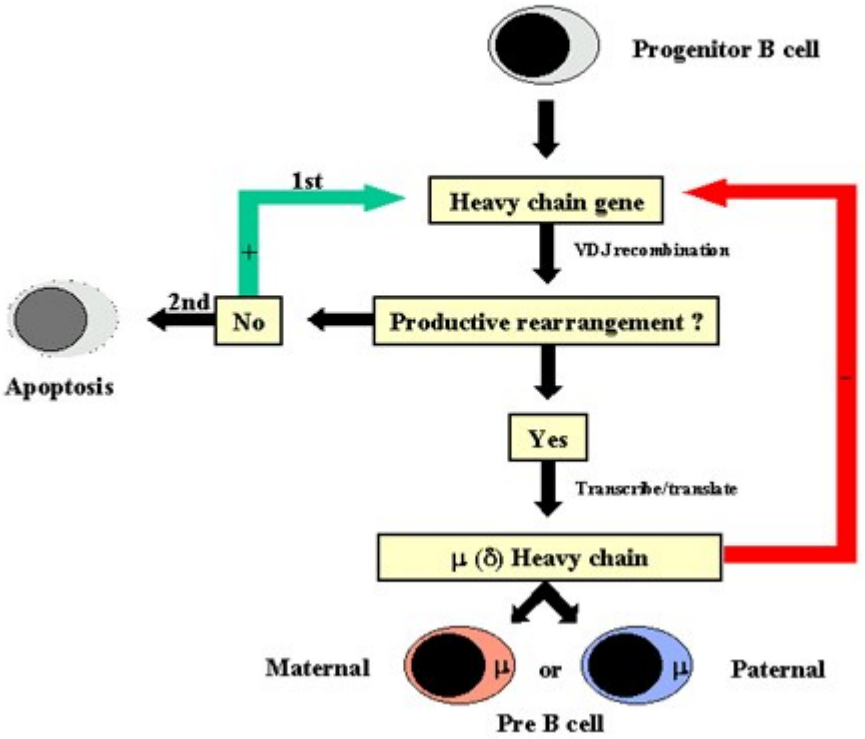


Aggiunta nucleotidi P (palindromici)

Aggiunta nucleotidi N

Nucleotidi possono essere tolti da esonucleasi

Order of Ig Gene Expression



SOPPRESSIONE RICOMBINAZIONE V CATENA PESANTE

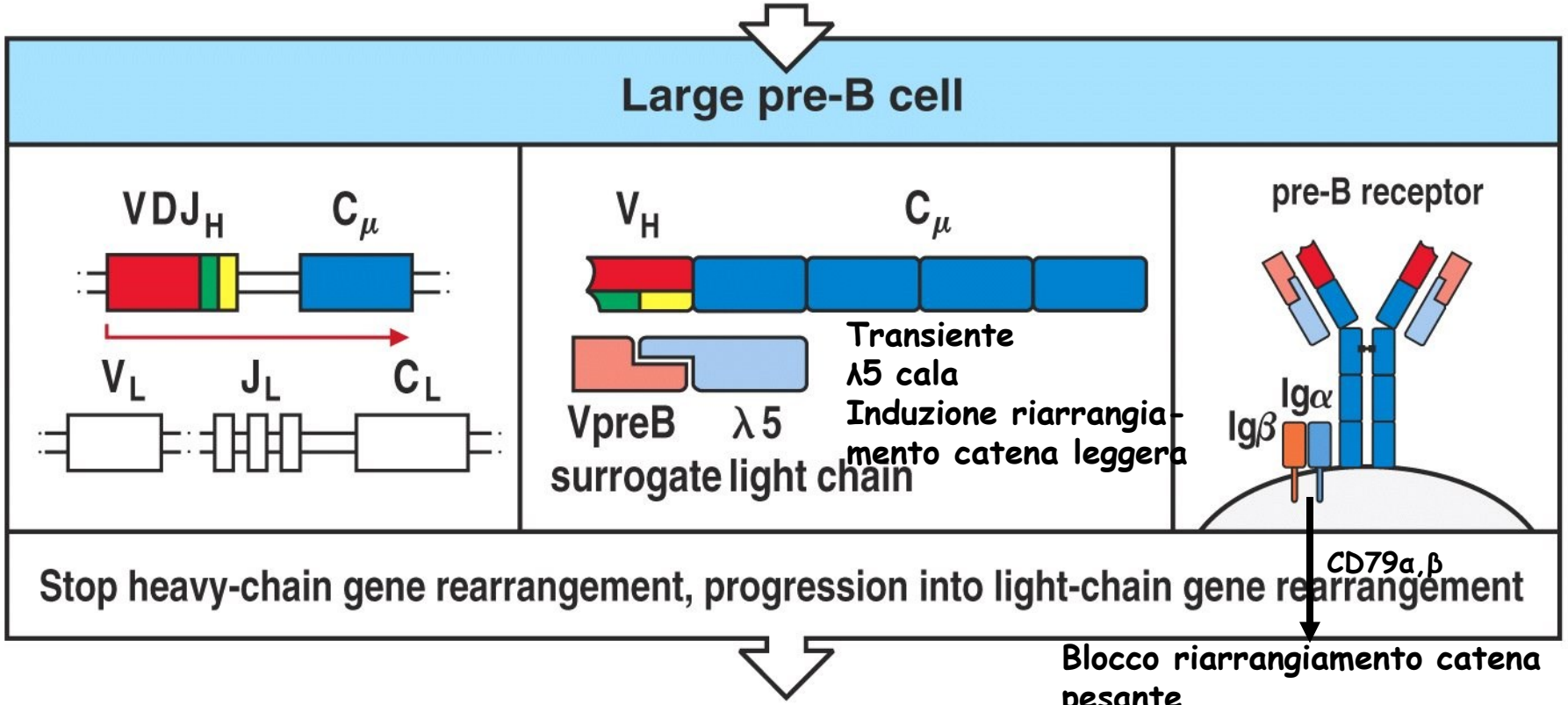
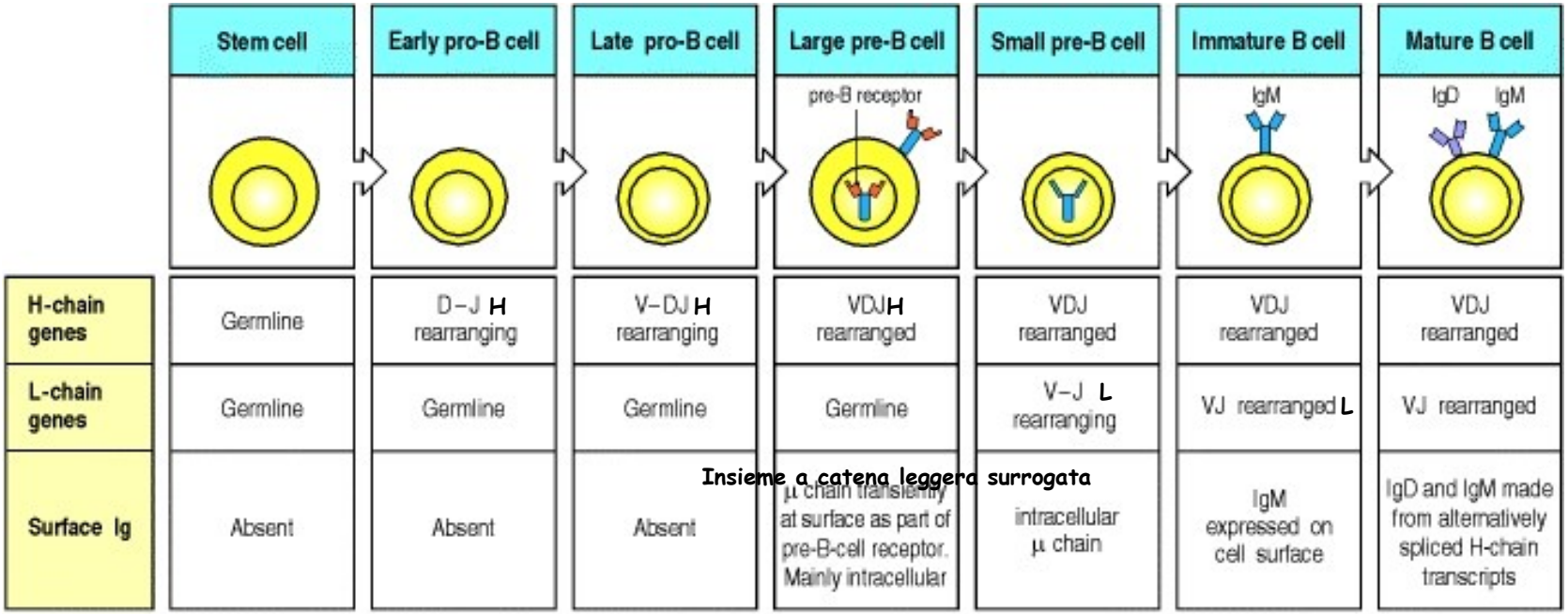


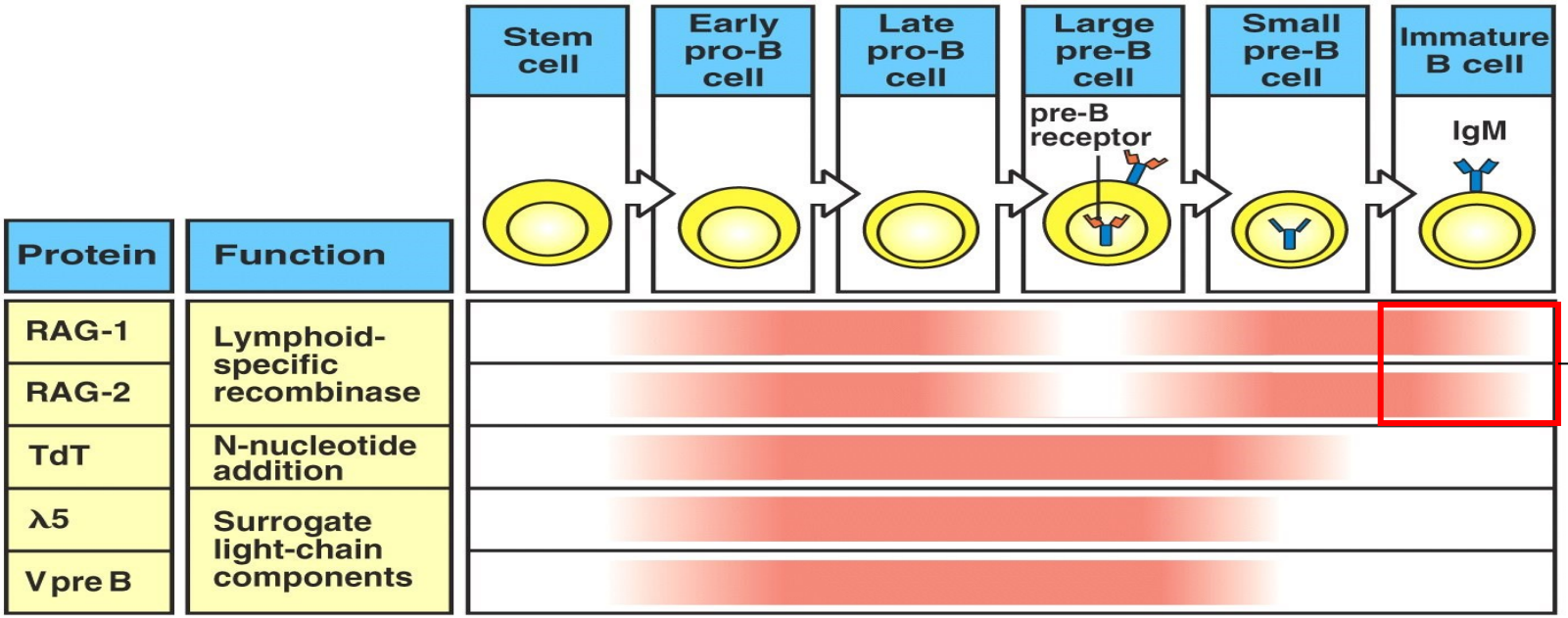
Figure 7-17 part 2 of 3 Immunobiology, 6/e. (© Garland Science 2005)

- ✓ Segnale catena pesante completa
- ✓ Soppressione espressione RAG2
- ✓ Inaccessibilitá regione V catena pesante
- ✓ Induzione ricombinazione catena κ

GLI STADI DI MATURAZIONE DEI LINFOCITI B SI DISINGUONO IN BASE ALL'ESPRESSIONE DELLE CATENE IMMUNOGLOBULINICHE



Insieme a catena leggera surrogata



Consentono possibile riarrangiamento catena leggera

Figure 7-19 part 1 of 2 Immunobiology, 6/e. (© Garland Science 2005)

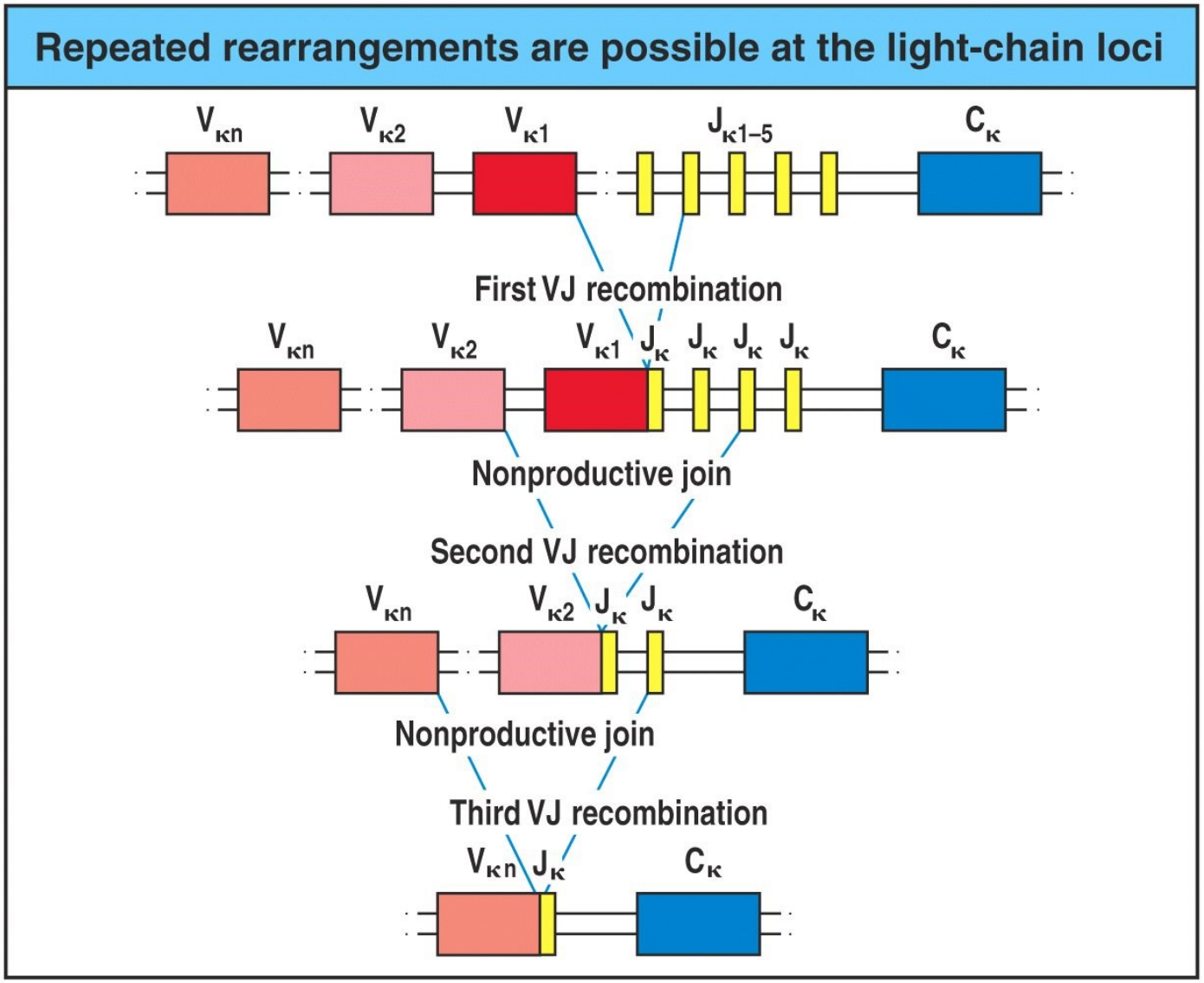
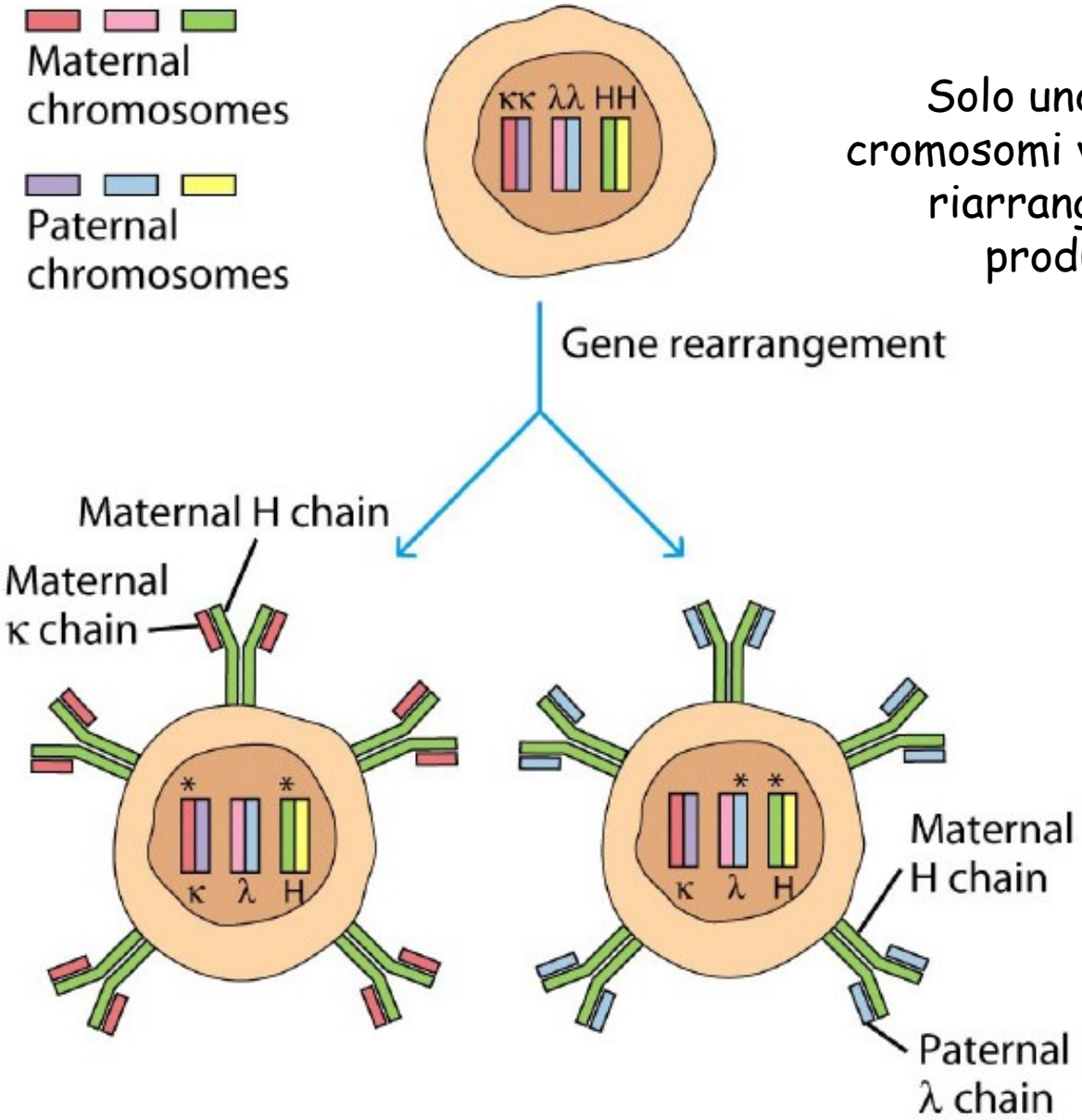


Figure 7-18 Immunobiology, 6/e. (© Garland Science 2005)

ESCLUSIONE ALLELICA



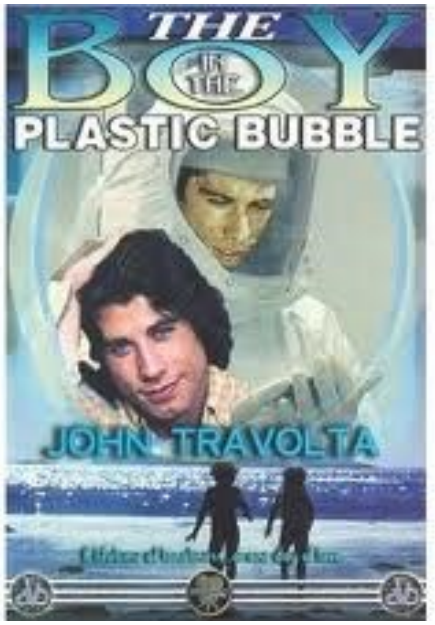
Solo uno dei due cromosomi va incontro a riarrangiamento produttivo

Mutazioni in RAG

Severe combined immunodeficiency (SCID)

Immunodeficienza ereditaria
Aumento rischio infezioni

David Phillip Vetter
(1971-1984)



1976

Linfocita B immaturo: esprime IgM di superficie

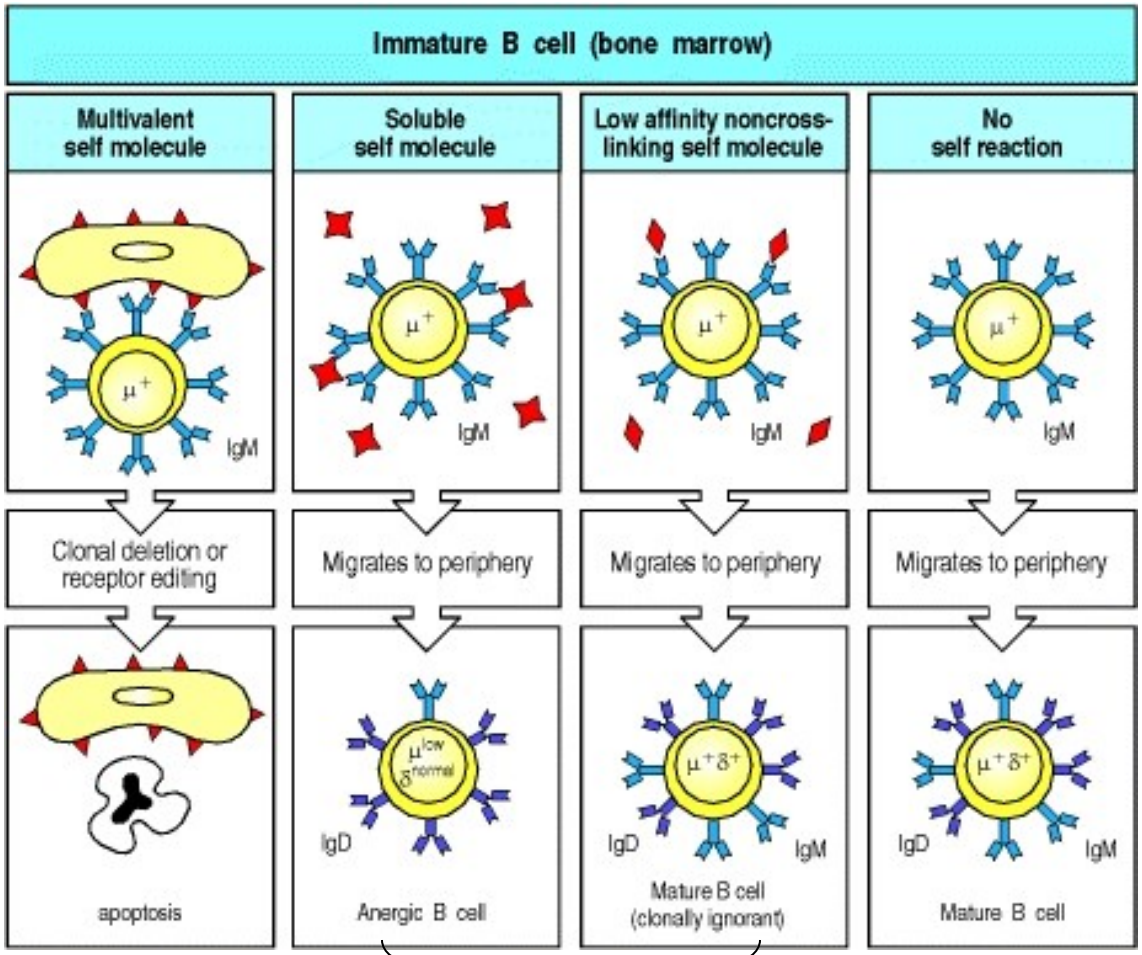
Selezione nel midollo……

SELEZIONE DEI LINFOCITI B A LIVELLO DEL MIDOLLO OSSEO

Linfociti B maturazione controllata da IgM di superficie (sIgM)

Ricombinazione IgL fino a che segmenti disponibili

(prima k poi λ)



Delezione clonale

Trasduzione del segnale bloccata

Neilinfonodi non entrano in zona follicolare

Cellule T tolleranti verso self

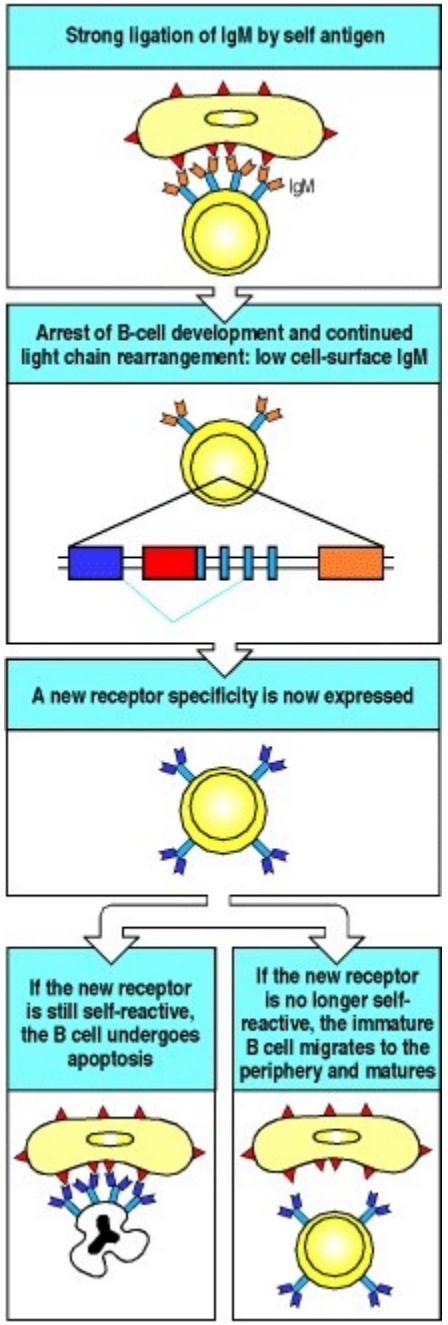
RECEPTOR EDITING

La cellule B reattiva al self può riarrangiare la catena leggera

Down-modulazione IgM

Continua sintesi RAG

Riarrangiamento catena leggera



Riarrangiamento continua fino a che sono disponibili segmenti V, J

Se finito locus κ inizia con locus λ

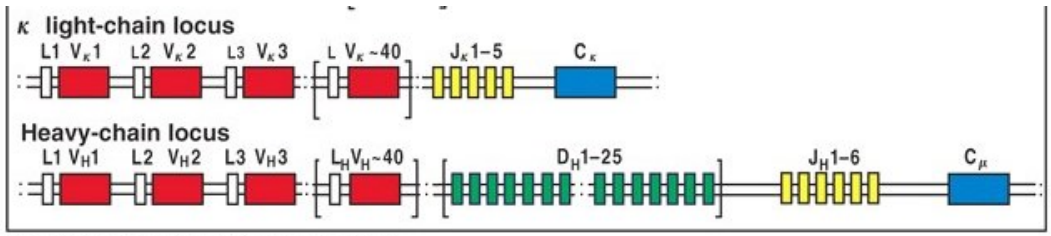
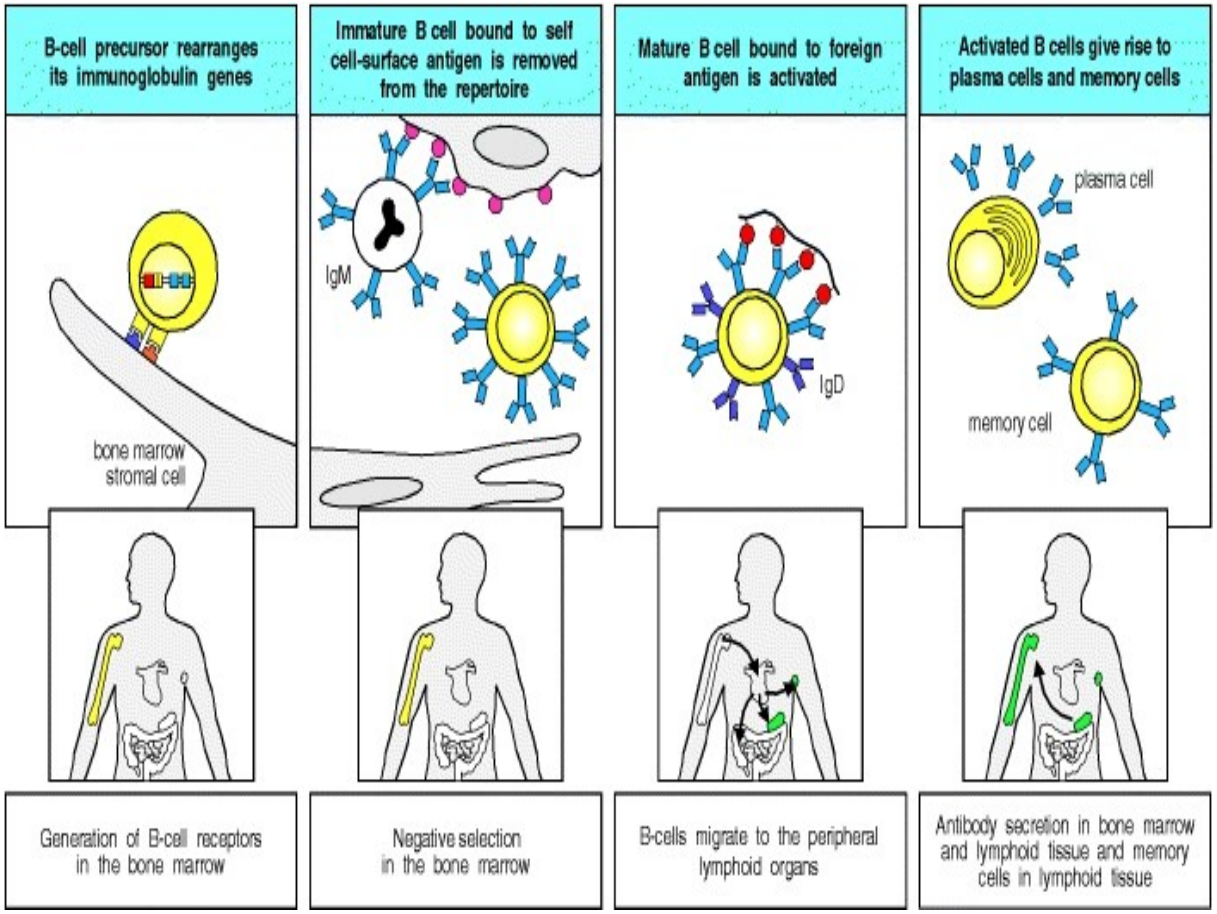


Figure 4-4 Immunobiology, 6/e. (© Garland Science 2005)

Linfocita B immaturo: esprime IgM di superficie (sIgM)

Se selezionato positivamente nel midollo:

Migra nella milza dove acquisisce l'espressione di IgD e completa la maturazione antigene-indipendente diventando un linfocita B maturo inattivo



SELEZIONE NEGATIVA

Linfociti B immaturi

Se sIgM lega peptidi self nel midollo osseo:

Tentativo di riarrangiamento catena leggera

Alta affinità : apoptosi

Bassa affinità : anergia

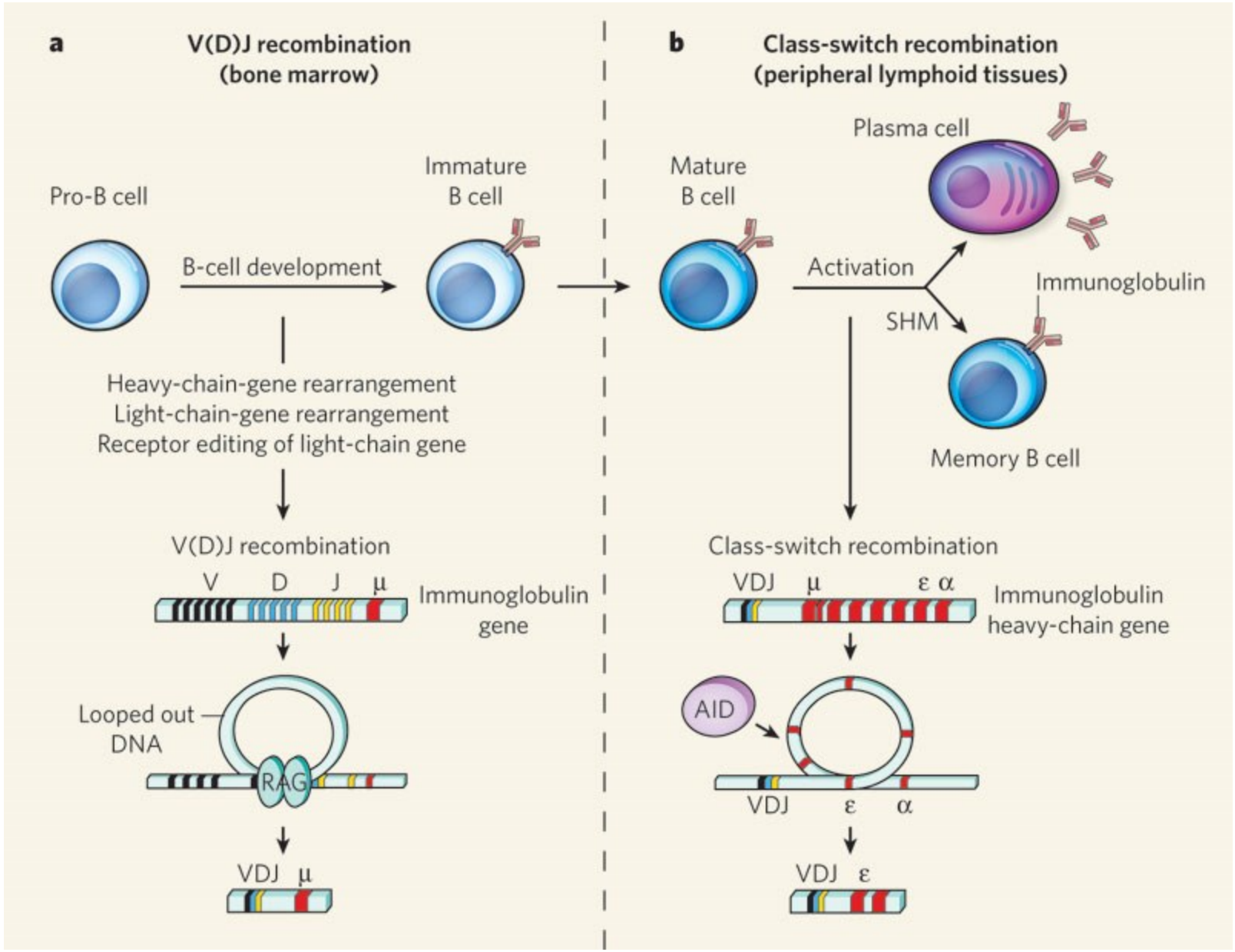
Linfociti B maturi

Se sIgM lega peptidi self in periferia:

Apoptosi immediata

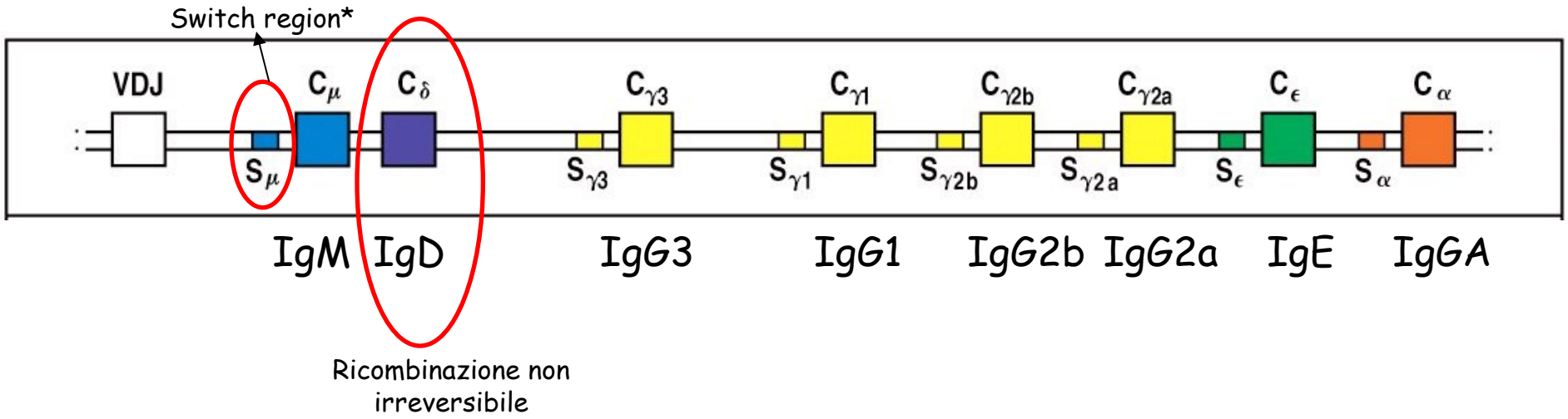
Legame BCR – Antigene

- ✓ Aggregazione BCR
- ✓ Attivazione linfocita B
- ✓ Aumento proliferazione
- ✓ Aumento B7-1 (CD86)/B7-2(CD80)
- ✓ Aumento recettori per citochine (IL-2, IL-4, BAFF)
- ✓ Aumento CCR7
- ✓ Migrazione ad aree T


a
V(D)J recombination
(bone marrow)
Pro-B cell
B-cell development
Immature
B cell
Heavy-chain-gene rearrangement
Light-chain-gene rearrangement
Receptor editing of light-chain gene
V(D)J recombination
V D J μ
Immunoglobulin
gene
Looped out
DNA
RAG
VDJ μ
b
Class-switch recombination
(peripheral lymphoid tissues)
Plasma cell
Mature
B cell
Activation
Immunoglobulin
SHM
Memory B cell
Class-switch recombination
VDJ μ ε α
Immunoglobulin
heavy-chain gene
AID
VDJ ε α
VDJ ε

DOMINI COSTANTI CATENA PESANTE

Cambio di classe (isotipico)

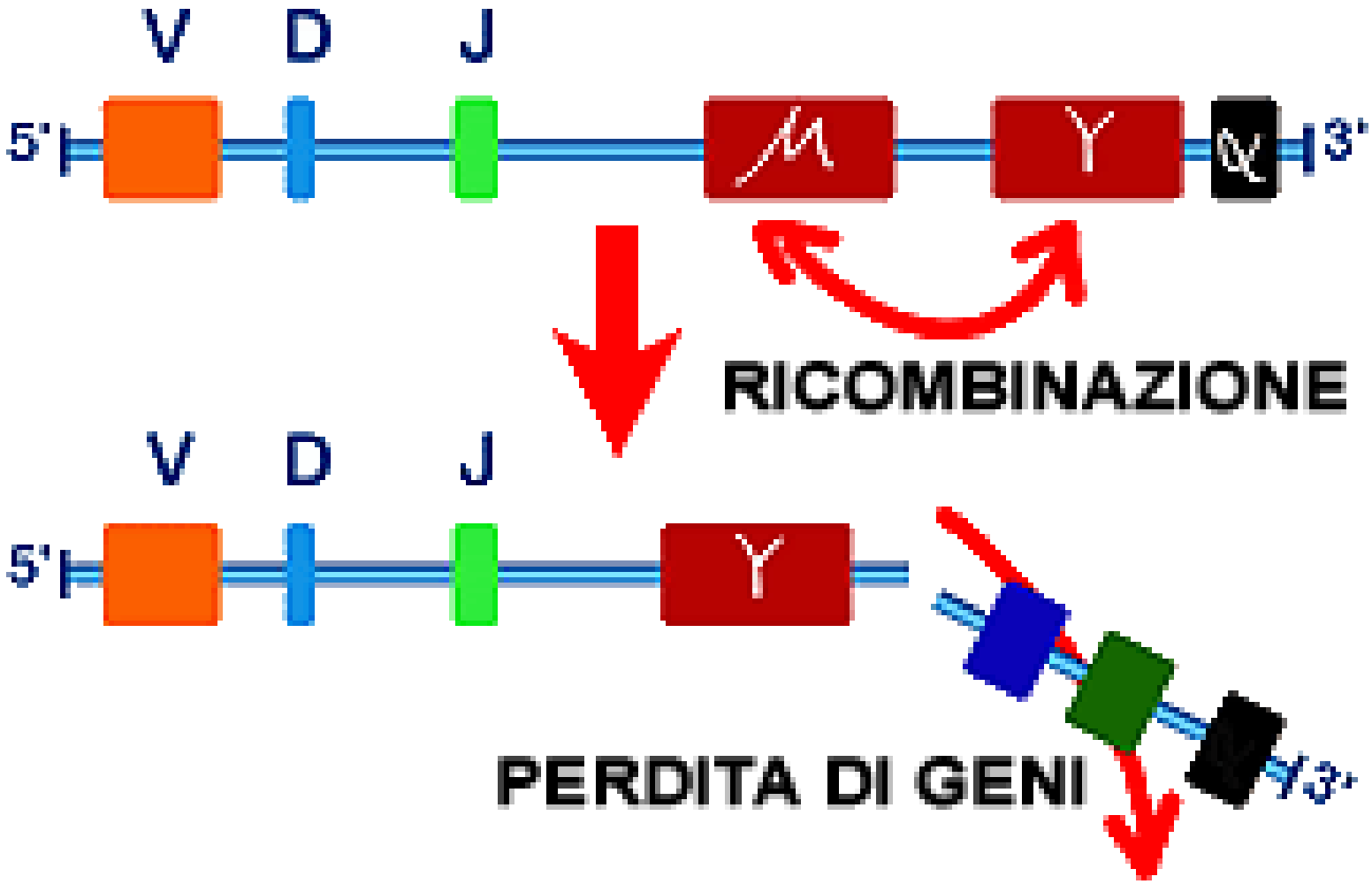


Linfocita B immaturo: esprime IgM di superficie

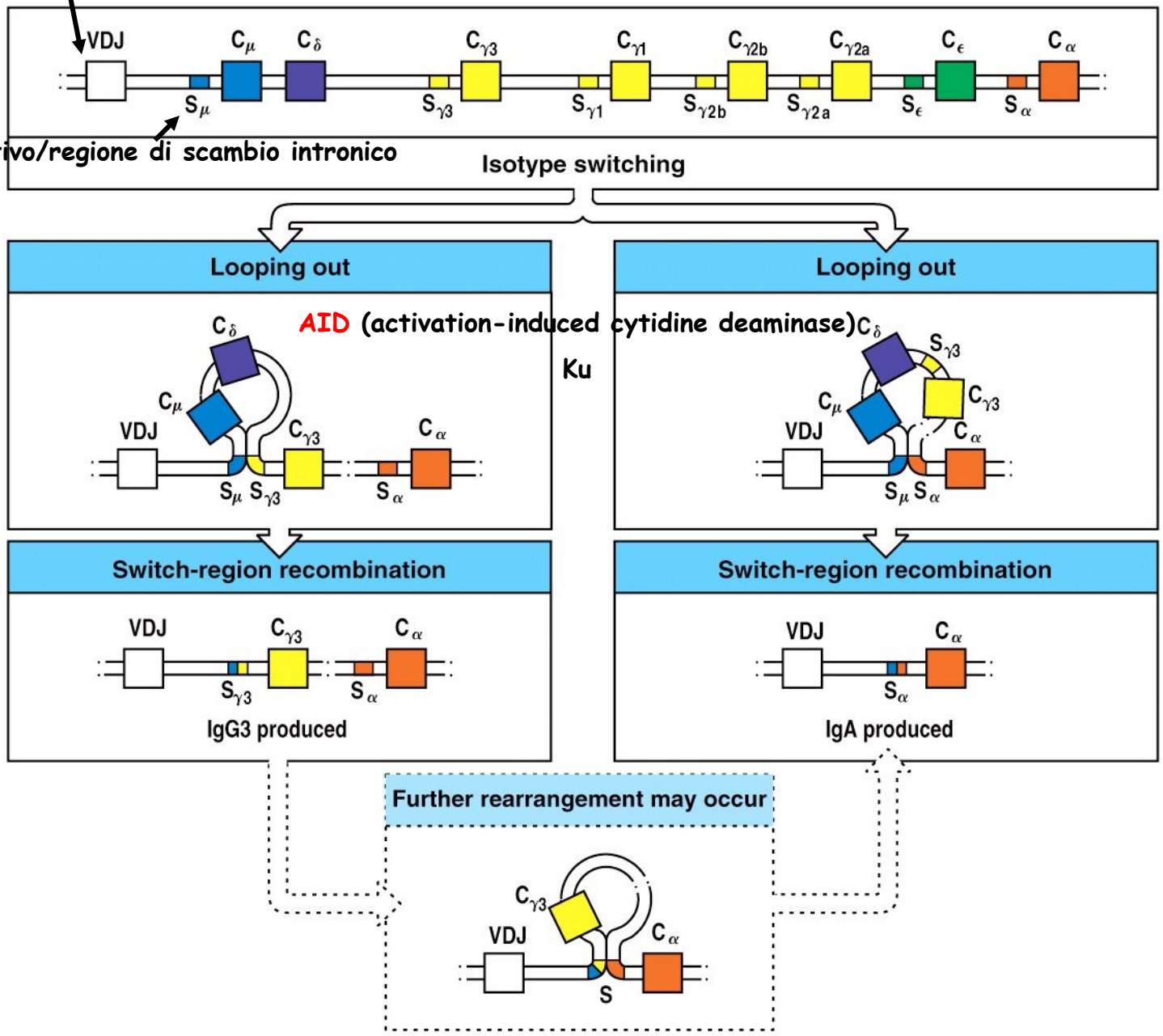
Se selezionato positivamente nel midollo:
Migra nella milza dove acquisisce l'espressione di IgD e completa la maturazione antigene-indipendente diventando un linfocita B maturo inattivo

*Ripetizioni *GAGCT*, *GGGGGT*

SCHEMA DELLO SCAMBIO DI ISOTIPO DELLE IMMUNOGLOBULINE

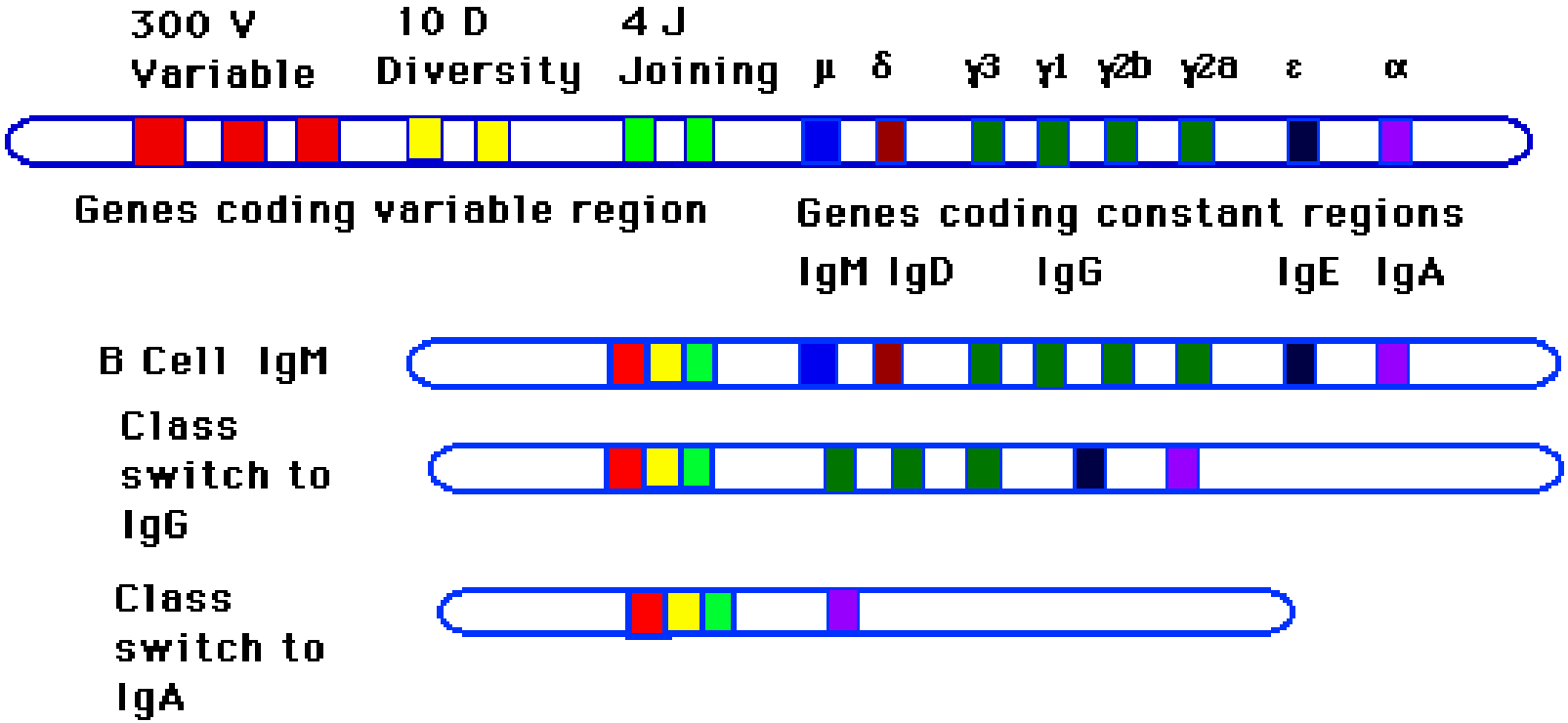


Ricombinazione irreversibile ma può associarsi a C diverse



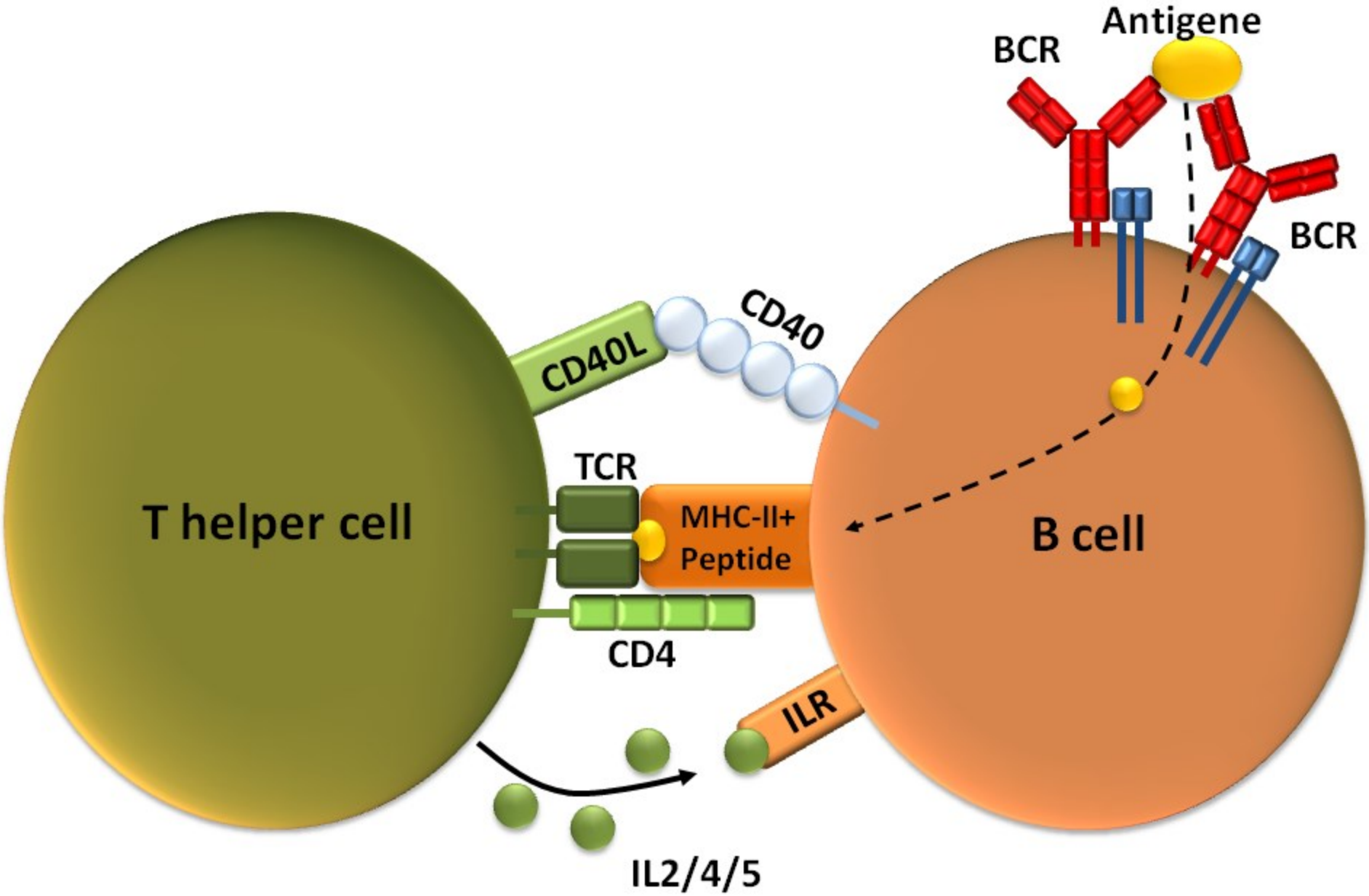
DNA ripetitivo/regione di scambio intronico

Figure 4-21 Immunobiology, 6/e. (© Garland Science 2005)



Scambio di classe

Citochine (IL-4 - IgE; IFN-gamma – IgG)
Legame CD40/CD40L (Linfocita T)


Antigene
BCR
BCR
CD40
CD40L
TCR
MHC-II+
Peptide
T helper cell
B cell
CD4
ILR
IL2/4/5

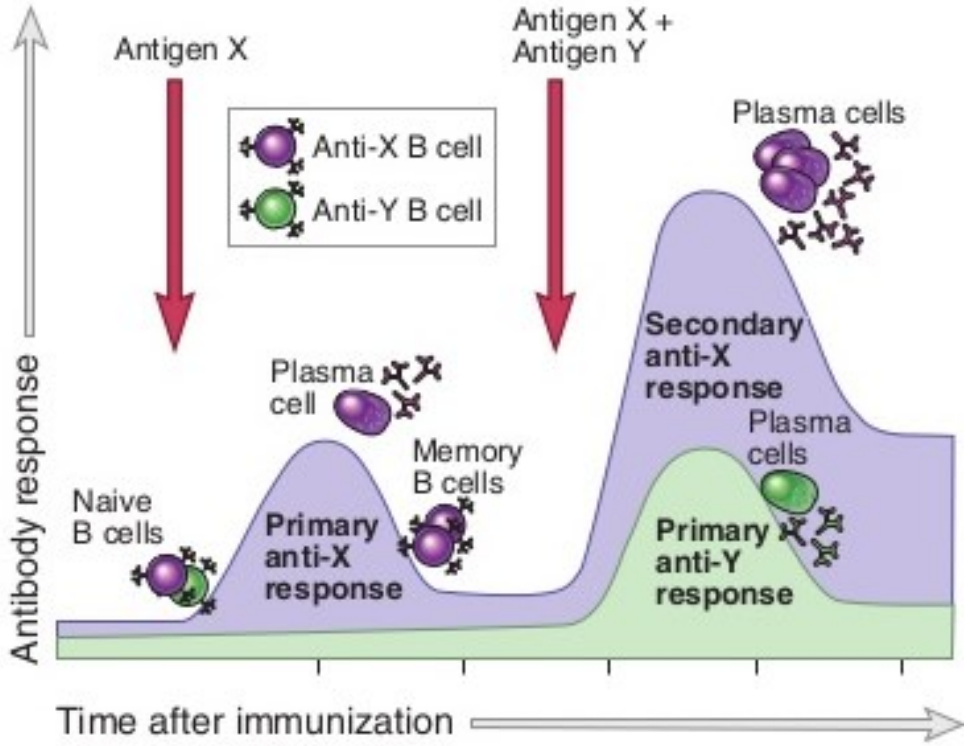
SCAMBIO ISOTIPICO

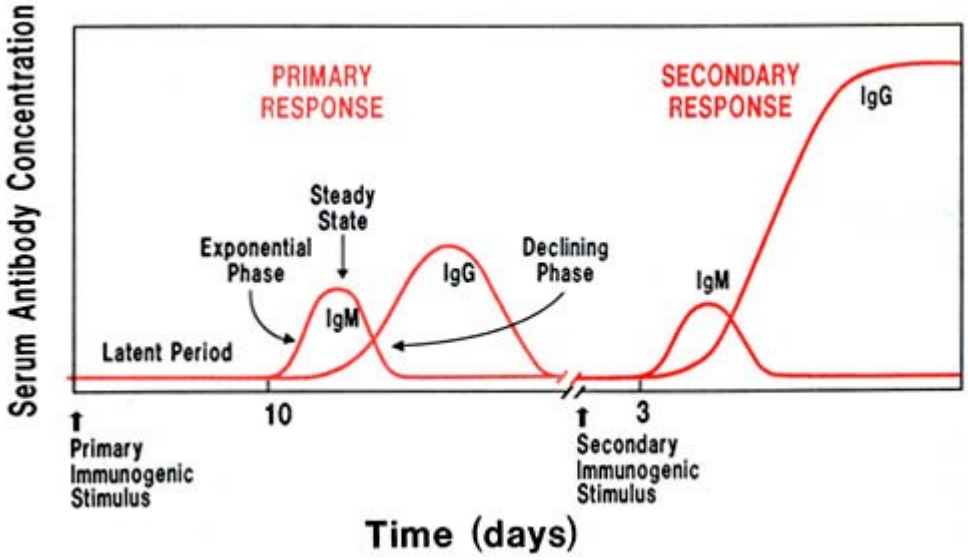
SWITCH DI CLASSE

- Avviene in cellule B attivate stimolate dall'antigene

- Permette alla stessa regione V, stessa specificitá antigenica, di svolgere diverse funzioni effetrici

FIGURE 1–7 Primary and secondary immune responses. Antigens X and Y induce the production of different antibodies (a reflection of specificity). The secondary response to antigen X is more rapid and larger than the primary response (illustrating memory) and is different from the primary response to antigen Y (again reflecting specificity). Antibody levels decline with time after each immunization. The level of antibody produced is shown as arbitrary values and varies with the type of antigen exposure. Only B cells are shown, but the same features are seen with T cell responses to antigens. The time after immunization may be 1-3 weeks for a primary response and 2-7 days for a secondary response, but the kinetics vary depending on the antigen and nature of immunization.





CAMBIO DI ISOTIPO

Indispensabile presenza CD40*

Controllato da citochine prodotte da T helper

	Role of cytokines in regulating Ig isotype expression						
Cytokines	**IgM**	**IgG3**	**IgG1**	**IgG2b**	**IgG2a**	**IgE**	**IgA**
IL-4	Inhibits	Inhibits	Induces		Inhibits	Induces	
IL-5							Augments production
IFN-γ	Inhibits	Induces	Inhibits		Induces	Inhibits	
TGF-β	Inhibits	Inhibits		Induces			Induces

*Individui senza CD40L sviluppano Immunodeficienza da Iper IgM: livelli elevati di IgM, infezioni ricorrenti, diminuzione estrema o assenza nel siero di immunoglobuline (IgG e IgA)

Anticorpi anti-isotipo

- Quantificare Ig in patologie
- Diagnosi immunodeficienze

Ig di MEMBRANA e SOLUBILI

Regione costante ha due esoni

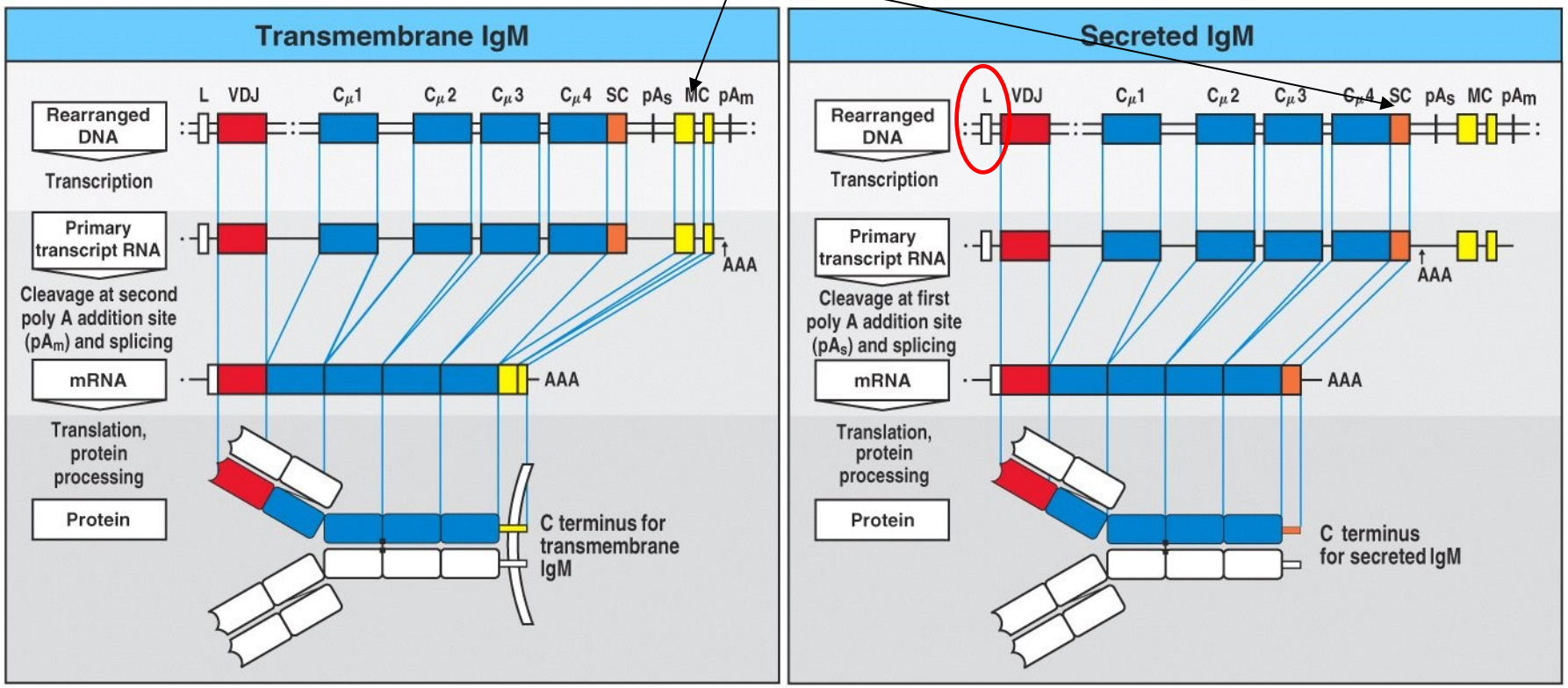


Figure 4-16 Immunobiology, 6/e. (© Garland Science 2005)

pA: sito di poliadenilazione

L: sequenza leader, direziona secrezione

MC: regione trans-membrana

SC: C-terminale secreta

Ig membrana: espansione clonale, maturazione

Ig solubili

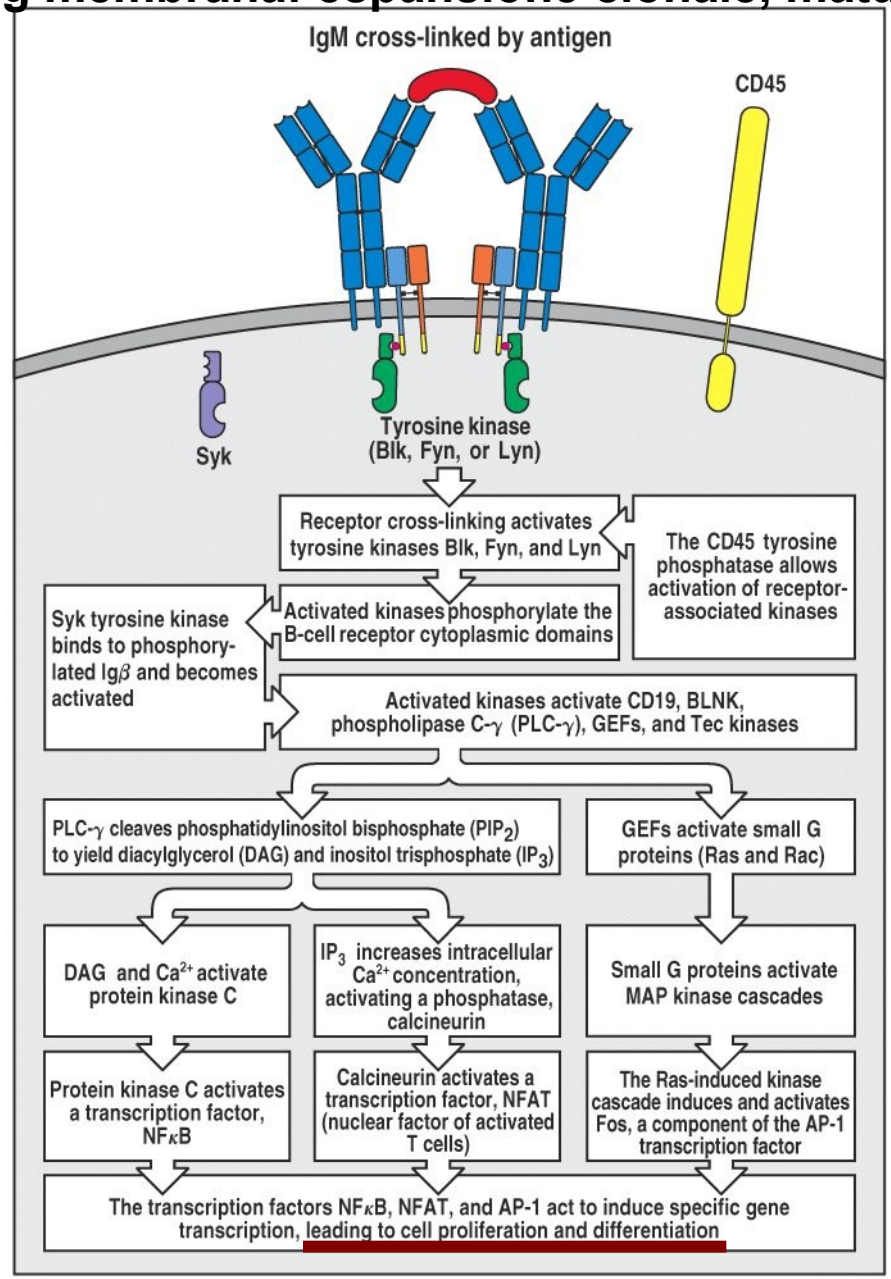


Figure 6-15 Immunobiology, 6/e. (© Garland Science 2005)

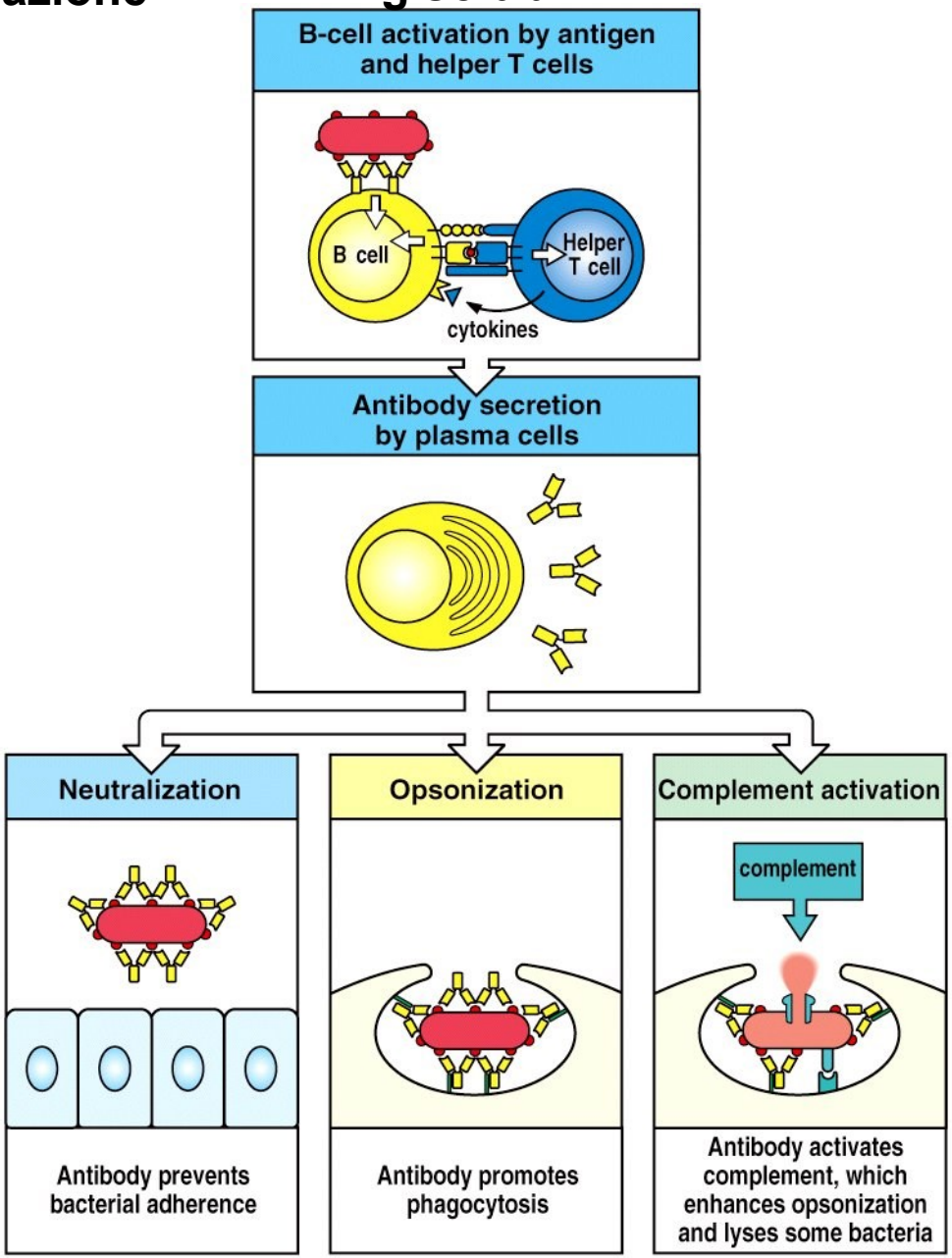
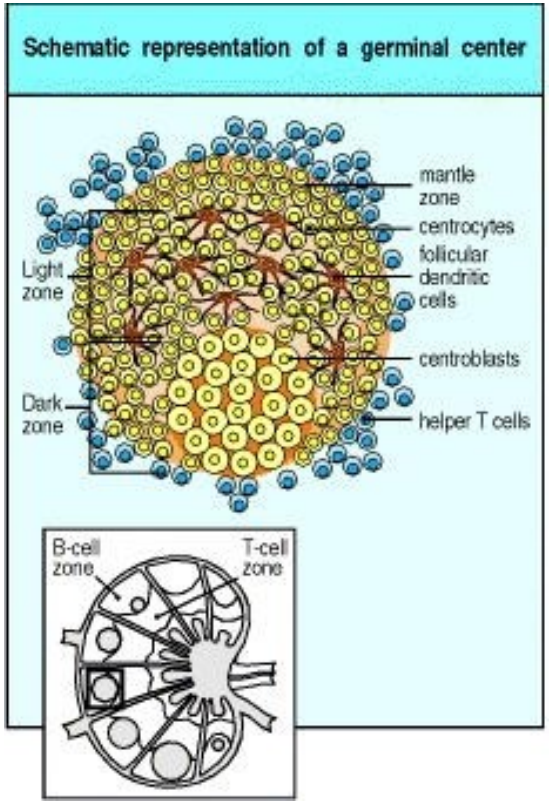


Figure 9-1 Immunobiology, 6/e. (© Garland Science 2005)

Alcuni linfociti B attivati migrano e formano un centro germinale



Nel centro germinale i linfociti B subiscono:

Cambio isotipico – regione C

Induzione secrezione Ig

Ipermutazione somatica – regione V

Maturazione d'affinità

V(D)J non puó subire ulteriori ricombinazioni ma puó subire ipermutazione somatica

IPERMUTAZIONE SOMATICA

V(D)J non puó subire ulteriori ricombinazioni ma puó subire ipermutazione somatica (linfonodi)

Giorno 0

Immunizzazione

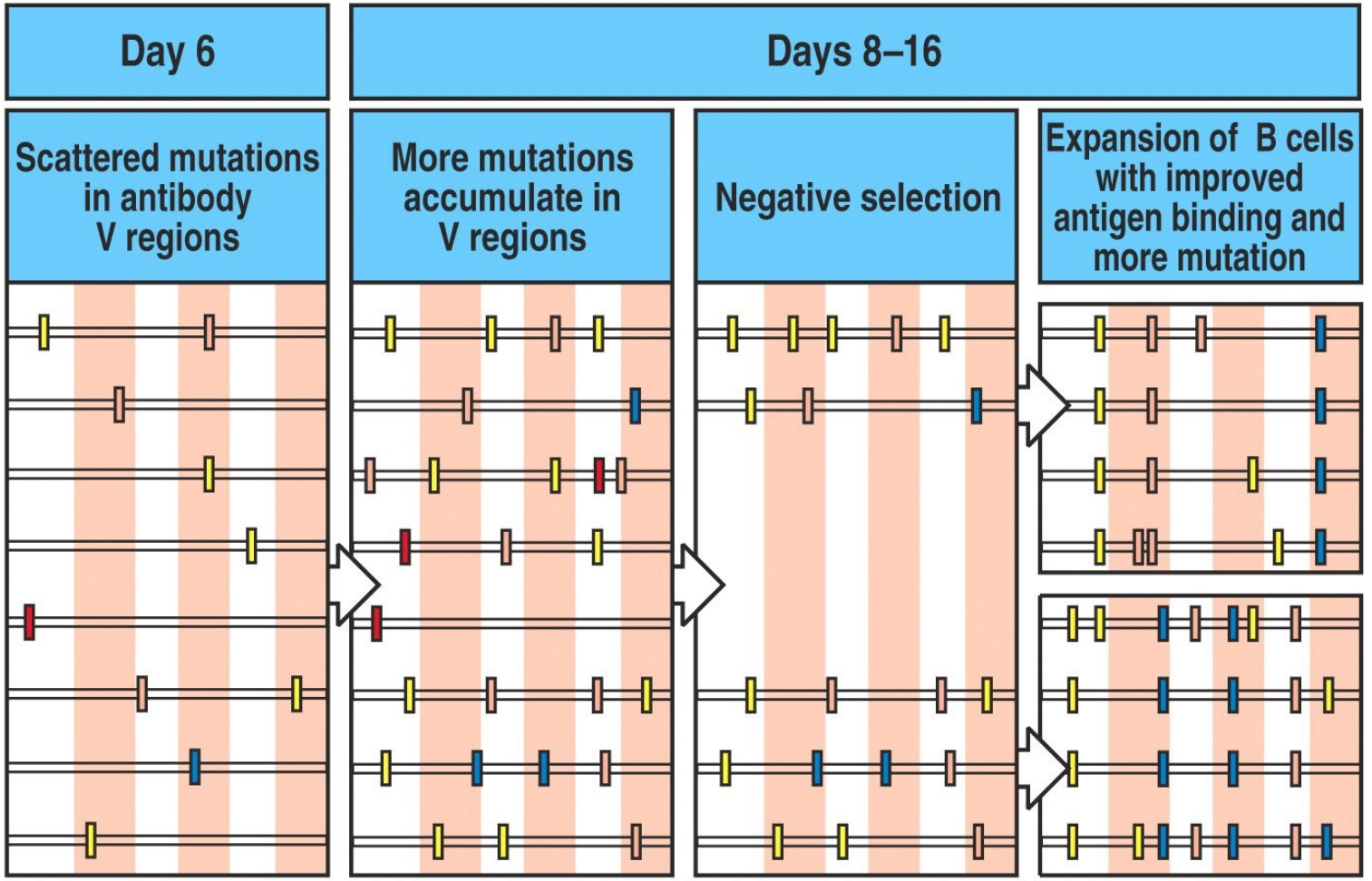


Figure 4-9 Immunobiology, 6/e. (© Garland Science 2005)

AID (activation-induced cytidine deaminase): deamina citosina

DNA riparato puó portare a cambio nucleotide

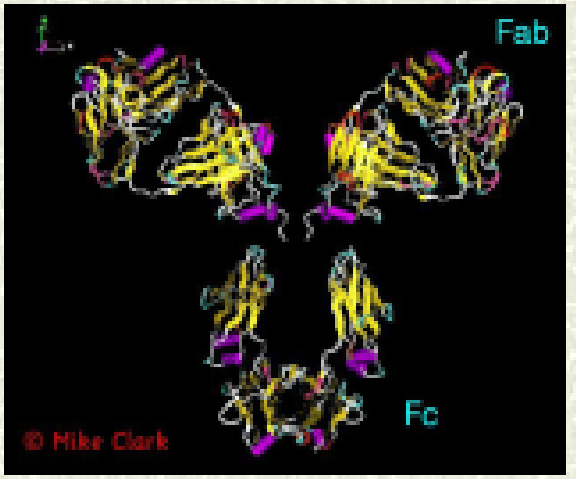
LE 2 FACCE DELLE IMMUNOGLOBULINE

RICONOSCIMENTO SPECIFICO DELL'ANTIGENE TARGET MEDIATO DAL DOMINIO VARIABILE AMINOTERMINALE DELLE DUE REGIONI Fab DELL'ANTICORPO.

↓

NEUTRALIZZAZIONE

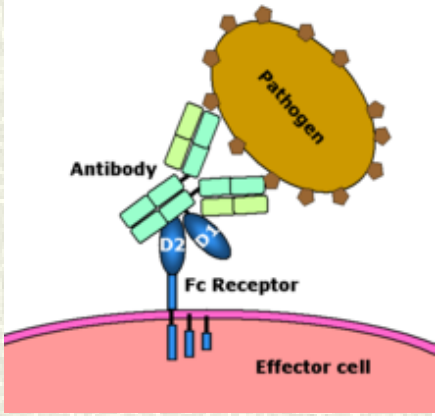
INTERAZIONE DEL DOMINIO COSTANTE DELLA REGIONE Fc DELL'ANTICORPO CON DIVERSE MOLECOLE EFFETTRICI.



↓

IMMUNITÀ INNATA ← **FcR** → IMMUNITÀ ADATTATIVA

FcR



I RECETTORI FcR SONO IN GRADO DI INTERAGIRE CON LA PORZIONE COSTANTE Fc DELLE IMMUNOGLOBULINE, NON RICONOSCONO DIRETTAMENTE L'ANTIGENE

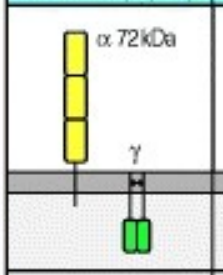
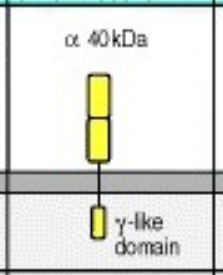
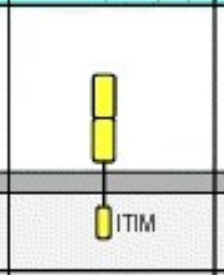
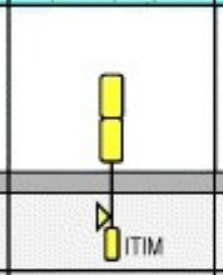
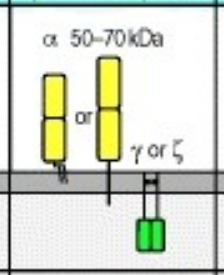
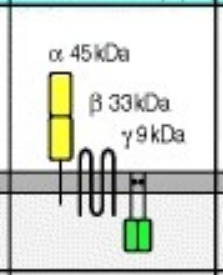
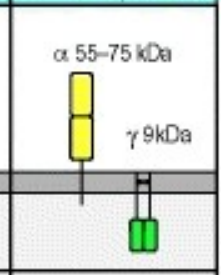
L'INTERAZIONE CON IL LIGANDO REGOLA LA RISPOSTA BIOLOGICA DELLA CELLULA SU CUI IL RECETTORE È ESPRESSO (ATTIVAZIONE/INIBIZIONE)

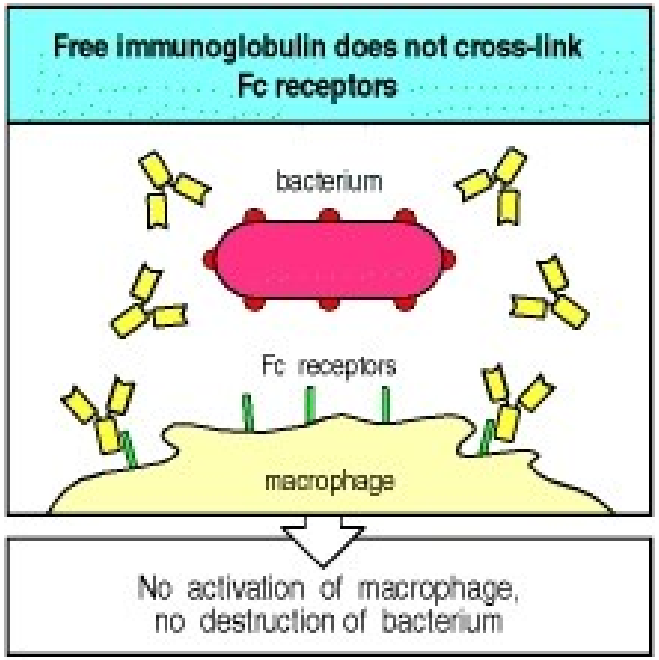
LA FUNZIONE EFFETTRICE DIPENDE DALLA CELLULA, DALLA SOTTOCLASSE DI ANTICORPO E DAL TIPO DI RECETTORE.

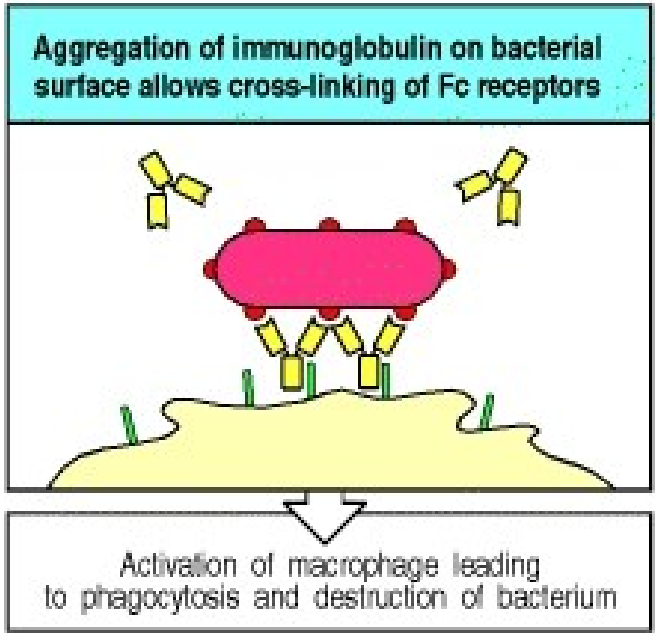
SONO PRESENTI RECETTORI SPECIFICI PER LE DIVERSE CLASSI DI IMMUNOGLOBULINE

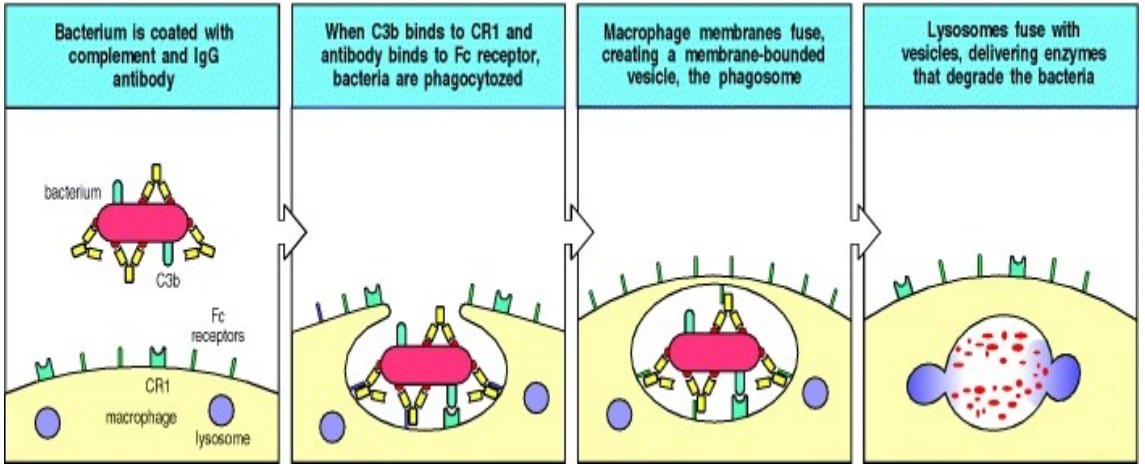
- -ALTA AFFINITA'/BASSA AFFINITA'
- -ESPRESSIONE COSTITUTIVA/INDOTTA
- -AFFINITA'SPECIFICA PER LE SOTTOCLASSI

QUESTI RECETTORI SONO MEMBRI DELLA SUPERFAMIGLIA DELLE IMMUNOGLOBULINE

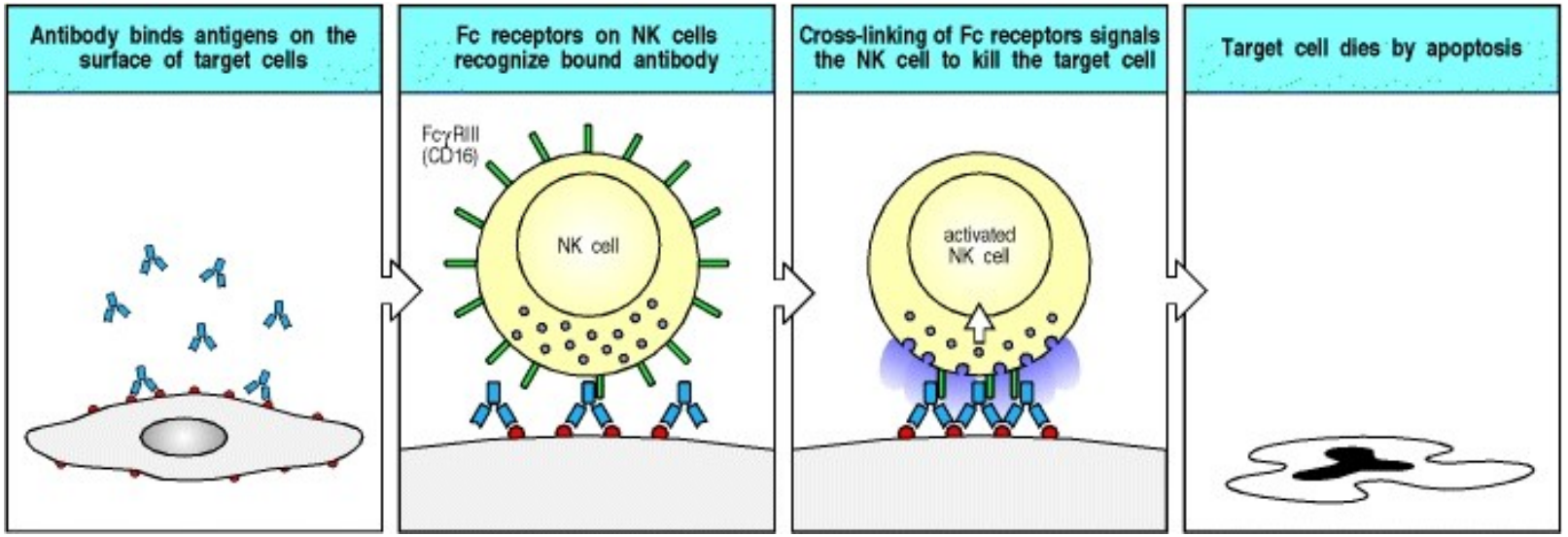
Receptor	FcγRI (CD64)	FcγRII-A (CD32)	FcγRII-B2 (CD32)	FcγRII-B1 (CD32)	FcγRIII (CD16)	FcεRI	FcαRI (CD89)
Structure							
Binding Order of affinity	IgG1 10^8 M^{-1} 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 2×10^6 M^{-1} 1) IgG1 2) IgG3=IgG2* 3) IgG4	IgG1 2×10^6 M^{-1} 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 2×10^6 M^{-1} 1) IgG1=IgG3 2) IgG4 3) IgG2	IgG1 5×10^5 M^{-1} IgG1=IgG3	IgE 10^{10} M^{-1}	IgA1, IgA2 10^7 M^{-1} IgA1=IgA2
Cell type	Macrophages Neutrophils† Eosinophils† Dendritic cells	Macrophages Neutrophils Eosinophils Platelets Langerhans' cells	Macrophages Neutrophils Eosinophils	B cells Mast cells	NK cells Eosinophils Macrophages Neutrophils Mast cells	Mast cells Eosinophils† Basophils	Macrophages Neutrophils Eosinophils‡
Effect of ligation	Uptake Stimulation Activation of respiratory burst Induction of killing	Uptake Granule release (eosinophils)	Uptake Inhibition of stimulation	No uptake Inhibition of stimulation	Induction of killing (NK cells)	Secretion of granules	Uptake Induction of killing

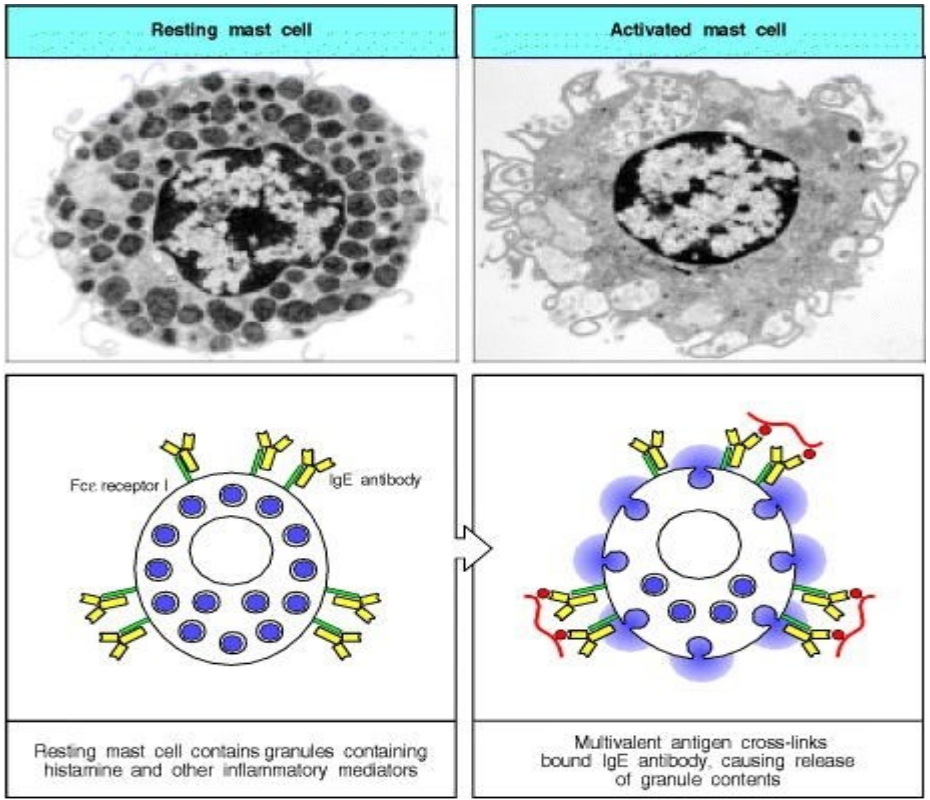

Free immunoglobulin does not cross-link Fc receptors
bacterium
Fc receptors
macrophage
No activation of macrophage, no destruction of bacterium


Aggregation of immunoglobulin on bacterial surface allows cross-linking of Fc receptors
Activation of macrophage leading to phagocytosis and destruction of bacterium

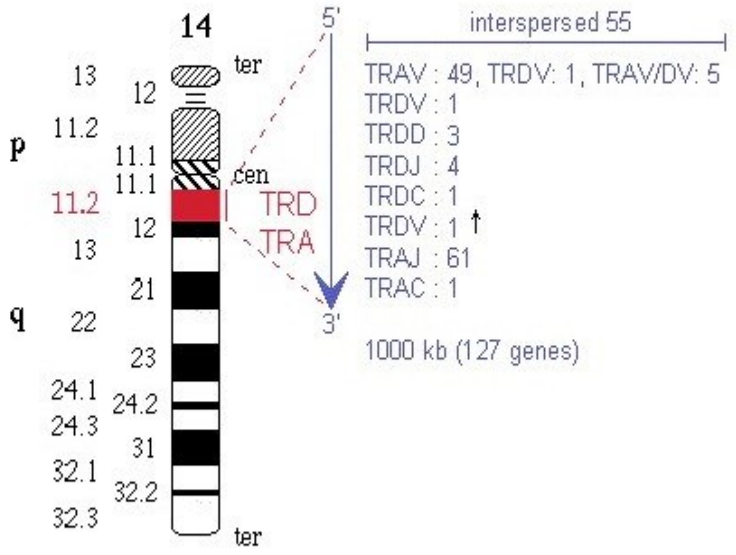

Bacterium is coated with complement and IgG antibody
When C3b binds to CR1 and antibody binds to Fc receptor, bacteria are phagocytozed
Macrophage membranes fuse, creating a membrane-bounded vesicle, the phagosome
Lysosomes fuse with vesicles, delivering enzymes that degrade the bacteria
bacterium
C3b
Fc receptors
CR1
macrophage
lysosome

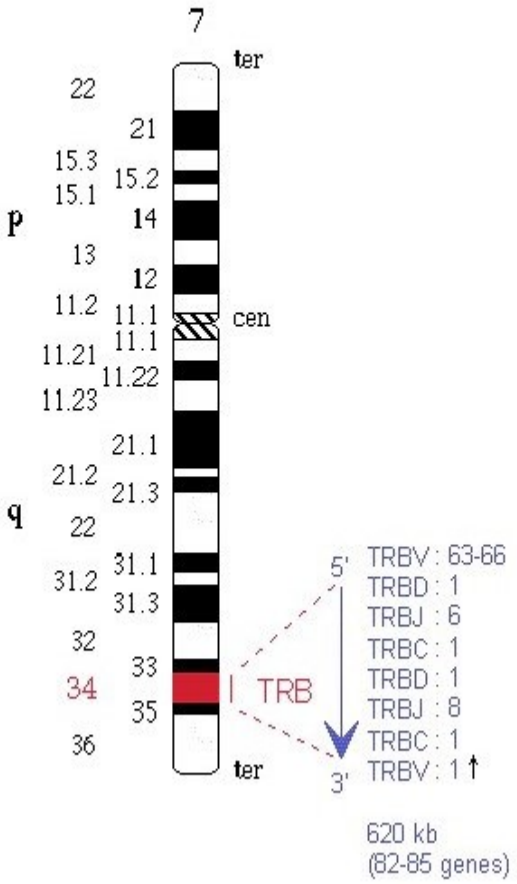
ADCC: Citotossicità cellulare mediata da anticorpi

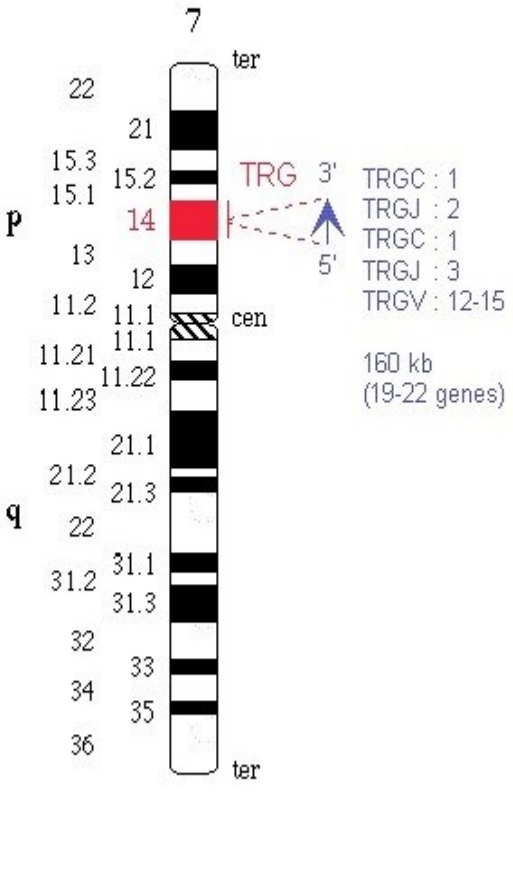




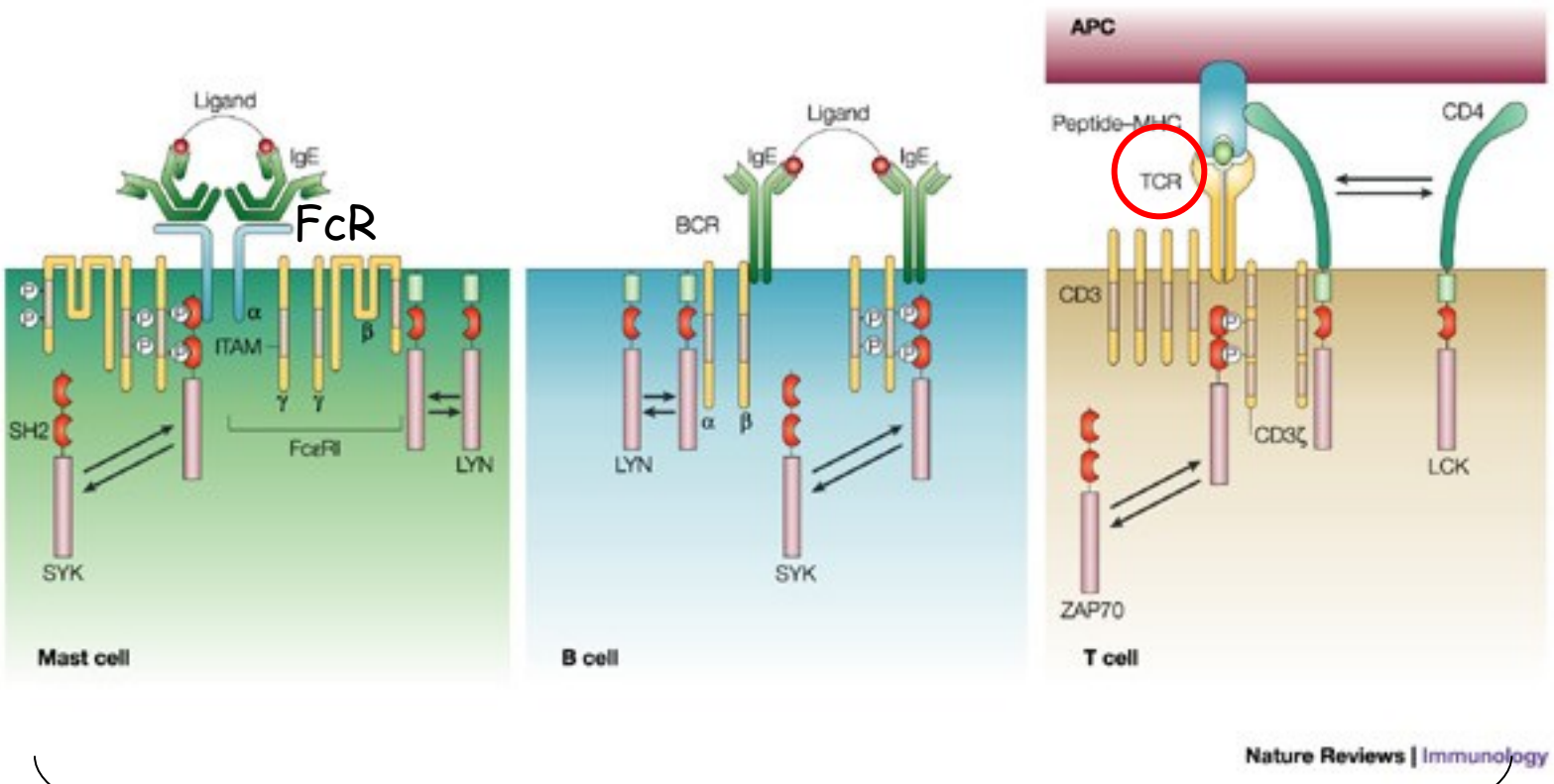
Chromosomal location of the TCR α/δ, β and γ chain loci in man







locus representations from the International Immunogenetics Information System (IMGT) server (http://www.imgt.org/)



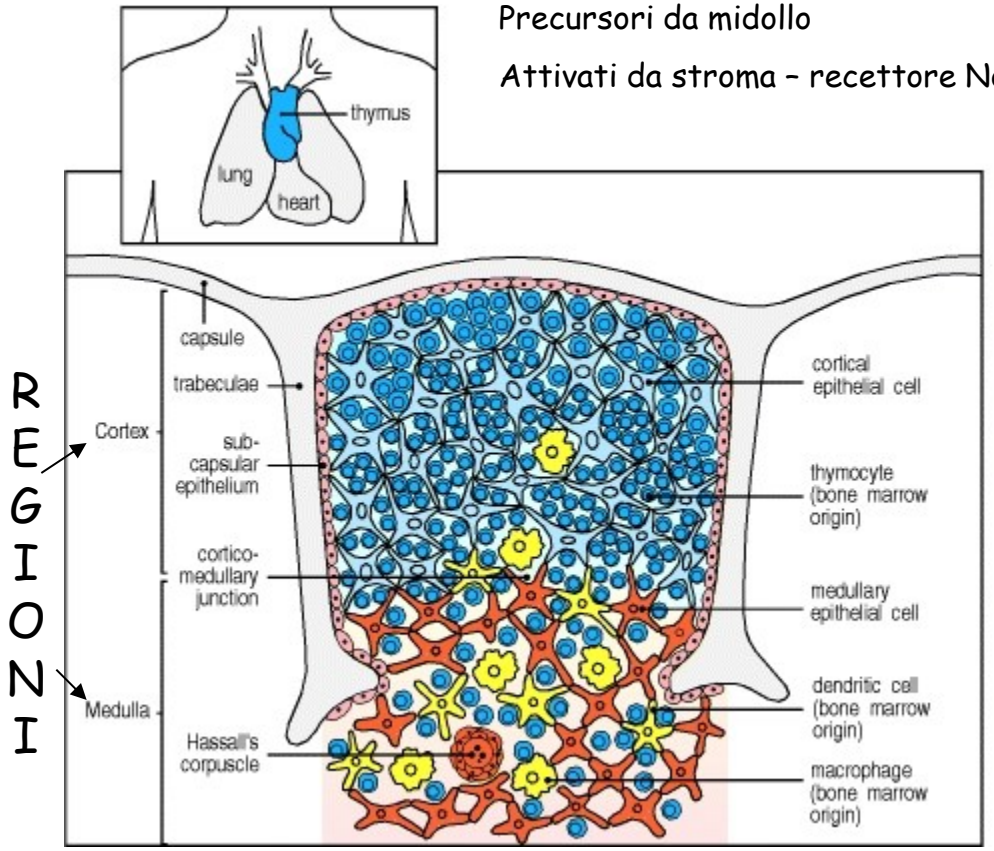
Attivazione risposta immunitaria

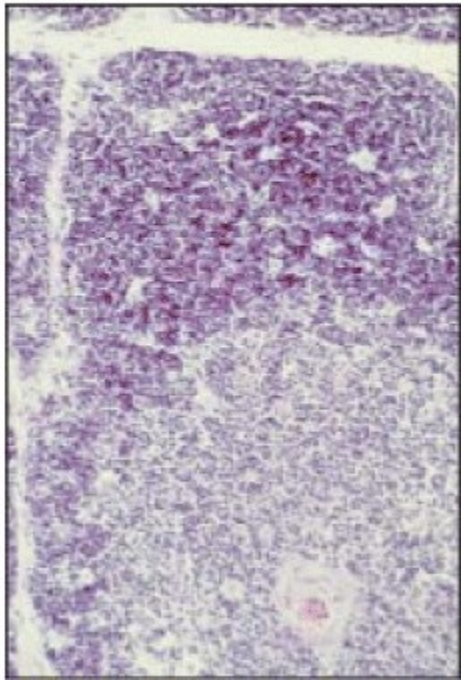
MATURAZIONE LINFOCITI T

(Thymus-dependent cells)

Precursori da midollo

Attivati da stroma – recettore Notch1: commissionati a cellule T





Immaturi

Selezione:

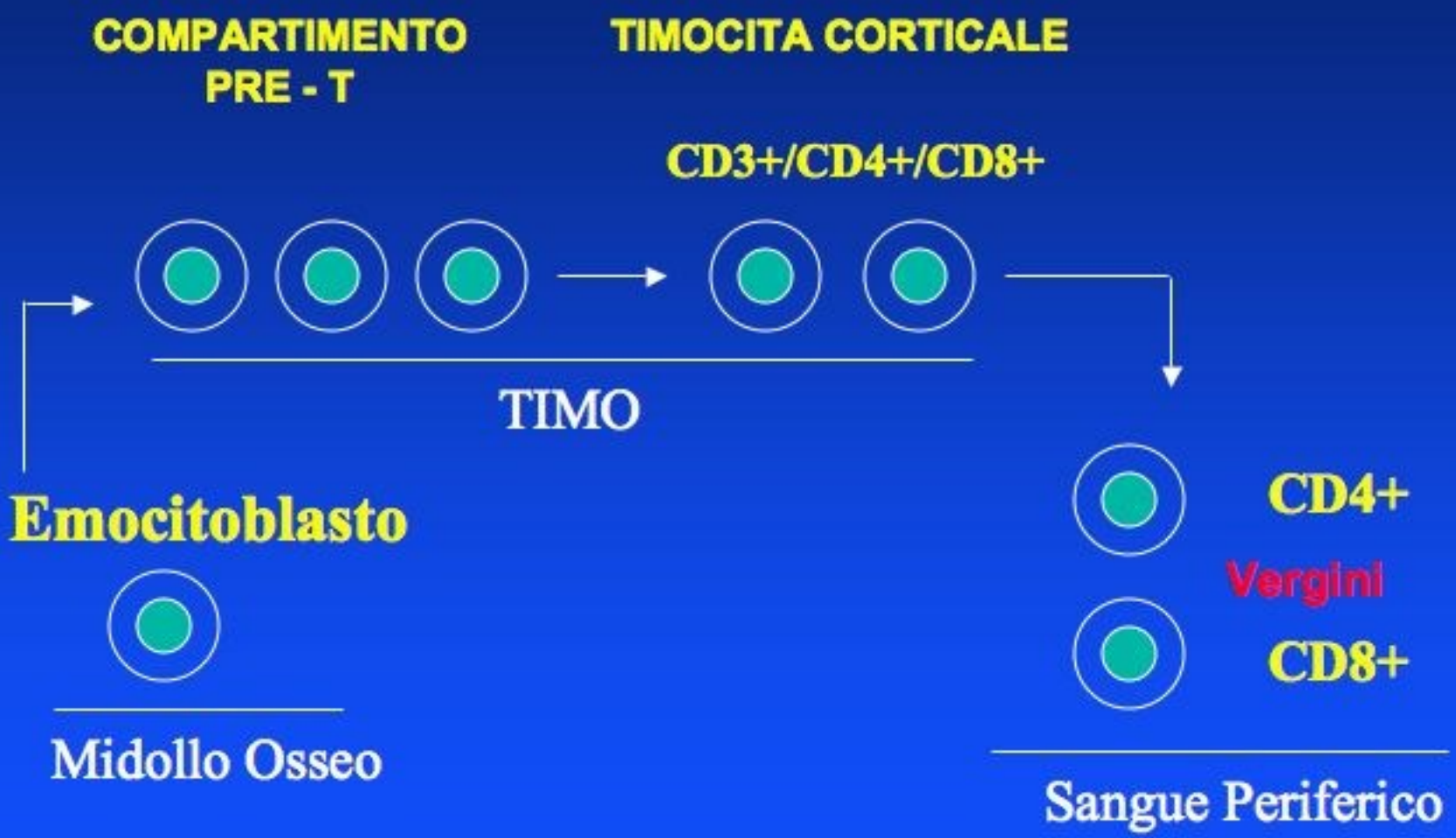
98% selezione -

Formato da numerosi lobuli

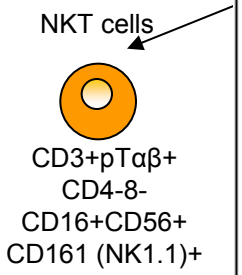
Coteccia: Stroma timico, timociti immaturi, epitelio

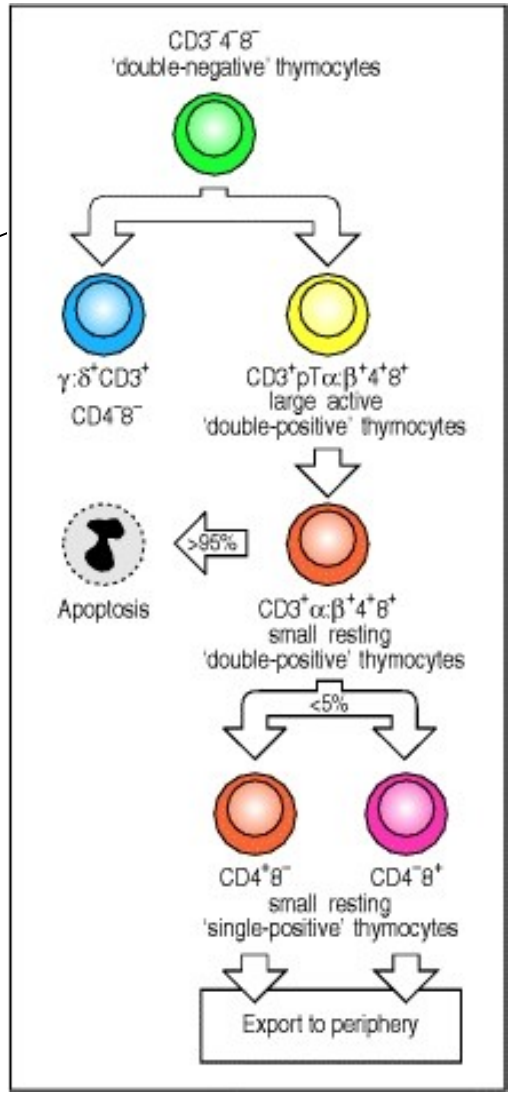
Midollo: Timociti maturi, macrofagi, cellule denritiche

Ontogenesi T

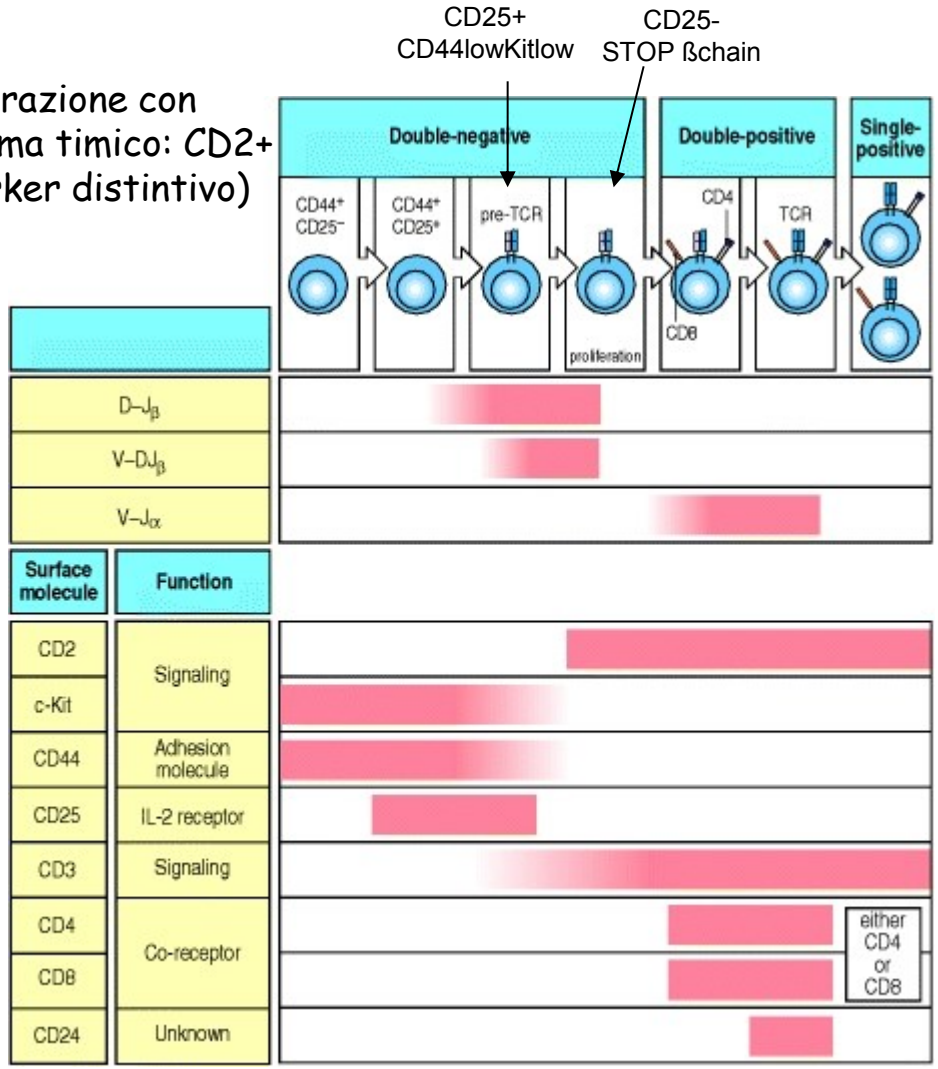


GLI STADI DI MATURAZIONE DEI LINFOCITI T SI DISINGUONO IN BASE ALL'ESPRESSIONE DEL TCR e DELLE PROTEINE DI SUPERFICIE





Interazione con stroma timico: CD2+ (marker distintivo)



Timo: sviluppato alla nascita

Pubertà: massima produzione cellule T

Dopo pubertà regredisce con diminuzione produzione nuove cellule T

Adulto: immunità sostenuta da cellule T periferiche

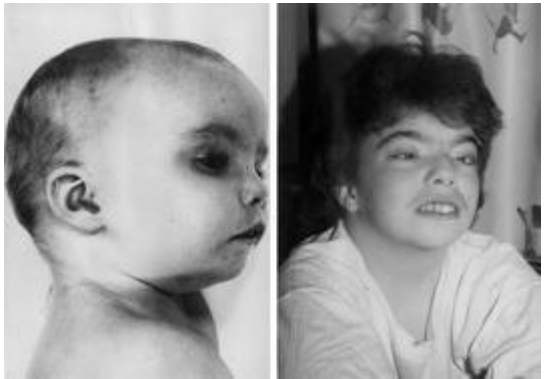
Sindrome di DeGeorge (o **aplasia timica**)

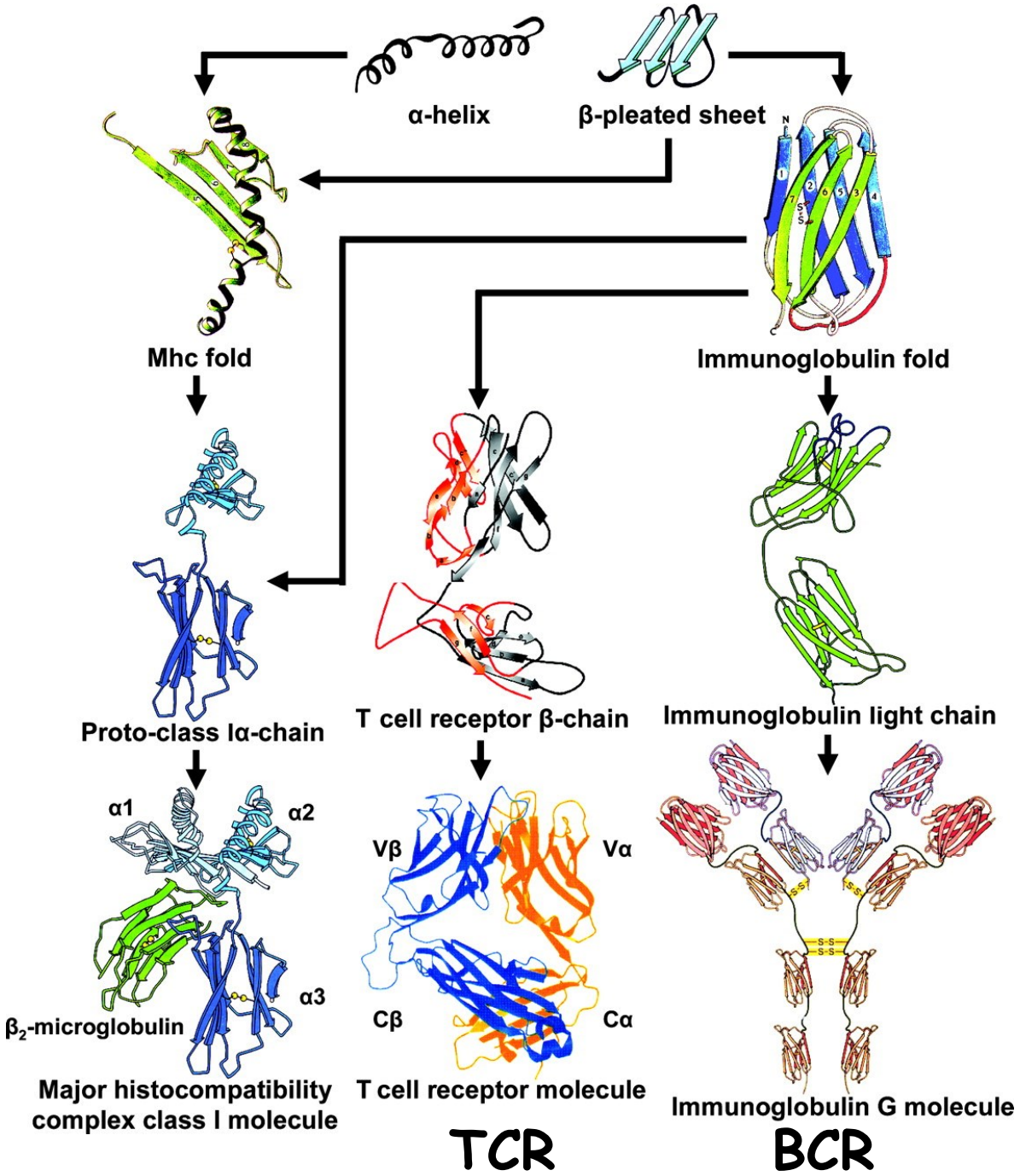
Carenza immunitaria da deficit da linfociti T i cui sintomi si manifestano subito dopo la nascita, determinata da un difetto embrio-morfogenetico.

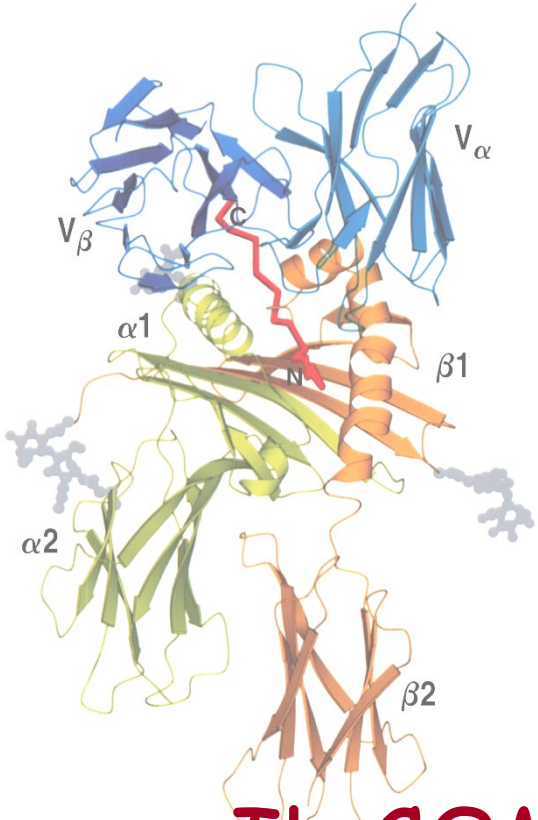
I pazienti presentano ipoplasia del timo e delle paratiroidi, con la caratteristica sintomatologia ipocalcemica (tetania, convulsioni) che si verifica nelle prime 24 ore di vita, malformazioni cardiache con difetti settali e interruzione dell'arco aortico e mancata chiusura del dotto arterioso, basso impianto auricolare, ipoplasia mandibolare e palatoschisi.

Questa sindrome causa l'insorgenza di infezioni spesso letali.

In un piccolo numero di casi è indicato il trapianto di timo fetale il più presto possibile e l'ipoparatiroidismo va curato con calcio al quale si deve aggiungere vitamina D o paratormone




α-helix
β-pleated sheet
Mhc fold
Immunoglobulin fold
Proto-class Iα-chain
T cell receptor β-chain
Immunoglobulin light chain
α1
α2
α3
β2-microglobulin
Major histocompatibility complex class I molecule
Vβ
Vα
Cβ
Cα
T cell receptor molecule
Immunoglobulin G molecule
TCR
BCR



IL COMPLESSO RECETTORIALE DELLA CELLULA T :

STRUTTURA E FUNZIONI

Un solo binding site

Non secreto

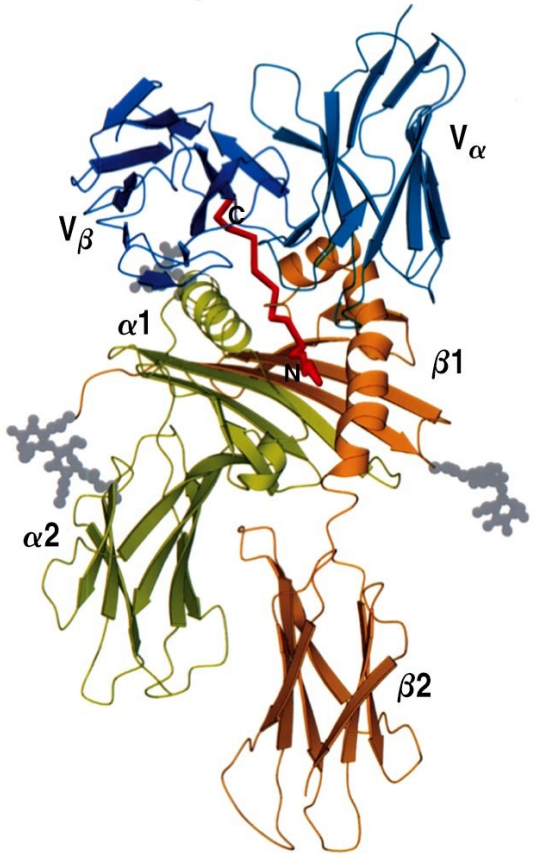


Figure 3-28 Immunobiology, 6/e. (© Garland Science 2005)

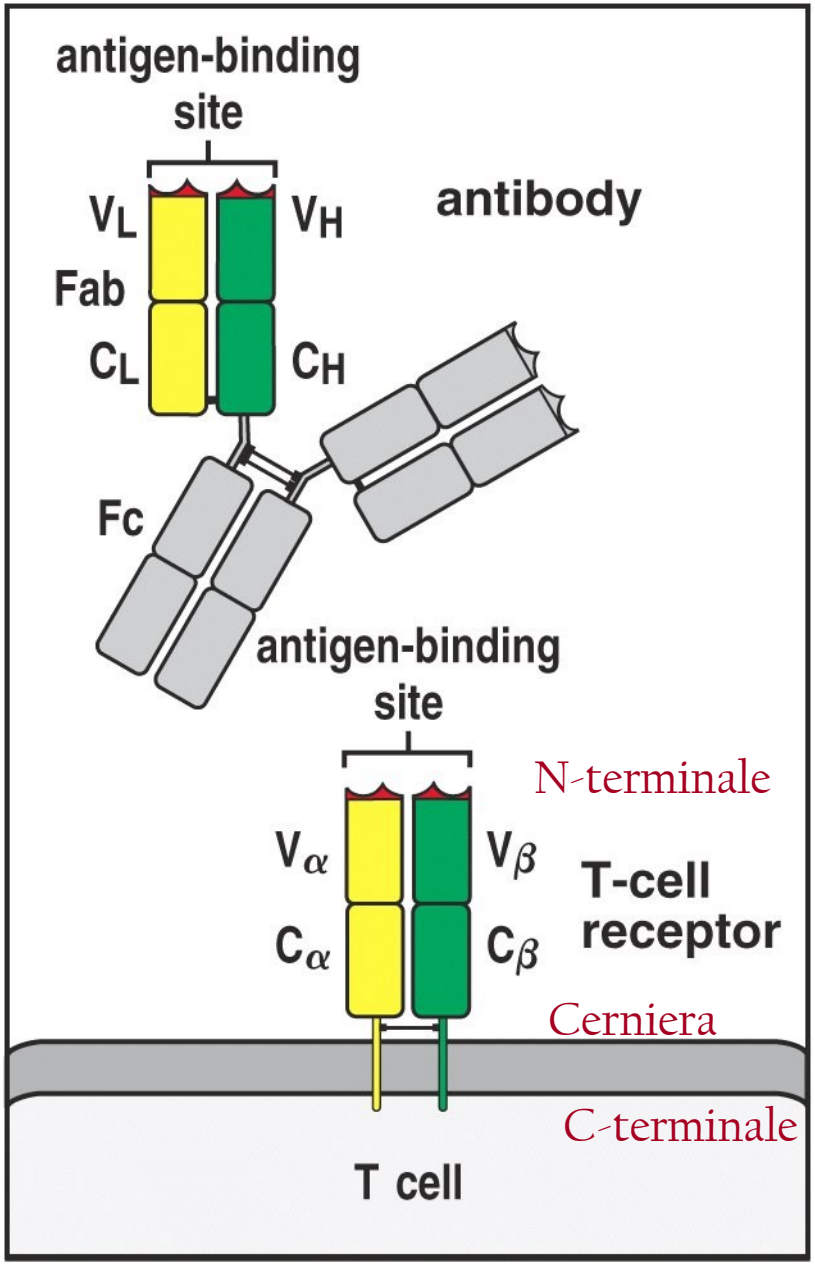


Figure 3-11 Immunobiology, 6/e. (© Garland Science 2005)

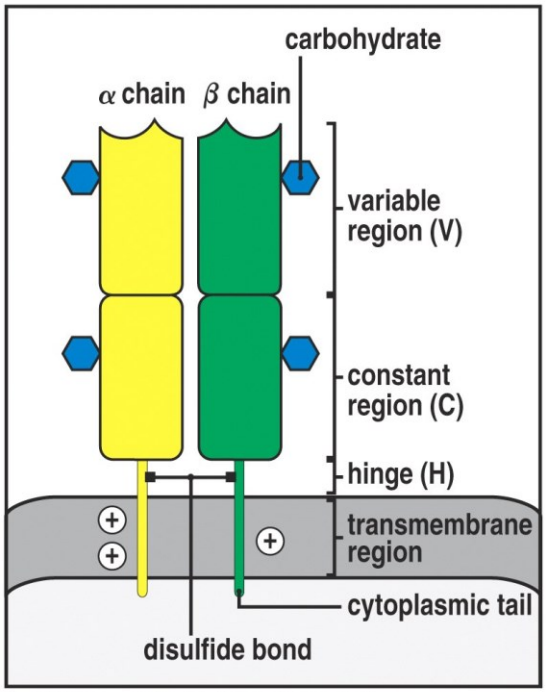


Figure 3-12 Immunobiology, 6/e. (© Garland Science 2005)

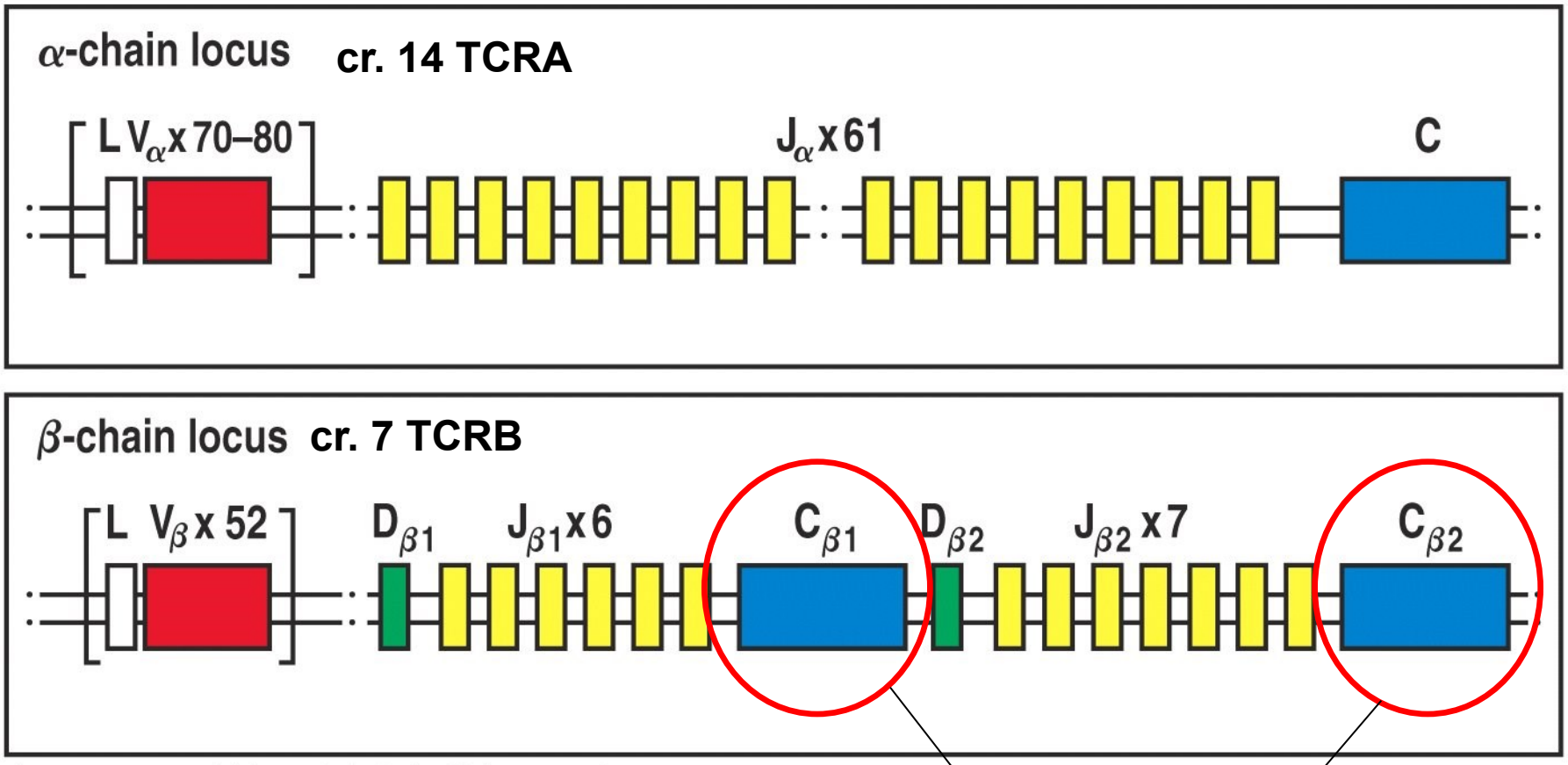
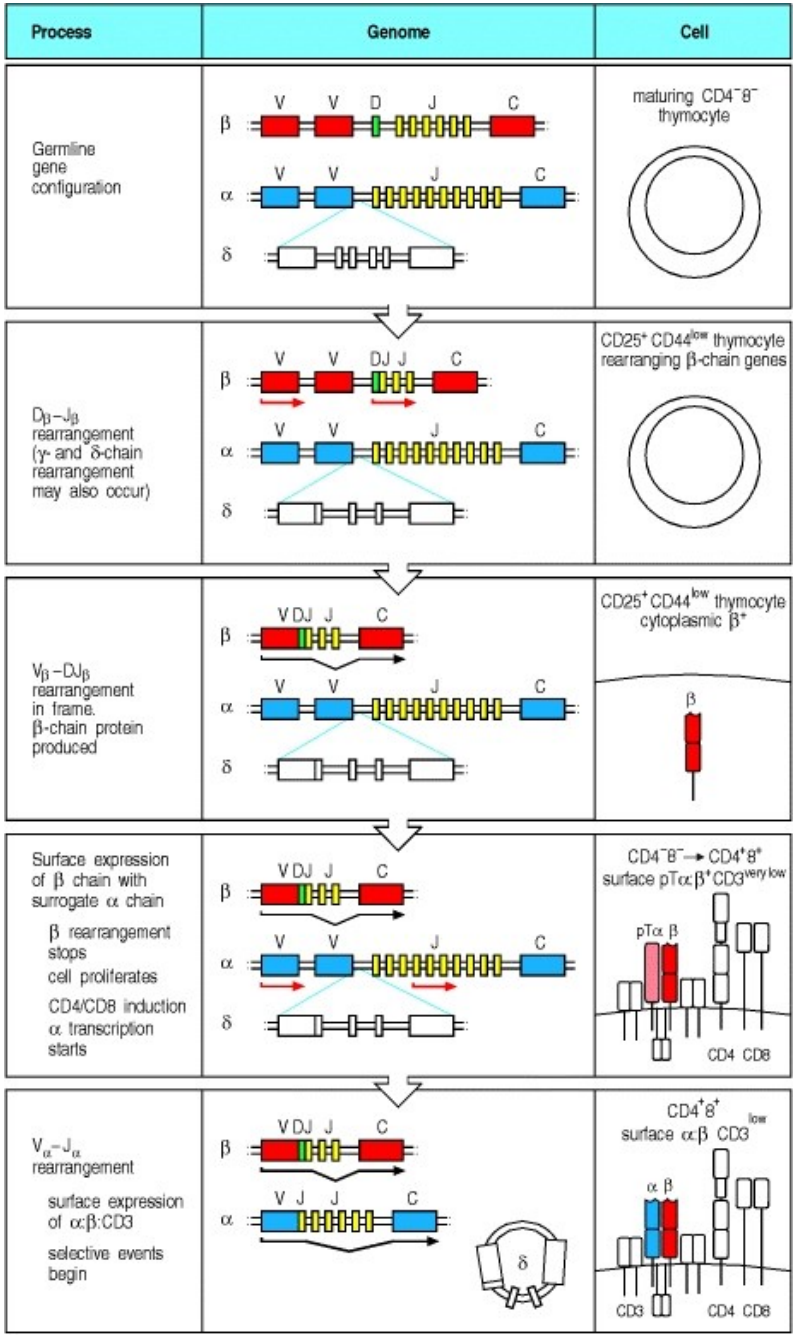


Figure 4-11 Immunobiology, 6/e. (© Garland Science 2005)

2 possibili riarrangiamenti se non produttivo

L: leader per indirizzo a RE



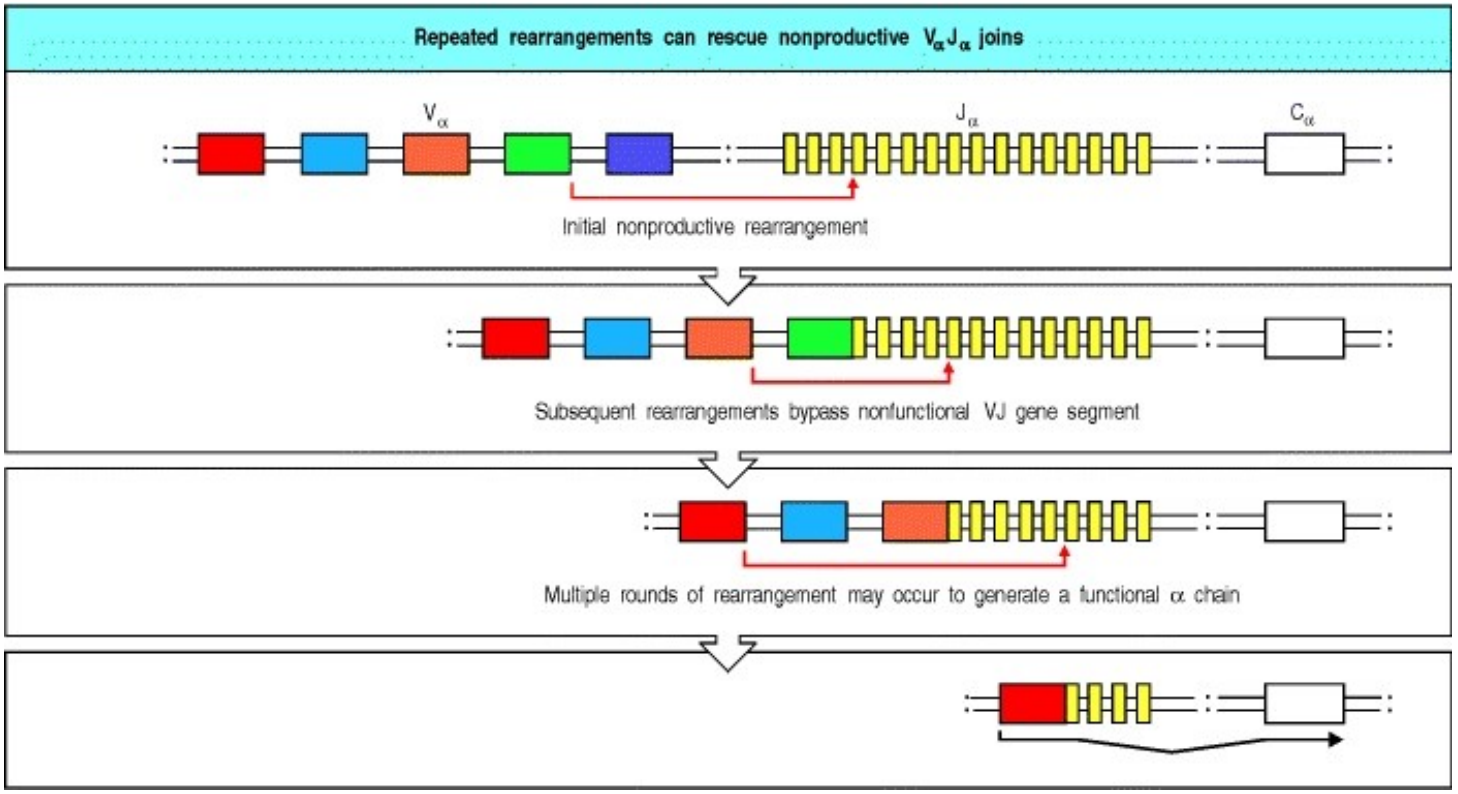
Segnali di ricombinazione

Nucleotidi P/N

Non esiste ipermutazione

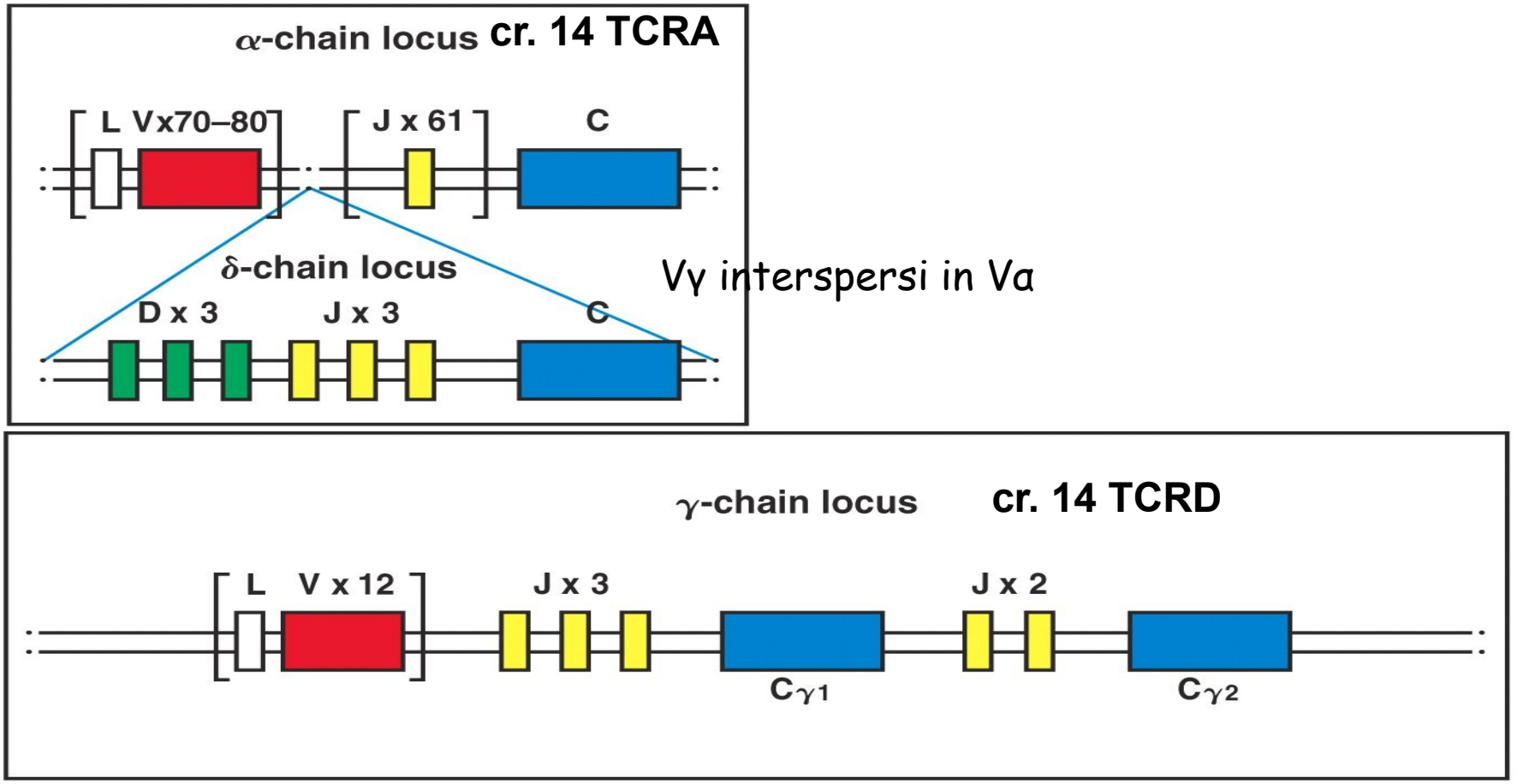
Diversitá strutturale data da ricombinazione somatica e modifiche di giunzione (P-, N-nucleotidi nella regione di legame con l'antigene)

RIARRANGIAMENTO CATENA ALFA



Continua fino alla selezione positiva MHC-PEPTIDE

Cellule T γδ



Vγ interspersi in Va

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

Sottotipo cellulare

Intraepiteliali

Riconoscono Ag direttamente senza MHC

Riconoscono Ag cellulari espressi in seguito ad infezione

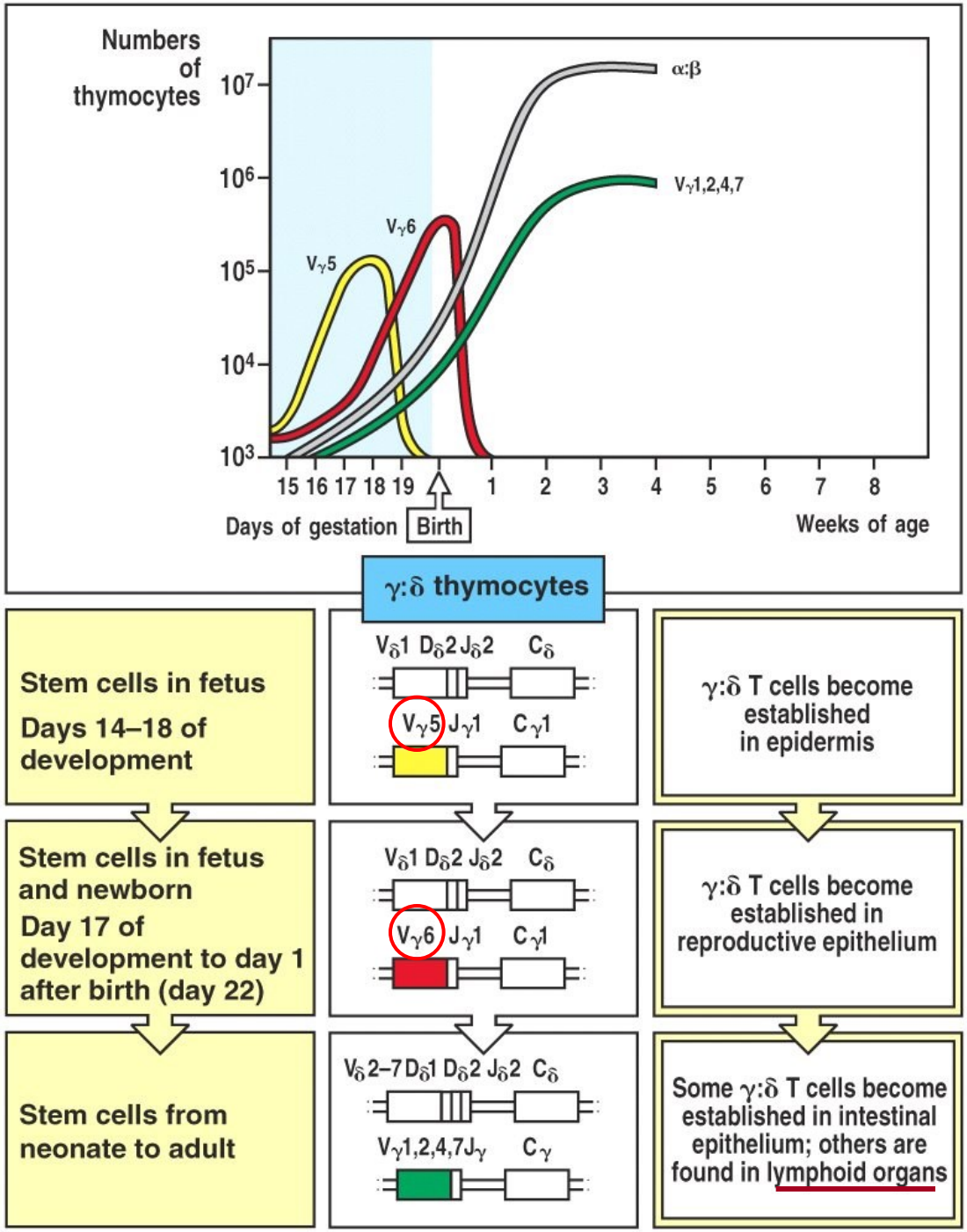


Figure 7-25 Immunobiology, 6/e. (© Garland Science 2005)

Omogenee:

stesse combinazioni

Da fegato fetale

Diverse:

diverse regioni V

Dendritic epidermal T cells (dETCs)

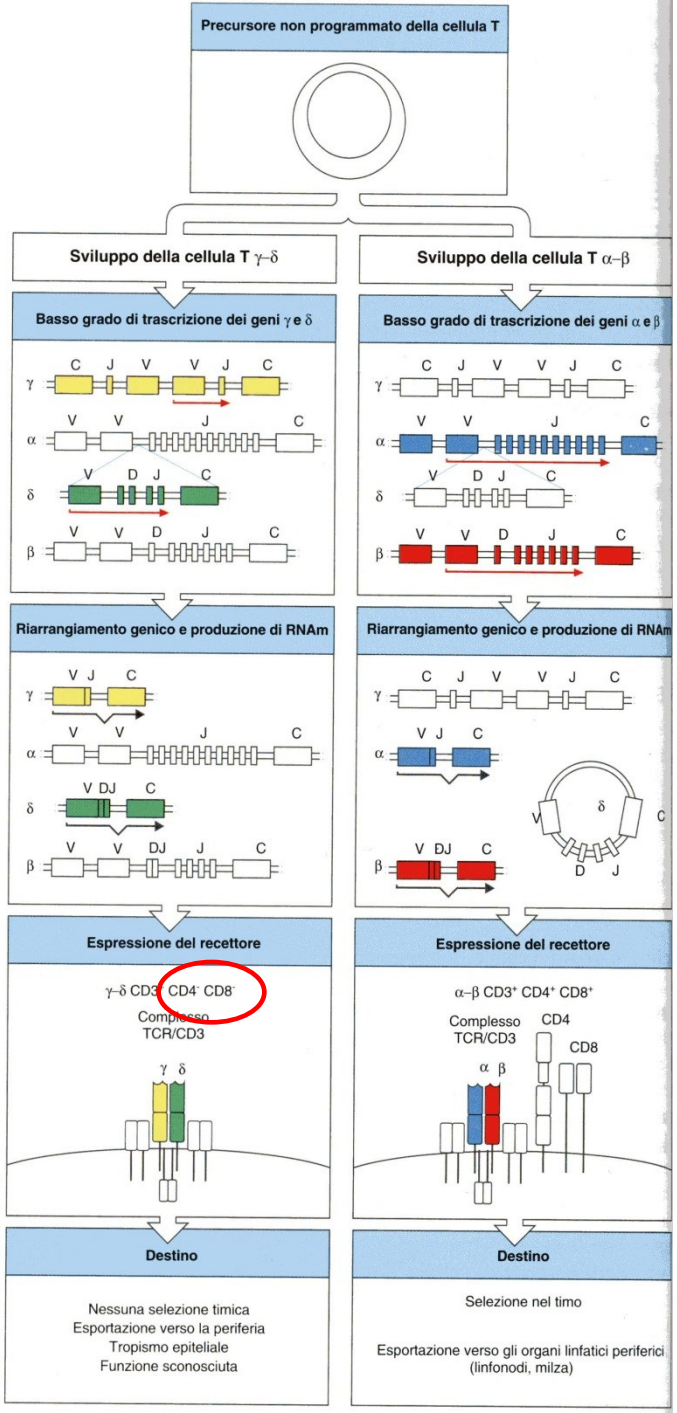
Si localizzano a livelli della mucosa intestinale

Gamma espressa a basso livello

Delta espresso a basso livello

Riarrangiamento gamma

Riarrangiamento delta



Gene delta eliminato dal riarrangiamento alpha

Element	Immunoglobulin		α:β T-cell receptors	
	H	κ+λ	β	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	1.9×10^6		5.8×10^6	
Junctional diversity	$\sim 3 \times 10^7$		$\sim 2 \times 10^{11}$	
Total diversity	$\sim 5 \times 10^{13}$		$\sim 10^{18}$	

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

CORECETTORI

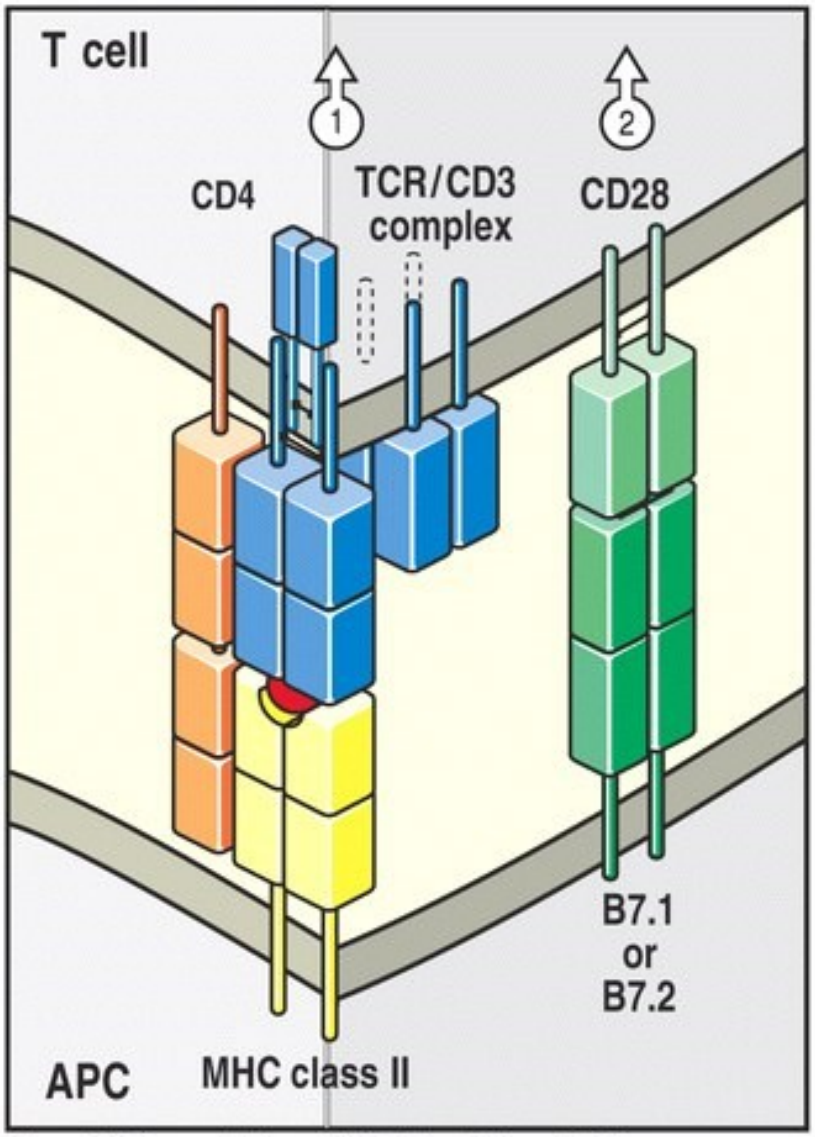


Figure 8-11 Immunobiology, 6/e. (© Garland Science 2005)

CD28: dimero (V)

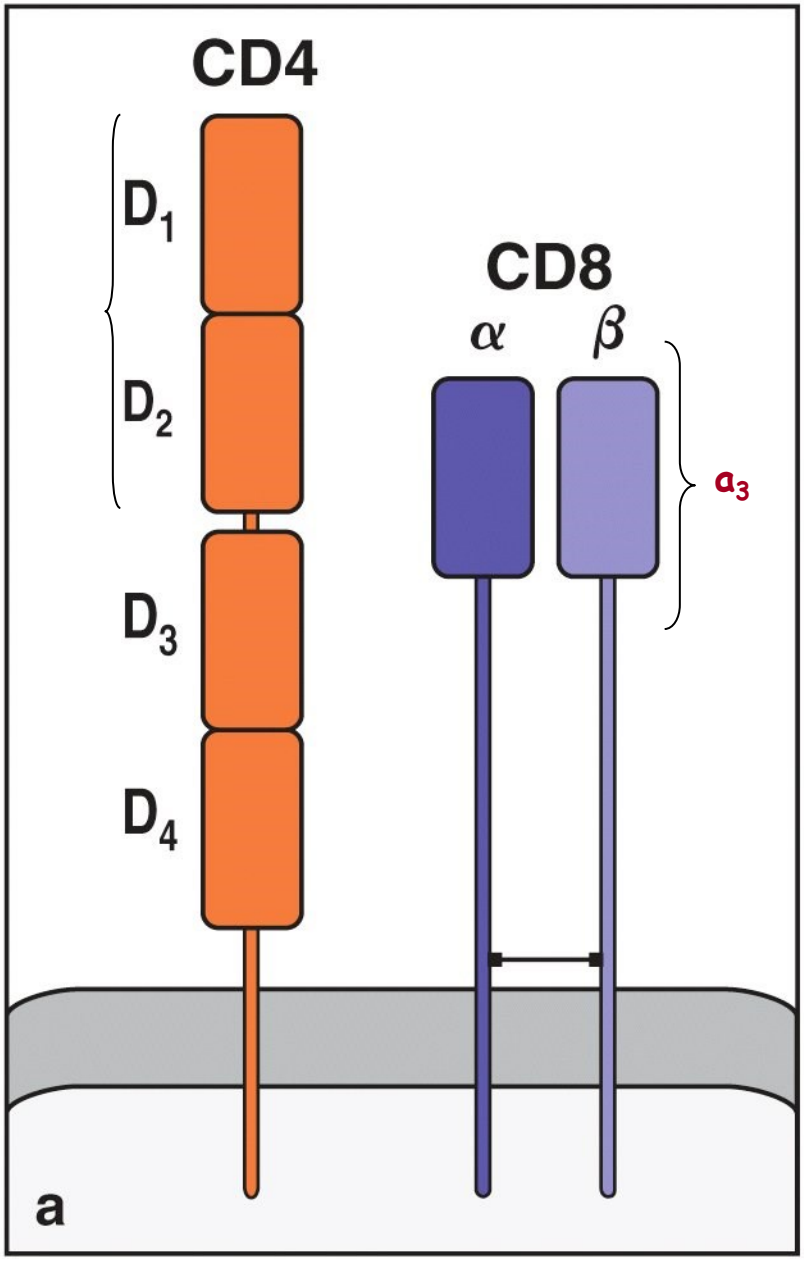
B7: dimero (V+C)

Assenza corecettori : ANERGIA

Prevenire risposte autodistruttive

MHC II MHC I

Beta chain



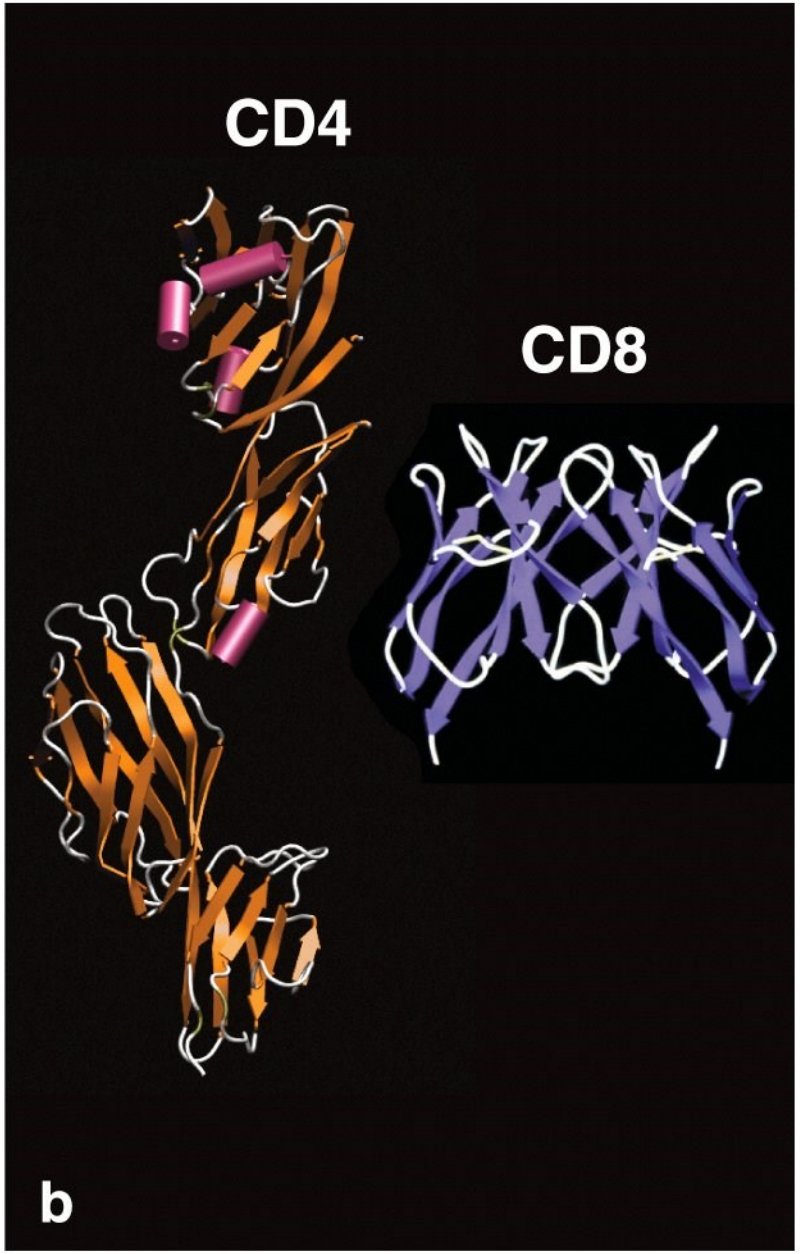
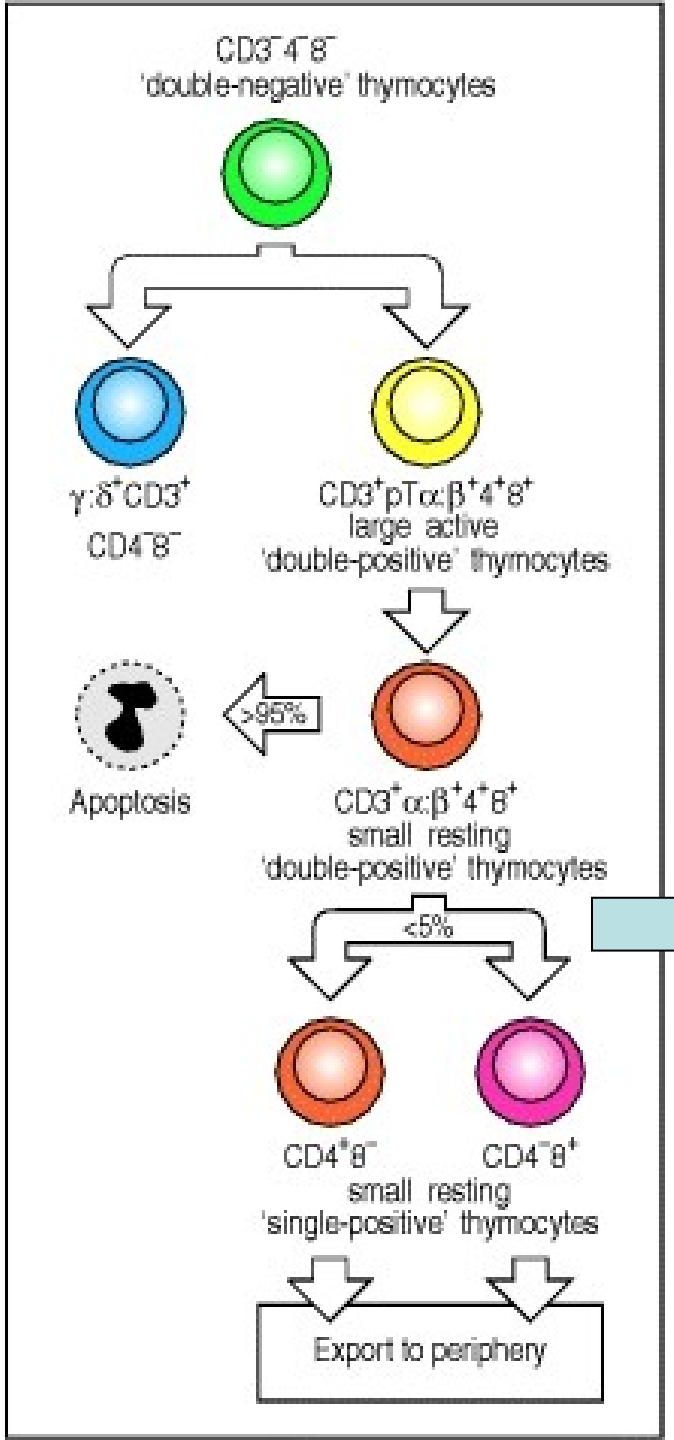


Figure 3-15 Immunobiology, 6/e. (© Garland Science 2005)



Riarrangiamento catena beta

Riarrangiamento catena alfa

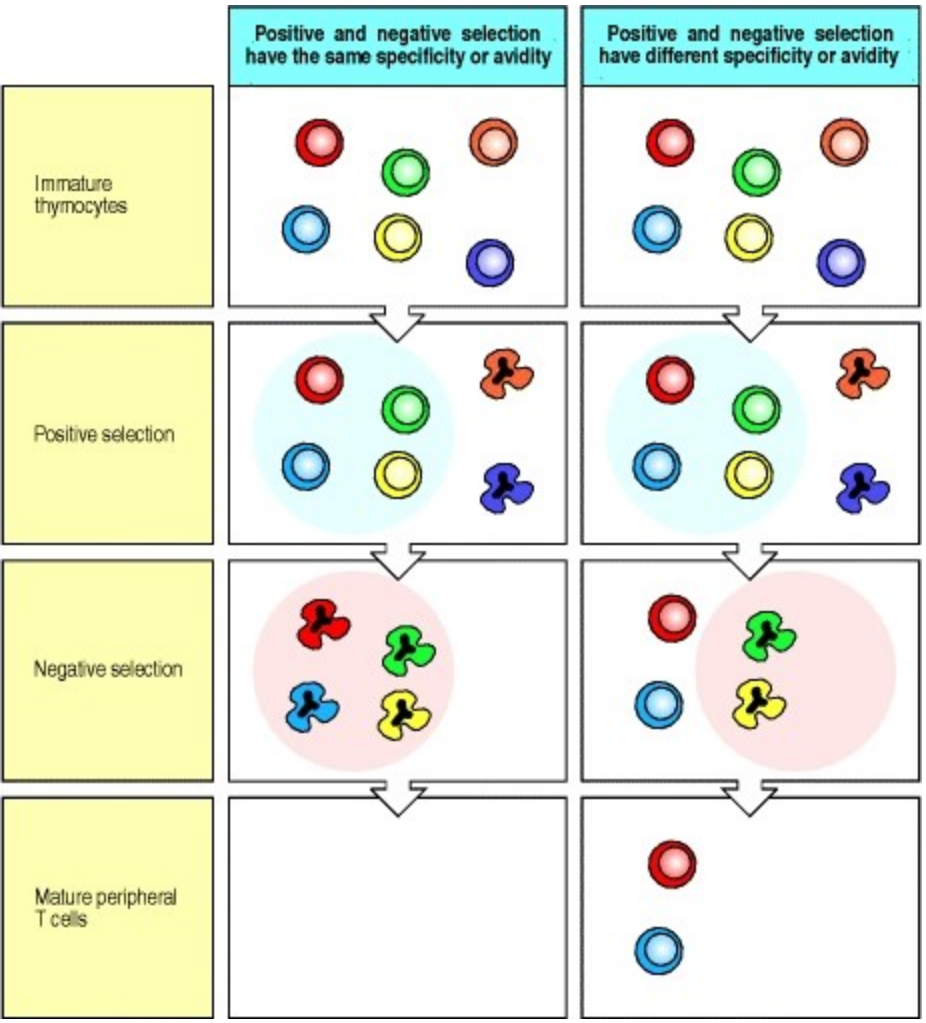
Selezione a livello timo

APC e macrofagi esprimenti MHC-I, MHC-II self-peptide self

CD4 - MHC-II

CD8 - MHC-I

TIMO



Linfociti T immaturi doppi positivi CD4+ CD8+

Selezione positiva: mantenuti linfociti T che riconoscono MHC-I+peptide, diventeranno CD8+CD4-

MHC-II+peptide, diventeranno CD8-CD4+

Linfociti T maturi naive

Selezione negativa: linfociti T che riconoscono MHC + self* (APC) : apoptosi o Treg

PERIFERIA

Selezione negativa: apoptosi dei linfociti T che riconoscono MHC + self

*Gene AIRE induce espressione antigeni tessuto specifici nel timo

SINDROME POLIENDOCRINA AUTOIMMUNE DI TIPO I

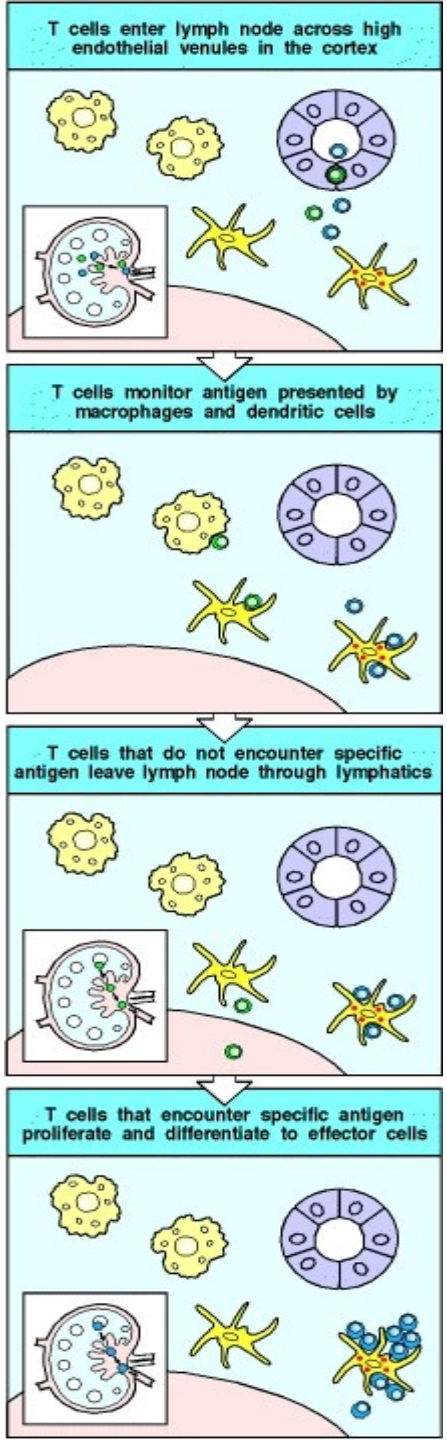
Sindrome di Witahcker o **APECED** (acronimo inglese di "Autoimmune Polyendocrinopathy- Candidiasis-Ectodermal Distrophy")

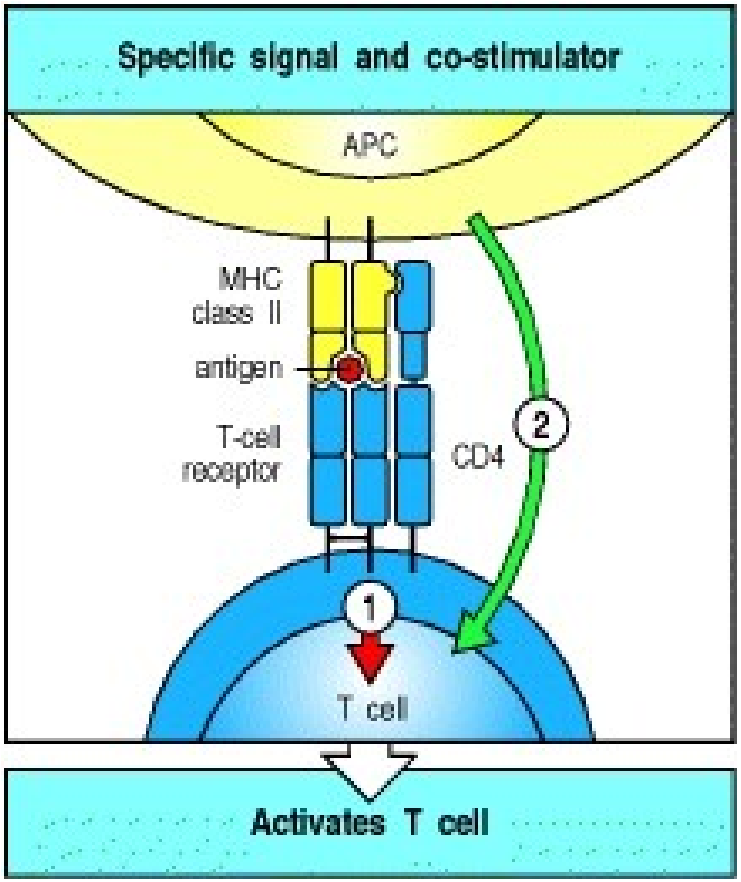
Micosi mucocutanea cronica (Candida), ipoparatiroidismo e Morbo di Addison (insufficienza corticosurrenale cronica autoimmune)
Malattia molto rara ad insorgenza precoce, sebbene possa manifestarsi in maniera sporadica anche in età adulta
Eccezione: Sardegna la sua prevalenza è di 1 caso ogni 14400 abitanti

Mutazioni a carico del gene AIRE (AutoImmune REgulator) localizzato sul cromosoma 21q22.3

Terapia : sintomatica

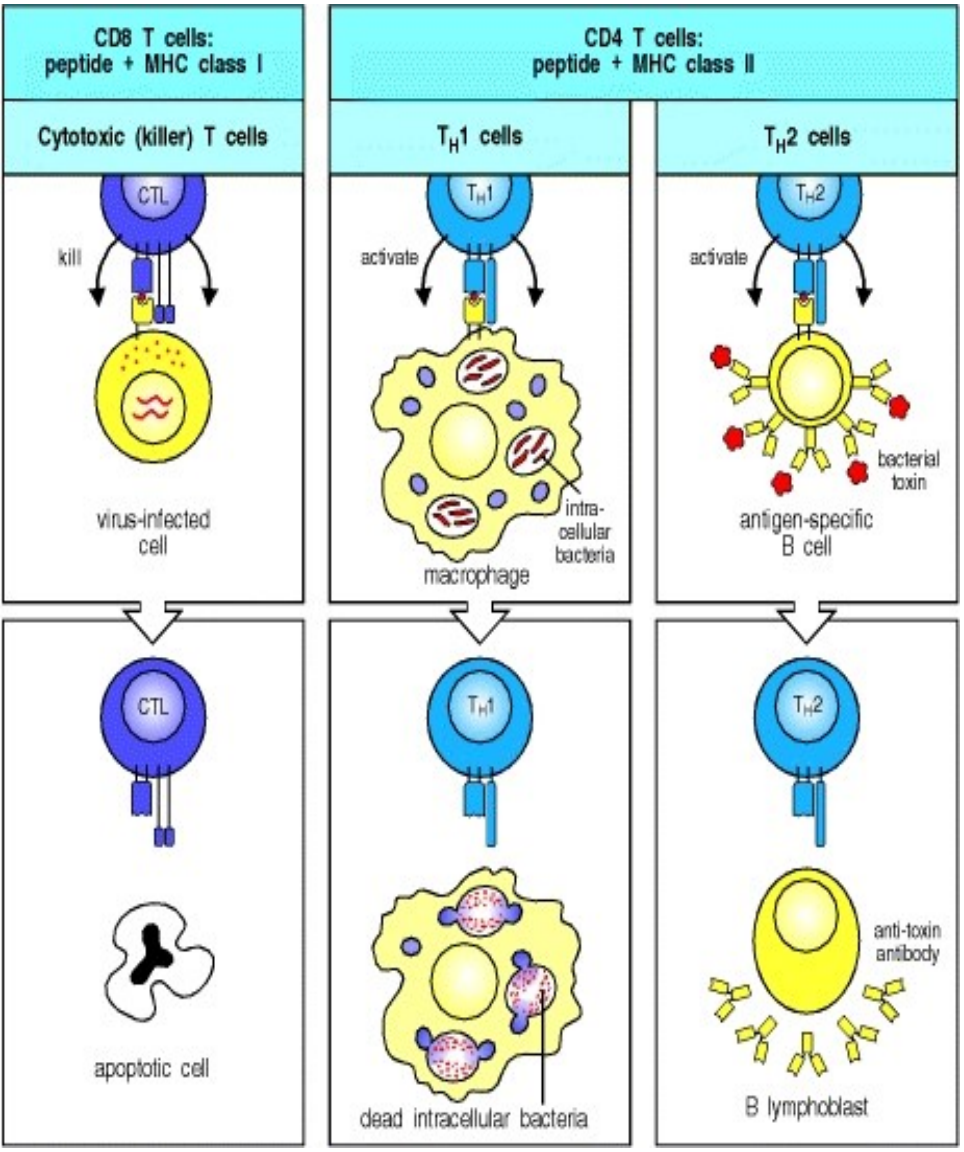
ATTIVAZIONE LINFOCITI T

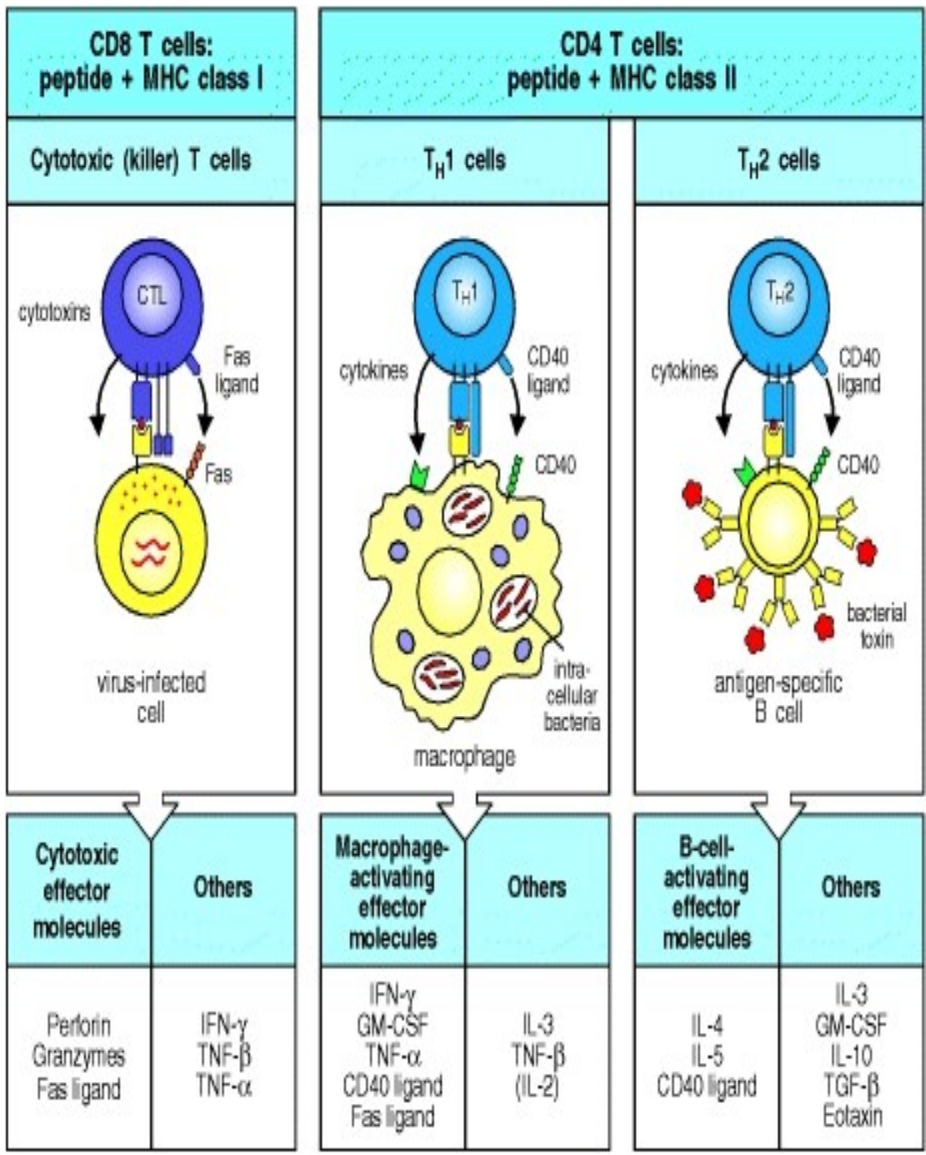




Espressione IL-2 e recettore IL-2 (CD25)

Induzione proliferazione e funzione effettrice





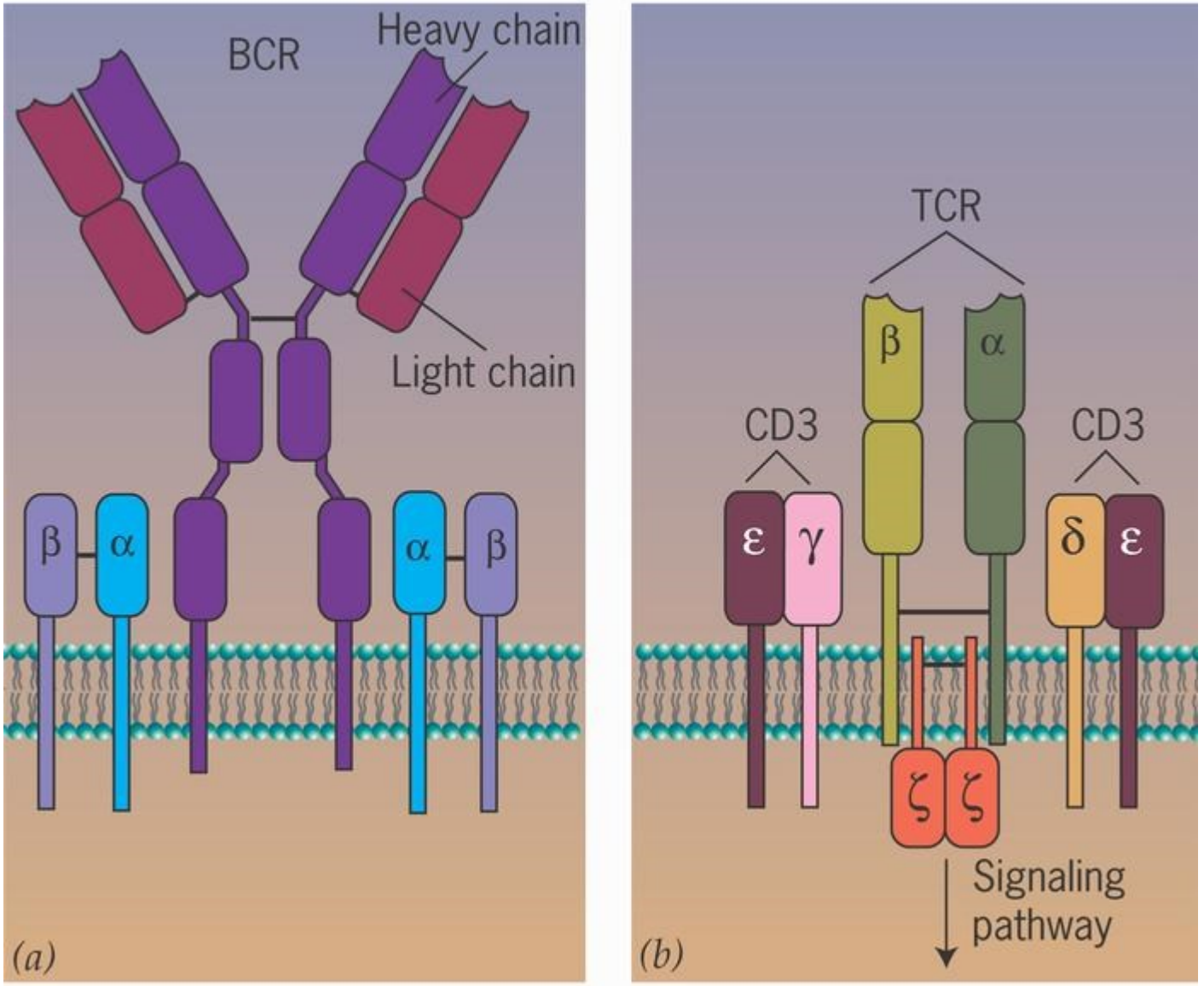
Cytotoxic effector molecules	Others
Perforin Granzymes Fas ligand	IFN-γ TNF-β TNF-α

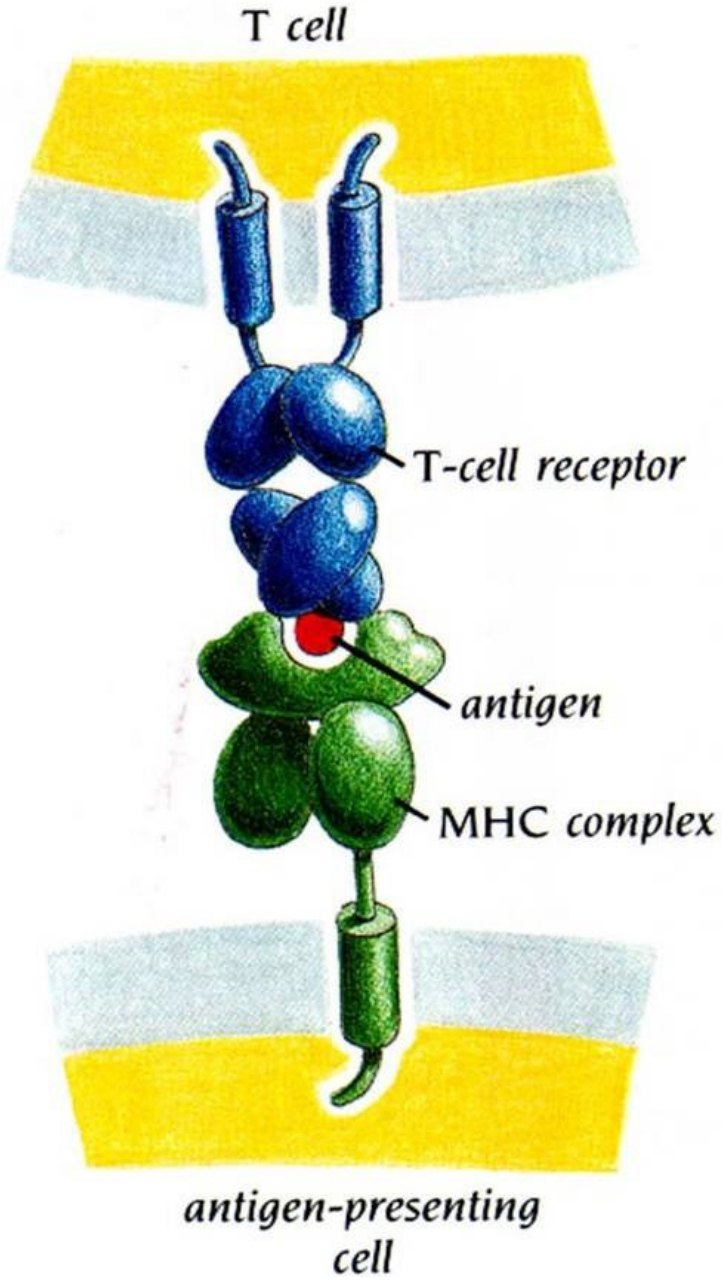
Macrophage-activating effector molecules	Others
IFN-γ GM-CSF TNF-α CD40 ligand Fas ligand	IL-3 TNF-β (IL-2)

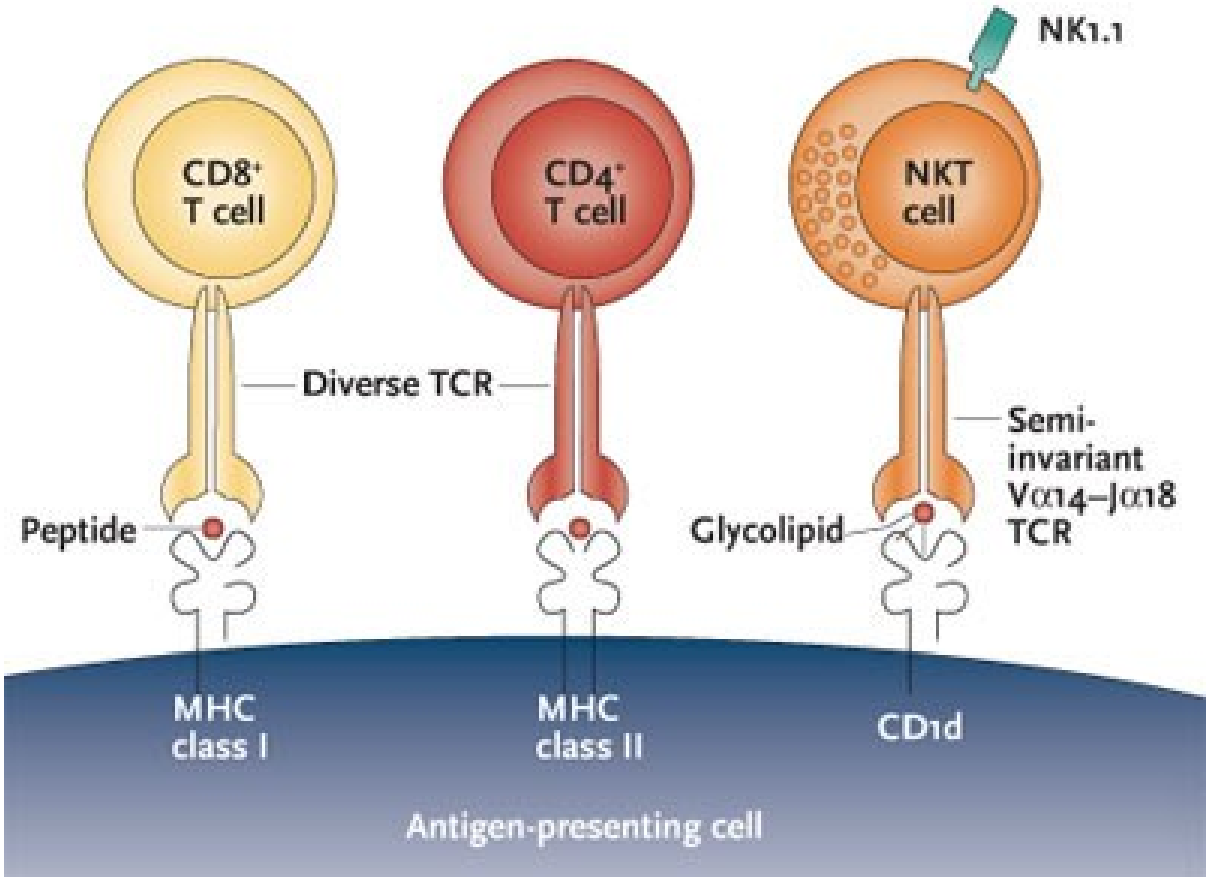
B-cell-activating effector molecules	Others
IL-4 IL-5 CD40 ligand	IL-3 GM-CSF IL-10 TGF-β Eotaxin

LINFOCITI B

LINFOCITI T




T cell
T-cell receptor
antigen
MHC complex
antigen-presenting cell


NK1.1
CD8+ T cell
CD4+ T cell
NKT cell
Diverse TCR
Semi-invariant Vα14–Jα18 TCR
Peptide
Glycolipid
MHC class I
MHC class II
CD1d
Antigen-presenting cell

Cellule T Natural Killer: CD16+, CD56+, produzione granzima

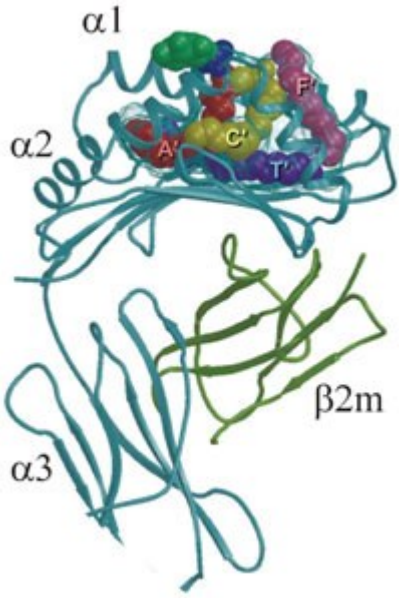
CD1

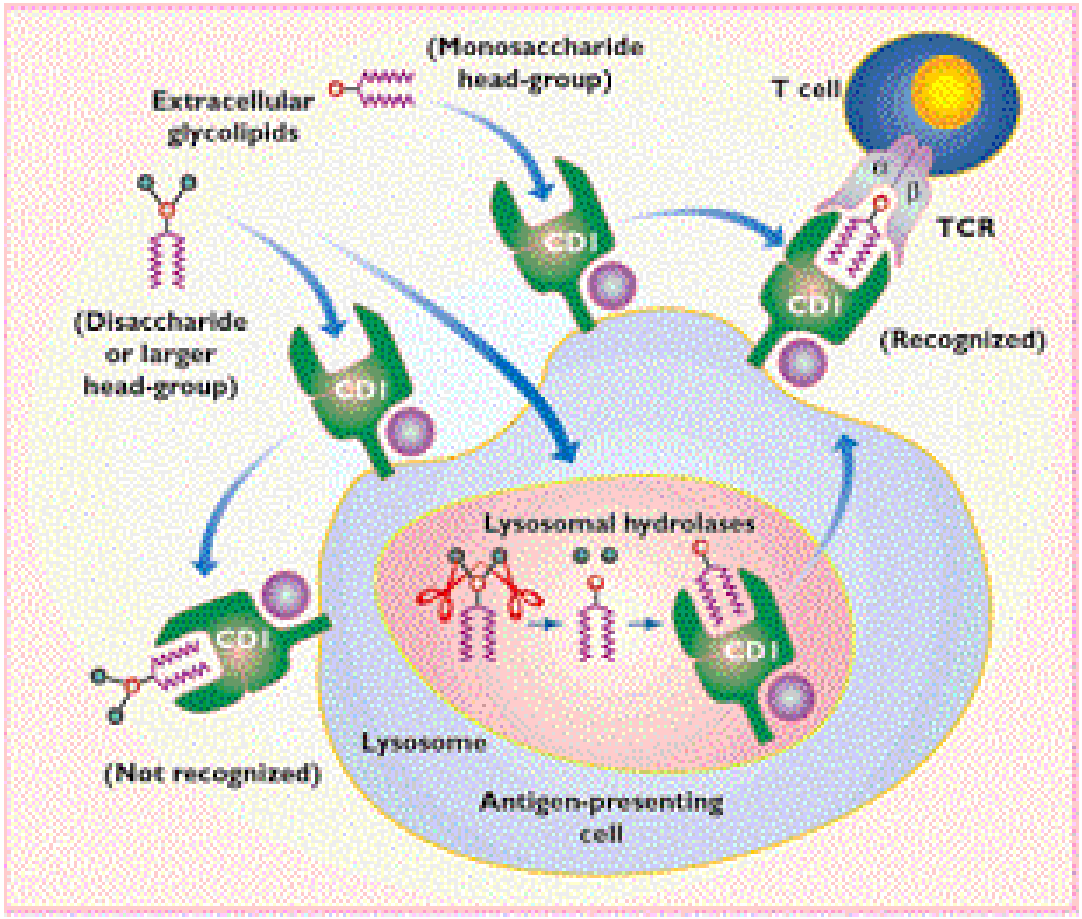
Famiglia di 5 glicoproteine (CD1A-E) di membrana o solubile eterodimeriche PM 43-49 kD appartenente alla superfamiglia delle immunoglobuline codificate da geni sul cr.1.

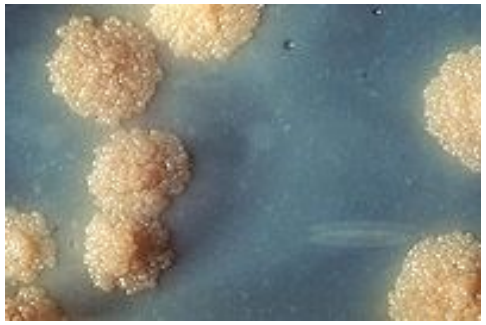
Somigliante per struttura a HLA-I, si associa con la β2-microglobulina, come funzione a HLA-II.

Presenta ai linfociti T antigeni lipo-glicidici o lipidici.

Ogni proteina possiede tre domini: citoplasmatico, transmembrana e extracellullare







Mycobacterium tuberculosis

Riconosce componenti membrana micobatteri

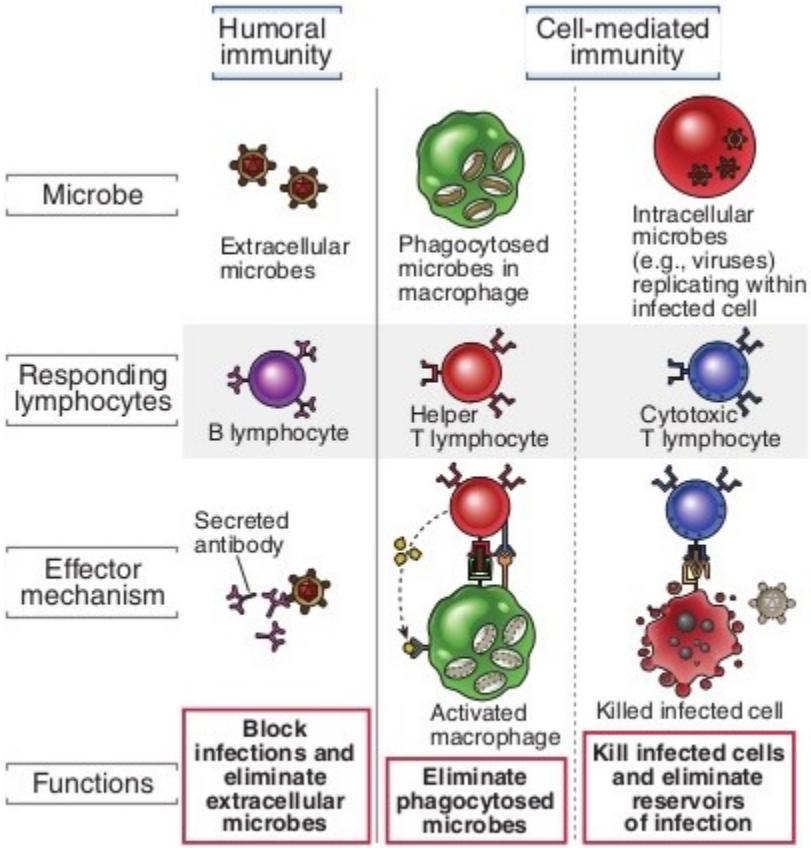


FIGURE 1–4 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, different types of T lymphocytes recruit and activate phagocytes to destroy ingested microbes and kill infected cells.