

Sélection positive et négative des répertoires lymphocytaires

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IF2009 IF-VIb
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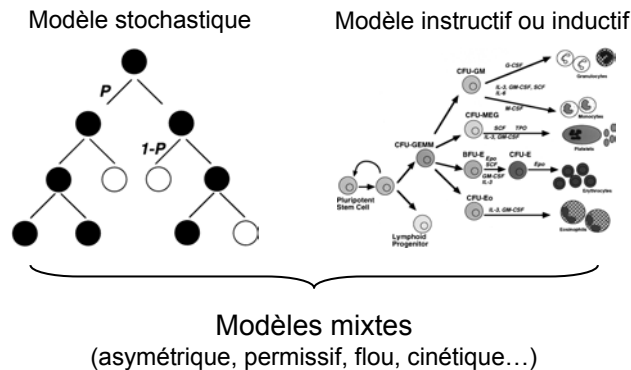
Sélection positive et négative des répertoires lymphocytaires

1. Introduction

2. Notion de répertoires
3. Sélection des répertoires B
4. Sélection des répertoires T
5. Conclusion

2

Modèles de différenciation & sélection



Socolovsky *et. al.* (1998) PNAS 95:6573

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Engagement vs. Sélection

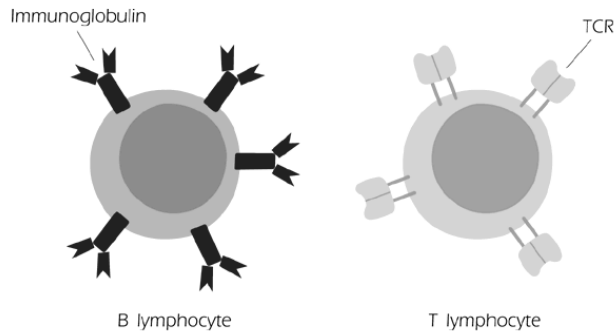
→ Par quel mécanisme les précurseurs s'engagent-ils dans un lignage donné?

→ L'engagement est-il le fruit du hasard?
Est-il contrôlé par un mécanisme de sélection?

→Au contraire, existe-t-il un signal (contact cellulaire, cytokine...) qui détermine l'engagement?

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Les lymphocytes B et T

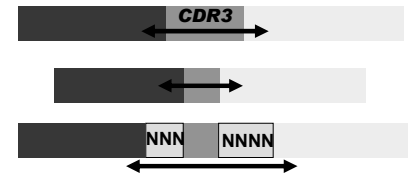


→ caractérisés par leur récepteur spécifique d'antigène

5

Diversité des chaînes Ig et TCR

- La diversité des chaînes d'Ig et de TCR est le produit de :
 - Combinatoire des segments V(D)J
 - Appariement IgH/L, TCR α / β or TCR γ / δ
 - Ajout/élimination aléatoire de nucléotides à la jonction des segments géniques (CDR3)



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Estimation de la diversité (2)

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

Mechanism of diversity	IMMUNOGLOBULINS		$\alpha\beta$ 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	$101 \times 13 \times 4$	85×4	79×38	$21 \times 2 \times 11$	7×3	$6 \times 2 \times 2$
and V-D-J joining	5.3×10^3	3.4×10^2	3.0×10^3	4.6×10^2	21	24
Alternative joining of D gene segments	-	-	-	+	-	+
Junctional flexibility	+	+	+	+	+	+
N-region nucleotide addition [†]	+	-	+	+	+	+
P-region nucleotide addition	+	+	+	+	+	+
Somatic mutation	+	+	-	-	-	-
Combinatorial association of chains	+	+	+	+	+	+

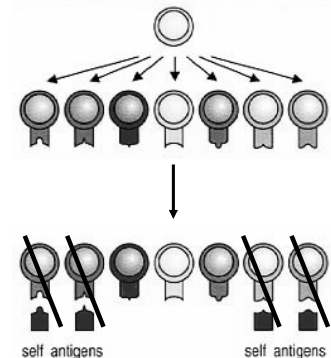
*Immunoglobulin data from Table 5-2; TCR data from Baum et al., 2004, Nucleic Acids Research 32:D51.
[†]A plus sign (+) indicates mechanism makes a significant contribution to diversity but to an unknown extent.
 A minus sign (-) indicates mechanism does not operate.
[‡]See Figure 9-8d for theoretical number of combinations generated by N-region addition.

Table 9-3
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Théorie de la sélection clonale (1) Burnet (1899–1985)

- Chaque lymphocyte exprime un type unique de récepteur spécifique d'antigène
- Les lymphocytes exprimant un récepteur dirigé contre un antigène du soi sont éliminés lors de la différenciation



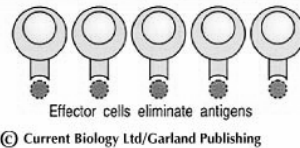
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Théorie de la sélection clonale (2)

- La liaison avec une bonne affinité d'une molécule étrangère et d'un récepteur entraîne l'activation du lymphocyte



- Les cellules effectrices différenciées à partir d'un lymphocyte activé donné expriment des récepteurs de même spécificité



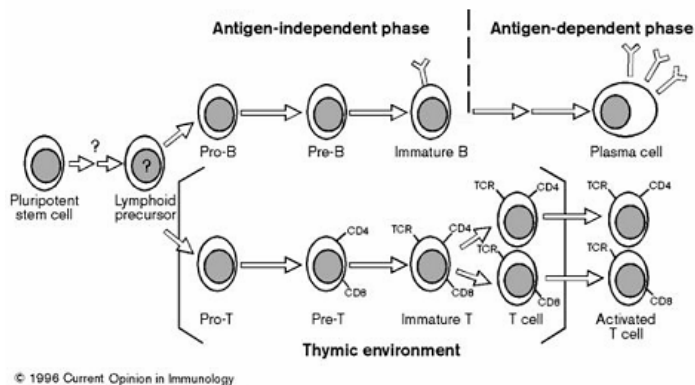
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Sélection positive et négative des répertoires lymphocytaires

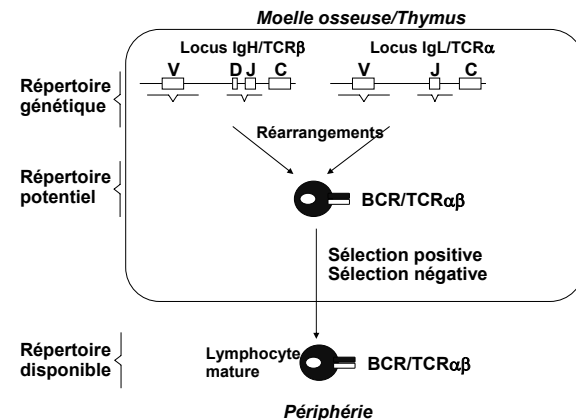
1. Introduction
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4. Sélection des répertoires T
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Parallèle différenciations B et T

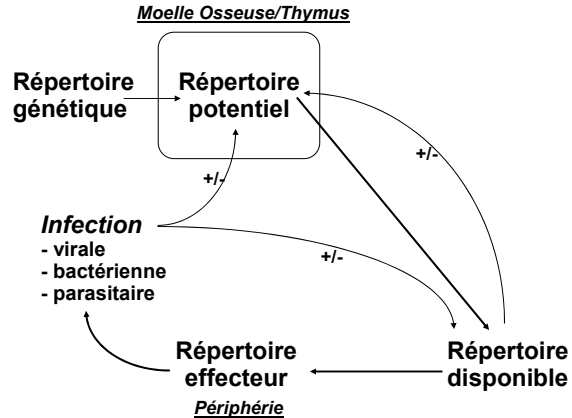
D'après Fitzsimmons et Hagman (1996) *Curr. Op. Immunol.* 8:166. 11

Notions de répertoires (1)



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Notions de répertoires (2)



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Notions de répertoires (3)

- La diversité des récepteurs spécifiques de l'antigène du répertoire disponible de lymphocytes matures périphériques conditionne la capacité à répondre aux **antigènes du non-soi**.
- Cette diversité disponible est en fait façonnée, notamment pendant la différenciation lymphocytaire, par les **antigènes du soi**.

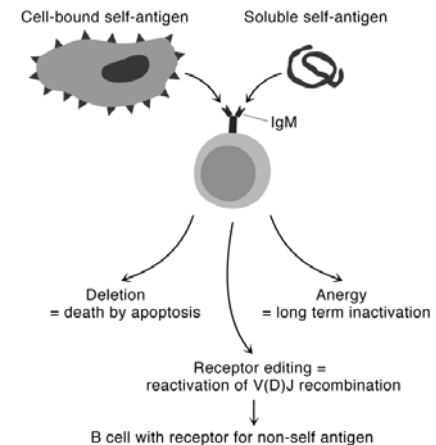
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Sélection positive et négative des répertoires lymphocytaires

1. Introduction
2. Notion de répertoires
3. **Sélection des répertoires B**
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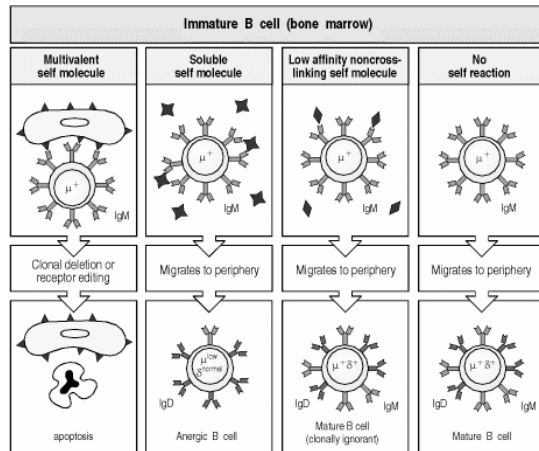
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Sélection des lymphocytes B (1)



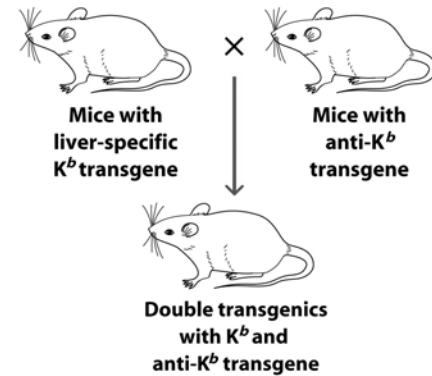
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Sélection des lymphocytes B (2)



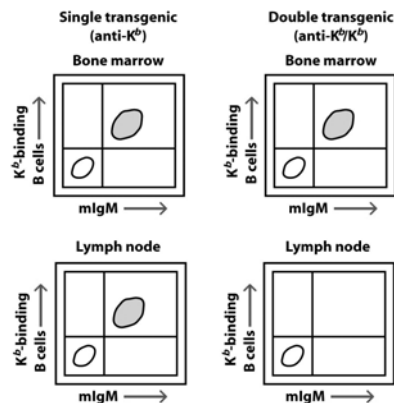
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Délétion clonale (1)

Figure 11-15a
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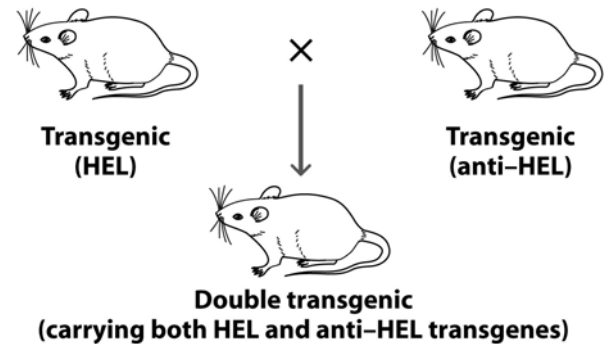
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Délétion clonale (2)

Figure 11-15b
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Anergie (1)

Figure 11-16a
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Anergie (2)

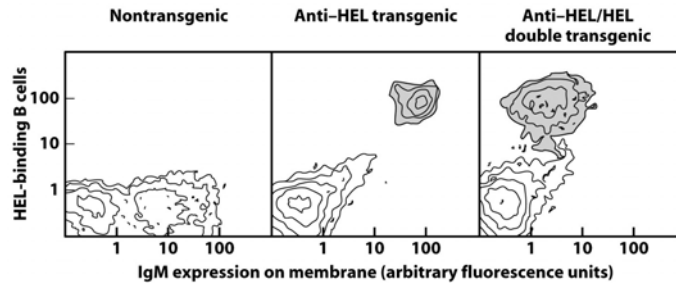
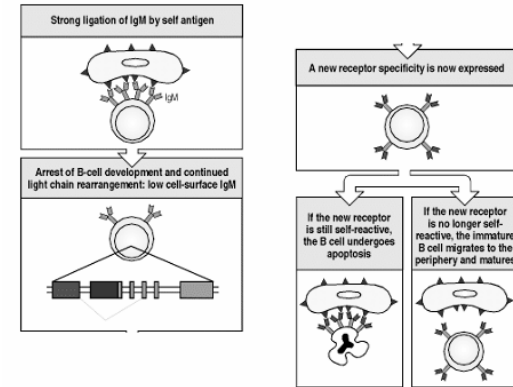


Figure 11-14b
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Sélection des lymphocytes B (3)



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Édition du BCR (1)

H-2^{d/k} transgenics

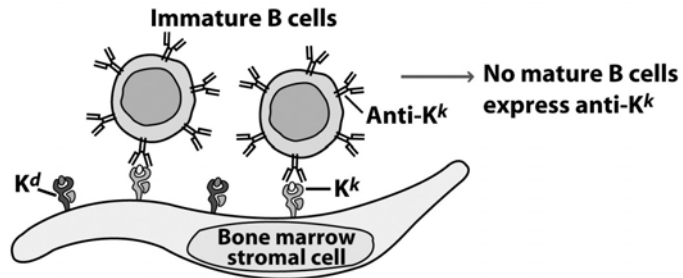


Figure 11-6a
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Édition du BCR (2)

H-2^d transgenics

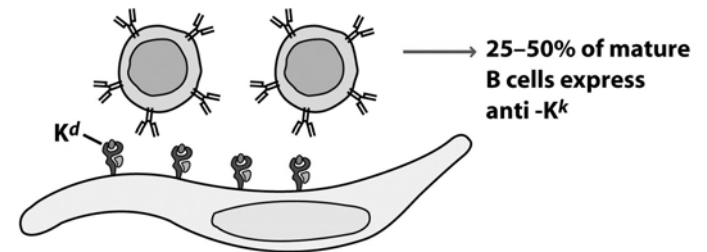


Figure 11-6b
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Édition du BCR (3)

TABLE 11-1 Expression of transgene encoding IgM antibody to H-2 ^k class I MHC molecules			
Experimental animal	Number of animals tested	EXPRESSION OF TRANSGENE	
		As membrane Ab	As secreted Ab (µg/ml)
Nontransgenics	13	(-)	<0.3
H-2 ^k transgenics	7	(+)	93.0
H-2 ^{dk} transgenics	6	(-)	<0.3

SOURCE: Adapted from D. A. Nemazee and K. Burki, 1989, *Nature* 337:562.

Table 11-1
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Édition du BCR (4)

H-2^{dk} transgenics

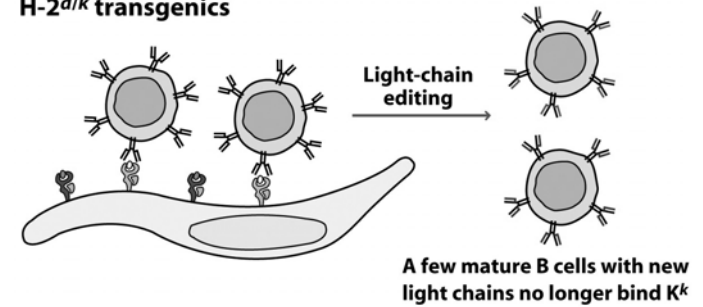
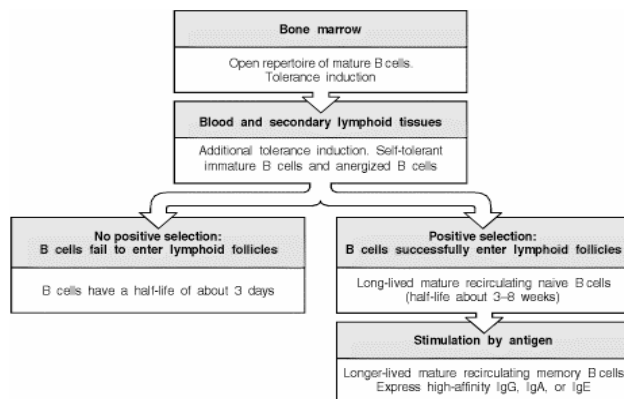


Figure 11-6c
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Sélection des lymphocytes B (4)



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Sélection des lymphocytes B (5)

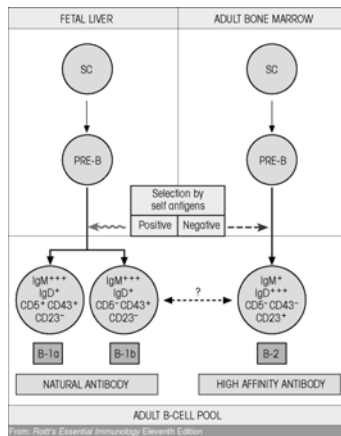


Attribute	Conventional B cells (B-2 B cells)	B-1 B cells
Major sites	Secondary lymphoid organs	Peritoneal and pleural cavities
Source of new B cells	From precursors in bone marrow	Self-renewing (division of existing B-1 cells)
V-region diversity	Highly diverse	Restricted diversity
Somatic hypermutation	Yes	No
Requirements for T-cell help	Yes	No
Isotypes produced	High levels of IgG	High levels of IgM
Response to carbohydrate antigens	Possibly	Definitely
Response to protein antigens	Definitely	Possibly
Memory	Yes	Very little or none
Surface IgD on mature B cells	Present on naive B cells	Little or none

Figure 11-5
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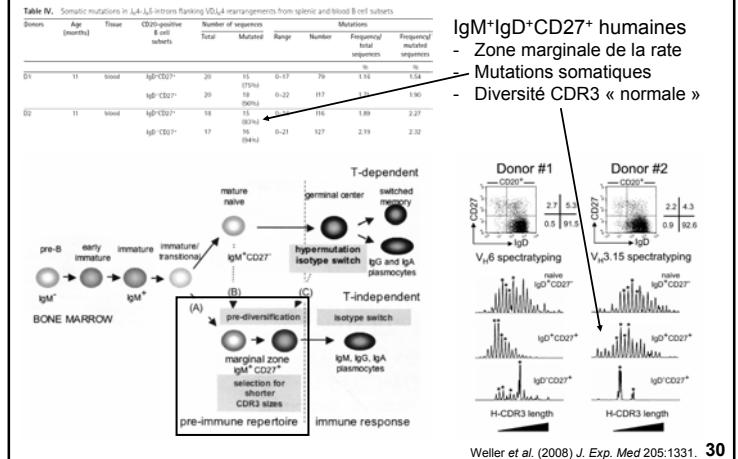
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Sélection des lymphocytes B (6)

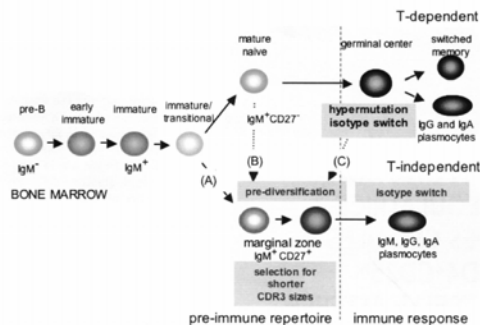


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Hypermutations en absence d'antigène



Hypermutations en absence d'antigène



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Compétition antigénique

TABLE 11-7 Antigenic competition between sheep and horse RBCs

IMMUNIZING ANTIGEN		HEMOLYTIC PLAQUE ASSAY (DAY 8)	
Ag1 (day 0)	Ag2 (day 3)	Test Ag	PFC / 10 ⁶ spleen cells
None	HRBC	HRBC	205
SRBC	HRBC	HRBC	13
None	SRBC	SRBC	626
HRBC	SRBC	SRBC	78

*PFC = plaque-forming cells.

Table 11-7
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Dominance clonale: idiotype T15 (1)

Anticorps inhibiteurs	Nombre de PFC anti-PC/rate
-	120 000
S1 60	115 000
S1 04	117 000
2E8	800
F6	950

-S160, S104, 2E8 et F6 sont quatre anticorps monoclonaux anti-T15, une immunoglobuline IgA, κ anti-phosphorylcholine.

-S160 est dirigé contre un épitope de IgA; κ ; S104 est spécifique de IgA, κ ; 2E8 et F6 sont des anticorps anti-idiotypiques.

-Les quatre anticorps ont été utilisés pour tenter d'inhiber des plages d'hémolyses locales (PFC) obtenues en mélangeant *in vitro* des cellules de souris BALB/c anti-PC, de la PC couplée à des globules rouges de mouton et du complément.

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Dominance clonale: idiotype T15 (2)

TABLE 1
Number of PC-Specific Foci and Percentages of T15⁺ Foci as a Function of Development

Age of donor mice in days ^a	Number of donor mice ^b	Total number of cells analyzed	Number of PC ⁺ foci	Frequency (in 10 ⁶ spleen cells) ^c	Number of T15 ⁺ foci	%T15 ⁺
2	58	2×10 ⁶	0	0	0	0
3	52	2×10 ⁶	0	0	0	0
4	31	2×10 ⁶	1	0.125	0	0
6	17	2×10 ⁶	7	0.875	2	28.5
7	13	3×10 ⁶	15	1.2	6	40.0
8	7	10 ⁶	7	1.7	4	57.1
9	5	10 ⁶	13	3.2	9	69.2
10	6	1.8×10 ⁶	30	4.1	24	80.0
12	4	1.5×10 ⁶	28	4.6	25	89.2
21	1	1.2×10 ⁶	18	3.7	16	88.8
42-46	1	2×10 ⁶	69	8.6	63	91.3

^aThe day of birth was counted as day 1. Thus, an age of 2 indicates 1 day after birth, age of 3 indicates 2 days after birth, etc.

^bSpleen cells from mice born within 12 hr of each other were pooled. Results from experiments performed on different days were pooled for the table.

^cCalculated as per Sigal et al. (1977).

Vakil, Briles & Kearney (1991) *Dev. Immunol* 1:203.

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Dominance clonale: idiotype T15 (3)

Injection néonatale de R36A *S. pneumoniae* + challenge R36A à 7 semaines
→ Dosage Ac anti-PC

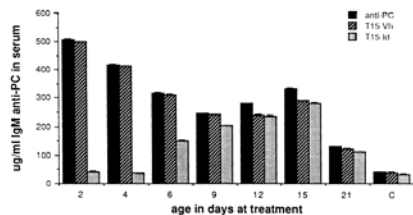


TABLE 3

Treatment of serum donor		Alive/dead postchallenge	
neonatal	adult	3 days	10 days
None	R36A	7/0	5/2
R36A	R36A	0/4 ^a	0/4 ^a
None	None	0/7 ^b	0/7 ^b
No serum		0/7 ^c	0/7 ^c

^aDifferent from none/R36A at $p < 0.01$.

^bDifferent from none/R36A at $p < 0.001$.

^cDifferent from none/R36A at $p < 0.06$.

Challenge léthal *S. pneumoniae*
→ Pouvoir protecteur du sérum de souris préalablement exposées?

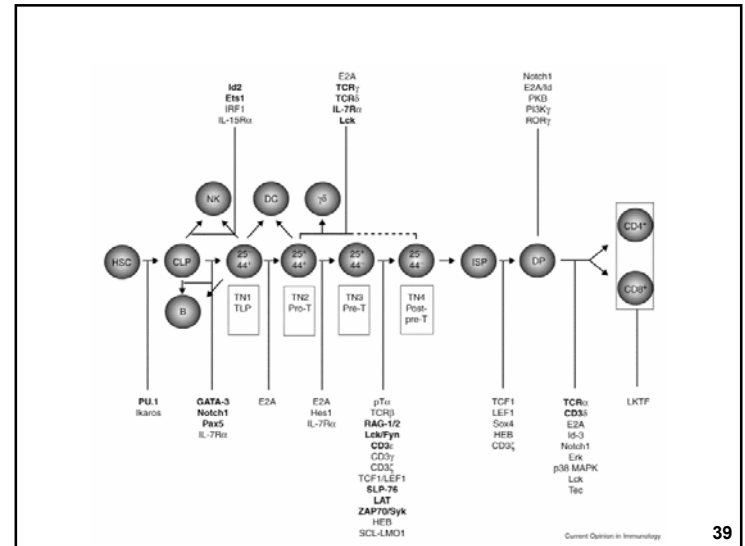
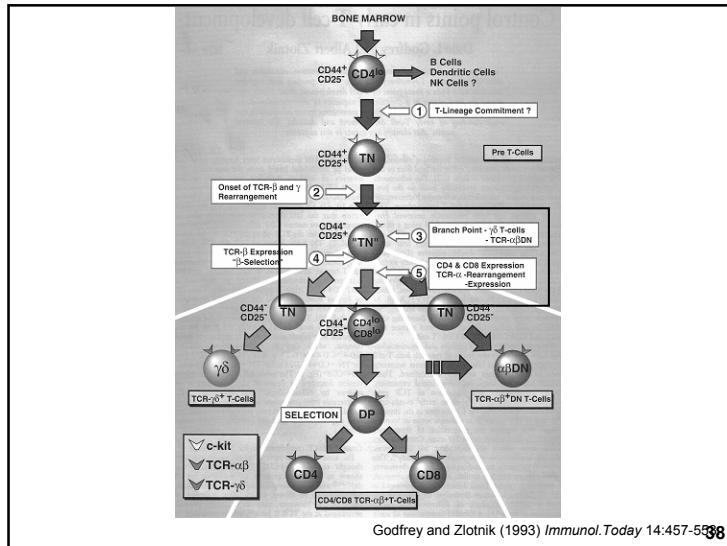
Vakil, Briles & Kearney (1991) *Dev. Immunol* 1:203.

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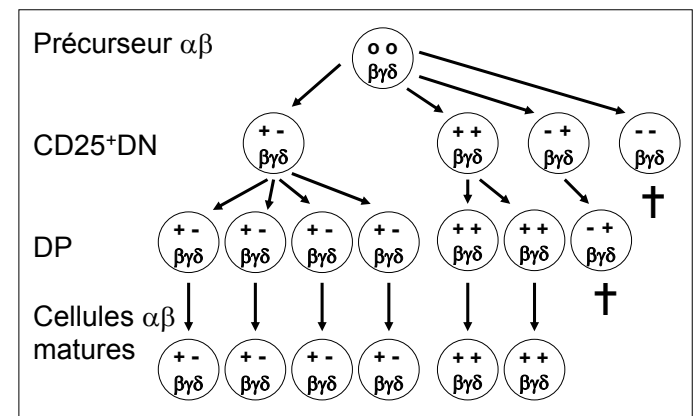


Lignées $\alpha\beta$ versus $\gamma\delta$

- Controverse concernant le mécanisme contrôlant le choix vers les lignées T $\alpha\beta$ et T $\gamma\delta$
- Certaines cellules T $\gamma\delta$ expriment TCR β
 Certaines cellules T $\alpha\beta$ expriment TCR γ
- Différents modèles proposés :
 - Réarrangements séquentiels
 - Réarrangements compétitifs
 - Lignées séparées

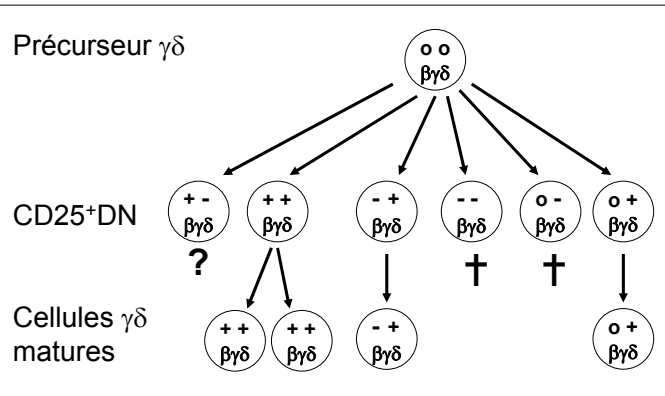
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Modèle modifié de lignée séparée (1)



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Modèle modifié de lignée séparée (2)

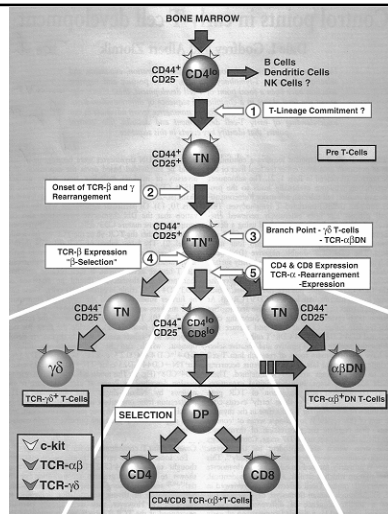


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Nouveau modèle instructif

T cell receptor-instructed $\alpha\beta$ versus $\gamma\delta$ lineage commitment revealed by single-cell analysis

$\alpha\beta$ and $\gamma\delta$ T cell lineages develop in the thymus from a common precursor. It is unclear at which stage of development commitment to these lineages takes place and in which way T cell receptor signaling contributes to the process. Recently, it was demonstrated that strong TCR signals favor $\gamma\delta$ lineage development, whereas weaker TCR signals promote $\alpha\beta$ lineage fate. Two models have been proposed to explain these results. The first model suggests that commitment occurs after TCR expression and TCR signaling directly instructs lymphocytes to adopt one or the other lineage fate. The second model suggests that commitment occurs before TCR expression and that TCR signaling merely confirms the lineage choice. By tracing the fate of single T cell precursors, this study shows that there is no commitment to either the $\alpha\beta$ or $\gamma\delta$ lineage before TCR expression and that modulation of TCR signaling in progeny of a single TCR-expressing cell changes lineage commitment.

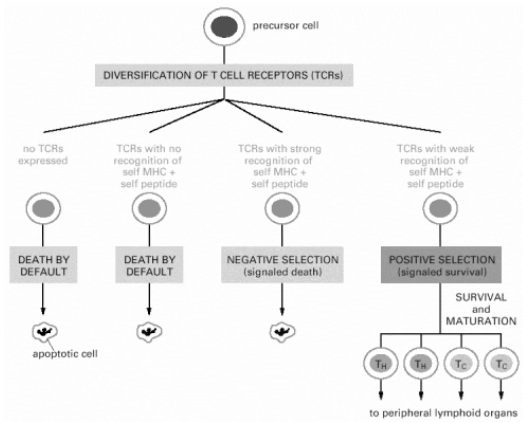
Kreslavsky et al. (2008) *J. Exp. Med.* 205:1173. **43**Godfrey and Zlotnik (1993) *Immunol.Today* 14:457. **44**

Sélections positive et négative (1)

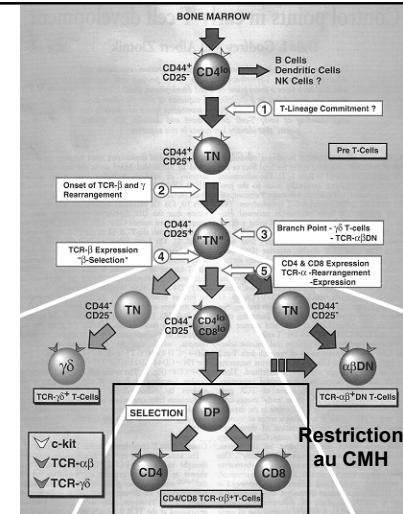
- Sélection positive: le TCR doit avoir une certaine réactivité avec une molécule du CMH du soi
- L'expression du co-récepteur CD4/CD8 suit la restriction pour le CMH
→ CD4/classe II et CD8/classe I
- Sélection négative: les cellules T autoréactives (reconnaissant CMH + peptide du soi) sont éliminées

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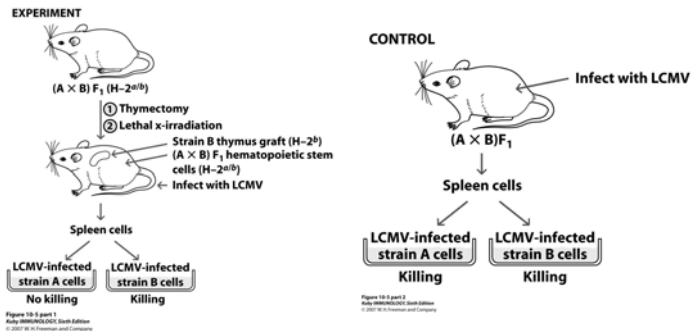
Sélections positive et négative (2)



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Godfrey and Zlotnik (1993) *Immunol Today* 14:457. 47

Rôle de l'épithélium thymique dans la sélection positive (1)



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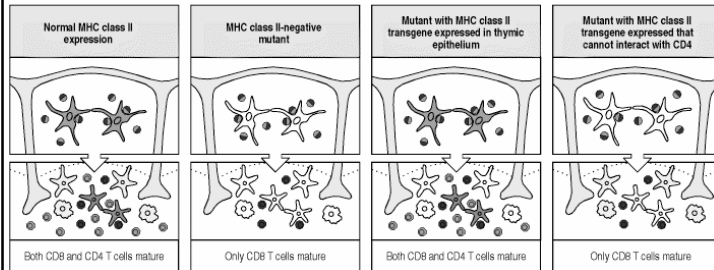
Rôle de l'épithélium thymique dans la sélection positive (2)

Thymectomize <i>b x k</i> mice	Graft with thymus of haplotype	Irradiate and reconstitute with <i>b x k</i> bone marrow	Prime with KLH	Proliferative response of primed T-cells to KLH on antigen-presenting cells of haplotype	
				H-2 ^b	H-2 ^k
	<i>b x k</i>	→	→	++	++
	<i>b</i>	→	→	++	-
	dGuo- treated <i>b</i>	→	→	++	-
	<i>k</i>	→	→	-	++
	dGuo- treated <i>k</i>	→	→	-	++

From: Roitt's *Essential Immunology* Eleventh Edition

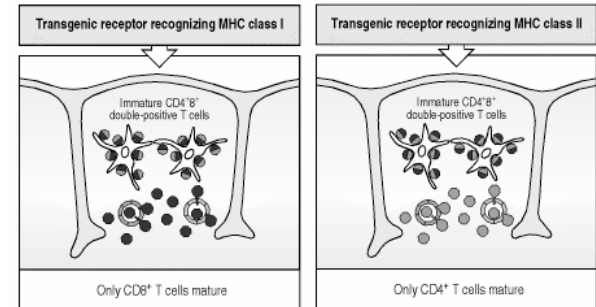
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Sélection positive & CMH (1)



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Sélection positive & CMH (2)



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Sélection positive & CMH (3)

TABLE 10-1		Effect of class I or II MHC deficiency on thymocyte populations*	
Cell type	Control mice	KNOCKOUT MICE	
		Class I deficient	Class II deficient
CD4 ⁻ CD8 ⁻	+	+	+
CD4 ⁺ CD8 ⁺	+	+	+
CD4 ⁺	+	+	-
CD8 ⁺	+	-	+

*Plus sign indicates normal distribution of indicated cell types in thymus. Minus sign indicates absence of cell type.

Table 10-1
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Sélection positive & CMH (4)

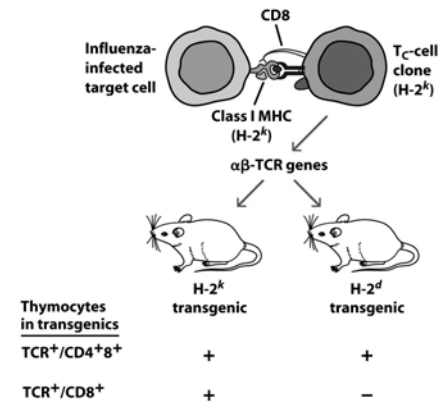
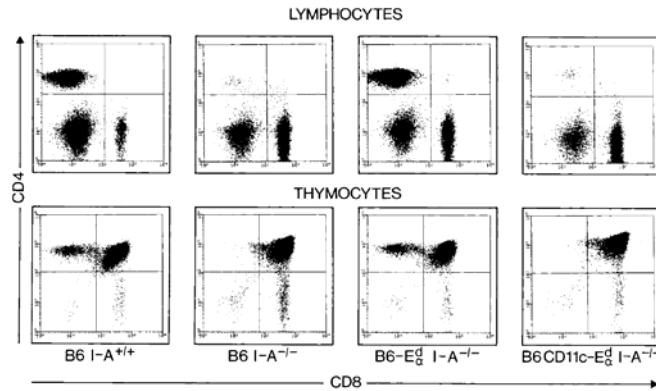
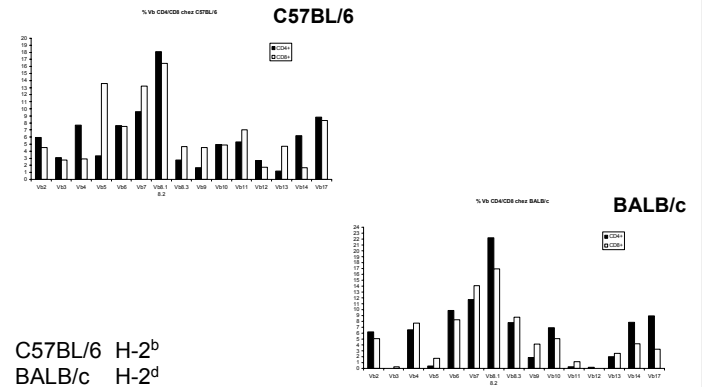
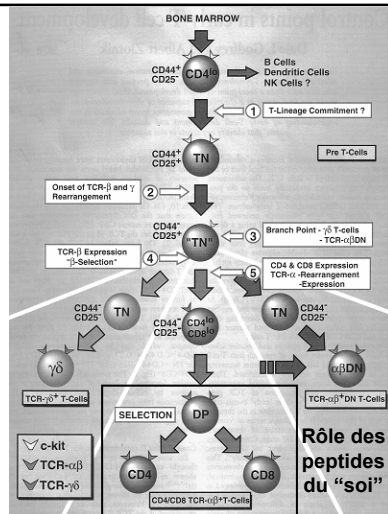


Figure 10-7
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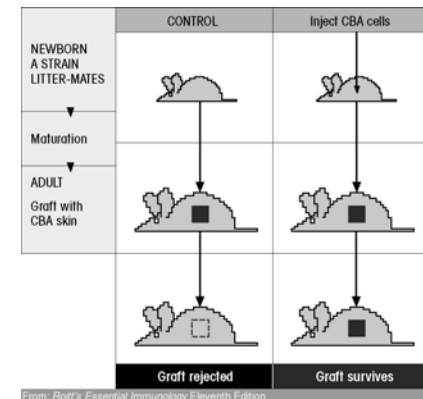
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Sélection positive & CMH (5)

Fonds C57BL/6 I-E⁻(I-E α ⁻), I-A⁺Brocker, Riedinger & Karjalainen (1997) *J. Exp. Med.* 185:541. **56**Baey & Thomas-Vaslin (2009) non publié. **57**

Godfrey and Zlotnik (1993) *Immunol.Today* 14:457.

Induction de la tolérance



From: Roitt's Essential Immunology Eleventh Edition

→ Rôle des peptides du soi → Délétion clonale



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Délétion clonale et superantigènes (1)

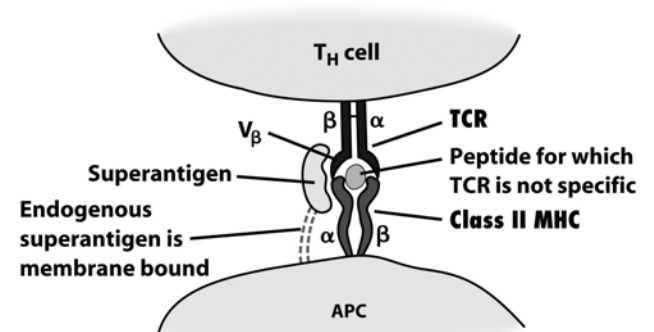


Figure 10-16
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Délétion clonale et superantigènes (2)

TABLE 10-3 Exogenous superantigens and their V _β specificity				
Superantigen	Disease ^a	V _β SPECIFICITY		
		Mouse	Human	
Staphylococcal enterotoxins				
SEA	Food poisoning	1, 3, 10, 11, 12, 17	nd	
SEB	Food poisoning	3, 8, 1, 8, 2, 8, 3	3, 12, 14, 15, 17, 20	
SEC1	Food poisoning	7, 8, 2, 8, 3, 11	12	
SEC2	Food poisoning	8, 2, 10	12, 13, 14, 15, 17, 20	
SEC3	Food poisoning	7, 8, 2	5, 12	
SED	Food poisoning	3, 7, 8, 3, 11, 17	5, 12	
SEE	Food poisoning	11, 15, 17	5, 1, 6, 1–6, 3, 8, 18	
Toxic shock syndrome toxin (TSST1)	Toxic shock syndrome	15, 16	2	
Exfoliative dermatitis toxin (ExFT)	Scalded skin syndrome	10, 11, 15	2	
Mycoplasma arthritidis supernatant (MAS)	Arthritis, shock	6, 8, 1–8, 3	nd	
Streptococcal pyrogenic exotoxins (SPE-A, B, C, D)	Rheumatic fever, shock	nd	nd	
^a Disease results from infection by bacteria that produce the indicated superantigens.				

*Disease results from infection by bacteria that produce the indicated superantigens.

Table 10-3
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Délétion clonale et superantigènes (3)

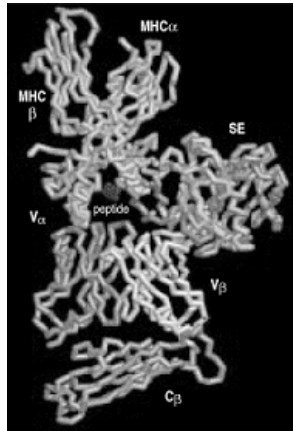
TABLE II V _β Specificity of MMTV Encoded Super-antigens				
Mtv	Chromosome	Super-antigen	V _β specificity	References
1	7	Mls-2	3	41
2	18		14	44
3	11		3, 17a	89, 92
6	16	Etc-2/Mls-3	3, 5, 1, 5, 2	35, 40, 41
7	1	Mls-1	6, 7, 8, 1, 9	41
8	6	Dvb11-1	5, 1, 5, 2, 11, 17a	39, 40
9	12	Etc-1/Dvb11-2	5, 1, 5, 2, 11, 12, 17a	33, 34, 38, 39, 40, 55
11	14	Dvb11-3	11	39
13	4	Mls-2	3	41
?	?		16*	26, 27
?	?		19a*	— [†]
?	?		20	29
C3H-exo			14, 15	42, 43
BALB/c tumor			2	90

*Super-antigen implicated but not yet demonstrated.

[†]R. J. Hodes, unpublished.

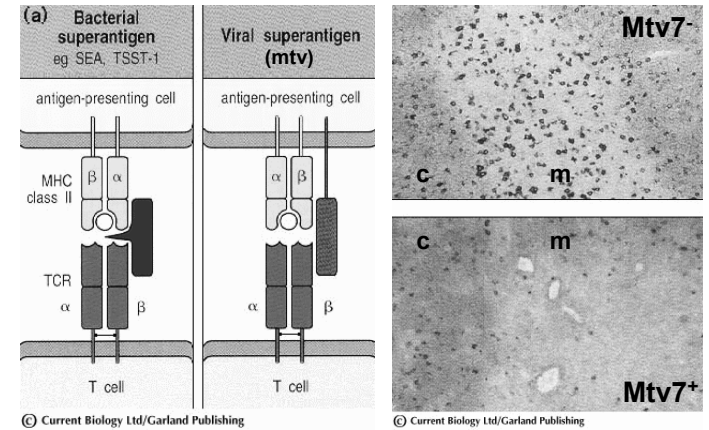
Woodland & Blackman (1992) *Int. Rev. Immunol.* 8:311. **63**

Délétion clonale et superantigènes (4)



64

Délétion clonale et superantigènes (5)



65

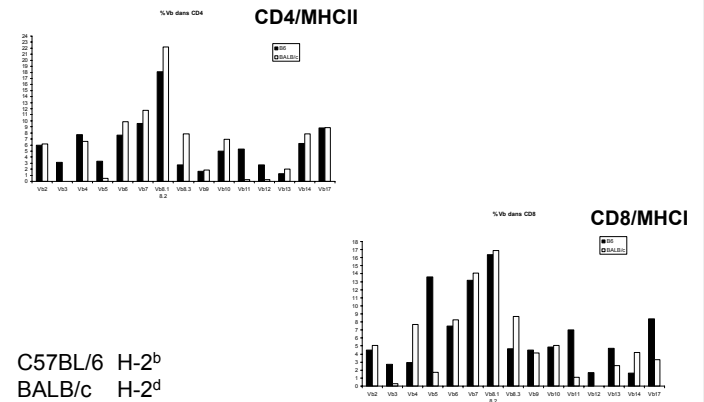
Délétion clonale et superantigènes (6)

Table 1. Strain distribution of some MTV proviruses, (adapted from Annu. Rev. Cell Biol. 1993 9:101-26)

MTV	1	3	6	7	8	9	11	13	14	17	23	29	30	31	†
Chromosome	7	11	16	1	6	12	14	4	4	4	6	6	12	Y	
cM from centromere	31	72	31	73	31	40	8	47	10	20	32	20-24	2		
Vb Specificity (Vb allele if not b)	3, 17?	3, 5, 17?	3, 5, 8.1, 17?	6, 7, 11, 12	5, 11, 12	11, 12	3, 17?	NE	NE	7	16	NE	7		
Strains	H2	IE		17?	9	17?	17?	17							
A/J	a	k	-	+	+	-	-	+	-	+	-	-	-	-	-
AKR/J	k	k	-	-	+	+	+	-	-	+	+	-	+	+	+
BALB/cByJ	d	d	-	-	+	+	+	-	-	-	-	-	-	-	-
B10.BR	k	k	-	-	+	+	+	-	-	+	-	-	+	-	-
C3H/HeJ	k	k	+	-	+	+	+	+	+	-	-	-	-	-	-
C57BL/6J	b	-	-	-	+	+	+	-	-	+	-	-	+	-	-
C57BR/cdJ(a)	k	k	-	-	+	+	+	+	+	+	+	+	?	-	-
C57L/J (a)	b	-	-	-	+	+	+	-	-	+	-	-	+	-	?
C58/J	k	k	-	+	+	-	-	-	-	+	-	-	+	-	-
CBA/CaJ	k	k	-	-	+	+	+	-	+	-	-	-	-	-	-
CBA/J	k	k	-	-	+	+	+	-	+	+	-	-	-	-	-

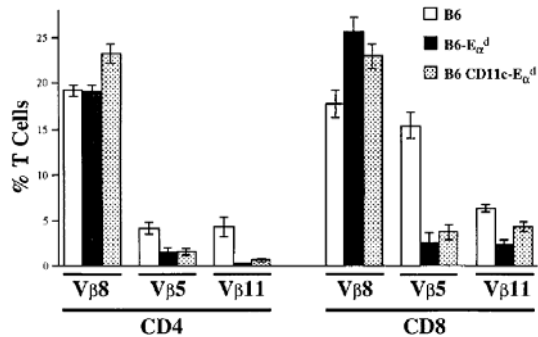
Scherer et al. (1993) Annu. Rev. Cell Biol. 9:101. 66

Sélection négative & superantigène (7)

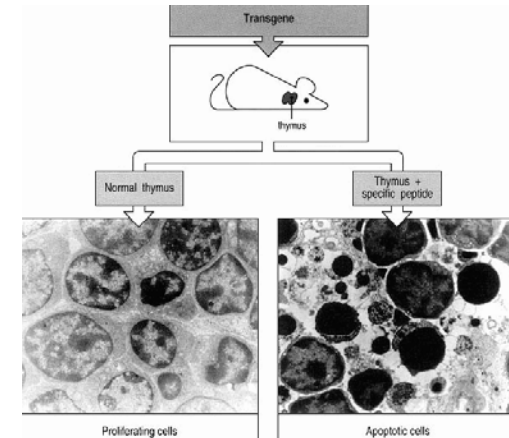
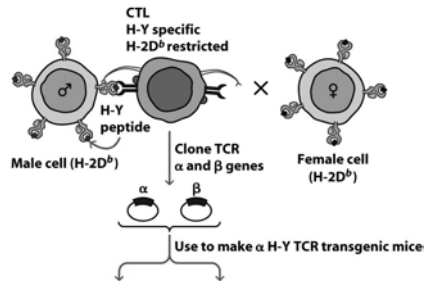


Baey & Thomas-Vaslin (2009) non publié. 67

Sélection négative & superantigène (8)

Fonds C57BL/6 I-E(I-E α), I-A⁺Brocker, Riedinger & Karjalainen (1997) *J. Exp. Med.* 185:541 **68**

Délétion clonale et TCR transgénique

**69**

	Male H-2D ^b	Female H-2D ^b
H-Y expression	+	-
Thymocytes		
CD4 ⁺ 8 ⁻	++	+
CD4 ⁺ 8 ⁺	+	++
CD4 ⁺	+	+
CD8 ⁺	-	++

Figure 10-8
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Sélection et TCR transgénique

Selection in SCID mice transgenic for H-2D^b/H-Y TCR

Phenotype	Positive selection		Negative selection	
	Transgenic females		Transgenic H-2 ^b	
	H-2 ^{b/d}	H-2 ^{d/d}	Males	Females
CD4 ⁺ 8 ⁻ TCR ⁻	+	++	+++	+
CD4 ⁺ 8 ⁺ TCR [±]	++	++	-	+++
CD4 ⁺ 8 ⁺ TCR ⁺⁺	+	-	-	+
CD4 ⁺ 8 ⁻ TCR ⁺⁺	-	-	-	-

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Experimental procedure—fetal thymic organ culture (FTOC)

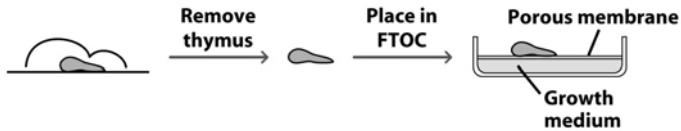


Figure 10-9a
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Development of CD8⁺ CD4⁻ MHC I-restricted cells

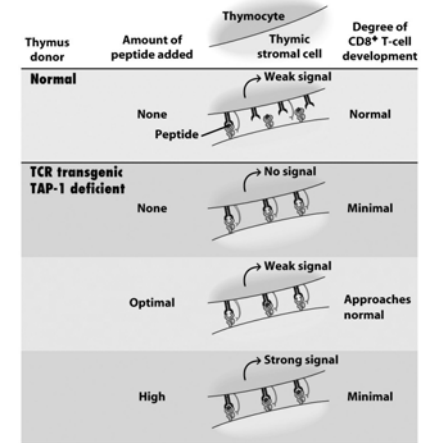
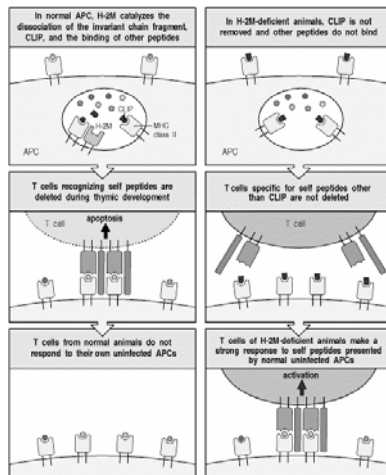


Figure 10-9b
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Peptides agonistes, antagonistes (1)

Peptide ligand altéré (APL)

= peptide analogue d'un peptide immunogène

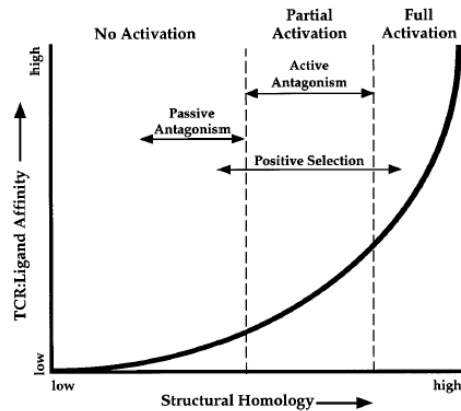
Agoniste → Conserve certaines fonctions d'activation

Antagoniste passif → Compétition pour le CMH

Antagoniste actif → induction d'anergie, modification de la cascade d'activation

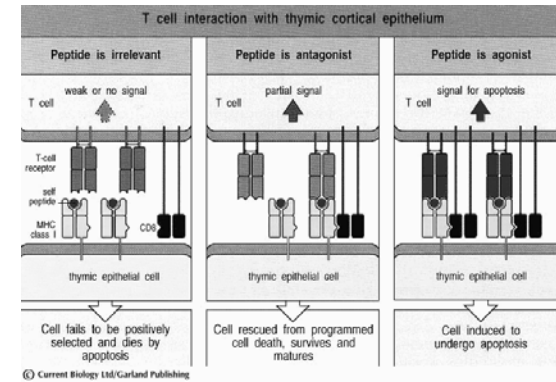
76

Peptides agonistes, antagonistes (2)



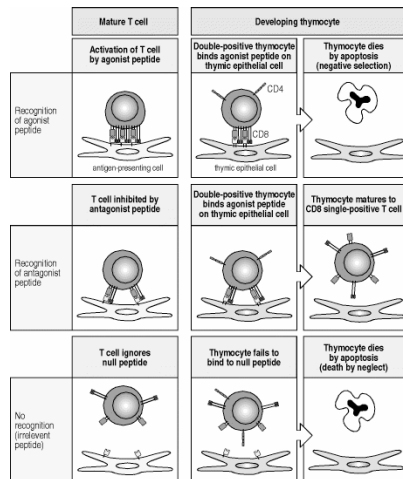
D'après Sloan-Lancaster et Allen (1996) *Annu. Rev. Immunol.* 14:1-37.

Peptides agonistes, antagonistes (3)

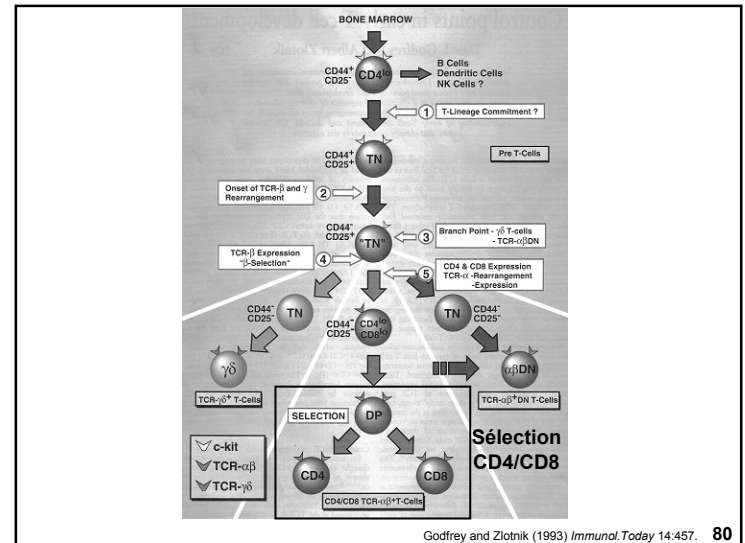


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Peptides agonistes, antagonistes (4)

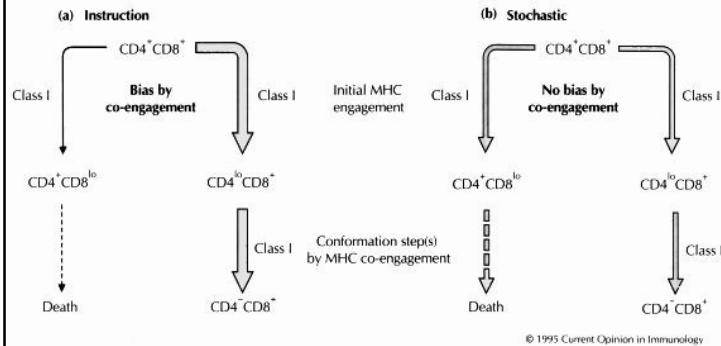


79



Godfrey and Zlotnik (1993) *Immunol. Today* 14:457. 80

Sélection CD8/CMHI & CD4/CMHII (1)



81

Sélection CD8/CMHI & CD4/CMHII (2)

INSTRUCTIVE MODEL

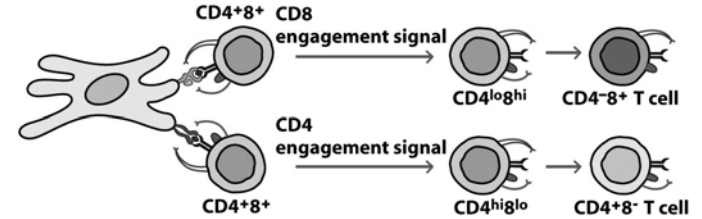


Figure 10-10 part 1
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Sélection CD8/CMHI & CD4/CMHII (3)

STOCHASTIC MODEL

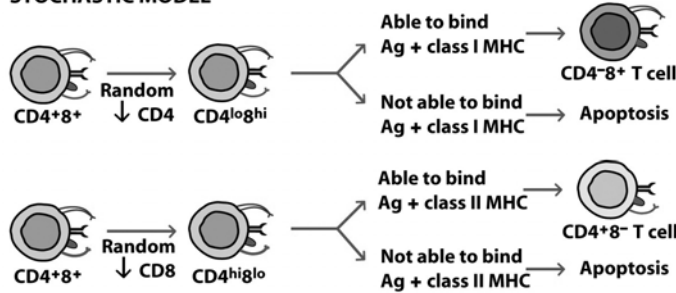
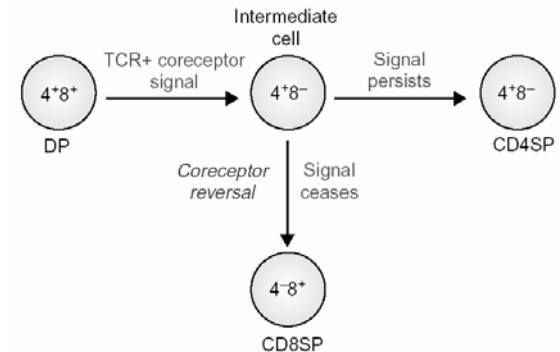


Figure 10-10 part 2
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Sélection CD8/CMHI & CD4/CMHII (4)

Modèle cinétique d'engagement CD4/CD8

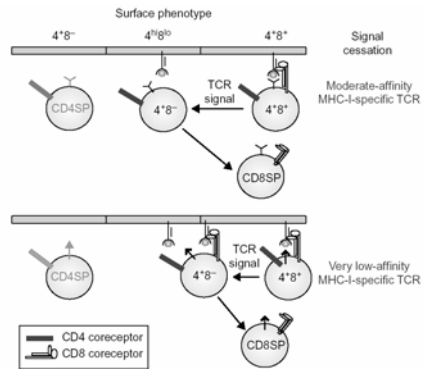


Current Opinion in Immunology

Singer, A. (2002) *Curr.Opin.Immunol.* 14, 207-285

Sélection CD8/CMHI & CD4/CMHII (5)

Modèle cinétique d'engagement CD4/CD8



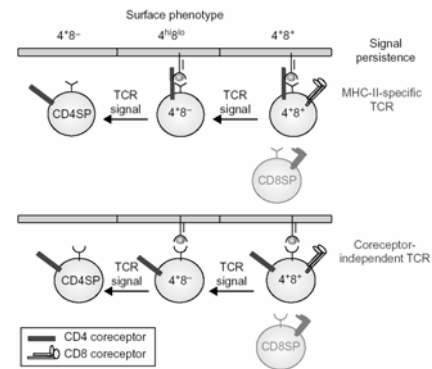
Current Opinion in Immunology

Singer, A. (2002) *Curr.Opin.Immunol.* 14, 207-216

Un arrêt du signal
promeut la
différenciation en
lymphocyte T CD8SP

Sélection CD8/CMHI & CD4/CMHII (6)

Modèle cinétique d'engagement CD4/CD8

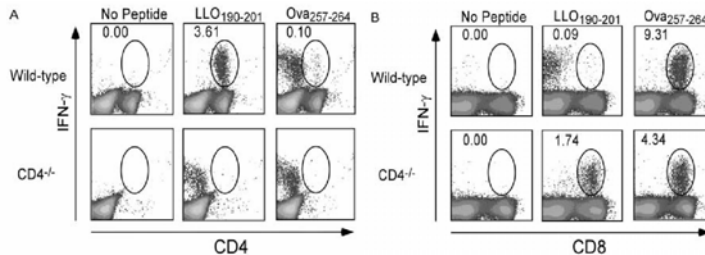


Current Opinion in Immunology

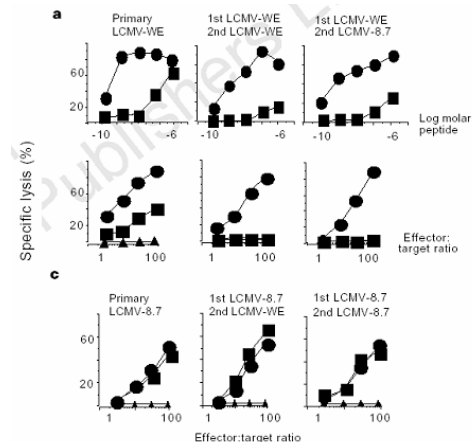
Singer, A. (2002) *Curr.Opin.Immunol.* 14, 207-216

Un signal persistant
promeut la
différenciation en
lymphocyte T CD4SP

Sélection CD8/CMHI & CD4/CMHII (7)

Tyznik, Sun & Bevan (2004) *J. Exp. Med.* 199:559. 88

Le « péché originel »



LCMV-WE
→ Sauvage
→ GP33-wt
→ H-2D^b

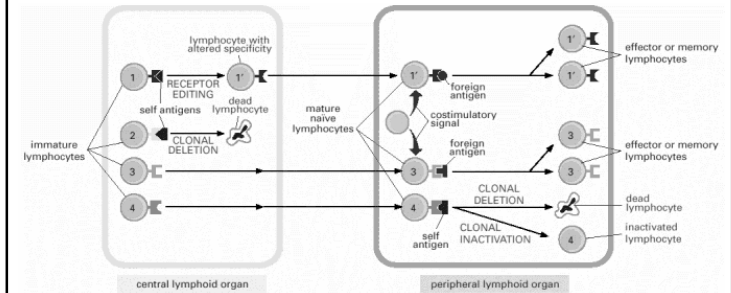
LCMV-8.7
→ Mutant
→ GP33-3L APL

Klenerman et Zinkernagel (1998) *Nature* 394:482-485. 89

Conclusion

90

Sélections centrale et périphérique



91

There is only one immune system! The view from immunopathology. A. M. Silverstein and N. R. Rose. *Semin. Immunol.* 12:173-178, 2000.

- The immune system does not 'decide' that a stimulus is deadly or harmless and respond accordingly.
- The world is not divided between the self and the not-self (foreign). The immune system does not 'know' the difference. Only obedience to the immunological rules defines what is tolerated and what is intolerable.
- SELF IS ONLY THAT COLLECTION OF POTENTIAL IMMUNOGENS THAT CANNOT STIMULATE A RESPONSE (or only a subliminal one) AT THAT TIME AND PLACE! This inability, which we name immunological tolerance [...] is the result of a multitude of central and peripheral down-regulatory mechanisms that have acted according to their own rules.
- Any 'foreign' epitope can become 'self' if administered appropriately, and any 'self' epitope can become 'foreign' and cause autoimmune disease, if tolerance is overcome with an adjuvant, by an intercurrent infection, by molecular mimicry, or by a variety of other means.
- Again, the immune system does not 'choose' immunoprotection or immunopathology in response to a challenge; both will occur in any event, and the fixed rules only determine the relative balance of the two.

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