Tolérance centrale
Sélection positive et négative des répertoires lymphocytaires

Adrien Six (adrien.six@upmc.fr)
Université Pierre et Marie Curie

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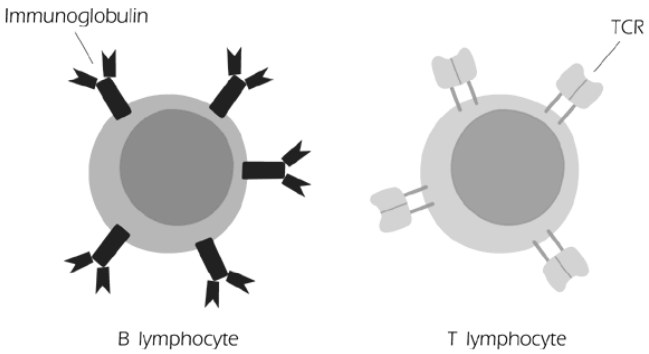
Sélection positive et négative des répertoires lymphocytaires

1. **Introduction**
2. Sélection des répertoires B
3. Sélection des répertoires T
4. Conclusion

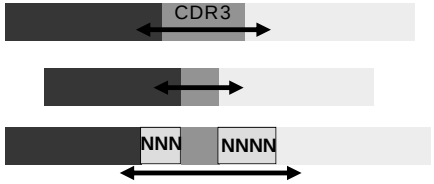
Les lymphocytes B et T



→ caractérisés par leur récepteur spécifique d'antigène

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, TCRα/β or TCRγ/δ
  - Ajout/élimination aléatoire de nucléotides à la jonction des segments géniques (CDR3)



Estimation de la diversité (2)

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

Mechanism of diversity	Ig H Chain	Ig κ Chain	αβ TCR α Chain	αβ TCR β Chain	γδ TCR γ Chain	γδ TCR 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 × 13 × 4	85 × 4	79 × 38	21 × 2 × 11	7 × 3	6 × 2 × 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				(some)		(often)
Junctional flexibility	+	+	+	+	+	+
N-region nucleotide addition‡	+ ~10^{12}	–	+ ~10^{15}	+	+ ~10^{18}	+
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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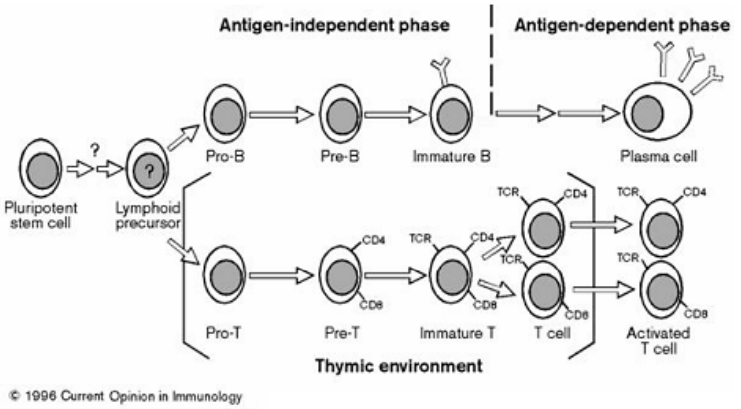
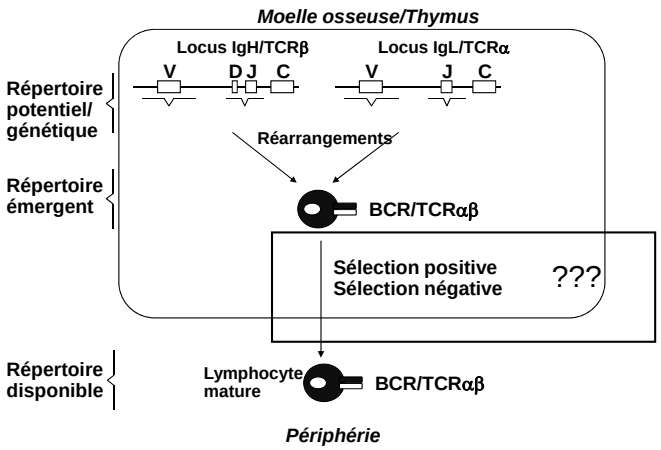
Parallèle différenciations B et T



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

Mise en place des répertoires



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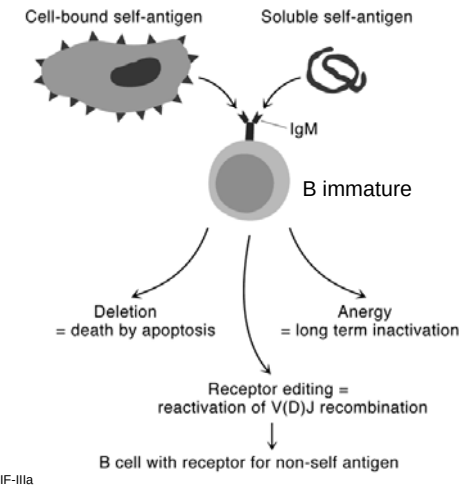
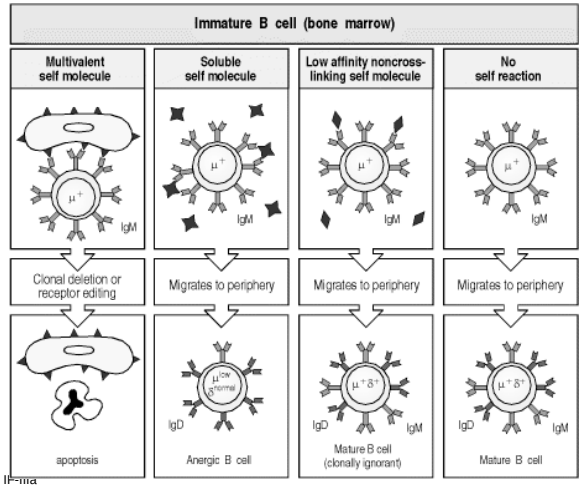
Sélection des lymphocytes B (1)



Sélection des lymphocytes B (2)



Délétion clonale (1)

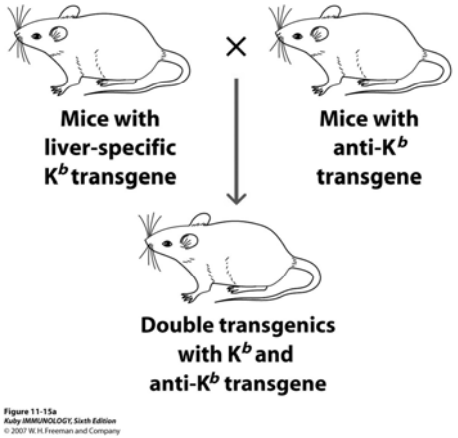


Figure 11-15a
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Délétion clonale (2)

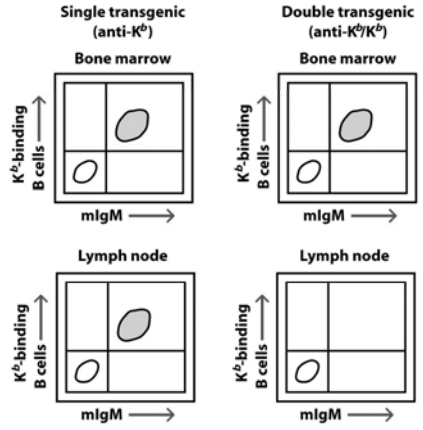

Figure 11-15b
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Anergie (1)

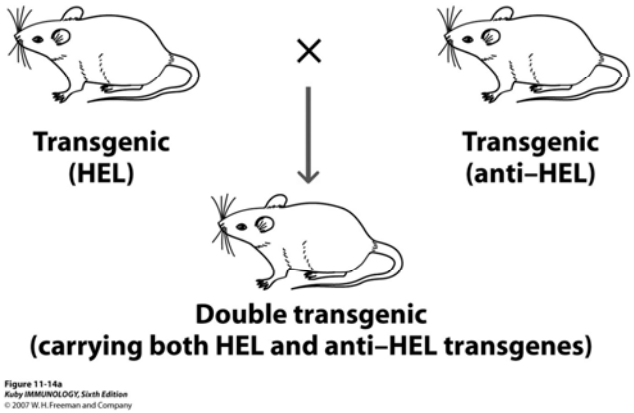

Figure 11-14a
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Anergie (2)

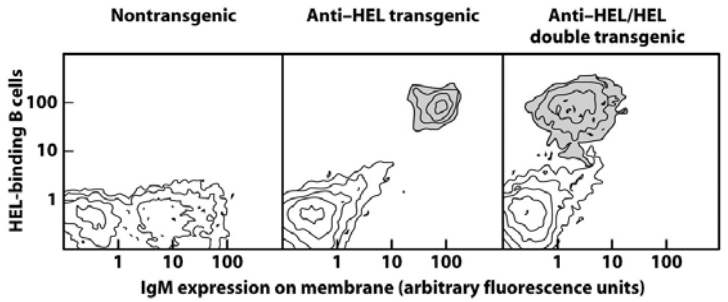

Figure 11-14b
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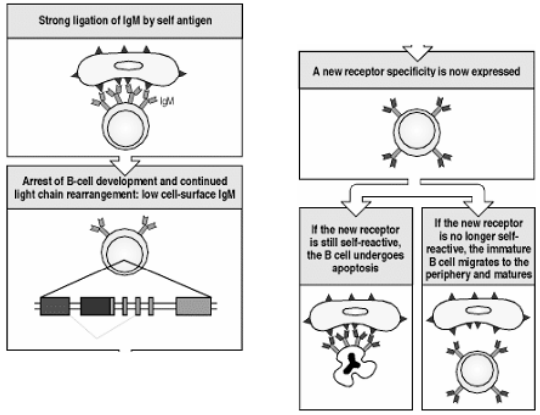
Sélection des lymphocytes B (3)



Édition du BCR (1)

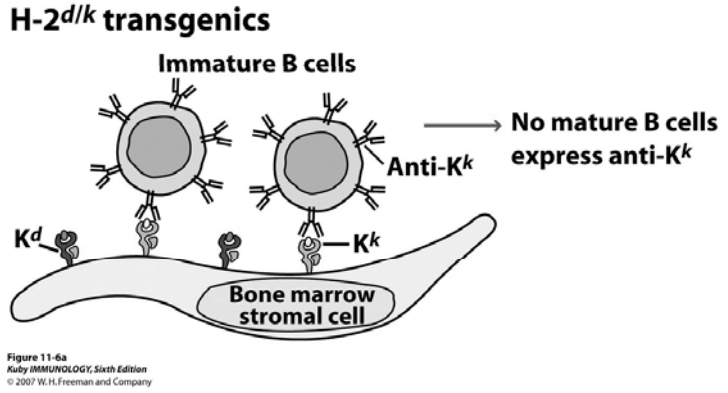


Figure 11-6a
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Édition du BCR (2)

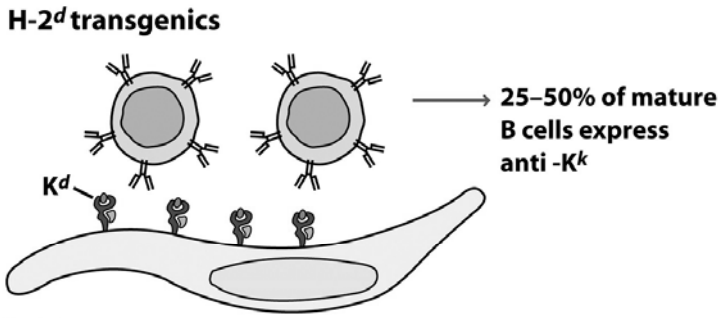

Figure 11-6b
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Édition du BCR (3)

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	Expression of transgene: As secreted Ab (μg/ml)
Nontransgenics	13	(−)	<0.3
H-2^d transgenics	7	(+)	93.0
H-2$^{d/k}$ 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)

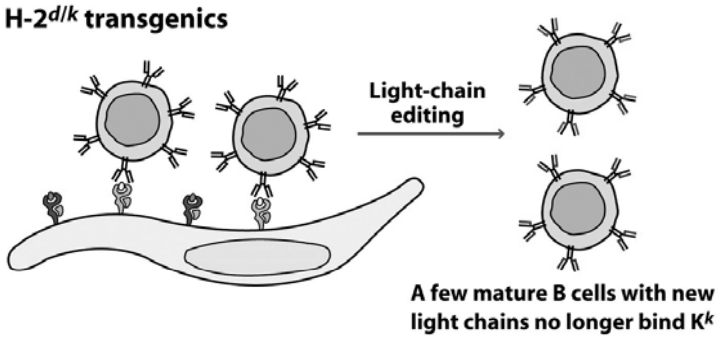

Figure 11-6c
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Sélection des lymphocytes B (4)

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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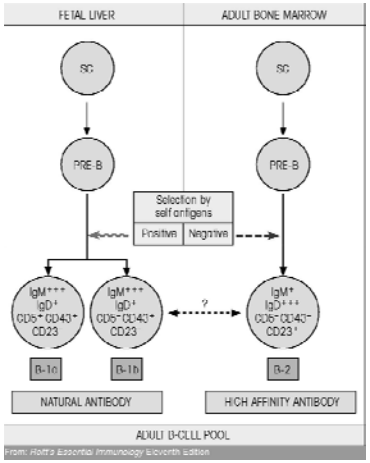
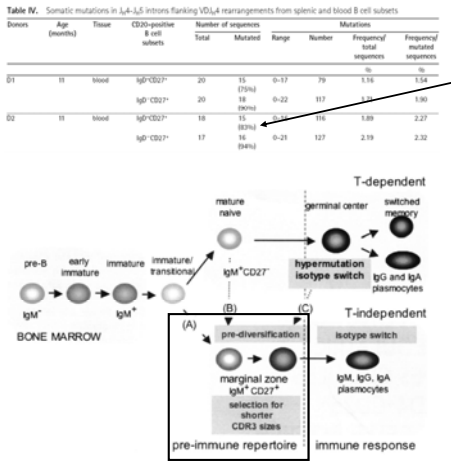
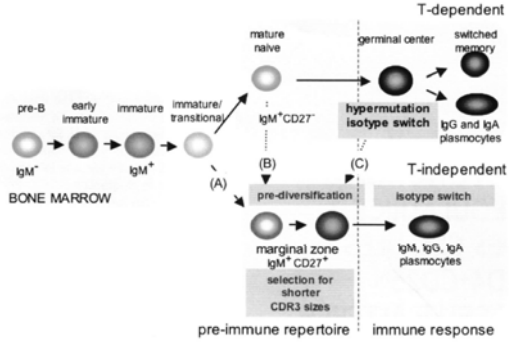
Sélection des lymphocytes B (5)



Hypermutations en absence d'antigène



Hypermutations en absence d'antigène



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 Igα; 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.

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	2×10^8	0	0	0	0
3	52	2×10^8	0	0	0	0
4	31	2×10^8	1	0.125	0	0
6	17	2×10^8	7	0.875	2	28.5
7	13	3×10^8	15	1.2	6	40.0
8	7	10^8	7	1.7	4	57.1
9	5	10^8	13	3.2	9	69.2
10	6	1.8×10^8	30	4.1	24	80.0
12	4	1.5×10^8	28	4.6	25	89.2
21	1	1.2×10^8	18	3.7	16	88.8
42–46	1	2×10^8	69	8.6	63	91.3

[a]The 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.
[b]Spleen cells from mice born within 12 hr of each other were pooled. Results from experiments performed on different days were pooled for the table.
[c]Calculated as per Sigal et al. (1977).

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

Dominance clonale: idiotype T15 (3)

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

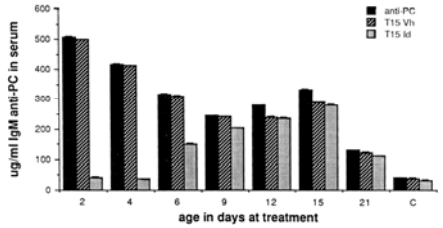


TABLE 3

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[c]
None	None	0/7[b]	0/7[a]
No serum		0/7[b]	0/7[a]

[a]Different from none/R36A at $p < 0.01$.
[b]Different from none/R36A at $p < 0.001$.
[c]Different 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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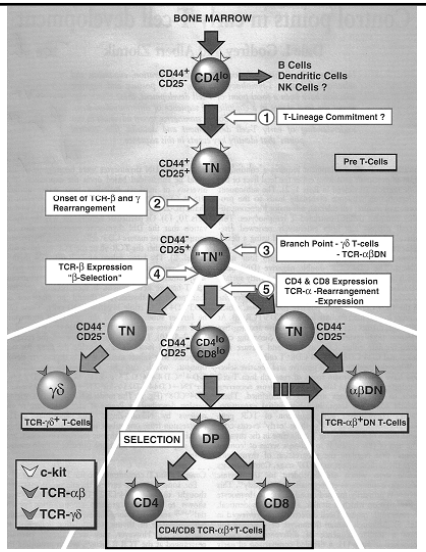
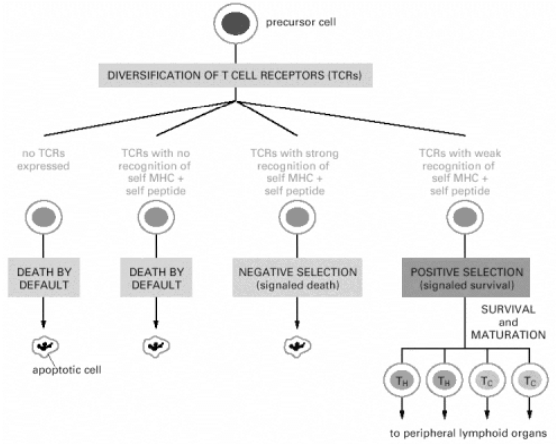


Godfrey and Zlotnik (1993) *Immunol.Today* 14:457.

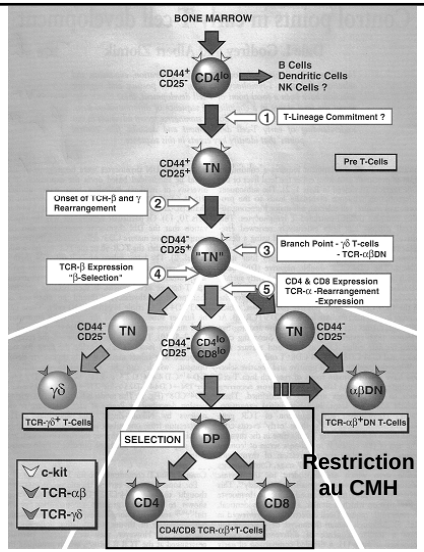
Sélections positive et négative (1)

- 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

Sélections positive et négative (2)

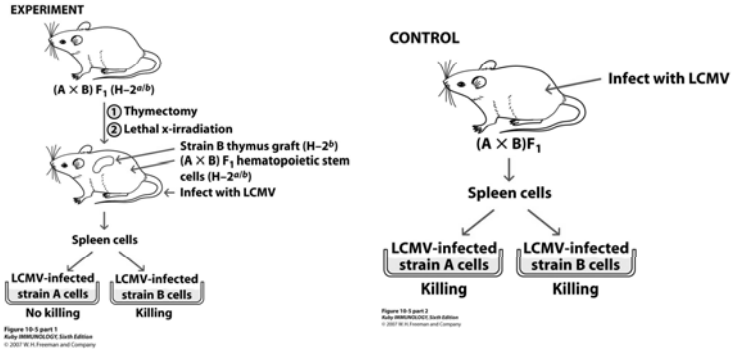


→ *Éducation thymique*



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

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

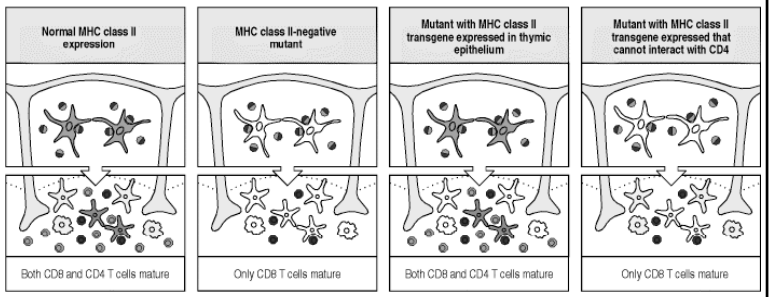


Rôle de l'épithélium thymique dans la sélection positive (2)

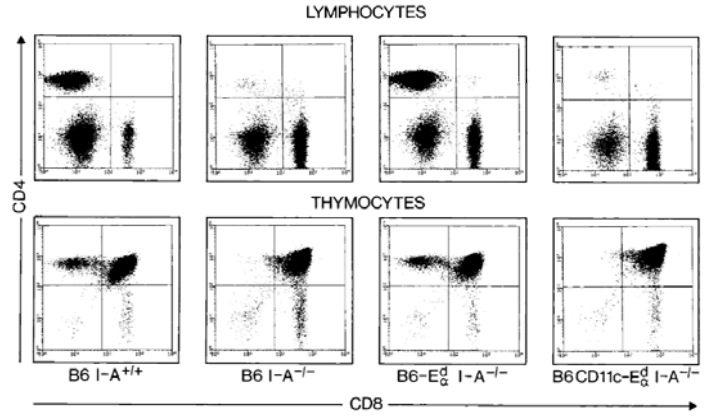
Thymectomize *b* x *k* mice	Graft with thymus of haplotype	Irradiate and reconstitute with *b* x *k* bone marrow	Prime with KLH	Proliferative response of primed T-cells to KLH on antigen-presenting cells of haplotype	
				$H\text{-}2^b$	$H\text{-}2^k$
	b x *k*	→		++	++
	b	→		++	–
	dGuo-treated *b*	→		++	–
	k	→		–	++
	dGuo-treated *k*	→		–	++

From: *Roitt's Essential Immunology* Eleventh Edition

Sélection positive & CMH (1)



Sélection positive & CMH (2)



Fonds C57BL/6 I-E$^-$(I-Eα^-), I-A$^+$

Brocker, Riedinger & Karjalainen (1997) *J. Exp. Med.* 185:541.

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	KNOCKOUT MICE: 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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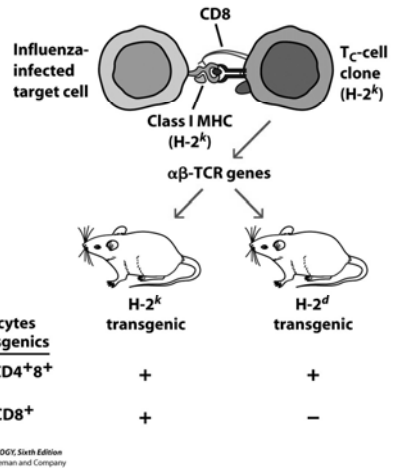
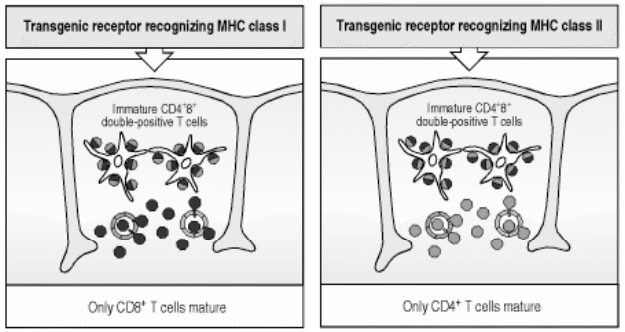
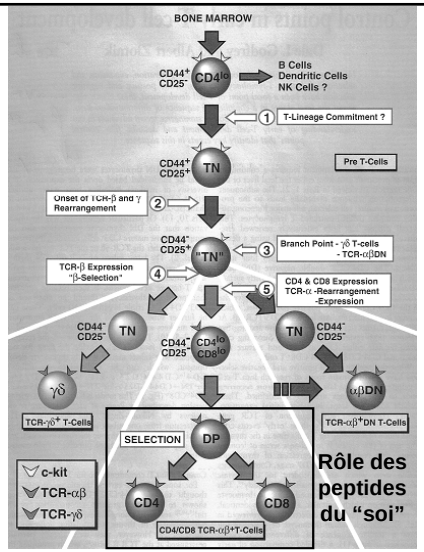
Sélection positive & CMH (4)



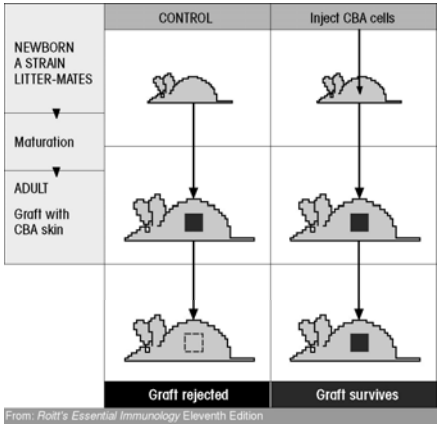
Sélection positive & CMH (5)



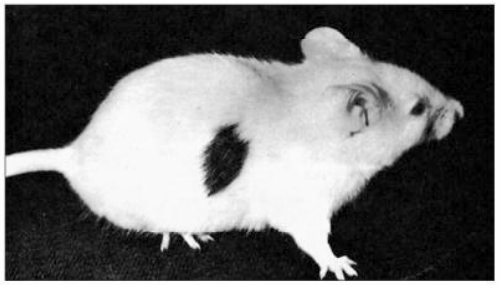


 Godfrey and Zlotnik (1993) *Immunol.Today* 14:457.

Induction de la tolérance



→ Rôle des peptides du soi → Délétion clonale



Délétion clonale et superantigènes (1)

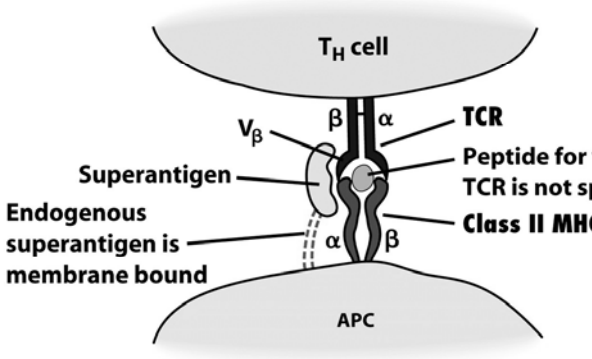


Figure 10-16
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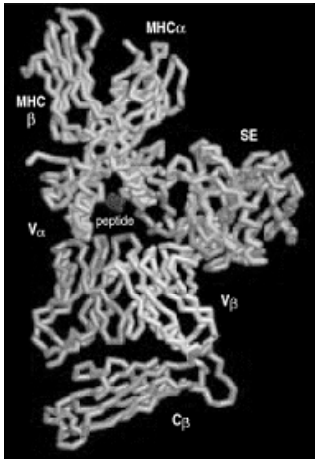
Délétion clonale et superantigènes (4)



Délétion clonale et superantigènes (2)

TABLE 10-3 Exogenous superantigens and their V_β specificity

Superantigen	Disease*	V_β SPECIFICITY: Mouse	V_β SPECIFICITY: 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

*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

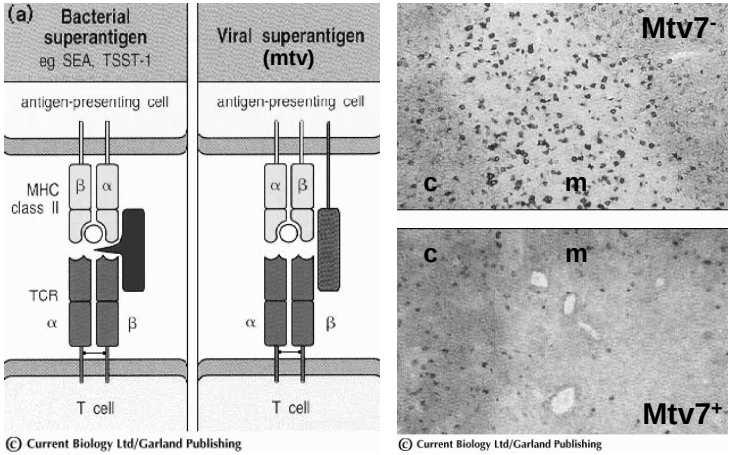
Vβ Specificity of MMTV Encoded Super-antigens

Mtv	Chromosome	Super-antigen	Vβ 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.

Délétion clonale et superantigènes (5)



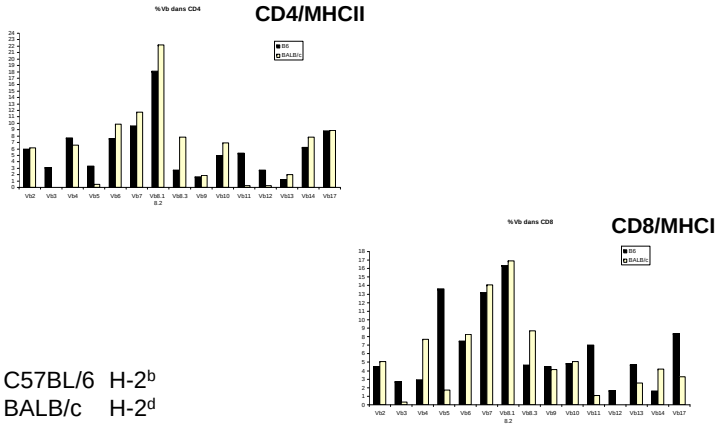
Délétion clonale et superantigènes (6)

Table 1. Stain distribution of some MTV proviruses. *(adapted from Annu. Rev. Cell Biol. 1993.9:101-28)*

	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 (Vβ allele if not b)		3, 17?	3,5 17	3, 5, 17?	6,7, 8.1, 9	5,7 11,12 17?	5, 11,12 17?	11, 12 17	3, 17?	NE	NE	7	16	NE	?
Strains	H2	IE													
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.

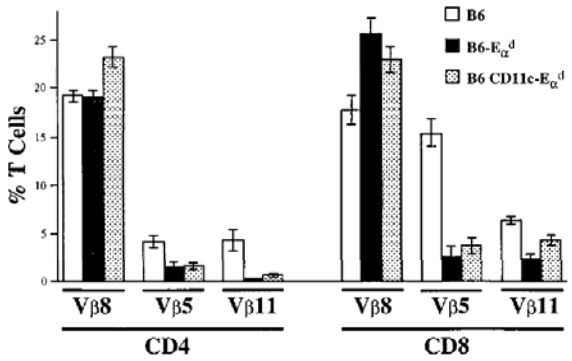
Sélection négative & superantigène (7)



C57BL/6 H-2^b
BALB/c H-2^d

Baey & Thomas-Vaslin (2009) non publié.

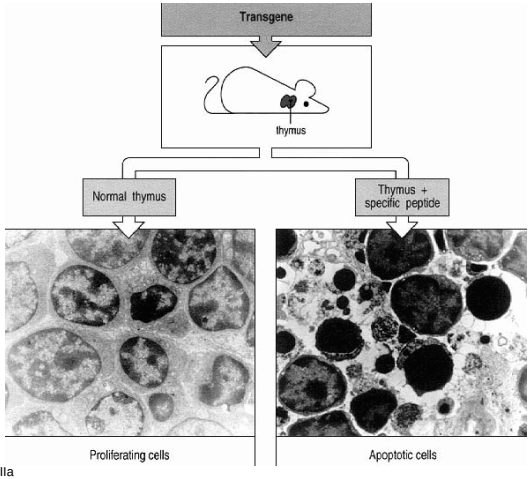
Sélection négative & superantigène (8)



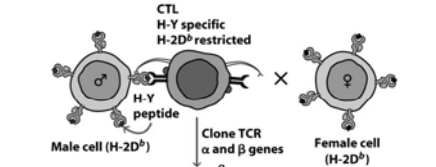
Fonds C57BL/6 I-E$^-$(I-Eα$^-$), I-A$^+$

Brocker, Riedinger & Karjalainen (1997) *J. Exp. Med.* 185:541.

Délétion clonale et TCR transgénique



Sélection et TCR transgénique



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

Figure 10-8
Kuby IMMUNOLOGY, Sixth Edition

Culture organotypique de thymus fœtal

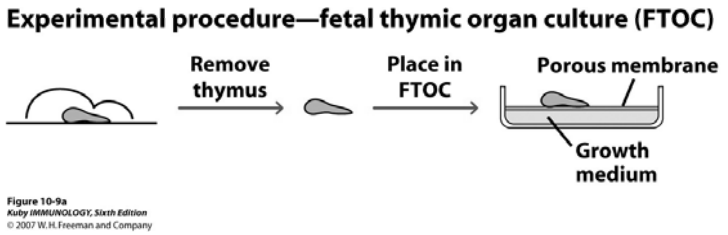
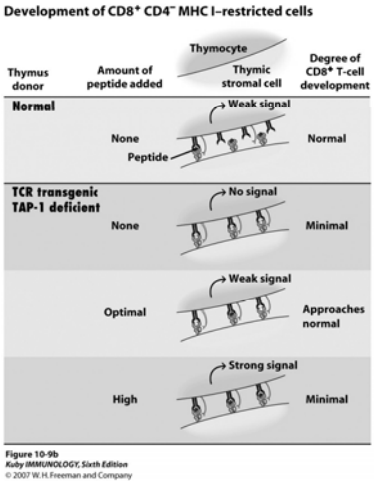
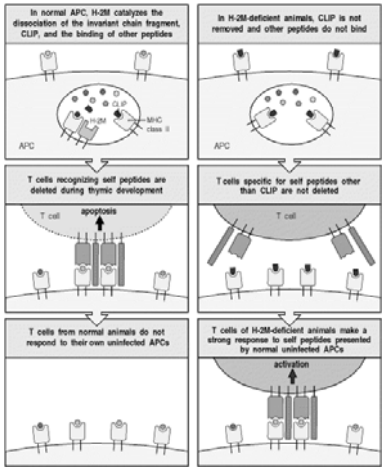


Figure 10-9a
Kuby IMMUNOLOGY, Sixth Edition

Rôle du peptide dans la sélection



Rôle du peptide dans la sélection



Peptides agonistes, antagonistes (1)

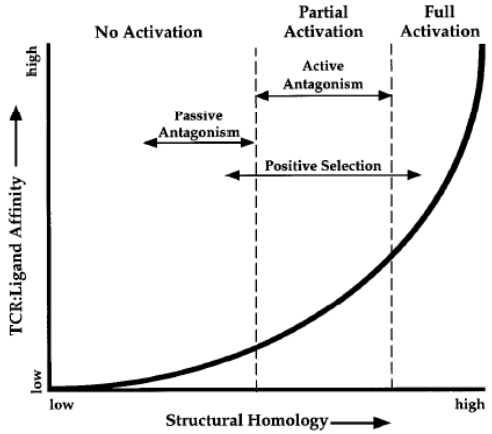
Peptide ligand altéré (APL)
= peptide analogue d'un peptide immunogène

Agoniste → Conserve certaines fonctions d'activation

Antagoniste passif → Compétition pour le CMH

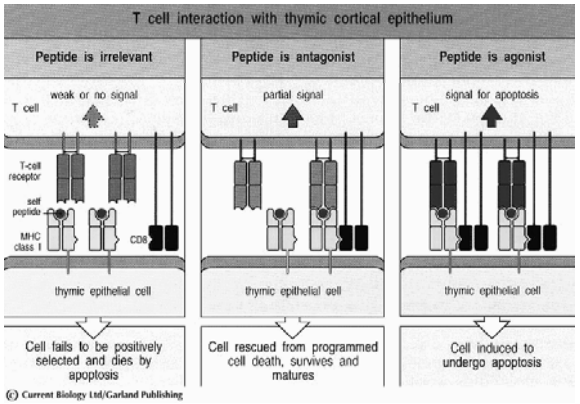
Antagoniste actif → induction d'anergie, modification de la cascade d'activation

Peptides agonistes, antagonistes (2)



D'après Sloan-Lancaster et Allen (1996) *Annu. Rev. Immunol.* 14:1-27

Peptides agonistes, antagonistes (3)



Expression des peptides du soi dans le thymus sous contrôle de AIRE

- AIRE fait partie d'un complexe multiprotéique
- Activateur transcriptionnel ectopique
- Expression dans le thymus, en particulier au niveau des cellules épithéliales médullaires (mTEC)

Table 1. Summary of the cell type–specific pattern of promiscuous gene expression

	SAP	CRP	Complement C5	α-fetoprotein	Albumin	Haptoglobin	α1-antitrypsin	PLP	MOG	S100β	GAD67	GAD65	Somatostatin	Trypsin2	Elastase	Insulin	Tyrosinase	Gp100	P1A	Thyroglobulin	Lactalbumin	α1-crystallin	Retinal S antigen	NAChRα1	IRBP	Amylase1
cTECs	–	–/+	+	–	–	–	–	+	–	–	–	–	–/+	–/+	+	–	–	+	–/+	+	–/+	+	+	–	–/+	+
mTECs	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
DCs	–	–	–/+	–	–	–	–	–/+	–	–	–	–	–/+	–	–/+	–	–	–	–	–	–	–	–	–	–	–
Macrophages	–	–	–/+	–	–	–	–	–/+	–	+	–	–	–	–	+	–	–	+	–	–	–/+	–/+	+	–	–	–/+

Derbinski *et al.* (2001) *Nat. Immunol.* 2:1032.

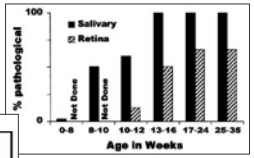
- Déficience de AIRE (souris knock-out; syndrome APECED chez l'homme) → autoimmunité +++

AIRE prévient l'autoimmunité

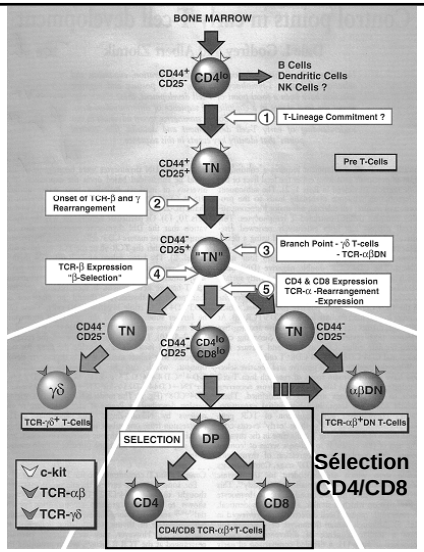
- Génération de souris knock-out pour AIRE:
  → augmentation avec l'âge de la fréquence de pathologies autoimmunes spécifiques d'organes
  → infiltrat lymphocytaire dans de nombreux organes
  → production d'autoanticorps spécifiques d'organes

Infiltrats lymphocytaires:

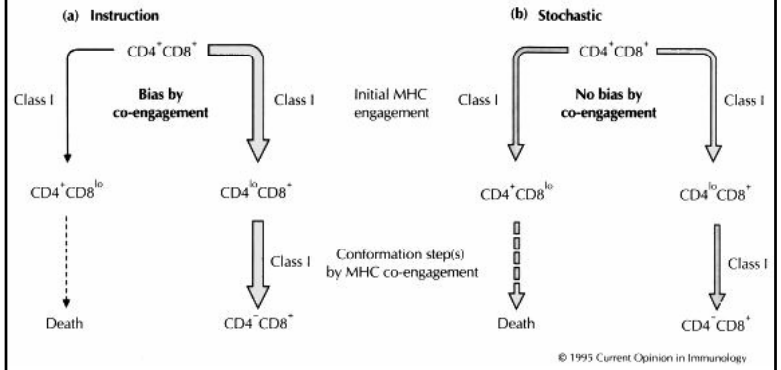
Sex	Age	Salivary	Reproduc.	Thyroid	Retina	Liver	Stomach
F	3	-	-	+	ND	-	-
M	4	-	-	-	ND	-	-
M	4	-	-	-	ND	-	-
F	9	+	-	-	ND	-	-
F	9	+	-	ND	ND	ND	ND
M	9	-	-	ND	-	ND	ND
M	10	tr	-	ND	+	ND	ND
M	15	+	-	-	ND	-	-
F	15	+	+	+	+	tr	-
F	15	+	-	-	-	tr	-
F	22	+	-	NA	+	tr	-
M	30	+	+	NA	-	+	+
F	31	+	tr	-	+*	+	+
M	35	+	+	NA	+	+	-



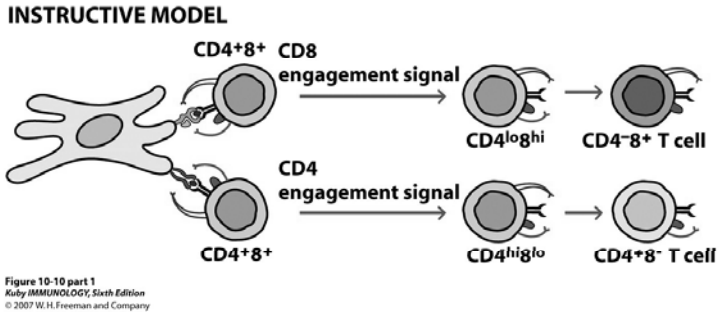
Derbinski *et al.* (2001) *Nat. Immunol.* 2:1032.



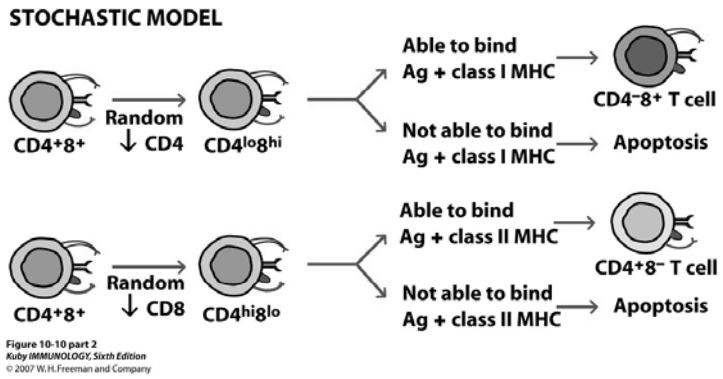
Sélection CD8/CMHI & CD4/CMHII (1)



Sélection CD8/CMHI & CD4/CMHII (2)

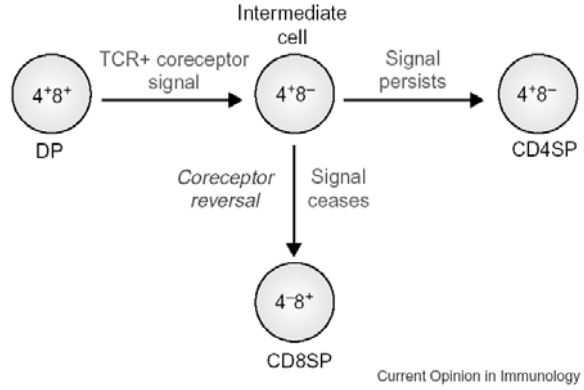


Sélection CD8/CMHI & CD4/CMHII (3)



Sélection CD8/CMHI & CD4/CMHII (4)

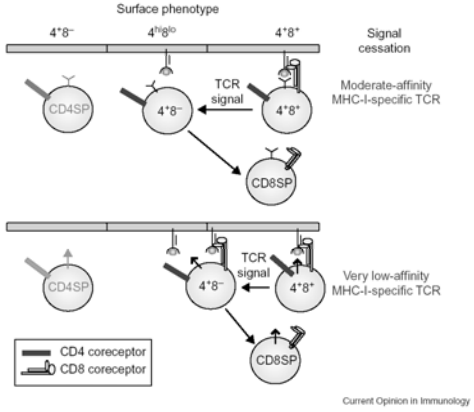
Modèle cinétique d'engagement CD4/CD8



Singer, A. (2002) *Curr.Opin.Immunol.* 14, 207-215

Sélection CD8/CMHI & CD4/CMHII (5)

Modèle cinétique d'engagement CD4/CD8

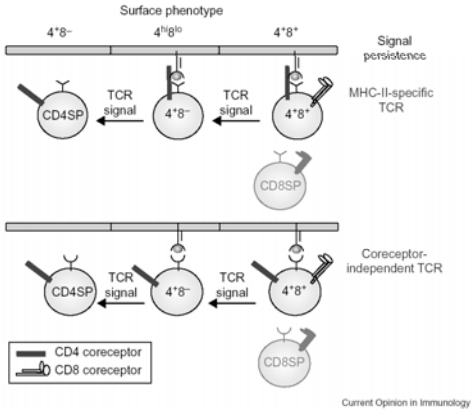


Un arrêt du signal promeut la différenciation en lymphocyte T CD8SP

Singer, A. (2002) *Curr.Opin.Immunol.* 14, 207-215.

Sélection CD8/CMHI & CD4/CMHII (6)

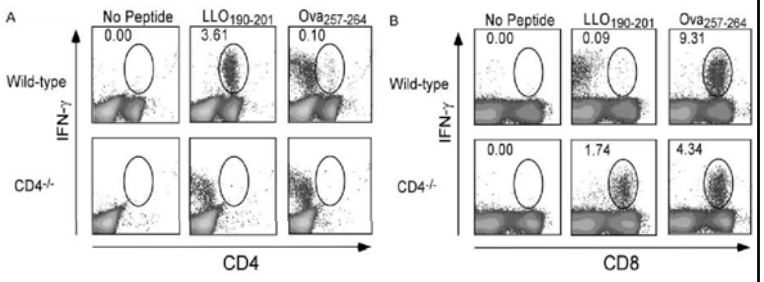
Modèle cinétique d'engagement CD4/CD8



Un signal persistant promeut la différenciation en lymphocyte T CD4SP

Singer, A. (2002) *Curr.Opin.Immunol.* 14, 207-215.

Sélection CD8/CMHI & CD4/CMHII (7)

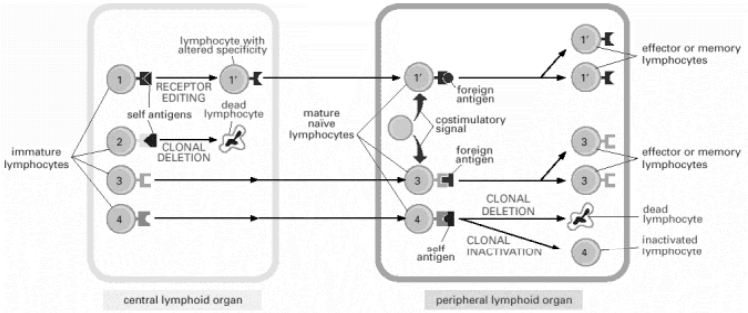


Fonds C57BL/6 H-2^b
$LLO_{190-201}$ → I-A^b
$OVA_{257-264}$ → K^b

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

Conclusion

Sélections centrale et périphérique



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***.

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.