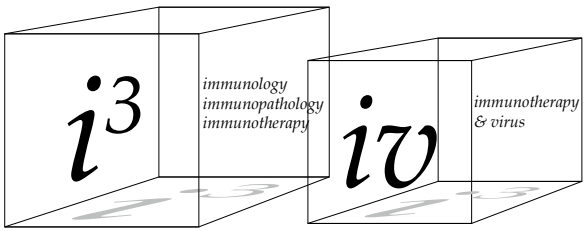
UPMC BMC423 IF

Tolérance Immunitaire:
Mécanismes de tolérance périphérique



Bertrand Bellier
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bertrand.bellier@upmc.fr

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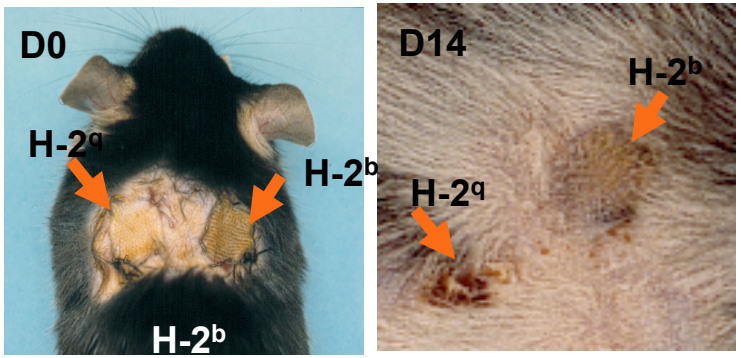
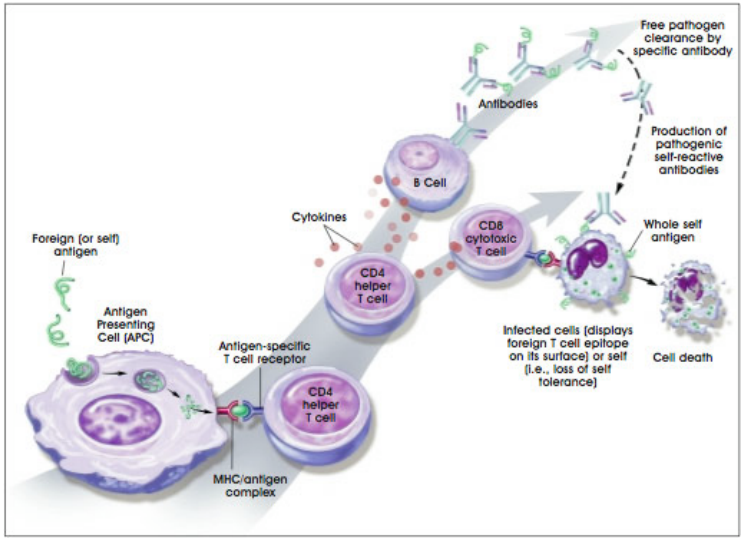
B. Bellier

Tolérance immunitaire

- **Propriété essentielle du sytème immuniatire**
- **Assure la discrimination du soi / non-soi**

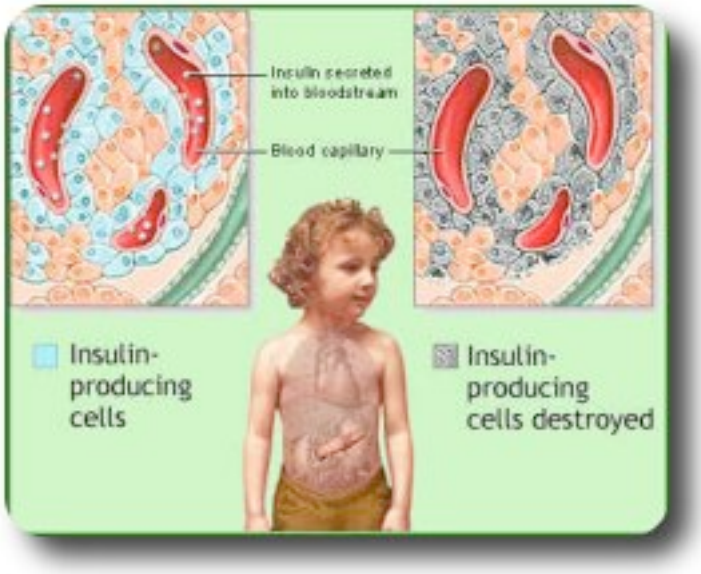
- **Tolérance naturelle**
  - La tolérance naturelle au soi a été acquise après des centaines de millions d'années d'évolution qui ont sélectionné des récepteurs permettant de différencier les produits microbiens ou les cellules infectées des produits du soi …
- **Tolérance induite**
  - Induction d'une non-réactivité immunitaire contre le non-soi
  - Infections chroniques
  - Immunothérapies actives
- **Conséquences:**
  - Tolérance au soi
  - Réponse immunitaire et élimination des pathogènes
  - Rejet des greffes allogéniques
  - En cas de rupture de la tolérance : Maladies Auto Immunes

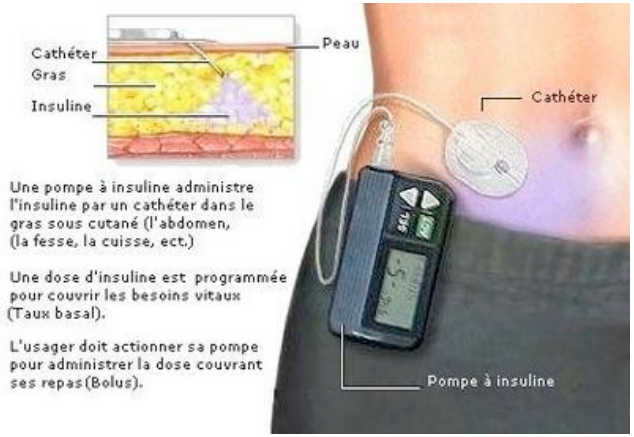




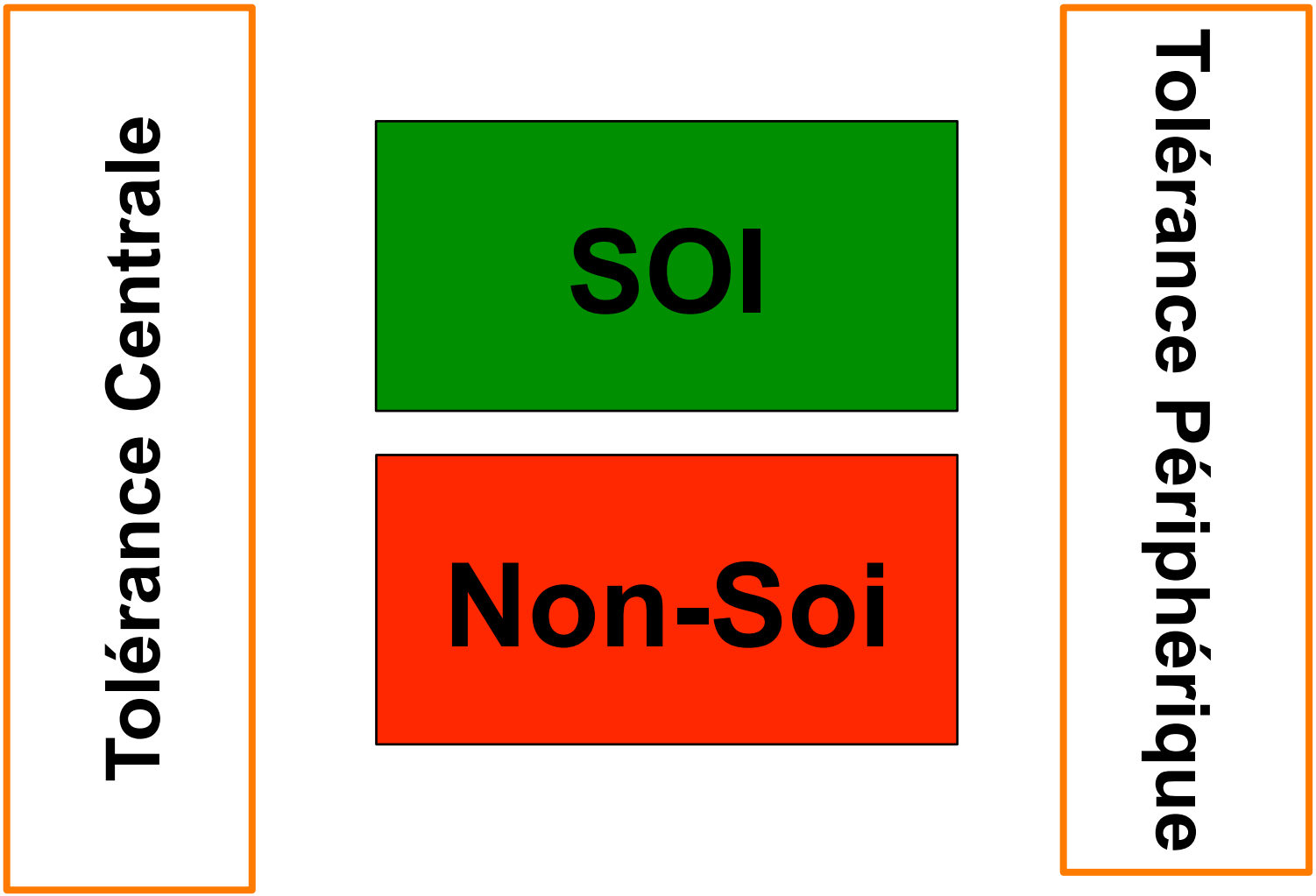
Rupture de Tolérance / Rejet du soi

- **Maladies auto-immunes:**
  - EX: les thyroïdites auto-immunes, la polyarthrite rhumatoïde, la spondylarthrite ankylosante, le diabète type 1, la maladie de Crohn, etc…





Tolérance immunitaire



B. Bellier

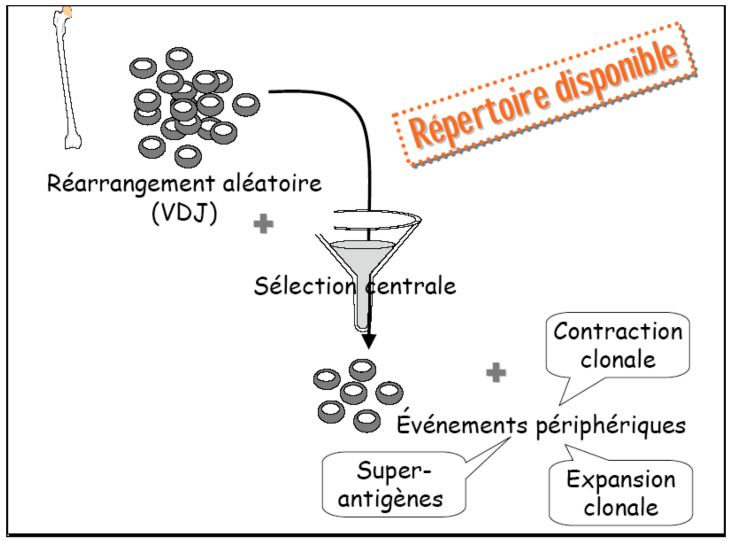
Tolérance centrale

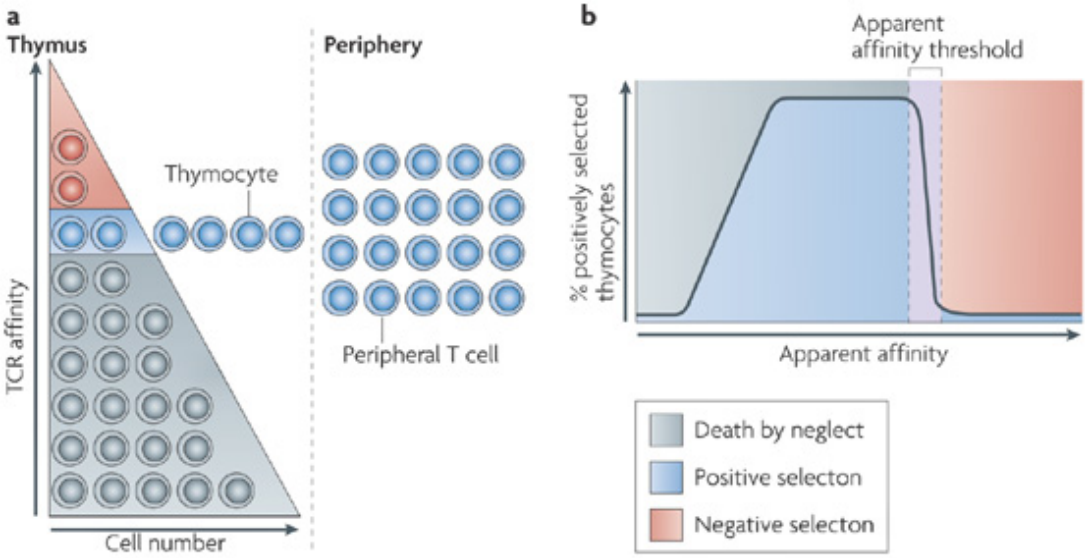
- Cf cours A. Six
- Etape déterminante de l'ontogénie lymphocytaire
- Tolérance T (thymus) et B (MO)
- Ontogénie T:

  -Sélection du répertoire disponible sur la base du CMH-AgSoi

  -Absence de sélection des clones non-fonctionnels (non-restreints au CMH)

  -Elimination des clones de forte affinité pour CMH-AgSoi





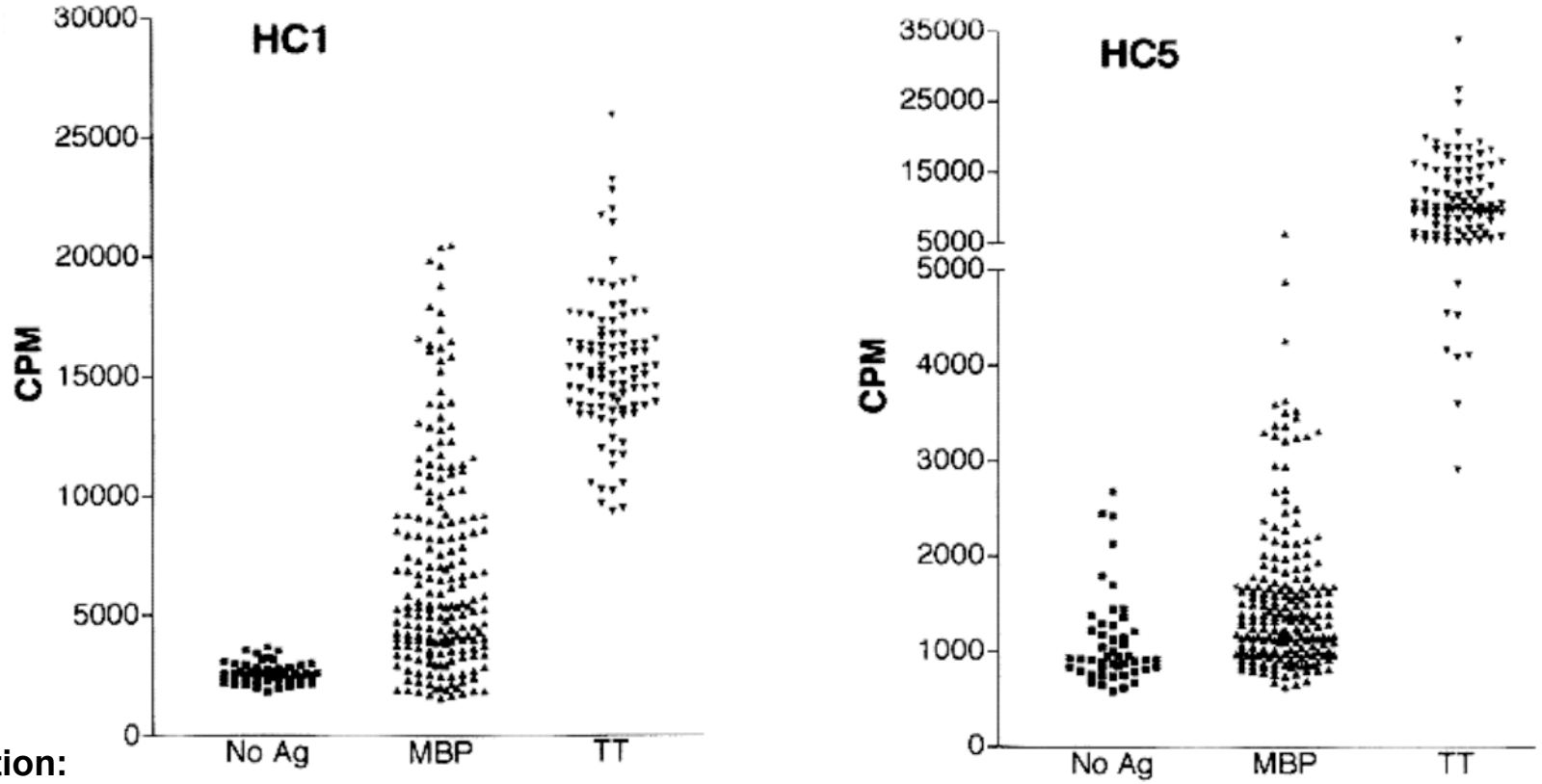
B. Bellier

Présence de lymphocytes autoréactifs en périphérie: un danger potentiel

B. Bellier

Echappement des clones de faible affinité à la sélection centrale

Reconnaissance de la MBP chez des individus sains



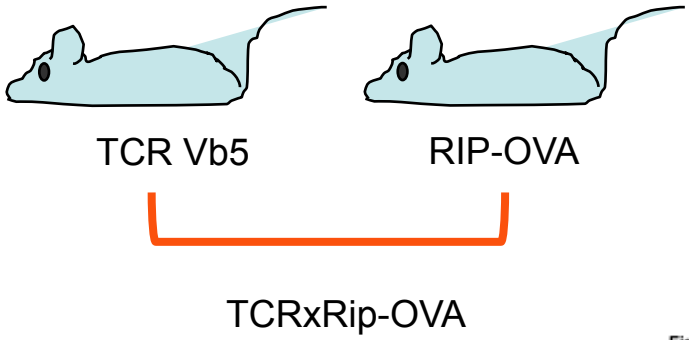
Lovett-Racke *et al.* 1998

Il existe donc dans le sang des sujets sains des lymphocytes T dont le TCR reconnaît des peptides d'une protéine de la myéline

…mais absence de réponse des clones auto-réactives

Zehn D 2006 Immunity

Modele TCR Vb5 / rip OVA



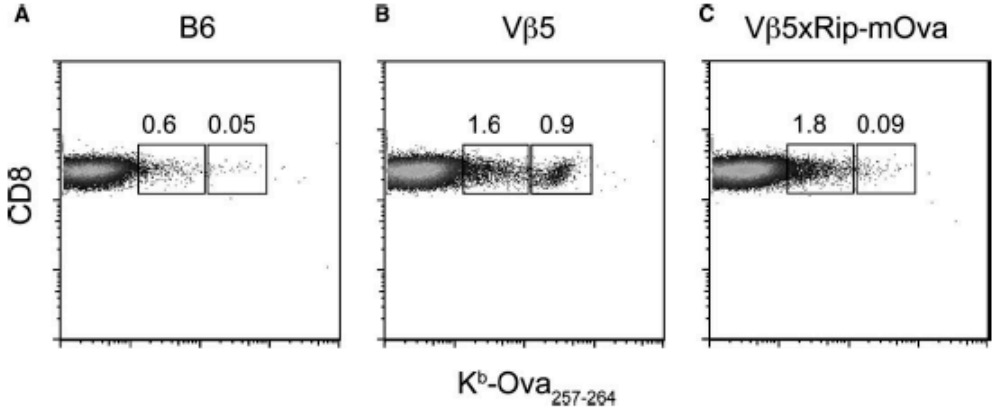
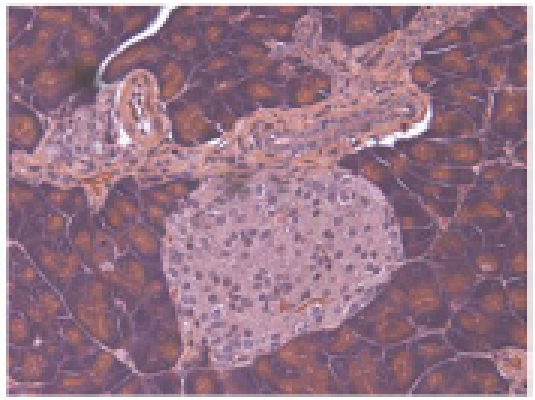


Figure 1. Tetramer Staining of Naive B6, Vβ5, and Vβ5xRip-mOva (C) Mice

Peripheral blood cells from B6 (A), Vβ5 (B), and Vβ5xRip-mOva (C) mice were stained with anti-CD8 and K^b-Ova tetramer. The representative plots shown are gated on $CD8^+$ T cells. The regions highlight cells staining at high and low levels with tetramer, and the numbers represent their frequency within the $CD8^+$ T cell population. The data are representative of three independent experiments.

TCRβ-only transgenic mice (Vβ5) expressing the same TCRβ chain as OT-I that skews CD8+ T cells to recognition of the Kb-Ova ligand (Dillon et al., 1994). The TCRβ transgene, in combination with endogenously rearranged TCRα chains, results in a detectable polyclonal population of CD8+ T cells with heterogeneous avidity for Kb-Ova. Thus, we were able to visualize TRA-specific T cells of a range of avidities in the naive repertoire

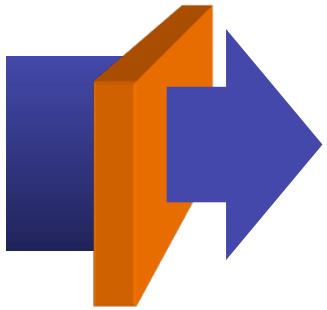
Vβ5xRip-mOva



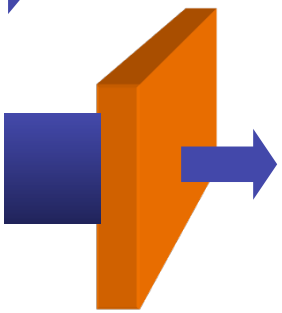
No diabetis

…contrôle en périphérie des clones auto-réactives

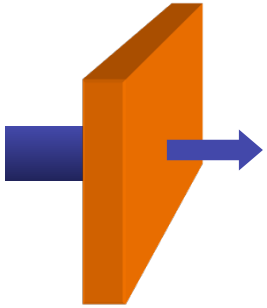
Etapes déterminantes au déclenchement des réponses:



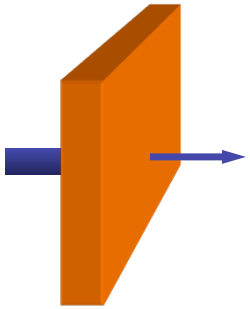
Atteindre **le tissu cible (Ag+)**



Percevoir **le signal**



Proliférer **et** ***se différencier***

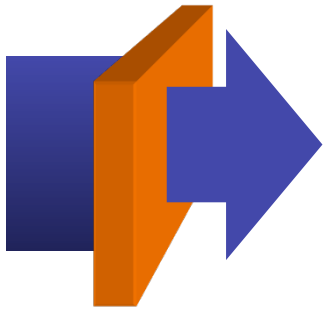


Atteindre **le tissu cible**

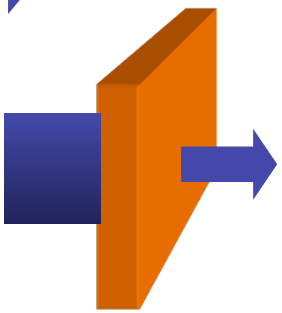
REPONSE

contrôle en périphérie des clones auto-réactives

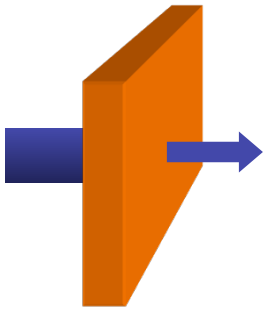
Etapes limitantes au déclenchement des réponses:



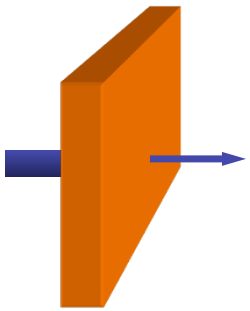
Atteindre **le tissu cible :**
Accès limité aux tissus



Percevoir **le signal**



Proliférer **et** ***se différencier***



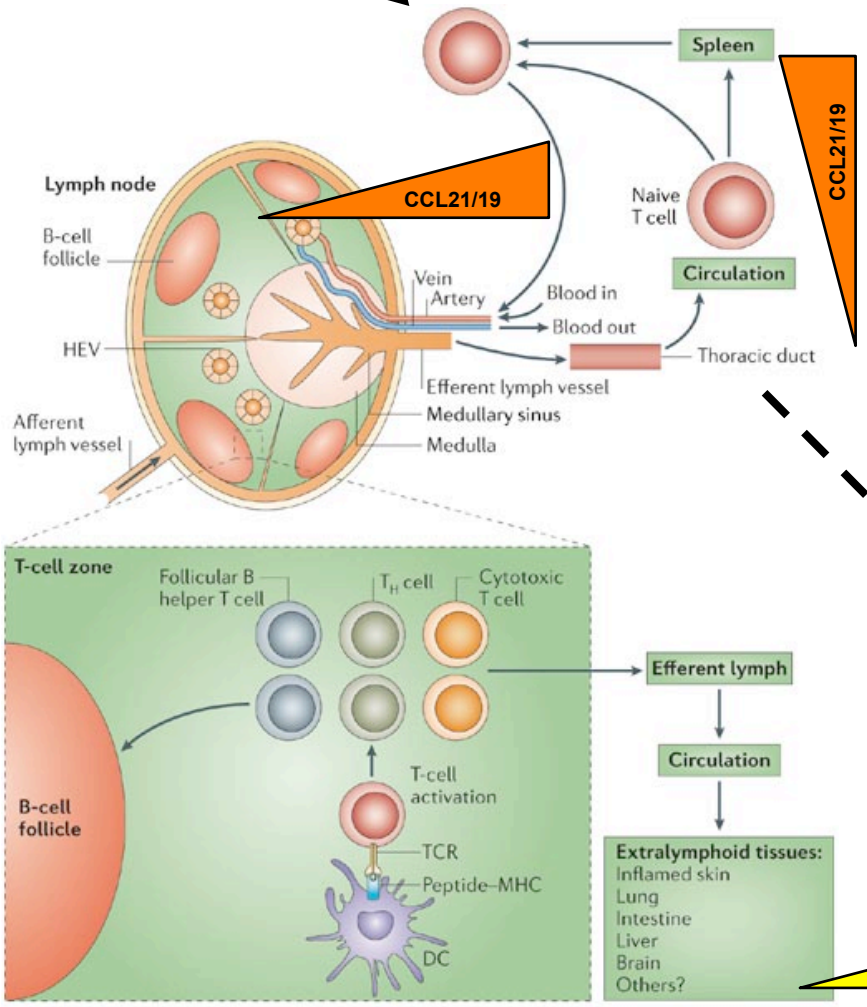
Atteindre **le tissu cible**

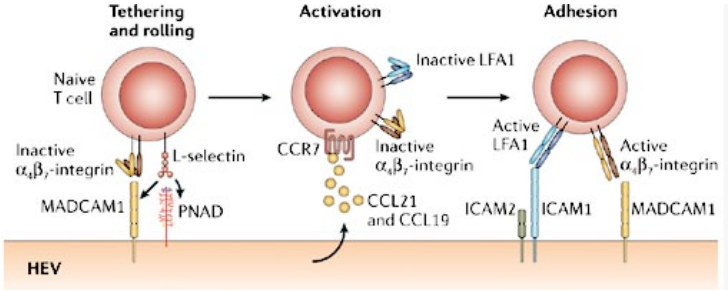
REPONSE

Ignorance des Ag périphériques
Accès limité aux tissus

Thymus

CCR7+
CD62Lhi





Tissus (Ag+)

Accès restreint pour les lymphocytes T naïfs

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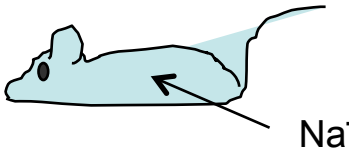
B. Bellier

Ignorance des Ag périphériques
Accès limité aux tissus

Maintenance of Peripheral Tolerance through Controlled Tissue Homing of Antigen-Specific T Cells in K14-mOVA Mice

Teresa Bianchi, Laura B. Pincus, Marc-André Wurbel, Benjamin E. Rich, Thomas S. Kupper, Robert C. Fuhlbrigge and Marianne Boes

J. Immunol. 2009;182;4665-4674

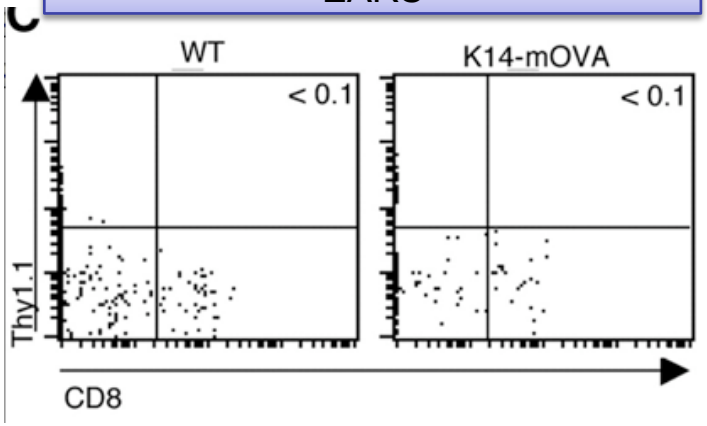


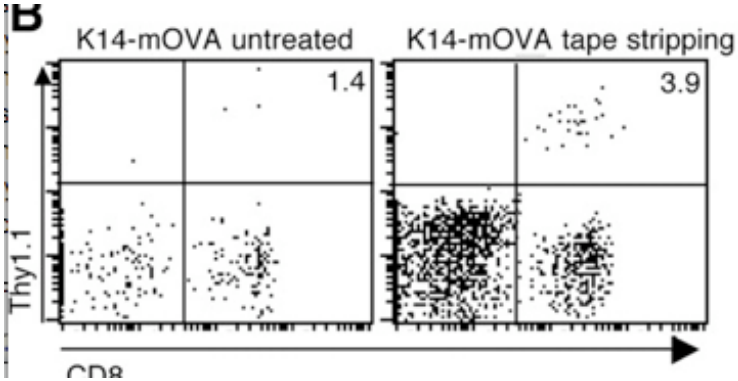
K14-OVA
vs WT
(Thy1.2+)

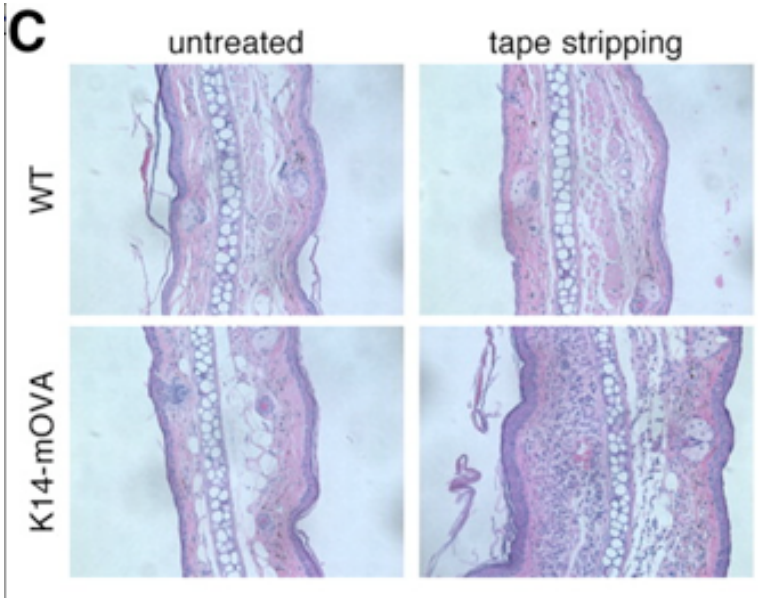
Naïf CD8+ OT-1+
(TCR OVA) Thy1.1+

We generated new transgenic mice expressing a membrane-bound form of OVA in skin under the human keratin 14 (K14) promoter (K14-mOVA mice). In contrast to other transgenic mice expressing similar self-Ags in skin, adoptive transfer of Ag-specific T cells does not induce inflammatory skin disease in our K14-mOVA mice. Additional inflammatory signal, here induced by tape stripping, is required in K14-mOVA mice to induce T cell migration to skin and development of inflammatory skin disease.

EARS

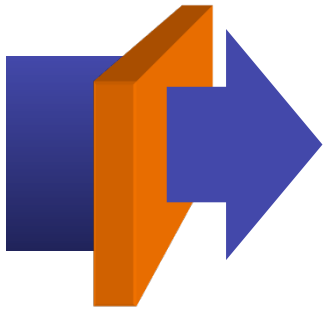




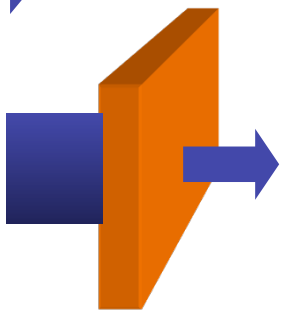


…contrôle en périphérie des clones auto-réactives

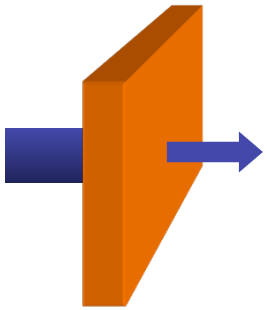
Etapes limitantes au déclenchement des réponses:



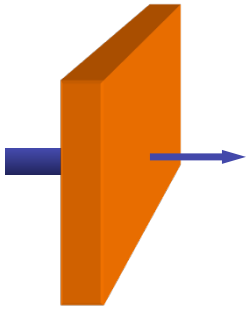
Atteindre **le tissu cible (Ag+)**



Absence d'activation:
Anergie
Absence de signaux de danger
Dendritiques tolérogènes
Délétion



Proliférer **et** ***se différencier***



Atteindre **le tissu cible**

REPONSE

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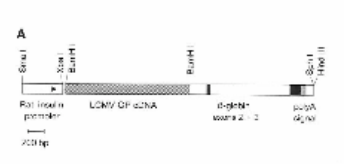
B. Bellier

Rôle des molécules de costimulation dans le contrôle de la réactivité

Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 3137–3141, April 1994
Immunology

Mice expressing both B7-1 and viral glycoprotein on pancreatic beta cells along with glycoprotein-specific transgenic T cells develop diabetes due to a breakdown of T-lymphocyte unresponsiveness

DAVID M. HARLAN*†, HANS HENGARTNER‡, MARK L. HUANG*, YUAN-HSU KANG*, RYO ABE*, RANDALL W. MOREADITH§, HANSPETER PIRCHER‡, GARY S. GRAY¶, PAMELA S. OHASHI‖, GORDON J. FREEMAN**, LEE M. NADLER**, CARL H. JUNE*, AND PETER AICHELE‡



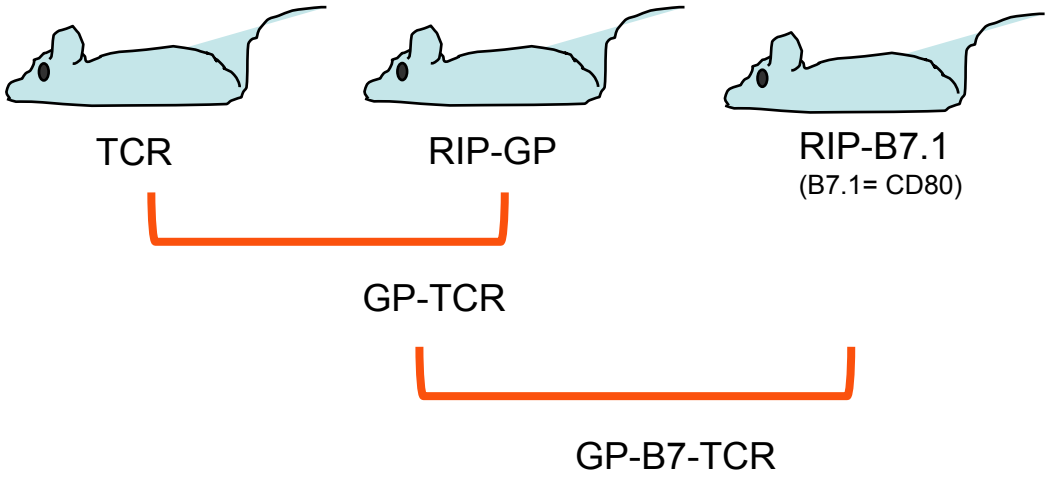


Table 1. Onset of diabetes in B7-GP, B7-TCR, and GP-TCR double-transgenic and GP-B7-TCR triple-transgenic mice

Transgenic mouse line	Animal no.	Proportion with diabetes	Age
B7-GP	27	0/27	4 weeks–11 months
B7-TCR	36	0/36	4 weeks–11 months
GP-TCR	24	0/24	4 weeks–11 months
GP-B7-TCR	14	14/14	7–14 weeks at onset of hyperglycemia

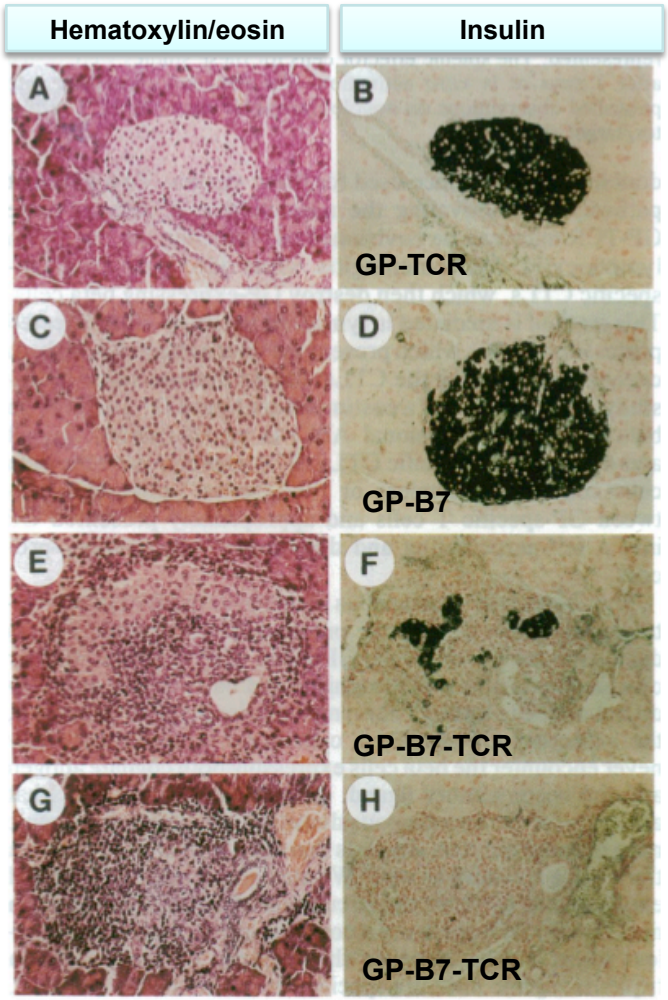
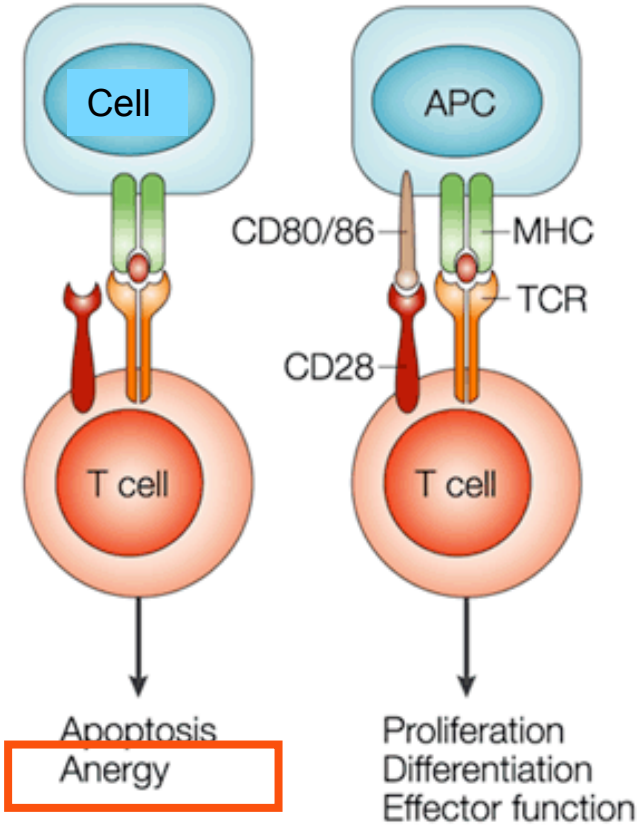


FIG. 2. Histologic analysis of double (GP-TCR and B7-GP) and triple (GP-B7-TCR) transgenic mice. Photos are paired and are stained as follows: Hematoxylin/eosin (*Left*) and antiinsulin antibodies (*Right*). Sections from GP-TCR animals (*A* and *B*) and from B7-GP animals (*C* and *D*) reveal normal islet architecture, no lymphocytic infiltrate, and normal immunostaining for insulin. Sections from prediabetic (*E* and *F*) and diabetic (*G* and *H*) triple-transgenic mice reveal an intense lymphocytic infiltrate and a loss (*F*) or absence (*H*) of islet cells staining for insulin.

Anergie

Pas d'activation T en l'absence de molécules de co-stimulation



Nature Reviews | Immunology

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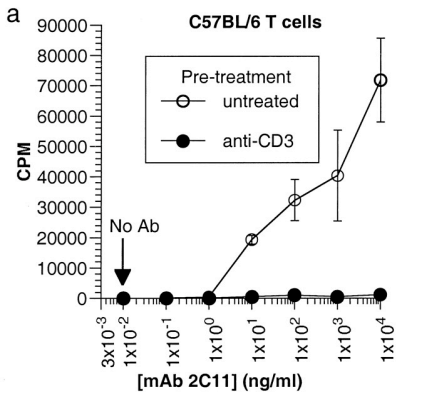
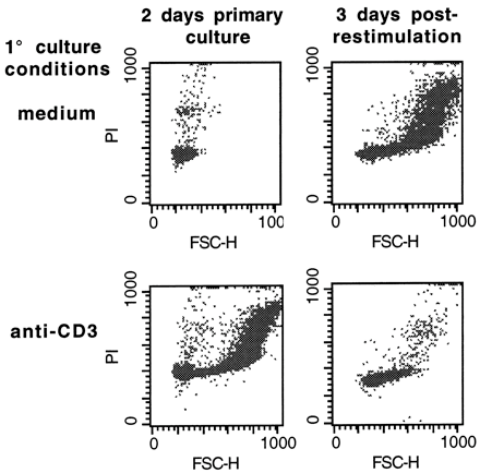
B. Bellier

Anergie: Un état de non-réponse réversible par l'IL-2

Induction of T cell anergy in the absence of CTLA-4/B7 interaction.
J Immunol. 2000 Mar 15;164(6):2987-93.

In vitro





Anergized cells enter cell cycle,
but arrest in G_1 phase upon restimulation.

C57BL/6 Bcl-X

Absence of co-stimulation and not the intensity of TCR signaling is critical for the induction of T cell unresponsiveness *in vivo*

Martin F. Bachmann[1], Daniel E. Speiser[2], Tak W. Mak[2, 3] and Pamela S. Ohashi[2]

In vivo

In vitro

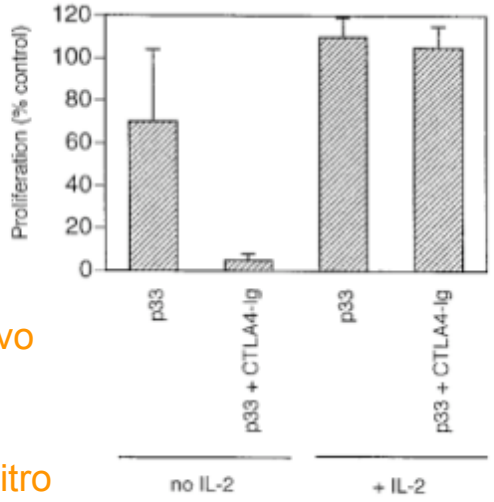


Figure 7. Blocking CD28 with CTLA-4-Ig induces T cell unresponsiveness *in vivo* after peptide injection. TCR-transgenic mice were immunized i.v. with 1 μg peptide and at the same time treated on 3 consecutive days with 50 μg CTLA-4-Ig or saline. Three days later, single-cell suspensions were prepared from spleens and cells were restimulated with p33-pulsed APC *in vitro*. Proliferation was assessed 2 days later by [^{3}H]thymidine incorporation. One representative experiment of two is shown.

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B. Bellier

Anergie
Mécanisme moléculaire

Nature Immunology **6**, 472 - 480 (2005)
Published online: 17 April 2005; | doi:10.1038/ni1193

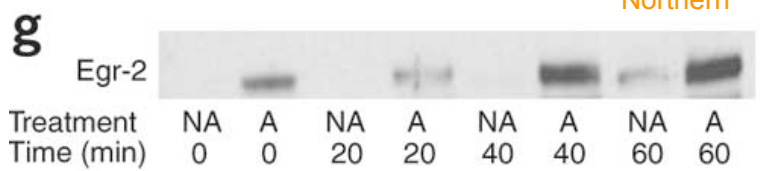
There is an Erratum (July 2005) associated with this Article.

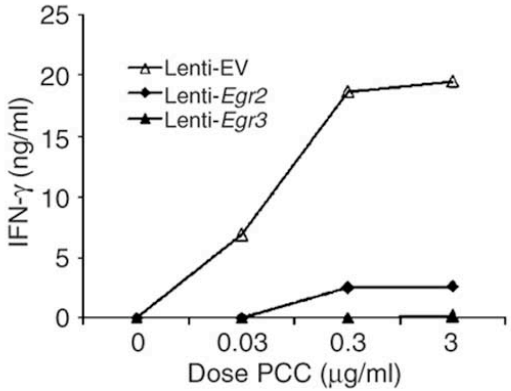
Egr-2 and Egr-3 are negative regulators of T cell activation

Meredith Safford[1, 5], Samuel Collins[1, 5], Michael A Lutz[1, 5], Amy Allen[1], Ching-Tai Huang[2],

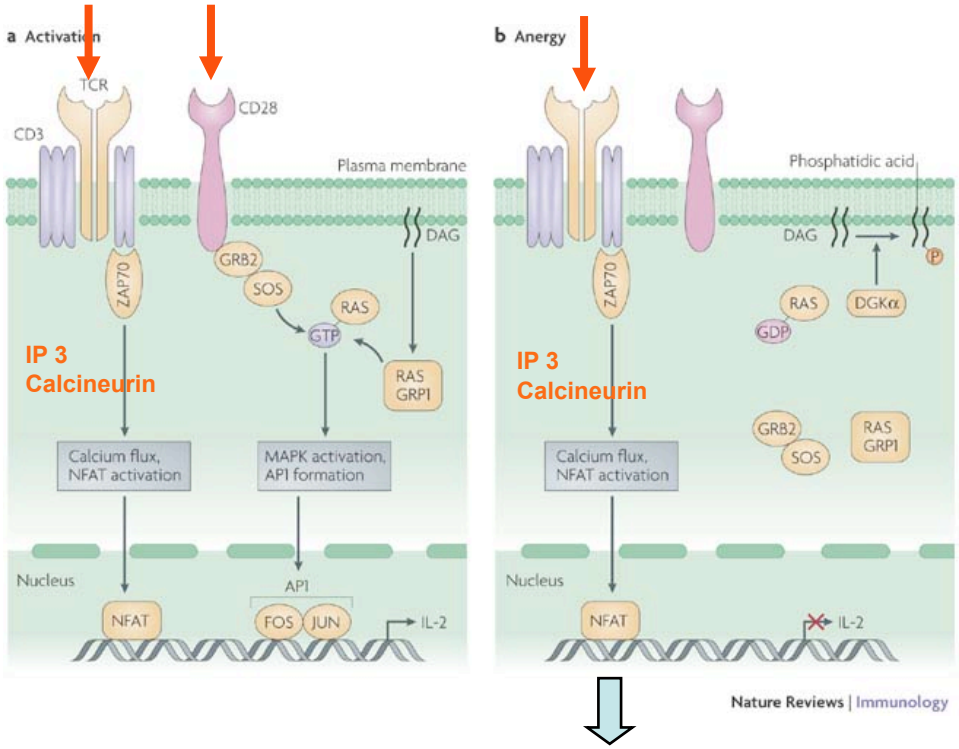
NA: Non-anergic, A: anergic

Northern





T cells were transfected with an *Il2 promoter driving luciferase reporter construct along with an empty vector (Lenti-EV) or lentivirus vector containing Egr2 (Lenti-Egr2), Egr3 (Lenti-Egr3) or mutated Egr2 (Lenti-MutEgr2).*

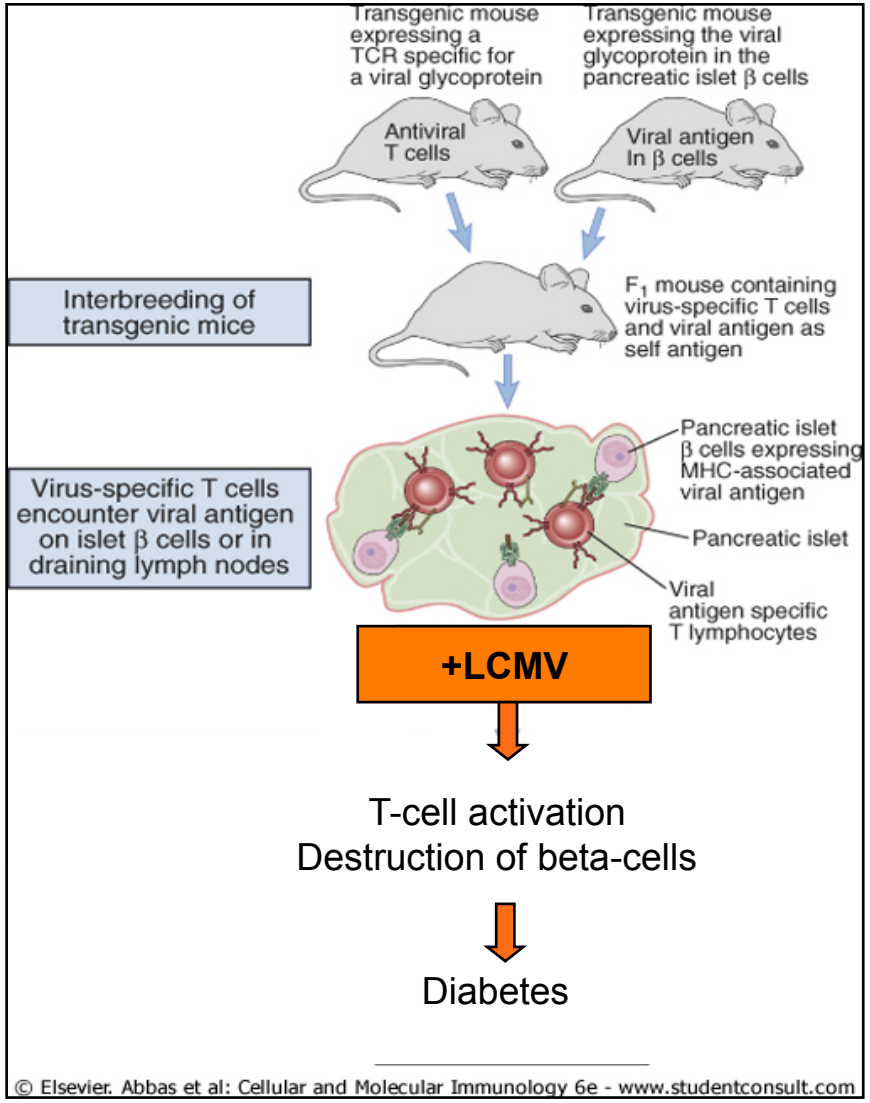


Inhibiteurs:
Egr2, Egr3
DGKa

B. Bellier

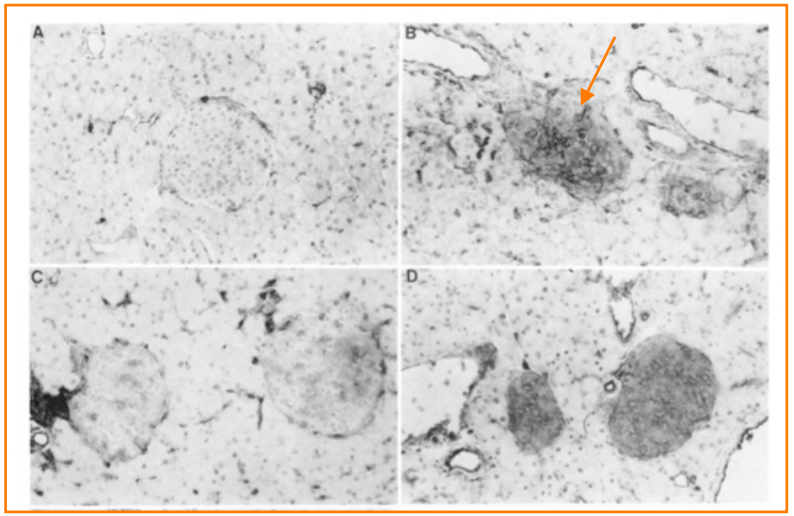
Rupture de la tolérance aux Ag tissulaires

Modèle Diabète induit



Mice	Infectious Agent	MHC Levels [a]	Diabetes
C57BL/6	None	Low	–
C57BL/6	LCMV	High	–
C57BL/6	vacc-gp	Low	–
RIP-gp	None	Low	–
RIP-gp	LCMV	High	+
RIP-gp	vacc-gp	Low	–
TCR	None	Low	–
RIP-gp/TCR	None	Low	–
RIP-gp/TCR	LCMV	High	+
RIP-gp/TCR	vacc-gp	High	+

[a] Class I MHC expression on β-islet cells.



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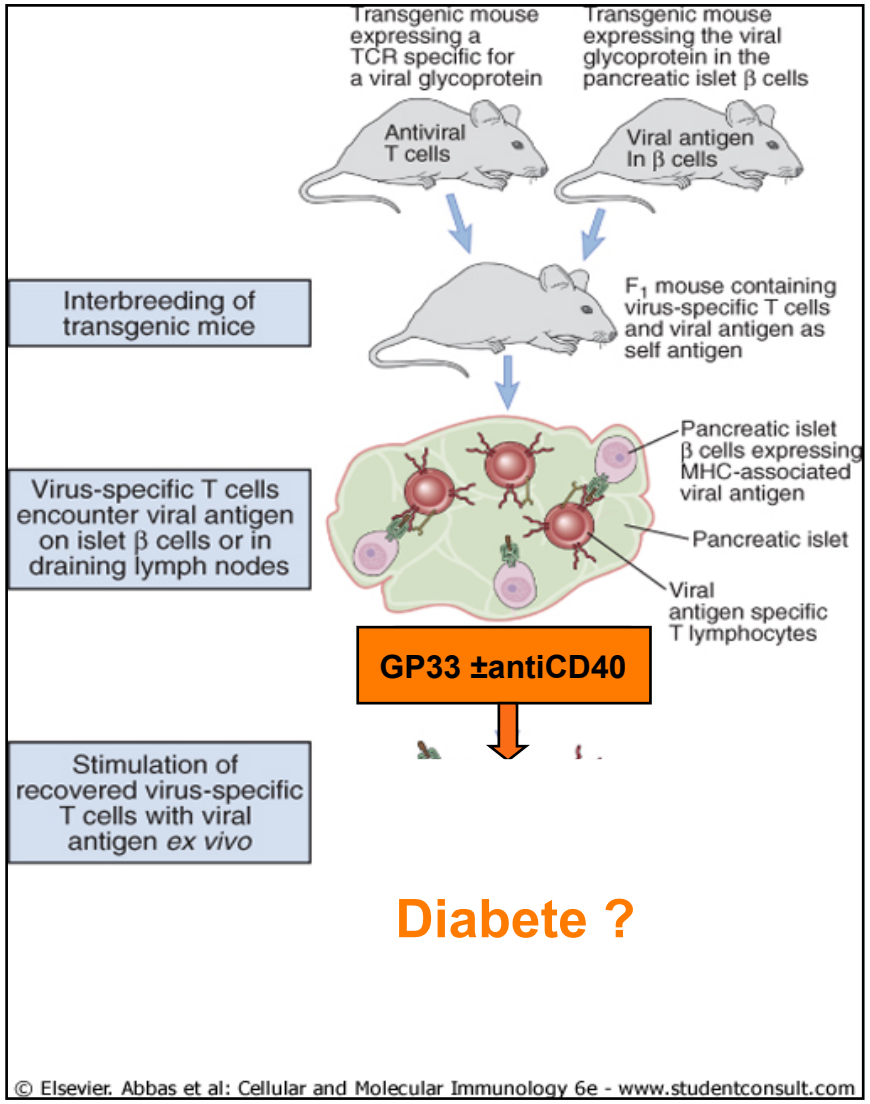
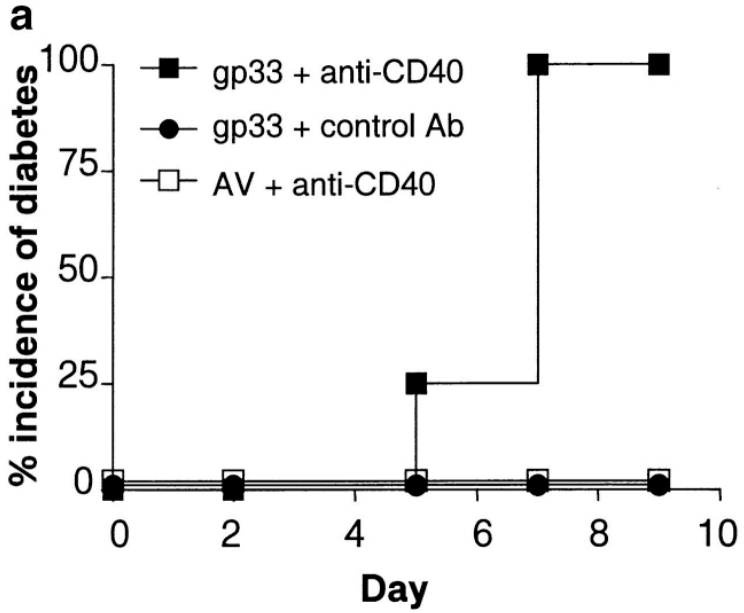
Rôle des cellules dendritiques dans la tolérance périphérique

Role of Antigen-Presenting Cells in Mediating Tolerance and Autoimmunity
Kristine M. Garza, et al
J Exp Med. 2000 June 5; 191(11): 2021–2028.



Diabete ?



Activation of APCs together with peptide treatment leads to insulitis and diabetes. RIP-gp/P14 double-transgenic mice were treated with the indicated peptide on day 0 and antibody on days 0 and 2. Blood glucose levels were monitored over time (a) (*n* > *20)*.

>> Implication des DC
>> Etat d'activation des DC déterminant

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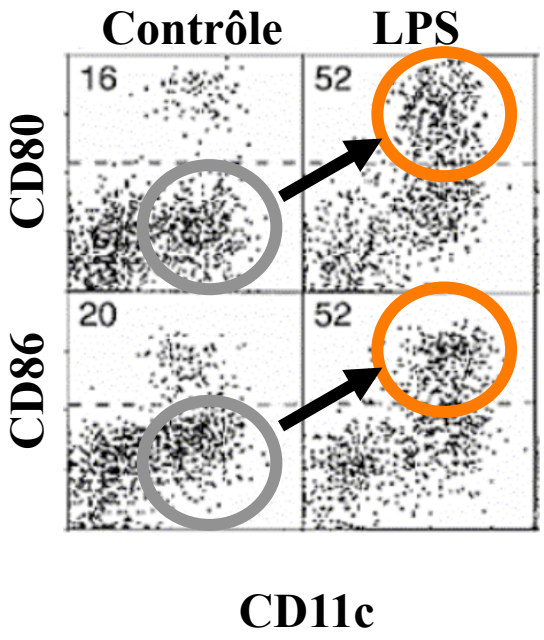
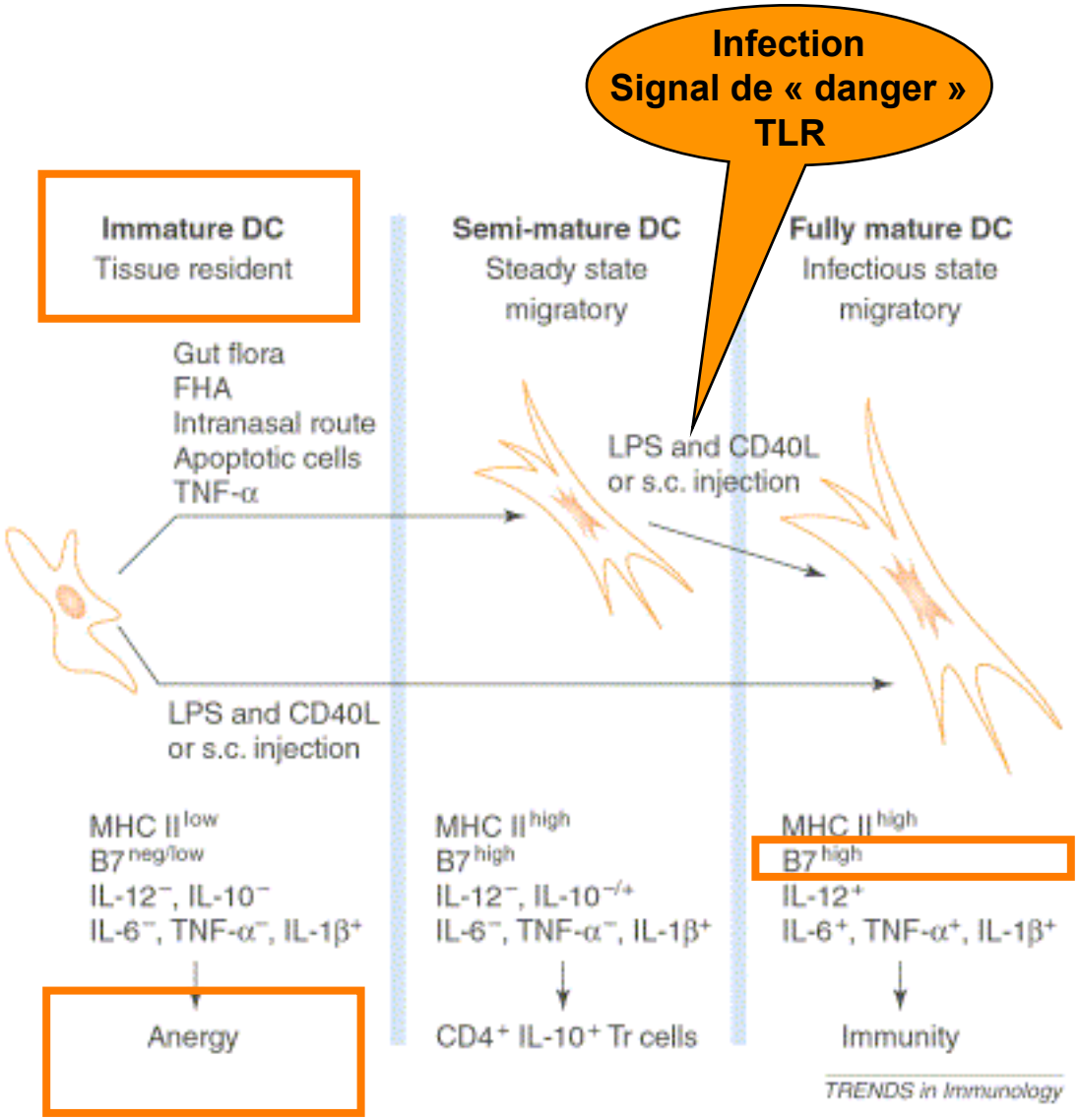
Environnement tolérogène dans les tissus: DC immatures

En conditions naturelles, non-pathologiques, la majorité de cellules dendritiques sont **immatures**

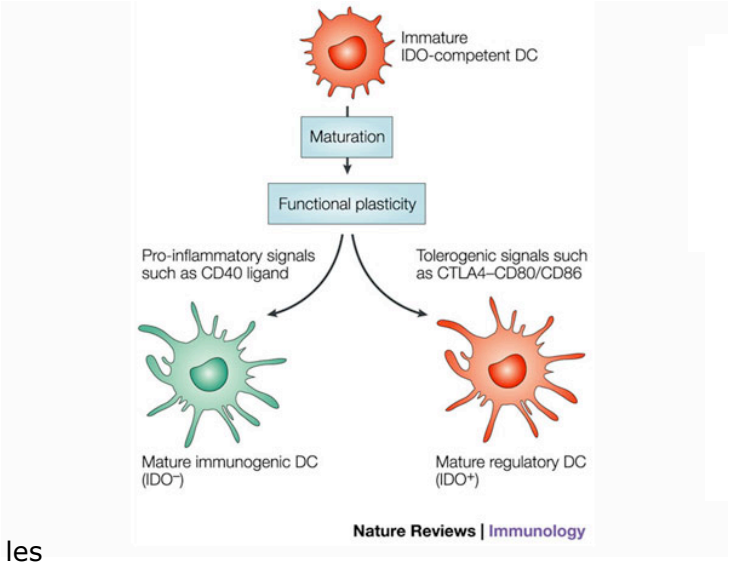
= Anergie

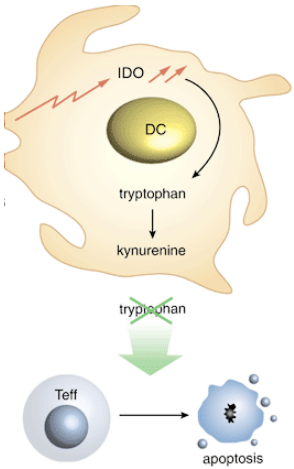




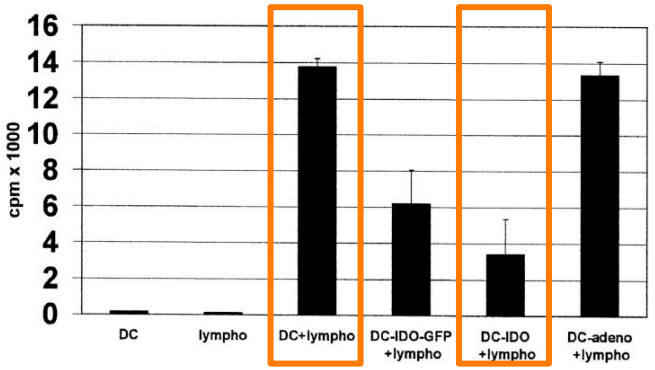
DC immatures / tolérogènes

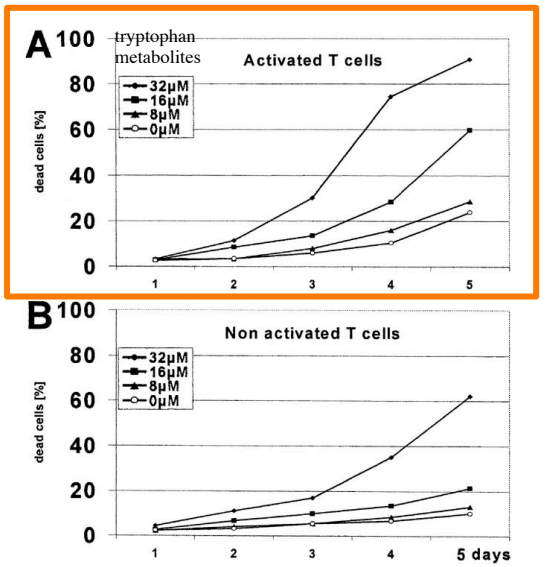
- **DC immatures**
  - CMHlo CD80- CD86- IL-12lo
- **DC tolérogènes:**
  - Réfractèrent à l'activation
  - IL-10+ IDO+
  - induit apoptose des T activés
- **Indoleamine 2,3-dioxygenase (IDO)**
  - Dégradation du Tryptophane dans les ganglions, rate, poumon, cœur, …
  - Régulation du taux sérique du Trp
  - Trp essentiel pour la prolifération des lymphocytes T
  - Exprimé par Mph, DC imm et DC tolérogènes





Inhibition of Allogeneic T Cell Proliferation by Indoleamine 2,3-Dioxygenase–expressing Dendritic Cells Mediation of Suppression by Tryptophan Metabolites
Peter Terness et al, J Exp Med. 2002





Tolérance orale: implication physiologique des DC tolérogènes

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Research article

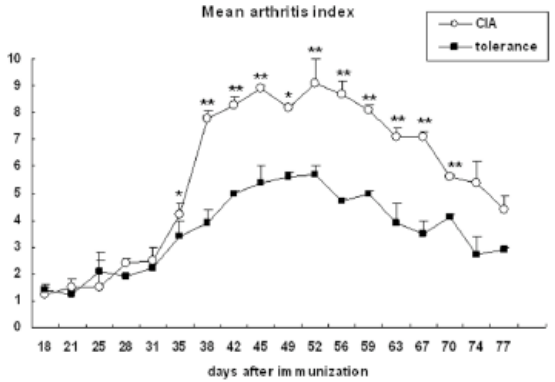
Open Access

Indoleamine 2,3-dioxygenase-expressing dendritic cells are involved in the generation of CD4+CD25+ regulatory T cells in Peyer's patches in an orally tolerized, collagen-induced arthritis mouse model

Min-Jung Park[1*], So-Youn Min[1*], Kyung-Su Park[1,2], Young-Gyu Cho[1], Mi-La Cho[1], Young-Ok Jung[1], Hyun-Sil Park[1], Soog-Hee Chang[1], Seok Goo Cho[3], Jun-Ki Min[1,2], Sung-Hwan Park[1,2] and Ho-Youn Kim[1,2]

Model: Arthritis induction

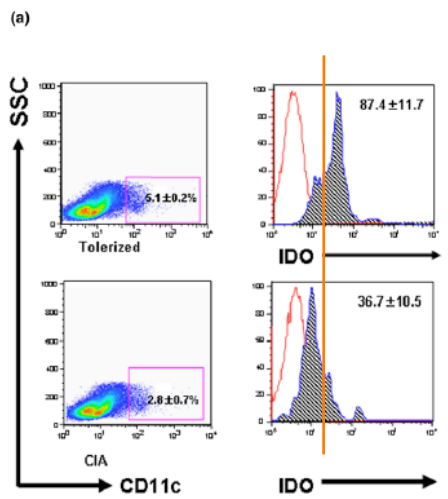
Figure 1



Inhibition of arthritis development in tolerized mice. Mice in the tolerance group were fed 100 μg type II collagen (CII) six times for 2 weeks before immunization. For collagen-induced arthritis (CIA) induction, CII emulsified with complete Freund's adjuvant was injected into the tail of mice in the tolerance group and in the CIA group as a primary immunization. Two weeks later, CII emulsified with incomplete Freund's adjuvant was injected into a hind leg as a booster injection. The mean arthritis index was significantly lower in the tolerance group than in the CIA group throughout the examination period. Values are presented as the mean ± standard deviation of three independent experiments involving 20 tolerized mice and 20 CIA mice per group. *P < 0.05, **P < 0.005.

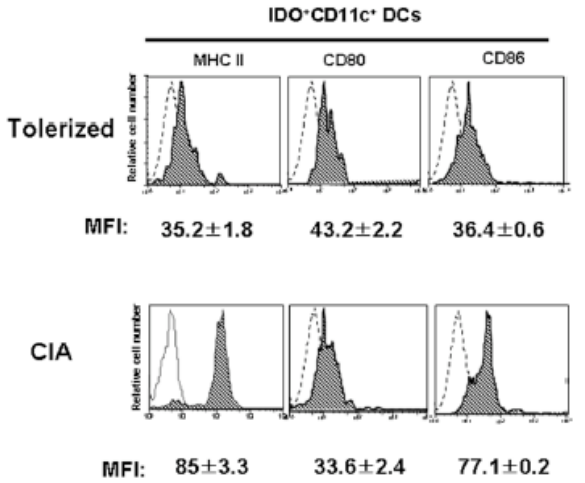
Expression of IDO in Payer's Patches DC

Figure 2



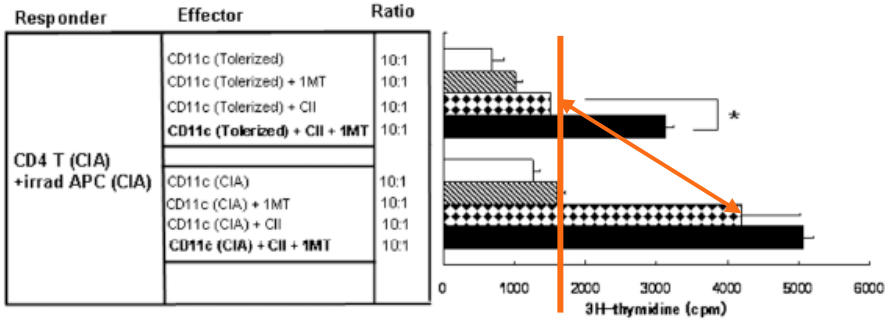
Immature phenotype of DC

Figure 3



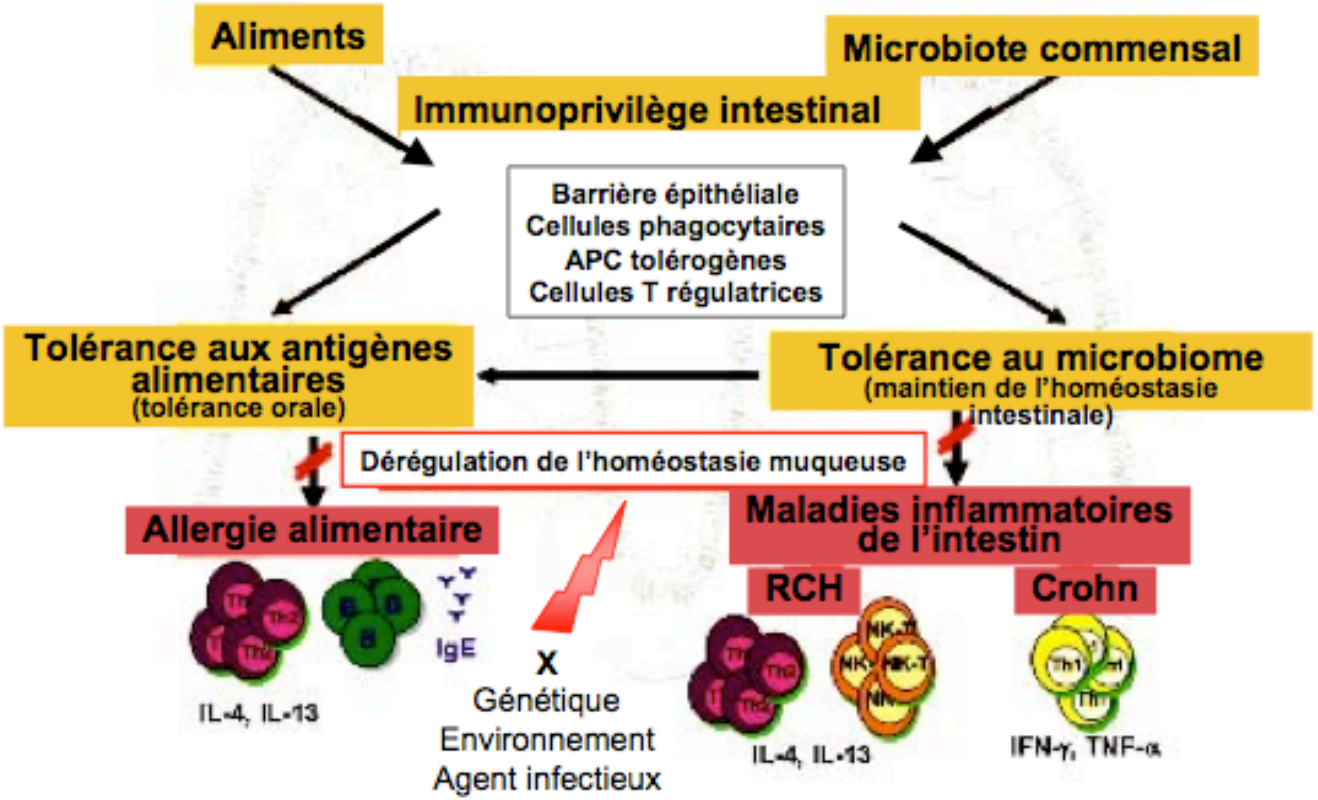
IDO-dependent suppression of CII specific T cells

Figure 4



Tolérance aux Ag alimentaires

Immunoprivilège intestinal: tolérance aux antigènes alimentaires et au microbiote commensal



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Activation périphérique contre les Ag du soi
Excès d'activation

- Délétion clonale des clones activés « chroniquement » par CMH-AgSoi
- Modèles d'immunisation témoigne de l'influence de la dose antigénique sur l'immunogénicité
- Mécanisme d'AICD
  Activation Induced Cell Death
- Différent mécanismes moléculaires de délétions
  - Fas
  - Bim

T Cell Priming Versus T Cell Tolerance Induced by Synthetic Peptides

By Peter Aichele, Karin Brduscha-Riem, Rolf M. Zinkernagel, Hans Hengartner, and Hanspeter Pircher

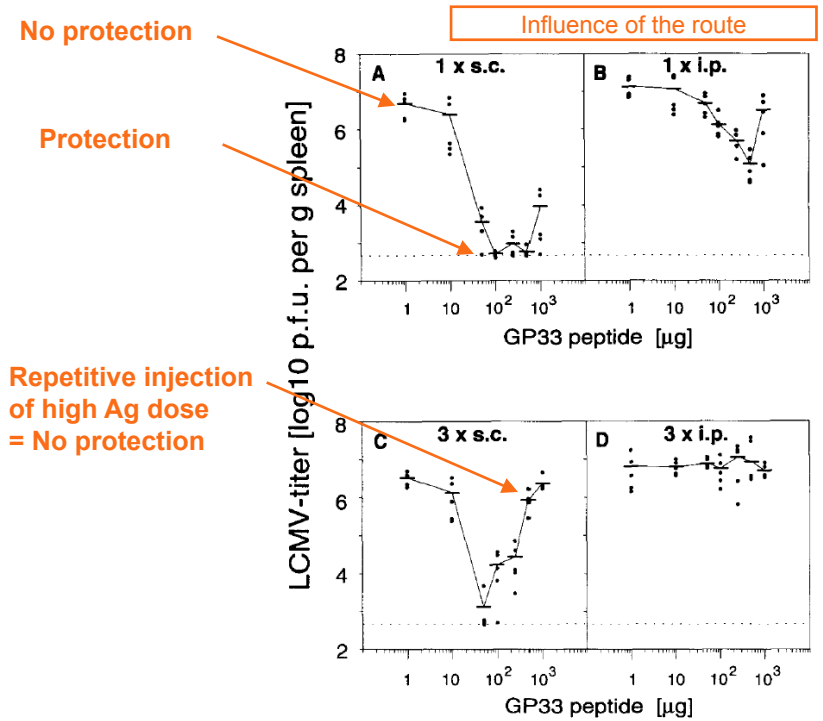

Figure 1. Parameters defining peptide-induced priming or tolerance of CTL. C57BL/6 mice were immunized with different amounts of GP33 peptide emulsified in IFA once s.c. (*A*) or i.p. (*B*) or three times at 3-d intervals s.c. (*C*) or i.p. (*D*). 10 d after the last peptide administration, mice were challenged i.v. with 200 PFU LCMV-WE, and virus titer in the spleen was analyzed 4 d later. Dots represent values from individual mice (five animals per group). Detection level is indicated as a dotted line.

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Implication de Fas dans le contrôle de la réactivité des T spécifiques des Ag Soi

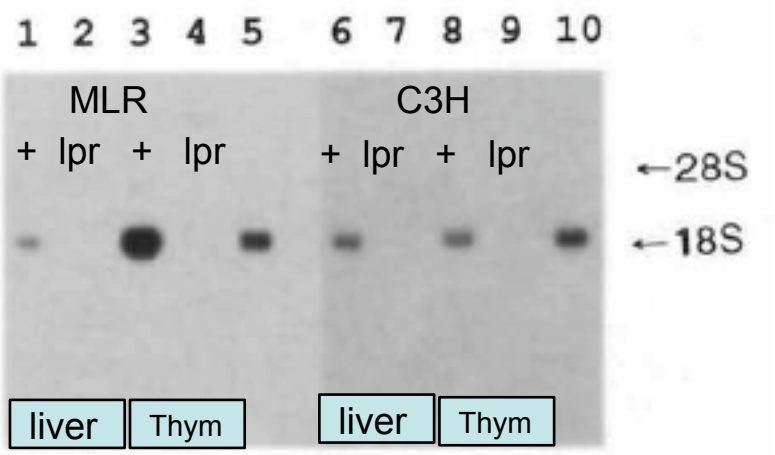
Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis

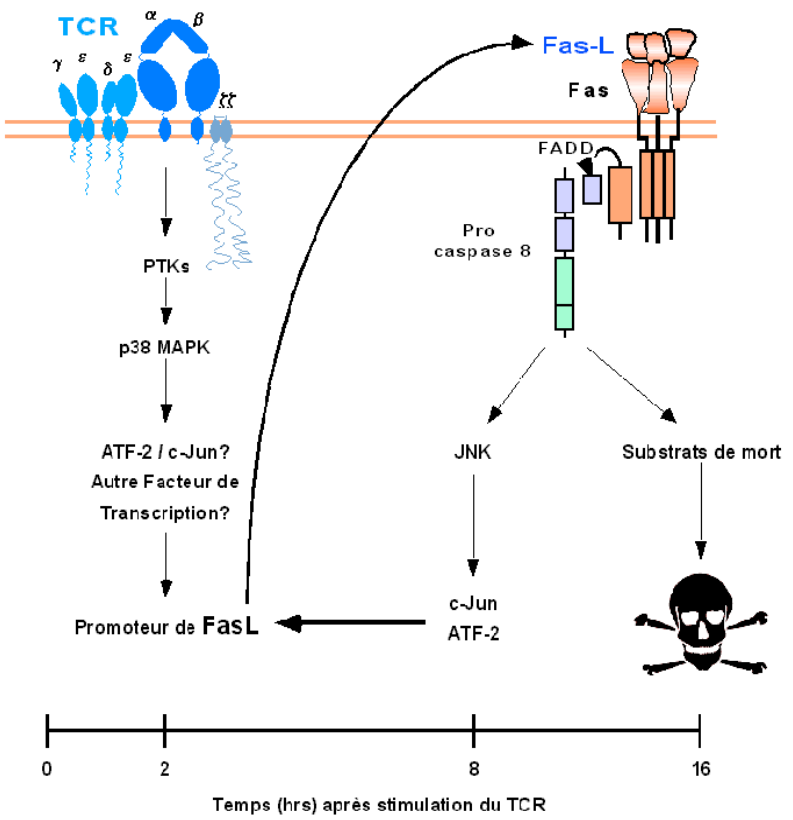
Rie Watanabe-Fukunaga*, Camilynn I. Brannan†, Neal G. Copeland†, Nancy A. Jenkins† & Shigekazu Nagata*‡

* Osaka Bioscience Institute, 6-2-4 Furuedai, Suita-shi, Osaka 565, Japan
† Mammalian Genetics Laboratory, ABL-Basic Research Program, NCI-Frederick Cancer Research and Development Center, Frederick, Maryland 21702, USA

factor receptor. Mice carrying the lymphoproliferation (*lpr*) mutation have defects in the Fas antigen gene. The *lpr* mice develop lymphadenopathy and suffer from a systemic lupus erythematosus-like autoimmune disease, indicating an important role for Fas antigen in the negative selection of autoreactive T cells in the thymus.

ARN

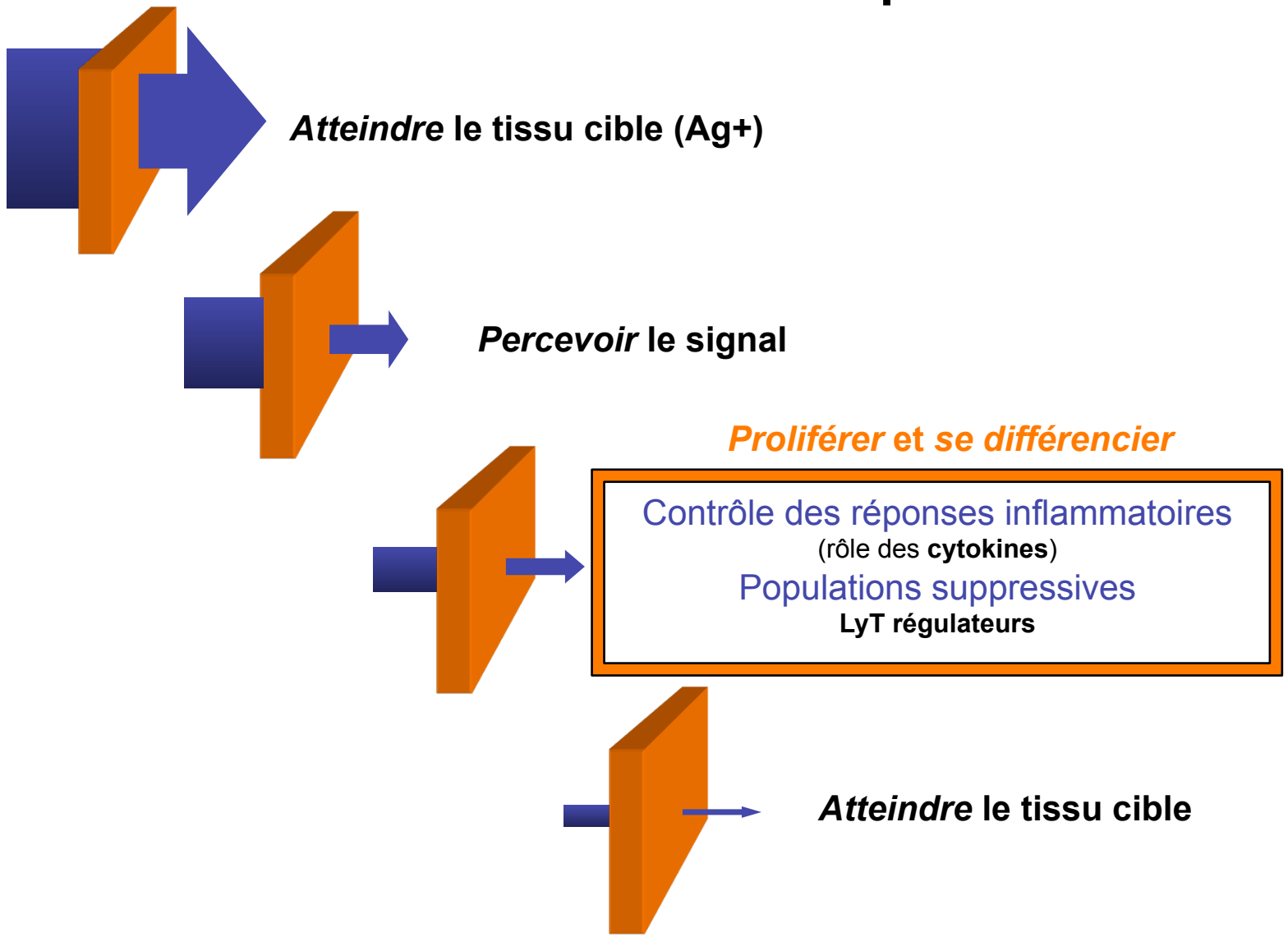




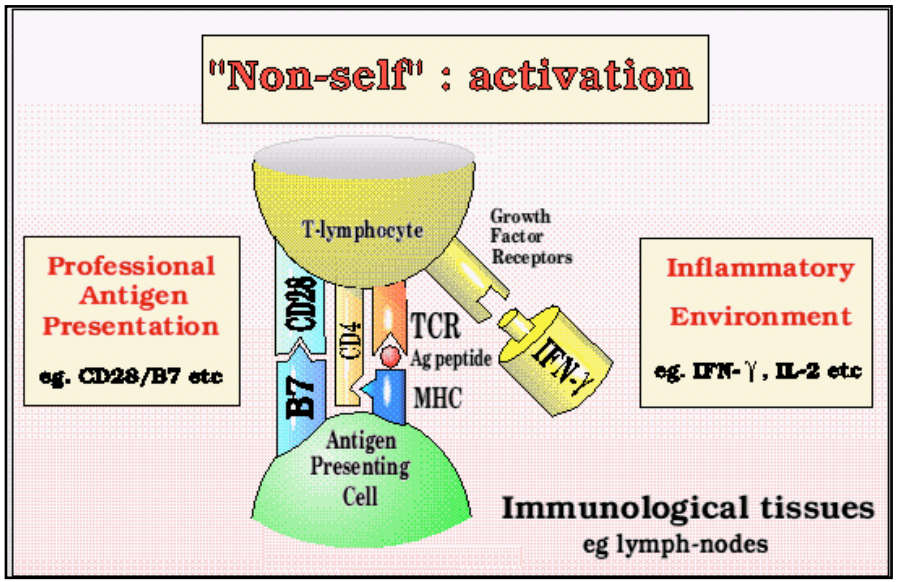
Déletion clonale
Mécanisme actif de tolérance périphérique

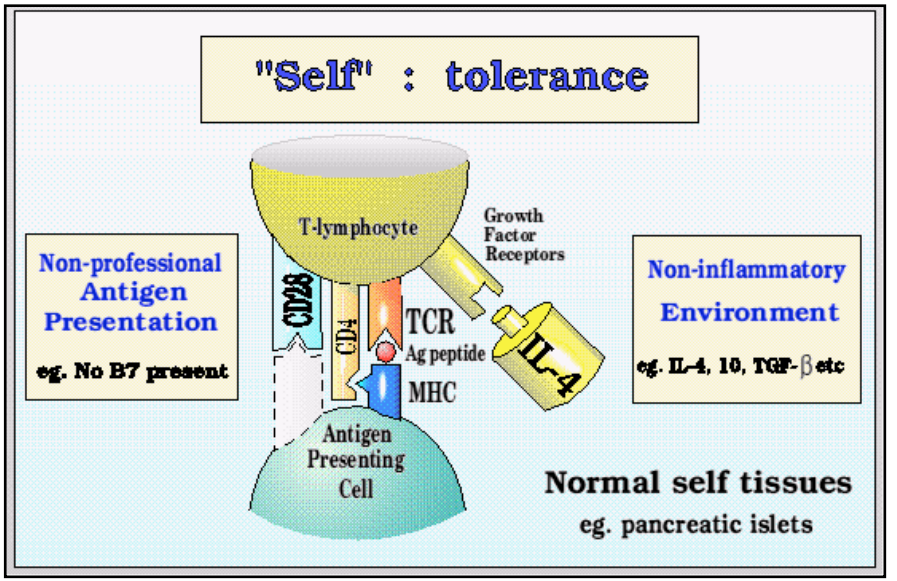
…contrôle en périphérie des clones auto-réactives

Etapes limitantes au déclenchement des réponses:

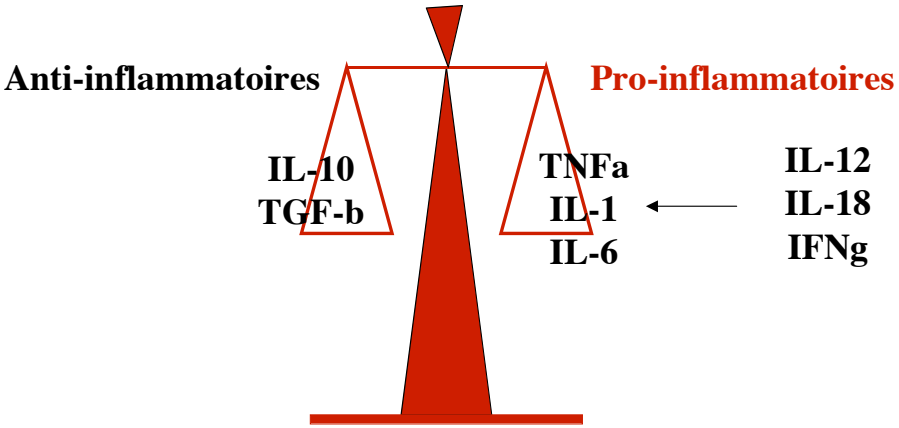


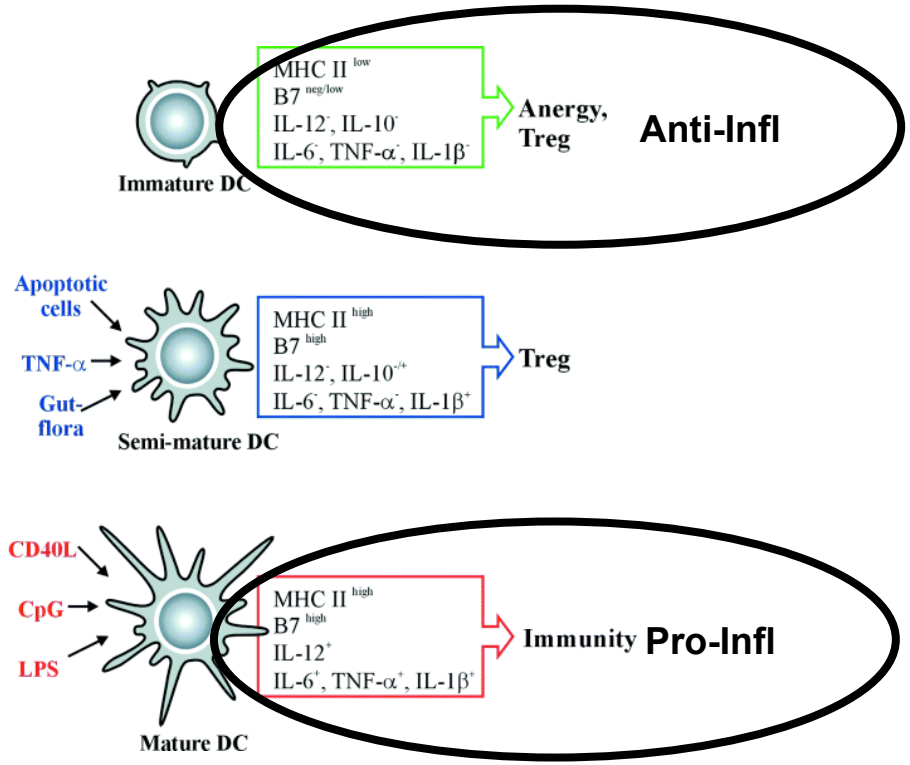
Cytokine: le 3eme signal d'activation





Environnement cytokinique





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Tolérance et cytokines

Autoimmunity

-IL-10-knockout mice develop an autoimmune colitis spontaneously, and **TGF-β**-knockout mice that develop a more extensive, multifocal autoimmunity

Default of IL-10 production in AID patients:

Colitis, Crohn disease: presence of cytokine-spe neutralizing Ab (**Fig 1**)

Serum samples (1:200 dilution) from patients with ulcerative colitis or Crohn's disease or from normal individuals were tested by enzyme-linked immunosorbent assay for antibodies recognizing (a) transforming growth factor-β, (b) interleukin (IL)-2, (c) IL-10 or (d) IL-4.

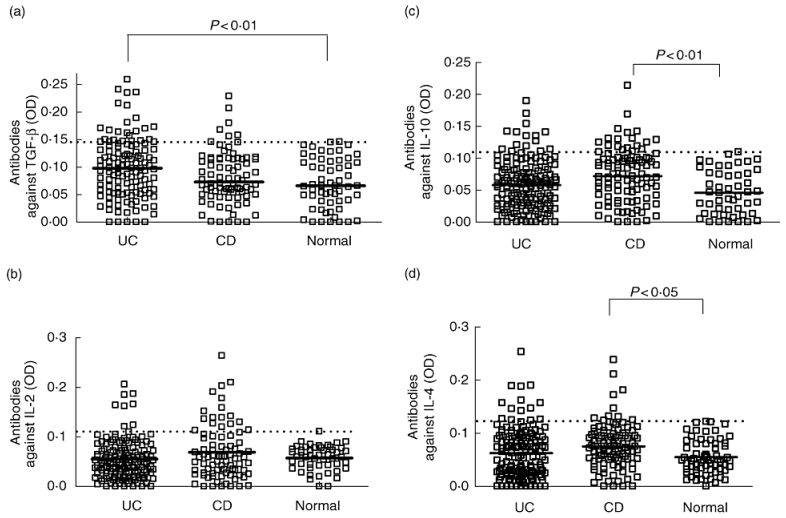
-IL-10 inhibits colitis induction in mice (**Fig. 2**)

-IL-4: Systemic injection of IL-4, gene therapy with IL-4 and transgene expression of IL-4 in β cells of the islets of Langerhans each prevent the onset of diabetes in NOD mice

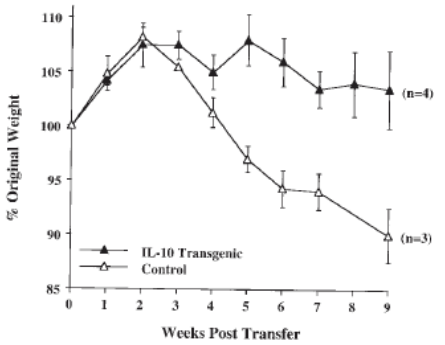
Mucosal tolerance

Tolerance to ubiquitous environmental antigens, : high frequency of **TGF-β+ cells** (Th3) that have suppressive functions

Patients with inflammatory bowel disease may have a transforming growth factor-β, interleukin (IL)-2- or IL-10-deficient state induced by intrinsic neutralizing antibodiesE. C. Ebert, Clin Exp Immunol. 2009



Colitis:



IL-10 tg

control

Figure 3. CD4+ CD45RB^{high} cells from IL-10 transgenic mice fail to induce colitis in SCID recipients. 4–5 • 10^5 FACS+ sorted CD4+ CD45RB^{high} cells from IL-10 transgenic or control littermate mice were injected into SCID mice. Weight gain/loss was scored weekly for 9 wk. Values are shown as a percentage of original weight at day 0, the time of cell injection. Number of mice in each group is indicated in parentheses. Regression analysis of the two curves shown indicated the data to be highly significant, P • 0.0012. (Similar results were obtained using Rag-2+/+ mice as T cell recipients.)

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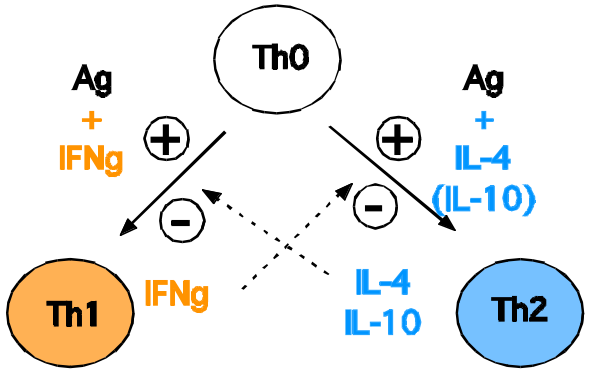
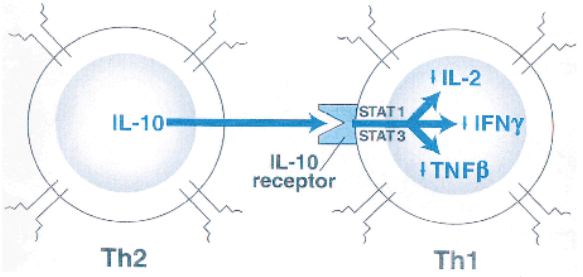
Cytokines anti-inflammatoires
IL-10, TGFb

- **Production**
  - IL-10: Mono, Macro, LyB, LyT Tr1
  - TGFb: tout type cellulaire, Th3

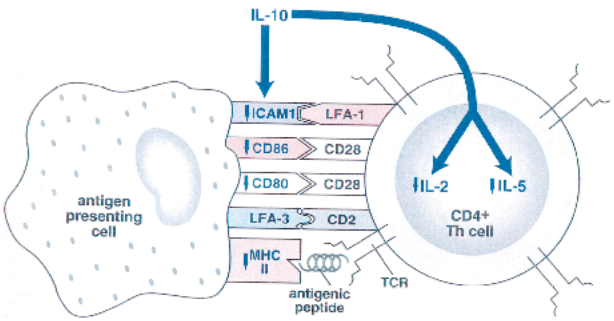


- **Cytokines anti-Th1:**
  >> Déviation immunitaire

- **Actions:**
  - Inhibition de production des cytokines pro-inflammatoires
  - Inhibition activité microbienne du Macro, PNneutro
  - Induit baisse d'expression MHC II et B7, ICAM-1



- **Génération de Lymphocytes suppresseurs:**
  - **Treg induits: Tr1**
  - **Th3**



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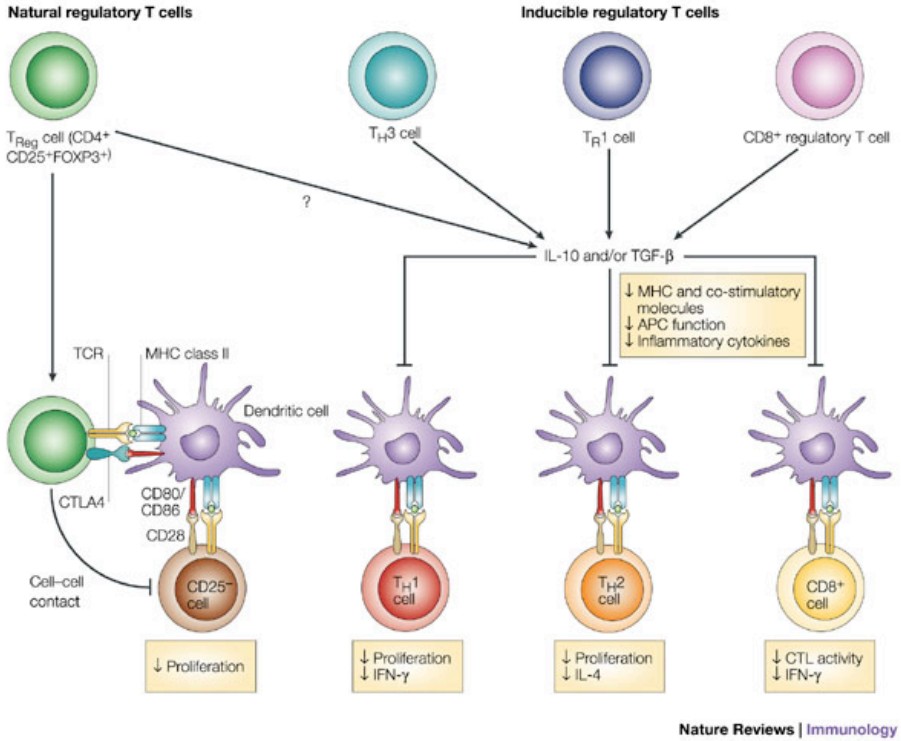
Lymphocytes T suppresseurs

	Th1	Th2	Th3	Tr1	CD25+(high)
					Treg naturels
Interferon gamma	++++	–	+/–	+	+/–
IL-4	–	++++	+/–	–	+/–
TGF-beta	+/–	+/–	++++	++	+/–
IL-10	–	++	+/–	++++	+/–
Growth	IL-2	IL-2/Il-4	Il-4/TGF-β	IL-10, Ifna	IL2+++
B helper	IgG2a	IgG1/IgE	IgA	–	–
Suppression	Th2	Th1	Th1 ou 2	Th1	Th1 or 2
Proliferation	+++			+/– (IL-15)	IL-2
Affinity for self	+/–	+/–	+	+ ?	+++++



- **Th3**

sous-groupe de lymphocytes TCD4+ qui secrètent du TGF- (ainsi que de l'IL-4 et de l'IL-10),

favorisent la sécrétion d'IgA par les plasmocytes,

régulent à la baisse les Th1 et les Th2.

Leur maturation dépend de la présence de TGF-, d'IL-4, d'IL-10 et du blocage de l'IL-12 , ainsi que de l'expression à leur surface de CD86 et de CTLA-4.

Ces clones Th3 émergent surtout après pénétration de l'antigène par voie orale.

Leurs cibles ne sont pas les T effecteurs mais plutôt les cellules présentatrices en contact avec ces derniers, la libération de TGF- induisant un mécanisme de suppression paracrine sur celles-ci.

- **Tr1**

La production de taux élevés d'IL-10

suppriment la réponse immune par contacts cellulaires directs et/ou par sécrétion de cytokines.

faible capacité à proliférer (du fait des hautes concentrations d'IL-10.

se différencient après contacts avec des cellules présentatrices synthétisant de grandes quantités d'IL-10.

Cette situation est surtout rencontrée lorsque la cellule dendritique est encore assez « naïve », que l'antigène est en *faible concentration*, et que les contacts entre cellule présentatrice et lymphocyte TCD4+ sont *répétés*.

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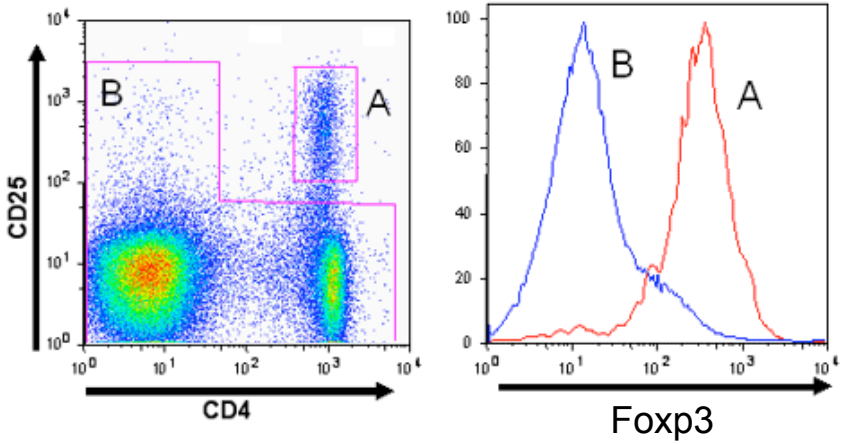
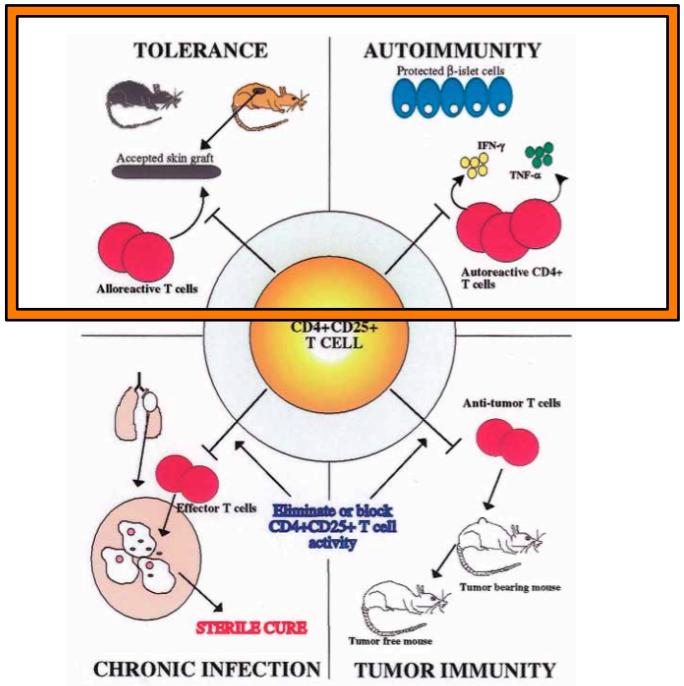
Lymphocytes T régulateurs CD4+ CD25+

- **Ly T régulateurs:**
  - (re)découverts par Sakagushi
  - Rôle dans maintien de la tolérance périphérique
  - Prévient l'apparition des MAI
  - Phénotype:
    - **CD4+ CD25+**
    - **Foxp3+**
  - 5-10% des T périphériques
  - Cellules anergiques, dépendantes de l'IL-2 et de CD28 pour leur survie
  - Action suppressive de proximité
    - Contact-dépendent
  - Rôle multiple
  - Suppression des réponses
    - auto-immunes
    - anti-tumorales
    - allogéniques
    - anti-infectieuses





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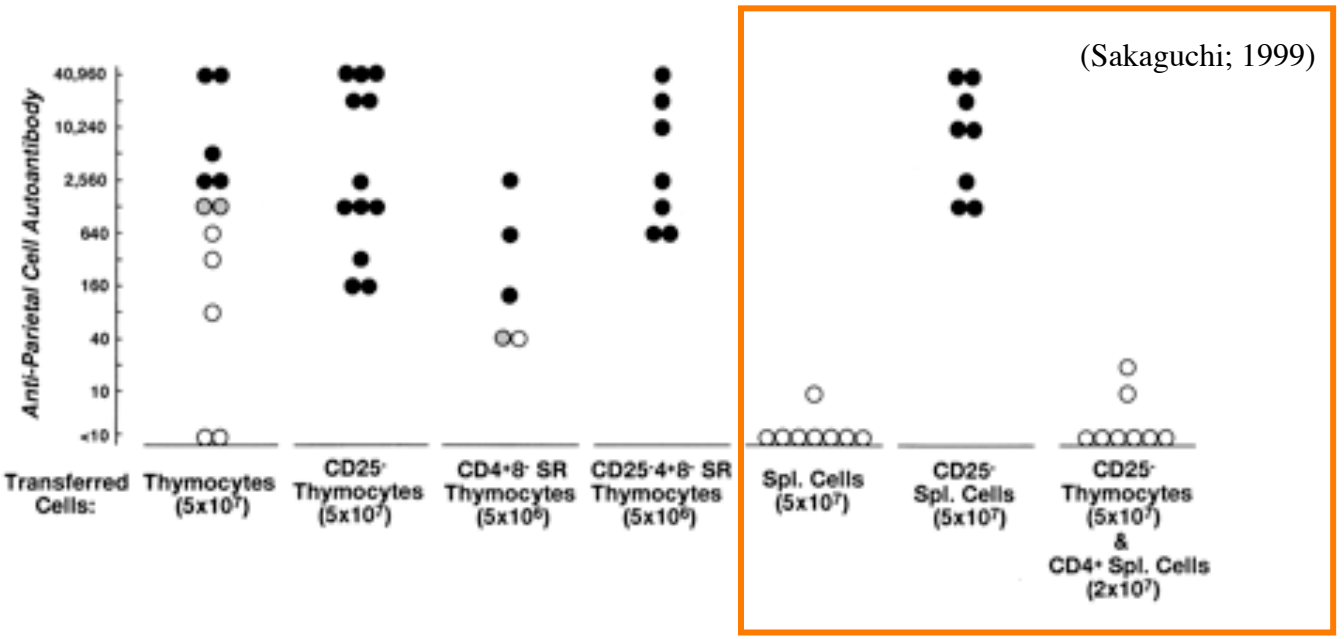
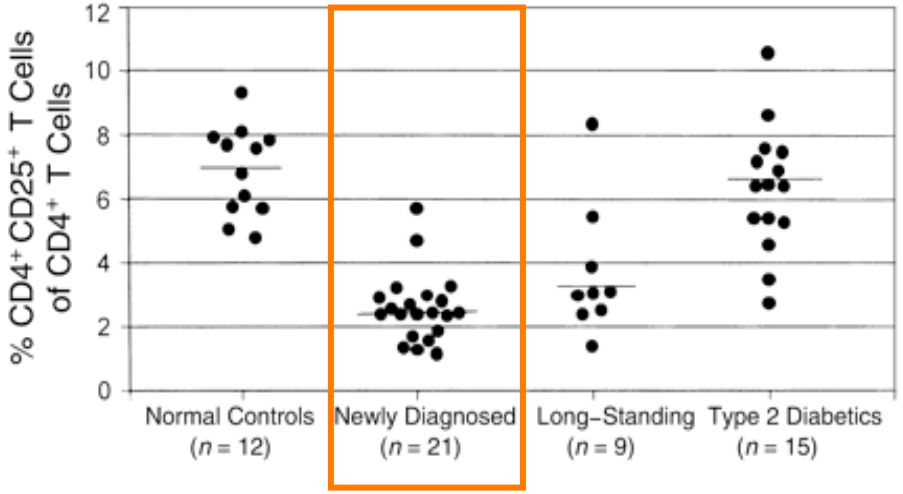
Lymphocytes T régulateurs:
mise en évidence de leur implication dans MAI

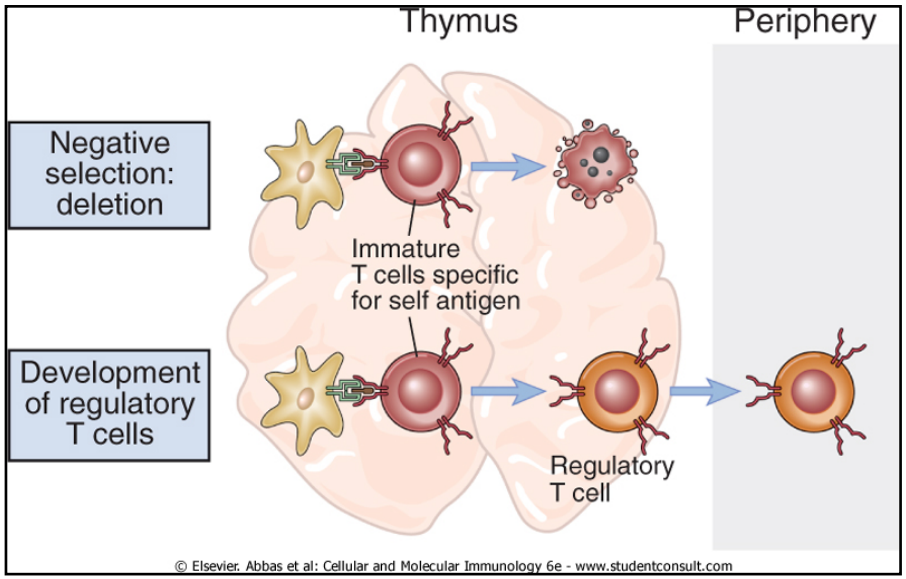
- **Chez la souris nude après transfert adoptif**

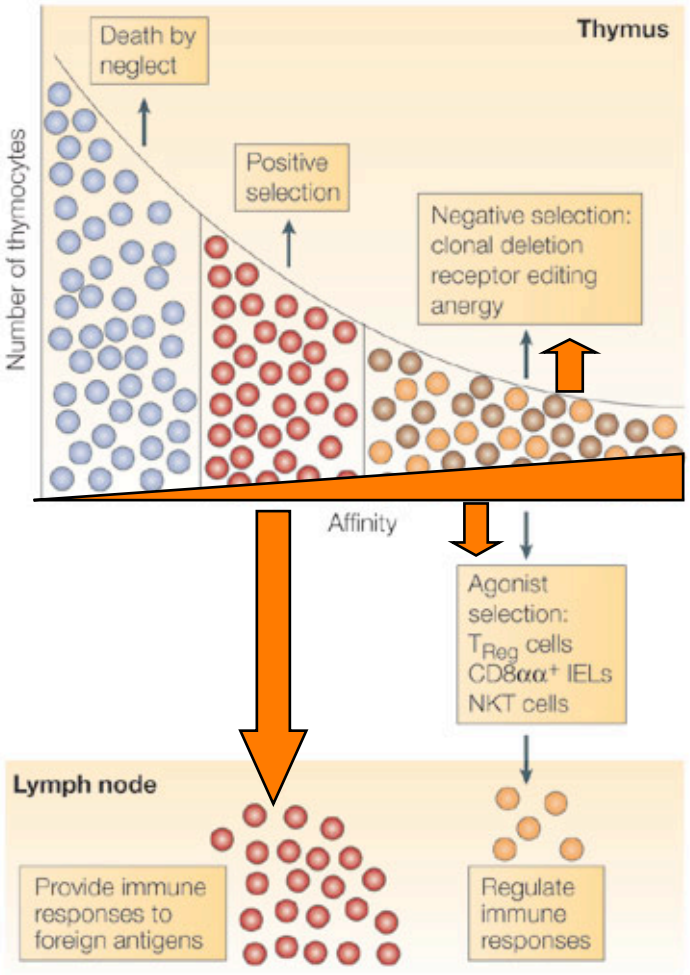


- **Chez les patients diabétiques insulino-dépendant (type 1)**

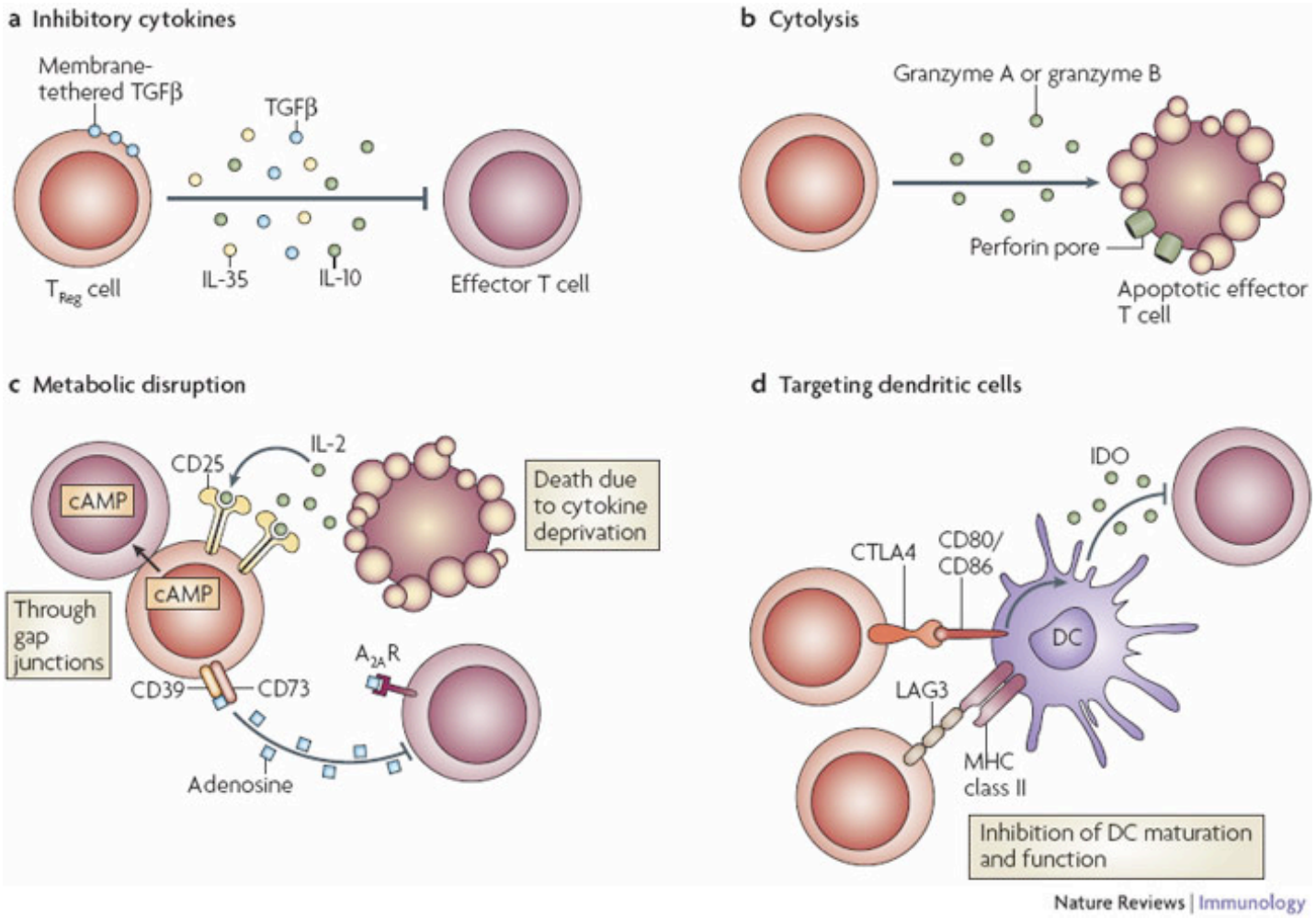


Ontogénie et Spécificité des Treg





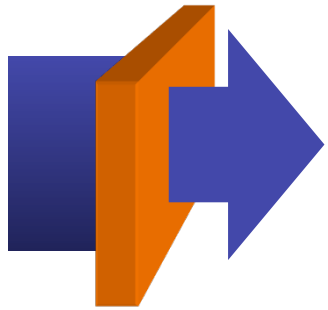
Mécanismes d'action



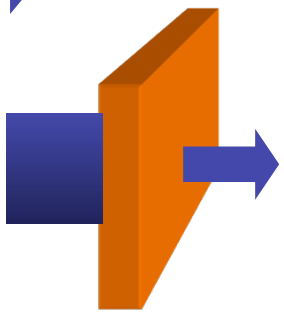
Nature Reviews | Immunology

…contrôle en périphérie des clones auto-réactives

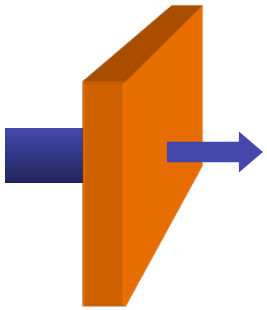
Etapes limitantes au déclenchement des réponses:



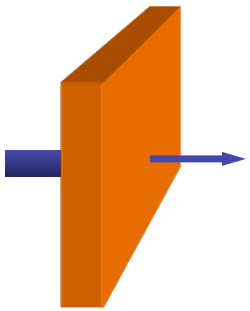
Atteindre **le tissu cible**



Percevoir **le signal**



Proliférer **et** ***se différencier***



REPONSE

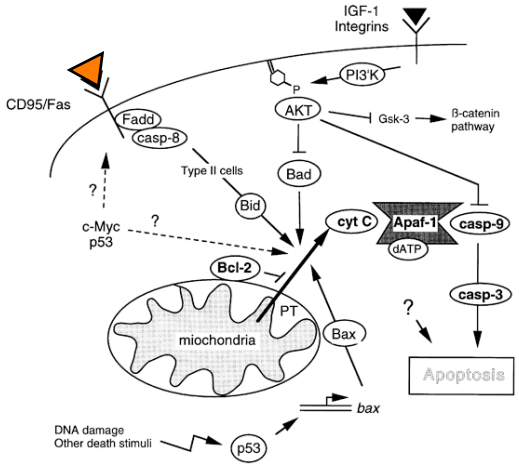
Accès limité aux tissus dits « immunoprivilégiès »

Tissus « immunoprivilégiés »

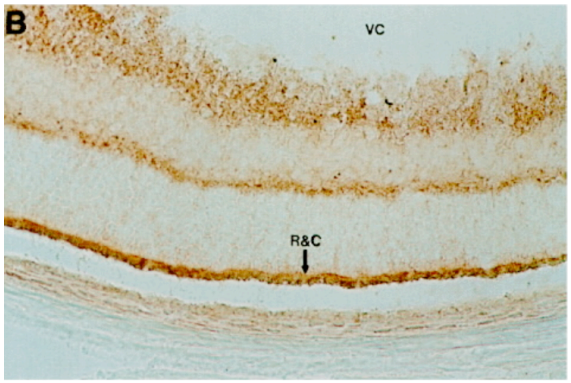
- **Accès limité de certains tissus aux lymphocytes T activés et potentiellement autoréactifs**

- **FasL+**
  - Œil, cerveau (astrocytes), testicules, l'utérus et le placenta (Rôle dans la tolérance du fœtus)

Les anomalies de l'apoptose lymphocytaire induite par Fas peuvent favoriser l'irruption de cellules immunitaires dans des sanctuaires immunoprivilégiés

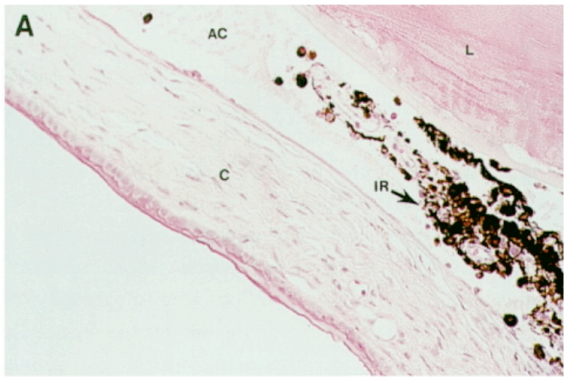


Oeil

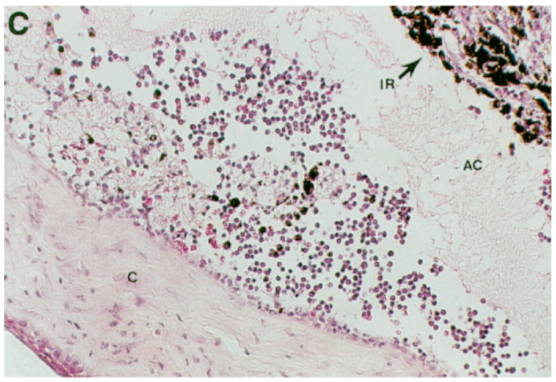


Infiltration lymphocytaire en réponse à une inoculation virale dans la chambre antérieure

WT



FasL-/-



Ferguson *et al.* 1997

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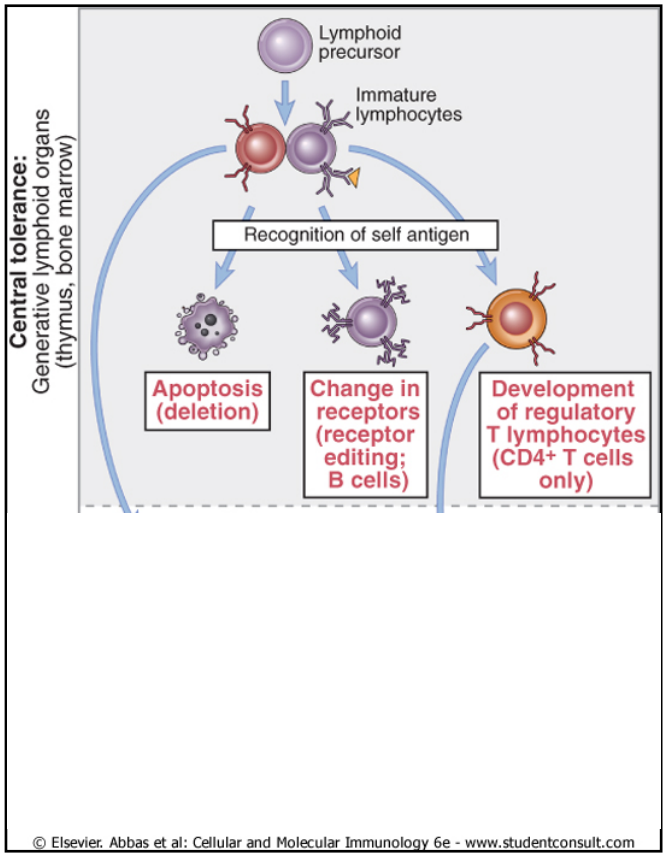
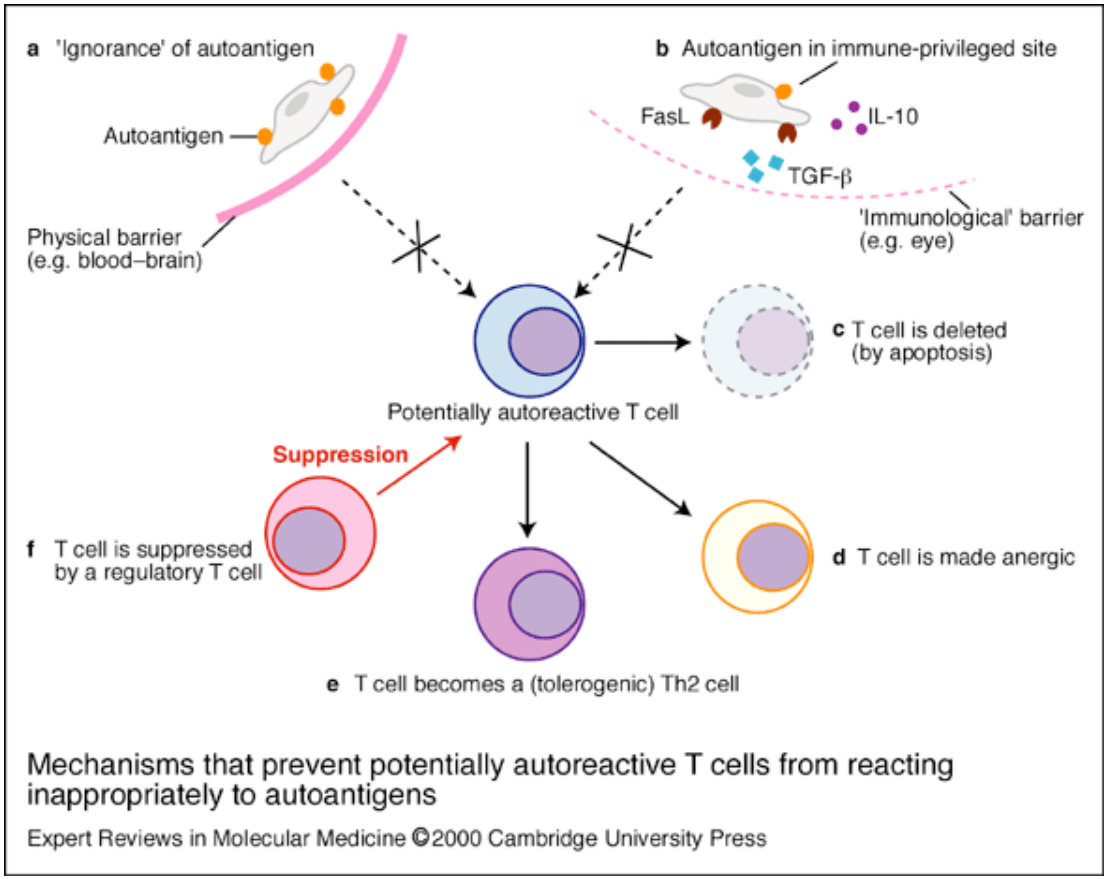
Conclusion
Mécanismes à l'origine de la tolérance

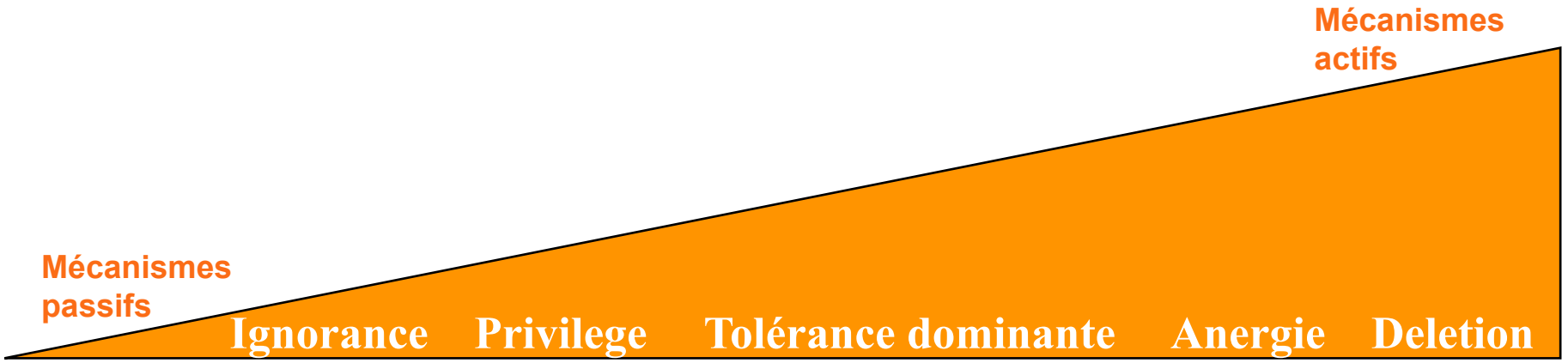
Tolérance centrale



Tolérance périphérique



conclusion



Absence d'activation suite à la reconnaissance des Ag du soi

Accès interdit à certains tissus

Suppression des fonctions effectrices des cellules auto-réactives

Mise en place d'un état de non réponse des cellules autoréactives

†

Mort Cellulaire Programmée

TOLERANCE CENTRALE

TOLERANCE PERIPHERIQUE

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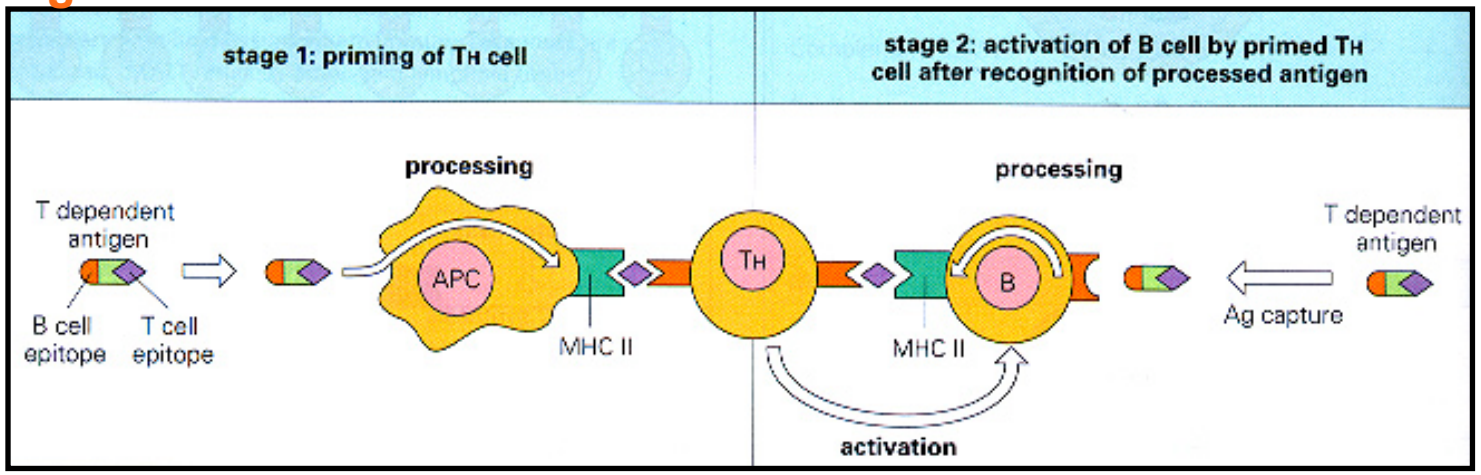
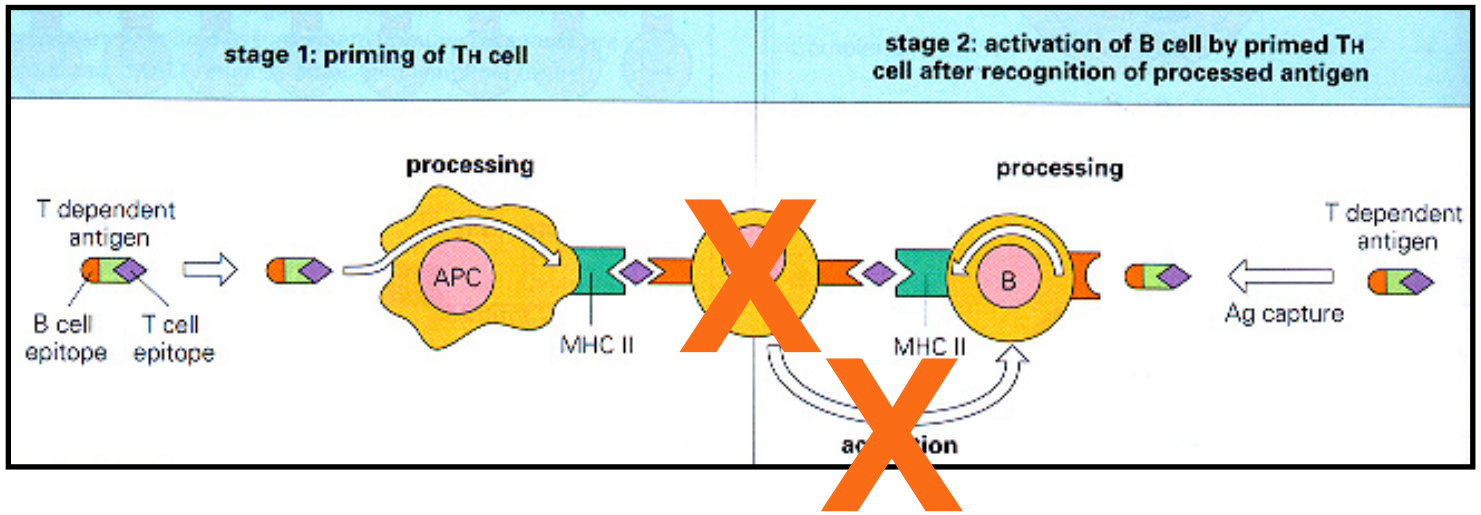
Importance de la tolérance T pour maintenir la tolérance B

B cells need T cell “help” to make high affinity antibody

Non-self Ag



Self Ag



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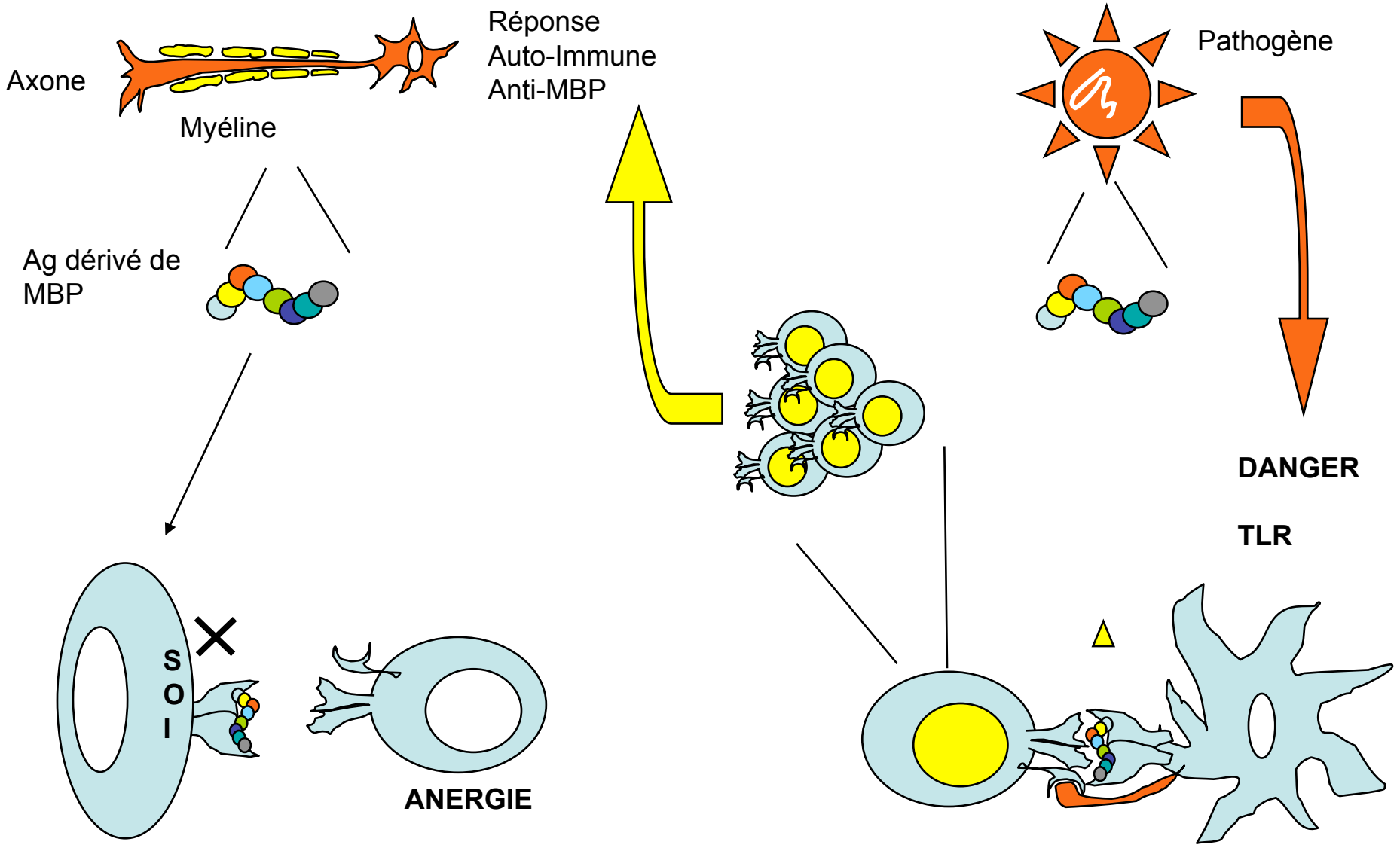
B. Bellier

Développement des maladies auto-immunes
Théorie du mimétisme moléculaire



Difficulté de l'établissement des réponses anti-tumorales

Tumeur = soi modifié

Ignorance
Anergie
Déviation immunitaire
Suppression
Treg
Echappement