

Les organes endocrines : une cible privilégiée de l'auto-immunité

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Maladies auto-immunes systémiques et d'organe

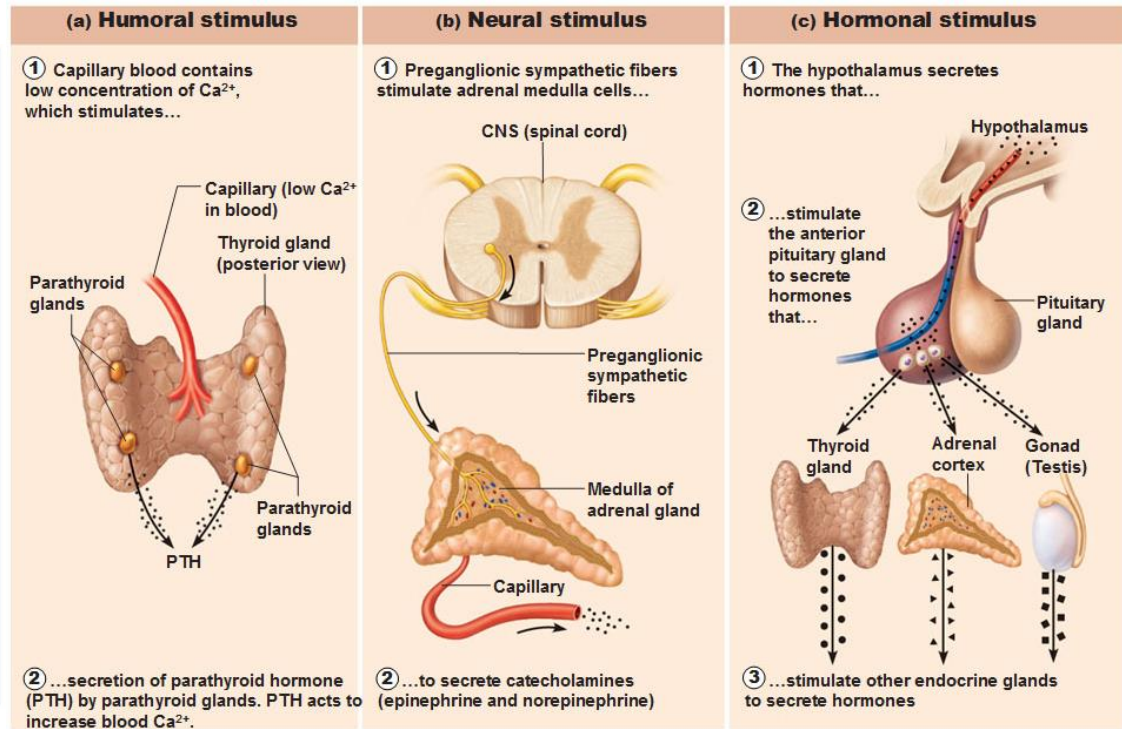
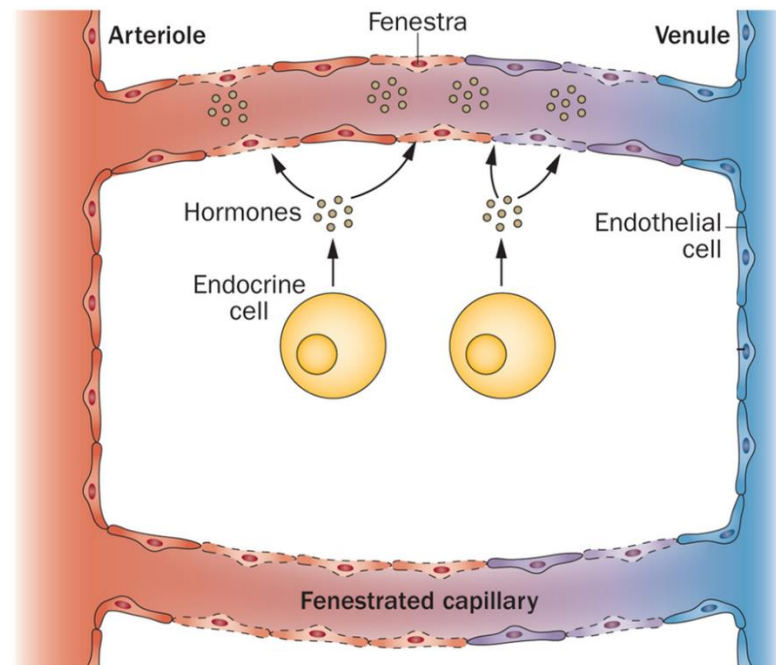
2 key differences:

- 1) Inflammation: systemic vs. local
- 2) Antigens: ubiquitous vs. tissue-restricted

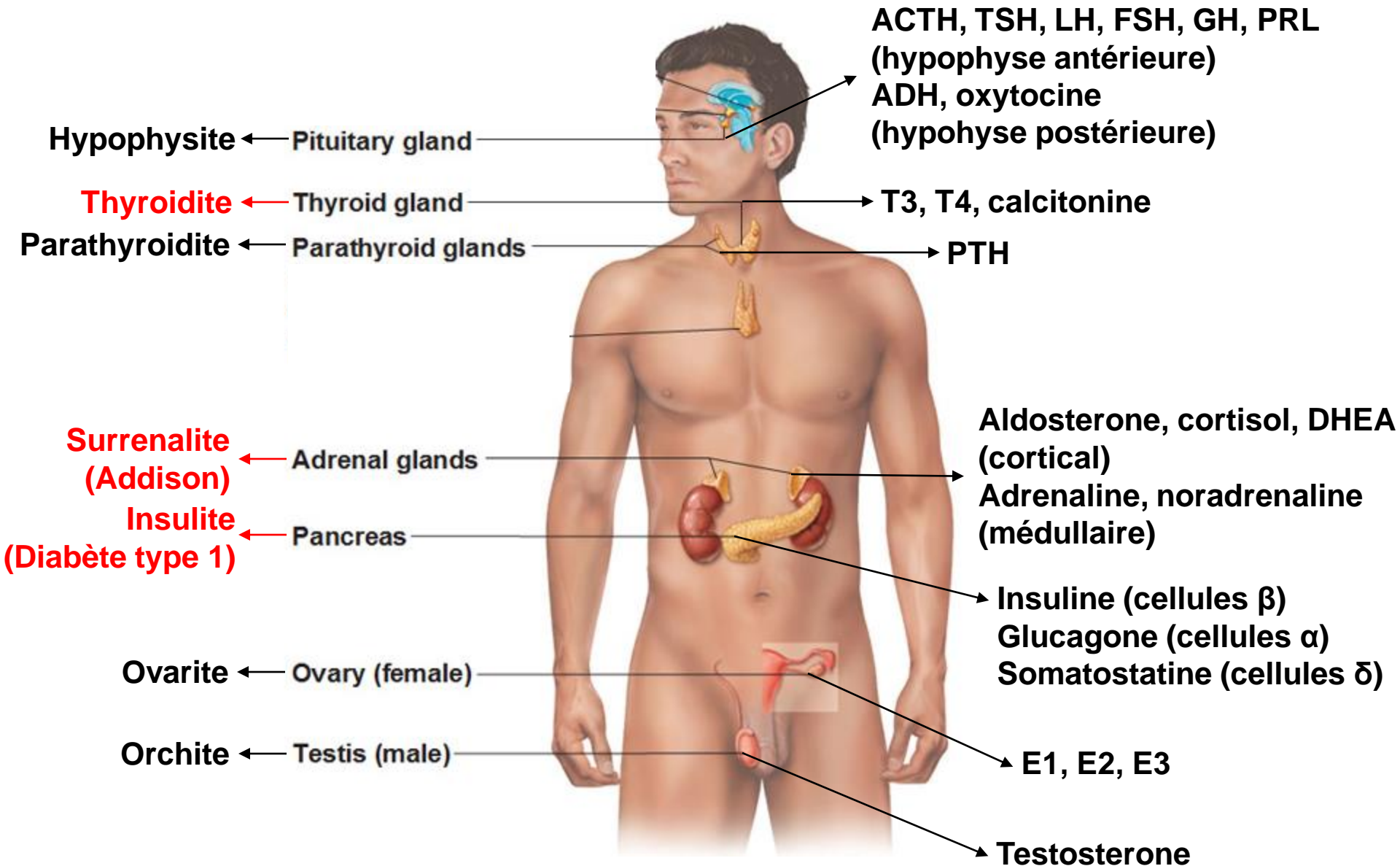
Systemic autoimmune diseases	Organ-specific autoimmune diseases
Rheumatoid arthritis	Psoriasis
Ankylosing spondylitis	Thyroiditides (Hashimoto & Graves/Basedow)
Systemic lupus erythematosus	Celiac disease
Sjogren's syndrome	Vitiligo
Polymyositis/dermatomyositis	Type 1 diabetes
Systemic sclerosis (scleroderma)	Alopecia areata
Wegener's granulomatosis	Pernicious anemia
CREST syndrome	Multiple sclerosis
	Addison's disease
	Myasthenia gravis
	Primary biliary cirrhosis
	Autoimmune polyglandular syndrome 2 (APS-2)

Définition de cellules endocrines

Secretory cells organized in glands that are devoid of a ductal system. They secrete hormones directly into the blood via their rich vascularization.



Les glandes endocrines: une cible privilégiée



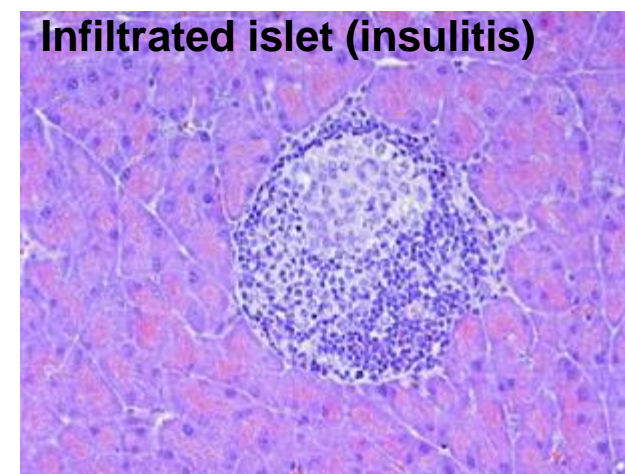
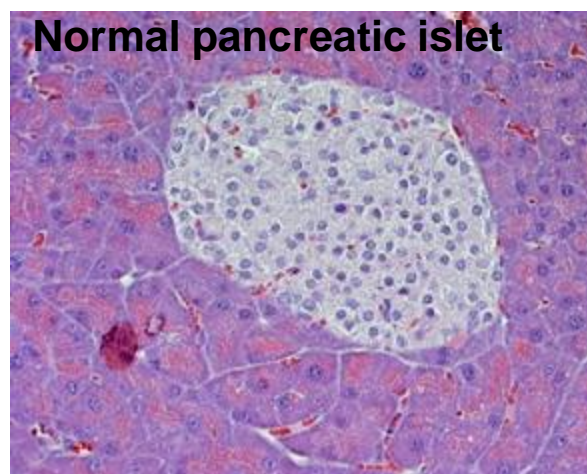
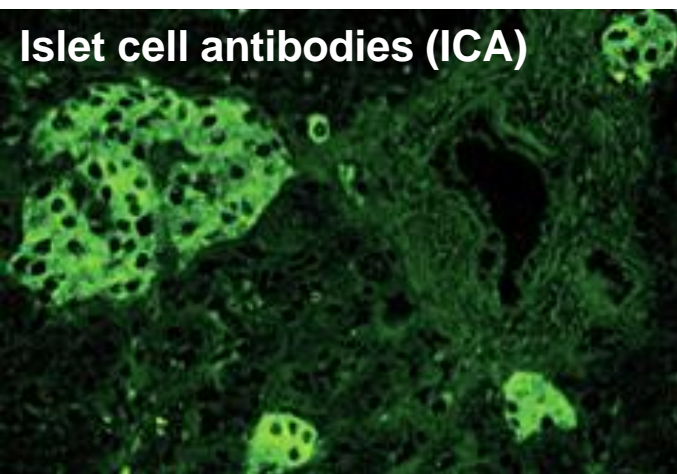
Prévalence des maladies auto-immunes

Autoimmune disease	Prevalence	Female/Male bias
Psoriasis	3.0%	93%
Hashimoto's thyroiditis	1.3%	90%
Graves' disease	1.2%	88%
Rheumatoid arthritis	1.0%	75%
Celiac disease	0.8%	75%
Inflammatory bowel disease	0.5%	Variable
Vitiligo	0.4%	52%
Type 1 diabetes	0.4%	40-50%
Ankylosing spondylitis	0.2%	30%
Alopecia areata	0.2%	50%
Pernicious anemia	0.2%	67%
Juvenile idiopathic arthritis	0.2%	68%
Multiple sclerosis	0.06%	64%
Systemic lupus erythematosus	0.02%	88%
Sjögren's syndrome	0.01%	94%
Addison's disease (50% as APS-2)	0.01%	70%
Myasthenia gravis	0.005%	73%
Polymyositis/dermatomyositis	0.005%	67%
Primary biliary cirrhosis	0.004%	89%
Systemic sclerosis (scleroderma)	0.004%	92%
Granulomatosis with polyangiitis (Wegener's)	0.003%	51%
APS-2	0.003%	75%
Uveitis	0.002%	50%
Autoimmune hepatitis	0.001%	88%
CREST syndrome	0.001%	80%
Idiopathic thrombocytopenic purpura	0.001%	Variable
APS-1 (APECED)	0.0007%	Variable
IPEX	Very rare	1%
TOTAL	2-5%	

Note: immune-mediated renal diseases not included

Comment a été démontré l'origine auto-immune des endocrinopathies?

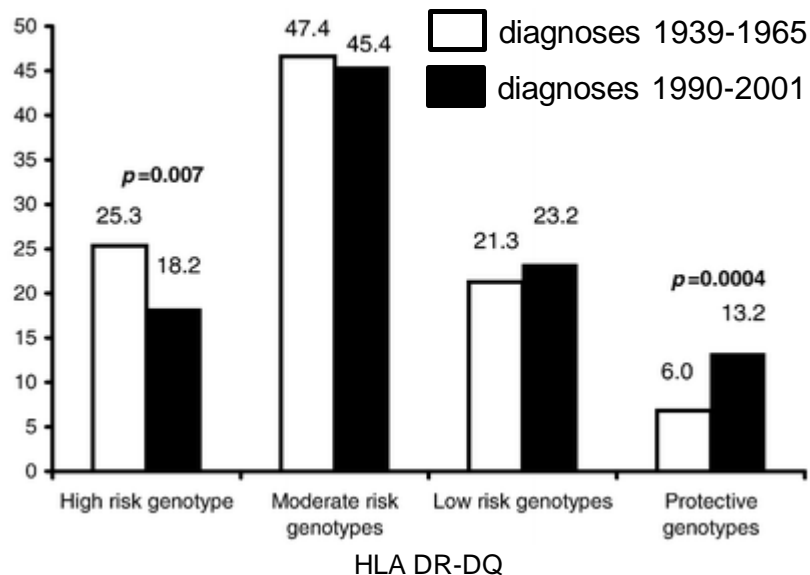
- Mouse models recapitulating the human diseases (spontaneous or induced)
- Antibodies or T lymphocytes from diseased mice transfer disease
- Organ-specific autoantibodies detectable in patients
- Strong association with HLA Class II alleles
- Immune infiltrates in diseased organs



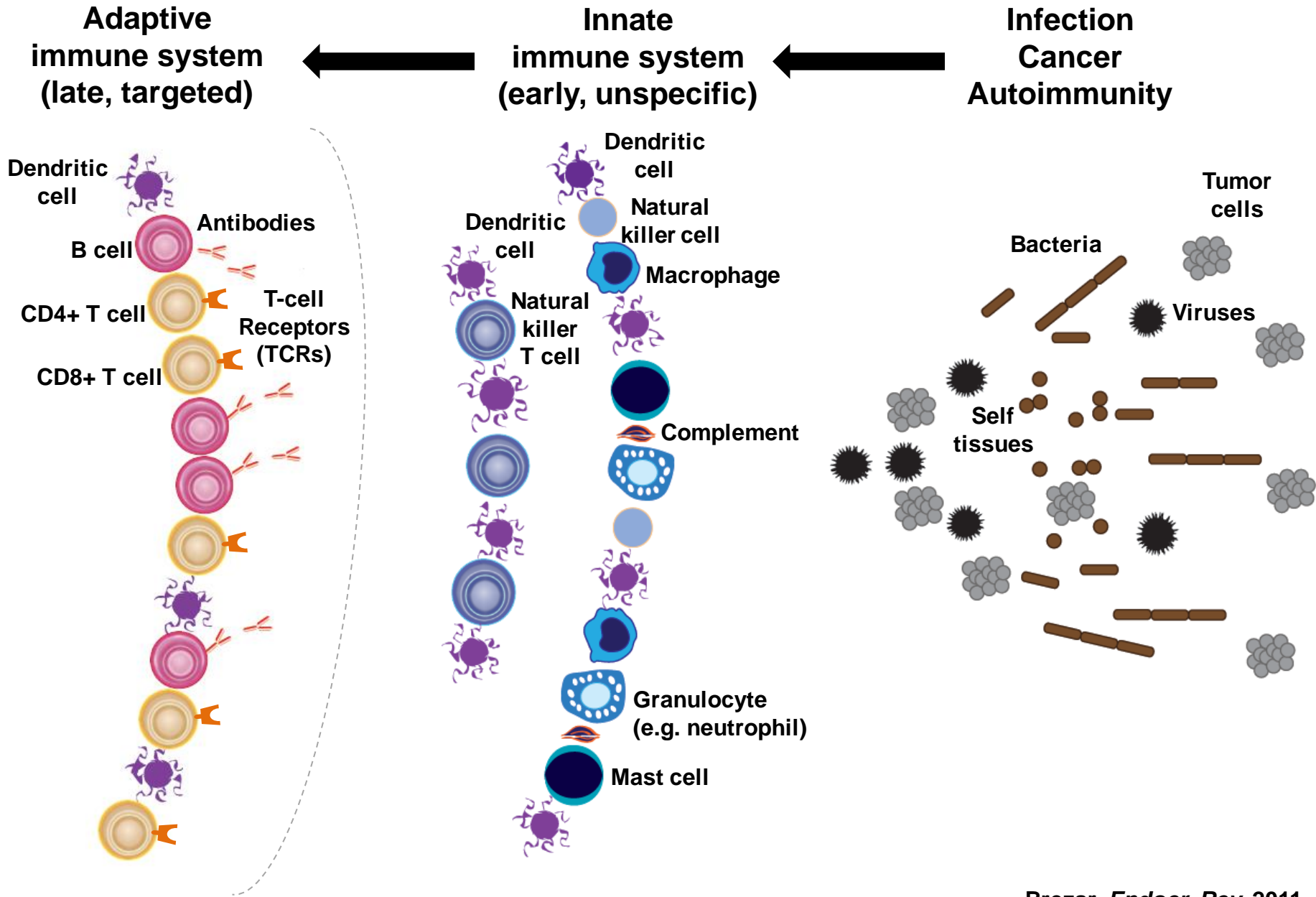
Génétique ou environnement? L'exemple du DT1

1) Environment weighs more than genetics:

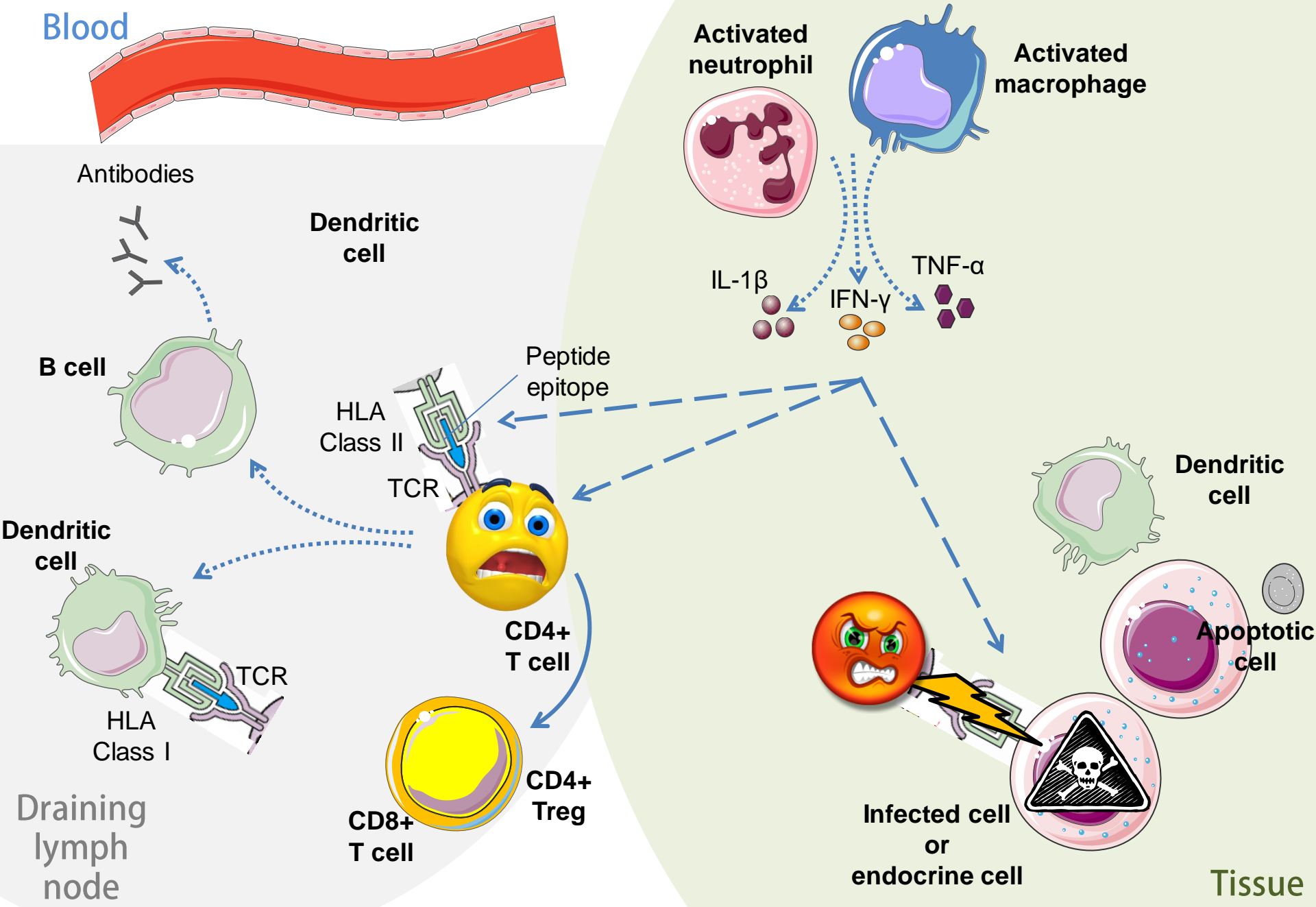
- 90% of cases are sporadic, only 10% arise in multiplex families
- Concordance between monozygotic twins: 30-65%
- Migrant studies: T1D incidence reflects that of the hosting region
- Comparison between regions with same genetic background and different environmental exposure
- 3-4%/year increase in T1D incidence and seasonality (spring, autumn)



Immunité innée et adaptative



Le canevas d'une réponse (auto)immune



Les trois ingrédients clés de l'auto-immunité

Blood

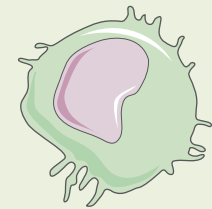
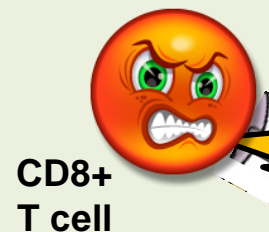
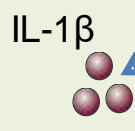
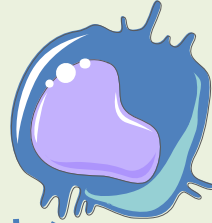
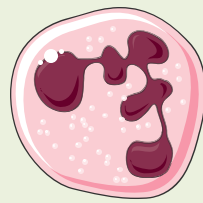
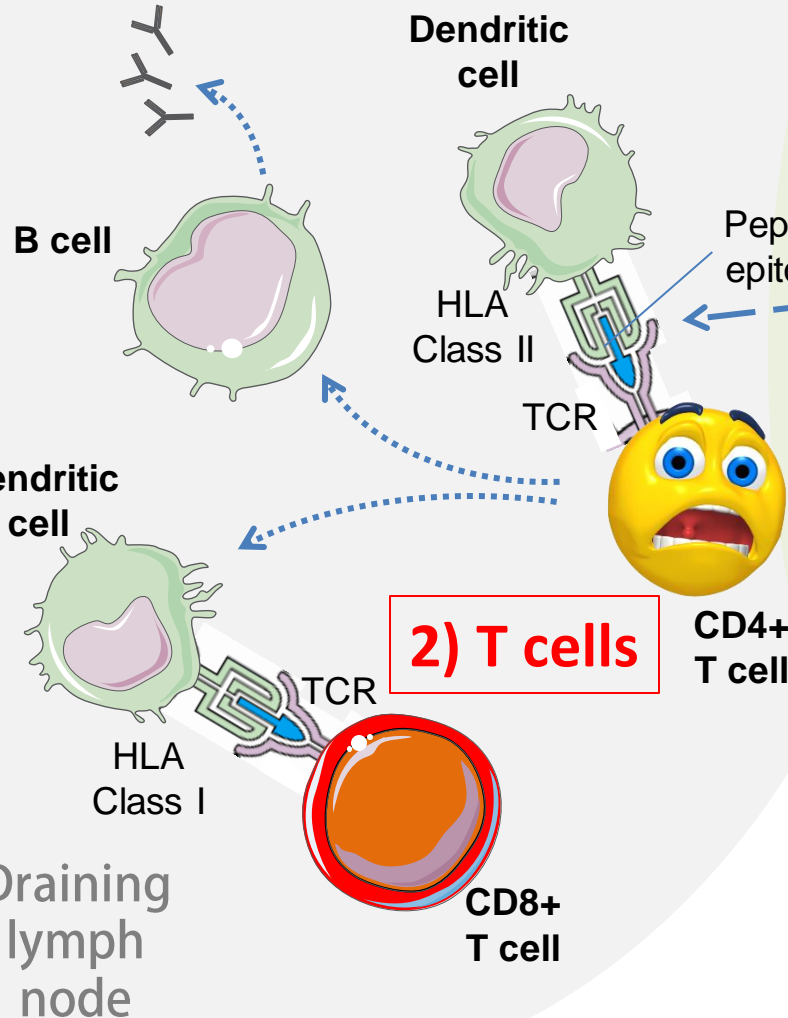
Activated neutrophil

Activated macrophage

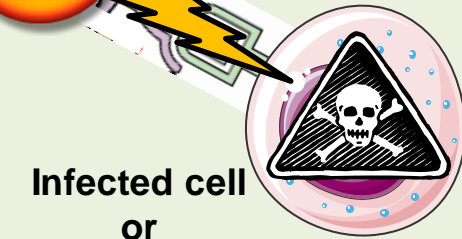
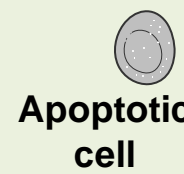
Antibodies

3) Autoantibodies

1) Inflammation

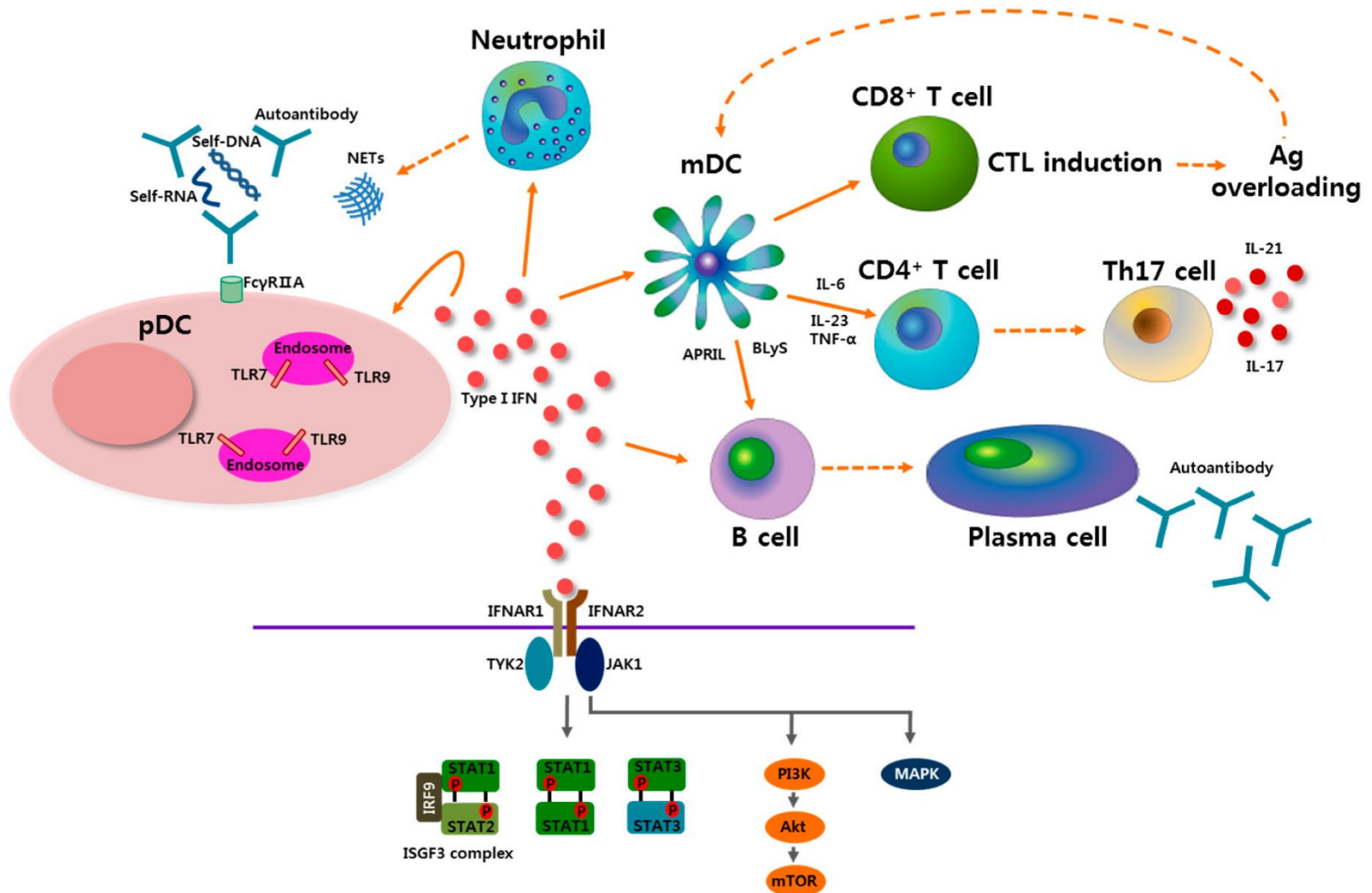


Dendritic cell

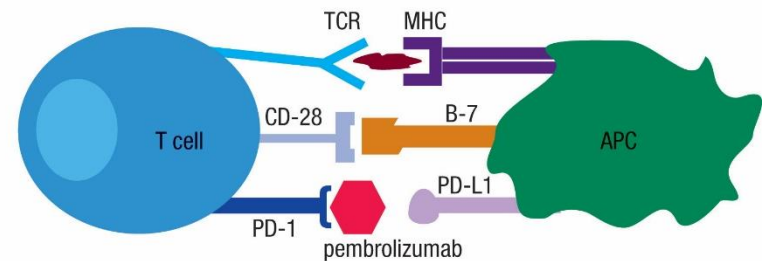
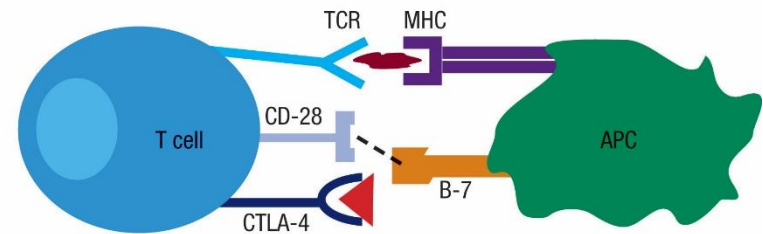
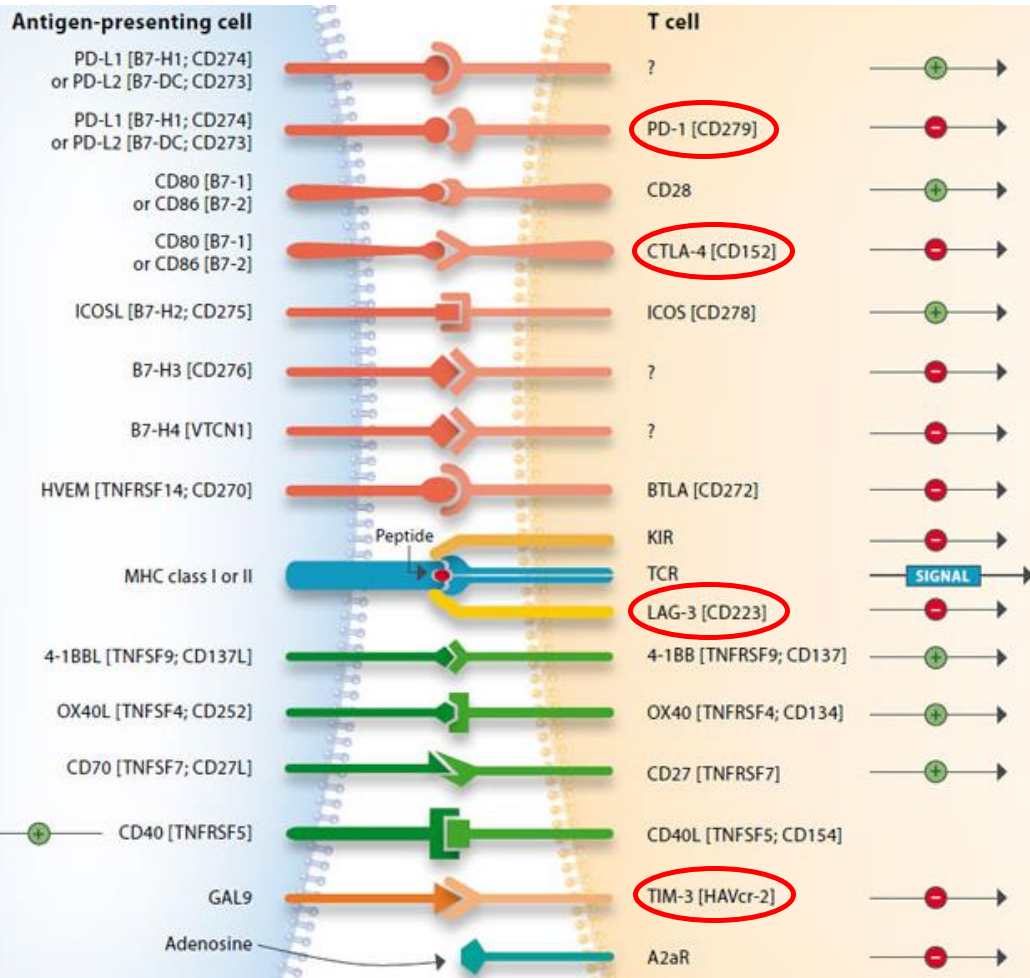


Tissue

Les enseignements à tirer des auto-immunités iatrogènes: IFN- α et hépatite C



Les enseignements à tirer des auto-immunités iatrogènes: Anti-CTLA-4/PD-1 et cancer



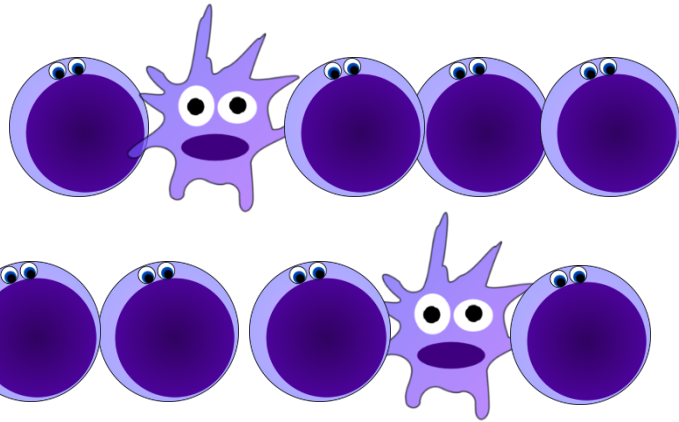
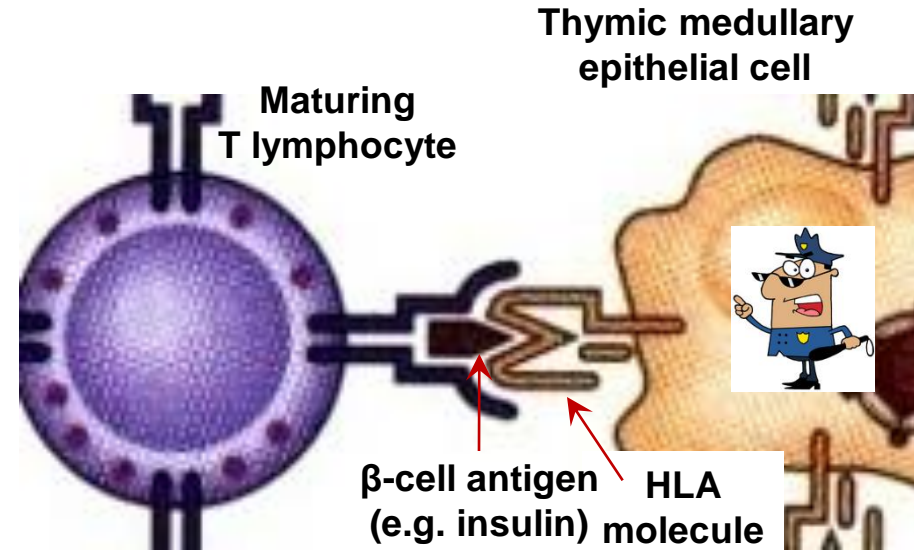
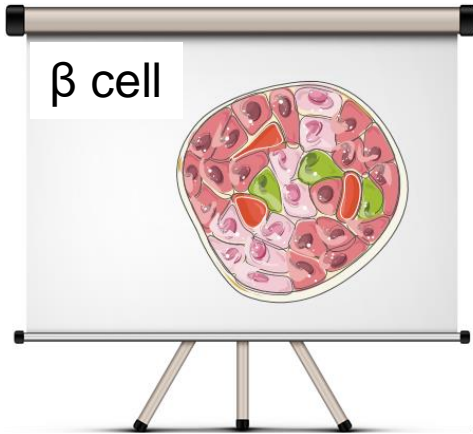
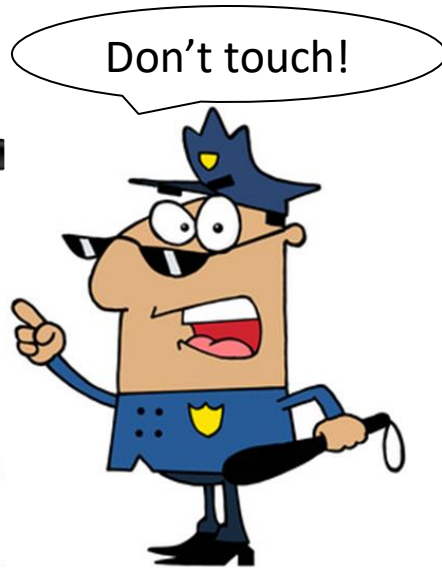
L'enjeu de l'auto-immunité : reconnaître le 'soi'



Caravaggio, "Narcissus", 1546-1548

L'apprentissage du soi a lieu dans le thymus

L'école thymique



T lymphocytes

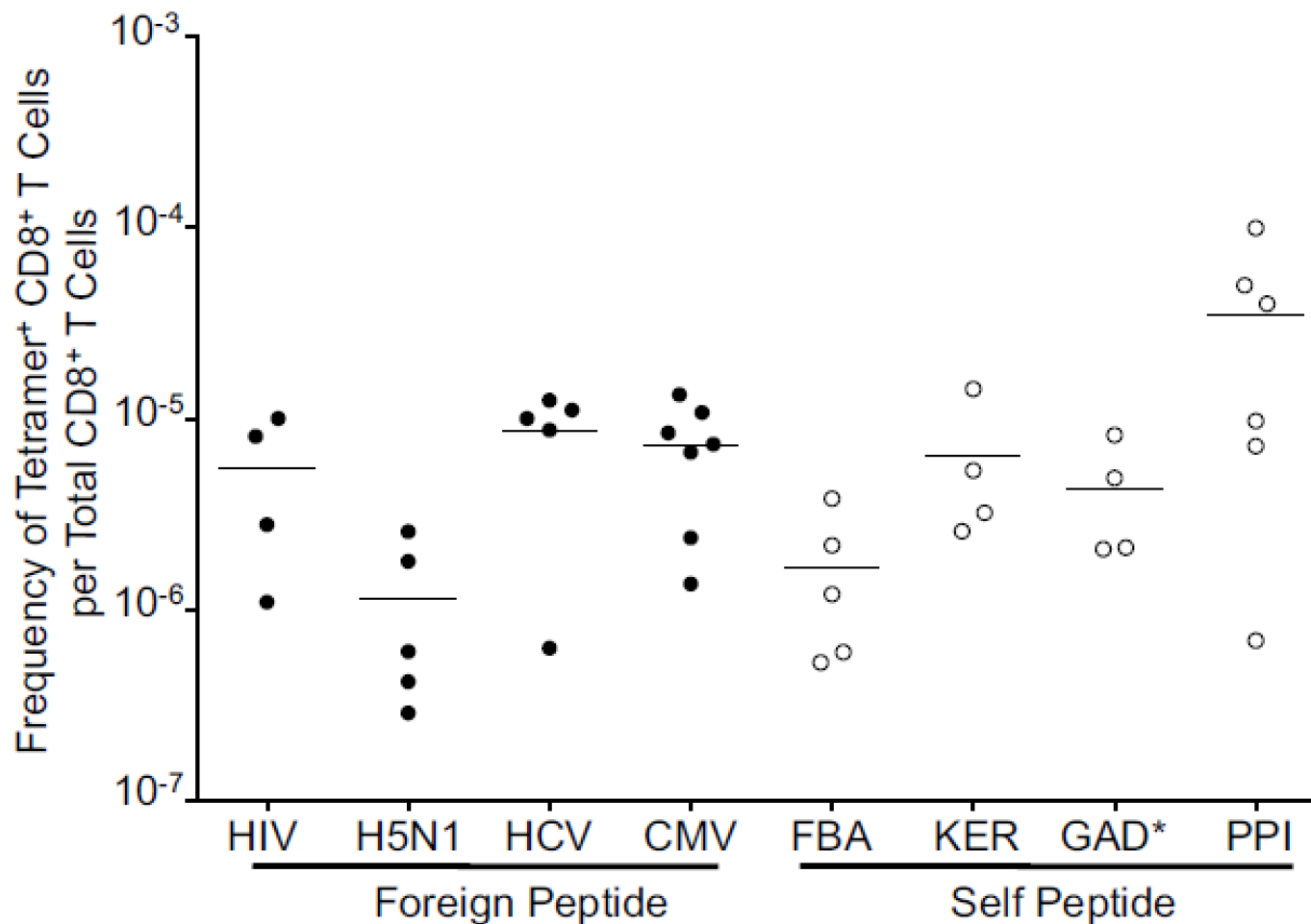


Autoreactive effector T cell:
pathogenic
→ eliminated

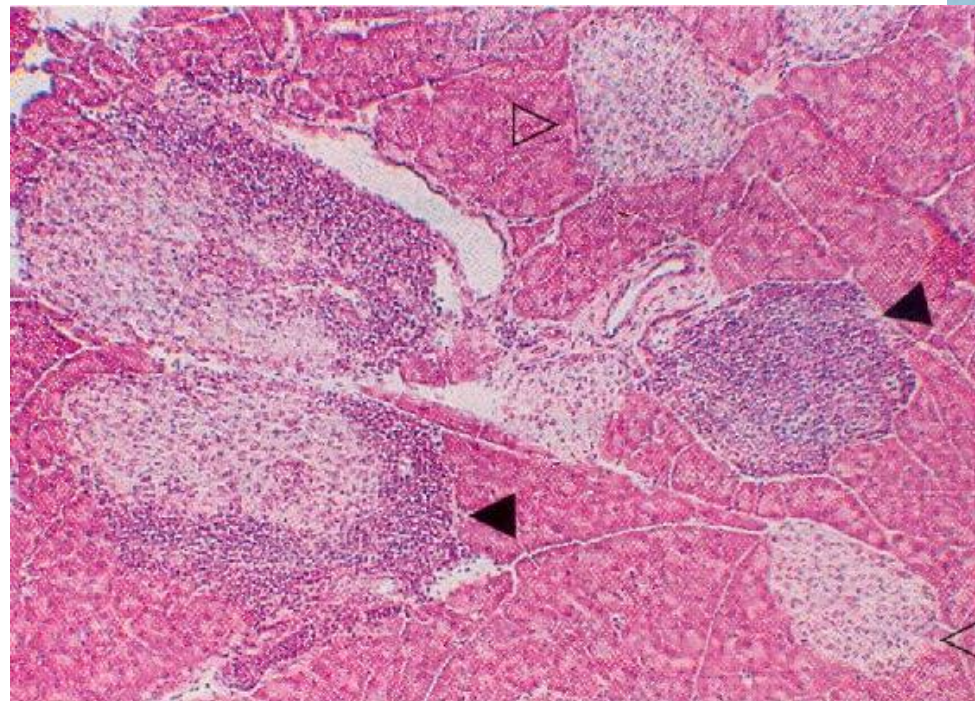


Autoreactive regulatory T lymphocyte:
protective
→ rescued

Nous sommes tous auto-immuns



La difference est-elle dans la cible?

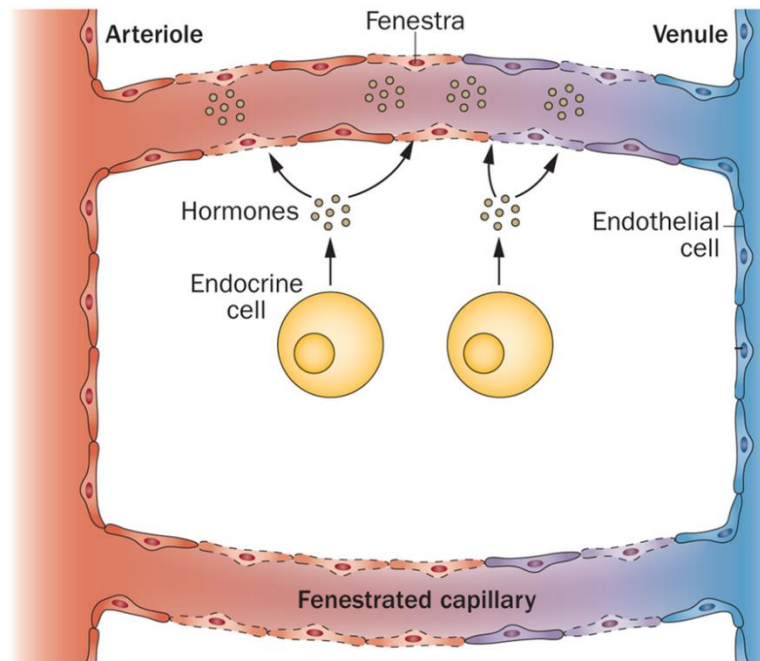


Pourquoi donc les cellules endocrines sont-elles une cible privilégiée?

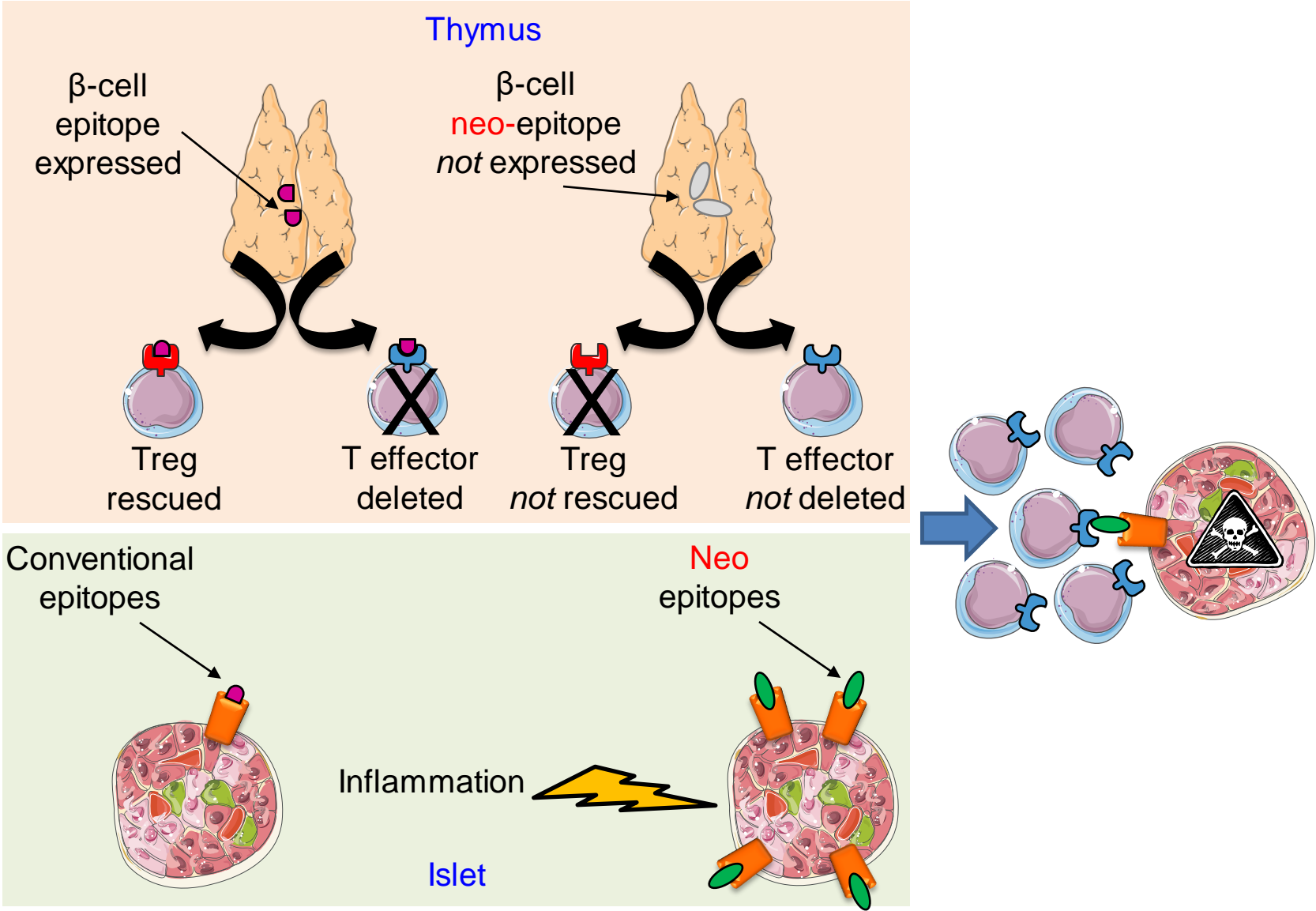
Definition of endocrine cell:

Secretory cells organized in glands that are devoid of a ductal system.

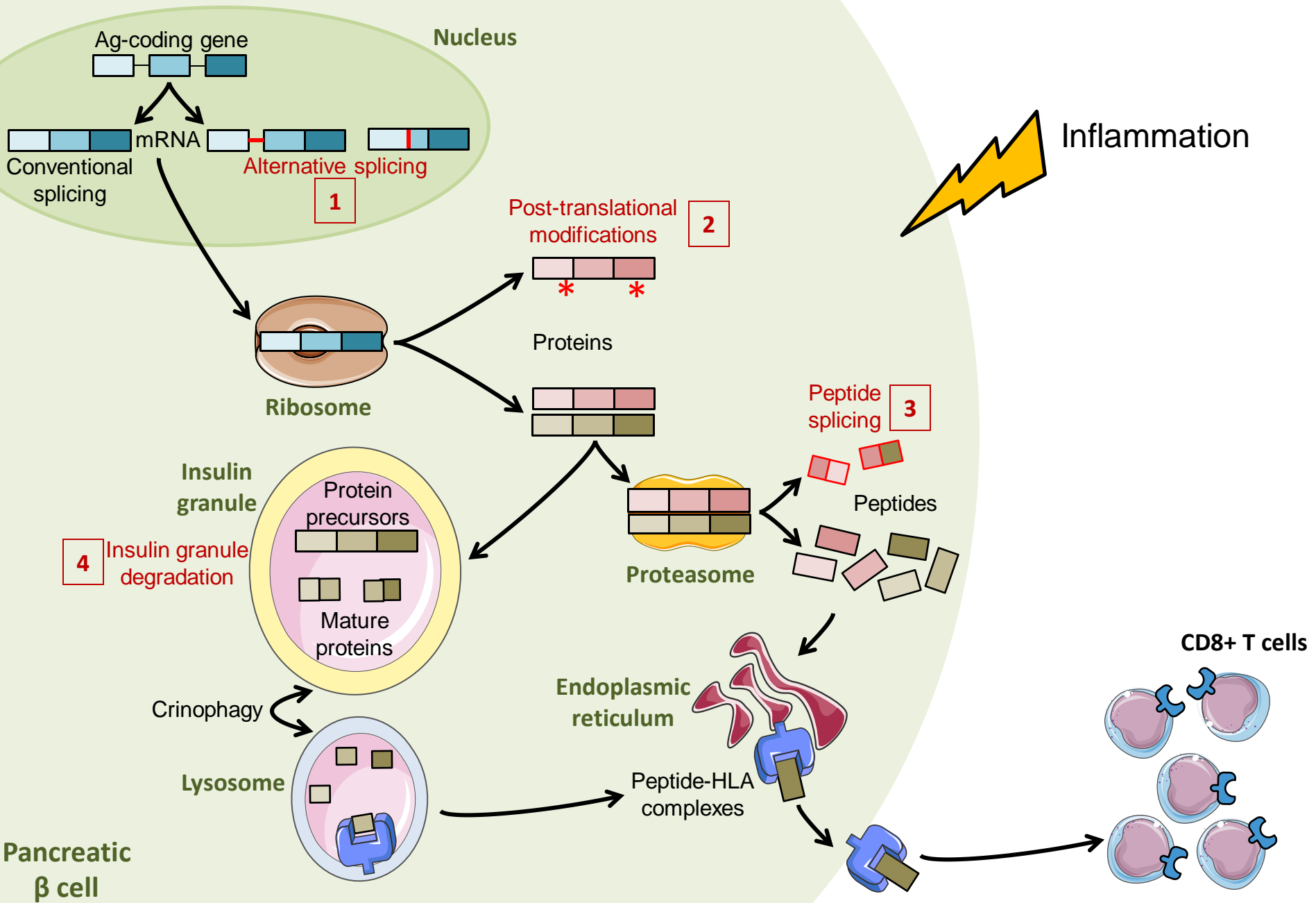
They secrete hormones directly into the blood via their rich vascularization.



Une cellule β inflammée pourrait devenir plus immunogène

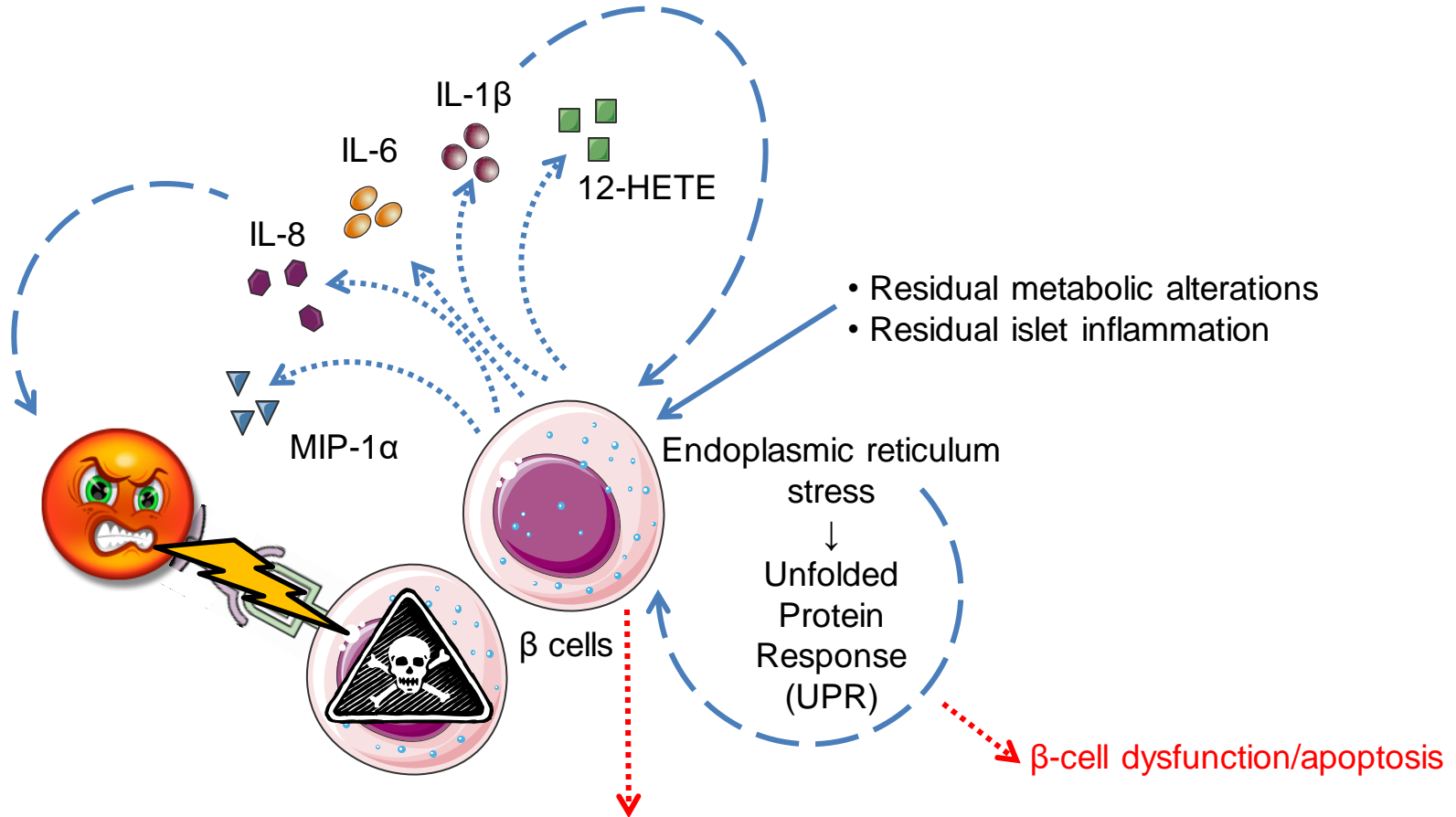


Les mécanismes de génération de néo-épitoques dans les cellules endocrines



Les cellules β restantes sont-elles normales?

L'homicide par les lymphocytes T ne deviendrait-il pas un suicide?



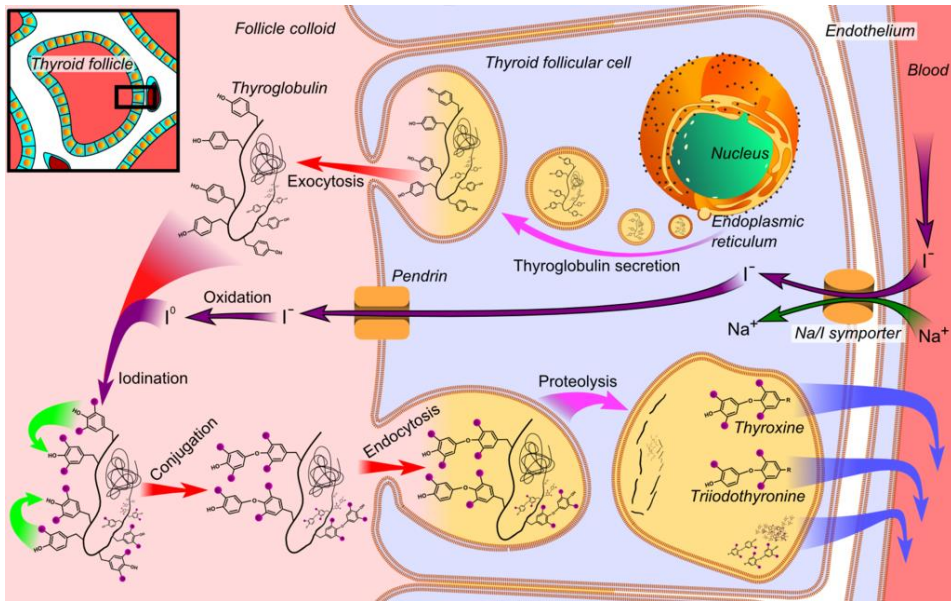
Neo-antigens:

- Alternative splicing
- Post-translational modifications
- Peptide splicing
- β -cell-specific epitope processing

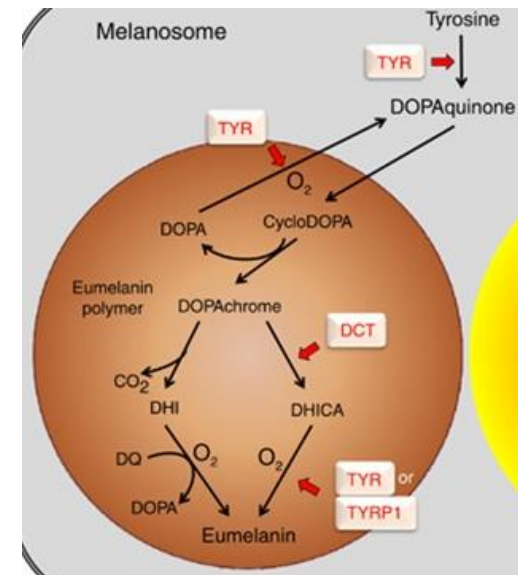
→ increased autoimmune vulnerability

Les similitudes avec l'Hashimoto et le vitiligo

Thyroid and iodine



Melanocyte and monobenzone





Les messages à réténir

- **Le diagnostic clinique est tardif, précédé d'une phase variable d'auto-immunité infra-clinique.**
- **La prédisposition génétique est majoritairement liée aux haplotypes HLA.**
- **Les facteurs environnementaux jouent le rôle plus important, mais restent méconnus.**
- **Une phase précoce de réponse immunitaire innée est suivie d'une réponse adaptative (lymphocytes T, anticorps).**
- **L'auto-immunité est un phénomène naturel, et la progression vers la maladie clinique est influencée par les facteurs environnementaux, par une bonne dose de chance et par la vulnérabilité de la cible endocrine.**
- **La cellule endocrine est une cible auto-immune privilégiée car elle est une 'usine à hormones': erreurs de synthèse de protéines, vulnérabilité inflammatoire.**

Les endocrinopathies auto-immunes: une mauvaise exemple d'approche diagnostique et thérapeutique

Maladie	Tests diagnostiques			Traitements
	Hormones	Anticorps	Lymphocytes T	
Thyroïdites: Basedow Hashimoto	TSH T3, T4	Thyropéroxydase Thyroglobuline Récepteur TSH (TRAK)	Non	Thyroxine Méthimazole Iode radioactive Thyroïdectomie
Addison	ACTH, rénine Aldostérone Cortisol DHEA	21-hydroxylase	Non	Hydrocortisone
Diabète de type 1	Peptide C Glycémie, HbA1c Cétonémie	Insuline (IAA) GAD IA-2 ZnT8	Non	Insuline
Hypoparathyroïdisme auto-immun	PTH Ca ²⁺ , phosphates	NALP5	Non	Calcium, magnesium 1,25OH vit. D

Du biomarqueur au traitement

First description: 1,700-1,500 B.C.



~3,500 years
later...

Insulin
1922

