Hormones et Système Immunitaire

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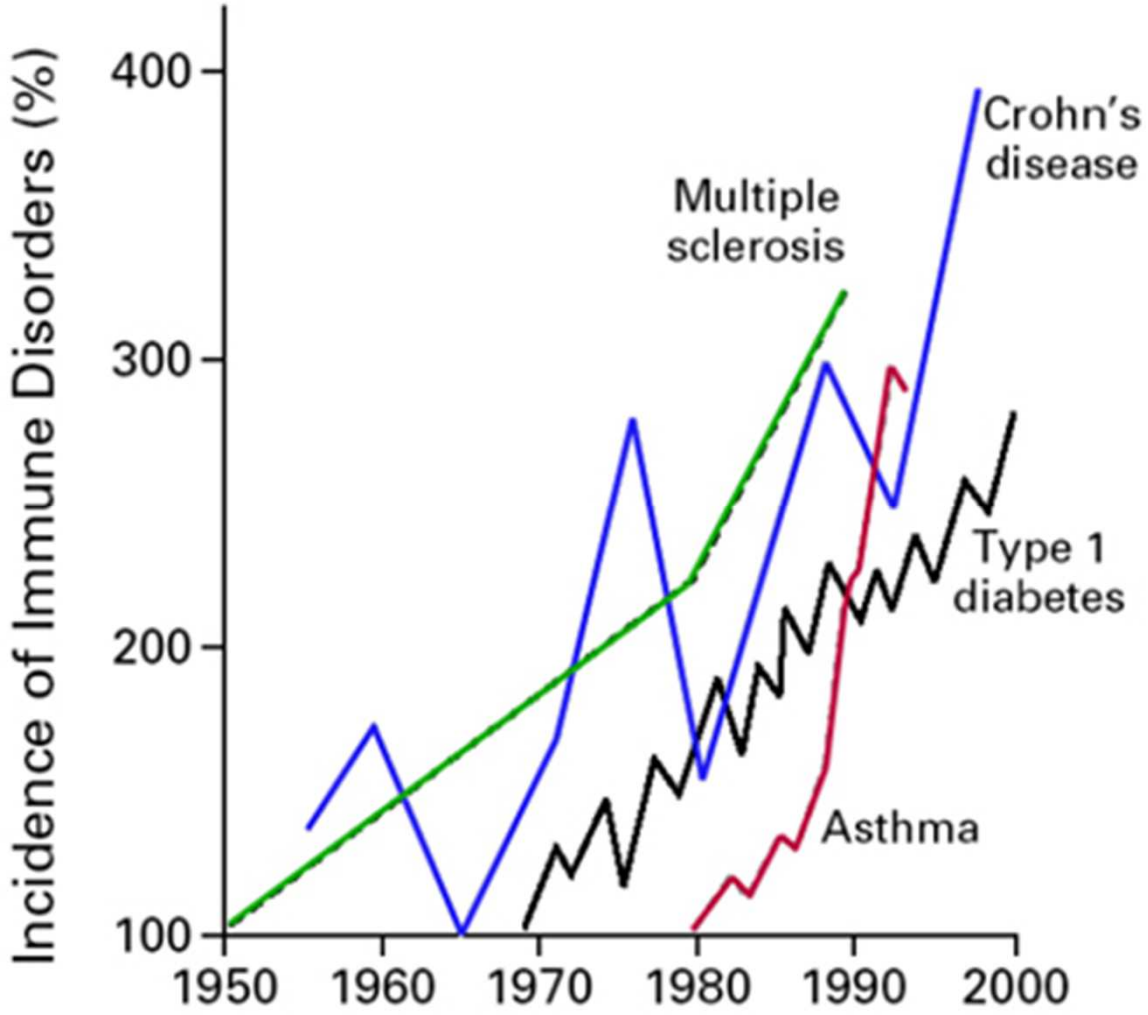
Service de Médecine Interne 2

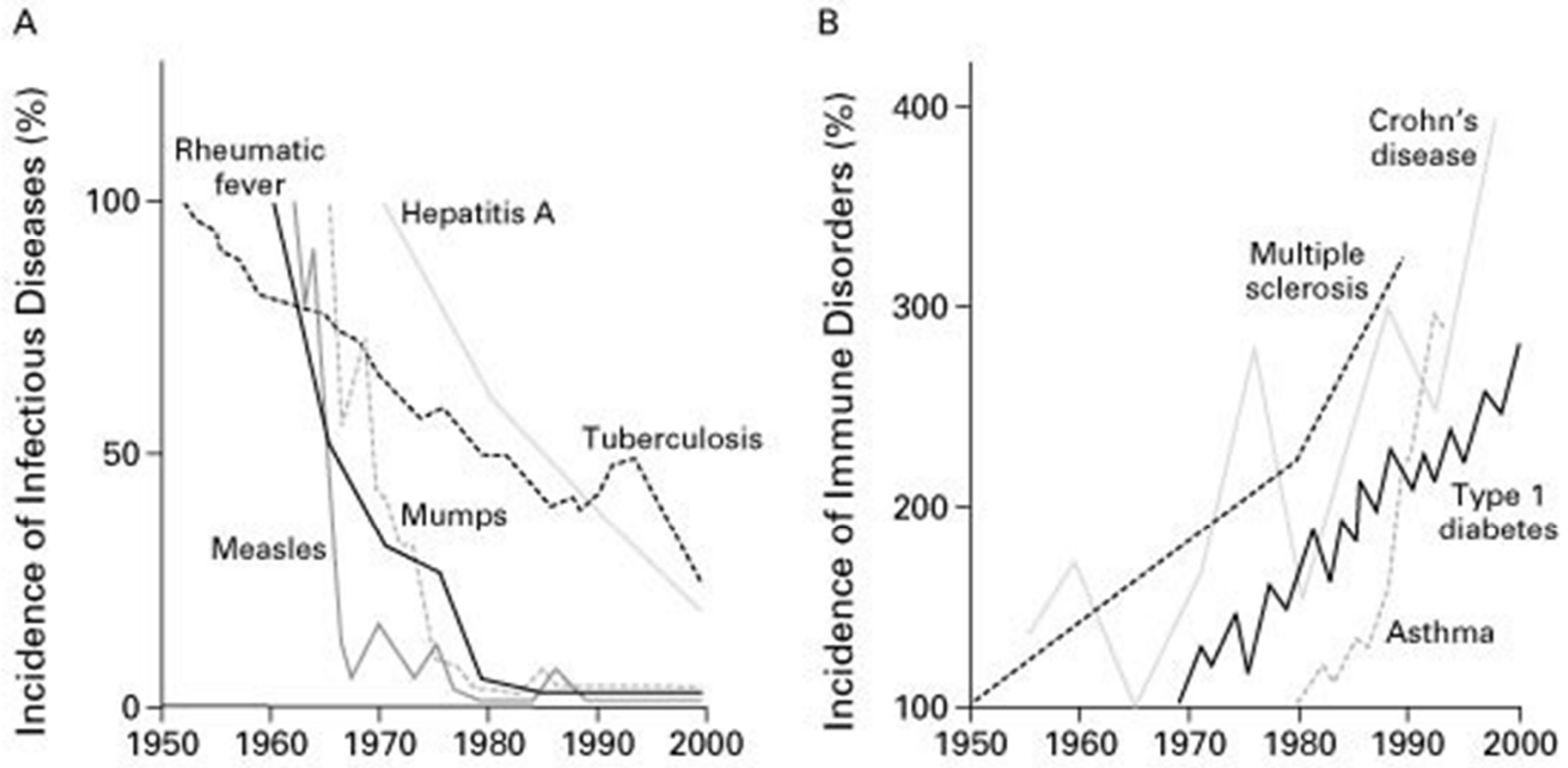
CIMI – UMRS 1135

Epidémiologie des maladies auto-immunes



Bach NEJM 2002

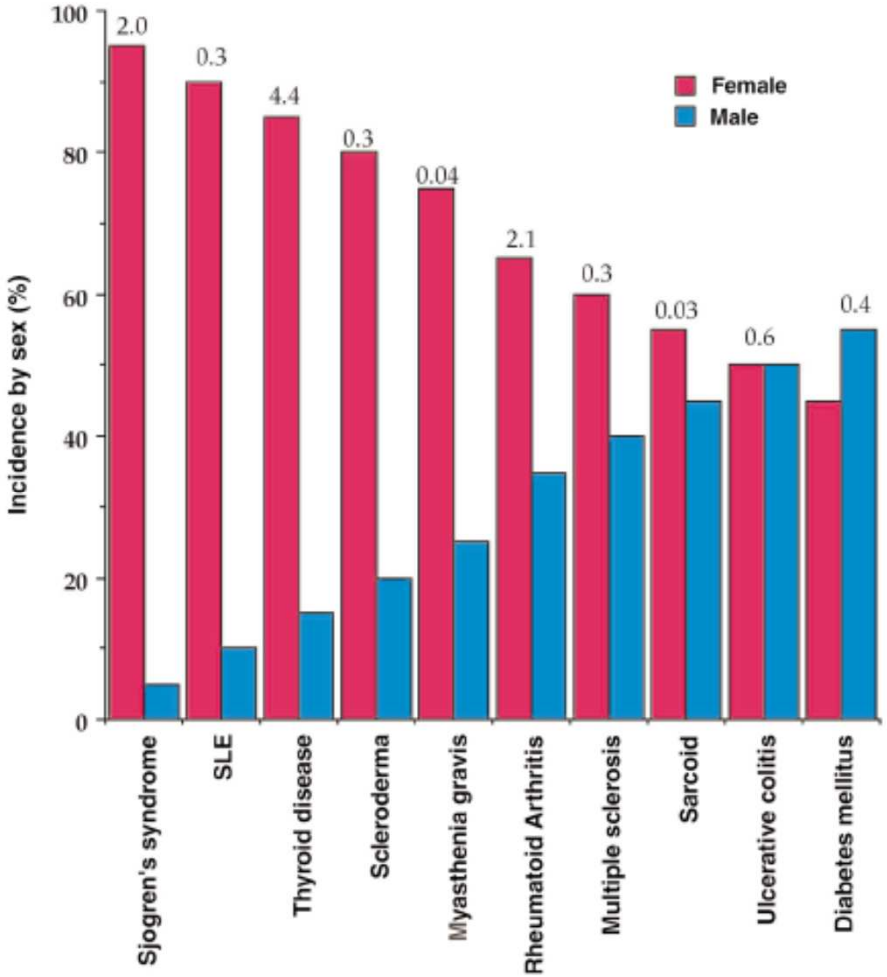
Epidémiologie des maladies auto-immunes



Epidémiologie des maladies auto-immunes

- diminution de l'incidence des maladies infectieuses
- augmentation de la pollution, du tabagisme
- augmentation de l'obésité
- moindre exposition solaire (moins de Vitamine D)
- nombre moindre de grossesses/ femme

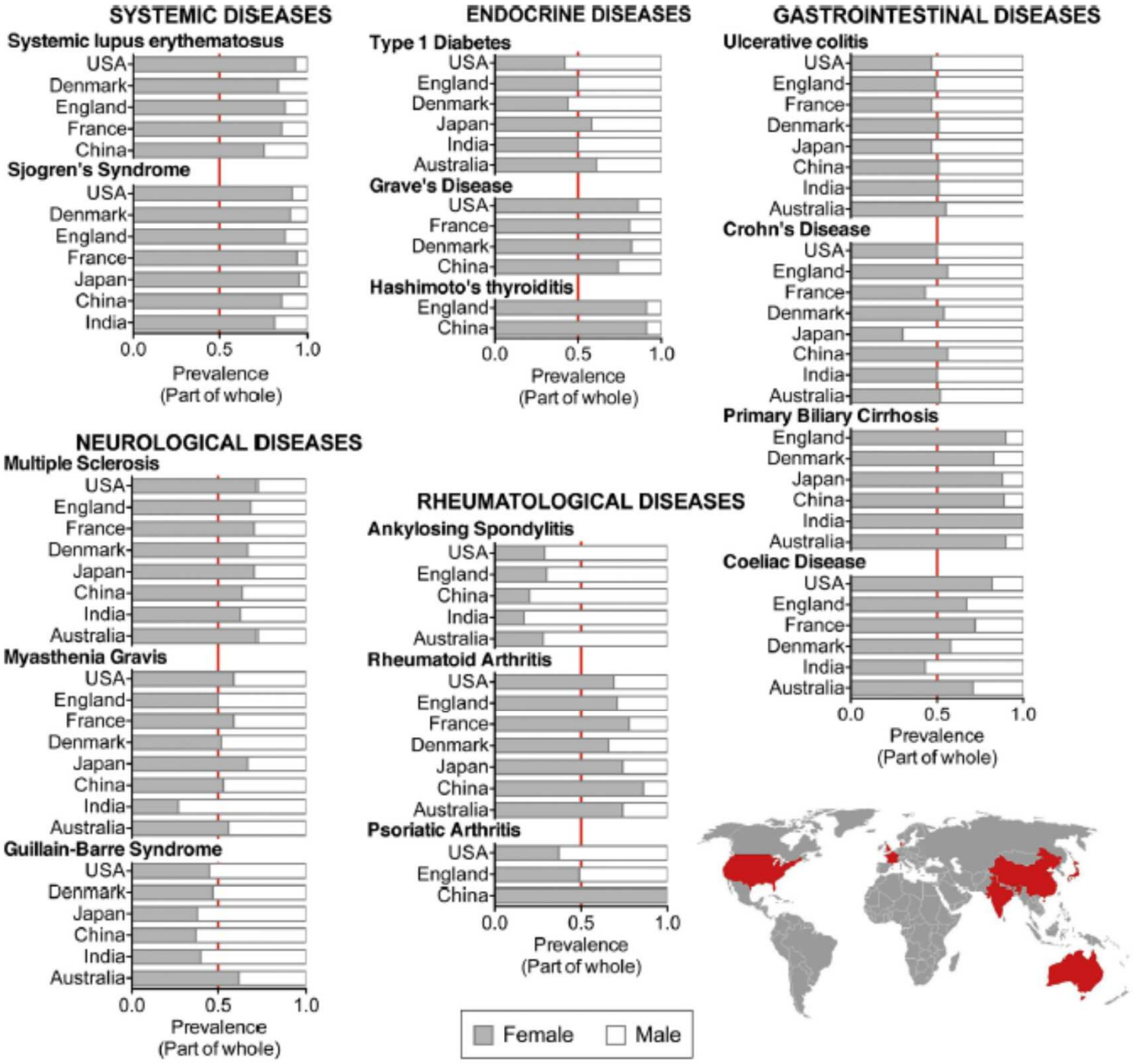
Prévalence féminine dans les maladies auto-immunes



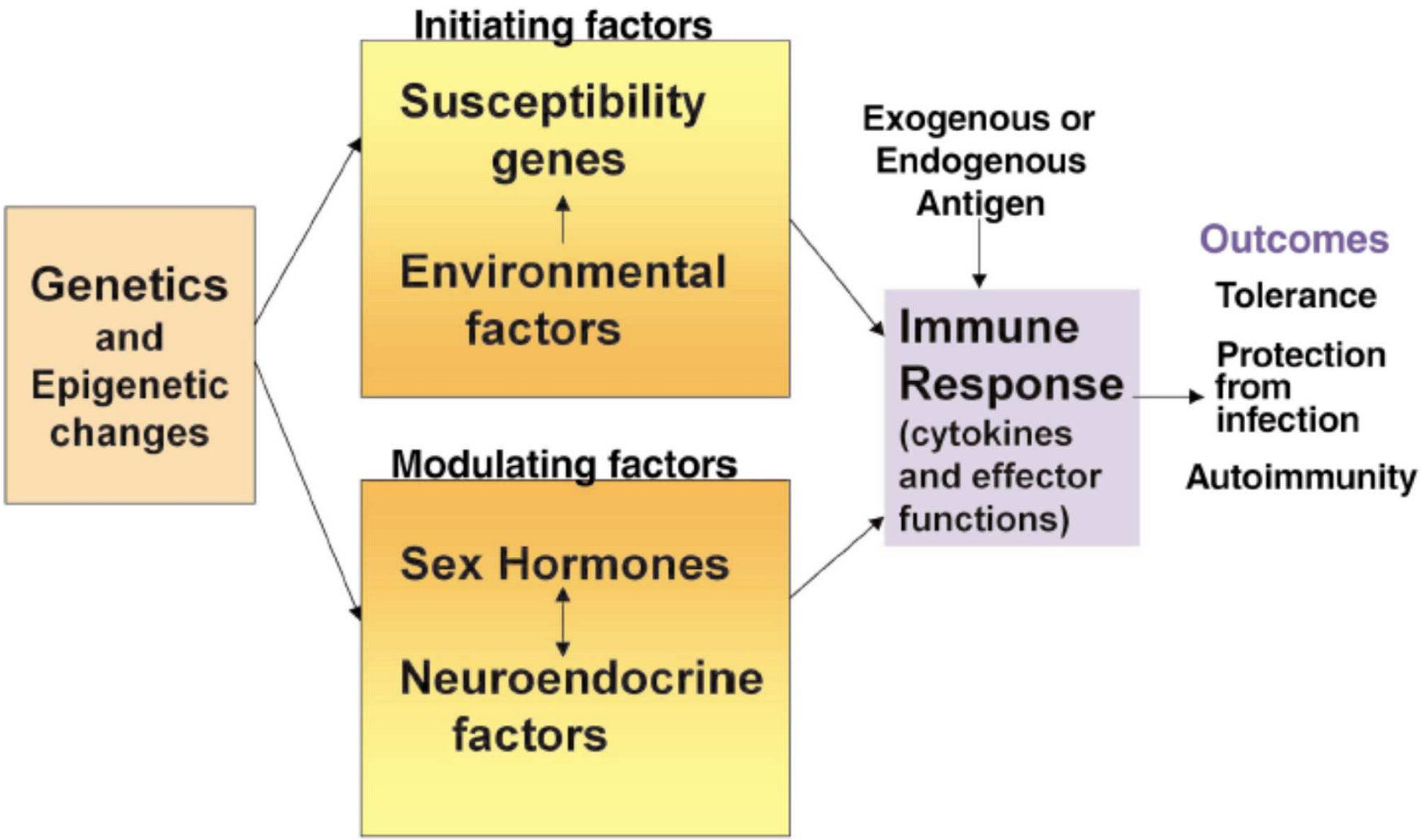
>8/1 : lupus, SGS, maladie de Takayasu, thyroïdites

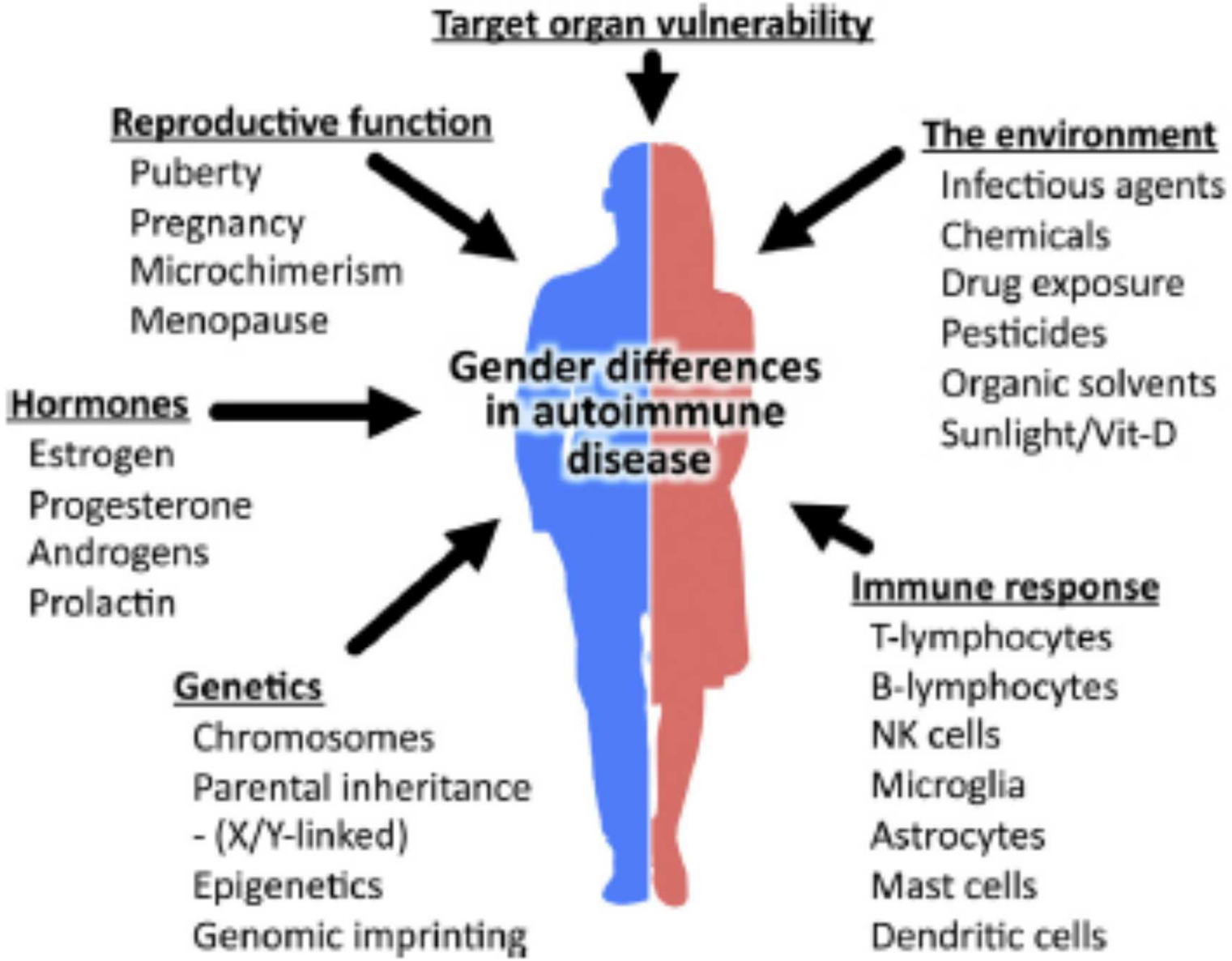
4/1 : PR, myasthénie, Biermer, SAPL

1.5-2/1 : sarcoïdose, vitiligo, SEP

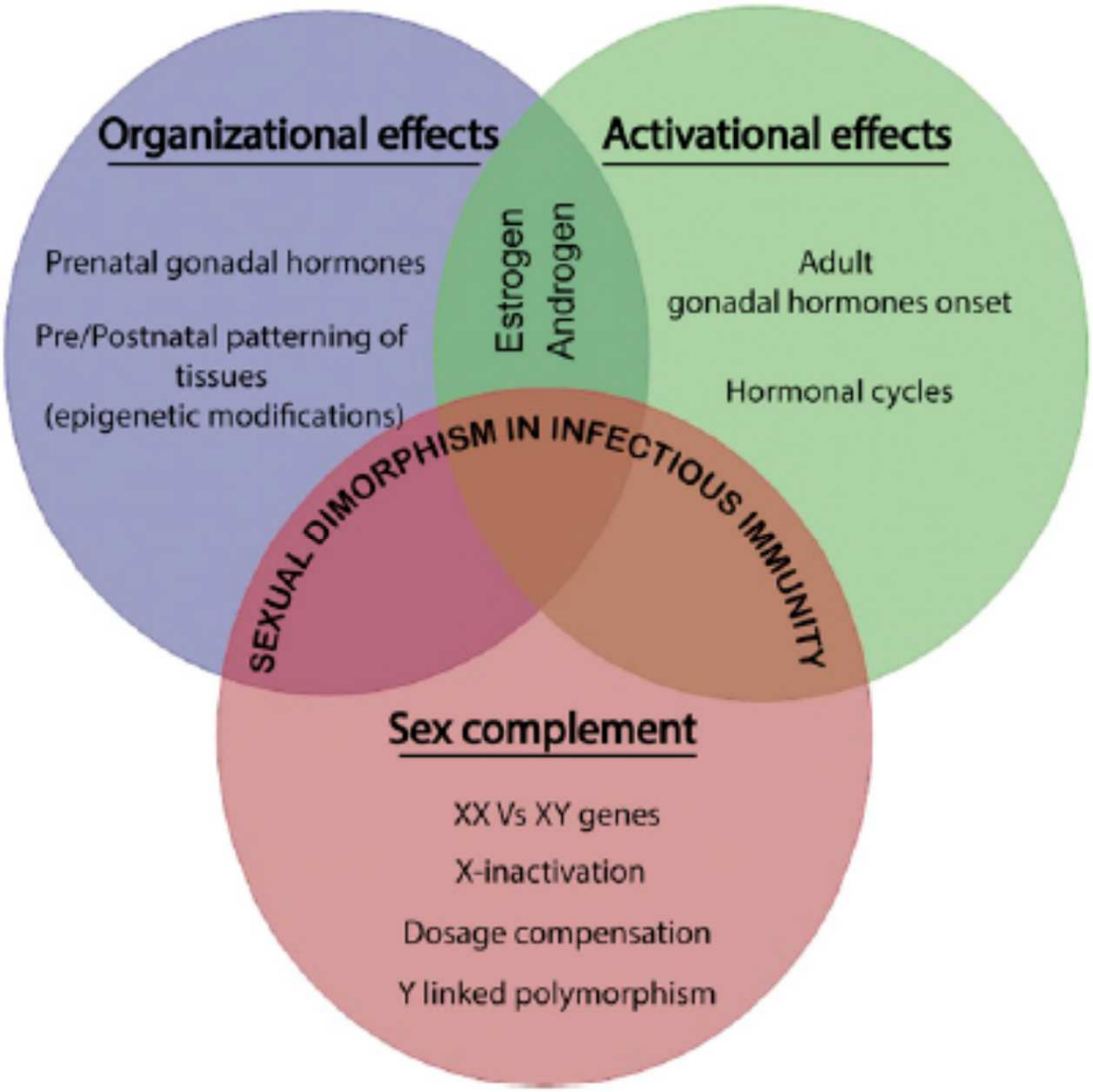

SYSTEMIC DISEASES
Systemic lupus erythematosus
USA
Denmark
England
France
China
Sjogren's Syndrome
USA
Denmark
England
France
Japan
China
India
0.0
0.5
1.0
Prevalence
(Part of whole)
ENDOCRINE DISEASES
Type 1 Diabetes
USA
England
Denmark
Japan
India
Australia
Grave's Disease
USA
France
Denmark
China
Hashimoto's thyroiditis
England
China
0.0
0.5
1.0
Prevalence
(Part of whole)
GASTROINTESTINAL DISEASES
Ulcerative colitis
USA
England
France
Denmark
Japan
China
India
Australia
Crohn's Disease
USA
England
France
Denmark
Japan
China
India
Australia
Primary Biliary Cirrhosis
England
Denmark
Japan
China
India
Australia
Coeliac Disease
USA
England
France
Denmark
India
Australia
0.0
0.5
1.0
Prevalence
(Part of whole)
NEUROLOGICAL DISEASES
Multiple Sclerosis
USA
England
France
Denmark
Japan
China
India
Australia
Myasthenia Gravis
USA
England
France
Denmark
Japan
China
India
Australia
Guillain-Barre Syndrome
USA
Denmark
Japan
China
India
Australia
0.0
0.5
1.0
Prevalence
(Part of whole)
RHEUMATOLOGICAL DISEASES
Ankylosing Spondylitis
USA
England
China
India
Australia
Rheumatoid Arthritis
USA
England
France
Denmark
Japan
China
Australia
Psoriatic Arthritis
USA
England
China
0.0
0.5
1.0
Prevalence
(Part of whole)
Female
Male

Overview des déterminants multifactoriels de la réponse immunitaire




Target organ vulnerability
Reproductive function
Puberty
Pregnancy
Microchimerism
Menopause
The environment
Infectious agents
Chemicals
Drug exposure
Pesticides
Organic solvents
Sunlight/Vit-D
Gender differences in autoimmune disease
Hormones
Estrogen
Progesterone
Androgens
Prolactin
Genetics
Chromosomes
Parental inheritance
- (X/Y-linked)
Epigenetics
Genomic imprinting
Immune response
T-lymphocytes
B-lymphocytes
NK cells
Microglia
Astrocytes
Mast cells
Dendritic cells

Dimorphisme sexuel



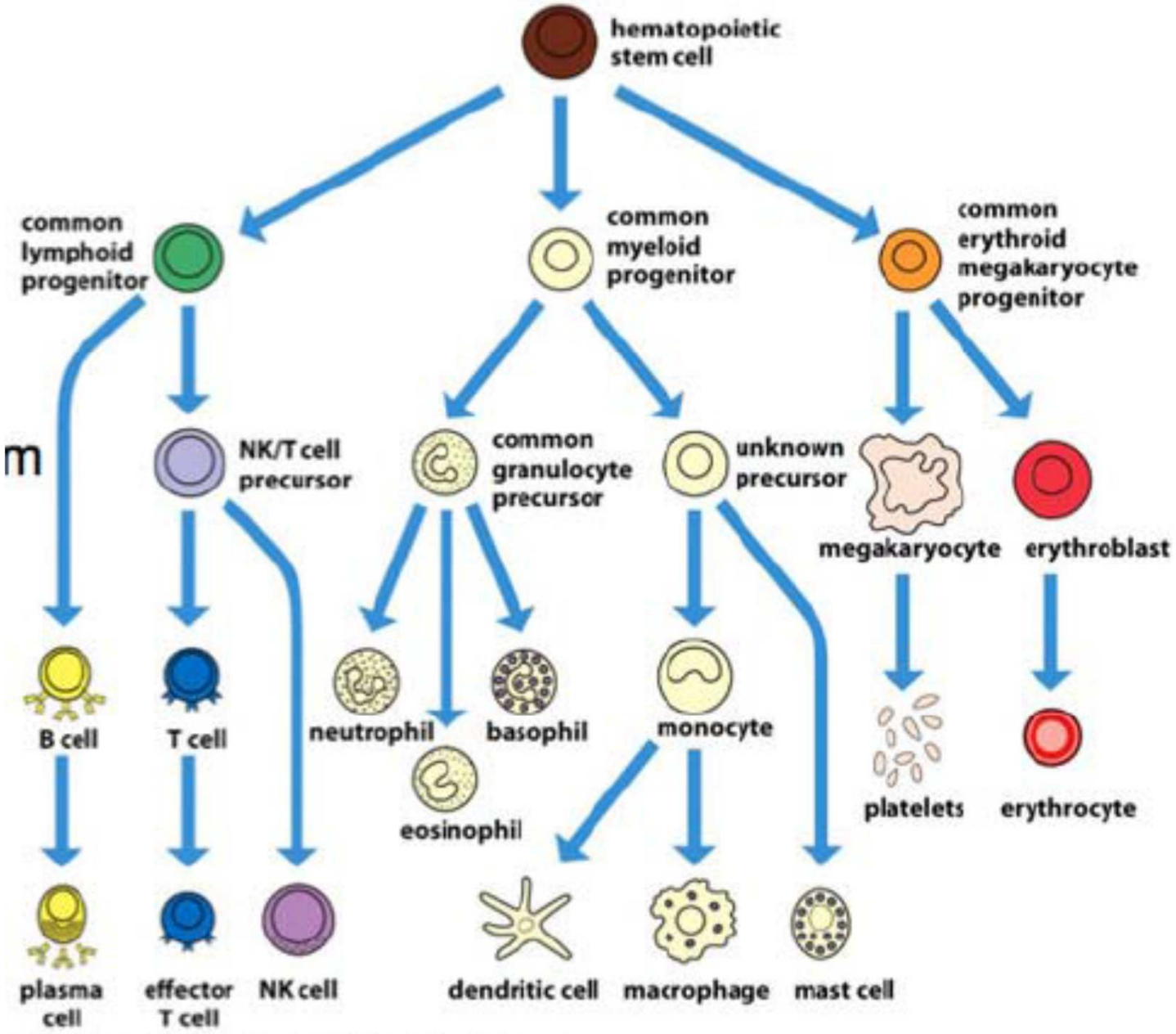
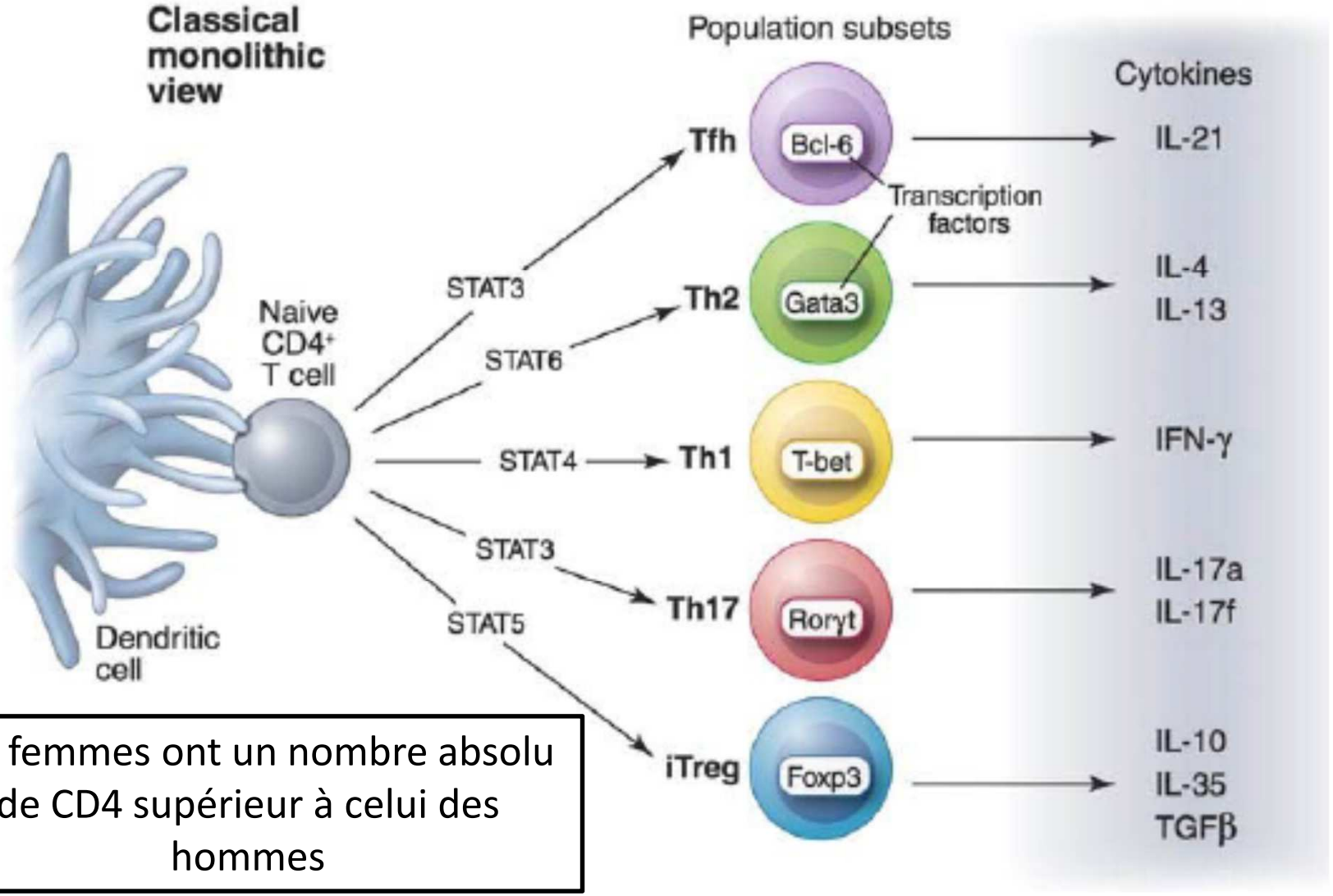
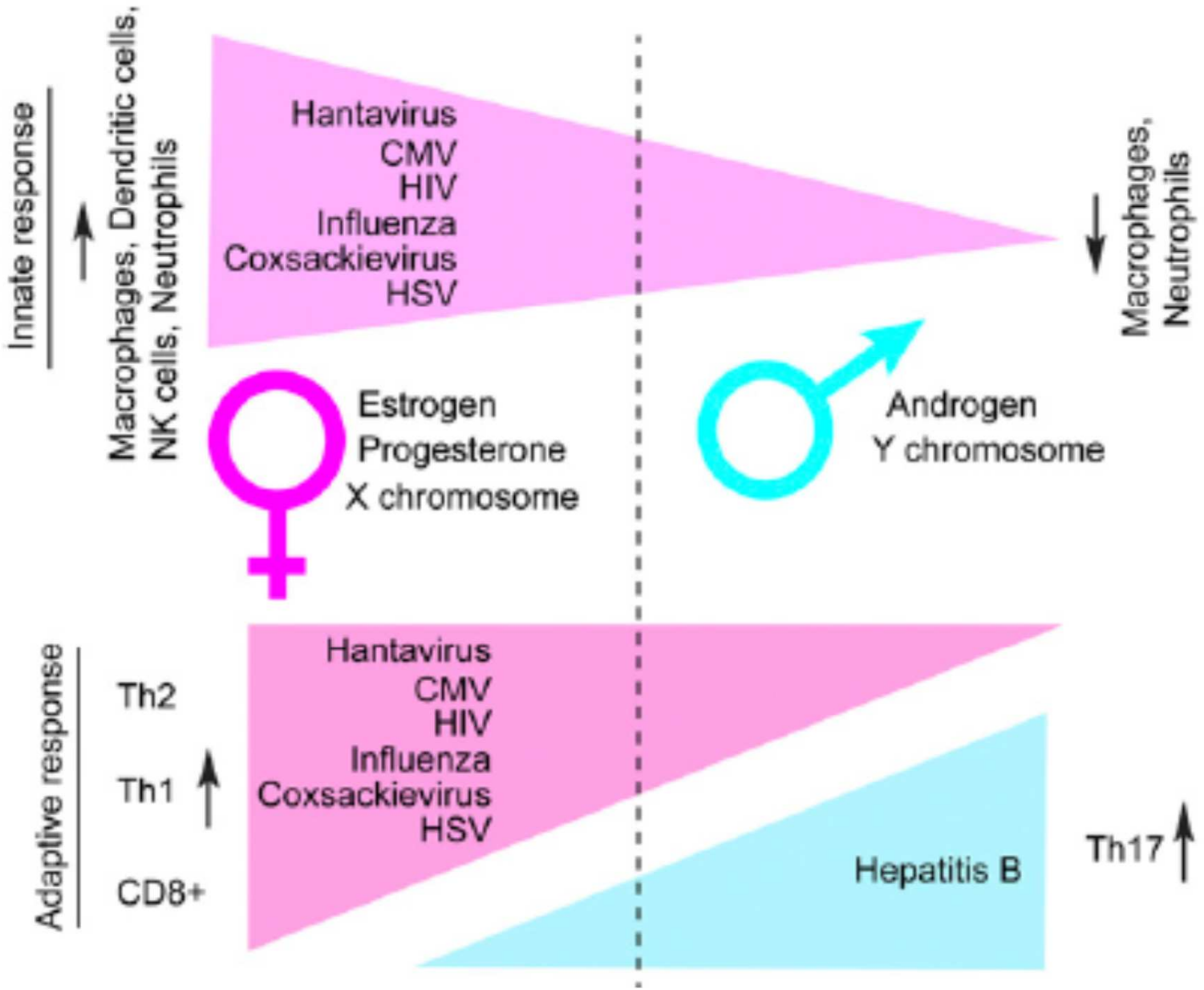


Figure 1.14 The Immune System, 3ed. (© Garland Science 2009)

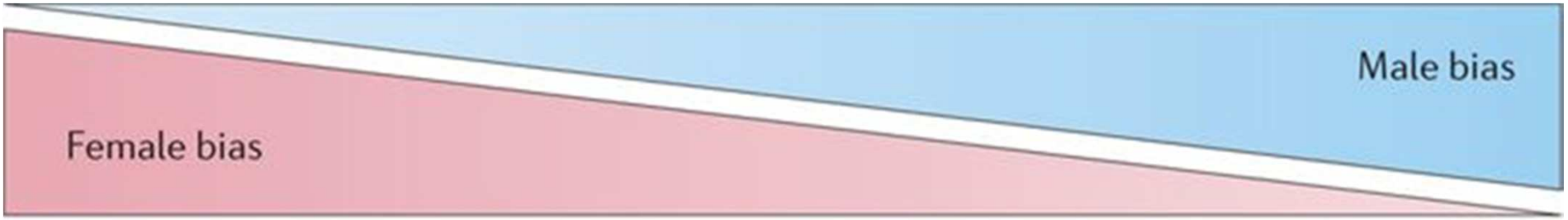
Sous population de cellules T CD4



Les femmes ont un nombre absolu de CD4 supérieur à celui des hommes



Ghosh J Immunol 2017



Autoimmune diseases	Infectious diseases		Non-reproductive cancers
• Graves disease • Hashimoto thyroiditis • Multiple sclerosis • Rheumatoid arthritis • Systemic lupus erythematosis • Type 1 diabetes	• HIV • Influenza • Toxoplasmosis • Legionella • Malaria • Zika	• Ebola • MERS • Hepatitis B • Tuberculosis • Leptospirosis • Campylobacter • Schistosomiasis • Amebiasis • Aspergillosis	• Bladder • Bowel • Kidney • Leukaemia • Liver • Lung • Malignant melanoma • Oesophagus • Stomach

Nature Reviews | Immunology

a Receptors & associated proteins

AR	Androgen receptor
AGTR2	Angiotensin receptor 2
CSF2RA	Colony-stimulating factor 2 receptor α (granulocyte-macrophage)
GPCR	G-protein coupled receptors 23, 50, 101, 112, 119, 174 and CX-chemokine receptor 3
CYSLTR1	Cysteinyl leukotriene receptor 1
IL-1RAP1	Interleukin-1 (IL-1) receptor accessory protein-like 1
IL-1RAP2	IL-1 receptor accessory protein-like 2
IL-2RG	IL-2 receptor γ-chain
IL-3RA	IL-3 receptor α-chain
IL-9R	IL-9 receptor
IL-13RA1	IL-13 receptor α1-chain
IL-13RA2	IL-13 receptor α2-chain
IRAK	IL-1 receptor-associated kinase
NGFRAP1	Nerve-growth-factor receptor associated protein 1
TLR7	Toll-like receptor 7
TLR8	Toll-like receptor 8

b Immune-response related proteins

XSCID	X-linked severe combined immunodeficiency
ELK1	Involved in B-cell development
EPAG	Early lymphoid activation protein
GATA1	GATA-binding protein 1
GTD	Gonadotropin deficiency
IDDMX	X-linked susceptibility to insulin-dependent diabetes
IGBP1	CD79A, immunoglobulin binding protein 1
IGSF1	Immunoglobulin superfamily member 1
ITGB1BP2	Integrin-β_1-binding protein 2
CD99	Also known as MIC2; associated with T-cell function
MTCP1	Mature T-cell proliferation 1
PFC	Properdin P factor, complement
TIMP1	Tissue inhibitor of metalloproteinase 1
CD40L	CD40 ligand
Z39IG	An immunoglobulin superfamily protein

c Transcriptional & translational control effectors

RHOGAP	RAS homologue (RHO) GTPase activating proteins 4, 6
CDC42GEF	Cell-division cycle 42 guanine-nucleotide-exchange factors 6, 9
ETK	Also known as BMX
BTK	Bruton agammaglobulinaemia tyrosine kinase
CDX4	Caudal homeobox transcription factor 4
TRAP170	A co-factor for SP1 transcription factor activation
DUSP	Dual specificity phosphatases 9, 21
EEF	Eukaryotic translation elongation factors 1α13, β4
EIF	Eukaryotic translation initiation factor 1A*, 2a
FOXP3	Forkhead box P3 (associated with the development and function of regulatory T cells)
GAB3	Growth-factor-receptor-bound protein 2-associated binding protein 3
HDAC	Histone deacetylases 6, 8
IKKγ	IκB kinase; also known as NEMO
MAPKKK15	Mitogen-activated protein kinase kinase kinase 15
NFκBRF	Nuclear factor-κB (NF-κB) repressing factor
NRK	NF-κB-inducing kinase-related kinase
NXF	Nuclear RNA export factors 2, 3, 4, 5
PAK3	p21 (also known as CDKN1A)-activated kinase 3
PPP	Protein phosphatases 1, 2*, 6
PRKCI	Protein kinase Cι
S6K	Ribosomal protein S6 kinase
SWI/SNF	SWI/SNF-related, matrix associated, actin-dependent regulator of chromatin
STK9	Serine/threonine kinase 9
TAF1	TATA-box-binding protein-associated factor 1, TFIID subunit
UBE1	Ubiquitin-activating enzyme E1
UBE2A	Ubiquitin-conjugating enzyme E2A
USP	Ubiquitin-specific proteases 9*, 11, 26, 27, 511
WASP	Wiskott–Aldrich syndrome protein

Nature Reviews Immunology 2008

La production de cytokines (IFN-G, IL-1, IL-10, est augmentée in vitro en présence d'oestrogènes et diminuée en présence d'androgènes

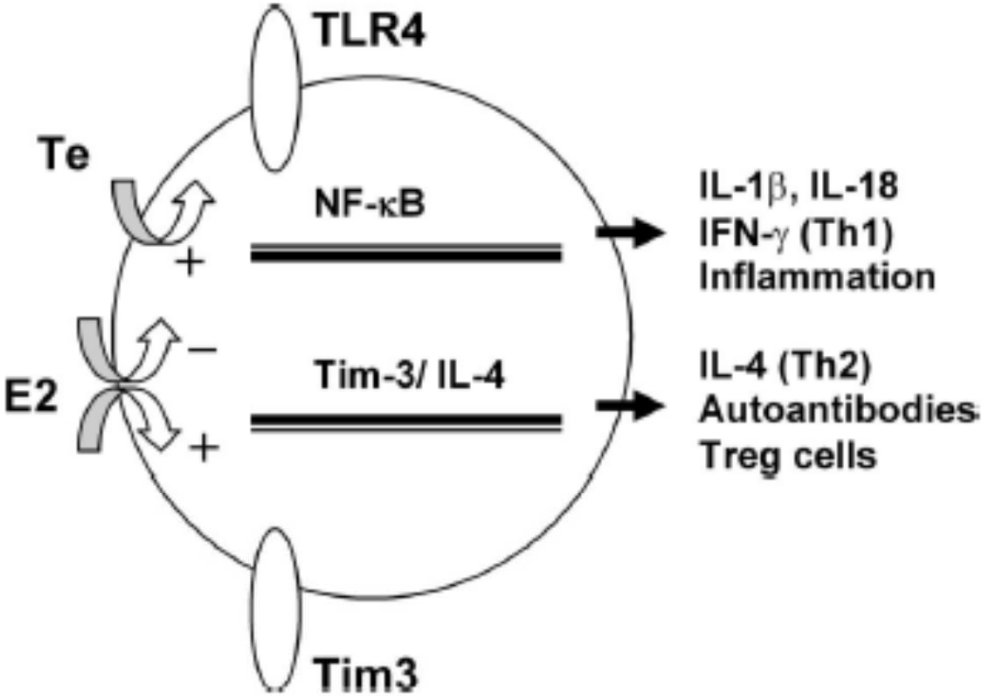


Figure 3. Role of sex hormones in regulating inflammation after infection. Testosterone (Te) increases MC and macrophage numbers, TLR4 expression, and NF-κB signaling in males resulting in increased levels of IL-1β, IL-18, and IFN-γ, increased inflammation, and a Th1-type immune response. Estrogen (E2) inhibits NF-κB signaling, reduces Th1 responses, and increases IL-4 transcription resulting in increased Th2 response, B-cell proliferation, autoantibody production, and Tim-3 expression in females. Tim-3 signaling increases Treg cell populations that dampen the TLR4-induced Th1 inflammatory response to infection.

T augmente le nombre de macrophages, l'expression de NF kappa B et la réponse Th1

E2 diminue l'expression de NF kappa B et augmente les réponses Th2

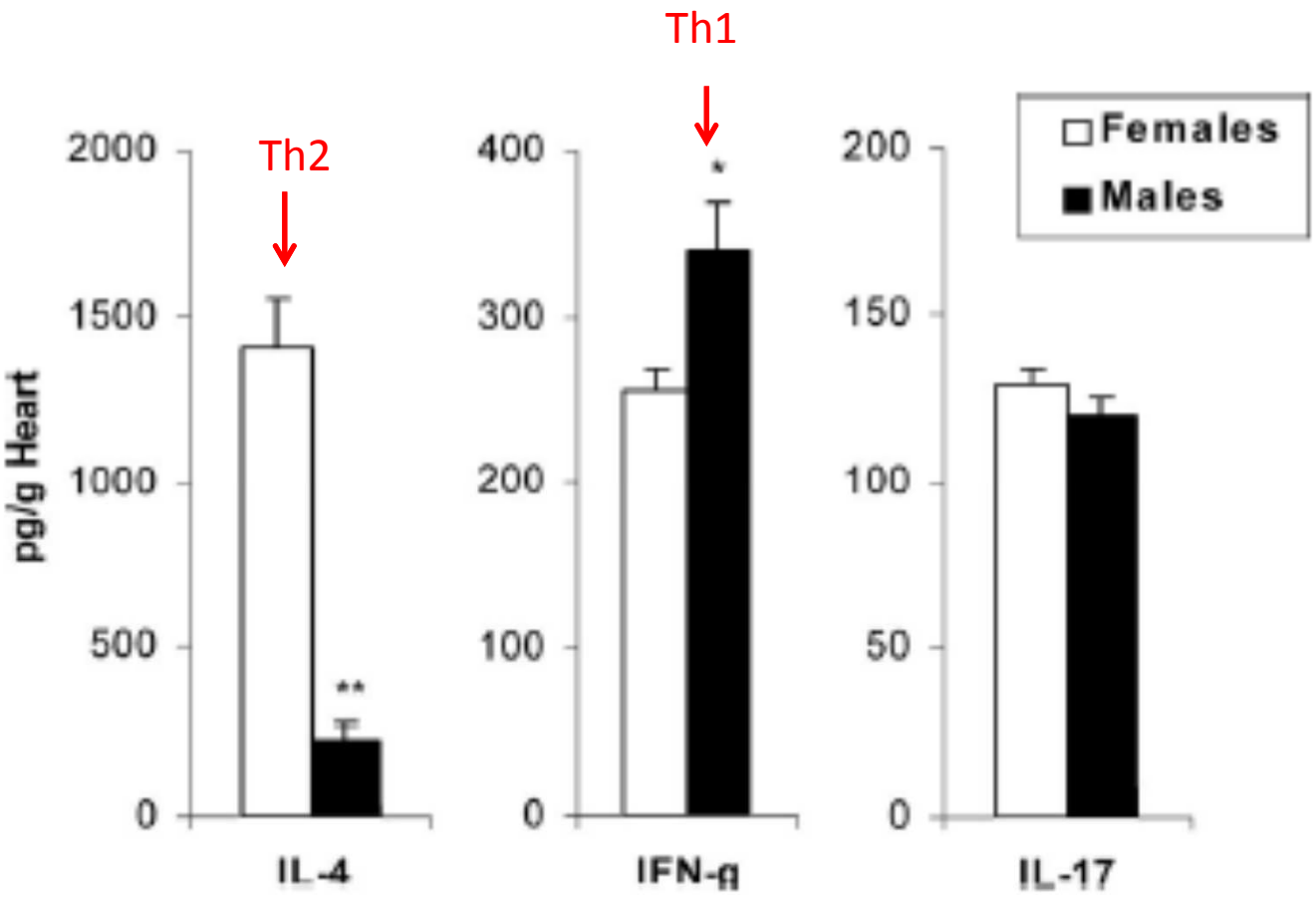
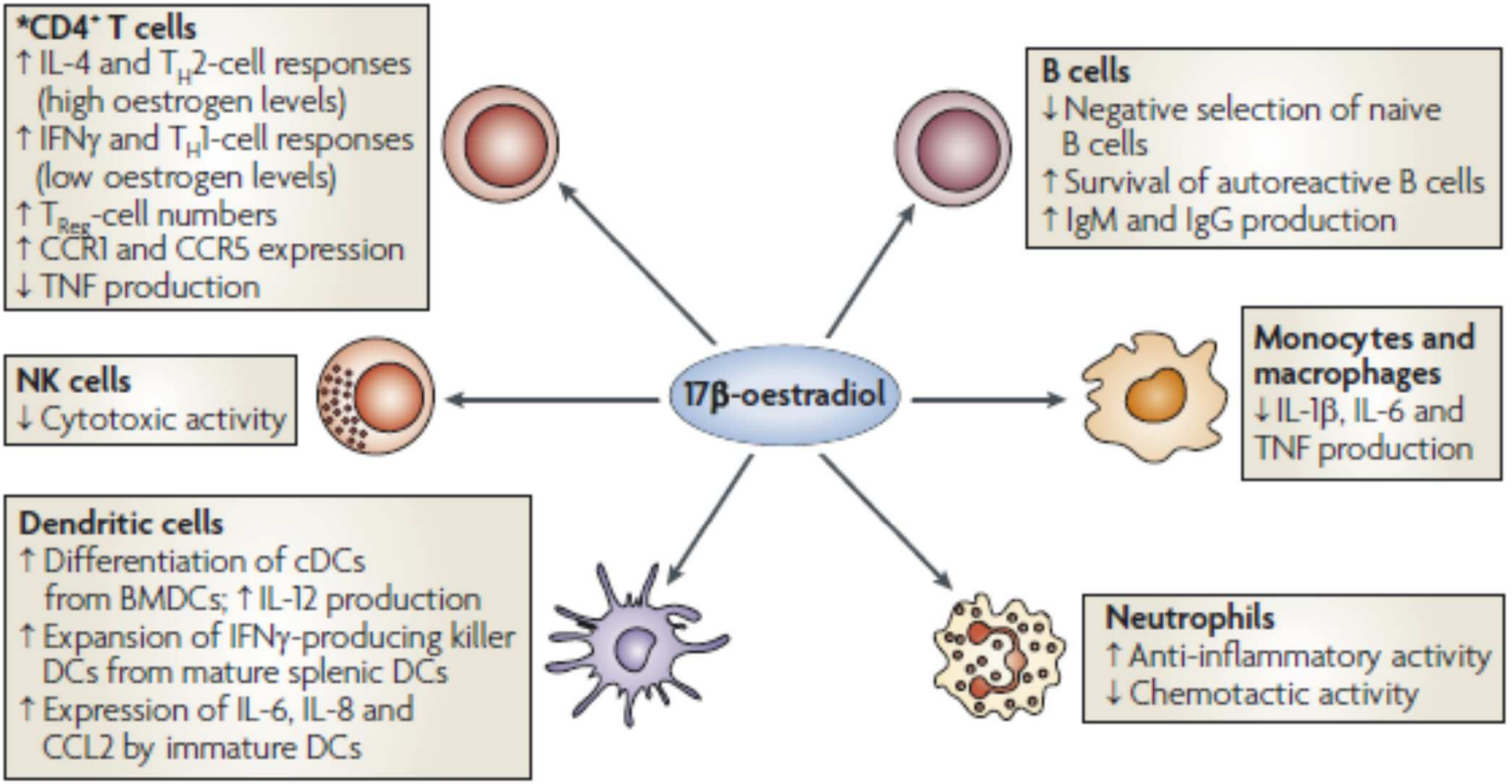
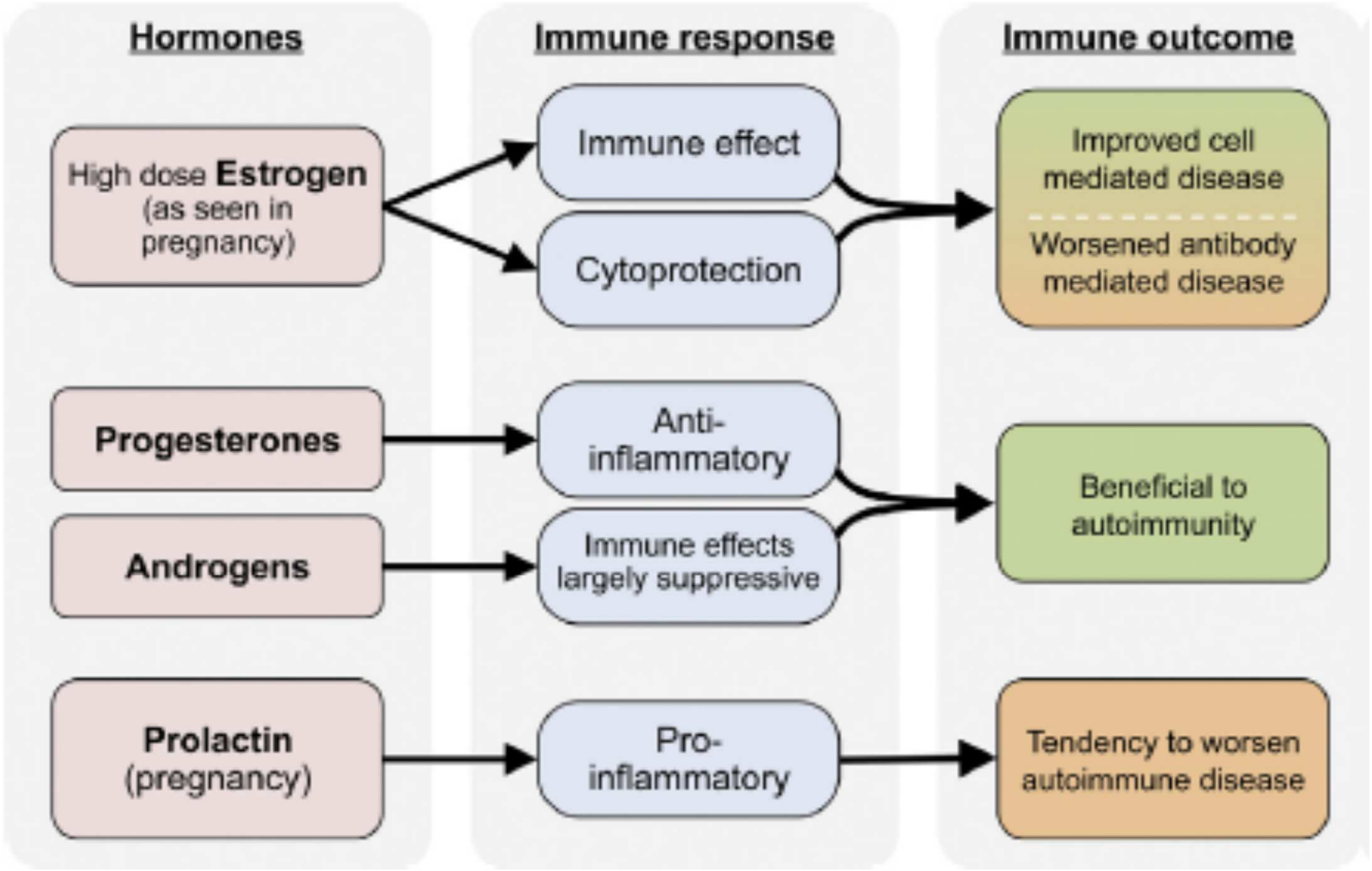


Figure 2. Males produce more IFN-γ (Th1 response) and females more IL-4 (Th2 response) during acute myocarditis. There is no significant difference in IL-17 (Th17 response) between males and females in three of four experiments, but IL-17 was significantly increased in males in one of four experiments. Female and male BALB/c mice were infected with CVB3 on day 0, and cytokine levels in the heart were assessed during acute myocarditis at days 10 or 12 after infection. Data show the SEM of 7 to 10 mice per group at day 12. Similar results were obtained in at least three separate experiments. $^{*}P < 0.05$, $^{**}P < 0.01$.

Effets du 17-B oestradiol sur le système immunitaire




Hormones
Immune response
Immune outcome
High dose Estrogen (as seen in pregnancy)
Immune effect
Cytoprotection
Improved cell mediated disease
Worsened antibody mediated disease
Progesterones
Androgens
Anti-inflammatory
Immune effects largely suppressive
Beneficial to autoimmunity
Prolactin (pregnancy)
Pro-inflammatory
Tendency to worsen autoimmune disease

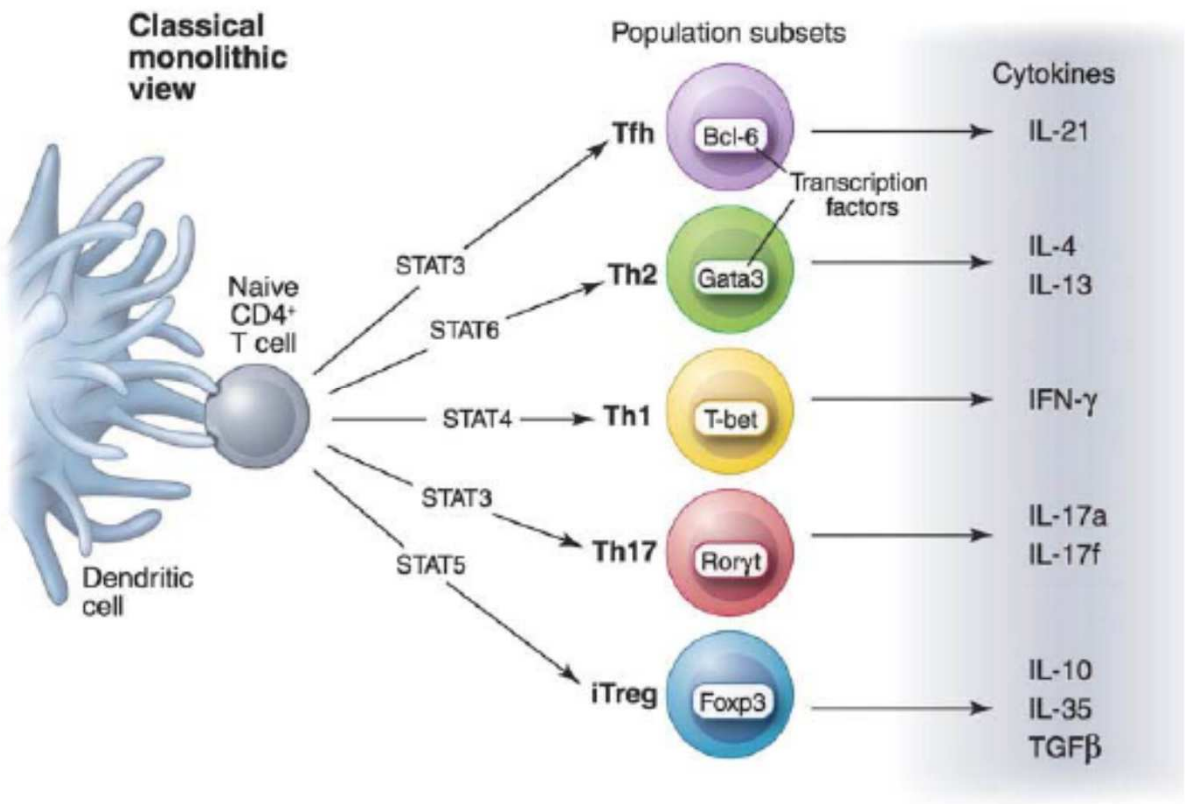
Grossesse et maladies auto-immunes

- L'effet des œstrogènes est variable pendant et en dehors de la grossesse (fonction de la concentration)
- Pendant la grossesse, les hormones (E2) favorisent une réponse Th2 (tolérogène)
- En dehors de la grossesse, les hormones favorisent une réponse Th1 (protection contre les infections)

Effet biphasique dose dépendant

Médiation Th1	**Médiation Th2**
SEP	NMO
Thyroïdite Hashimoto	Maladie de Basedow
Maladie de Crohn	RCH
Polyarthrite rhumatoïde	Lupus systémique

Grossesse et maladies auto-immunes



Poussée

Basedow

Myasthénie

Lupus

Mieux

PR

Hashimoto

SEP

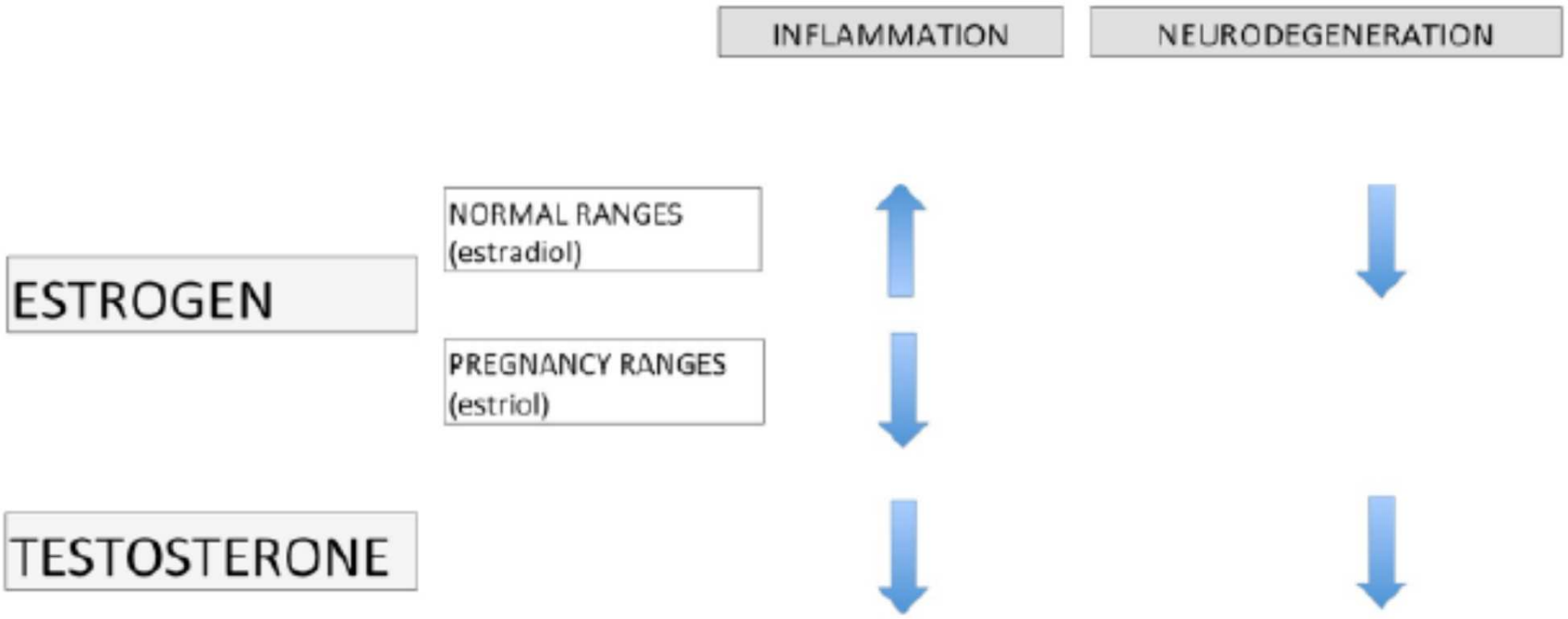
Augmentation des œstrogènes : switch Th1 => Th2

Grossesse et lupus

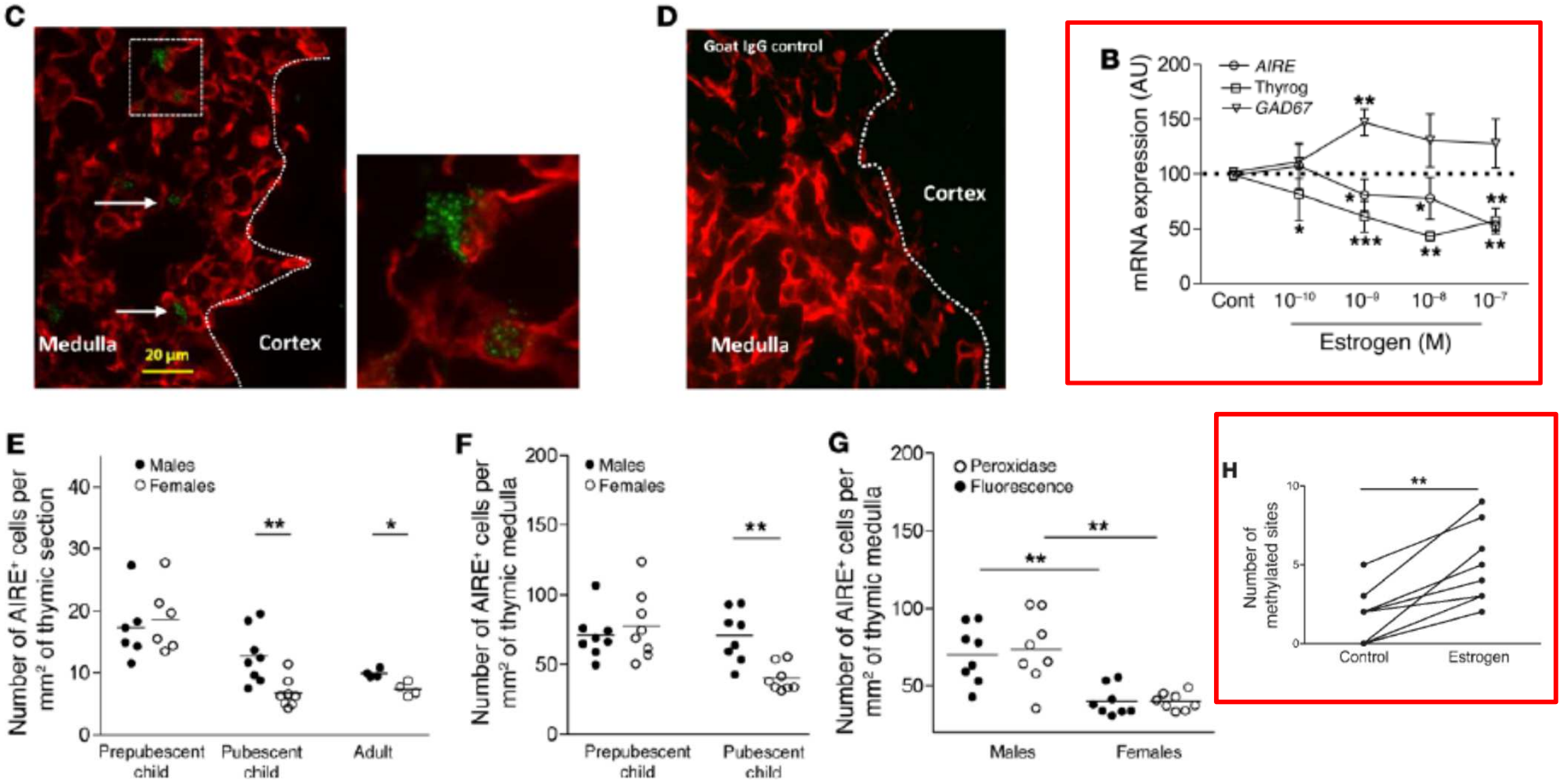
Table 2 Association of pregnancy and lupus flares defined by PGA*: the Hopkins Lupus Cohort, 1987–2015 (n=1349)

	Flares	PY	Crude incidence per 100 PY	Crude IRR (95% CI)
12-month postpartum period				
All patients (n=1349)				
Not pregnant/postpartum	2246	5583.2	40.2	1.0 (ref)
Pregnancy	134	220.8	60.7	1.51 (1.27 to 1.80)
12 months postpartum	148	370.9	39.9	0.99 (0.84 to 1.17)
Patients with ≥1 observed pregnancy in the cohort (n=304)				
Not pregnant/postpartum	642	1790.4	35.9	1.0 (ref)
Pregnancy	134	220.8	60.7	1.69 (1.40 to 2.04)
12 months postpartum	148	370.9	39.9	1.11 (0.93 to 1.33)
3-month postpartum period				
All patients (n=1349)				
Not pregnant/postpartum	2336	5786.3	40.4	1.0 (ref)
Pregnancy	134	220.8	60.7	1.50 (1.26 to 1.79)
3 months postpartum	58	95.6	60.7	1.50 (1.16 to 1.95)
Patients with ≥1 observed pregnancy in the cohort (n=304)				
Not pregnant/postpartum	732	1993.5	36.7	1.0 (ref)
Pregnancy	134	220.8	60.7	1.65 (1.38 to 1.99)
3 months postpartum	58	95.6	60.7	1.65 (1.26 to 2.16)

Effets différents au cours de la SEP

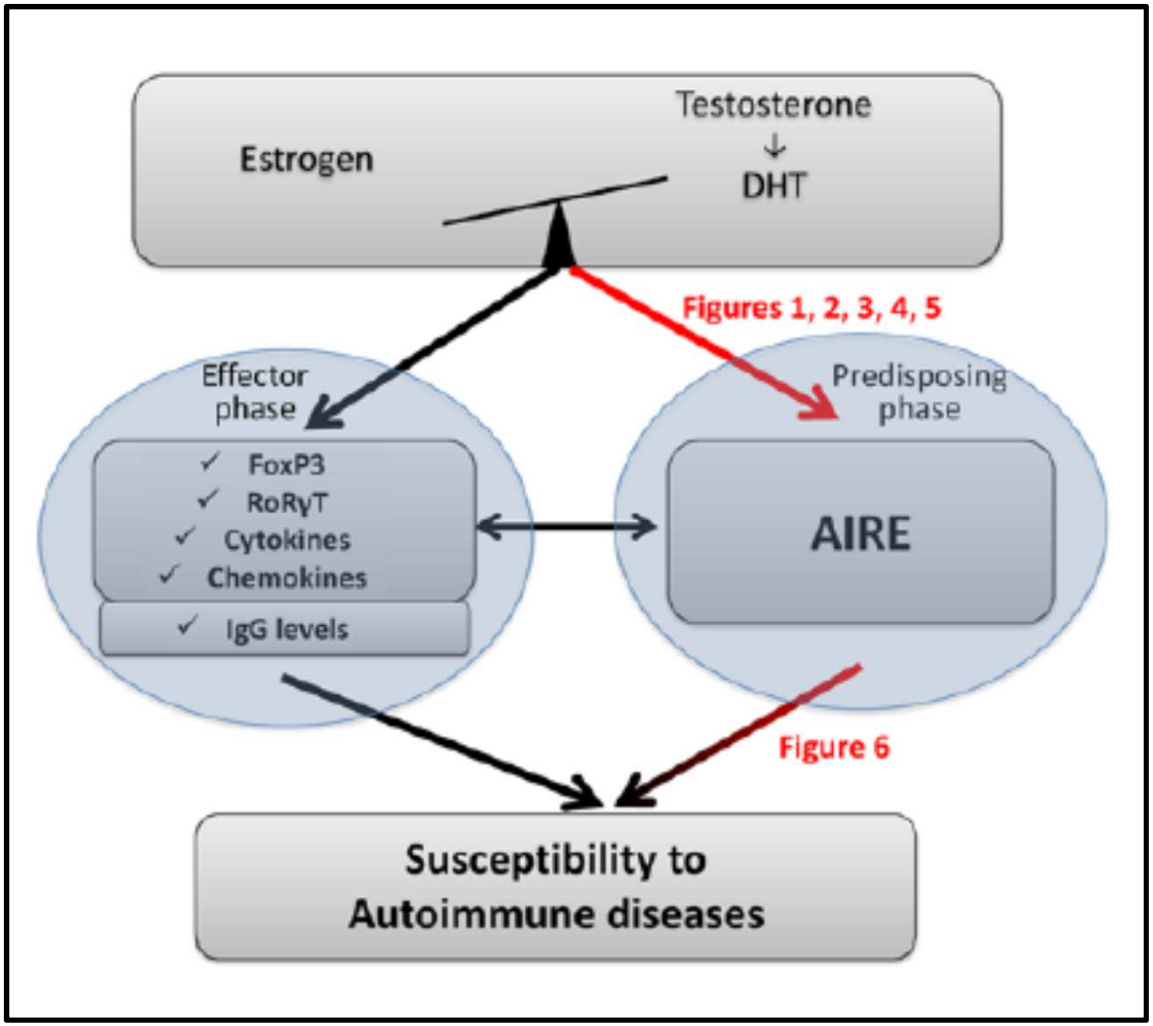


Oestrogènes et expression de AIRE



Dragin, JCI 2016

Oestrogènes et expression de AIRE



Vitamine D et auto-immunité

- Effet de la vitamine D sur l'inhibition de la prolifération des cellules T CD4 (plus marqué chez les femmes)
- Oestradiol augmente l'expression du récepteur à la vitamine D et diminue le CYP24A1 (qui dégrade la vitamine D)

Et les hommes ?

- Les androgènes diminuent la réponse vaccinale, diminuent l'auto-immunité et augmentent le risque de cancer
- Les hommes avec des concentrations basses de testostérone ont plus de risque de SEP, et des meilleures réponses anti-virales
- La mesure D2/D4 qui reflète l'exposition aux androgènes in utero est liée au risque de SEP

Take home messages

La modulation du système immunitaire par le sexe (genre) est bien documentée

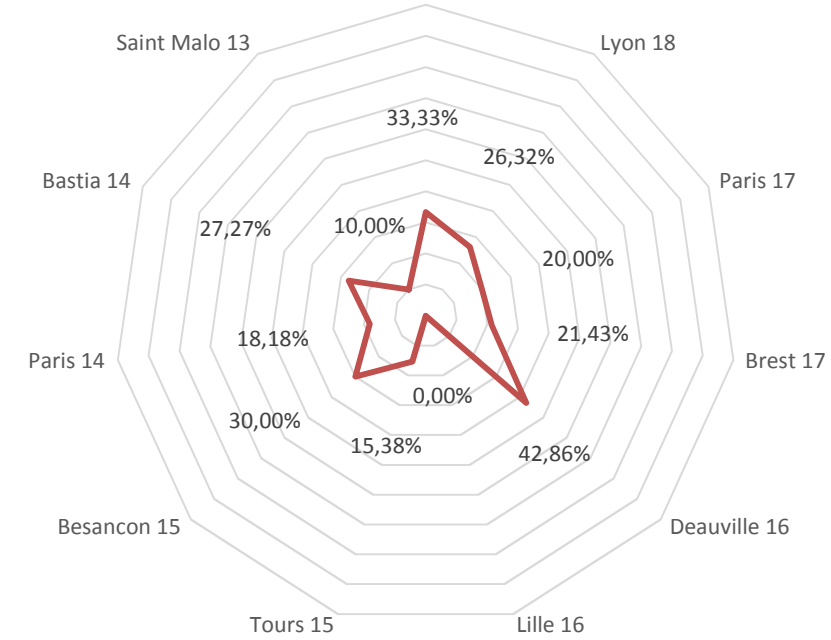
La plupart des maladies auto-immunes ont en commun la prédominance féminine

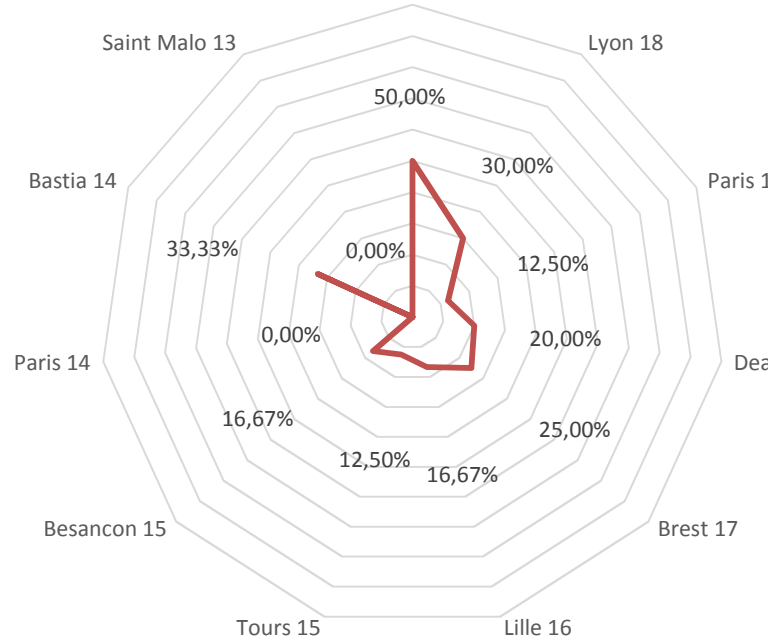
Au moins une partie est liée à l'action directe des hormones sur le système immunitaire

Les cellules immunitaires expriment des récepteurs aux hormones (ESR1, ESR2)

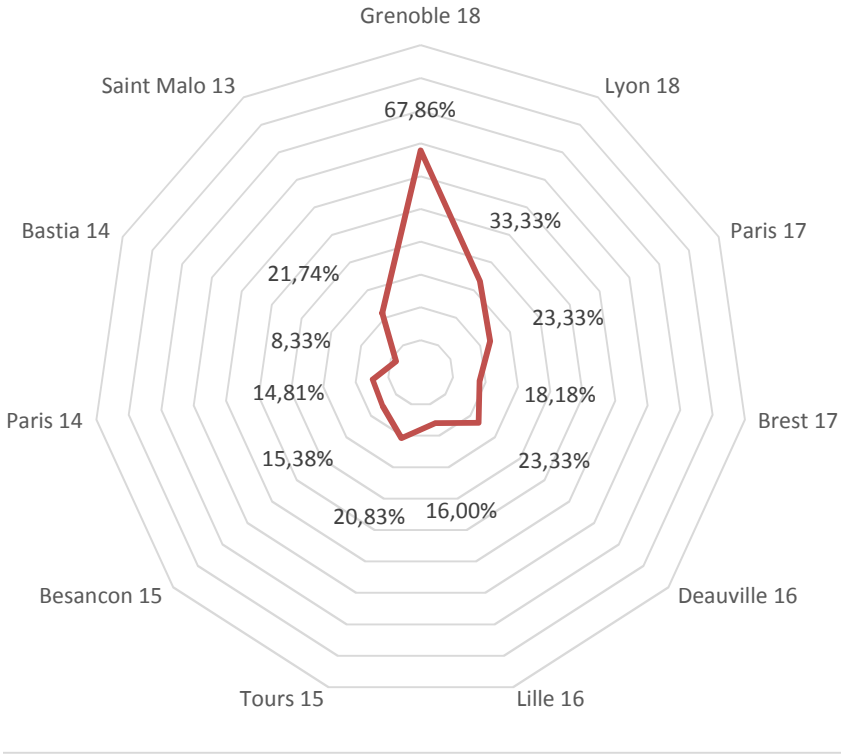
Ces hormones modulent les réponses immunes, l'initiation et la progression des maladies autoimmunes

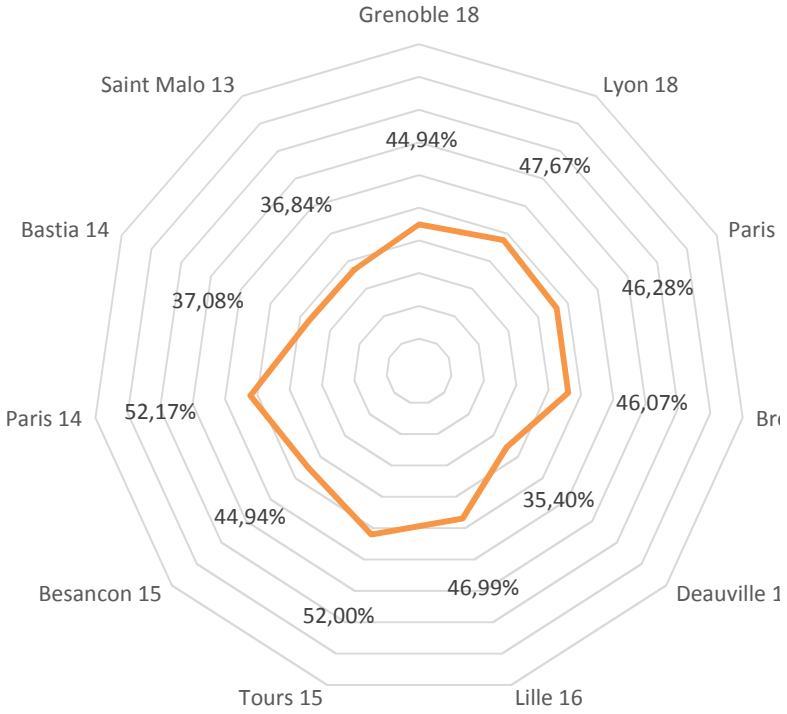
Au-delà, des facteurs génétiques et épigénétiques peuvent influencer la susceptibilité autoimmune et participer à la prédominance féminine


Saint Malo 13
Lyon 18
Paris 17
Brest 17
Deauville 16
Lille 16
Tours 15
Besancon 15
Paris 14
Bastia 14
33,33%
26,32%
20,00%
21,43%
42,86%
15,38%
30,00%
18,18%
27,27%
10,00%
0,00%


Saint Malo 13
Lyon 18
Paris 1
Brest 17
Besancon 15
Tours 15
Lille 16
Paris 14
Bastia 14
50,00%
30,00%
12,50%
20,00%
25,00%
16,67%
12,50%
16,67%
0,00%
0,00%
33,33%

B


Grenoble 18
Saint Malo 13
Lyon 18
Paris 17
Brest 17
Deauville 16
Lille 16
Tours 15
Besancon 15
Paris 14
Bastia 14
67,86%
33,33%
23,33%
18,18%
23,33%
16,00%
20,83%
15,38%
14,81%
8,33%
21,74%


Grenoble 18
Saint Malo 13
Lyon 18
Paris
Bre
Deauville 1
Lille 16
Tours 15
Besancon 15
Paris 14
Bastia 14
44,94%
47,67%
46,28%
46,07%
35,40%
46,99%
52,00%
44,94%
52,17%
37,08%
36,84%

D