Microbiote intestinal, santé et pathologies

SSMG 10/12/2016

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Médecine générale (UCL, 2009)
Licence en nutrition humaine (UCL, 1996)
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Comprendre cette grande journée

Rappels de base

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Film 1

http://www.nature.com/ni/multimedia/mucosal/index.html

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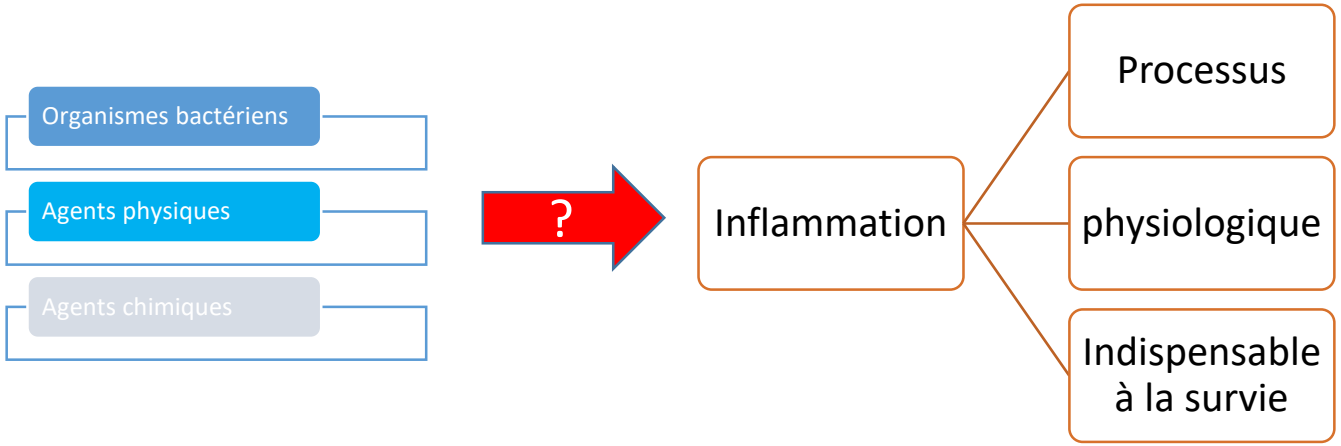
L’agression de l’organisme par des



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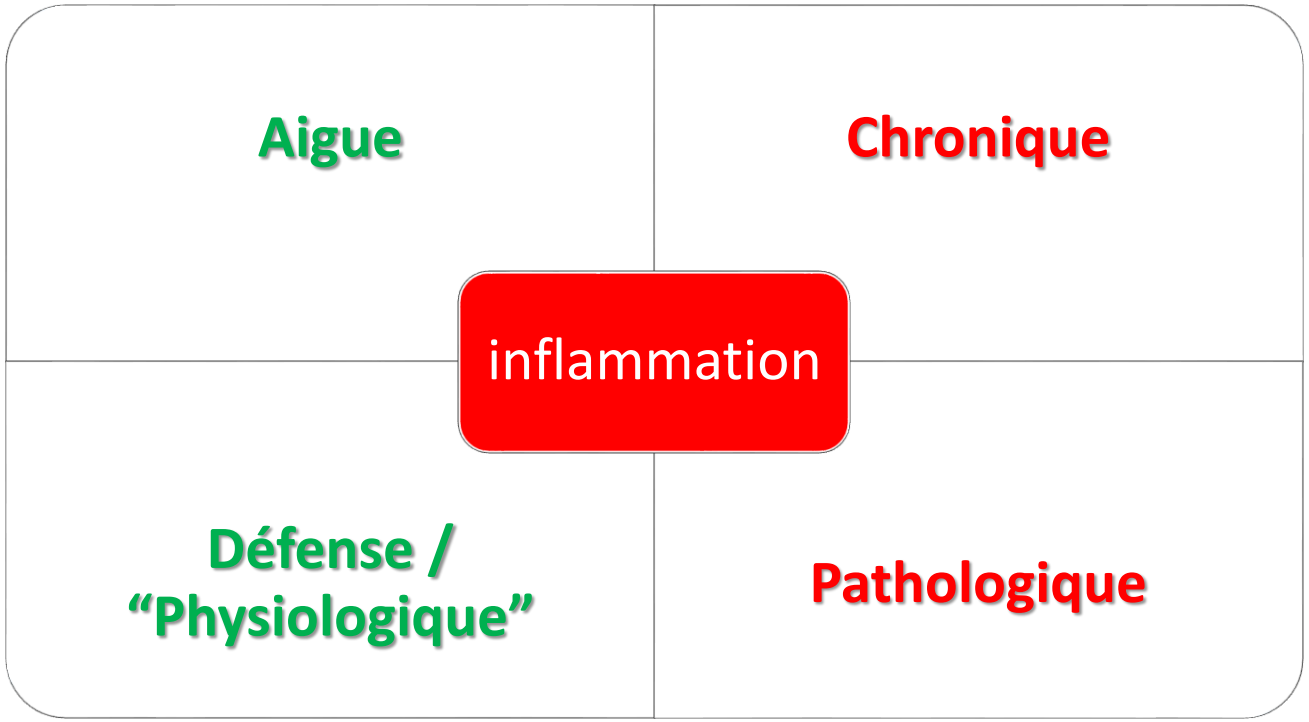
Aigue
Chronique
inflammation
Défense /
“Physiologique”
Pathologique

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Défense

Immunité

Acquise

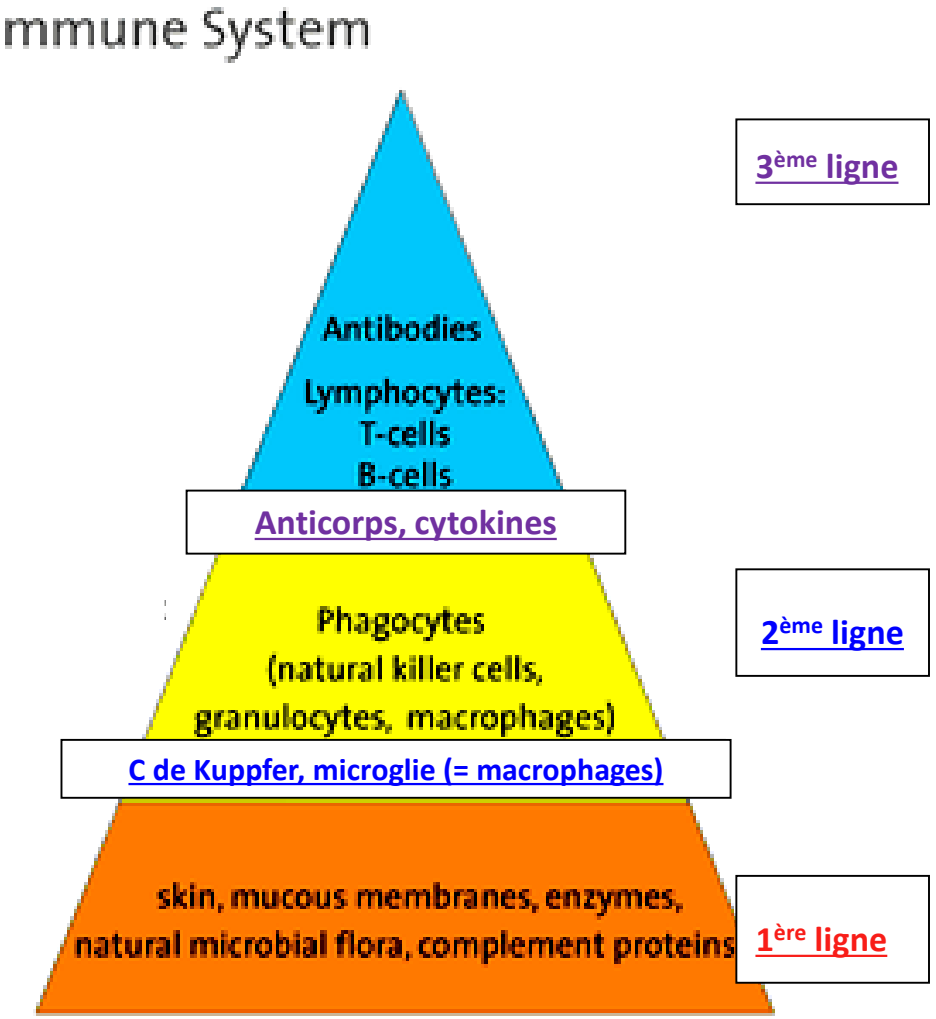
Immunité

innée non

spécifique

Fonction

de barrière



3ème ligne

2ème ligne

1ère ligne

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1ère ligne

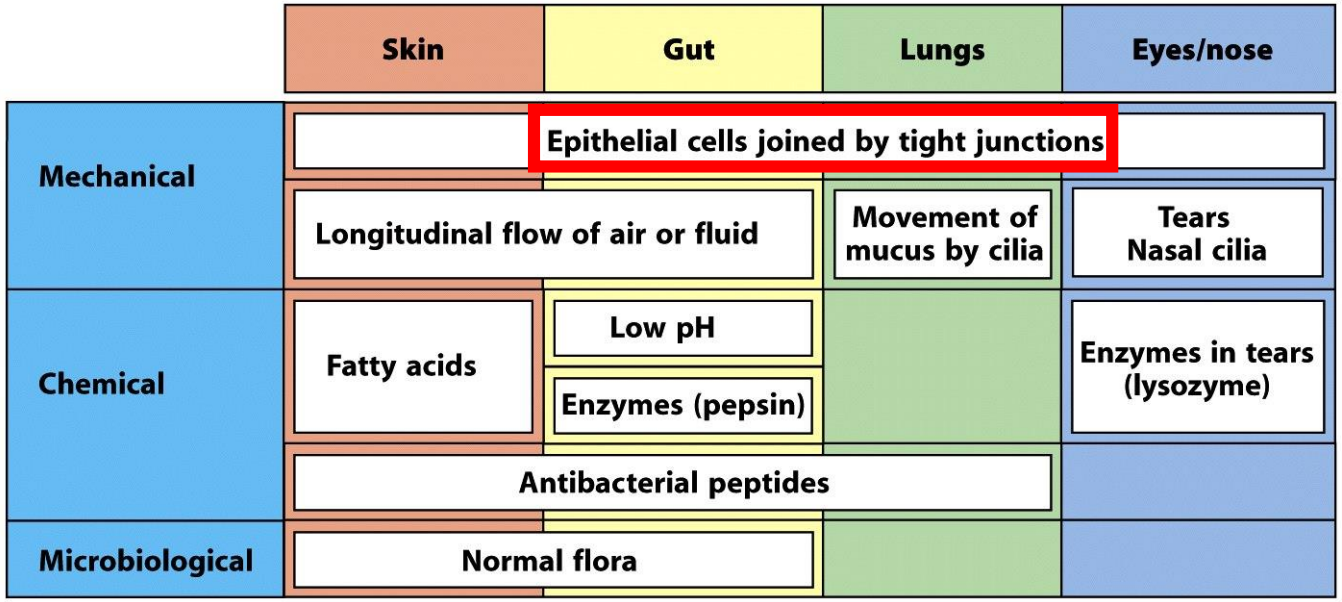

Figure 2-7 Immunobiology, 7ed. (© Garland Science 2008)

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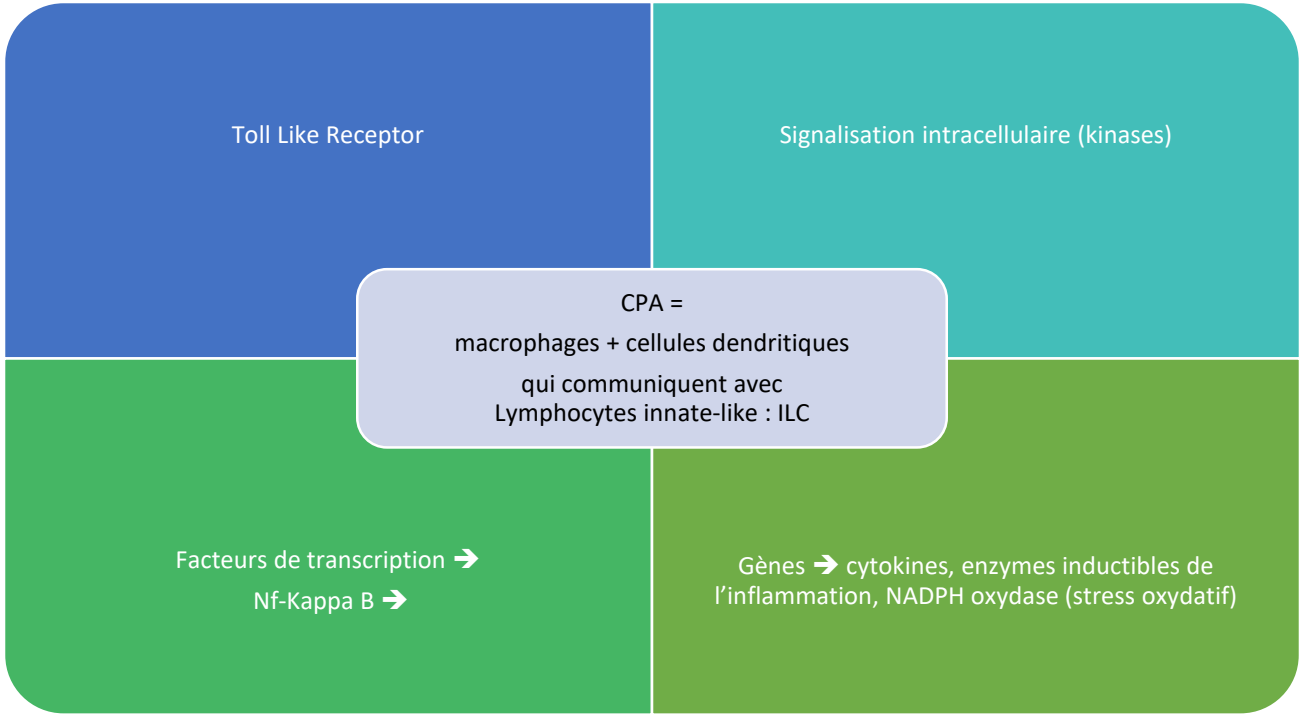
2ème ligne



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TLR, récepteur transmembranaire avec grande analogie avec récepteur Toll de la drosophile (développement)

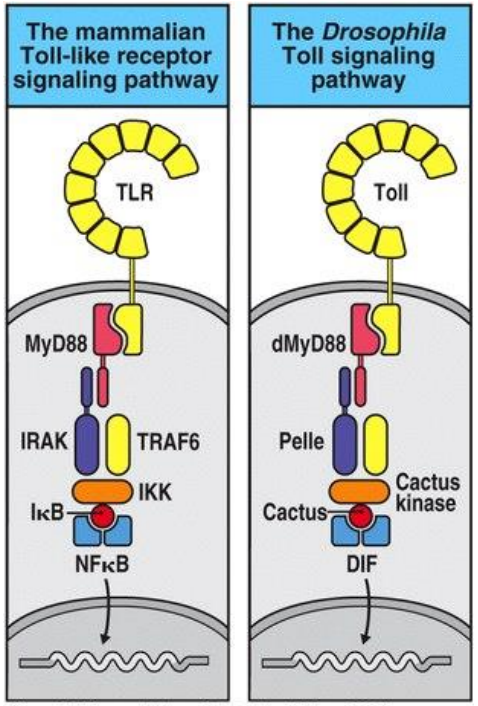

Figure 15-4 Immunobiology, 6/e. (© Garland Science 2005)

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Toll-Like Receptors (TLR's)

- ✓ **TLR4 cloned by Beutler's group in 1998 (Nobel prize 2011)**
- ✓ **10 TLR genes in humans**
- ✓ **12 TLR genes in mice**
- ✓ **1997 MyD88 was linked to innate immunity (IL1R)**

TLR = pathogen recognition receptor (**PRR**) ➔ pathogen-associated molecular patterns (**PAMPs**)

Innate immune recognition by Toll-like receptors	
Toll-like receptor	**Ligand ➔ PAMPs**
TLR-1:TLR-2 heterodimer	Peptidoglycan Lipoproteins Lipoarabinomannan (mycobacteria) GPI (*T. cruzi*) Zymosan (yeast)
TLR-2:TLR-6 heterodimer	
TLR-3	dsRNA
TLR-4 dimer (plus MD-2 and CD14)	LPS (Gram-negative bacteria) Lipoteichoic acids (Gram-positive bacteria)
TLR-5	Flagellin
TLR-7	ssRNA
TLR-8	G-rich oligonucleotides
TLR-9	Unmethylated CpG DNA

Figure 2-16 Immunobiology, 7ed. (© Garland Science 2008)

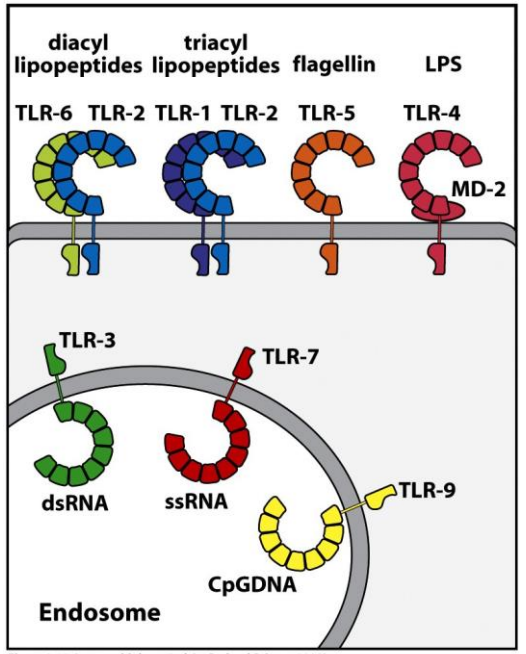

Figure 2-17 Immunobiology, 7ed. (© Garland Science 2008)

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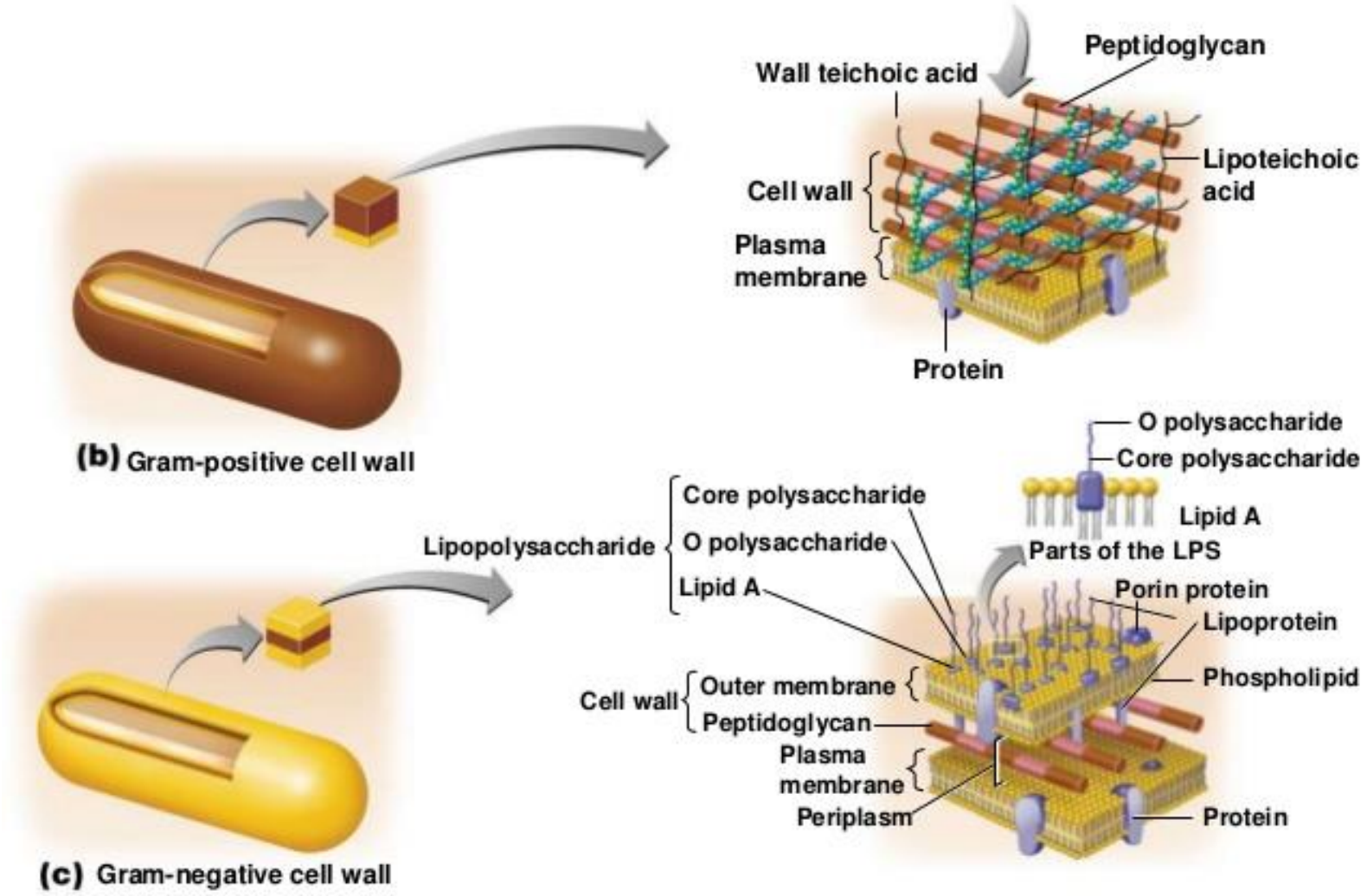
Gram positive vs negative

Figure 4.13b-c Bacterial cell walls.



En simple

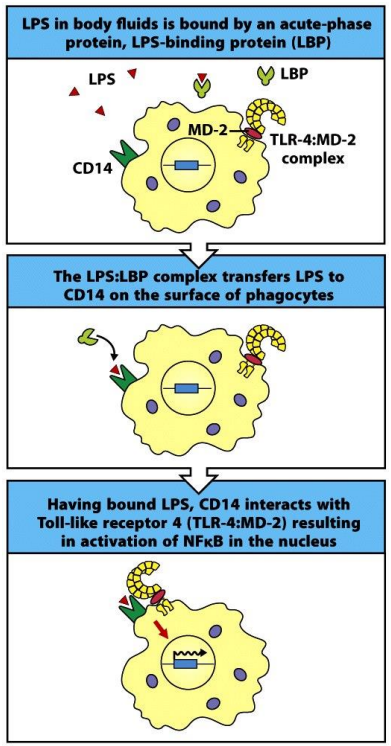
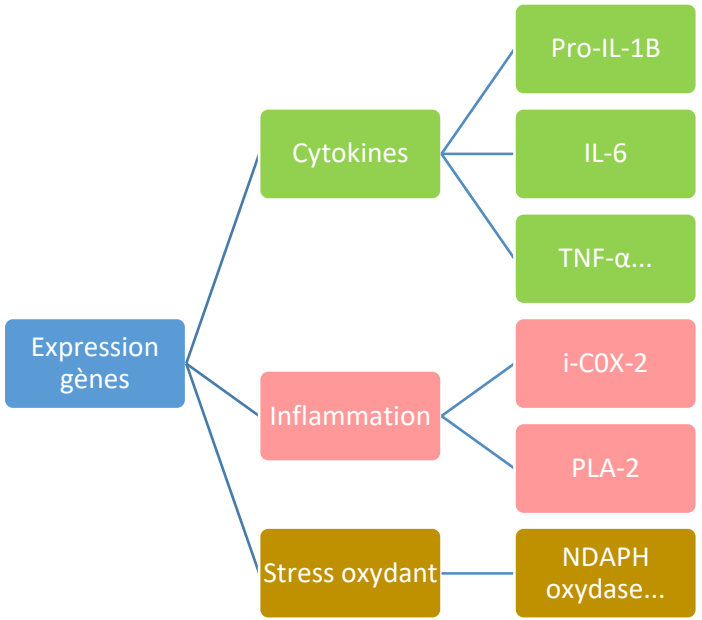


Figure 2-19 Immunobiology, 7ed. (© Garland Science 2008)



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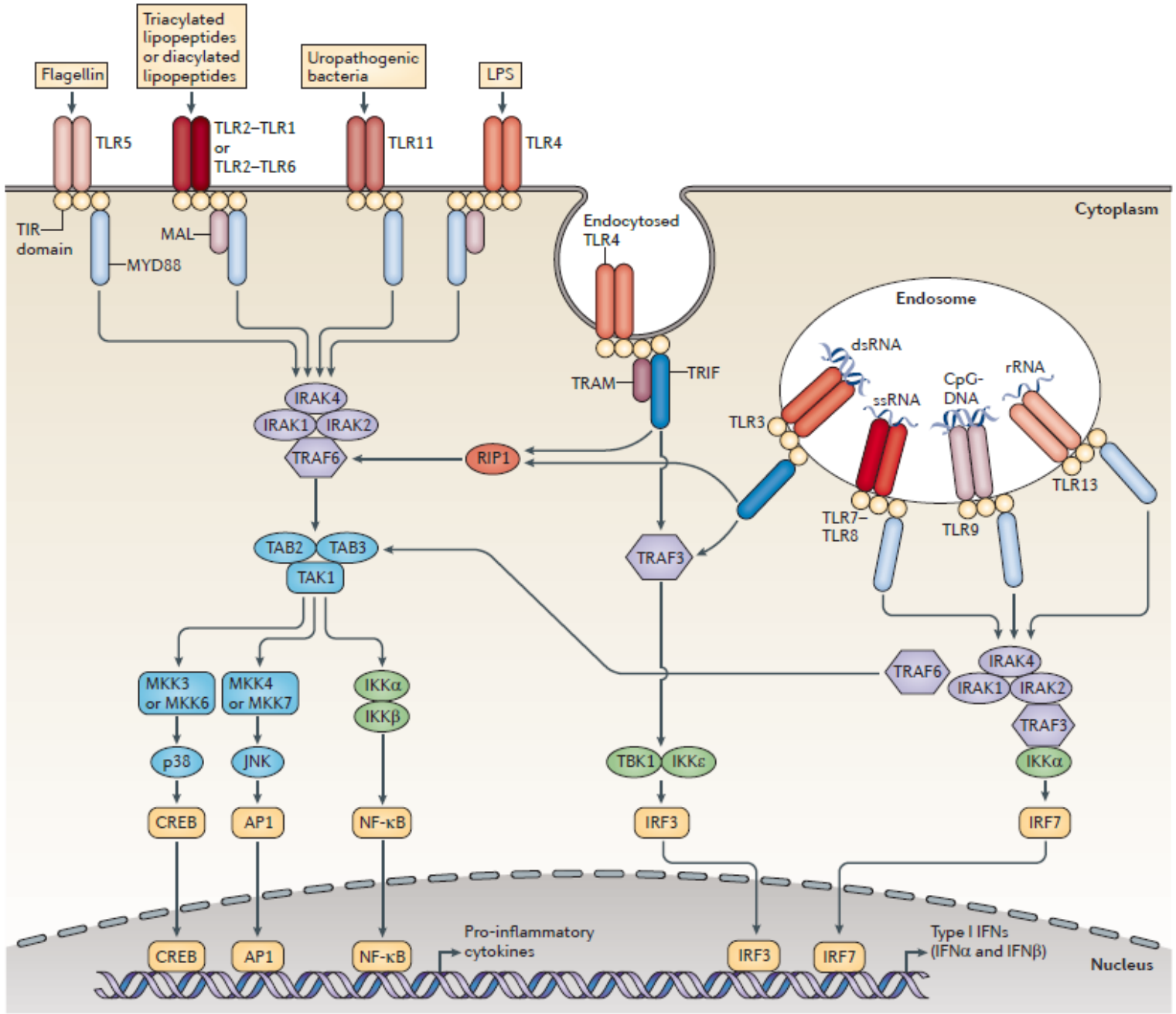
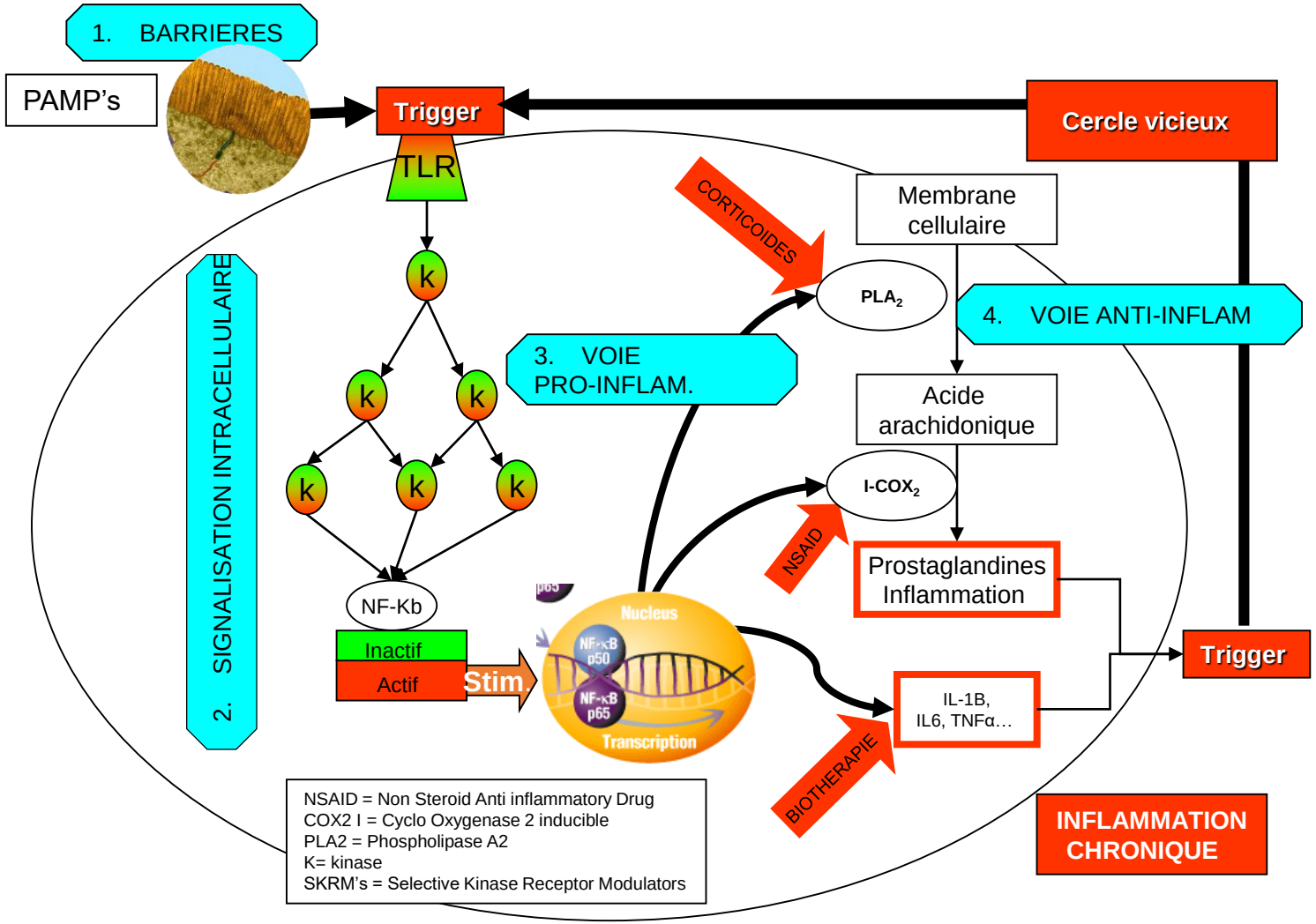
Plus élaboré



O'Neill et al · Nat Rev Immunol 2013


1. BARRIERES
PAMP's
Trigger
TLR
Cercle vicieux
Membrane cellulaire
CORTICOIDES
PLA2
4. VOIE ANTI-INFLAM
3. VOIE PRO-INFLAM.
Acide arachidonique
I-COX2
NSAID
Prostaglandines Inflammation
2. SIGNALISATION INTRACELLULAIRE
k
NF-Kb
Inactif
Actif
Stim
Nucleus
NF-κB p50
NF-κB p65
Transcription
IL-1B, IL6, TNFα…
Trigger
BIOTHERAPIE
INFLAMMATION CHRONIQUE
NSAID = Non Steroid Anti inflammatory Drug
COX2 I = Cyclo Oxygenase 2 inducible
PLA2 = Phospholipase A2
K= kinase
SKRM's = Selective Kinase Receptor Modulators

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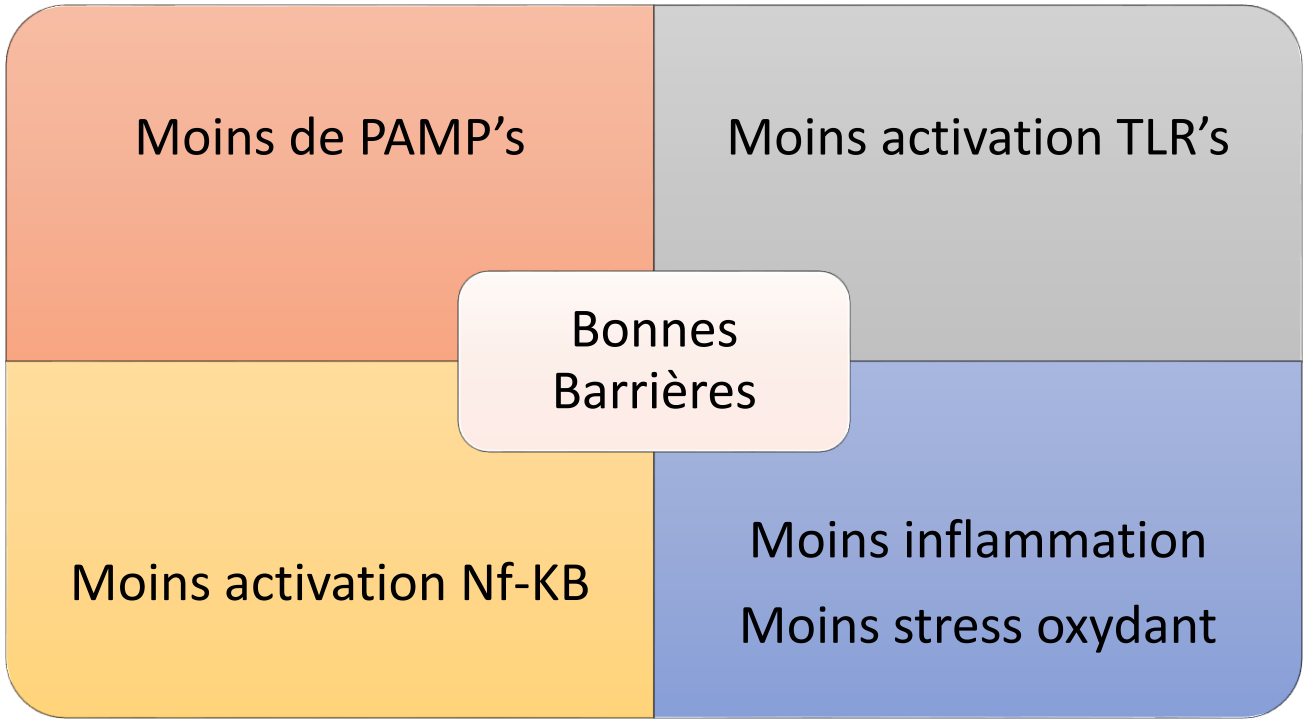
Conclusions



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Film 2

Réponse immunitaire et Toll like récepteurs

https://www.youtube.com/watch?v=iVMIZy-Y3f8

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Surfaces et barrières

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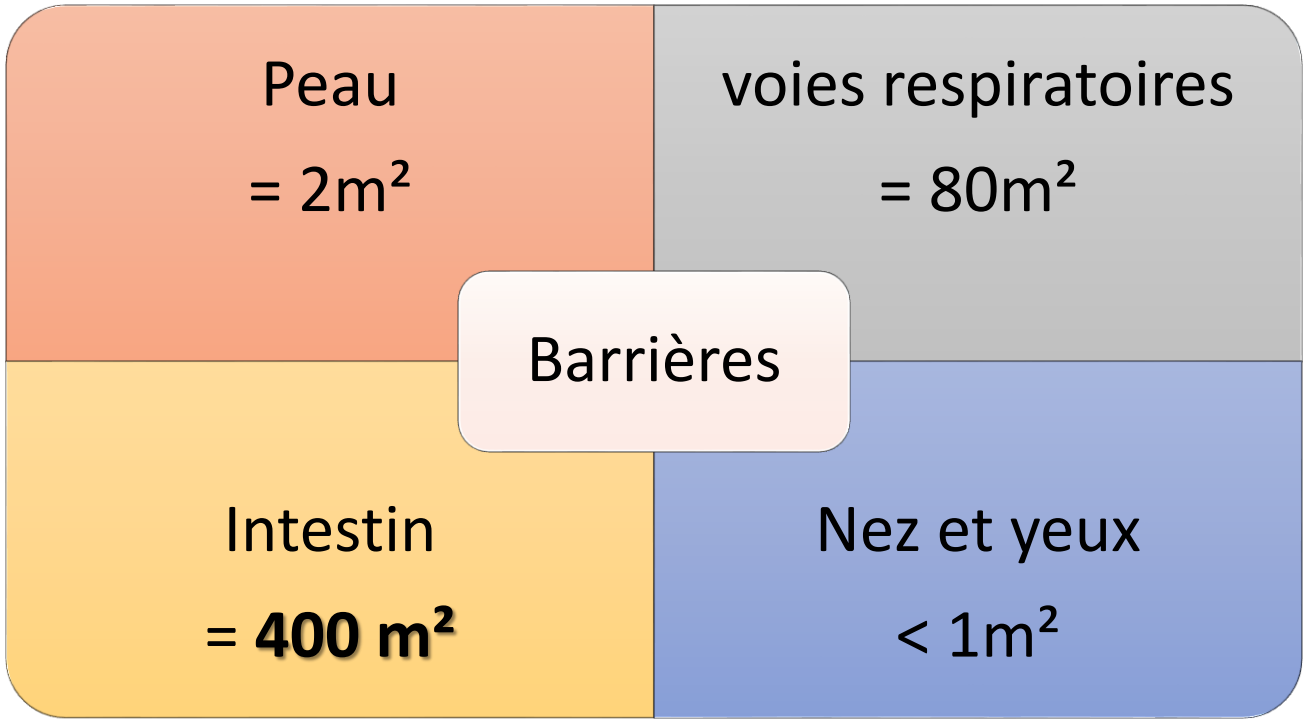
Surfaces


Peau
= 2m²
voies respiratoires
= 80m²
Barrières
Intestin
= 400 m²
Nez et yeux
< 1m²

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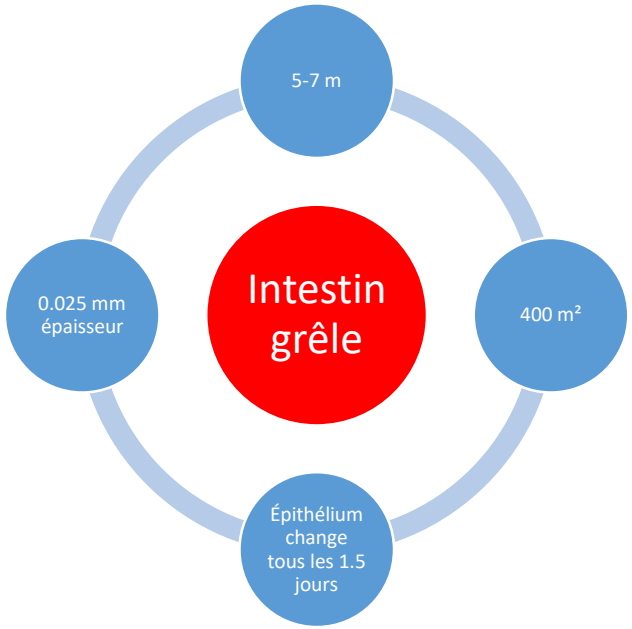
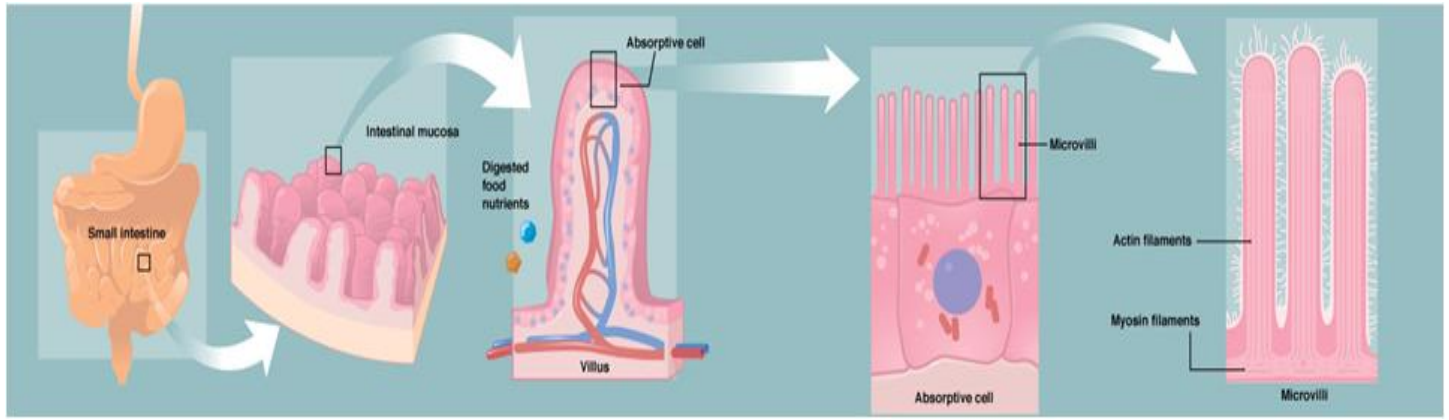
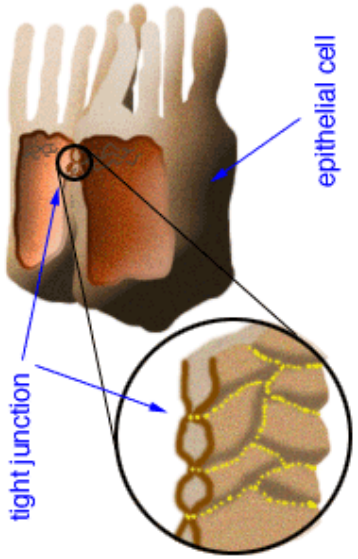
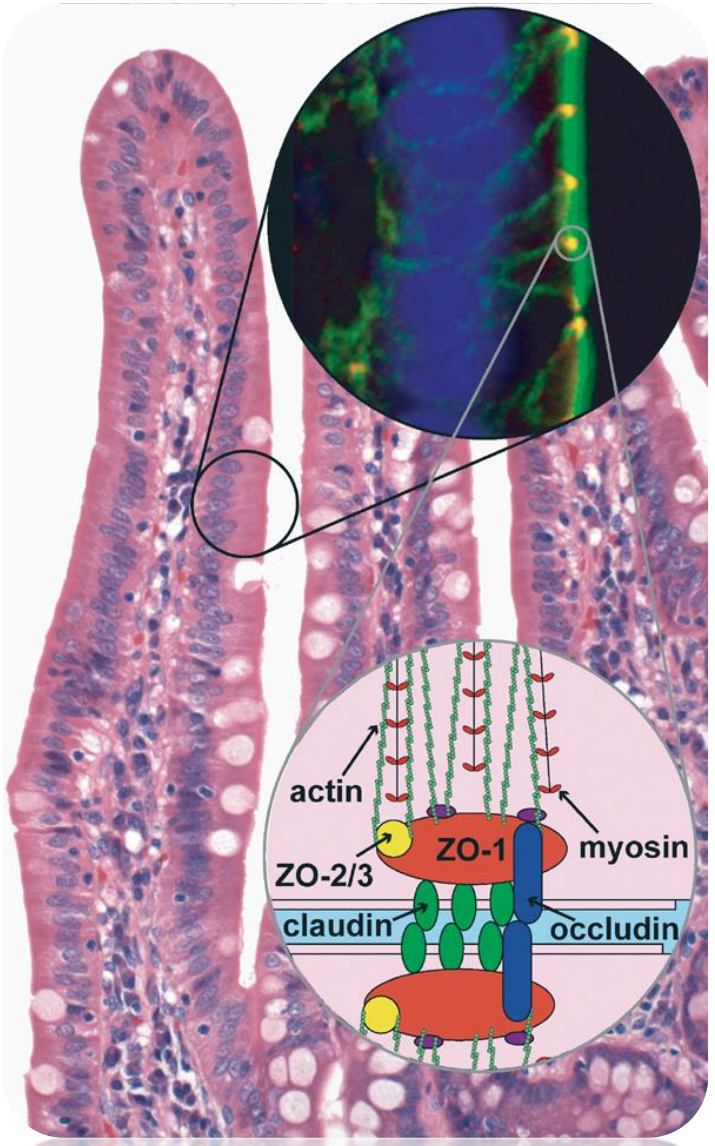
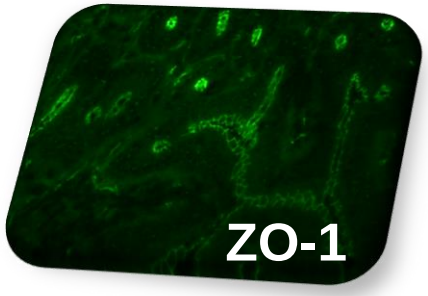

5-7 m
0.025 mm
épaisseur
Intestin
grêle
400 m²
Épithélium
change
tous les 1.5
jours

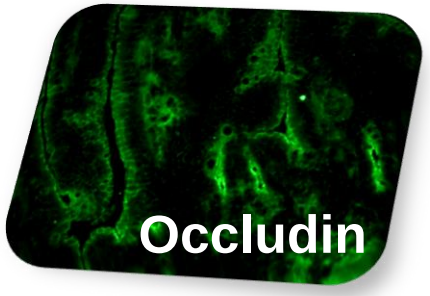

Small intestine
Intestinal mucosa
Digested
food
nutrients
Absorptive cell
Villus
Microvilli
Absorptive cell
Actin filaments
Myosin filaments
Microvilli

Barrière intestinale– jonctions serrée

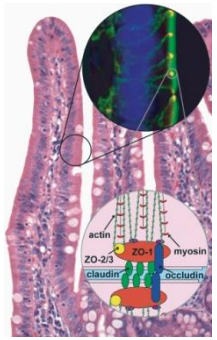


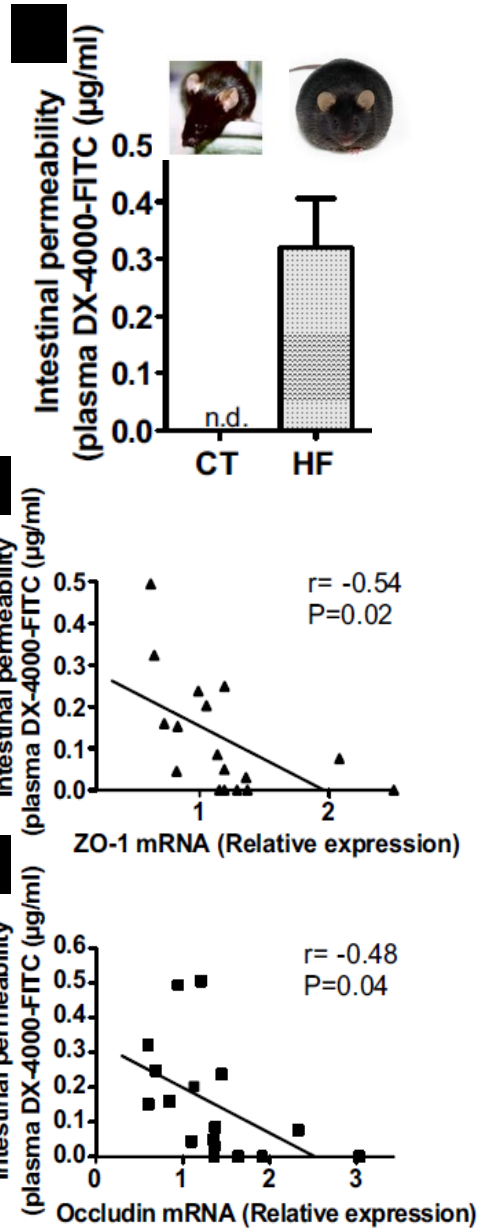


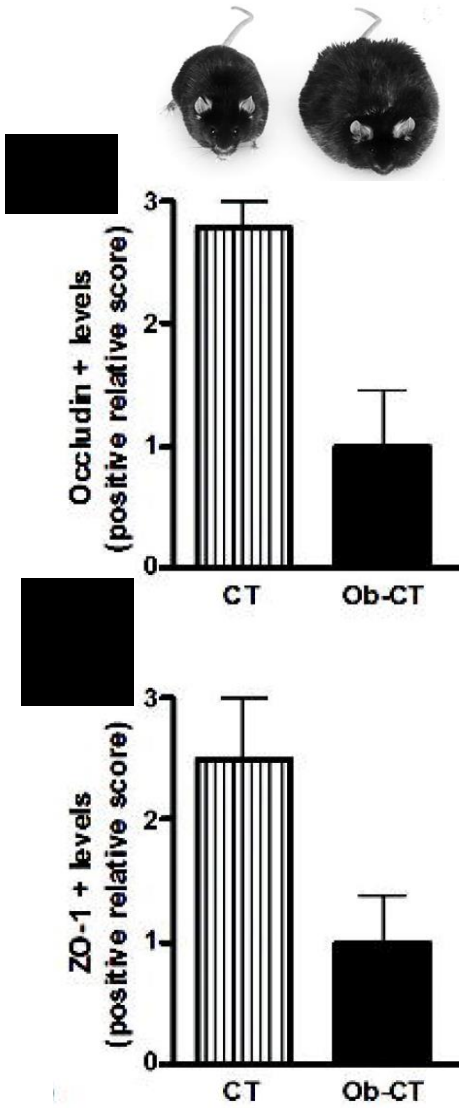




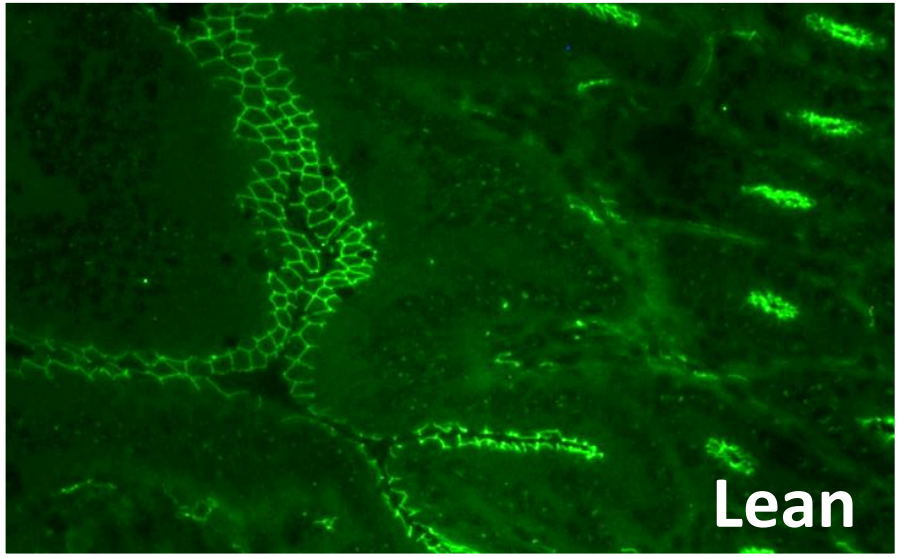
Gut barrier function

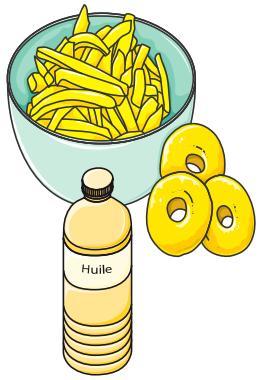


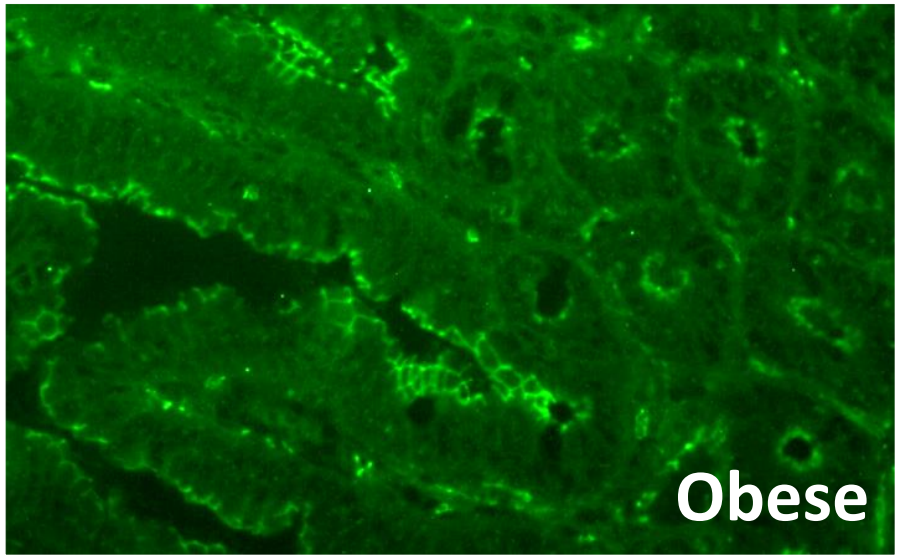




Cani P.D. *et al. Diabetes* 2008
Cani P.D. *et al. Gut* 2009


Lean

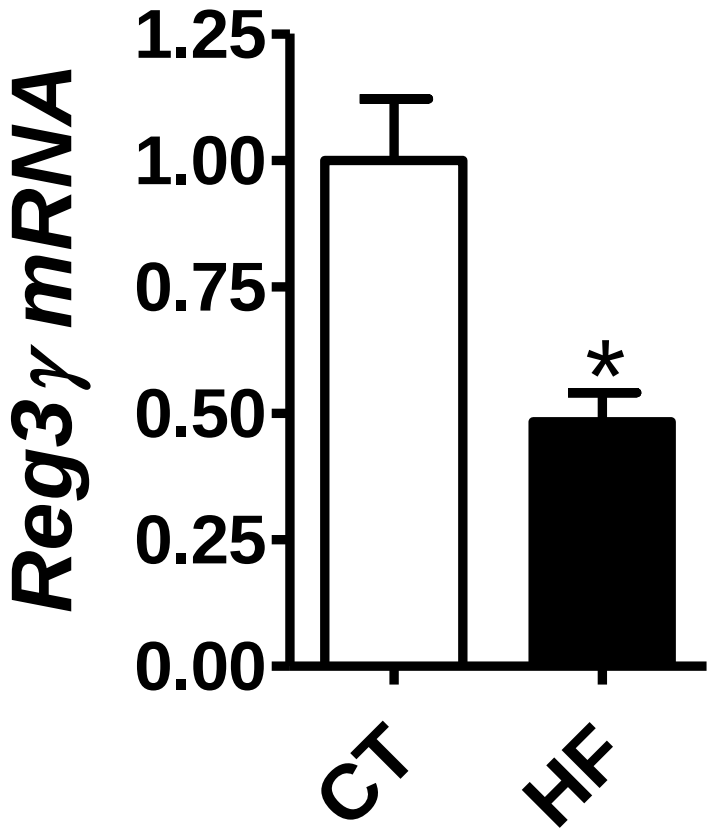

Huile

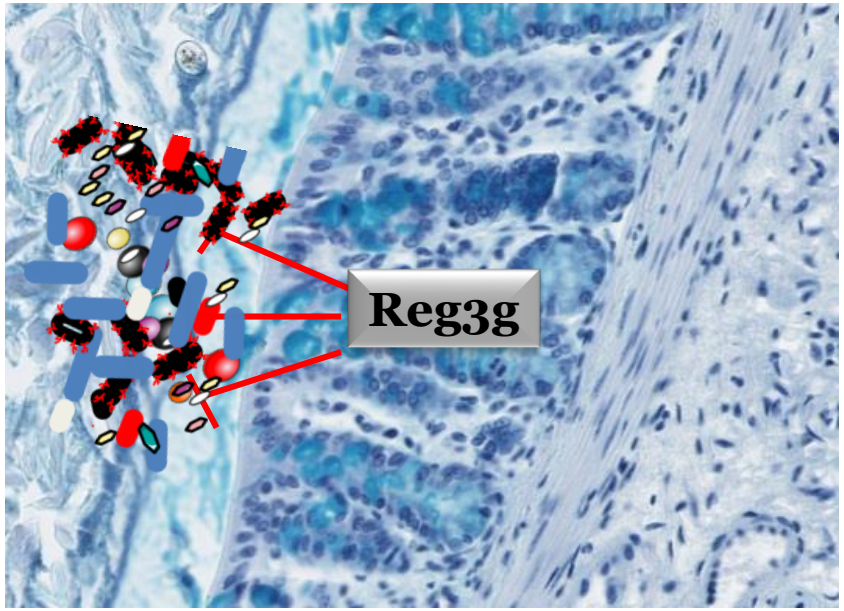

Obese

Microbiota to host : Harmful

- ↘ antimicrobial peptides

High-Fat diet feeding reduces Reg3γ in the gut

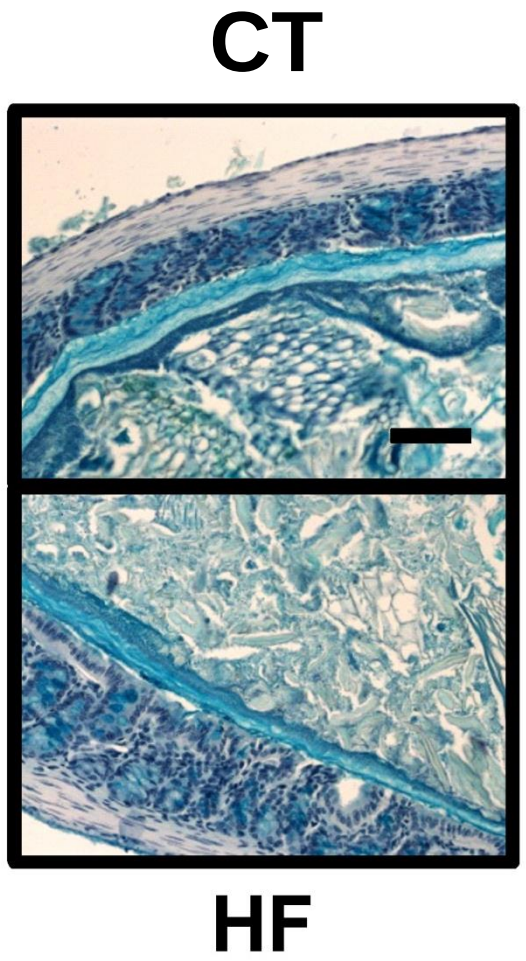


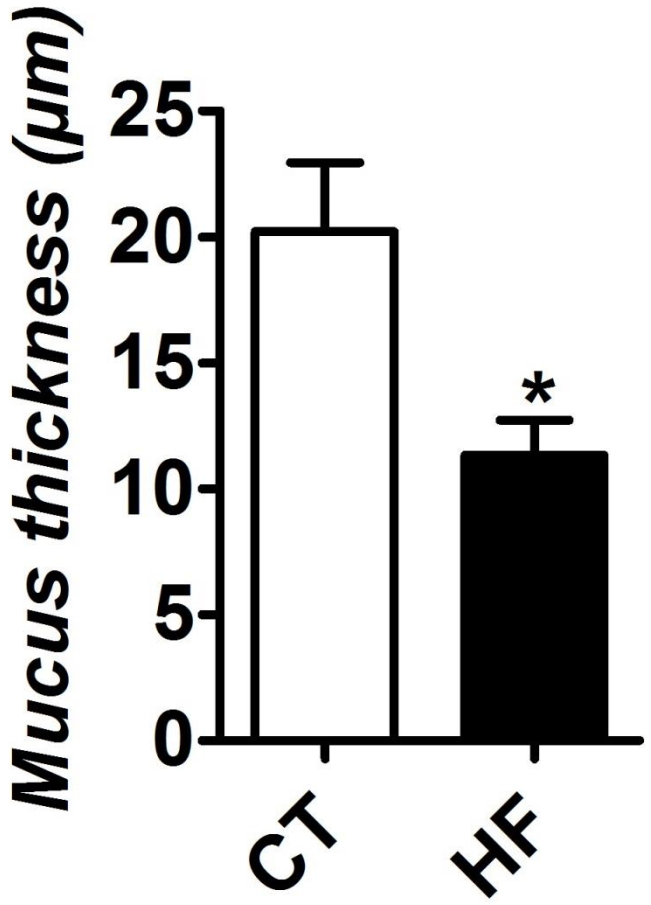


Les cellules de paneth produisent EG3G (or REG3 gamma) via la stimulation des toll-like receptors (TLRs) par les PAMP's. Les REG3 gamma, peptides antibactériens, ciblent spécifiquement les bactéries gram +.

Everard et al *PNAS* 2013
Everard et al ISME J 2014
Everard et al Nature Commun 2014

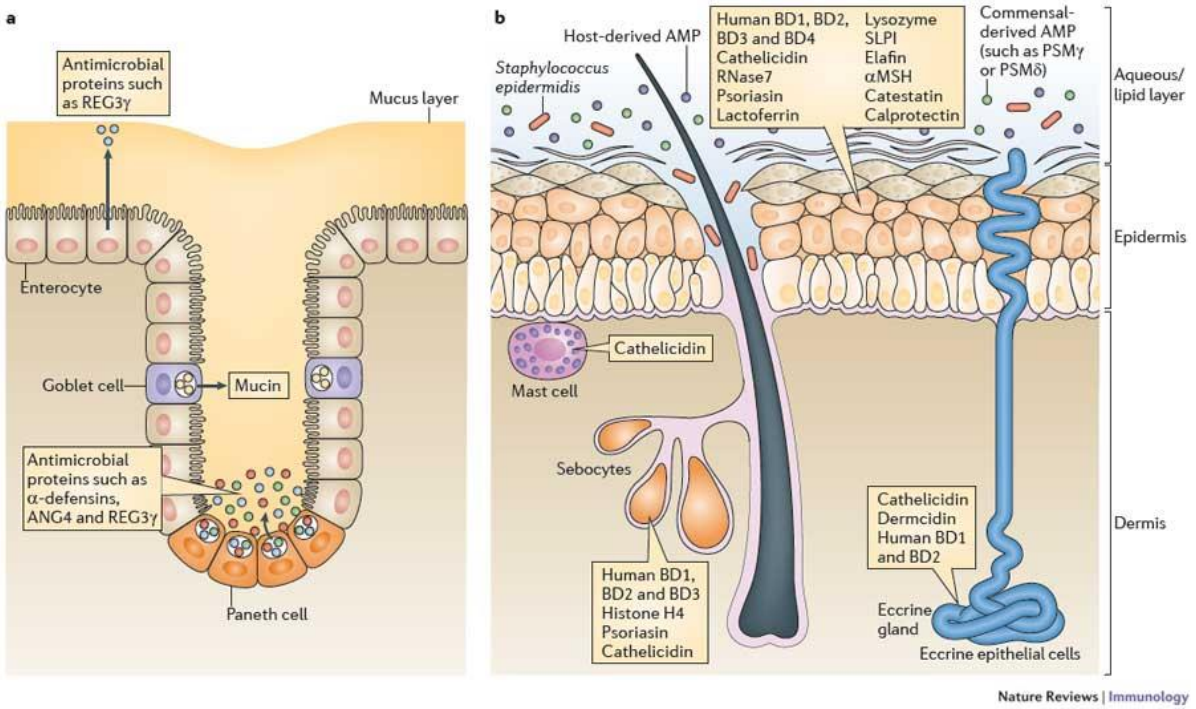
High-Fat diet feeding reduces mucus layer thickness





Everard et al *PNAS* 2013

Barrières épithéliales intestin et peau: flore , mucus, lipides, AMP



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REVIEW 2005
www.nature.com/clinicalpractice/gasthep

Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases

Alessio Fasano* and Terez Shea-Donohue

Le tractus gastro-intestinal joue le rôle de barrière qui régule étroitement le passage de macro-molécules entre le milieu extérieur (aliment / microbiote) et le milieu interne (cellules/tissus/organes…)

Quand cette fonction complexe de barrière est perturbée , des molécules extérieures peuvent entrer et interagir avec le système immunitaire pour induire une réponse inflammatoire susceptible de se manifester sous différentes pathologies intestinales et extra-intestinales.

Fasano and Shea-Donohue,
NATURE CLINICAL PRACTICE GASTROENTEROLOGY & HEPATOLOGY SEPTEMBER 2005 VOL 2 NO 9

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Leaky “Tissue”, c’est quoi?

Simplement un problème de barrière

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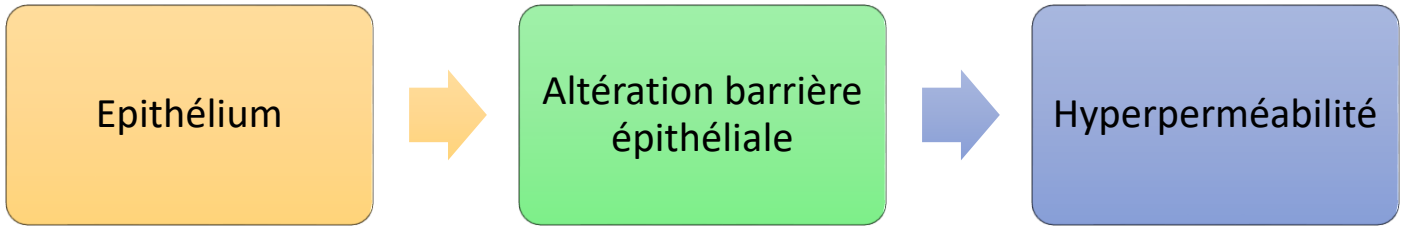
Leaky Gut, c’est quoi?…



Simplement un problème de barrière

JM

Leaky gut syndrome

Simple mais beaucoup plus complexe que ça

Altération – stress de l’épithélium versus intégrité – bon état des épithélia

L’épimmunome par le Dr Isabelle Dequenne