Inflammation - and the innate immune system

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Biomedicine Discovery Institute,
Department of Microbiology

MONASH University

Australian Government
National Health and Medical Research Council
NHMRC

State Government Victoria

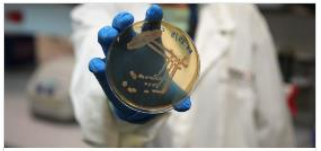
Inflammation

While the immune system protects us from invaders (viruses, bacteria), out-of-control inflammation is the cause of 50 per cent of deaths worldwide and underpins hundreds of chronic diseases and conditions.

Hudson Institute houses Australia's largest group of inflammation and immunity scientists and clinicians. By finding the complex interconnections that control inflammation, they are discovering new ways to diagnose, detect and treat inflammatory diseases and conditions.

LISTEN TO Professor Elizabeth Hartland, CEO, discussing inflammation.

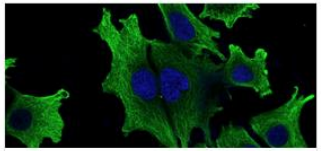
Inflammation diseases we research



Antimicrobial resistance >

COVID-19 >

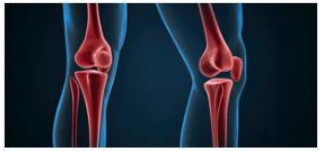
Gastroenteritis >



Inflammation and cancer >

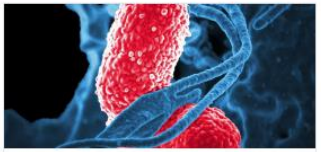
Inflammatory bowel disease (IBD) >

Influenza >



Lupus >

Microbiome in health and disease >



Pneumonia >

https://www.hudson.org.au/disease/inflammation/

Seminar outline

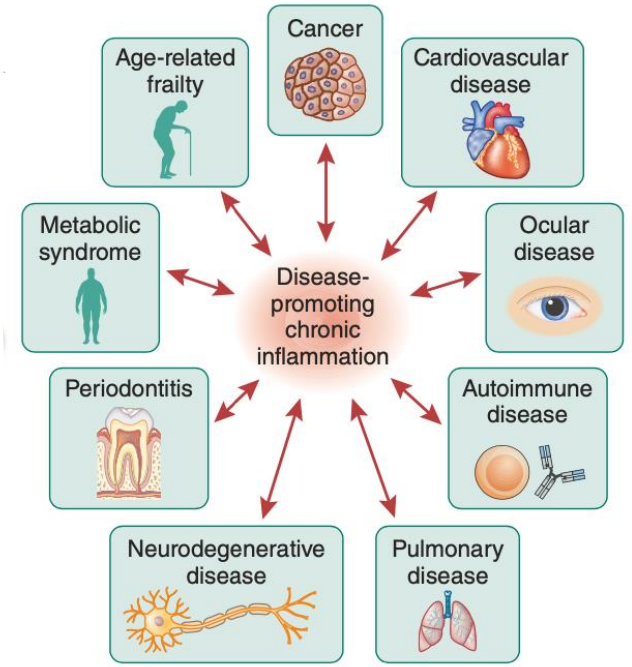
1. What is inflammation?
2. Historical perspective on inflammation
3. The innate immune system – What is it and how does it control inflammation?
4. Key factors in skin immunity
5. Questions and conclusions

What is inflammation?

"A localized physical condition in which part of the body becomes reddened, swollen, hot, and often painful, especially as a reaction to injury or infection."

- Oxford Dictionary

The root cause of many diseases



Potential contributors and therapeutic targets:

- Accumulation of senescent cells
- Unresolved infection
- Dysbiosis
- Activated microglia and macrophages
- Cytokine and chemokine dysregulation
- Imbalance between pro-inflammation mediators and pro-resolution mediators
- Gene mutations
- Epigenetic modifications
- Lifestyle risk factors

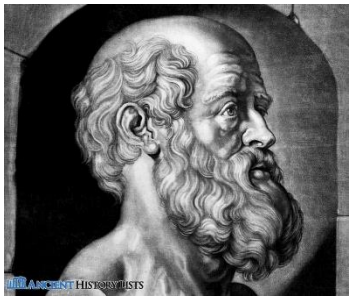
Liu *et al. Nat Immunol.* **18,** 1175-1180

Inflammation: Historical perspective - 1

The Egyptians (3,000 B.C.)

- Ebers papyrus

Hippocrates (5thc B.C.)



- oedema
- sepsis

Celsus (30 B.C.-38 A.D.)

- *rubor* (redness)
- *calor* (warmth)
- *dolor* (pain)
- *tumor* (swelling)

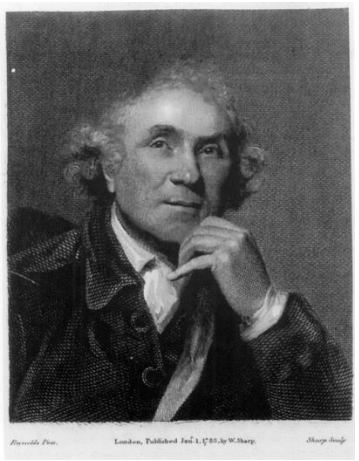
Galen (129 – 210 A.D.)?

- *functio laesa* (loss of function)

Cavaillon *J Venom Anim Toxins incl Trop Dis* ***27***, e20200147

Inflammation: Historical perspective - 2

John Hunter (18th c. A.D.)
A Treatise on the Blood, Inflammation and Gun-shot Wounds



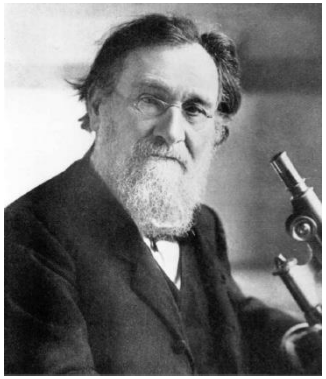
"*Inflammation in itself is not to be considered as a disease, but as a salutary operation, consequent either to some violence or some disease.*"

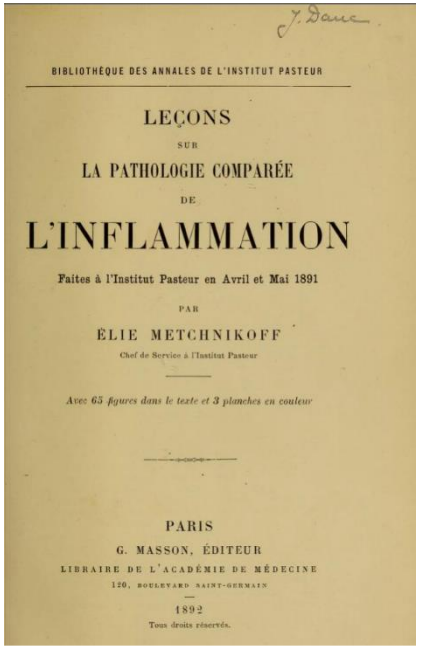
- **Described 3 types of inflammation: adhesive, suppurative, ulcerative**
- **Pus, formation and treatment of abscesses and wounds, infection**

Turk *Int J Exp Path* **75**, 385-395

Inflammation: Historical perspective - 3

E. Metchnikoff (1890s)





BIBLIOTHÈQUE DES ANNALES DE L'INSTITUT PASTEUR

LEÇONS
SUR
LA PATHOLOGIE COMPARÉE
DE
L'INFLAMMATION

Faites à l'Institut Pasteur en Avril et Mai 1891

PAR

ÉLIE METCHNIKOFF

Chef de Service à l'Institut Pasteur

Avec 65 figures dans le texte et 3 planches en couleur

PARIS
G. MASSON, ÉDITEUR
LIBRAIRE DE L'ACADÉMIE DE MÉDECINE
120, BOULEVARD SAINT-GERMAIN

1892

Tous droits réservés.

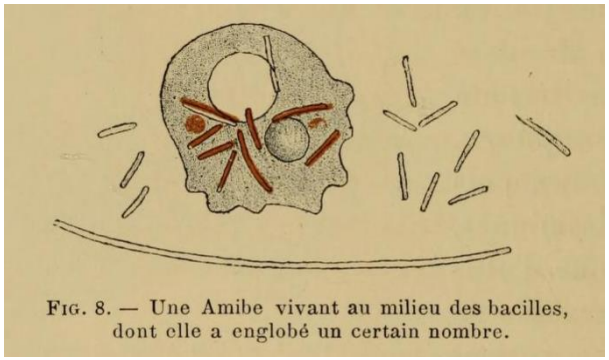
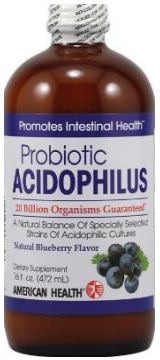


FIG. 8. — Une Amibe vivant au milieu des bacilles, dont elle a englobé un certain nombre.



Discovery of the innate immune system (2011)

- Nobel Prize in Medicine

Photo: Mosimann for Balzan

Bruce A. Beutler

Photo: Mosimann for Balzan

Jules A. Hoffmann

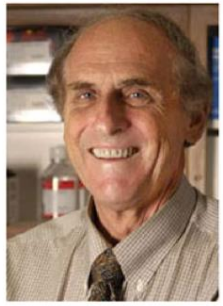
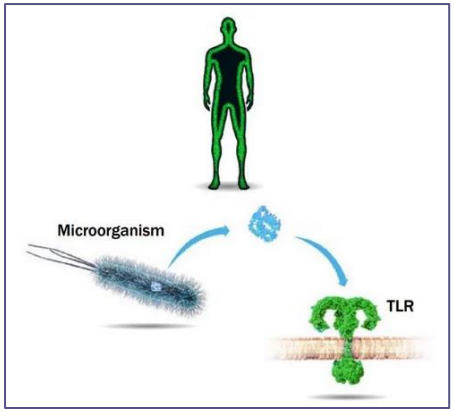


Photo: Rockefeller University Press

Ralph M. Steinman



https://www.nobelprize.org

Innate immune recognition of molecular patterns

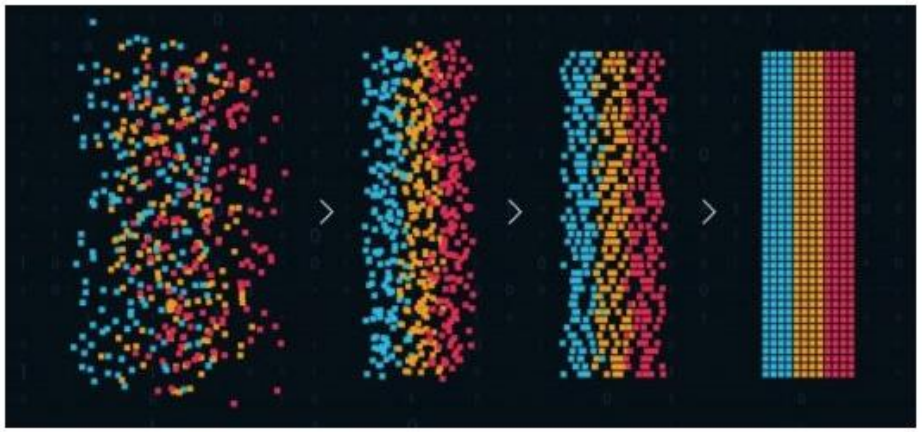
REFLECTIONS ON SELF: IMMUNITY AND BEYOND

VIEWPOINT

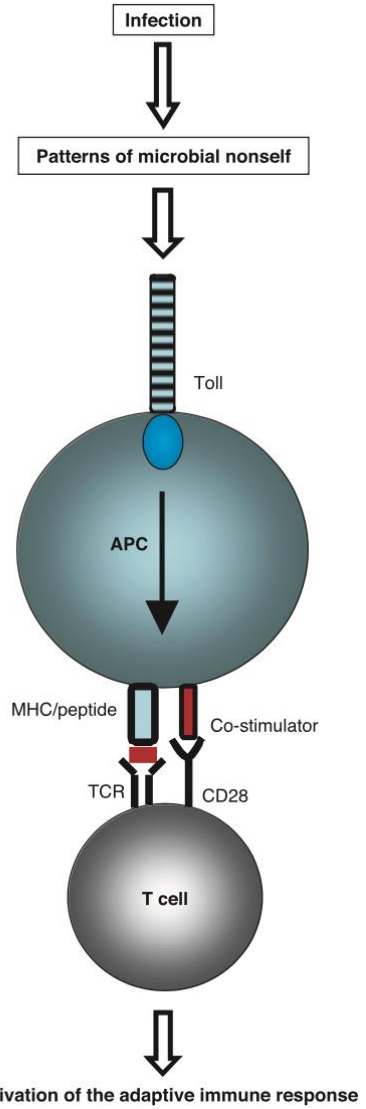
Decoding the Patterns of Self and Nonself by the Innate Immune System

Ruslan Medzhitov* and Charles A. Janeway Jr.

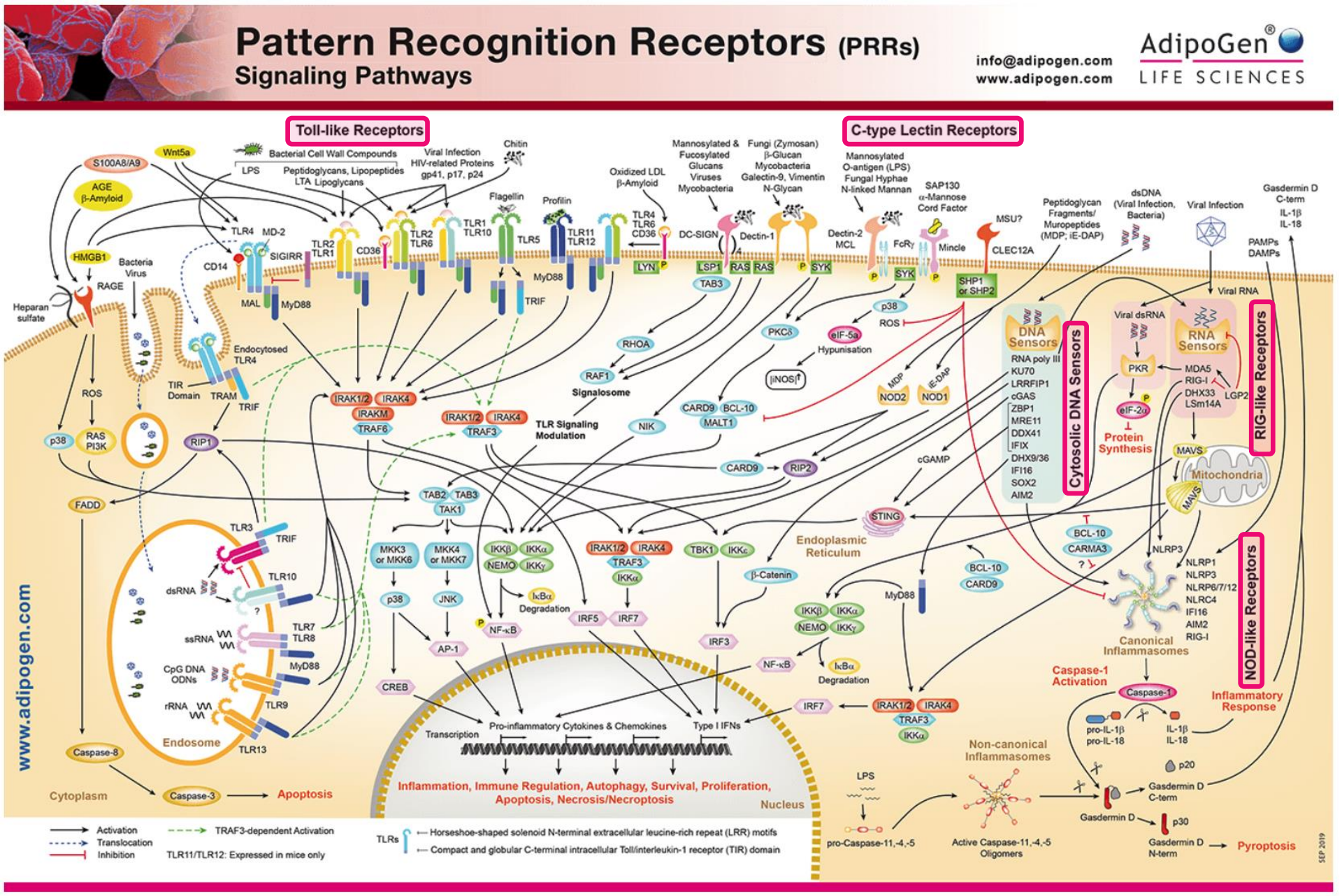
The innate immune system evolved several strategies of self/nonself discrimination that are based on the recognition of molecular patterns demarcating infectious nonself, as well as normal and abnormal self. These patterns are deciphered by receptors that either induce or inhibit an immune response, depending on the meaning of these signals.



https://www.edureka.co/blog/pattern-recognition/



Medzhitov & Janeway *Science* **296**, 298-300 (2002)


Pattern Recognition Receptors (PRRs)
Signaling Pathways
info@adipogen.com
www.adipogen.com
AdipoGen LIFE SCIENCES
Toll-like Receptors
C-type Lectin Receptors
Bacterial Cell Wall Compounds
LPS
Peptidoglycans, Lipopeptides
LTA Lipoglycans
Viral Infection
HIV-related Proteins
gp41, p17, p24
Chitin
Flagellin
Profilin
Oxidized LDL
β-Amyloid
Mannosylated & Fucosylated Glucans Viruses Mycobacteria
Fungi (Zymosan) β-Glucan Mycobacteria Galectin-9, Vimentin N-Glycan
Mannosylated O-antigen (LPS) Fungal Hyphae N-linked Mannan
SAP130 α-Mannose Cord Factor
MSU?
Peptidoglycan Fragments/ Muropeptides (MDP; iE-DAP)
dsDNA (Viral Infection, Bacteria)
Viral Infection
Gasdermin D C-term
IL-1β
IL-18
PAMPs
DAMPs
S100A8/A9
Wnt5a
AGE β-Amyloid
HMGB1
Bacteria
Virus
RAGE
Heparan sulfate
TLR4
MD-2
CD14
SIGIRR
MAL
MyD88
TLR2 TLR1
CD36
TLR2 TLR6
TLR1 TLR10
TLR5
TLR11 TLR12
TLR4 TLR6 CD36
LYN
DC-SIGN
Dectin-1
Dectin-2 MCL
FcRγ
Mincle
CLEC12A
LSP1
RAS
RAS
SYK
SYK
TAB3
SHP1 or SHP2
p38
ROS
PKCδ
eIF-5a
Hypunisation
RHOA
RAF1
Signalosome
iNOS
MDP
iE-DAP
NOD2
NOD1
DNA Sensors
RNA poly III
KU70
LRRFIP1
cGAS
ZBP1
MRE11
DDX41
IFIX
DHX9/36
IFI16
SOX2
AIM2
Cytosolic DNA Sensors
Viral dsRNA
RNA Sensors
PKR
eIF-2α
Protein Synthesis
MDA5
RIG-I
DHX33
LSm14A
LGP2
Viral RNA
RIG-like Receptors
Endocytosed TLR4
TIR Domain
TRAM
TRIF
ROS
p38
RAS
PI3K
RIP1
IRAK1/2
IRAK4
IRAKM
TRAF6
IRAK1/2
IRAK4
TRAF3
TLR Signaling Modulation
NIK
CARD9
BCL-10
MALT1
CARD9
RIP2
cGAMP
MAVS
Mitochondria
FADD
TAB2
TAB3
TAK1
STING
Endoplasmic Reticulum
BCL-10
CARMA3
NLRP3
NLRP1
NLRP3
NLRP6/7/12
NLRC4
IFI16
AIM2
RIG-I
Canonical Inflammasomes
NOD-like Receptors
TLR3
TRIF
TLR10
dsRNA
TLR7
TLR8
ssRNA
MyD88
CpG DNA ODNs
TLR9
rRNA
TLR13
Endosome
MKK3 or MKK6
MKK4 or MKK7
IKKβ
IKKα
NEMO
IKKγ
IRAK1/2
IRAK4
TRAF3
IKKα
TBK1
IKKε
β-Catenin
MyD88
BCL-10
CARD9
p38
JNK
IκBα
Degradation
NF-κB
IRF5
IRF7
IRF3
AP-1
CREB
Caspase-1 Activation
Caspase-1
pro-IL-1β
pro-IL-18
IL-1β
IL-18
Inflammatory Response
Transcription
Pro-inflammatory Cytokines & Chemokines
Type I IFNs
Non-canonical Inflammasomes
LPS
p20
Gasdermin D C-term
Gasdermin D
p30
Gasdermin D N-term
Pyroptosis
pro-Caspase-11,-4,-5
Active Caspase-11,-4,-5 Oligomers
Caspase-8
Cytoplasm
Caspase-3
Apoptosis
Inflammation, Immune Regulation, Autophagy, Survival, Proliferation, Apoptosis, Necrosis/Necroptosis
Nucleus
www.adipogen.com
Activation
Translocation
Inhibition
TRAF3-dependent Activation
TLR11/TLR12: Expressed in mice only
TLRs
Horseshoe-shaped solenoid N-terminal extracellular leucine-rich repeat (LRR) motifs
Compact and globular C-terminal intracellular Toll/interleukin-1 receptor (TIR) domain
SEP 2019

The innate immune system

Patterns

“Pathogen-associated molecular patterns” (PAMPs)

Lipopolysaccharide
Chitin
Peptidoglycan
DNA
RNA

“Danger-associated molecular patterns”

Uric acid
High-mobility group box 1 (HMGB1)
Cholesterol
Fatty acids
Heat shock proteins (HSPs)

Receptors (PRRs)

TLR4
Dectins
RIG-I
NOD2
NLRP3
cGAS-STING

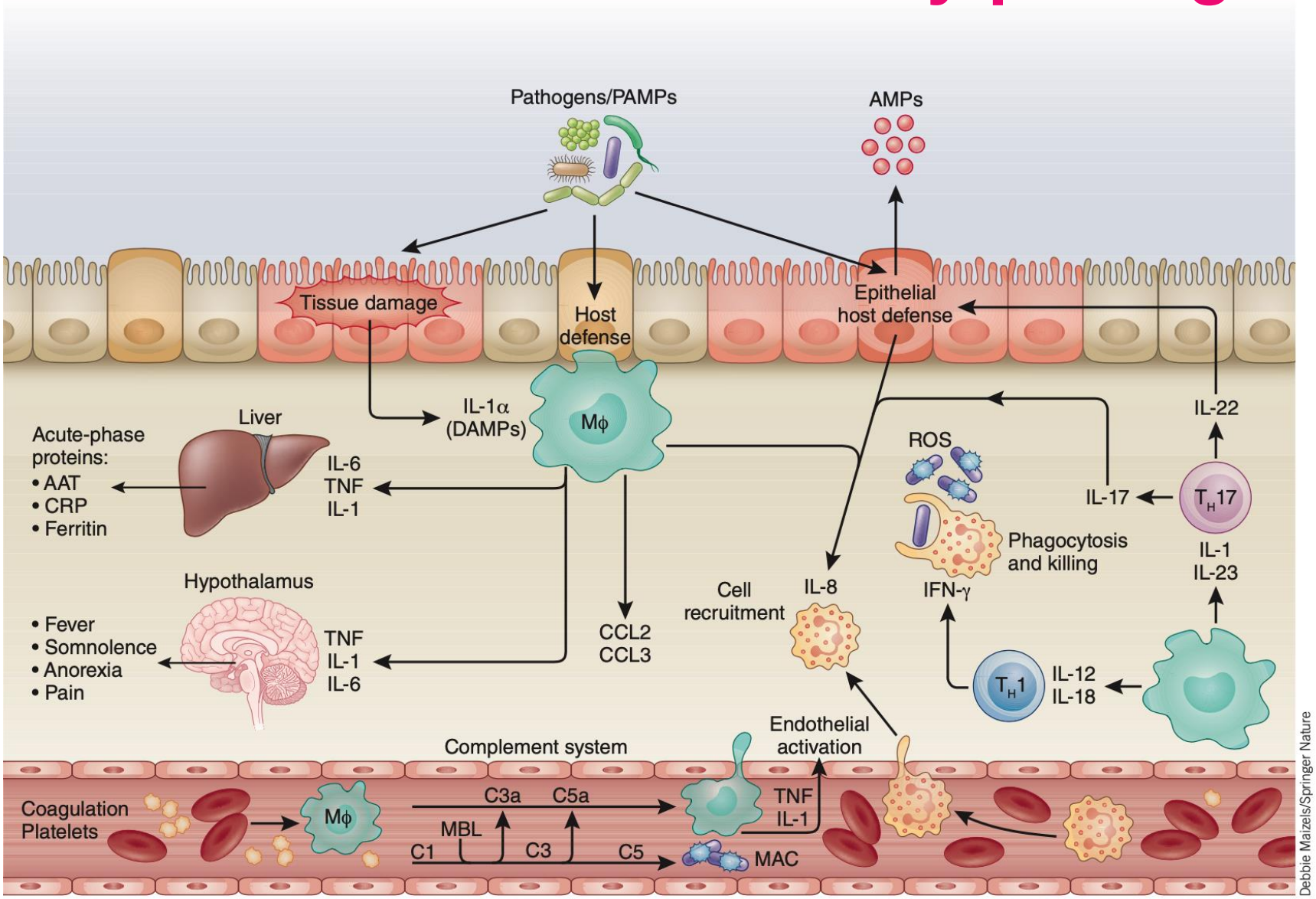
Cellular responses

Production of immune-mediators (*e.g.* cytokines, chemokines, antimicrobial peptides)
Autophagy
Cell proliferation
Cell death (apoptosis, pyroptosis, necroptosis, necrosis)
Unfolded protein response
Cell adhesion

Clinical/ pathological impact

Infection
Inflammation
Tissue repair
Innate immunity (phagocytosis)
Metabolic dysregulation
Adaptive immunity (B-, T-cells, antibodies)

Induction of inflammation by pathogens



Netea *et al*. *Nat Immunol.* **18**, 826-831

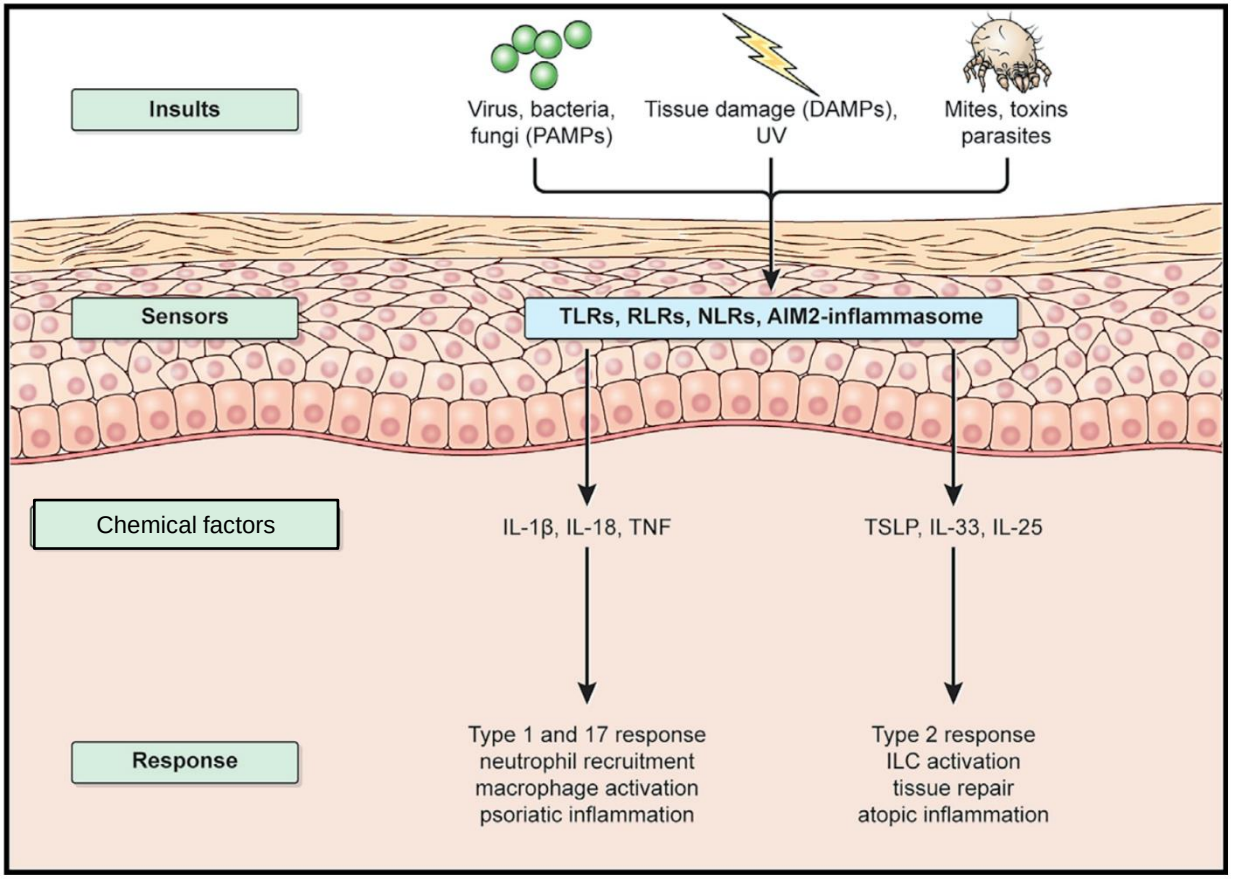
*"Choreographing immunity in the skin epithelial barrier"**

What is skin and what does it do?

- **multilayered (epidermis, dermis, hypodermis – each with its immune cell population)**
- **endothelial cells, fibroblasts, neurones, adipocytes epithelial cells acting in unison to ensure its function**
- **direct interactions between immune cells of innate and adaptive systems**
- **a barrier against environmental pressures *e.g*. UV, microbes, allergens..**
- **immune cell interactions with keratinocytes can promote antimicrobial responses or inflammatory disease**
- **emerging key factors: hair follicles, neurones, microbiota**

*Kobayashi *et al. Immunity* **50**, 552-565

What is skin and what does it do?

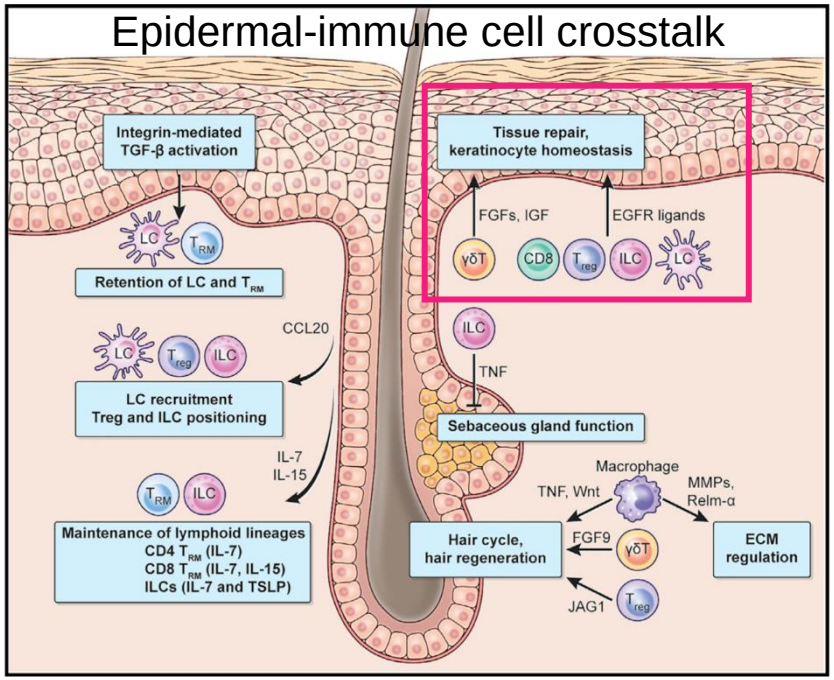


Dysregulation of immune pathways directed against infectious agents play key roles in inflammatory conditions *e.g.* psoriasis, dermatitis

Kobayashi *et al. Immunity* **50**, 552-565

Hair follicles and skin immunity

- Immune systems preceded occurrence of hair follicles in evolution *e.g.* hairless vertebrates
- Follicles - passageways for environmental signals, immunosurveillance and immune cell traffic?
- Chemical signals - chemokines, cytokines, growth factors
- Innate lymphoid cells – can regulate sebaceous gland size → sebum composition and amount → microbiota
- Epithelialisation in wounds mediated by immune factors *e.g.* epidermal growth factor receptor ligands, fibroblast growth factors

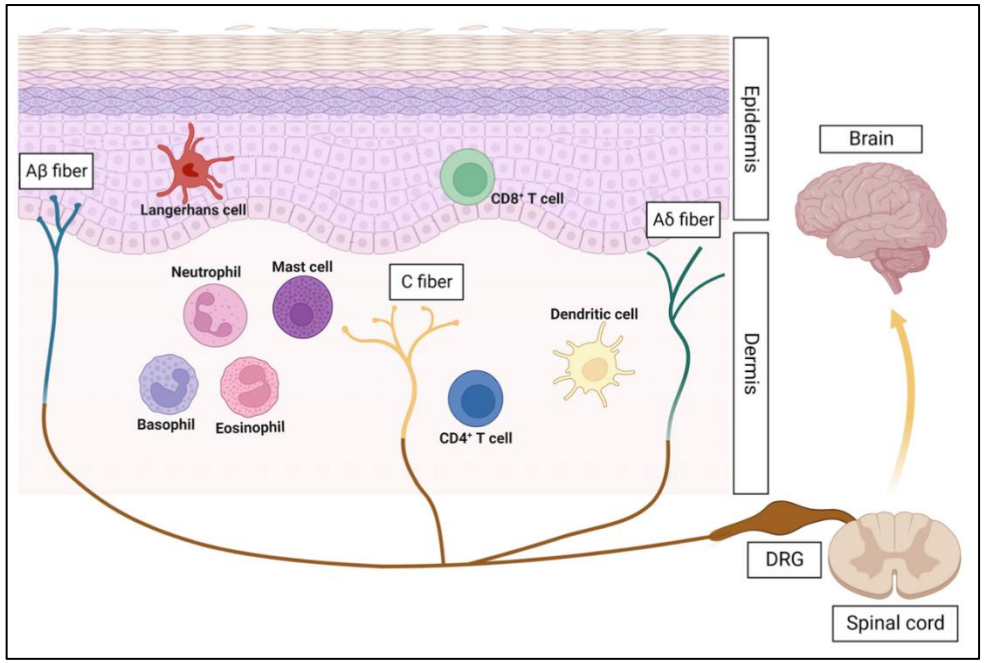


Kobayashi *et al. Immunity* **50**, 552-565

Neurones and skin immunity

- **Skin is innervated (role of nervous system in "barriers")**
- **Peripheral neurones recognise harmful stimuli**
  ***e.g.* microbes, allergens**
- **Neuronal activation leads to pain and itch responses**

Immune cell and sensory neurones in skin

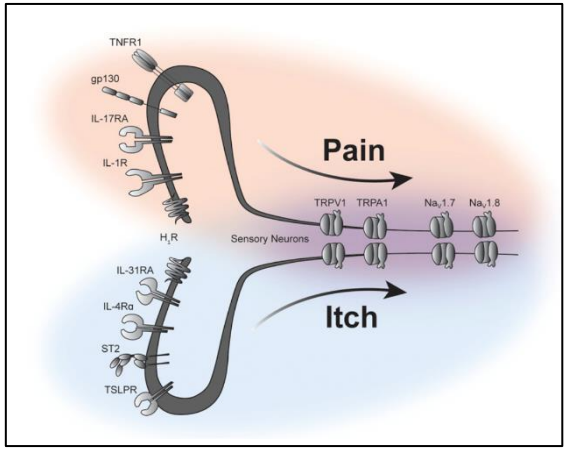


Huang et *al Pharmaceuticals* **16**, 246

Cytokine receptors - specialised functions for pain or itch

Pain – restrict movement, promote wound healing, prevent infection spread, conserve metabolic resources

Itch – expulsion of irritants

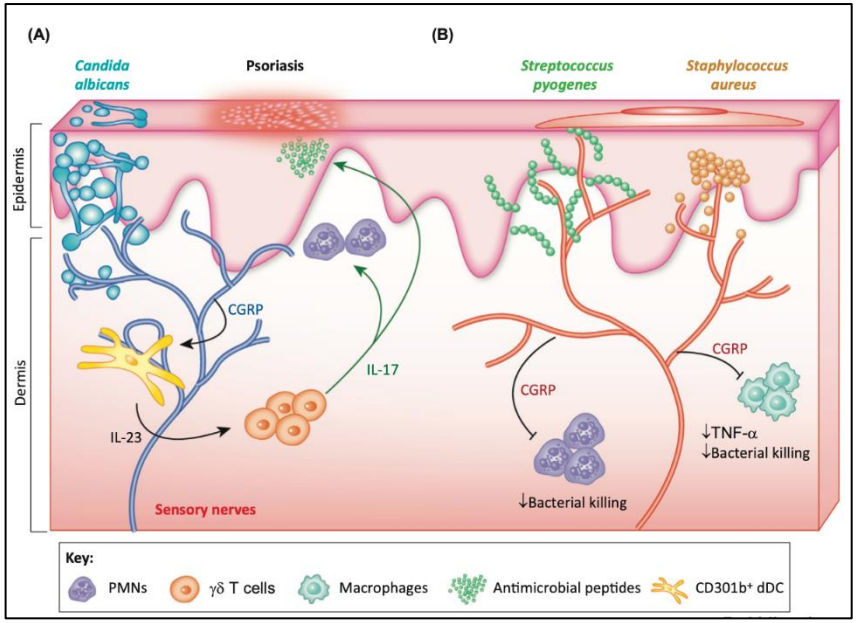


Trier et *al. J Immunol* **202**, 2829-2835

Neurones and skin immunity

- **Sensory neurones:**
  - **share some features with immune cells *e.g.* pathogen recognition, soluble factors**
  - **regulate immune cells**
  - **can be directly activated by pathogens**

- **primarily transmit signals from skin to CNS but can also do so to other cells in periphery via efferent route through release of neuropeptides *e.g.* calcitonin gene–related peptide, CGRP**

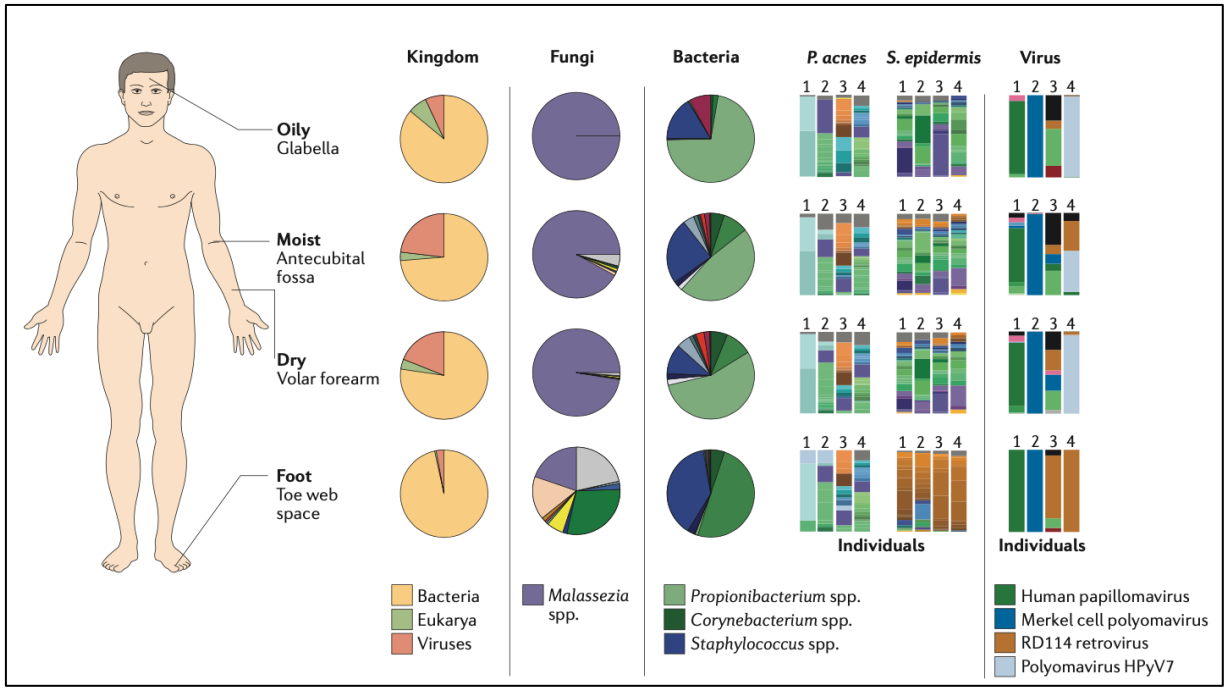


Blake *et al. Trends Neurosci* **42**, 537-551

The microbiota and skin

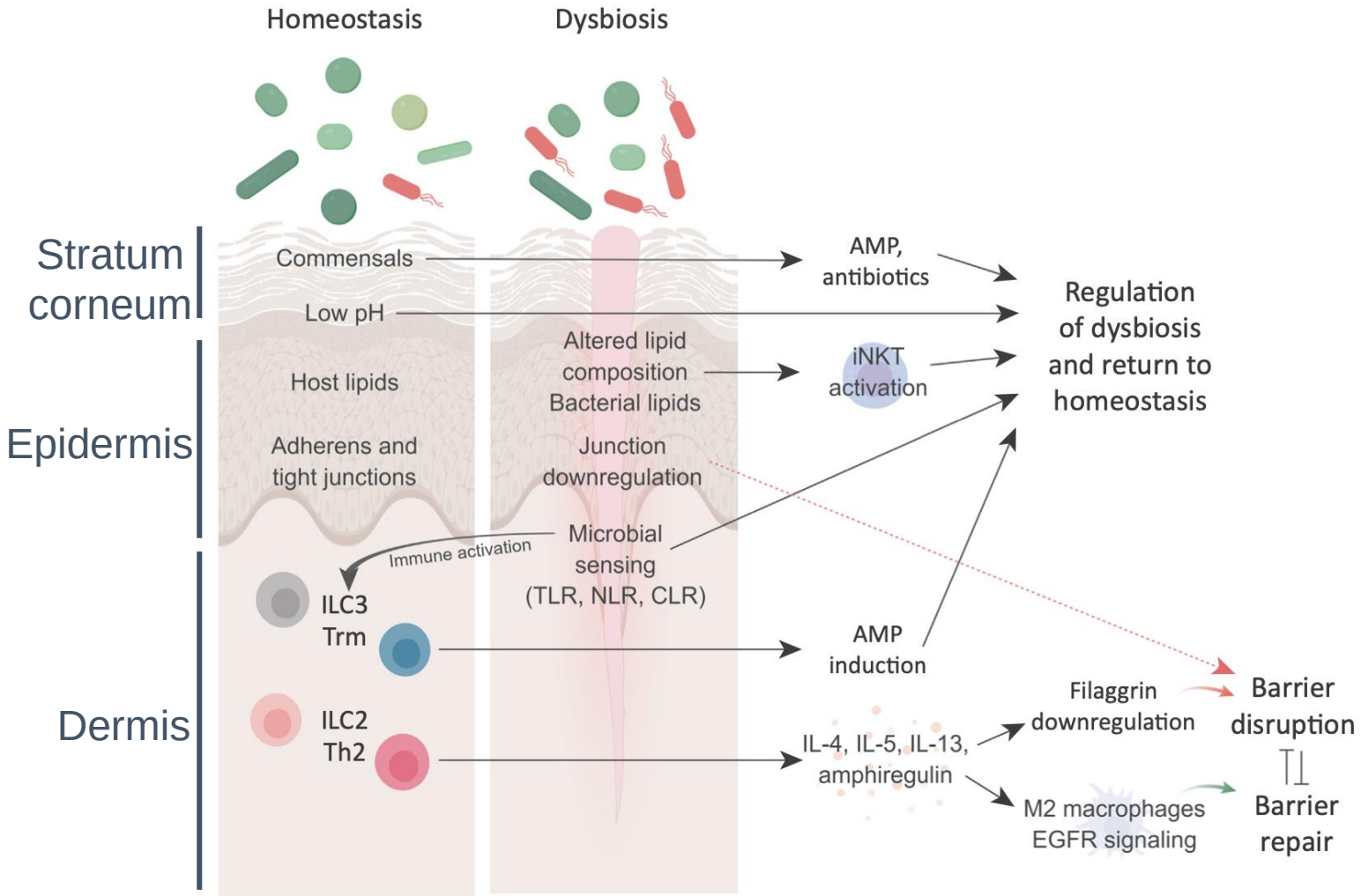
- The microbiota: resident microbes (bacteria, fungi, viruses, parasites)
- Skin microbial communities are shaped by the host immune system (maintain commensals, eliminate pathogens)

- Microbiota composition is shaped by physiological characteristics and individual



Byrd *et al. Nat Rev Microbiol* **16**, 143-155

The cutaneous barrier - homeostasis versus dysbiosis

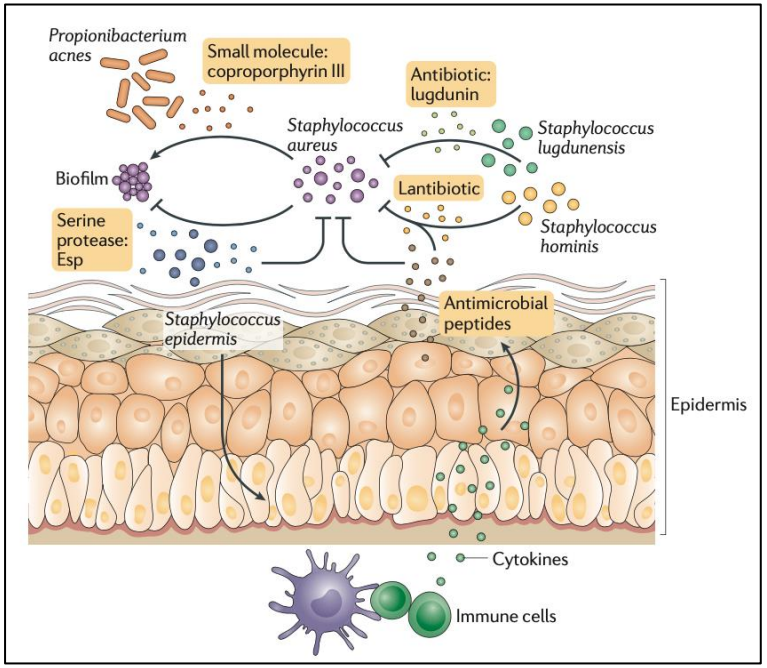


Eyerich *et al. Trends Immunol* **39**, 315-327

The microbiota and skin

Commensals:

- **"educate" skin immune responses**
- **interact with other commensals and also with pathogens**
- **have role in skin diseases *e.g.* atopic dermatitis**



Knowledge has been rapidly gained due to technical advances in sequencing ("metagenomics")

- need to better understand impact of commensals on immune system; how these microbes are sensed; and immunological tools to track commensal-specific responses

Byrd et *al. Nat Rev Microbiol* **16**, 143-155

The microbiota and skin

- **Both commensals and pathogens regulate neuronal function**
- **Can information about their impact on neurones be used to develop novel approaches to treat infection?**
- **Does the location of pathogen invasion affect neuroimmune interactions *i.e.*, the types of immune cells that are recruited, the neuroimmune modulation mechanism?**

Blake et *al. Trends Neurosci* **42**, 537-551

Conclusions

- **Inflammation can have beneficial effects - host defence, tissue repair**
- **Key role of the innate immune system in inflammation**
- **The need for a better understanding of the microbiome and commensal-pathogen interactions in inflammation**