COST Initiative Occupational Skin Diseases (OSD)
StanDerm Seminar
Etiology and Prevention of Occupational Contact Dermatitis: New Challenges

UNIVERSITÄTS KLINIKUM FREIBURG

Skin barrier and inflammation

Stefan F. Martin, PhD

YOUR SKIN. THE MOST IMPORTANT OF YOUR LIFE. 2m²

EADV - EUROPREVENTION
CAMPAIGN: HEALTHY SKIN @ WORK

ALLERGY Research Group

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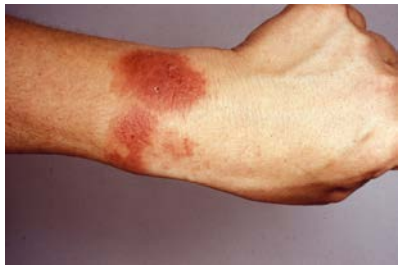
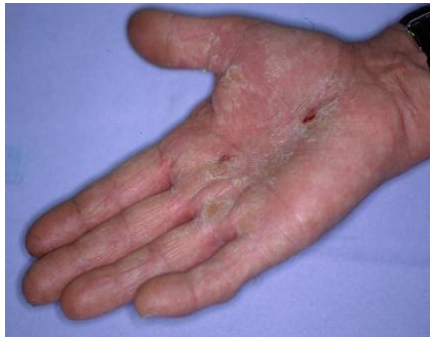
Skin barrier

- Mechanical barrier (Stratum corneum, tight junctions…)
- Biochemical/metabolic barrier (redox systems, detoxification systems)
- Immunological barrier (commensal flora (skin microbiota), antimicrobial peptides, structural cells, immune cells, extracellular matrix (ECM))

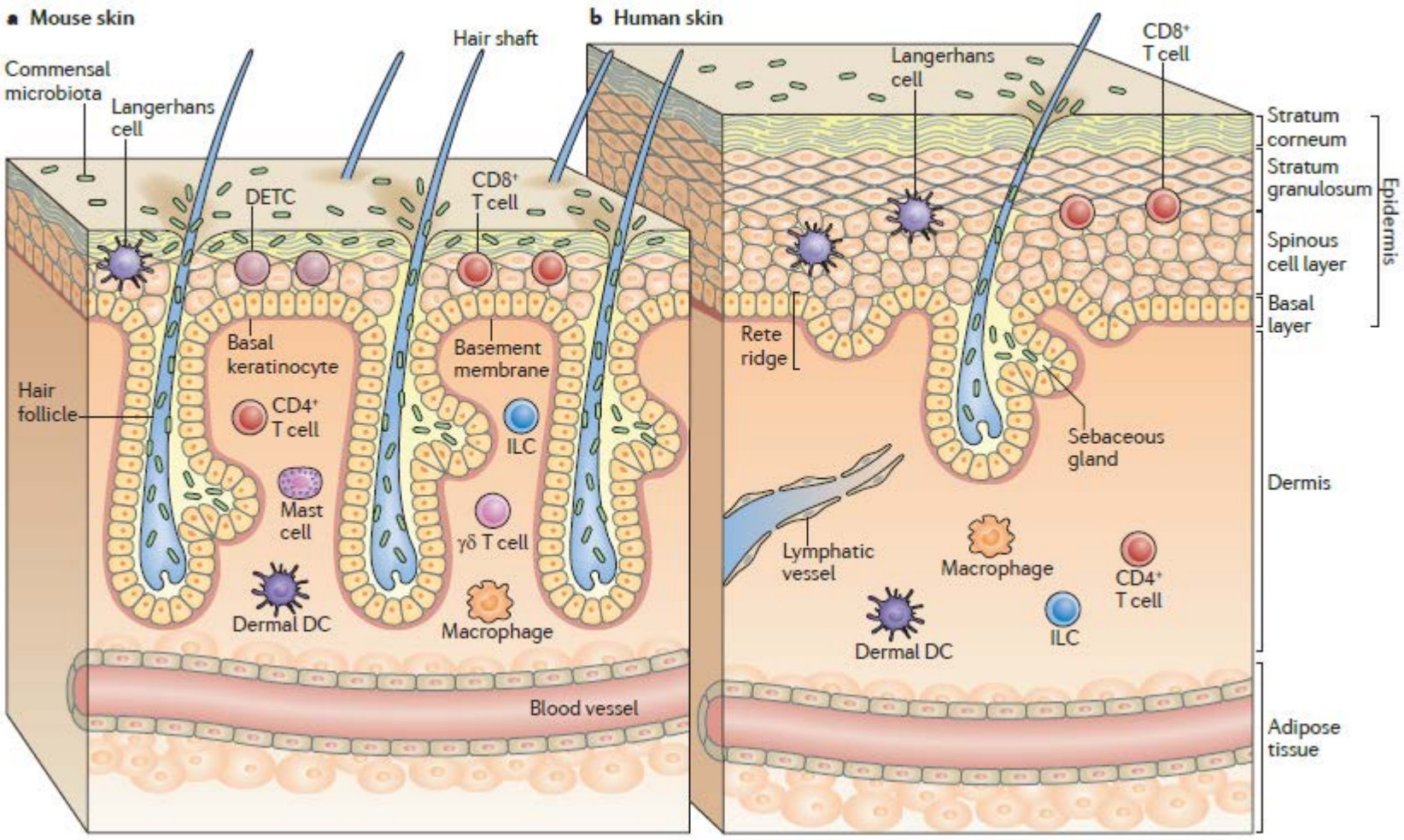
⇒ **Skin as a strong multifunctional barrier**

⇒ **Penetration, avoidance of detoxification and overcoming the immunological barrier in immunity and disease**



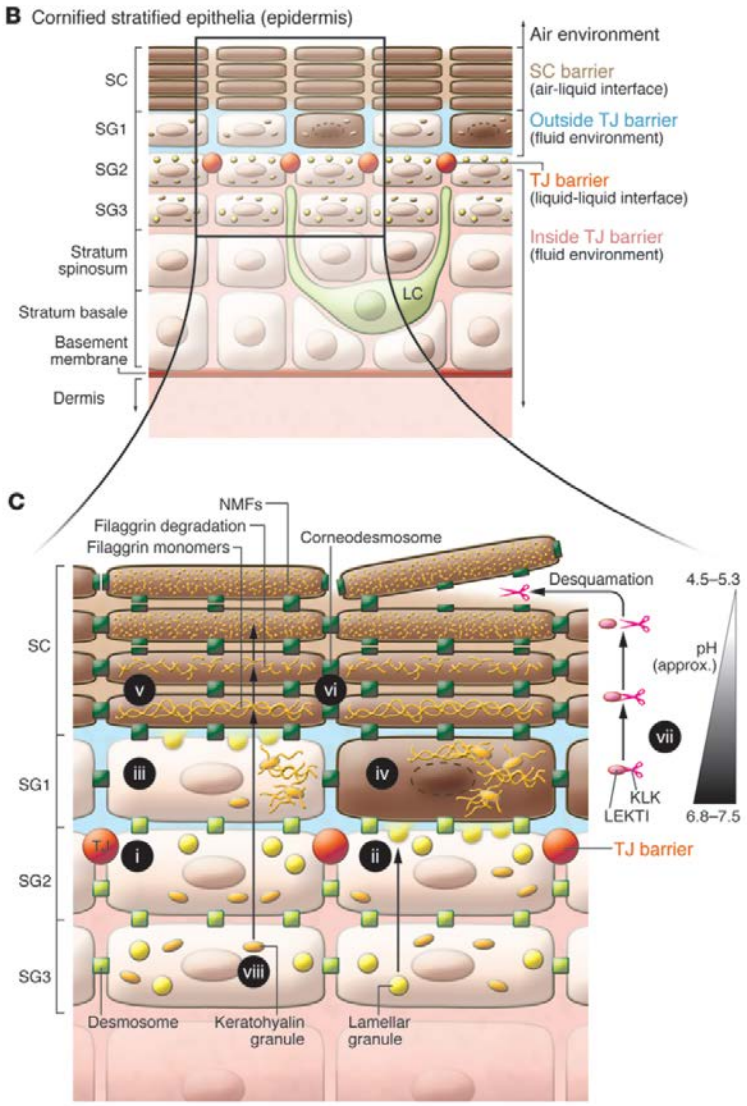


Structure and cellular components of skin in mice and humans



Pasparakis M. et al., *Nat. Rev. Immunol.* 14:289-301 (2014)

Structure and cellular components of skin in mice and humans



Kubo A. et al., *J. Clin. Invest.* 122:440-447 (2012)

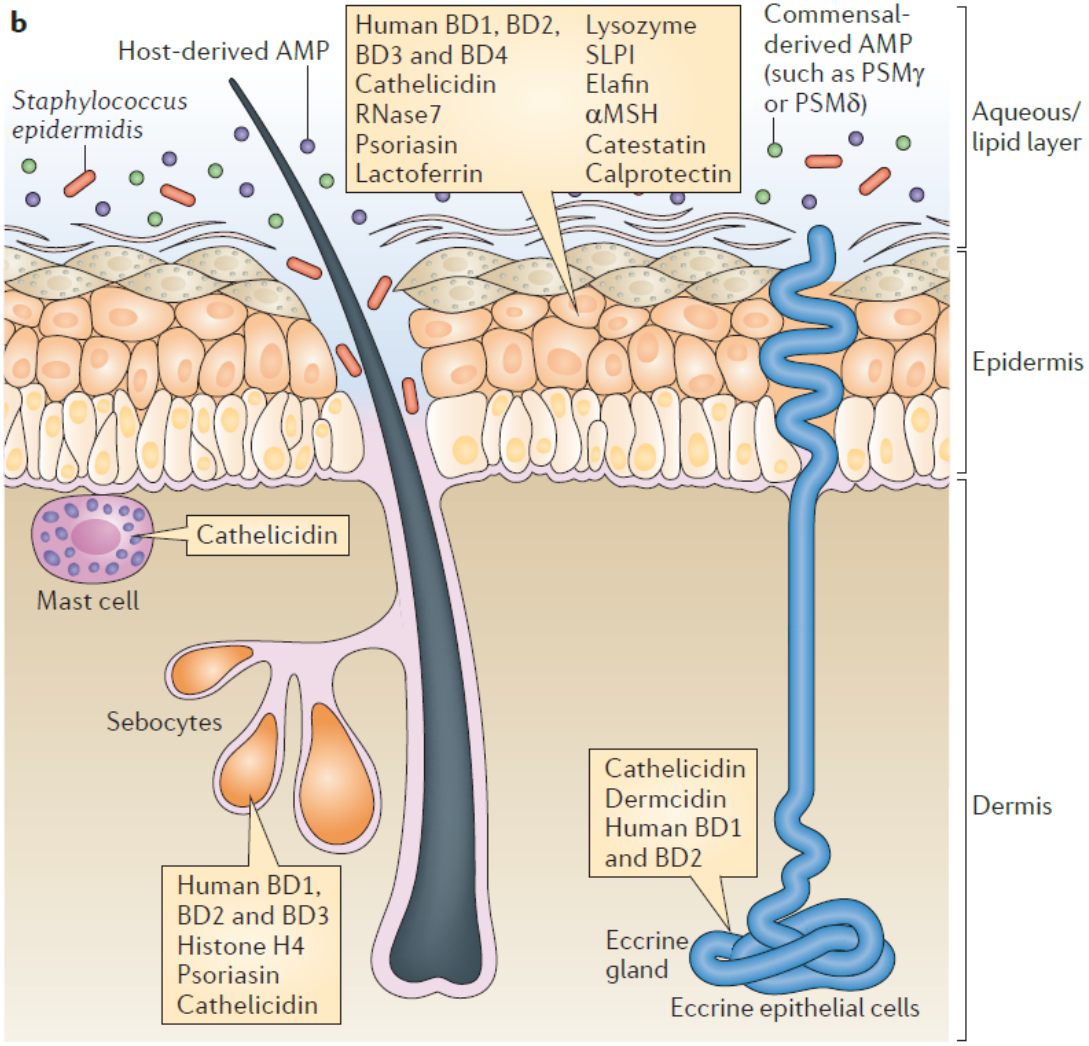
Table 1

Skin barrier–related genes associated with AD/AD-like dermatitis

Gene symbol	Gene name	Functions	Representative refs.[A]
Filaggrin system			
FLG	Filaggrin	Major constituent of keratohyalin granules; bundling keratin filament to form keratin pattern; degradation products are reported to have skin-moisturizing activity	62, 69
Desquamation			
SPINK5	Serine peptidase inhibitor, Kazal type 5	pH-dependent inhibition of KLK5 and KLK7	86
KLK7[B]	Kallikrein-related peptidase 7	Digestion of corneodesmosin	96
CDSN	Corneodesmosin	Structural protein of corneodesmosomes	97[C]
Others			
CSTA	Cystatin A	Cysteine protease inhibitor of house dust mite protease	125
CLDN1[D]	Claudin 1	Integral transmembrane protein of TJs	109

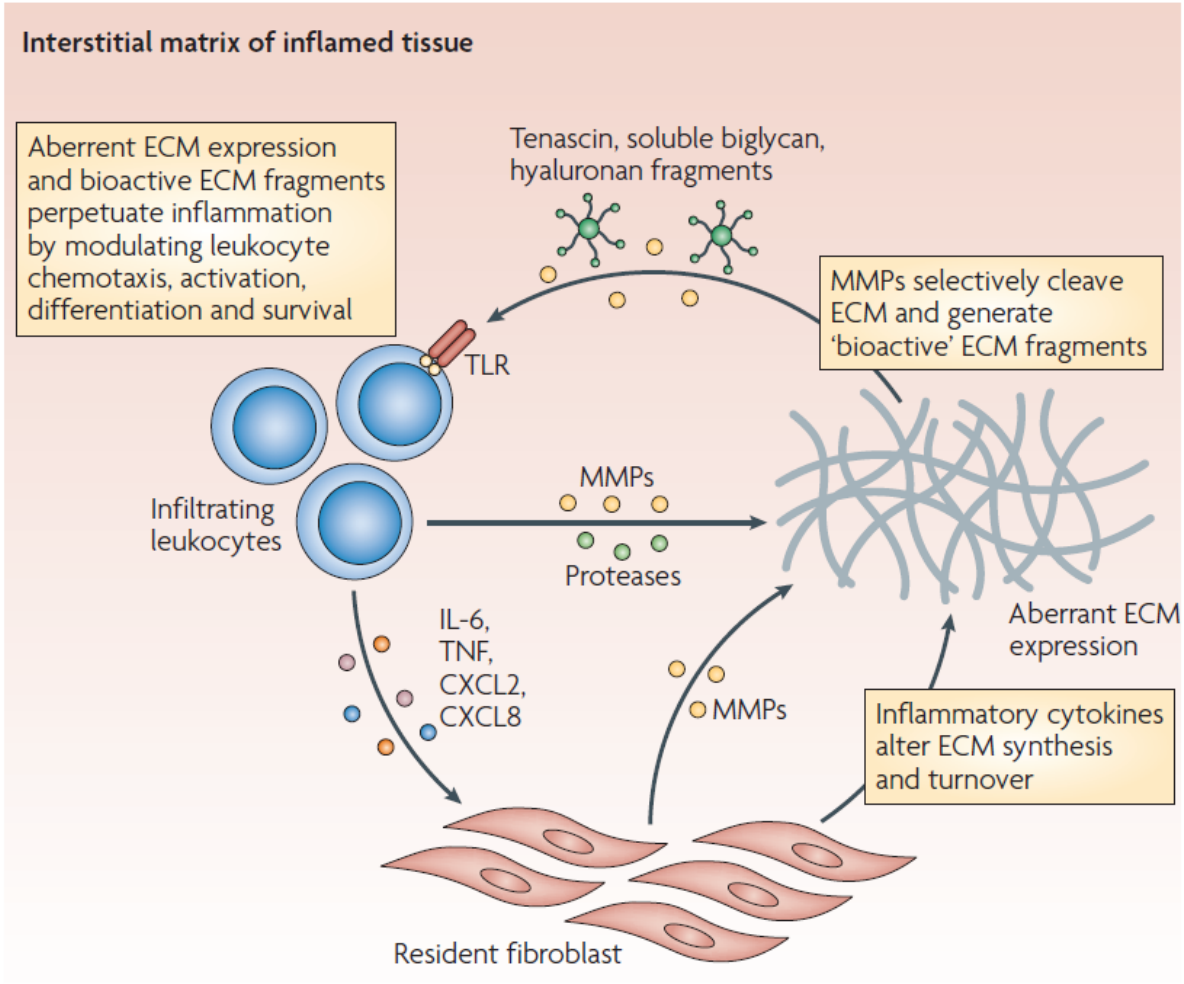
[A]For more detailed data on gene variants, see ref. 75. [B]The association with AD is still controversial (126). [C]Only reported as responsible for peeling skin syndrome type B. [D]No atopic disease has been reported to complicate in patients with NISCH, who totally lack claudin 1 protein (107, 108).

The epithlial barrier of the skin and antimicrobial peptides (AMP)



Gallo R.L. and L.V. Hooper, *Nat. Rev. Immunol.* 12:503-516 (2012)

Potential modes of ECM activation of immune cells



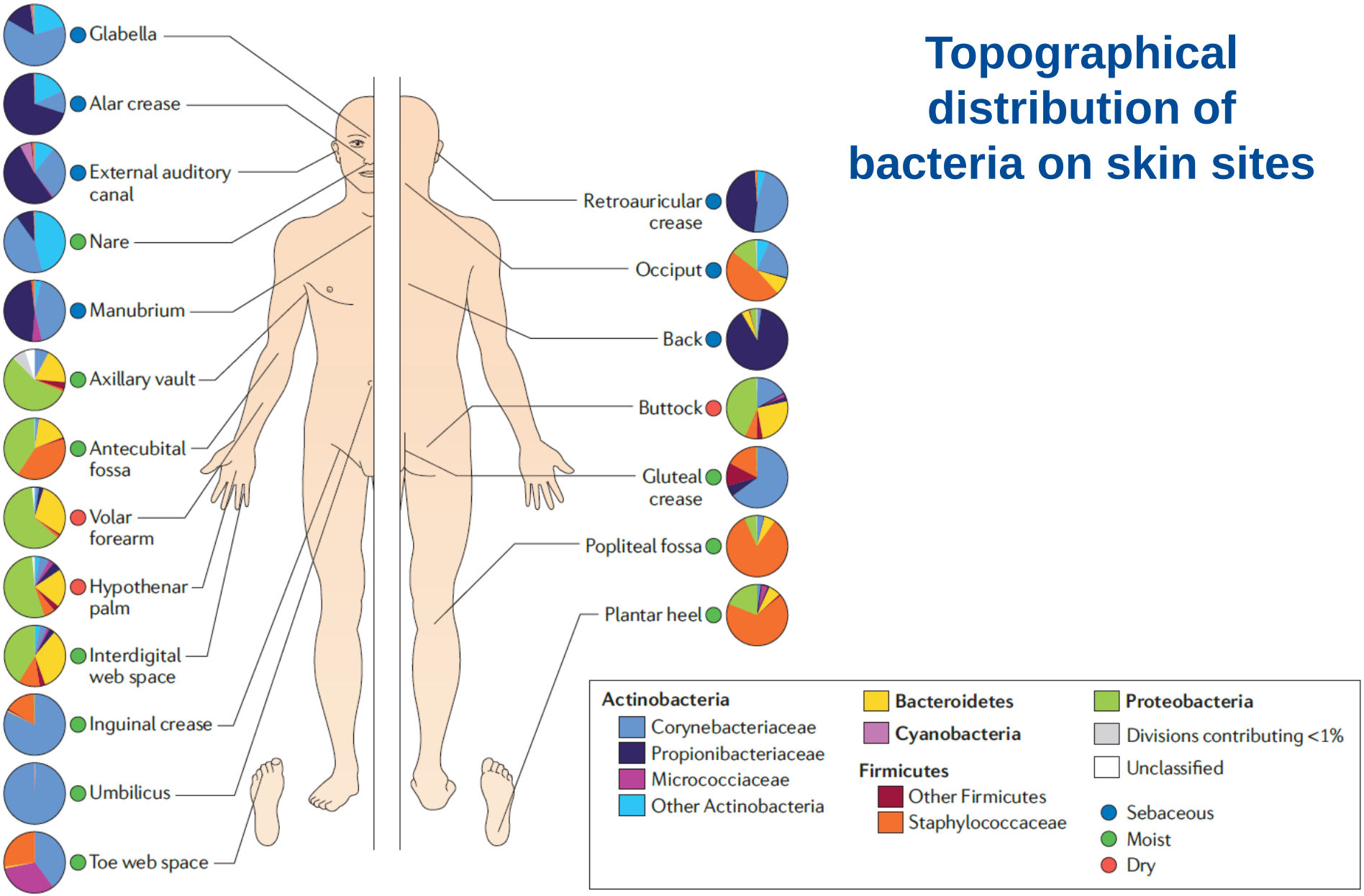
Sorokin J., *Nat. Rev. Microbiol.* 10:712-723 (2010)

Table 1 | **Examples of factors that can modulate the ECM in inflamed tissues**

Factor	Effects on ECM	Refs
Cytokines		
TNF	Upregulation of osteopontin, MMP9 and the vascular laminins α4 and α5; downregulation of most other ECM molecules	37,113, 124,125
IL-17	Upregulation of MMP9	114
TGFβ	Upregulation of most ECM molecules	125
IFNg	Downregulation of most ECM molecules; downregulation of MMP1, MMP2, MMP3, MMP7, MMP9 and MMP10	125,126
IL-1β	Upregulation of laminin α4; upregulation of MMP1, MMP3, MMP7 and MMP9;	37,39,121
Proteases		
MMP2, MMP9	Cleavage of cell–matrix receptors (for example, dystroglycan)	55
MMP2, MMP9	Inactivation of chemokines (for example, CXCL12)	127
MMP9	Activation of chemokines (for example, CXCL8, CXCL6 and CXCL5); surface release of TNF, which alters local concentrations	119,120
MMP2, MT1–MMP	Production of CXCR3 receptor antagonists (for example, CCL7); degradation of IL-1β, which alters local concentrations of this cytokine	118,121, 122
MMP1, MMP3	Production of CXCR3 receptor antagonists (for example, CCL2, CCL8 and CCL13)	128
MMP7	Cleavage of syndecan 1 and syndecan 4; cleaved syndecans bind to chemokines, which alters their local availability	129

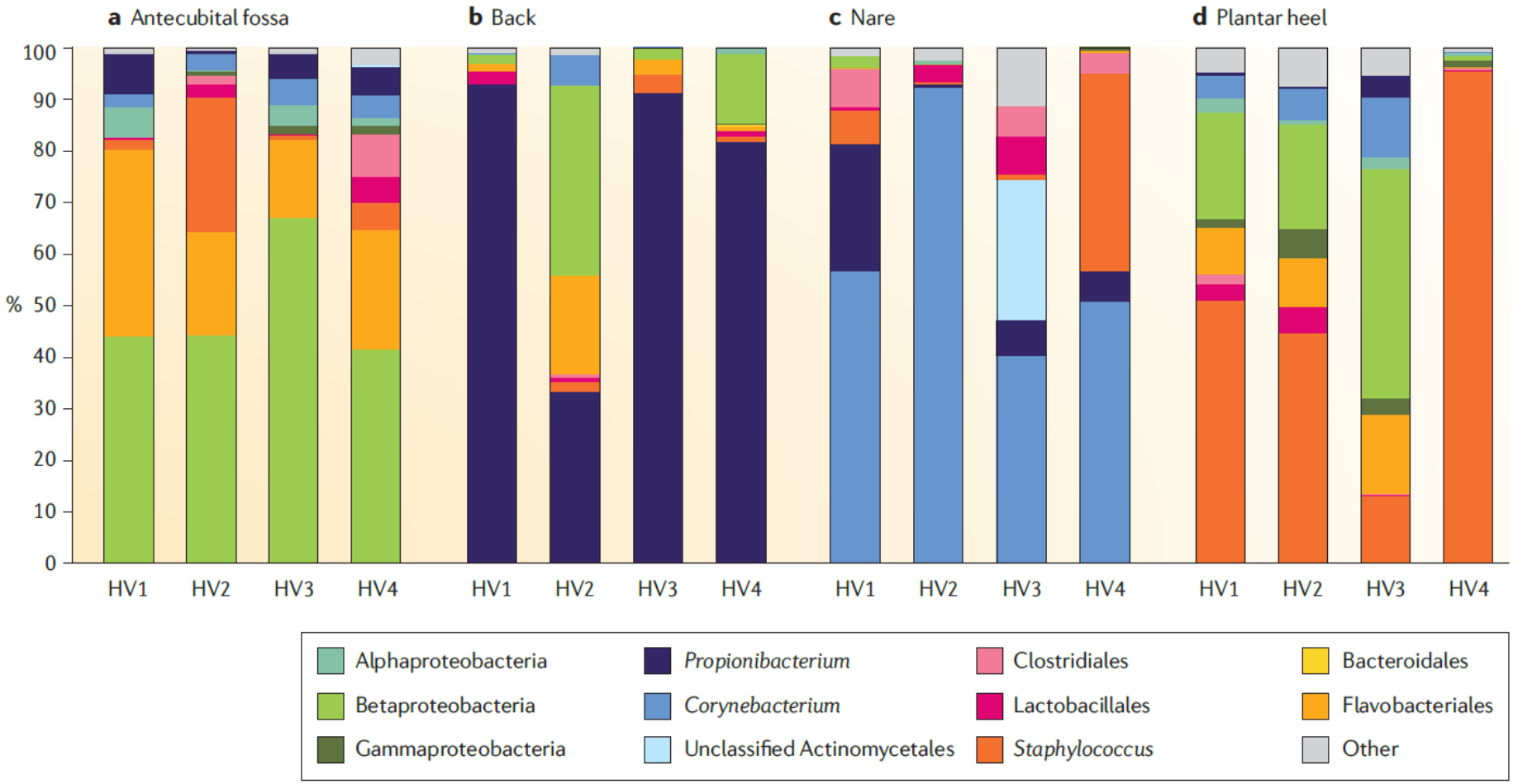
CCL, CC-chemokine ligand; CXCL, CXC-chemokine ligand; CXCR, CXC-chemokine receptor; ECM, extracellular matrix; IFNγ, interferon-γ; IL, interleukin; MMP, matrix metalloproteinases; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor.

Topographical distribution of bacteria on skin sites



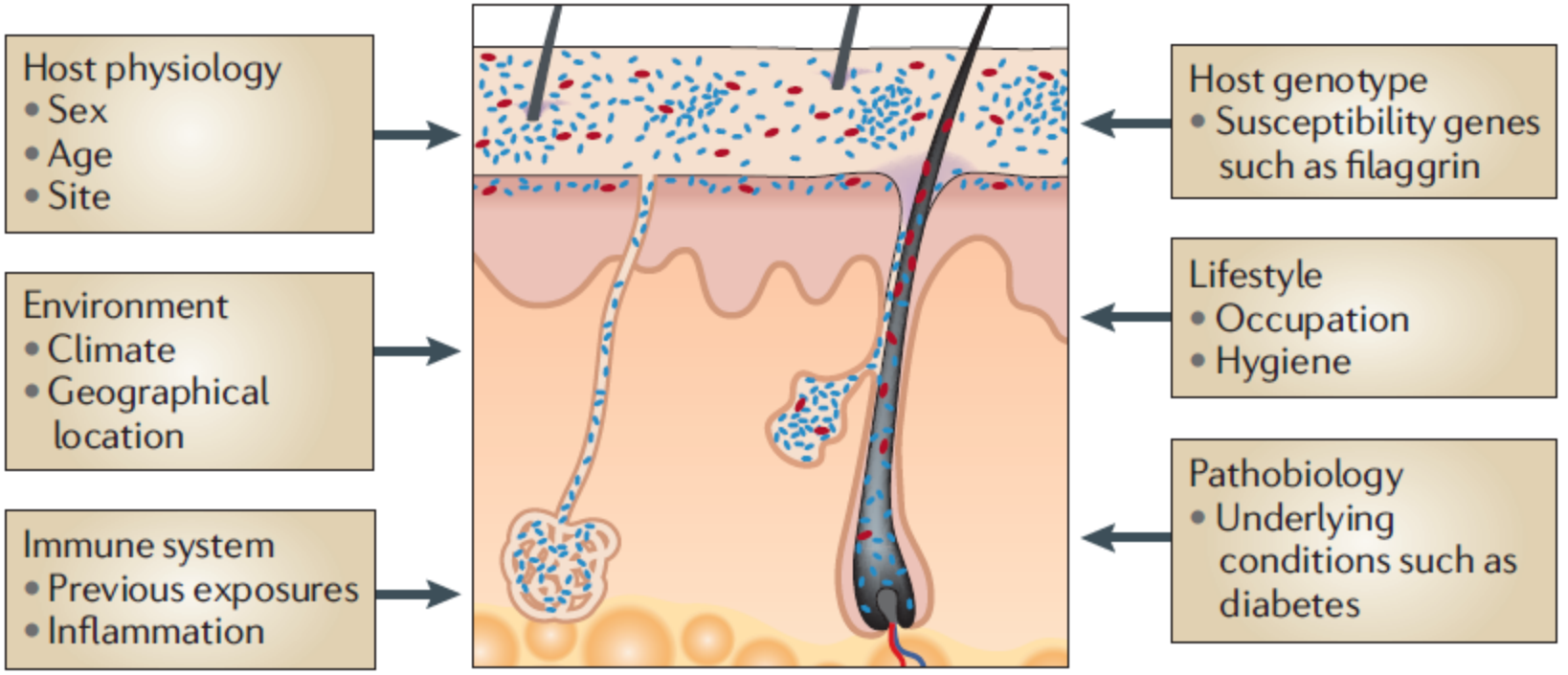
Grice E.A. and J. Segre, *Nat. Rev. Microbiol.* 9:244-253 (2011)

Interindividual variation of the skin microbiome



Grice E.A. and J. Segre, *Nat. Rev. Microbiol.* 9:244-253 (2011)

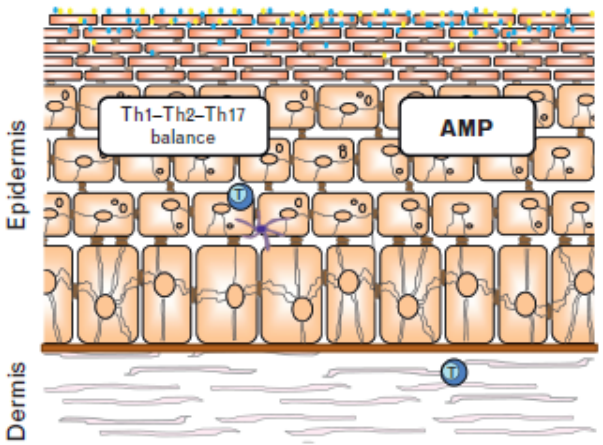
Factors contributing to the variation in the skin microbiome



Grice E.A. and J. Segre, *Nat. Rev. Microbiol.* 9:244-253 (2011)

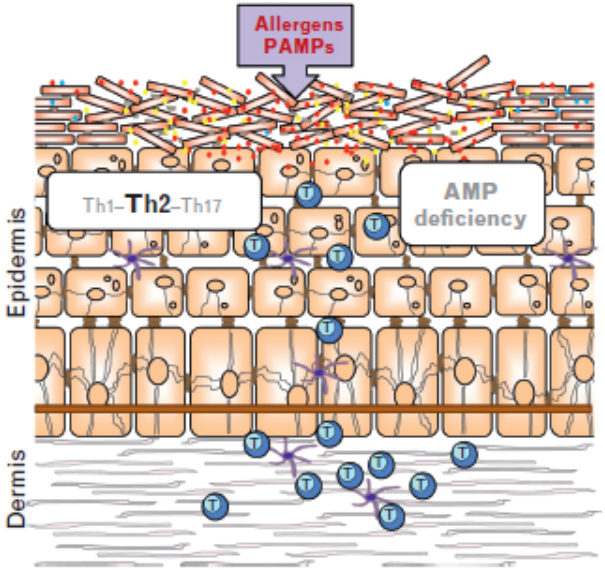
Skin microbiome, dysbiosis and inflammation

Homeostasis in normal skin



- Microbiome of healthy normal skin
- Intact epithelial barrier
- Adequate production of antimicrobial peptides
- Adequate response of innate and adaptive immune system (balanced Th1-Th2-Th17 response)

Dysbiosis and infection in atopic dermatitis

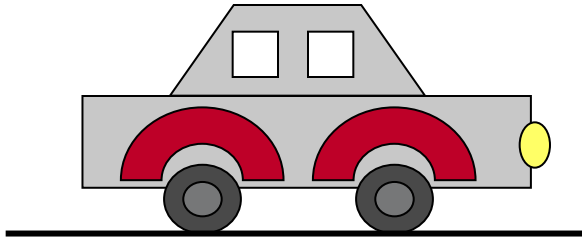


- Colonization by S. *aureus*
- Poor skin barrier
- Penetration of allergens and microbial components
- Inadequate production of antimicrobial peptides
- Th2 cytokine response predominates leading to poor skin barrier and suppression of innate host defense system

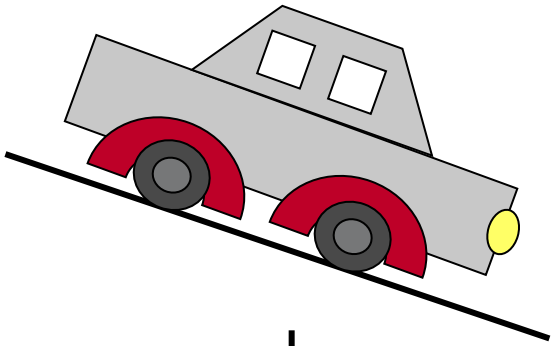
Zeeuwen P.L.J.M. et al., *Curr. Opin. Allergy Clin. Immunol.* 13:514-520 (2013)

Immune homeostasis – an active process

open break (passive)



closed break (active)

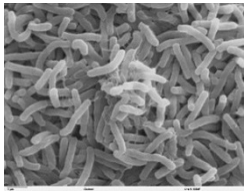


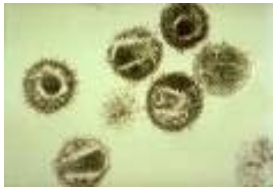
innate immune response
inflammation

overcome immunoregulatory default

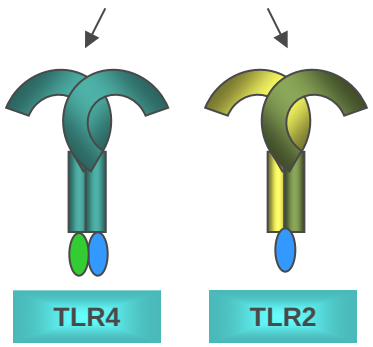
adaptive immune response

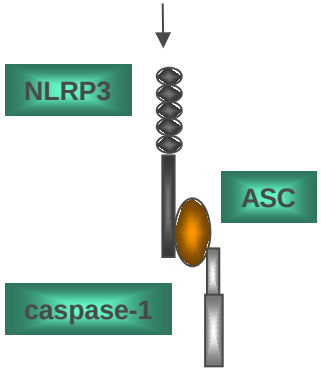
Danger signals activate the innate immune system and thereby trigger inflammation





LPS lipopeptide bact./viral RNA etc. bacteria/viruses





reactive oxygen species (ROS)

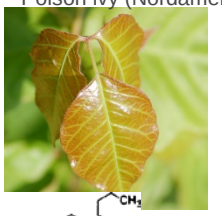
extracellular ATP

Toll-like receptors **NLRP3 inflammasome**

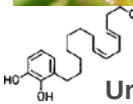
activation of the *innate* immune system -> inflammation: DC activation and migration

TLR, NLRP3 etc.: Pattern Recognition Receptors (PRR, Charles A. Janeway)

Danger signals activate the innate immune system and thereby trigger inflammation



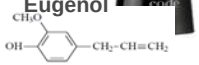
Poison ivy (Nordamerika)



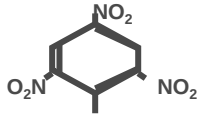
Urushiol

Chromium salts

fragrances



Eugenol



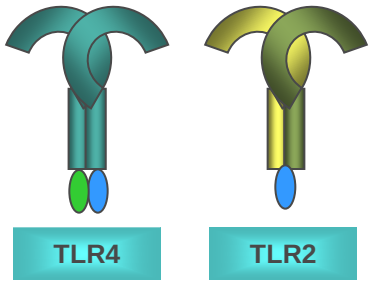
2,4,6-trinitrochlorobenzene

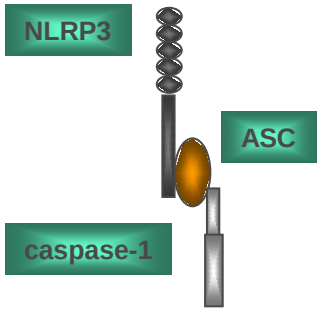
?

?

?

?





reactive oxygen species (ROS)

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Toll-like receptors

NLRP3 inflammasome

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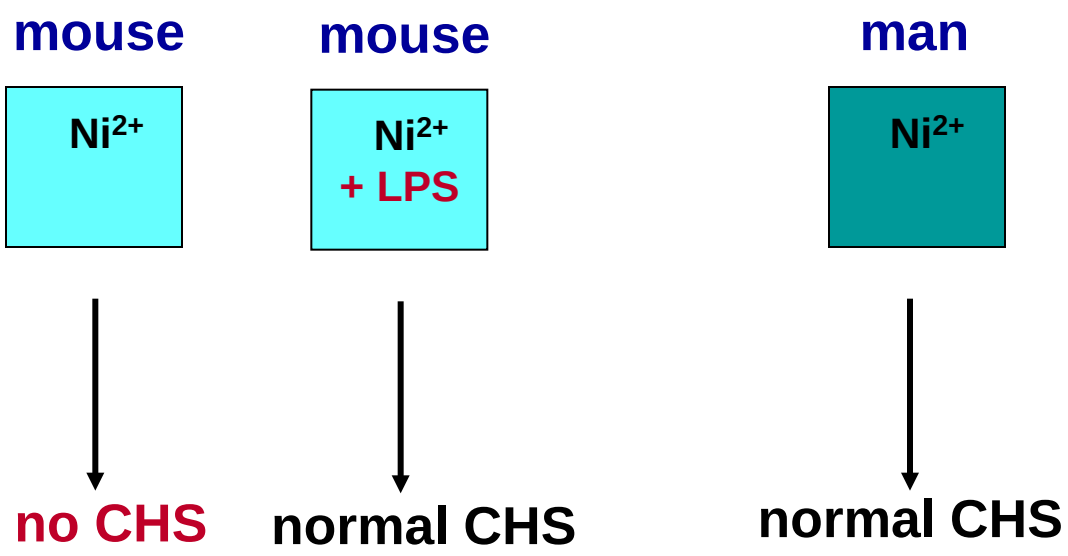
TLR, NLRP3 etc.: Pattern Recognition Receptors (PRR, Charles A. Janeway)

Species-specific differences in allergic contact dermatitis: LPS, a ligand for TLR4, povides the missing innate *danger signal*

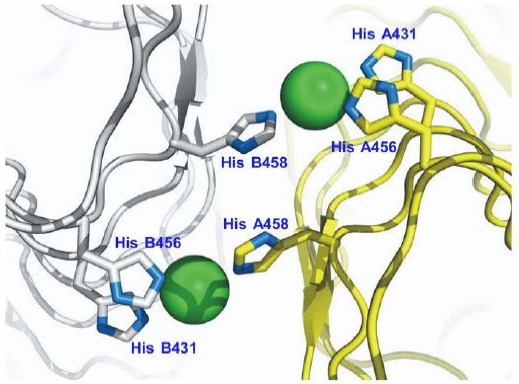


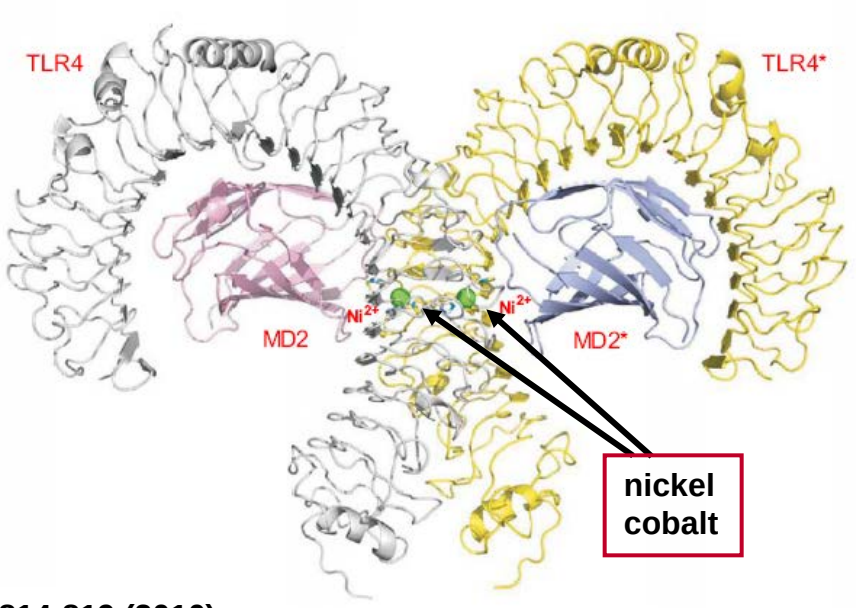
Nickel and cobalt bind directly to human but not mouse TLR4 and induce receptor dimerization

a

hTLR4	LRR14	DLPSLEFLDLSRNGLSFKGCCSQSDF	396
mTLR4	LRR14	ALPSLSYLDLSRNALSFSGCCSYSDL	394
hTLR4	LRR15	GTTSLKYLDLSFNGVITMSSNFL	419
mTLR4	LRR15	GTNSLRHLDLSFNGAIIMSANFM	417
hTLR4	LRR16	GLEQLEHLDFQHSNLKQMSEFSVFL	444
mTLR4	LRR16	GLEELQHLDFQHSTLKRVTEFSAFL	442
hTLR4	LRR17	SLRNLIYLDISHTHTRVAFNGIFN	468
mTLR4	LRR17	SLEKLLYLDISYTNTKIDFDGIFL	466
hTLR4	LRR18	GLSSLEVLKMAGNSFQENFLPDIFT	493
mTLR4	LRR18	GLTSLNTLKMAGNSFKDNTLSNVFA	491
hTLR4	LRR19	ELRNLTFLDLSQCQLEQLSPTAFN	517
mTLR4	LRR19	NTTNLTFLDLSKCQLEQISWGVFD	515
hTLR4	LRR20	SLSSLQVLNMSHNNFFSLDTFPYK	541
mTLR4	LRR20	TLHRLQLLNMSHNNLLFLDSSHYN	539
hTLR4	LRR21	CLNSLQVLDYSLNHIMTSKKQELQH	566
mTLR4	LRR21	QLYSLSTLDCSFNRIETSKGI-LQH	563
hTLR4	LRR22	FPSSLAFLNLTQNDFA	582
mTLR4	LRR22	FPKSLAFFNLTNNSVA	579
hTLR4	LRRCT	CTCEHQSFLQWIKDQRQLLVEVERM	607
mTLR4	LRRCT	CICEHQKFLQWVKEQKQFLVNVEQM	604

b

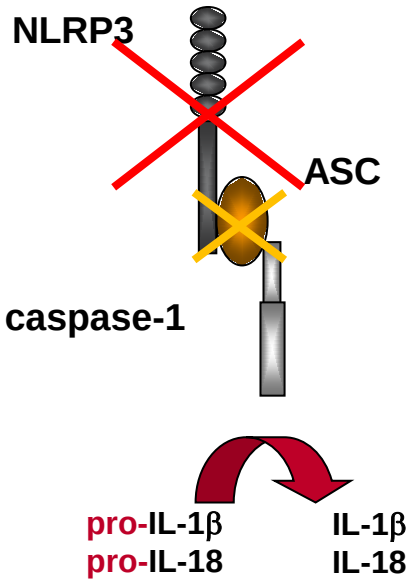


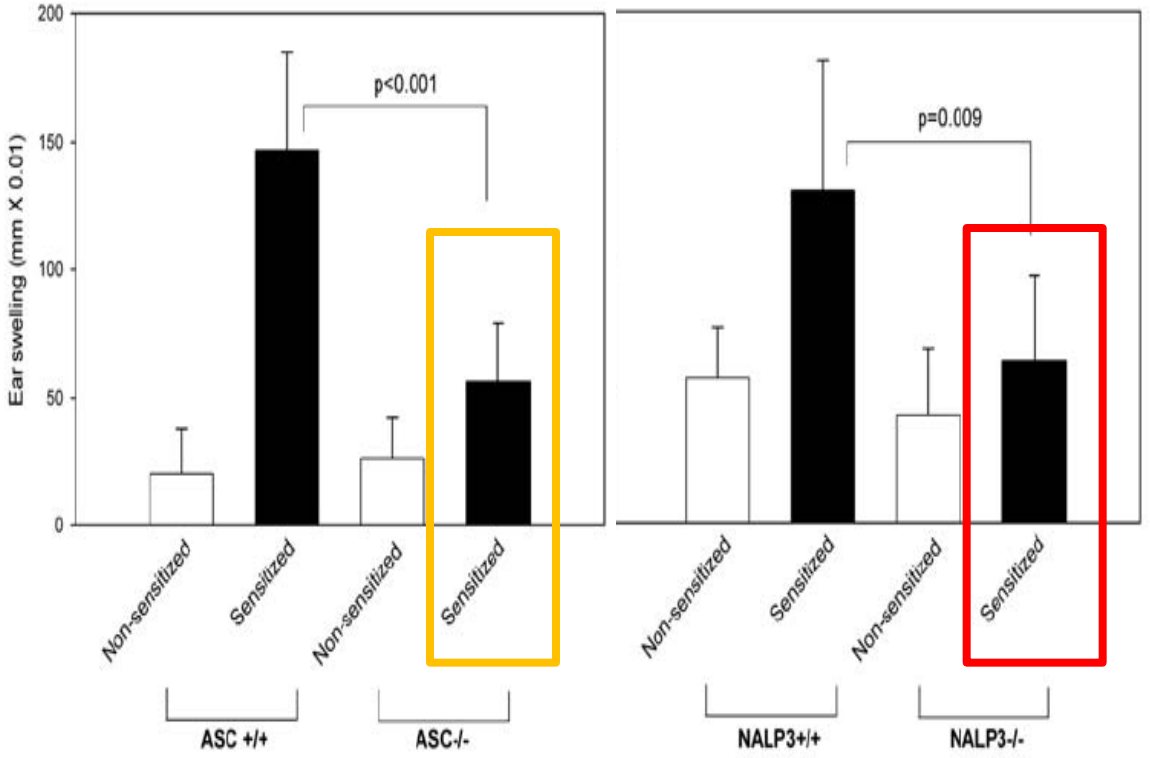


Schmidt, M. et al., *Nat. Immunol.* 11:814-819 (2010)
Raghavan B. et al., *EMBO Rep*. 13:1109-1115 (2012)

ALLERGY Research Group

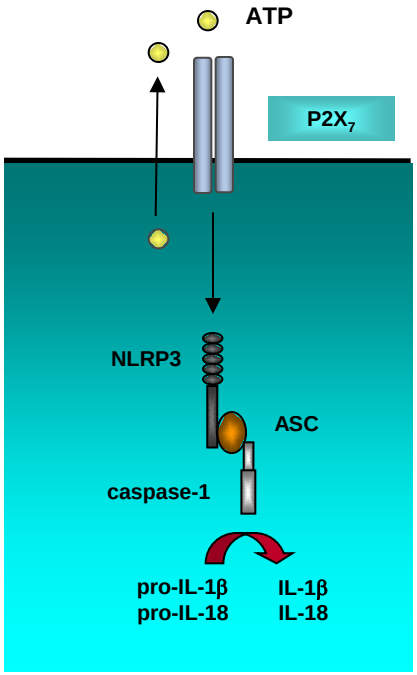
ASC- or NLRP3-deficient mice fail to develop CHS to TNCB



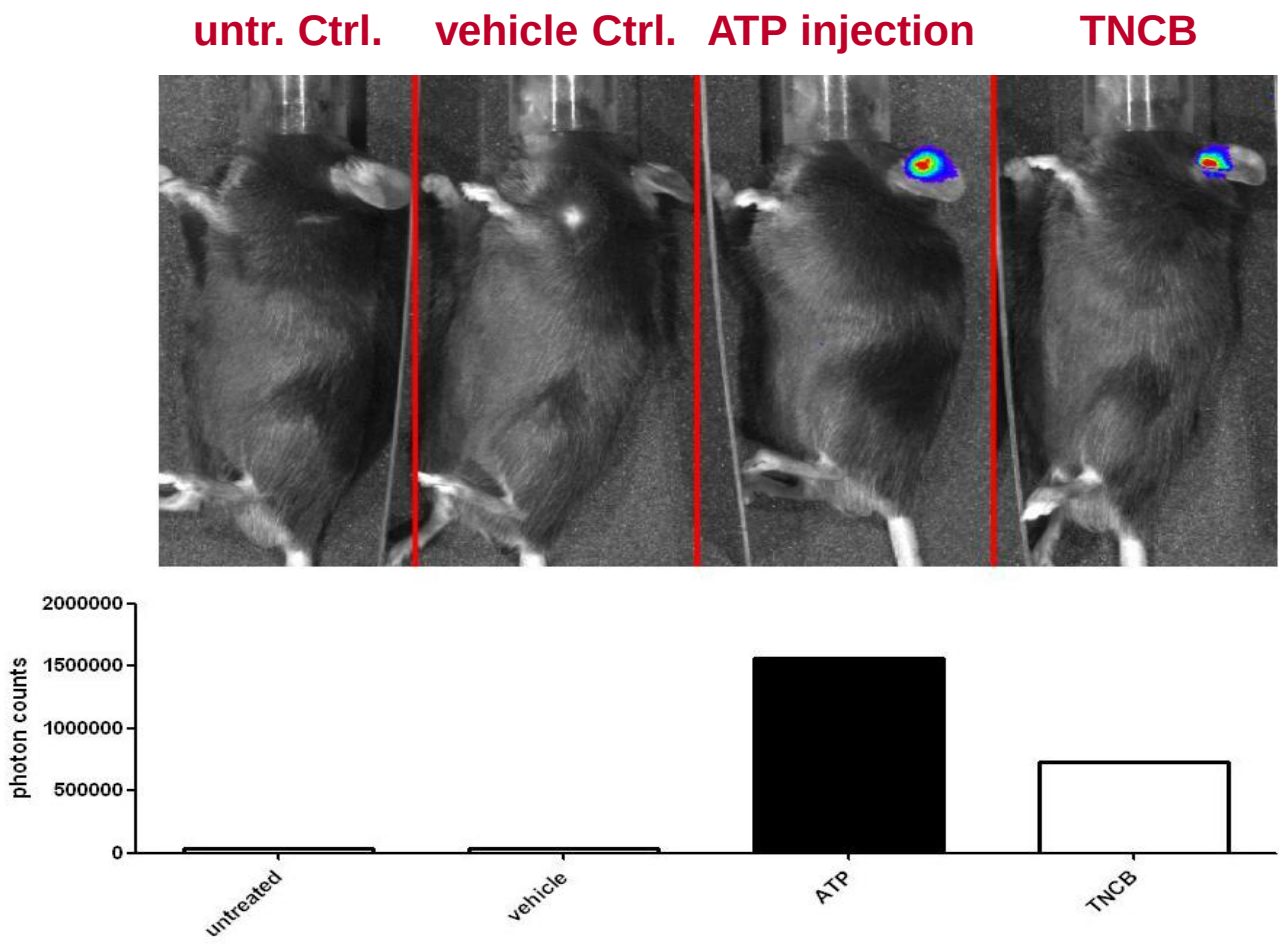


Sutterwala F.S. et al., *Immunity* 24:317-327 (2006)

NLRP3 inflammasome activation by the endogenous *danger signal* ATP and the purinergic receptor $P2X_7$

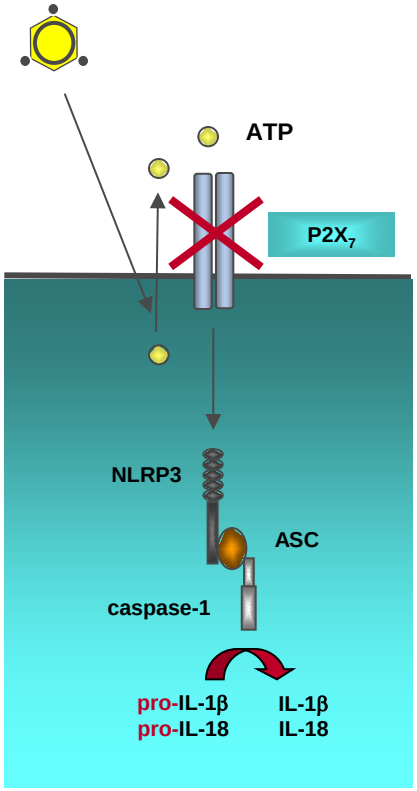


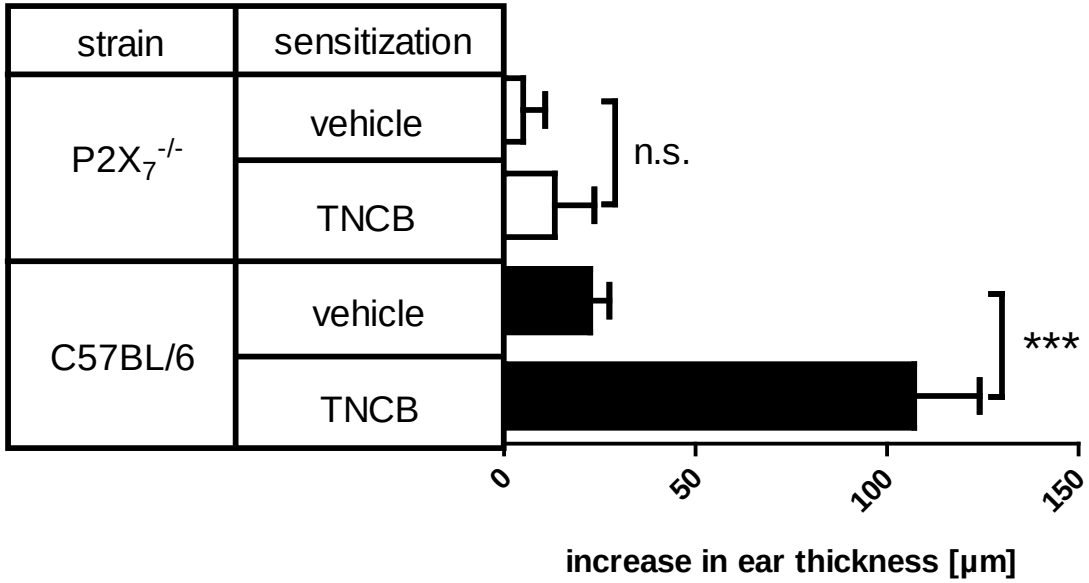
ATP release in the skin triggered by TNCB application



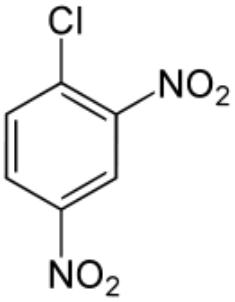
Weber F.C. et al., *J. Exp. Med.* 207:2609-2619 (2010)

$P2X_7$-deficient mice are resistant to contact hypersensitivity (CHS)

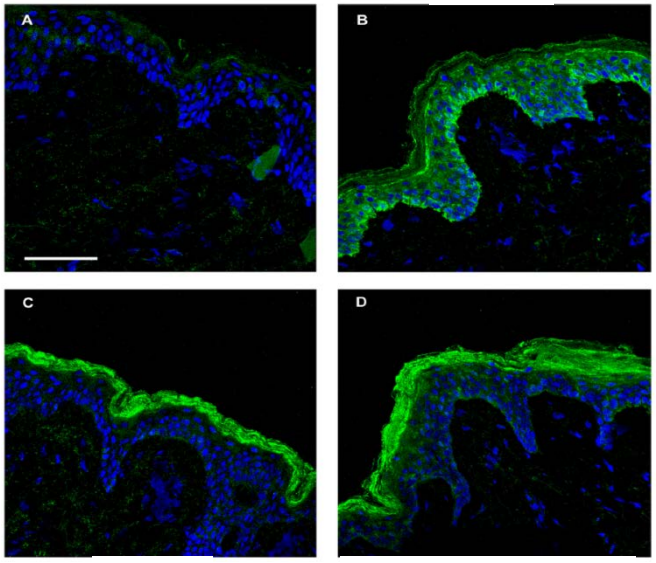




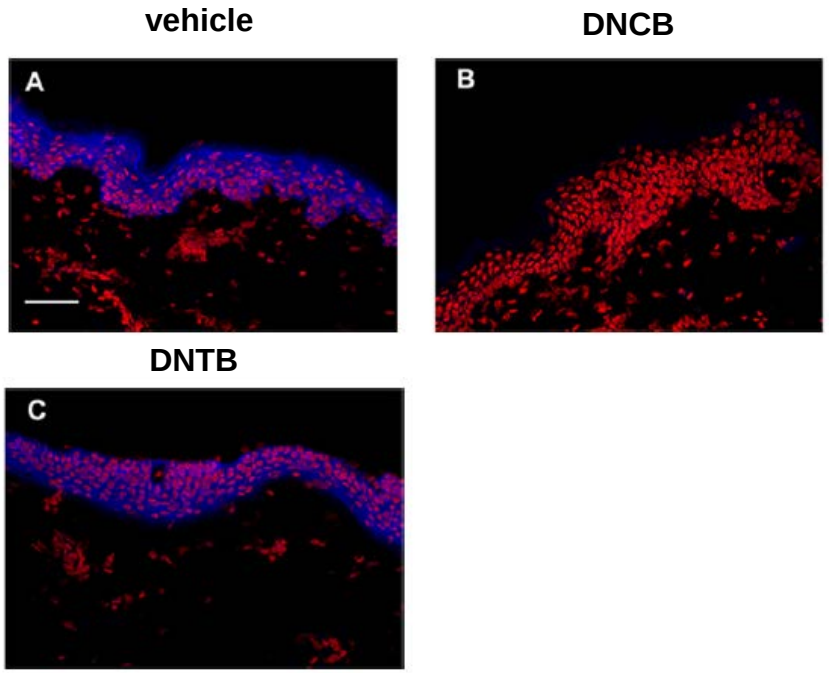
Differences between the strong contact allergen DNCB and the weak contact allergen/tolerogen DNTB

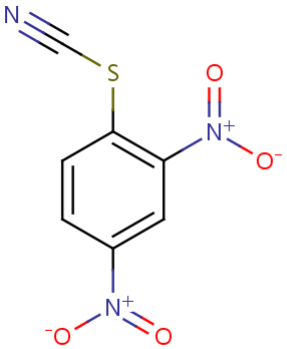


skin penetration

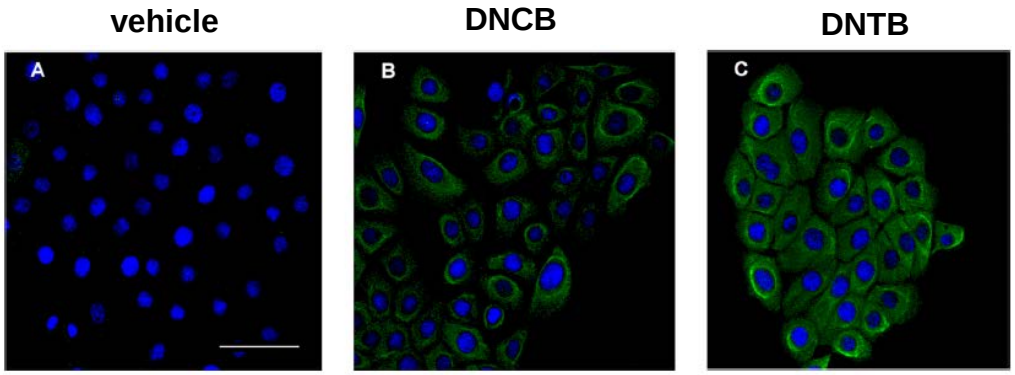


glutathione depletion





protein haptenation



Pickard C. et al., *J. Immunol.* 183:7576-7584 (2009)

Summary

- Danger signals are essential for activation of the innate immune system
- Contact allergens are danger signals (nickel, cobalt, palladium) or induce their release/formation
- Inflammation overcomes the immunological barrier (opening the brake)

Other mechanisms and therapeutic relevance to be discussed by Dr. Philipp Esser