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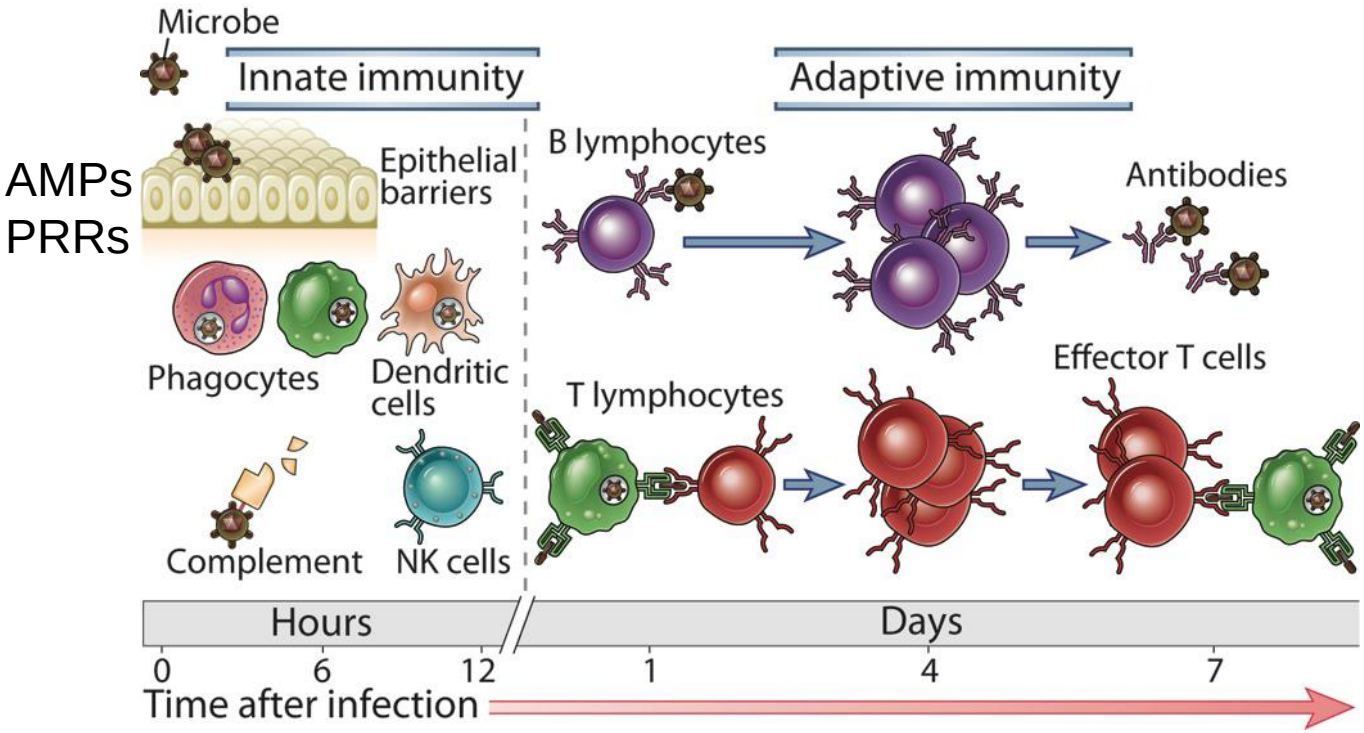
# Cutaneous Innate Immune Sensing of Toll-like Receptor 2-6 Ligands Suppresses T Cell Immunity by Inducing Myeloid-Derived Suppressor Cells

Skabytska Y. *et al.,* Immunity 41, 762–775 (2014)

Tanja Berger

# Immune system




Abbas *et al*., Cellular and Molecular Immunlogy (7th edition, 2012)

Innate immune system:

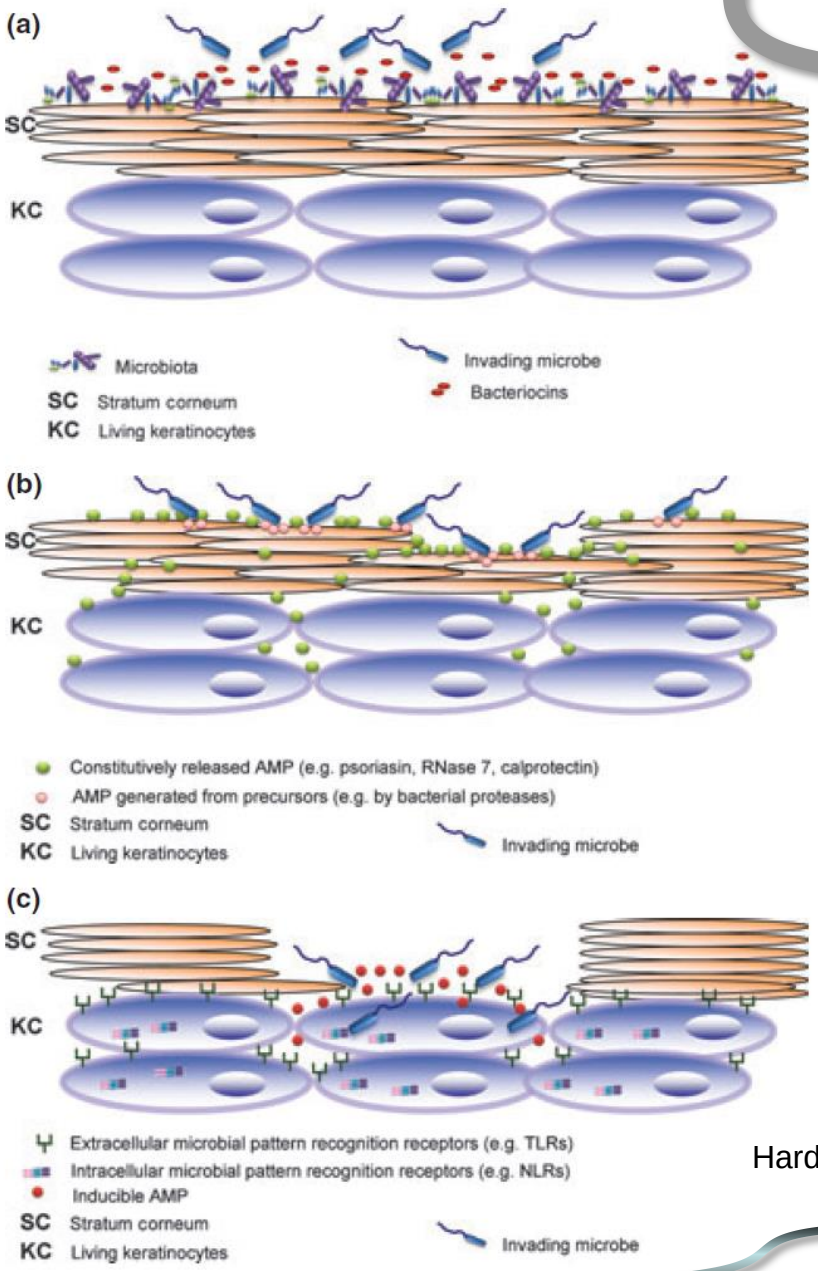
first line of host defense against microbes

One of the most potent skin pathogens: *Staphylococcus aureus* (*S. aureus*)

➔can cause life-threatening diseases

**Atopic dermatitis (AD):**

200-fold increased *S. aureus* colonization




Harder J. *et al.*, Exp.Dermatol (2013)

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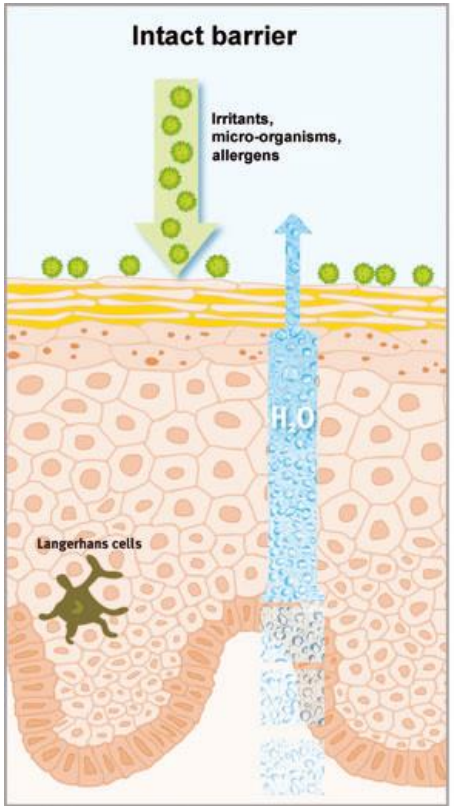
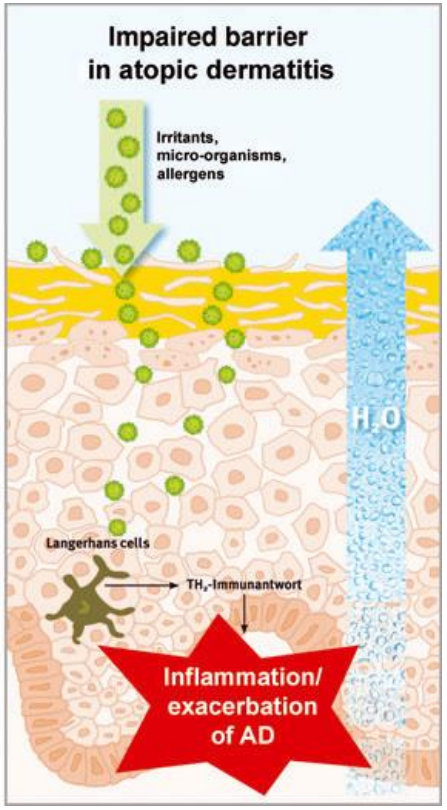
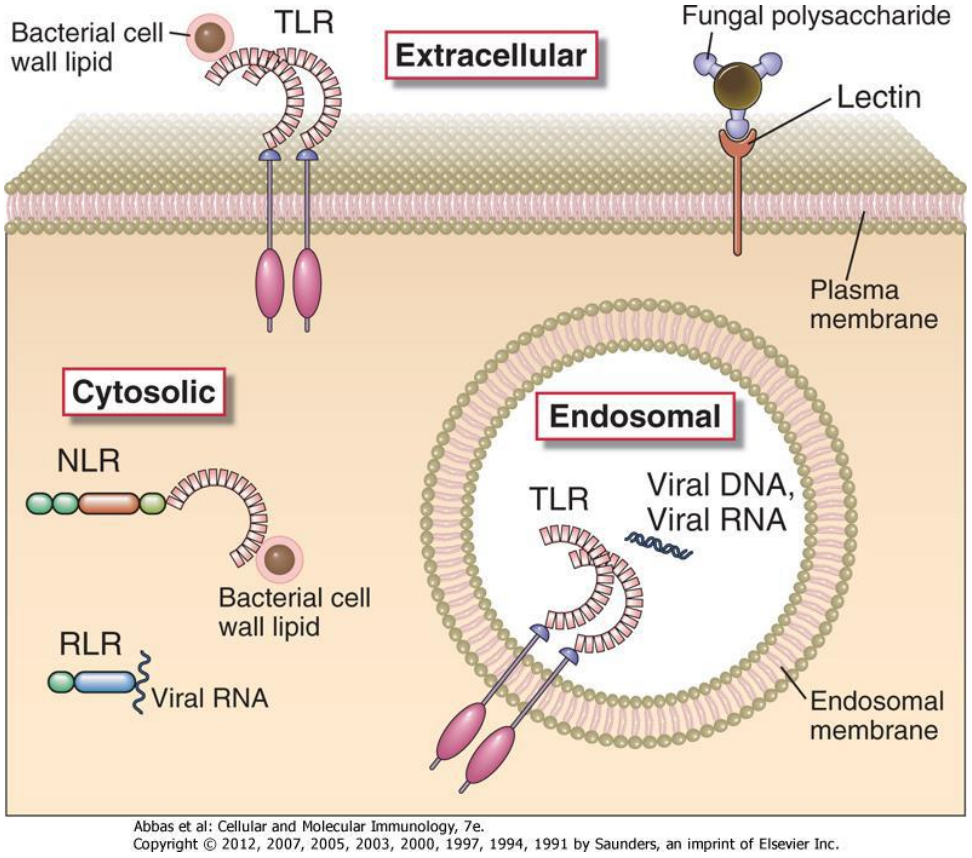


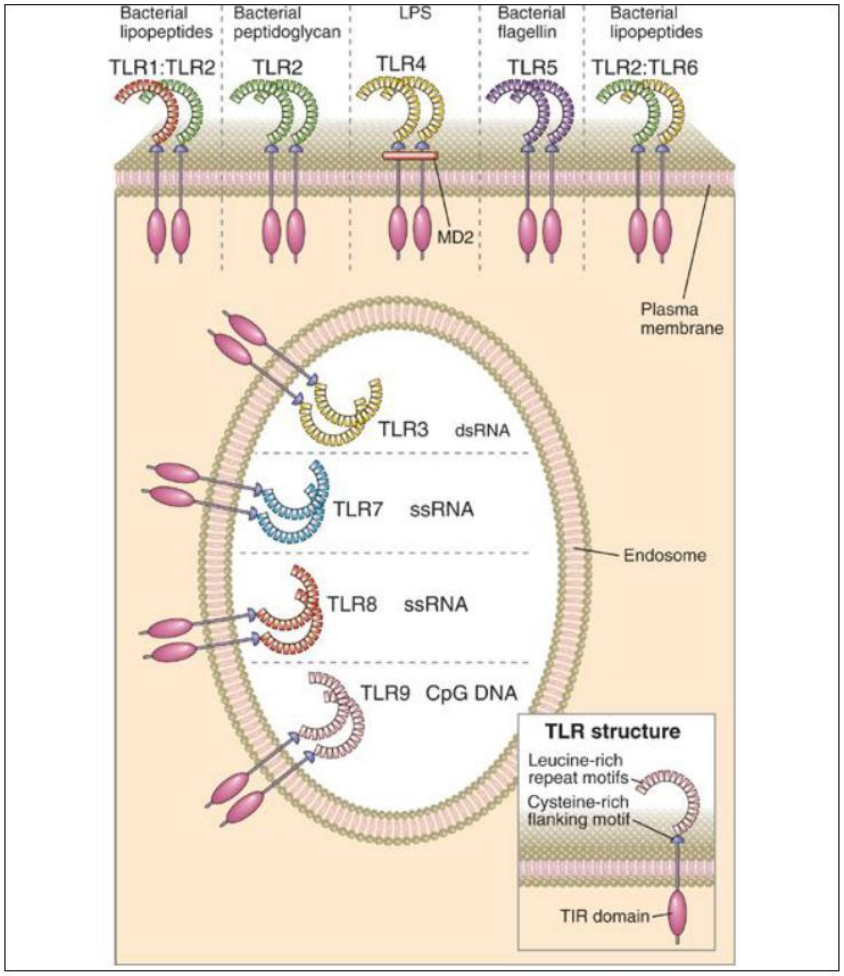




Proksch E. et al., JDDG; 7:899–910 (2009)

# Pattern recognition receptors




Abbas et al: Cellular and Molecular Immunology, 7e.


Abbas et al., Cellular and Molecular Immunlogy (7th edition, 2012)

TLR: Toll- like receptors
NLR: NOD- like receptors
RLR: RIG- like receptors

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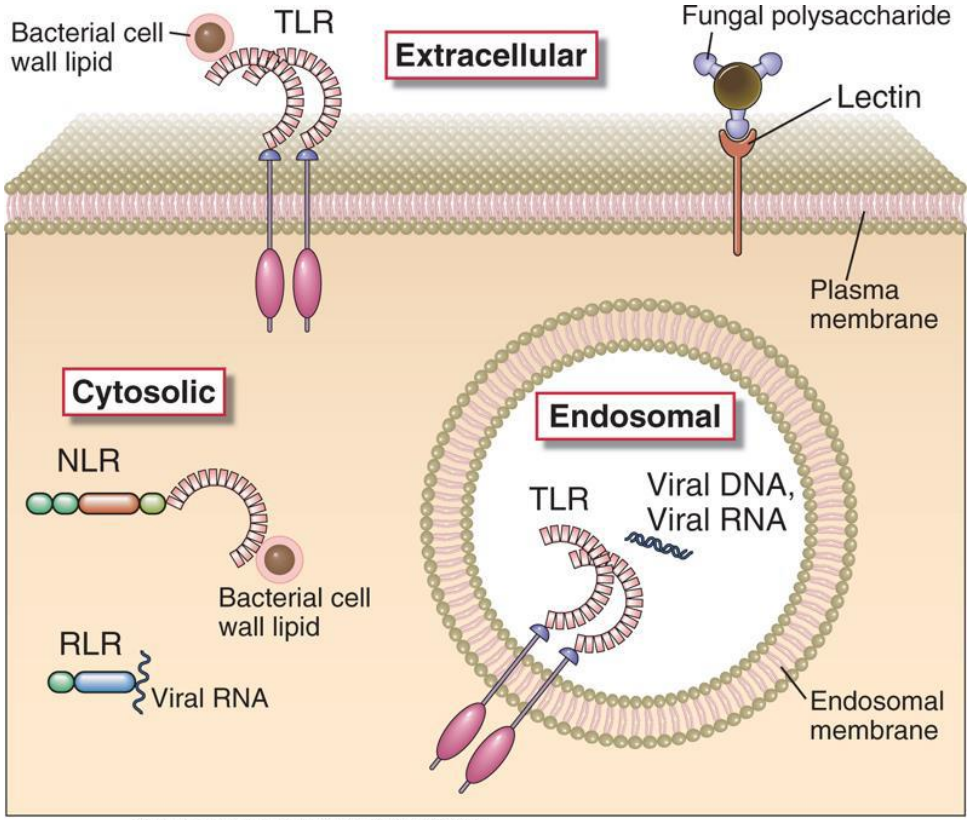
# Pattern recognition receptors

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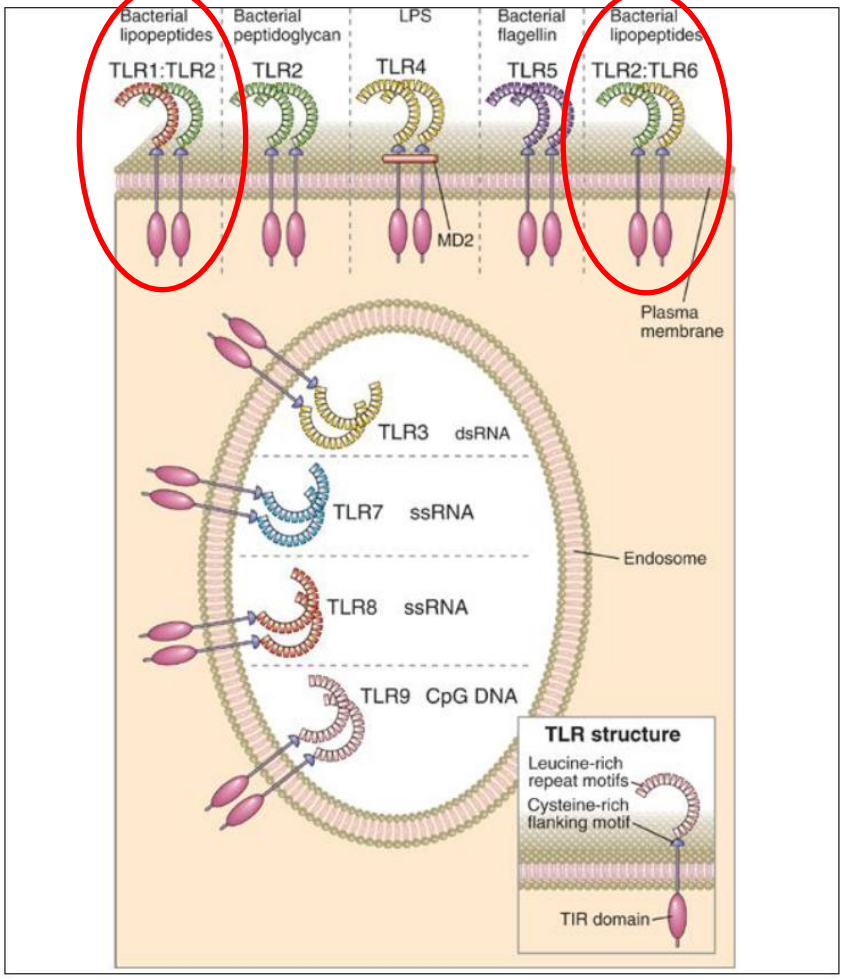


Abbas et al., Cellular and Molecular Immunlogy (7th edition, 2012)

TLR: Toll- like receptors
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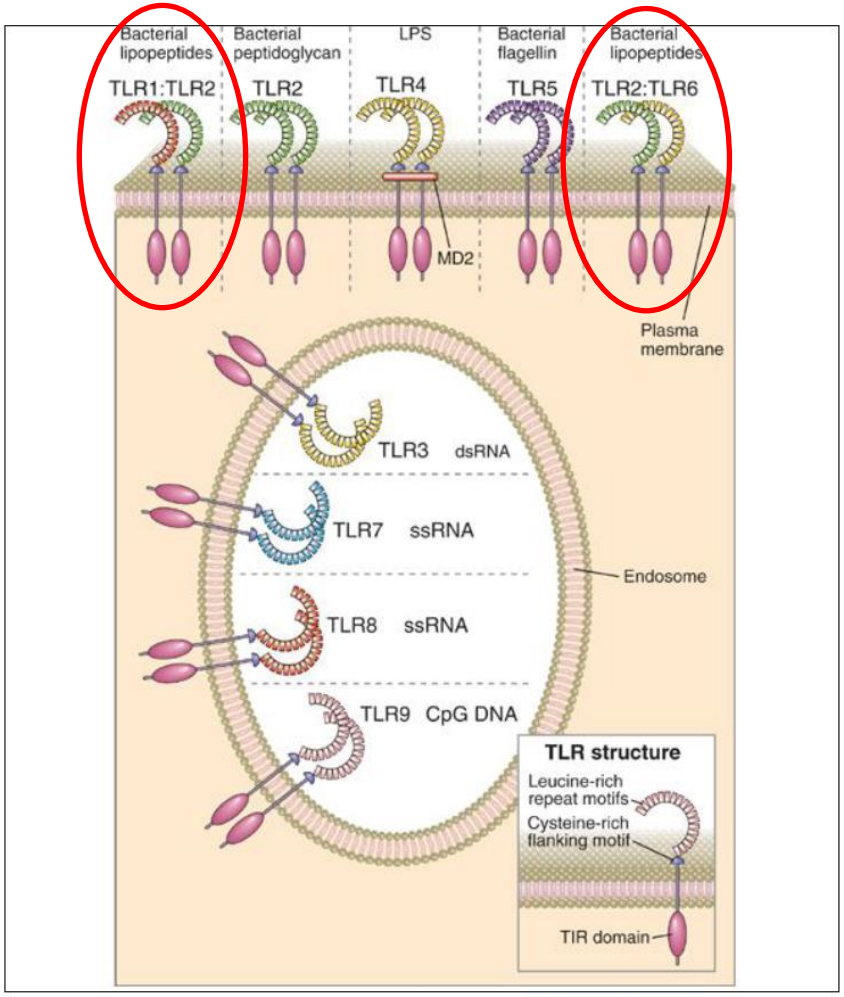
# Pattern recognition receptors

**TLR2 receptor for *S. aureus:***

TLR2-1 recognizes triacylated lipopeptids (e.g. Pam3Cys)

TLR2-6 recognizes diacylated lipopeptids (e.g. FSL-1, Pam2Cys)



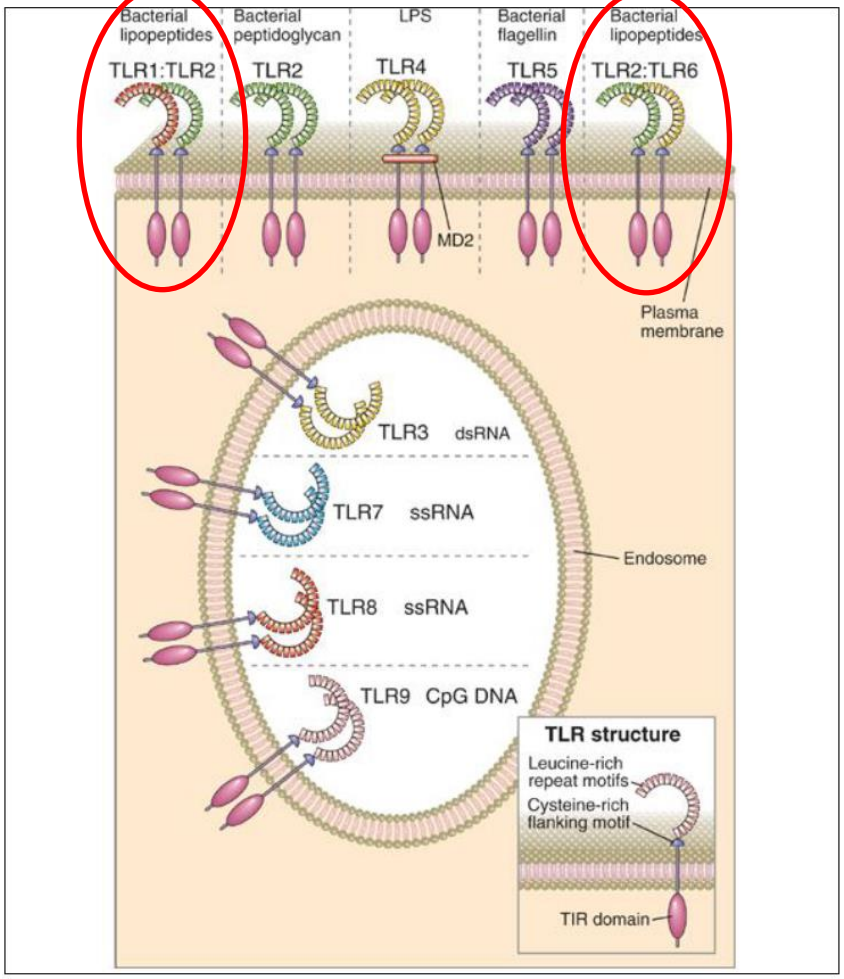

Abbas et al., Cellular and Molecular Immunlogy (7th edition, 2012)

# Pattern recognition receptors

Sustained activation of TLRs causes persistent production of proinflammatory cytokines:

- tumor necrosis factor (TNF)
- interleukin-6 (IL-6)

➔tissue damage

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# Pattern recognition receptors

Sustained activation of TLRs causes persistent production of proinflammatory cytokines:

- tumor necrosis factor (TNF)
- interleukin-6 (IL-6)

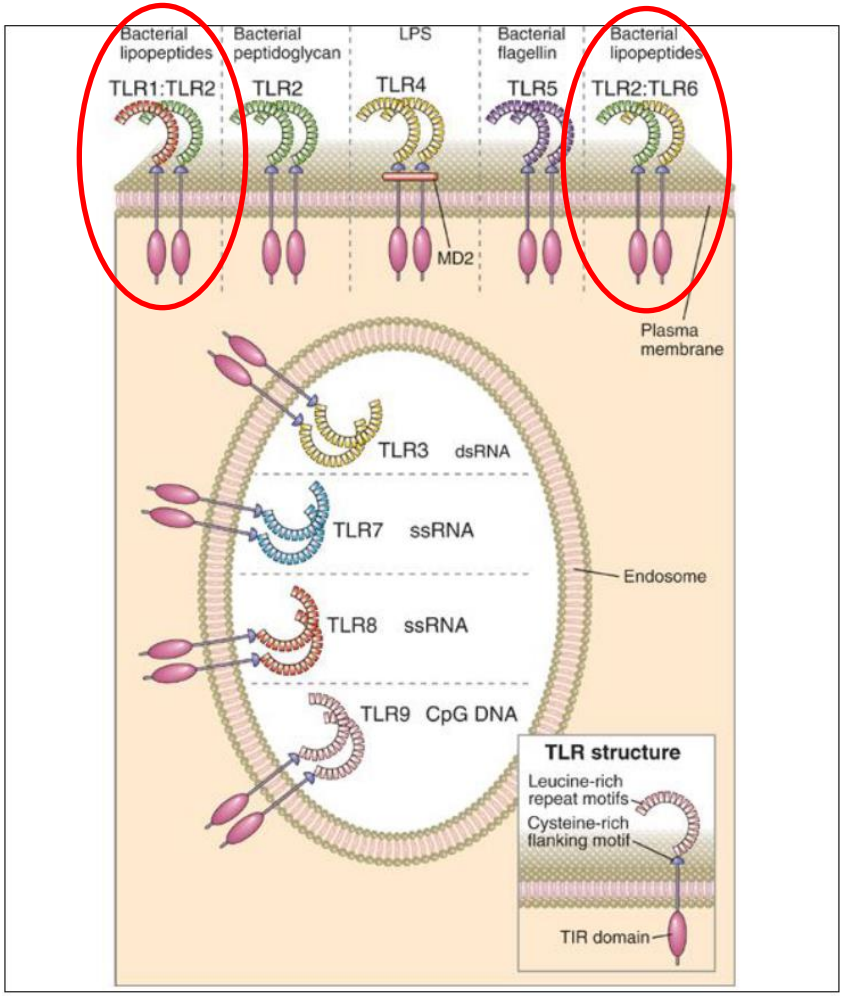
➔tissue damage

**Mechanisms to limit cutaneous inflammation:**

e.g. Gr1+CD11b+ myeloid-derived suppressor cells (MDSCs)

or regulatory T cells (Tregs)

➔ Suppression of T cells




Abbas et al., Cellular and Molecular Immunlogy (7th edition, 2012)

# Better characterization of skin-driven immunity

Specific functional consequences for the activation of different heterodimers *in vivo*

➔ Application of living *S. aureus* and specific lipopeptides onto healthy and dermatitis-induced skin

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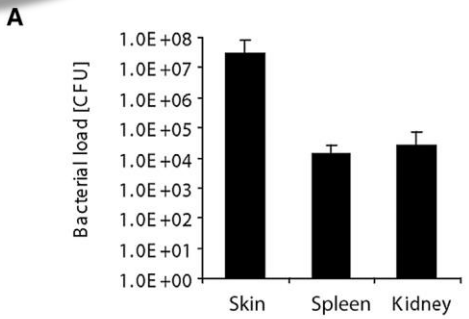
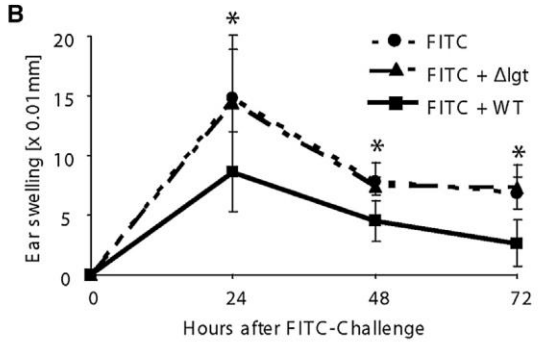
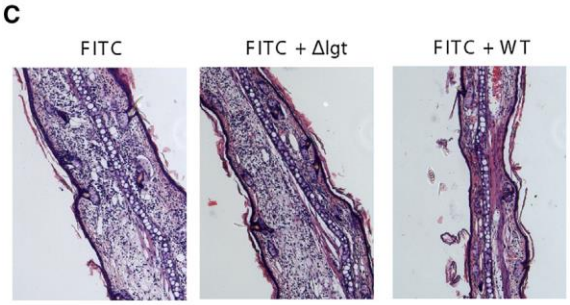
# *S. aureus* induces immune suppression

Application of living *S. aureus*

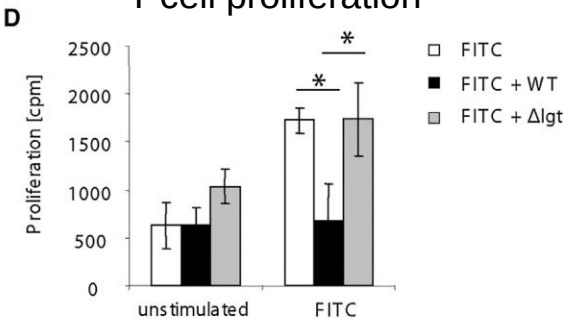


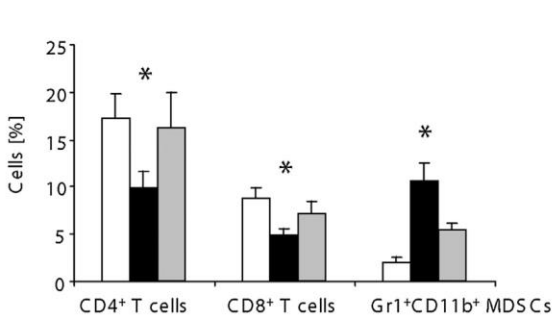

ΔIgt: lipoprotein-deficient *S. aureus*

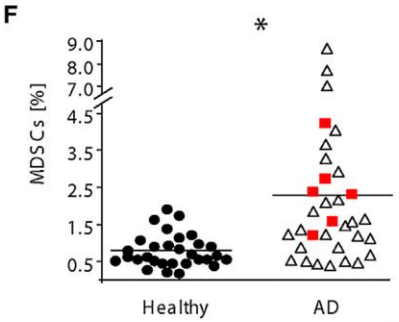



T cell proliferation




Gr1+CD11b+ myeloid-derived suppressor cells (MDSCs)




Human

Skabytska Y. *et al.*, Immunity 41, 762–775 (2014)

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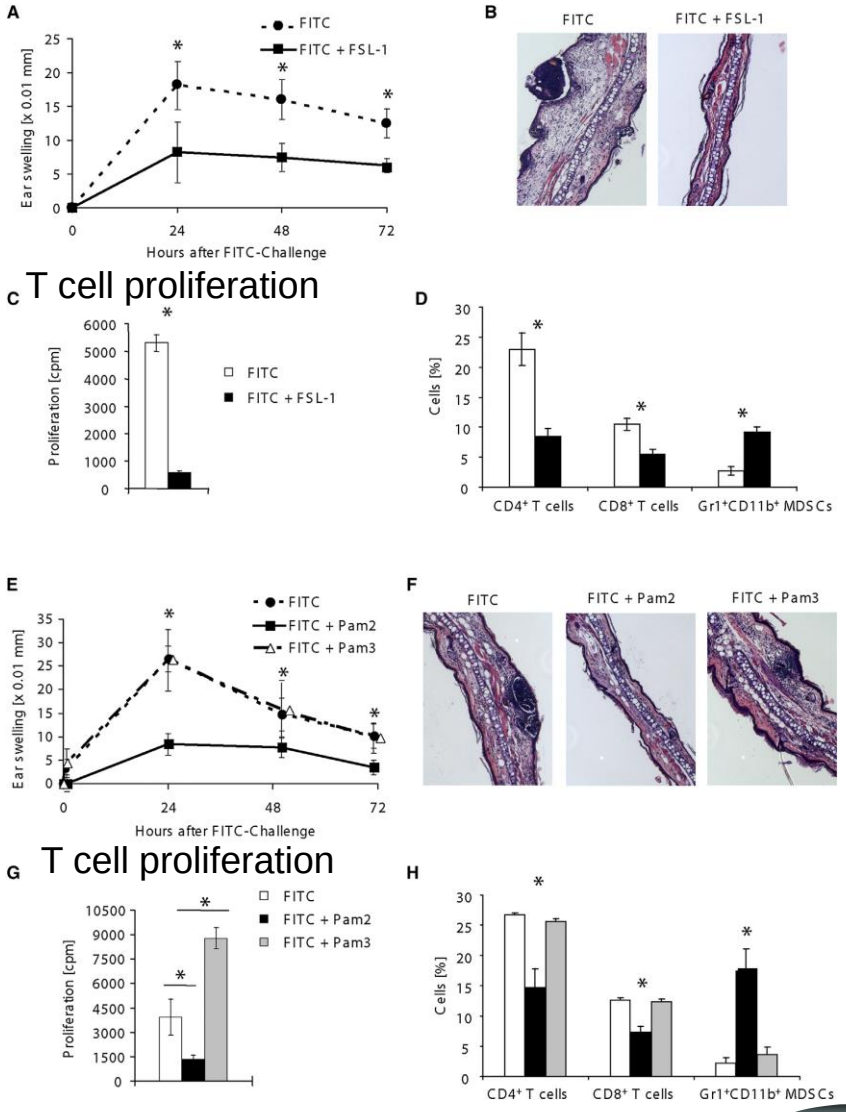
# TLR2-6 responsible for immune suppression

TLR2-1 recognizes triacylated lipopeptids (e.g. Pam3Cys)

TLR2-6 recognizes diacylated lipopeptids (e.g. FSL-1, Pam2Cys)

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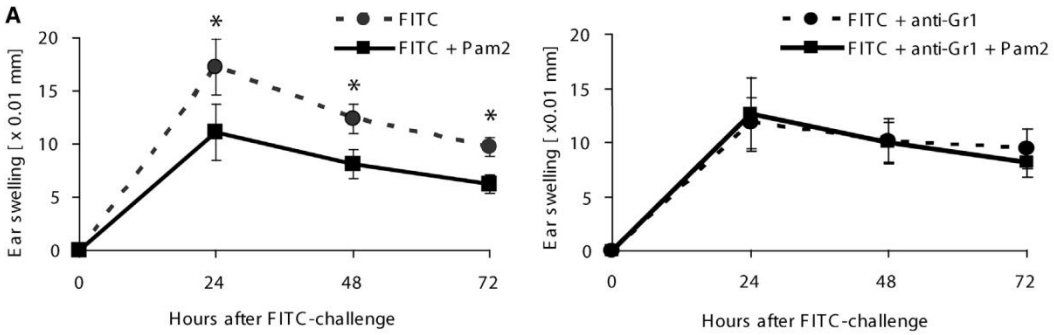
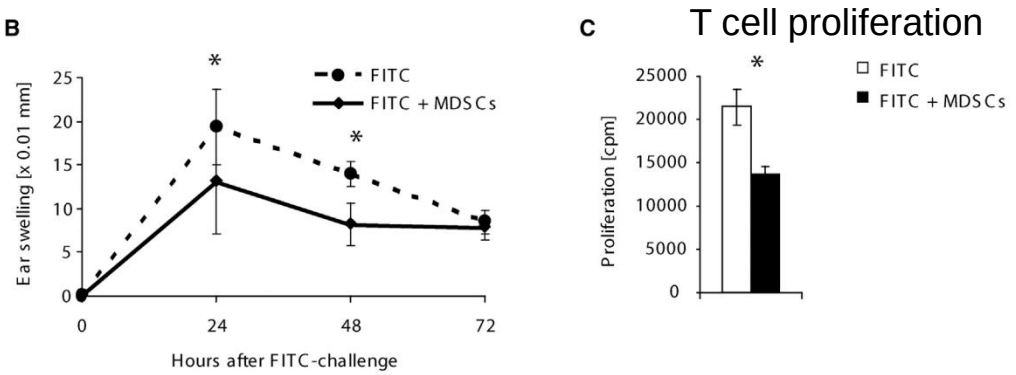
# Immune suppression mediated by MDSCs




Anti-Gr1:

Depletion of Gr1+ cells

Adoptive transfer of MDSCs

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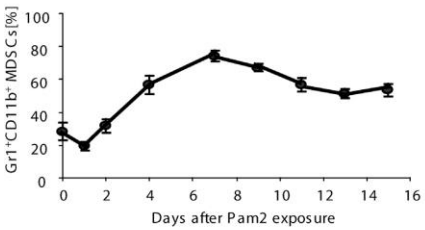
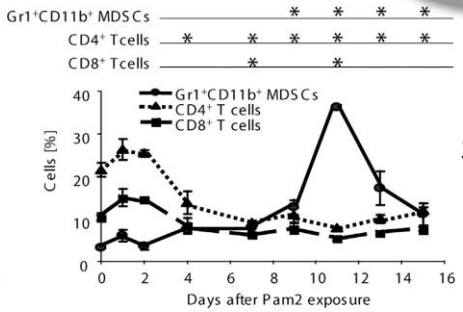
# MDSCs accumulation

Bone marrow

Spleen

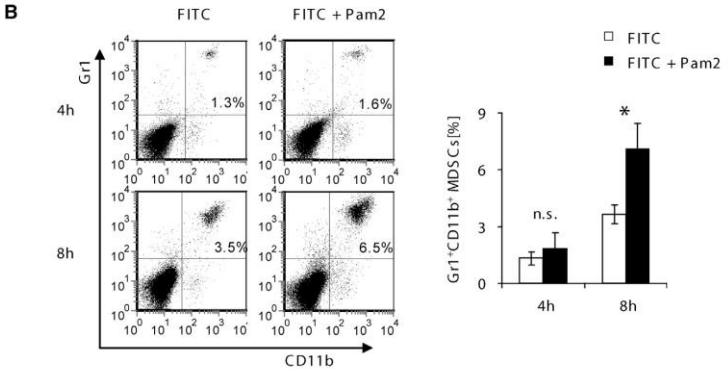
Mice



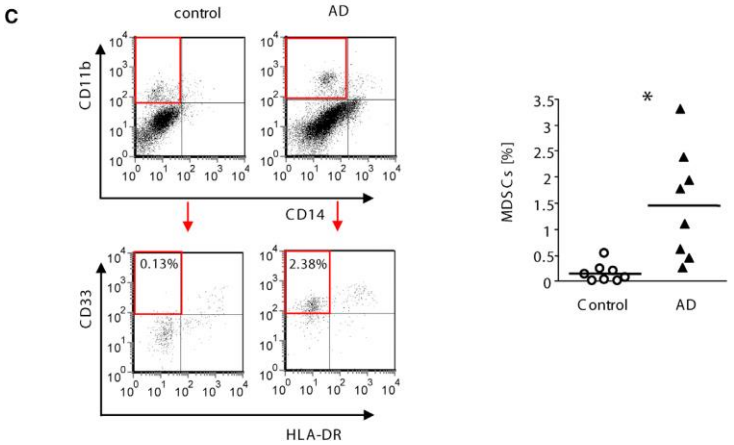

Mice

Skin




Human

Skin

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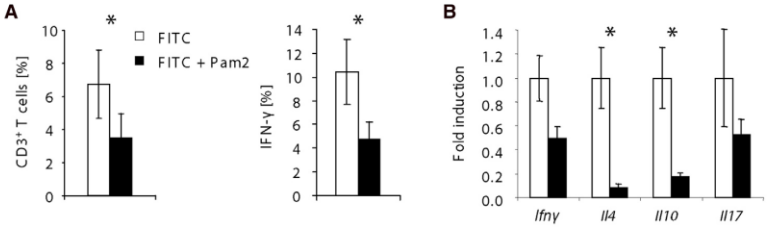
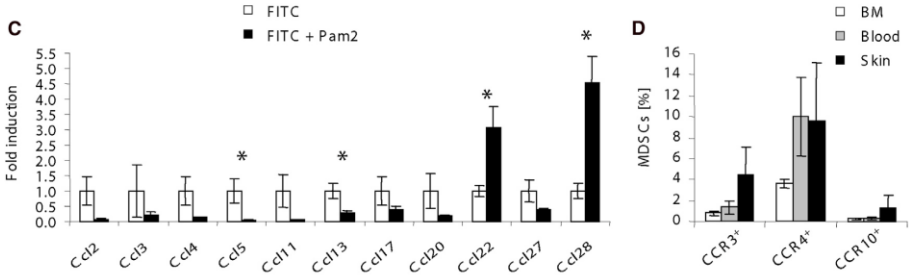
# Cytokine and chemokine expression

CD3 expressed on T cells




T cell attracting:

- Ccl22 ligand for CCR4
- Ccl28 ligand for CCR10




Chemokine receptors expressed on MDSCs

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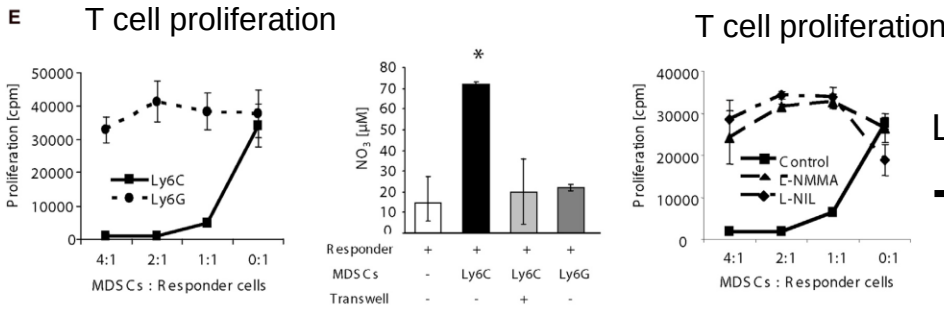
# MDSCs

## immunosuppressive activity

Anti-CD3-CD28 stimulation

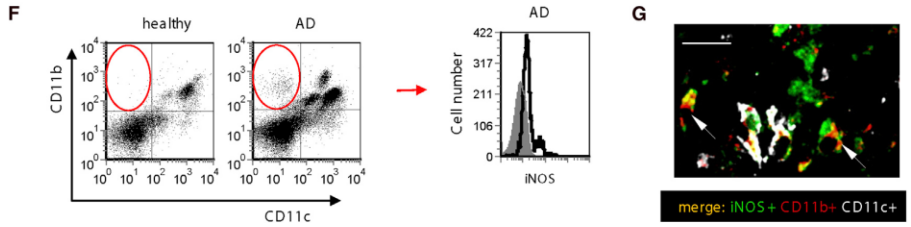
➔T cell activation/ proliferation




L-NMMA and L-NIL

➔inhibiting iNOS

Human




Skin tissue of AD

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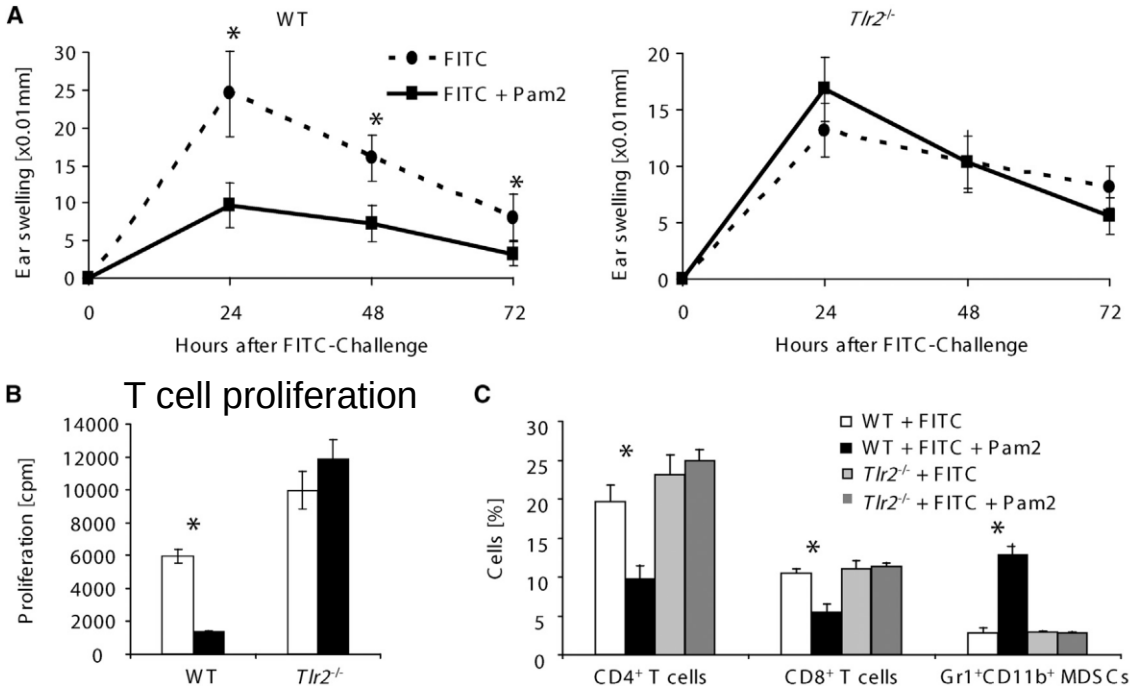
# Immune suppression dependent on TLR2

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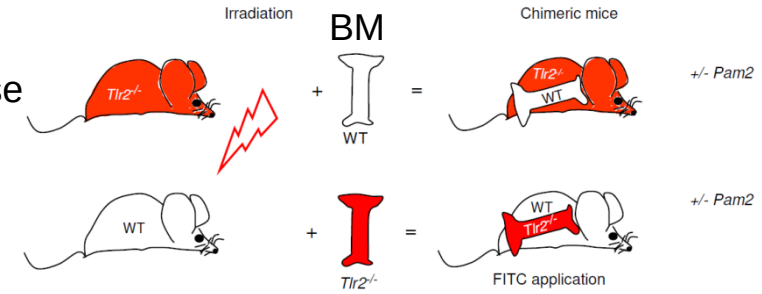
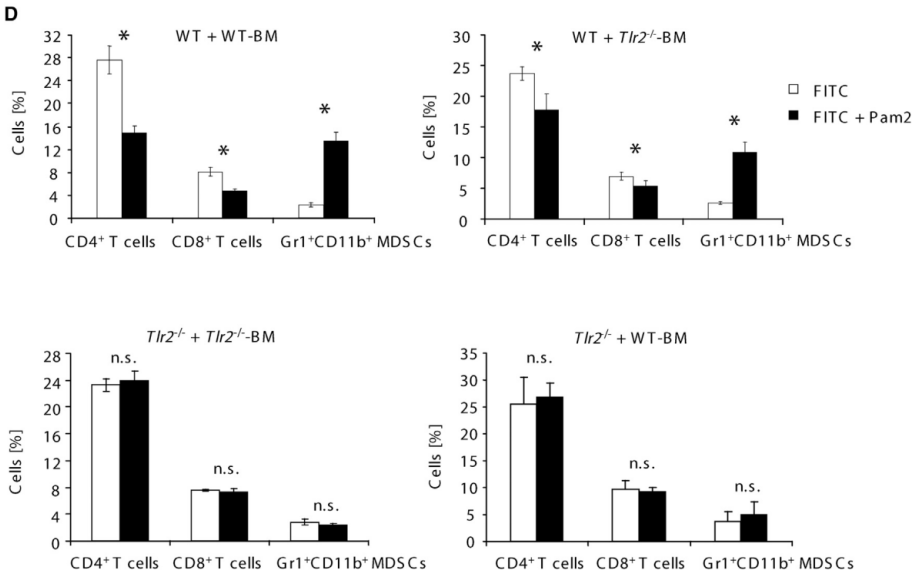
# TLR2 sensing through skin resident cells or hematopoietic cells?

Tlr2-/- means Tlr2 knock out mouse

BM= Bone marrow cells

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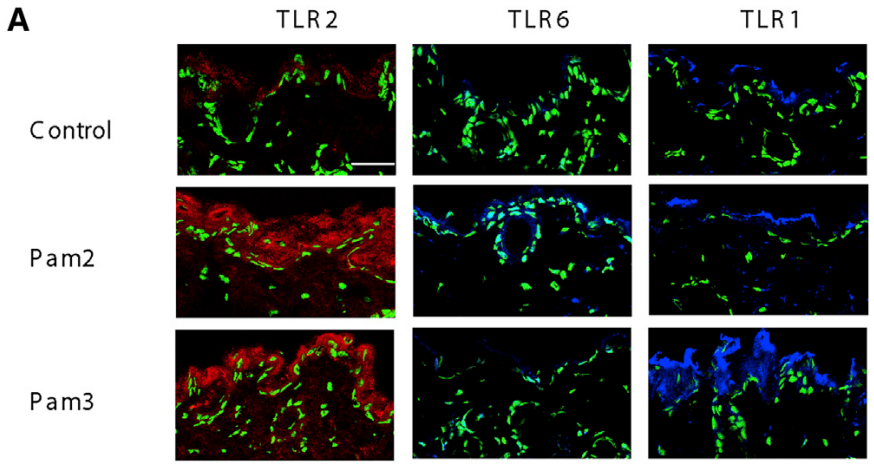
# TLR expression after stimulation




Red: TLR2 Blue: TLR6 Blue: TLR1

Green: nuclei

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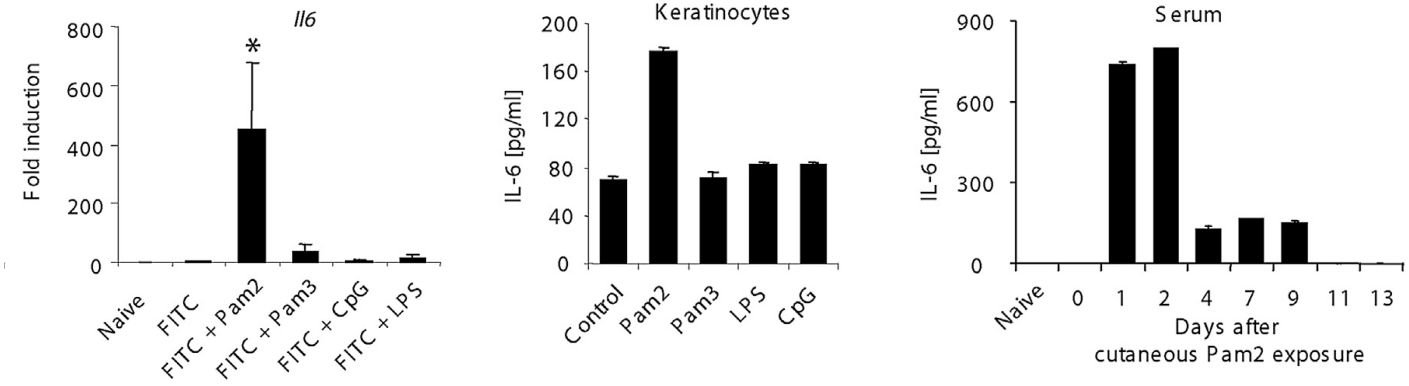
# Mechanism:

## Expression of IL-6 upon Pam2 stimulation




- CpG binds TLR9
- LPS binds TLR4

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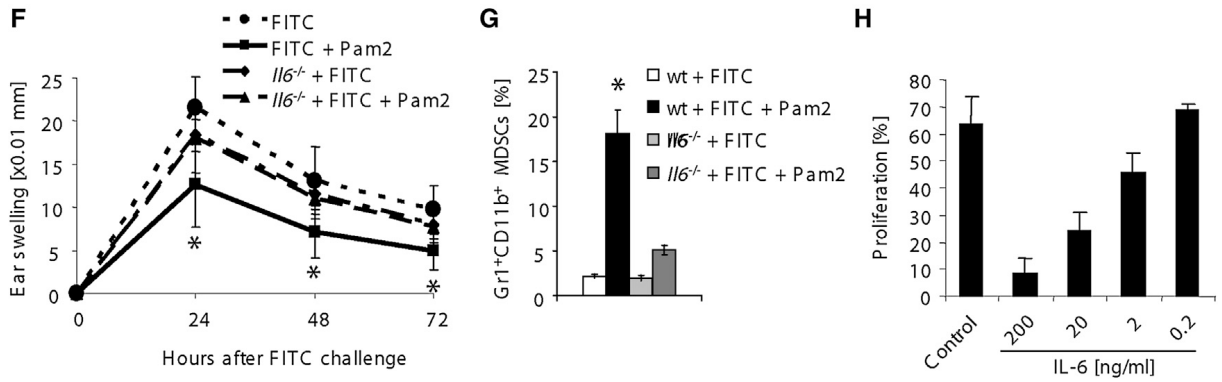
# IL-6 required for MDSC induction

IL6-/- means IL6 knock out mouse




BM-derived MDSCs treated with or without IL-6

→then cocultured with activated responder cells

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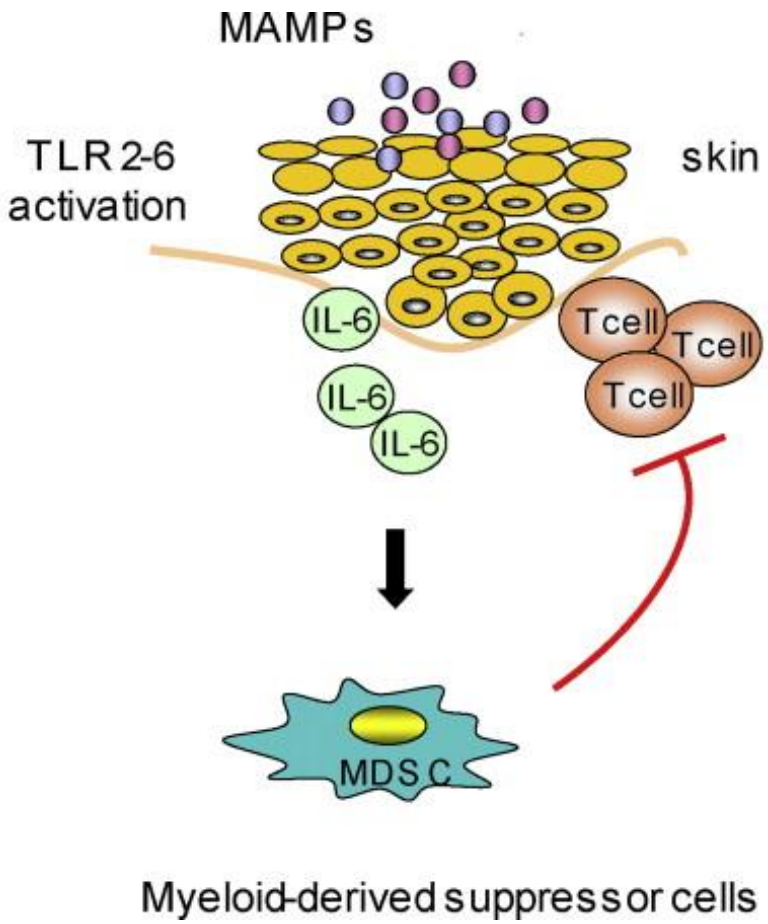
# Summary

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