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

Innate immune system:
first line of host defense against microbes

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

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

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

Abbas et al., Cellular and Molecular Immunology (7th edition, 2012)
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Abbas et al., Cellular and Molecular Immunology (7th edition, 2012)
**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 Immunology (7th edition, 2012)
Sustained activation of TLRs causes persistent production of proinflammatory cytokines:

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

→ tissue damage

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**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 Immunology (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
S. aureus induces immune suppression

Application of living S. aureus

Δlgt: lipoprotein-deficient S. aureus

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

Human

Skabytska Y. et al., Immunity 41, 762–775 (2014)
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Skabytska Y. et al., Immunity 41, 762–775 (2014)
Immune suppression mediated by MDSCs

Anti-Gr1:
Depletion of Gr1+ cells

Adoptive transfer of MDSCs

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

Bone marrow

Spleen

Mice

Skabytska Y. et al., Immunity 41, 762–775 (2014)
Cytokine and chemokine expression

T cell attracting:
- Ccl22 ligand for CCR4
- Ccl28 ligand for CCR10

Chemokine receptors expressed on MDSCs

CD3 expressed on T cells

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MDSCs

immunosuppressive activity

Anti-CD3-CD28 stimulation ➞ T cell activation/proliferation

T cell proliferation

L-NMMA and L-NIL ➞ inhibiting iNOS

Human

Skin tissue of AD

Skabytska Y. et al., Immunity 41, 762–775 (2014)
Immune suppression dependent on TLR2

Skabytska Y. et al., Immunity 41, 762–775 (2014)
TLR2 sensing through skin resident cells or hematopoietic cells?

Tlr2-/- means Tlr2 knock out mouse

BM= Bone marrow cells

Skabytska Y. et al., Immunity 41, 762–775 (2014)
TLR expression after stimulation

A

Control

Pam2

Pam3

Green: nuclei

Red: TLR2  Blue: TLR6  Blue: TLR1

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

Expression of IL-6 upon Pam2 stimulation

- CpG binds TLR9
- LPS binds TLR4

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

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

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