Skin Innate Immunity: Atopic Dermatitis and the Microbiome

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A problem for skin immunity
Some Microbes multiply quickly
62,914,560
Streptococcus pneumonia
15
6.5 hrs

AMPs are key to skin innate immunity

Physical and chemical barrier
(stratum corneum, pH, constitutively produced ROS, lipids, peptides)

Pattern recognition, inducible chemicals
(TLRs etc., IL-1, defensins, cathelicidins, complement)

Cell recruitment
(Neutrophils, Monocytes, Macrophages, NK, NKT cells)

Cell education and clonal proliferation
(Dendritic cells, T-cells, B-cells)

Cathelicidins and Defensins shown to be important
to disease resistance in multiple organ systems and
diseases

Urinary track

Blood Brain Barrier

Eye

Macrophage

Monocyte

Lung

The Physical structure, AMPs and Cellular Response form the barrier

Barriers to Bugs
Chemical
Physical
Detection system
Resident cells
Recruited cells

Gallo PNAS 1994
Psoriasis has defect in the physical barrier but these patients are less susceptible to infection than the normal population.

Atopic Dermatitis

Disrupted barrier  Infection

Psoriasis

Disrupted barrier  Protection


Atopics have less AMPs than expected in inflamed skin

Atopic Dermatitis with history of eczema herpeticum are most suppressed

Despite innate immunity, our skin has many microbes

How do we reconcile tolerance for abundant and diverse microbes with a potent skin antimicrobial system?

Today we are rediscovering the surface microbes and describing great diversity in detectable species.
1. S. epidermidis, a common skin microbe, protects against pathogens
2. S. epidermidis helps dampen excessive skin inflammation

**Overview of data to be presented**

**S. epidermidis inhibits Strep. pyogenes**

Group A Streptococcus

GAS is hemolytic (clear zones)

**S. pyogenes PSM peptide is AMP**

HPLC purification

Determine fractions with antimicrobial activity

PSM δ:

N-formyl-MAMDDSTKDQVKEIDTVNFKK

MS TOF-TOF sequence result from fraction 37

**PSM peptides are present on the skin and are colocalized in NETS**

Cogen AL. (2009) J. Invest Derm

Cogen et al. PLOS One 2010 5(1) e8557

**Conclusion:**

1. S. epidermidis helps us protect against pathogens

Next:

2. S. epidermidis helps dampen excessive skin inflammation
Start with a simple assay

Add pro-inflammatory stimuli to keratinocytes

Measure output of pro-inflammatory cytokines

Add products of S. epidermidis

Keratinocytes produce TNFα in response to Poly(I:C) (a stimulus of TLR3)

This is blocked in presence of S. epidermidis

Expand to animal model assays

Add pro-inflammatory stimuli to skin

Add products of S. epidermidis

SE blocks Poly(I:C) inflammation in vivo.

What is role of TLR-3-mediated detection in skin?

TLR3 is an endogenous sensor of tissue necrosis during acute inflammatory events

Karen A. Cavassani, Makoto Ishii, Haitao Wen, Matthew A. Schaller, Pamela M. Lincoln, Nicholas W. Lukacs, Cory M. Hogaboam, and Steven L. Kunkel

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JEM (2008) 205:2609-21
TLR3 required for inflammation after injury and SE suppresses inflammation after injury.

How does SE suppress TLR-3 induced inflammation in the skin?

Test the model: As predicted, LTA only blocks cytokines

What happens if a mouse is too clean?

A germ-free mouse has low TRAF-1

Take Home messages

1. Innate Immunity is essential for defense
2. Atopic Dermatitis is a defect in innate immunity
3. Normal resident microbes are part of skin immune defense
   - they produce antimicrobials
   - they can regulate inflammation

Does the microbiome influence disease in Atopics???
Still to come........

THANK YOU!!!!

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BBC NEWS

Dirt ‘can be good for children’

Children should be allowed to get dirty, according to scientists who have found being so more can improve the skin’s ability to heal.

The study suggests that the skin of babies is more vulnerable to damage from dirt than their adult counterparts.

The authors say it can reduce the risk of developing infections or allergies, which is important for the development of healthy skin.

This research has just been published in the online edition of Nature Medicine.

The findings provide an explanation for the ‘hygiene hypothesis’, which holds that too much cleanliness can lead to conditions like eczema and allergies.

The authors say the findings show that exposure to bacteria and other substances can help to develop a healthy skin microbiome, which can help to prevent diseases.

Researcher’s from Utah’s School of Medicine at the University of Utah.