


Skin Innate Immunity: Atopic Dermatitis and the Microbiome

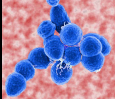
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University of California, San Diego



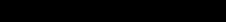
A problem for skin immunity

Some Microbes multiply quickly

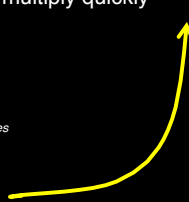
15
Streptococcus pyogenes



6.5 hrs



62,914,560
Streptococcus pneumoniae



AMPs are key to skin innate immunity

time

0

mins

hours

days

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


Early
Pattern recognition, inducible chemicals
(TLRs etc., iNOS, antimicrobial peptides, chemokines, complement)

Intermediate
Cell recruitment
(Neutrophils, Monocyte, Macrophage, NK, NKT cells)

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

AMPs

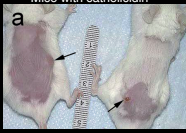
AMPs



Cathelicidin knock-outs are more susceptible to Invasive Group A *Streptococcus*

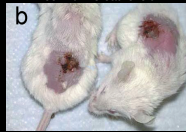
a

Mice with cathelicidin



b


Mice with no cathelicidin



Lesion culture at 7 day

+/+	+/-	-/-

Nizet et al. Nature, (2001) 414:454



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

Urinary track

Blood Brain Barrier

Intestine

Eye

Macrophage

Monocyte

Lung

Chromek et al. *Nat Med* (2006) 12(6) 636-41

Bergman et al. *Infect and Imm* (2006) 74: 6982-91

Imura et al. *J. Immunol* (2005) 174:4901-7

Huang et al. *Invest. Oph. Vis. Sci.* (2007) 48:4498-508

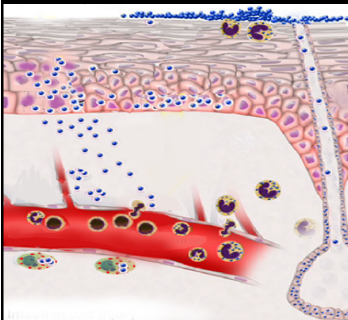
Rosenberger et al. *P.N.A.S.* (2004) 101(8):2422-7

Liu et al. *Science* (2006) 311(5768):1770-3

Moser et al. *Infect. Immun* (2002) 70:3068-3072




The Physical structure, AMPs and Cellular Response form the barrier



Barriers to Bugs

- Chemical
- Physical
- Detection system
- Resident cells
- Recruited cells

Gallo PNAS 1994

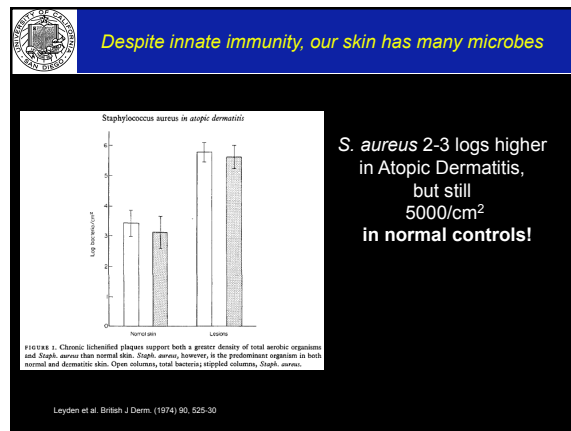
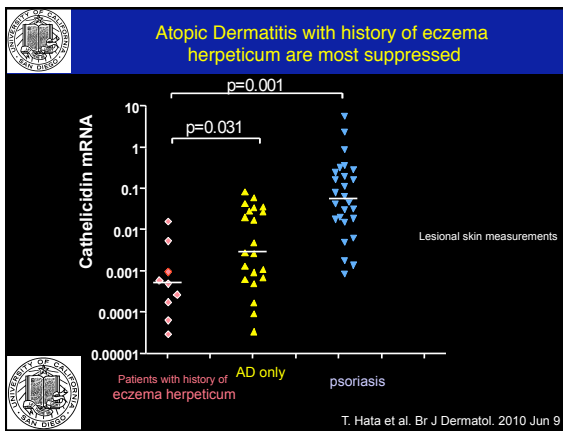
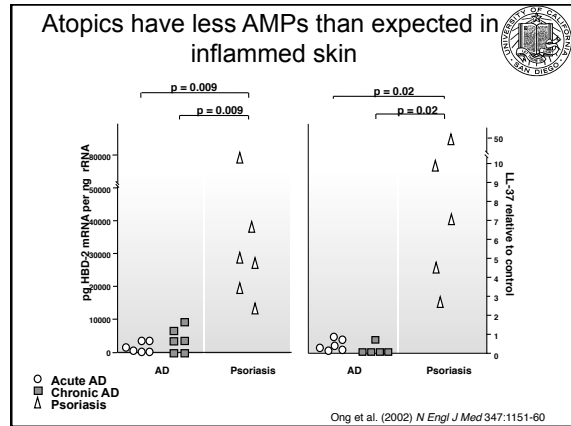


Psoriasis has defect in the physical barrier but these patients are less susceptible to infection than the normal population

Psoriasis
Disrupted barrier → Protection

???? Atopic Dermatitis
Disrupted barrier → Infection

Christophers E, Helseiser, T (1987) Arch Derm Res.



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

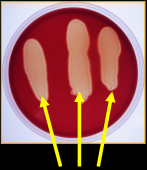
Today we are rediscovering the surface microbes and describing great diversity in detectable species.

Gao et al. 2007 PNAS 104:2927
Grice et al., 2009, Science 324, 1190
Grice and Segre. 2011 Nat Rev Microbiol 9:244

Overview of data to be presented

1. *S. epidermidis*, a common skin microbe, protects against pathogens
2. *S. epidermidis* helps dampen excessive inflammation

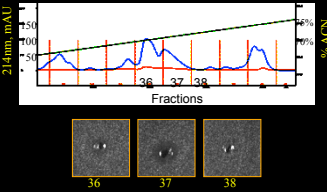
S. epidermidis* inhibits *Strep. pyogenes



Group A *Streptococcus*

GAS is hemolytic (clear zones)

***S. pyogenes* PSM peptide is AMP**



HPLC purification

Determine fractions with antimicrobial activity

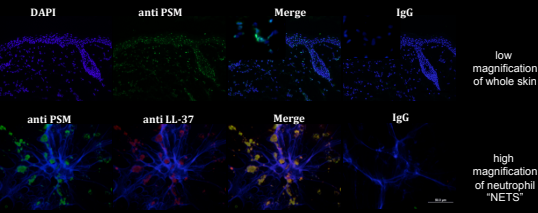
MS TOF-TOF sequence result from fraction 37

N-formyl-M₆₇AADIISTIGDLVKWIIDTVNKFKK

PSM δ :

Cogen AL. (2009) *J. Invest. Derm.*

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

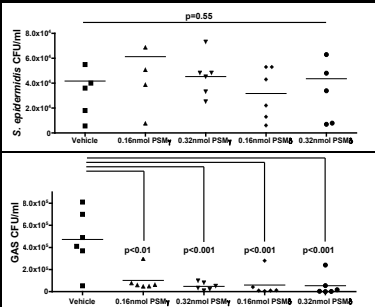


low magnification of whole skin

high magnification of neutrophil "NETS"

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

PSM selectively controls the skin microbiome



$p=0.55$

$p<0.01$ $p<0.001$ $p<0.001$ $p<0.001$

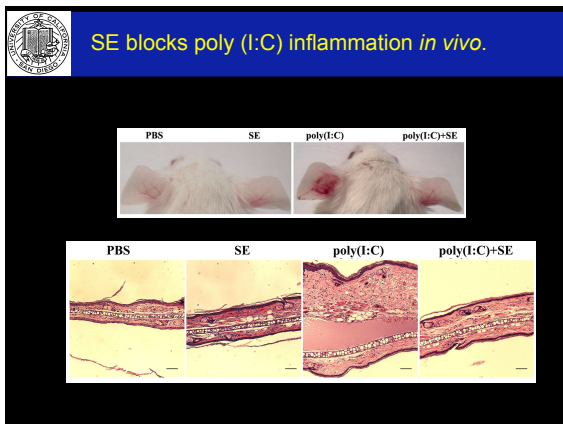
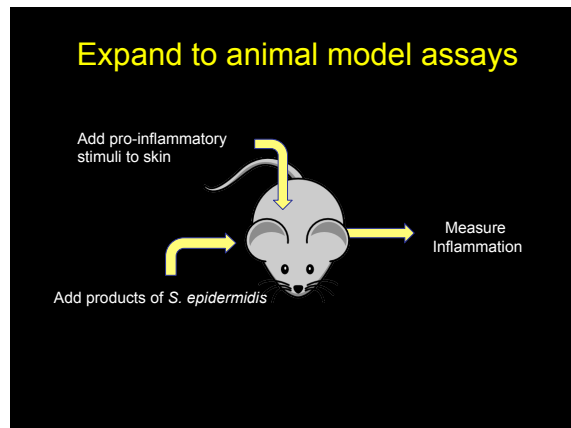
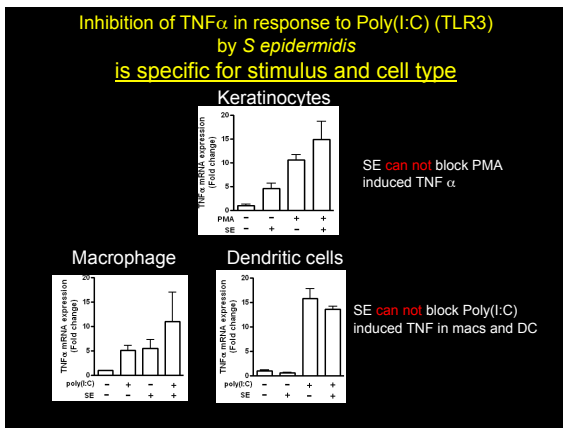
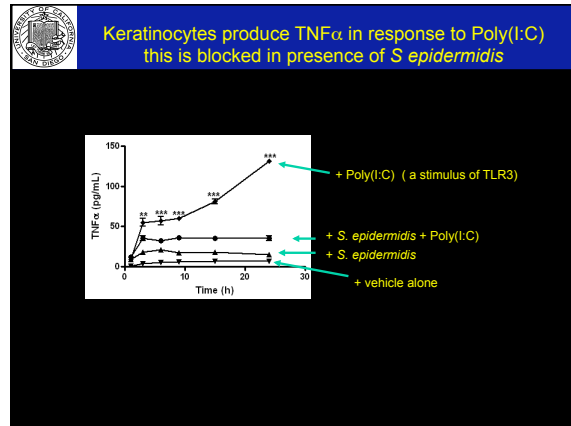
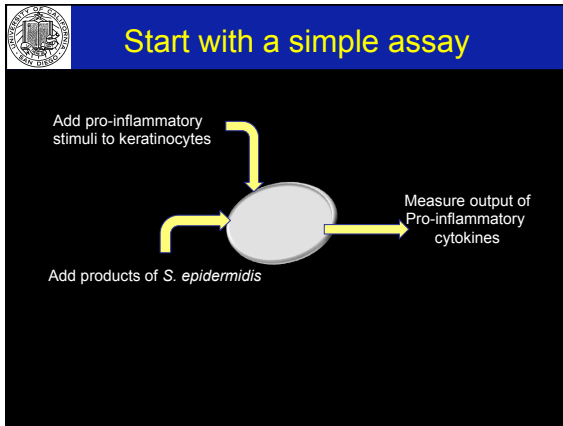
Cogen AL. (2009) *J. Invest. Derm.* (2010) *PLOS one*

Conclusion:

1. *S. epidermidis* helps us protect against pathogens

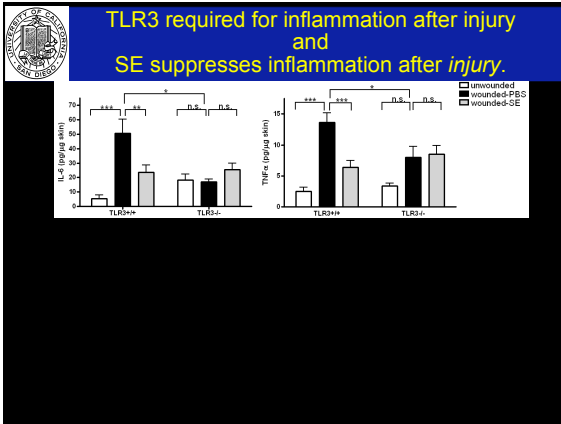
Next:

2. *S. epidermidis* helps dampen excessive skin inflammation

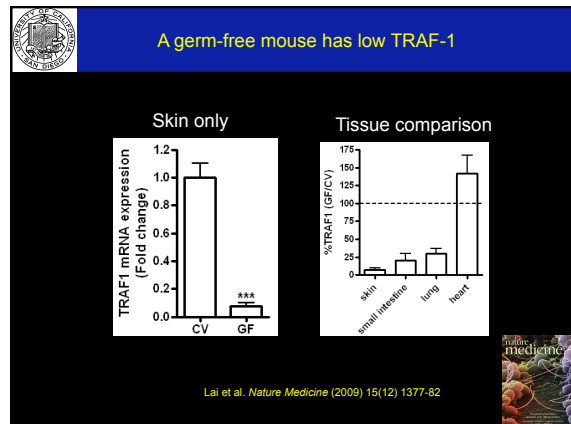
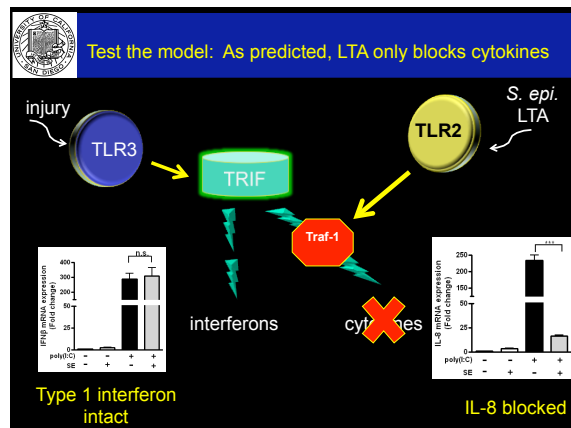
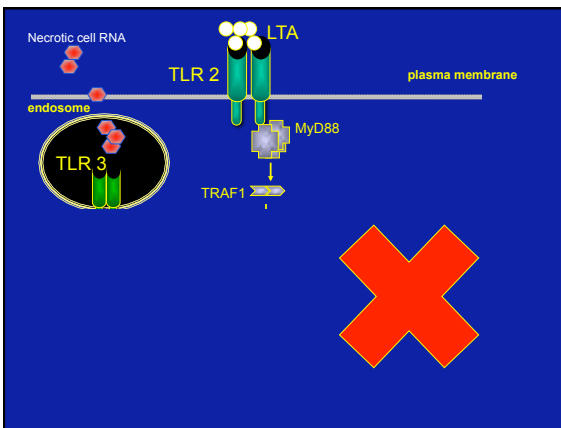


What is role of TLR-3-mediated detection in skin?

TLR3 is an endogenous sensor of tissue necrosis during acute inflammatory events
 Karen A. Cavassani, Makoto Ishii, Hailao Wen, Matthew A. Schaller, Patricia M. Lincoln, Nicholas W. Lukacs, Cory M. Hogaboam, and Steven L. Kunkel
 Department of Pathology, University of Michigan, Ann Arbor, MI 48109
JEM (2008) 205:2609-21



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







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.....

Dirt 'can be good for children'

Children should be allowed to get dirty, according to scientists who have found being too clean can impair the skin's ability to heal.

Normal bacteria living on the skin trigger a pathway that helps prevent inflammation when we get hurt, the US team discovered.

The bugs dampen down overactive immune responses that can cause cuts and grazes to swell, they say.


Their work is published in the online edition of Nature Medicine.

Experts said the findings provided an explanation for the "hygiene hypothesis", which holds that exposure to germs during early childhood primes the body against allergies.

Many believe our obsession with cleanliness is to blame for the recent boom in allergies in developed countries.

'Good' bacteria

Researchers from the School of Medicine at University of California, San Diego, found a common bacterial species, known as *Staphylococcus*, blocks a vital step in a cascade of events that led to inflammation.



THANK YOU!!!!

Gallo Lab

Work from past graduates

Anna Cogen
Yu Ping Lai

Key Collaborators

Anna Di Nardo
Tissa Hata
Eric Huang
Donald Leung
Victor Nizet

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NIH: (NIAMS, NIAID, NHLBI)
L'Oreal
Galderma
Colgate Palmolive

