Immunologic (and metabolic) competence of the skin and its implication in pharmaceutical safety assessment

PRECLINICAL SCIENCE

Dr. Lars Mecklenburg

DVM, PhD, DACVP

Skin in general

PRECLINICAL SCIENCE

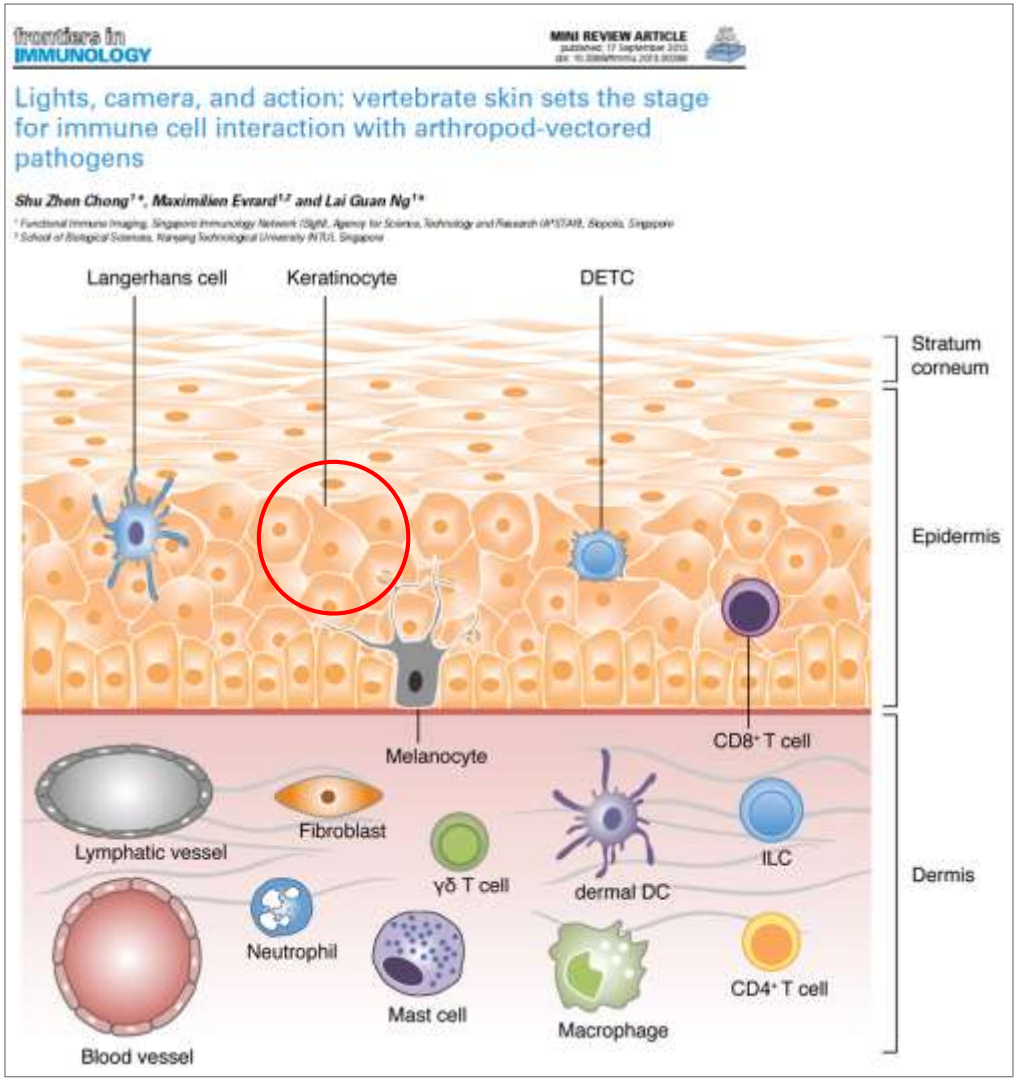
- First line of defense
- >1 million commensal bacteria, fungi, mites

- Adequate immune reaction against trauma, toxins and pathogens

Skin immune system

PRECLINICAL SCIENCE

- Epidermis
  - **Keratinocytes**
  - Langerhans cells
  - Epidermal T cells (DETC)
- Dermis
  - Dermal dendritic cells
  - Macrophages
  - Mast cells
  - T lymphocytes (T_{reg})
  - Innate lympoid cells (ILC)



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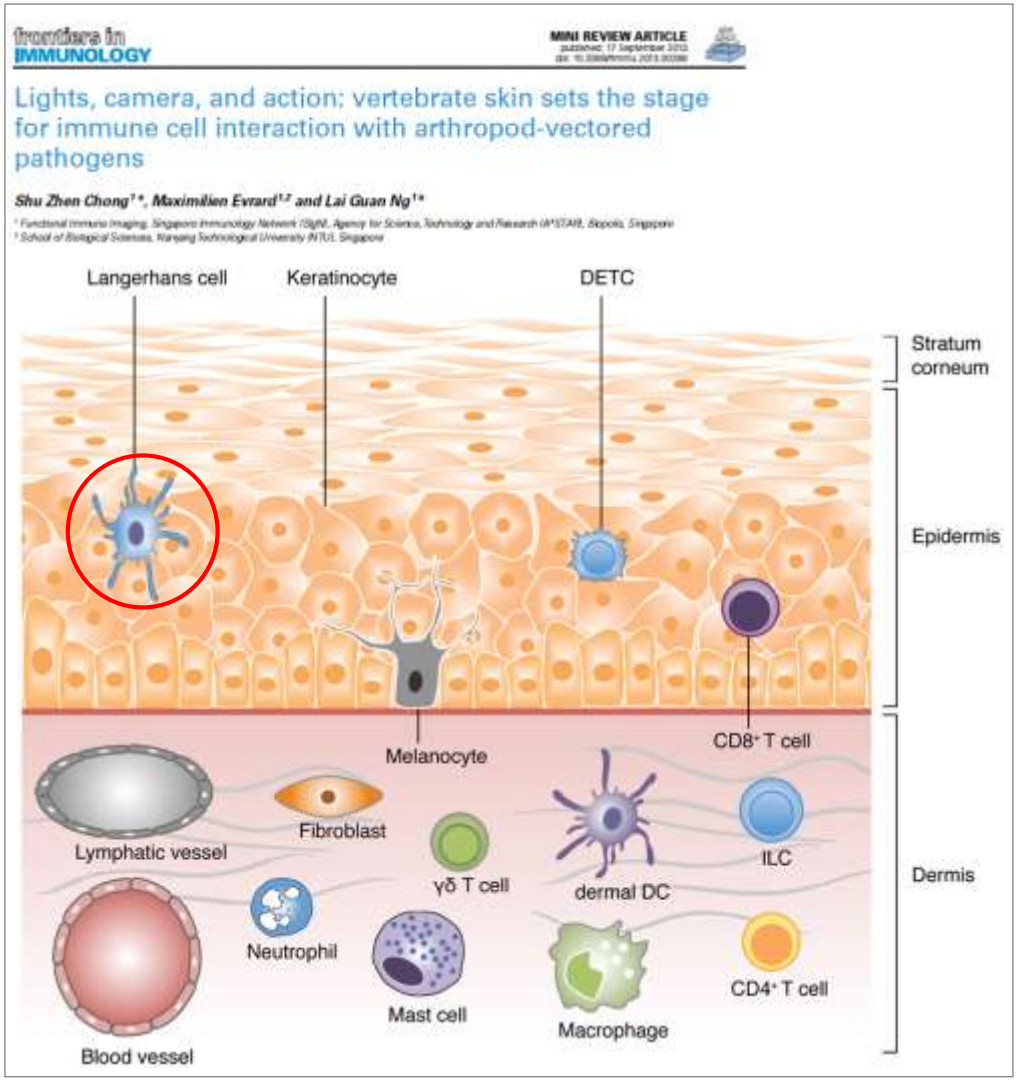

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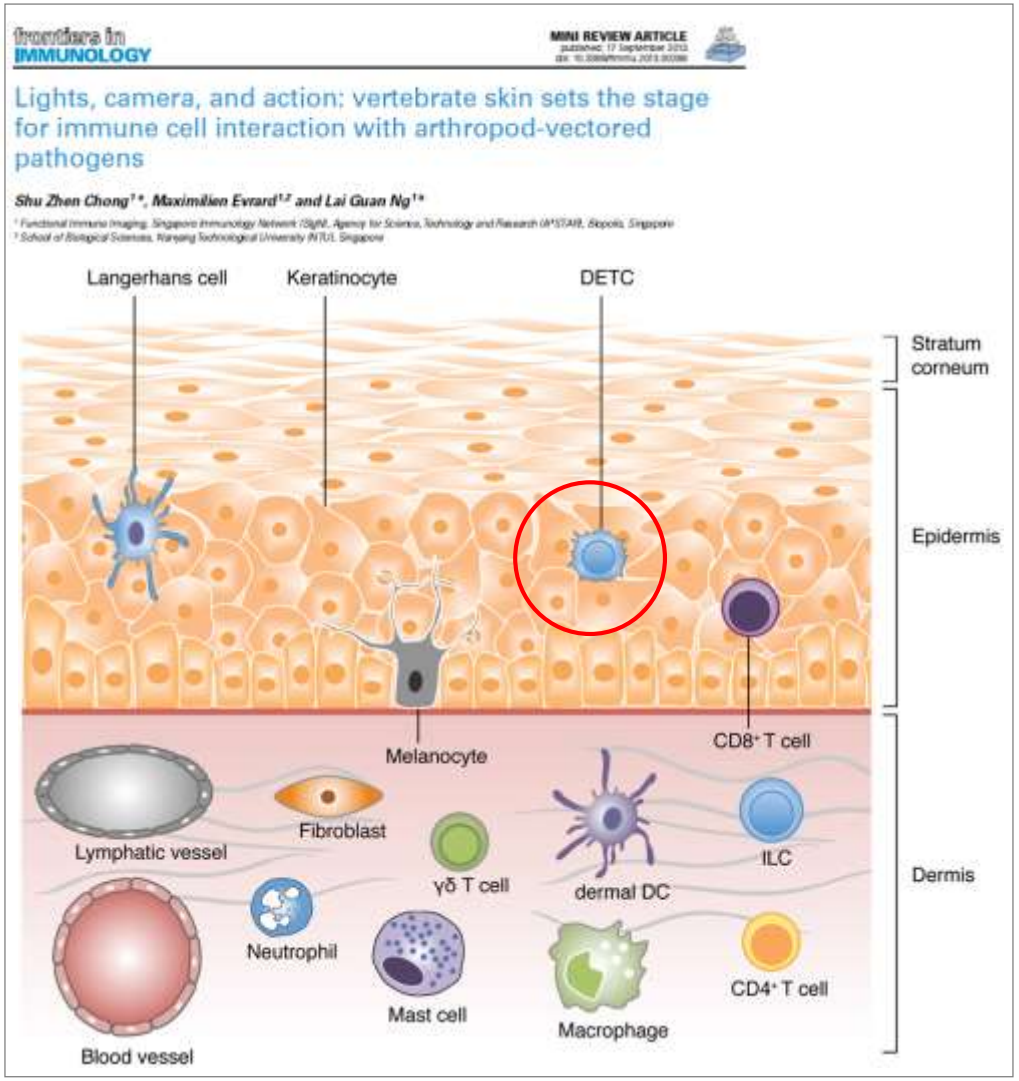

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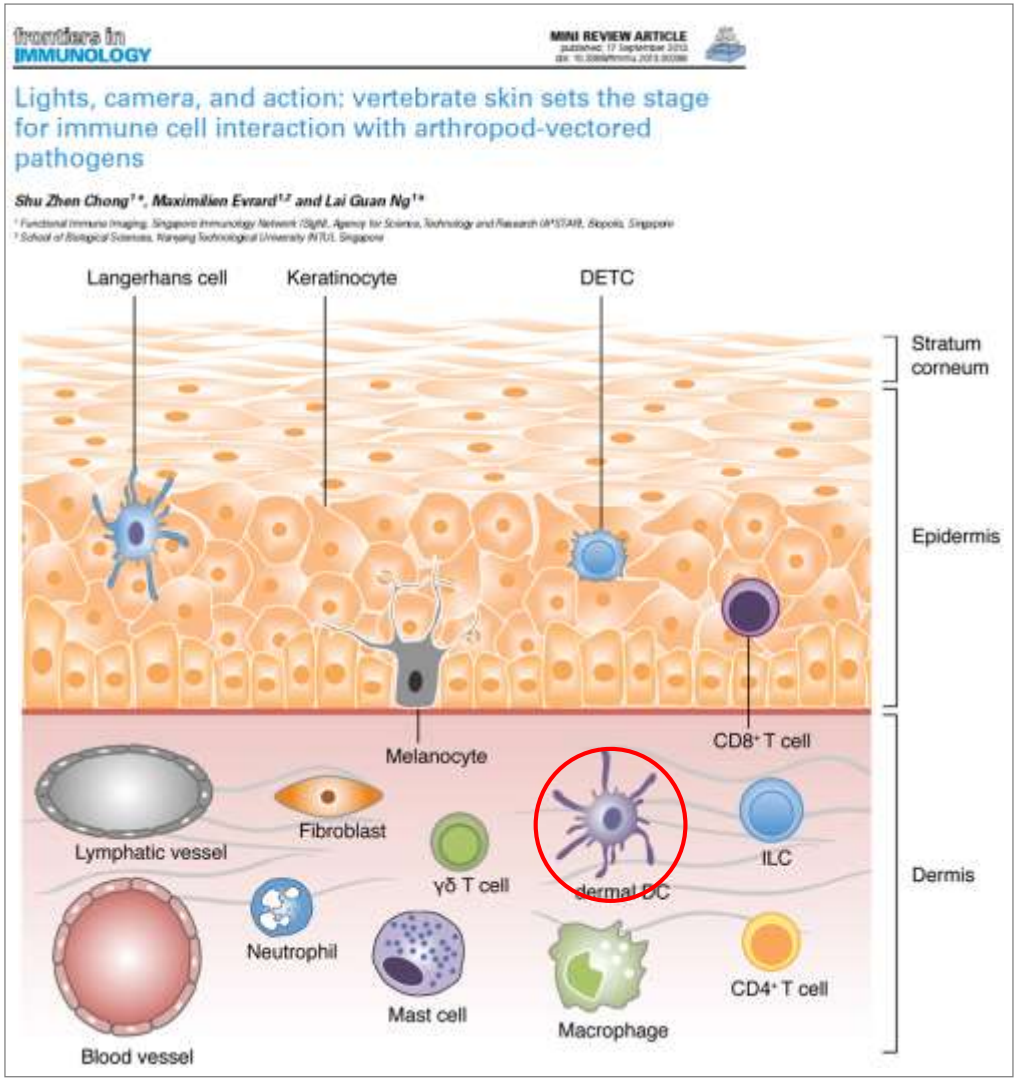

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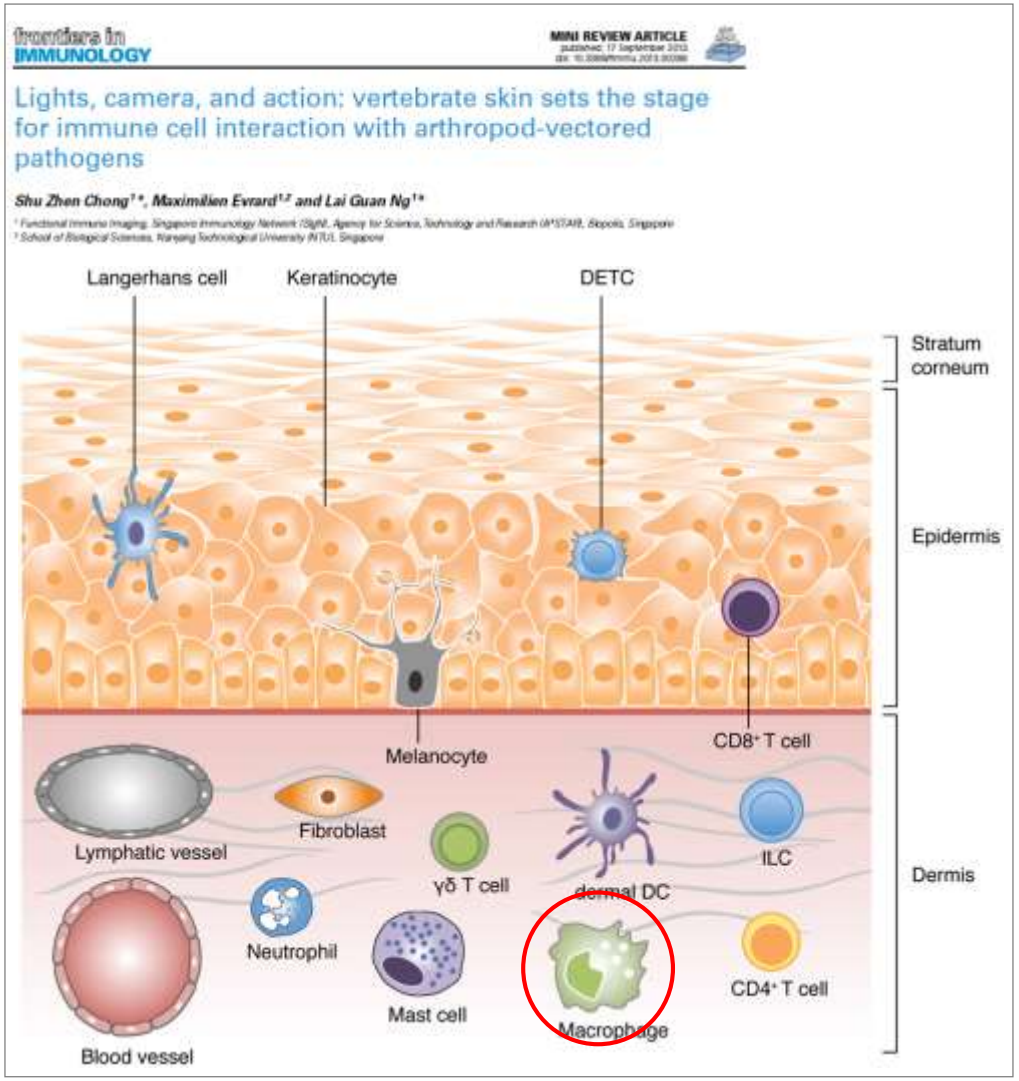

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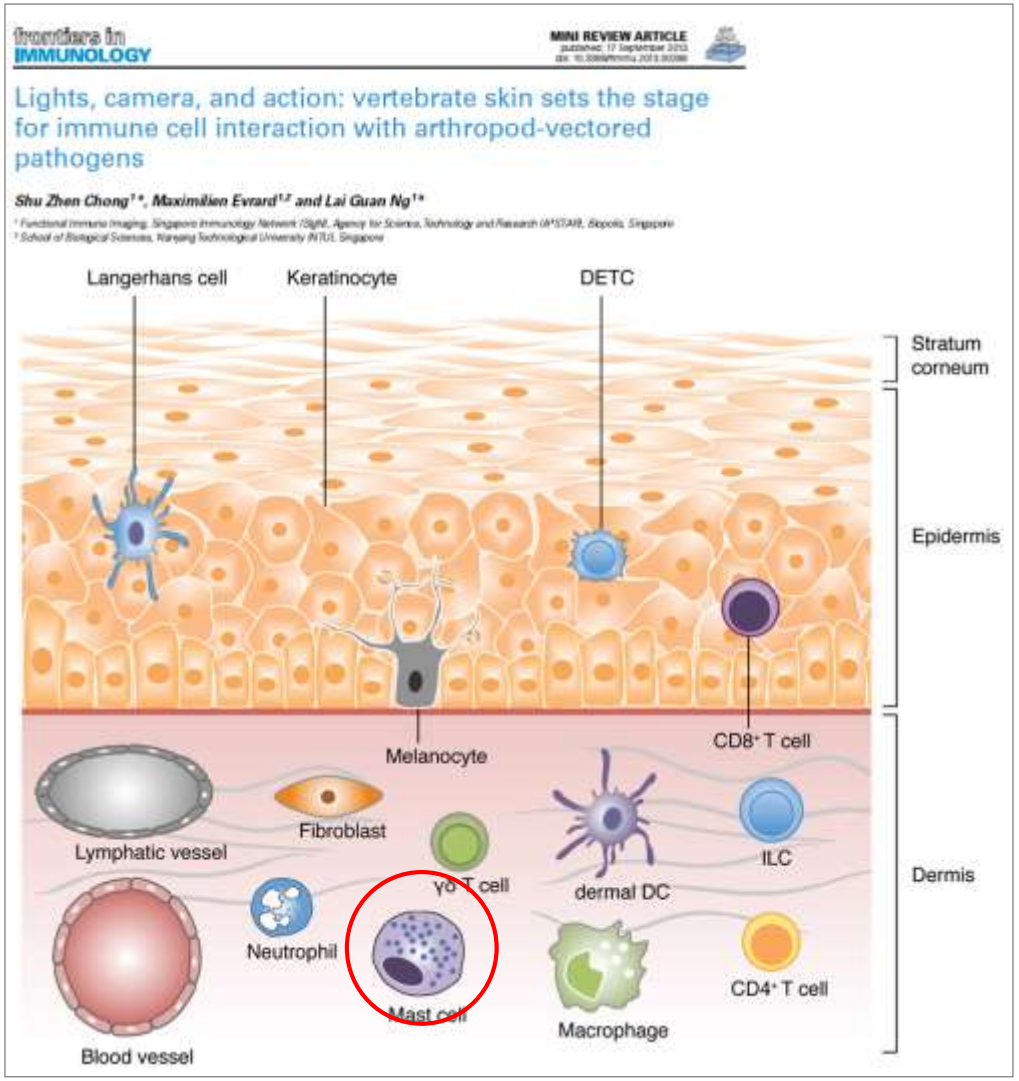

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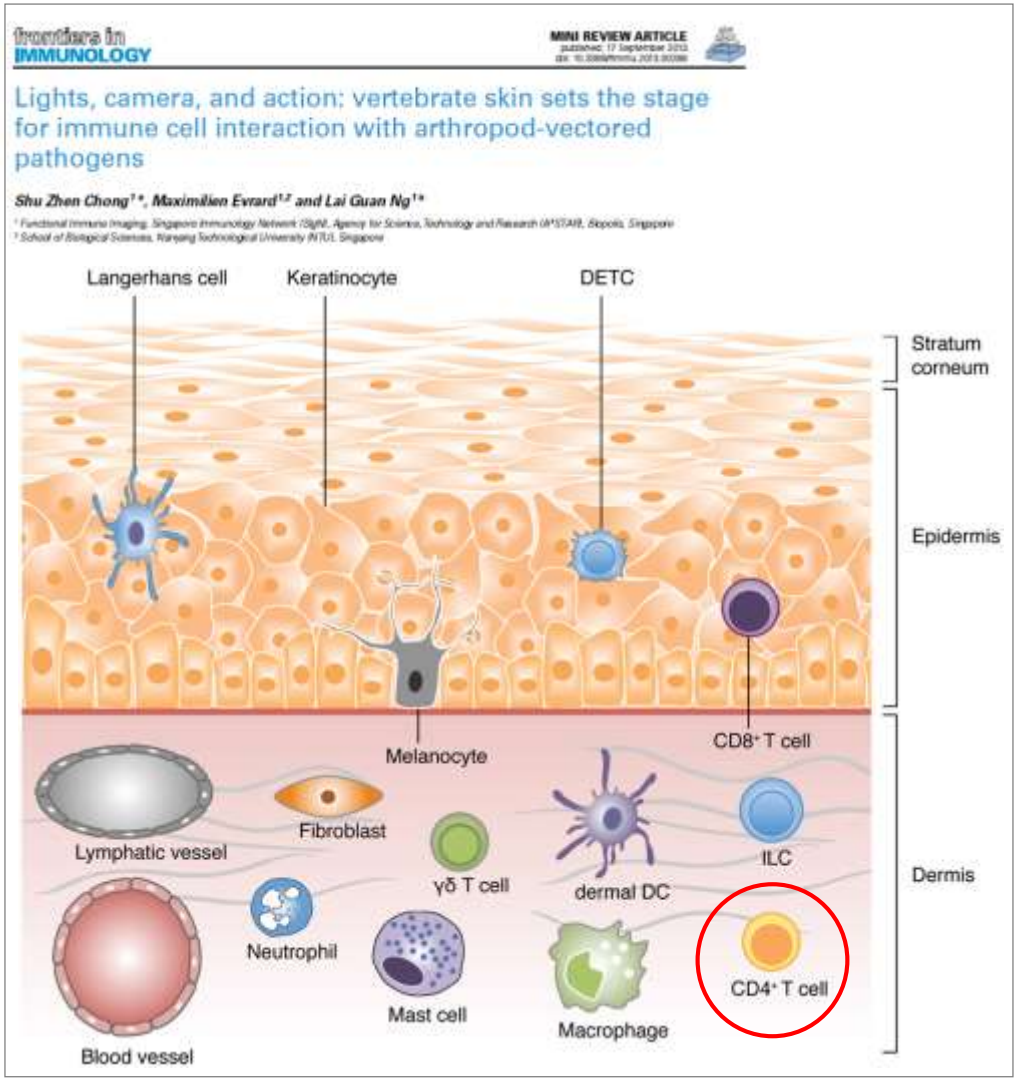

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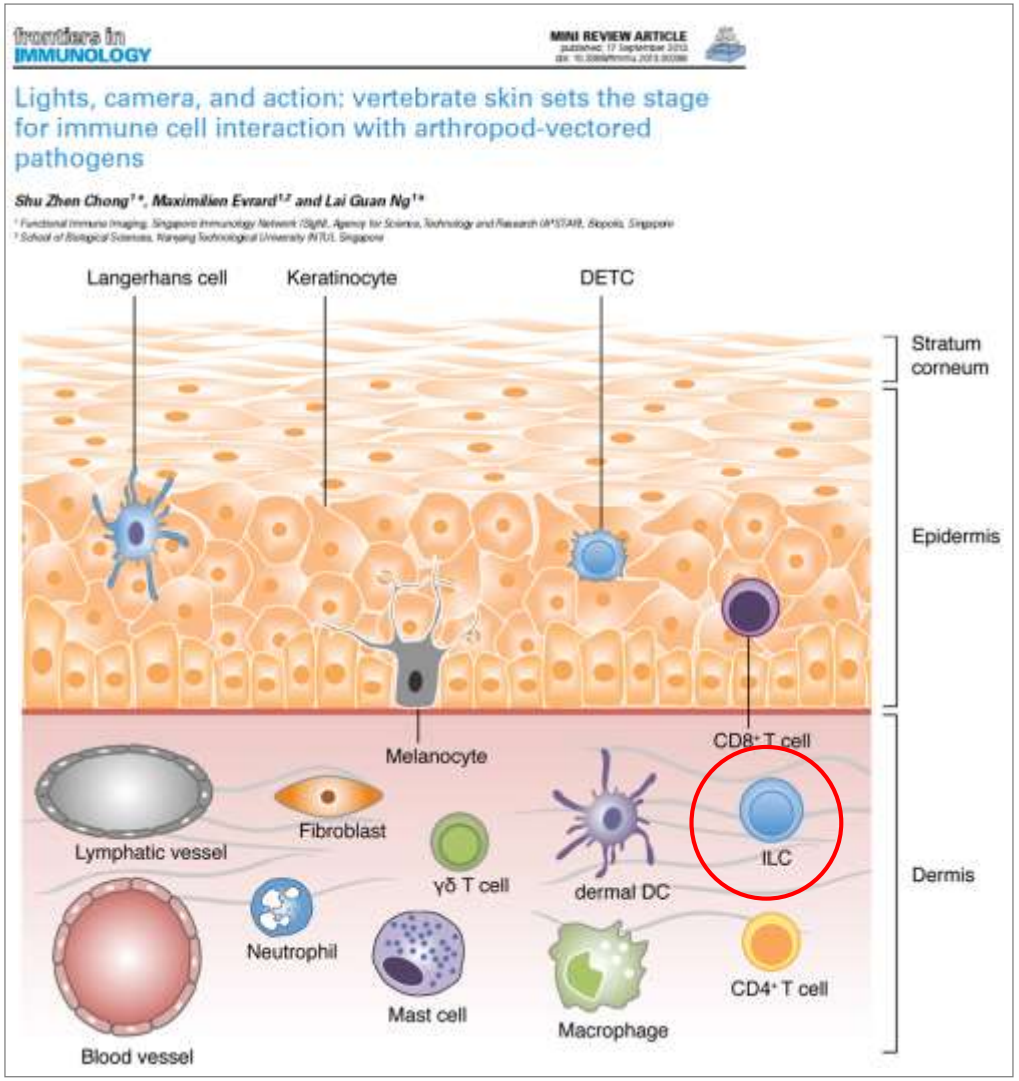
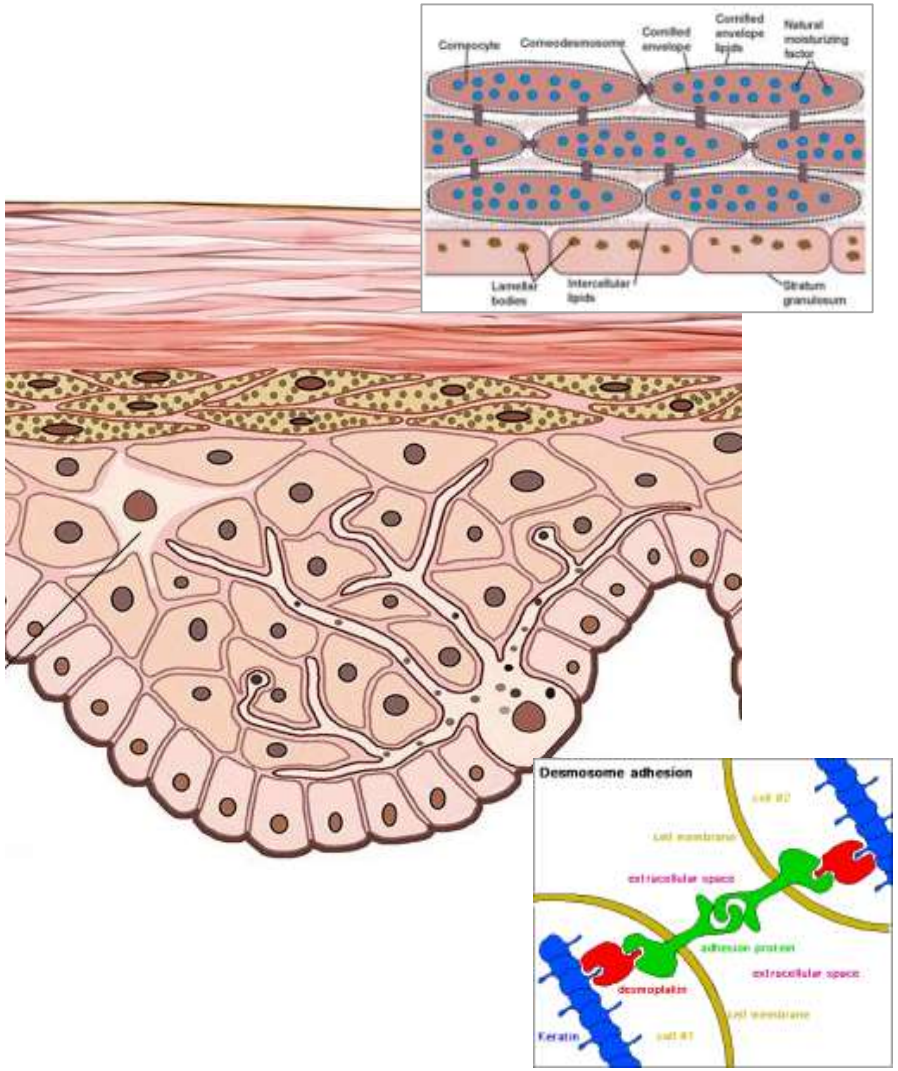


Keratinocytes

PRECLINICAL SCIENCE

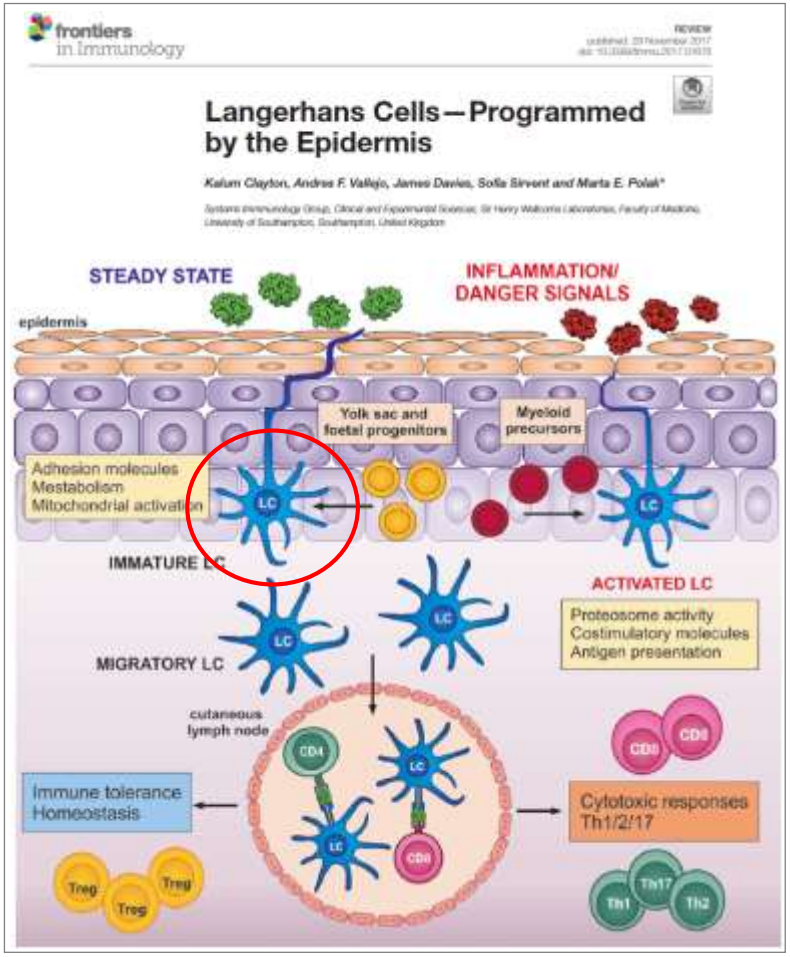
- Barrier integrity
- Limited intrusion of microbial pathogens and toxins
- Act as sentinels
  - Ag presentation despite lack of co-stimulatory molecules
- Can initiate a pro-inflammatory signaling cascade
  - IL-1a, IL-1b, IL-6, IL-17, IL-18, IL-23 and TNFa
- Activation of resident immune cells



Langerhans cells

PRECLINICAL SCIENCE

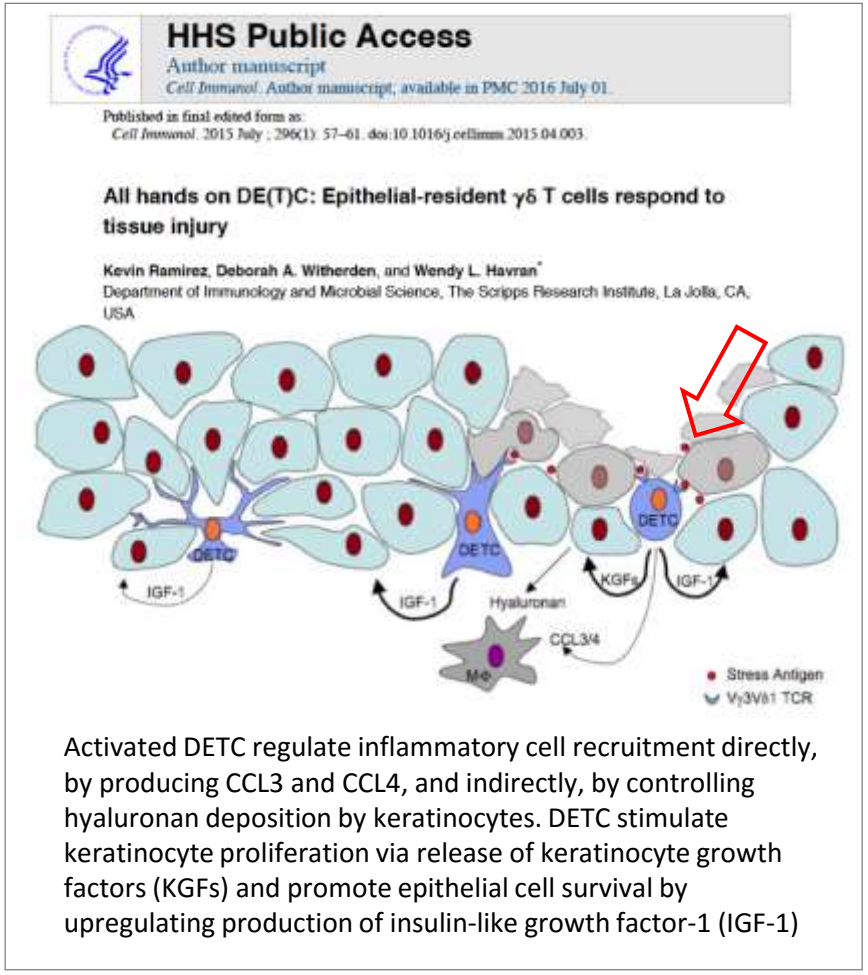
- Ag-presenting dendritic cells in epidermis and pilosebaceous unit
- Discovered in 1868
- Sentinels for the adaptive immune system
- Seeded in the epidermis from yolk sac and fetal liver progenitors
- Can be repopulated by local progenitors and myeloid precursors
- Express high levels of adhesion molecules
- Can migrate from the epidermis to draining lymph nodes for interaction with T cells associated with a change in surface marker expression
- Coordinate immune tolerance



Epidermal T cells

PRECLINICAL SCIENCE

- T cells found in the surface-contacting epithelia of all mammals
- Respond to ‚self' antigens expressed by ‚distressed' neighboring keratinocytes
- Involved in controlling epidermal integrity, response to environmental stimuli, regulation of inflammation, tumor surveillance, and would healing
- Mice: Dendritic Epidermal T cells (DETC)
- Expressing γ/δ TCR
  - Particularly dense in mice
- Expressing α/β TCR
  - More prevalent in humans
- Narrow range of antigen receptor diversity, recognizing highly selective ligands



Activated DETC regulate inflammatory cell recruitment directly, by producing CCL3 and CCL4, and indirectly, by controlling hyaluronan deposition by keratinocytes. DETC stimulate keratinocyte proliferation via release of keratinocyte growth factors (KGFs) and promote epithelial cell survival by upregulating production of insulin-like growth factor-1 (IGF-1)

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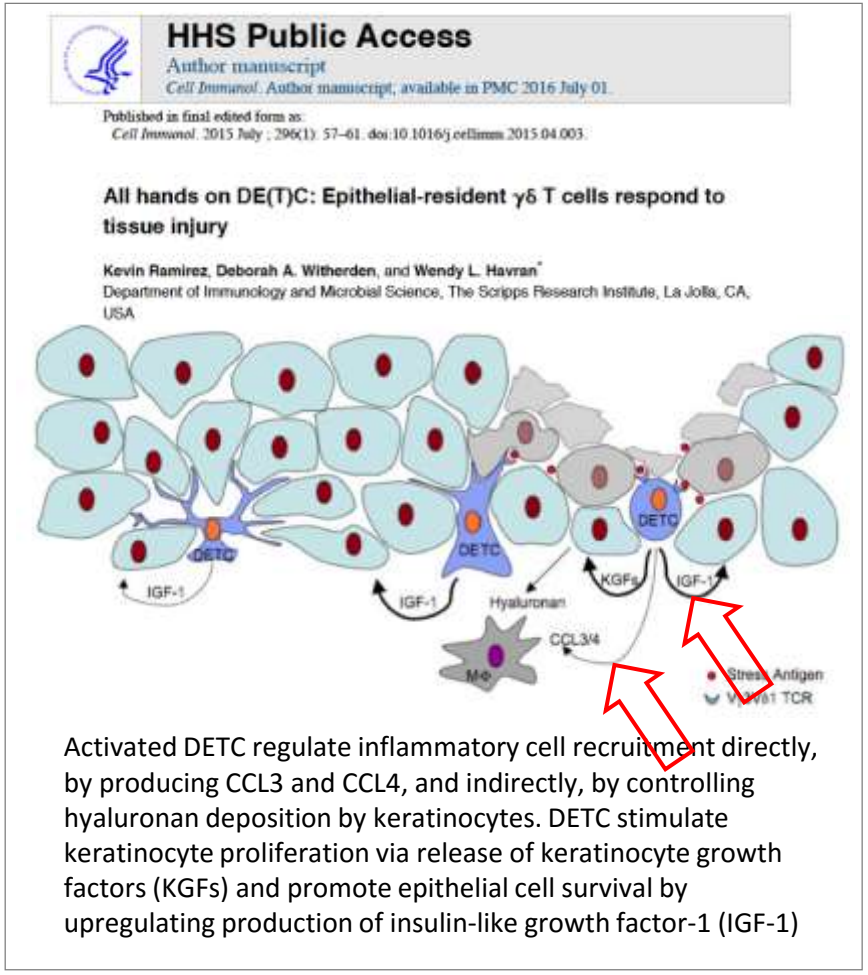

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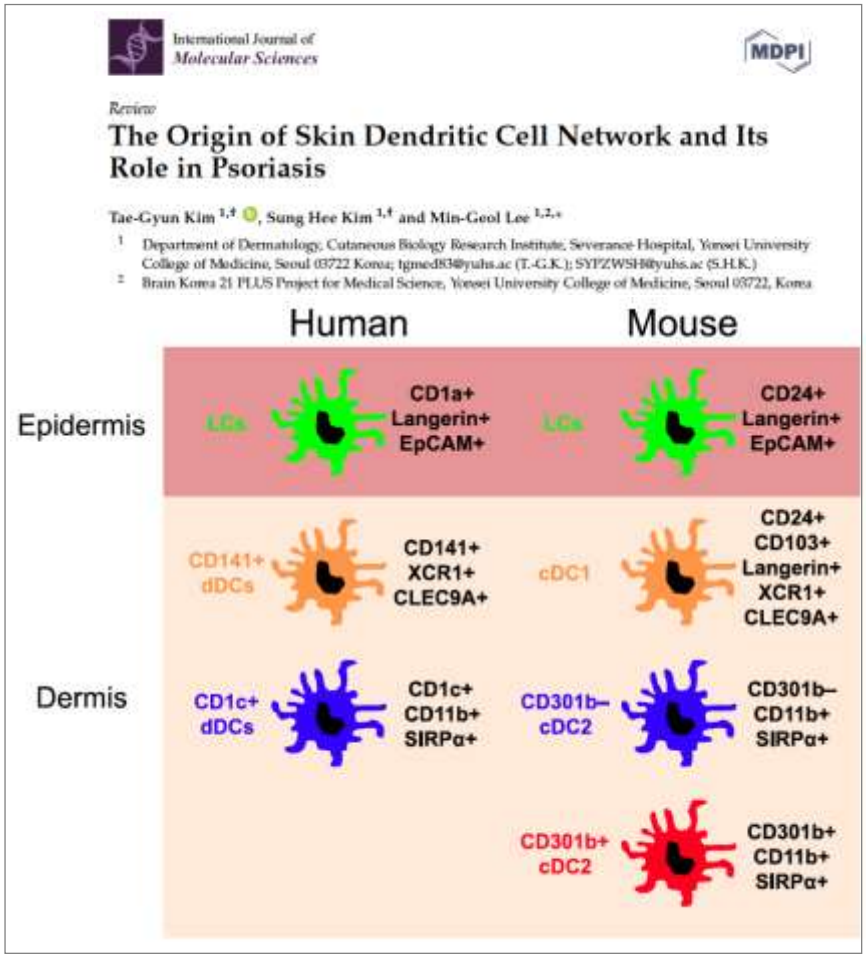
Ag-presenting cells in the skin

PRECLINICAL SCIENCE

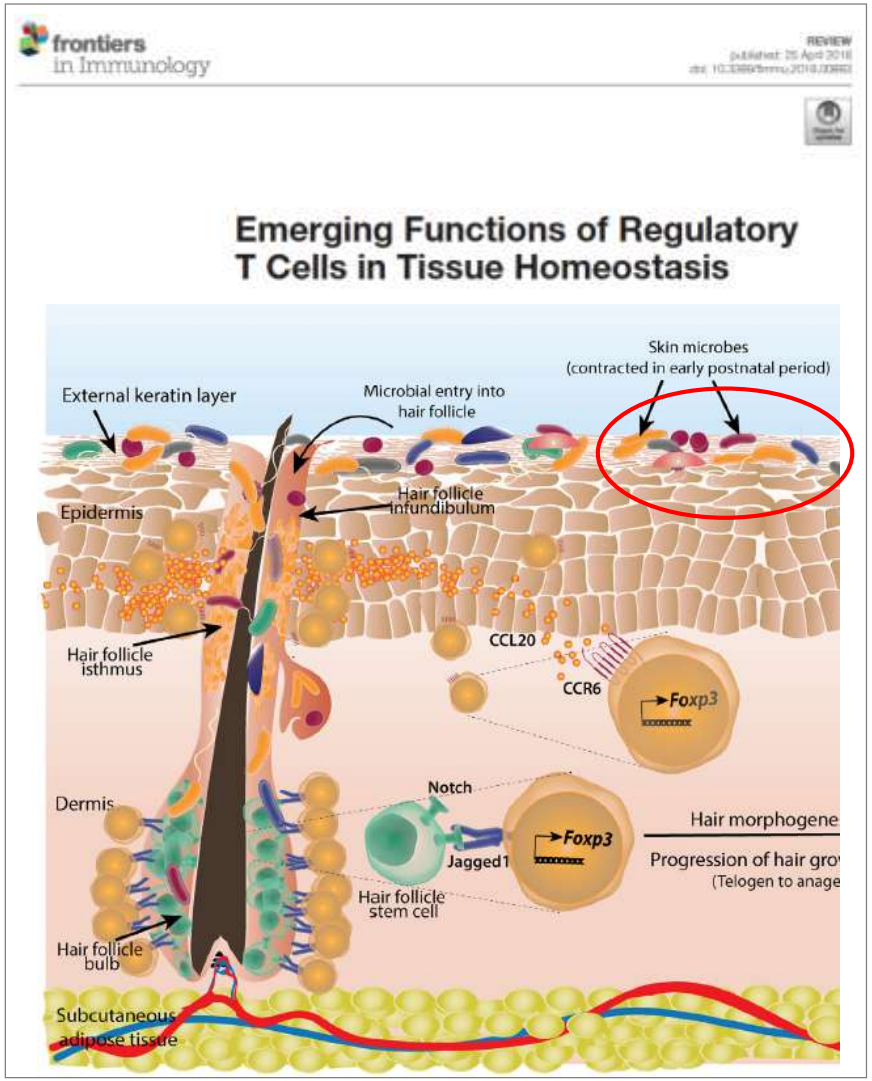
- ‚sample' extracellular antigens in the environment and induce immune response
- MHC-II expression
- Epidermal Langerhans cells
  - Embryo precursor-derived
- Dermal dendritic cells
  - Bone marrow-derived
  - Take up self-mRNA released by UVB damage
  - Unique ability to prime naïve T lymphocytes (adaptive immune response)
- Tissue-resident macrophages
  - Core phagocytes and activators of innate immune system
  - Fetal progenitors



Regulatory T cells

PRECLINICAL SCIENCE

- CD4+, CD25+, Foxp3+
- Promote immune tolerance
  - **Colonize skin in early postnatal period coinciding with microbial colonization**
  - Microbes enter hair follicles which produces CCL20
  - Attraction of T_{reg} expressing CCR6
  - Establish immune tolerance to commensal microbes
- Abnormal function relevant to the pathogenesis of several skin diseases



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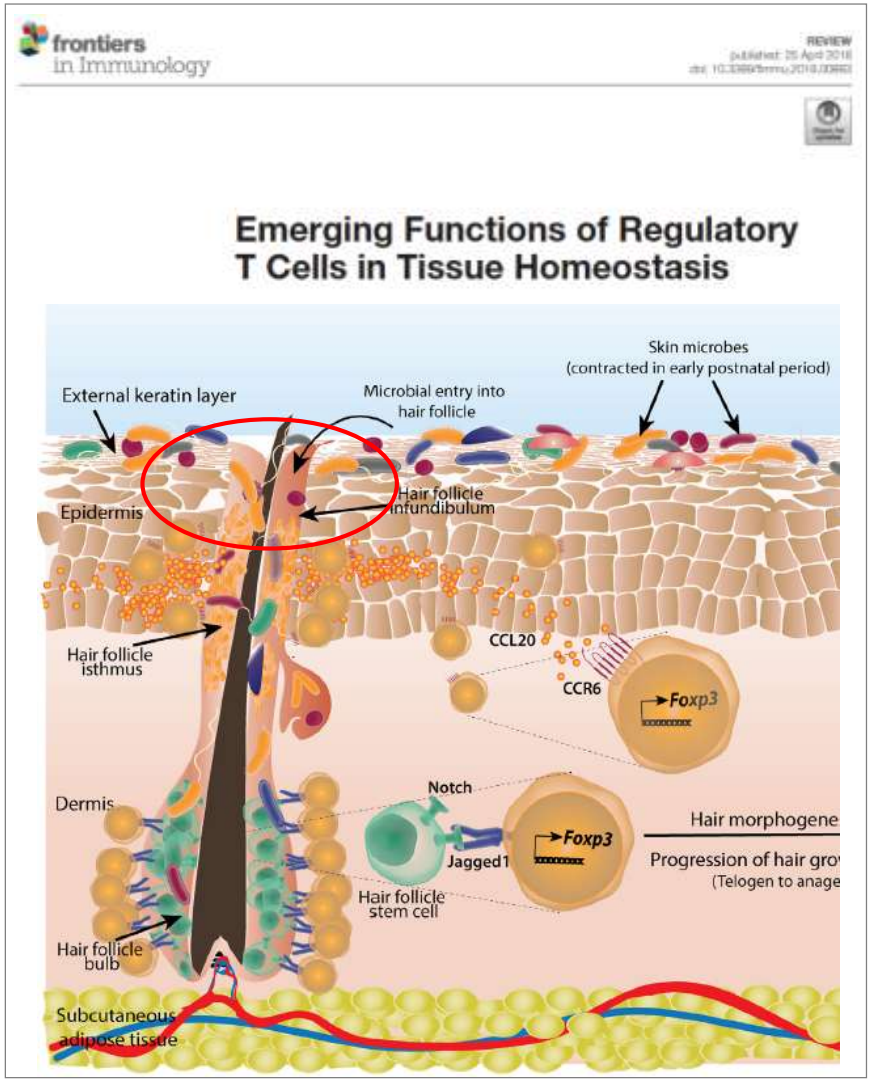

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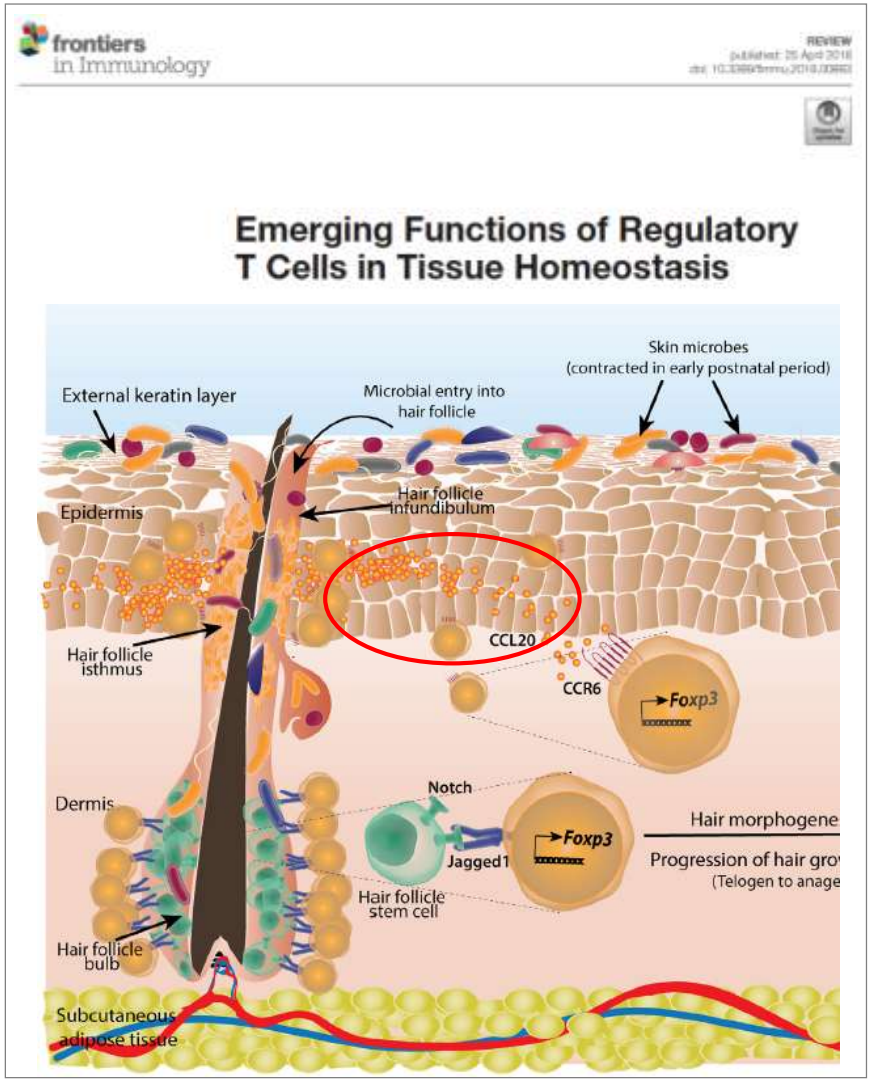

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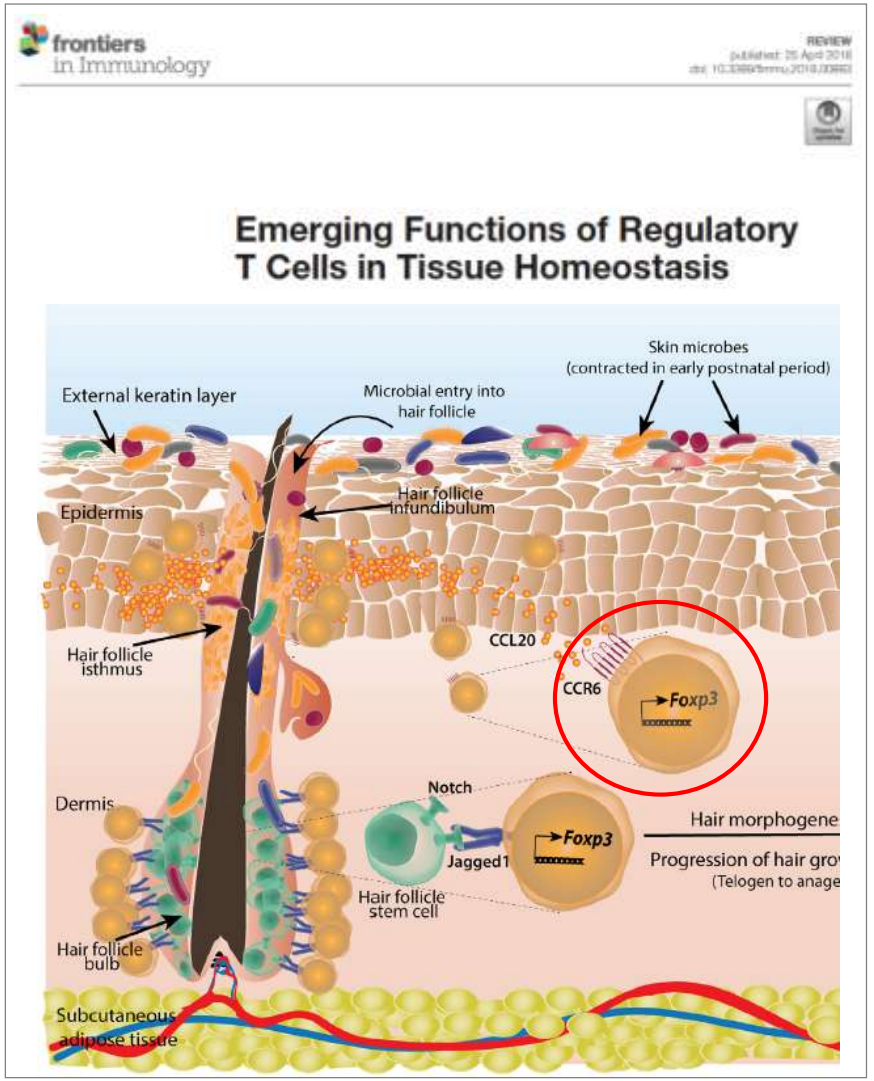
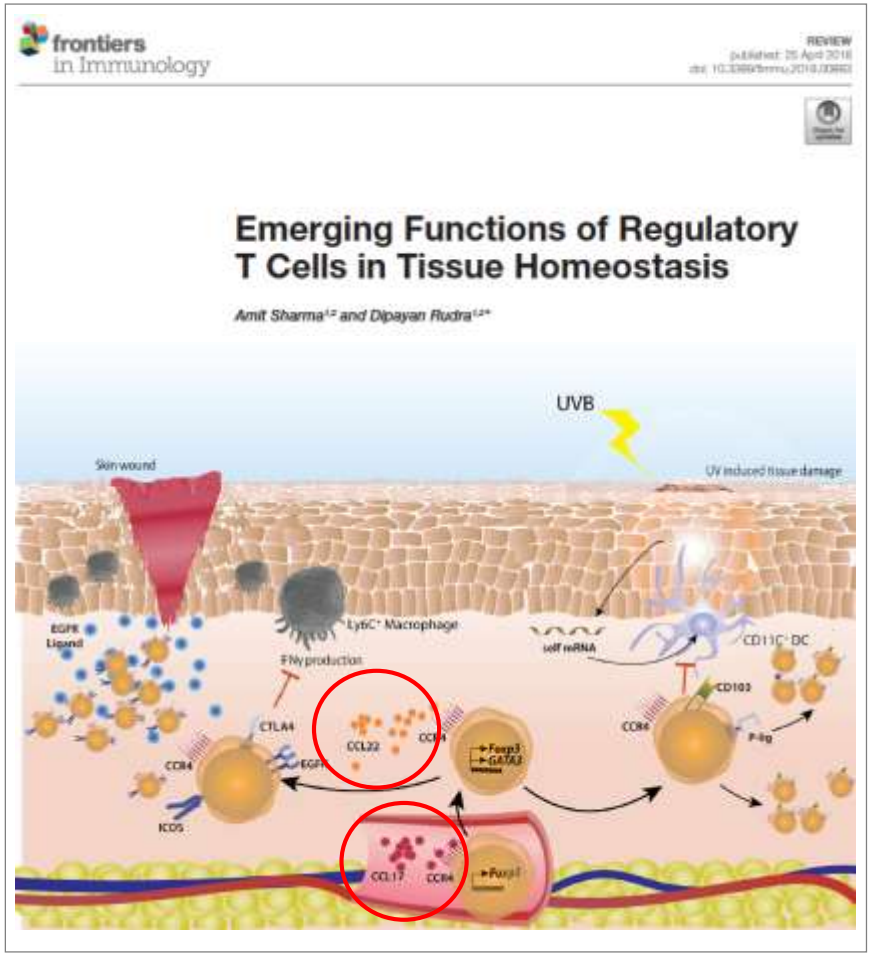


Regulatory T cells

PRECLINICAL SCIENCE

- Repair skin wounds
  - **Secretion of CCL17 and CCL22 by endothelial cells and immune cells**
  - **Attraction of T_{reg} via interaction with CCR4**
  - Induced expression of CTLA4 and ICOS
  - Suppress IFN-γ production from inflammatory macrophages
- Repair UV induced tissue damage
  - Express CD103 (Integrin αE) and P-lig (P-selectin ligand)
  - Suppress dendritic cells to respond to self-mRNA



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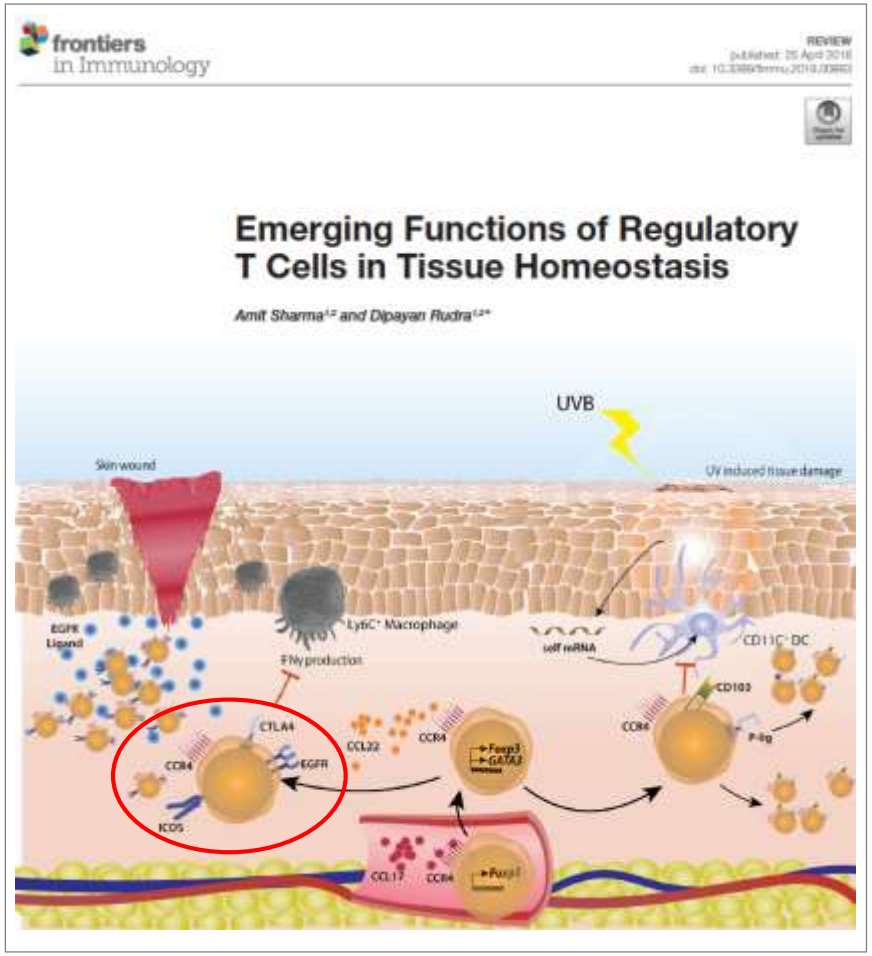

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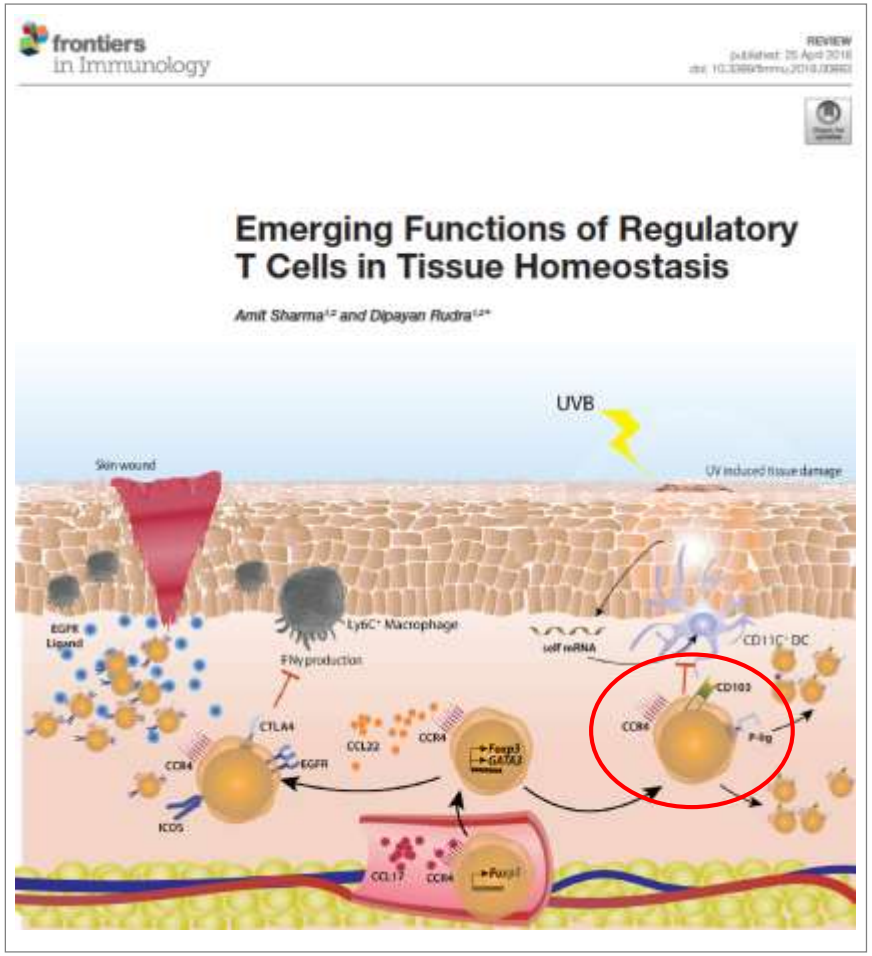
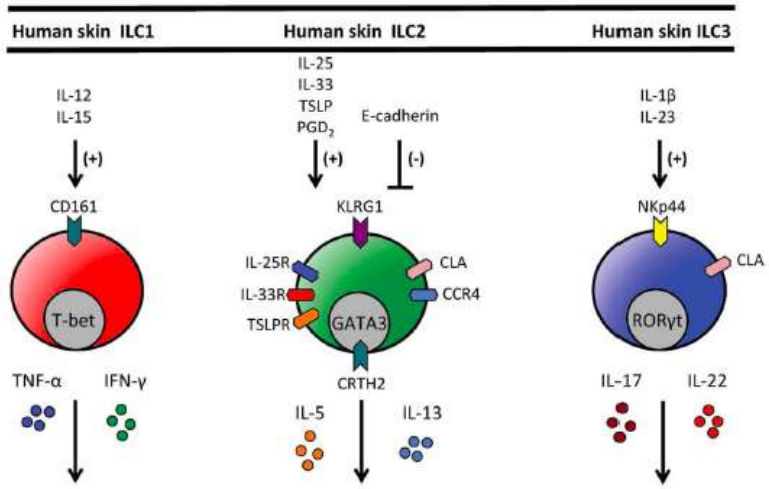


Innate lymphoid cells

PRECLINICAL SCIENCE

- Derive from common lymphoid progenitor
- Do not express cell lineage markers associated with T cells, B cells, DCs, macrophages and granulocytes
- ‚Innate' immune system
- Currently divided into 3 groups based on transcription factor/cytokine profile



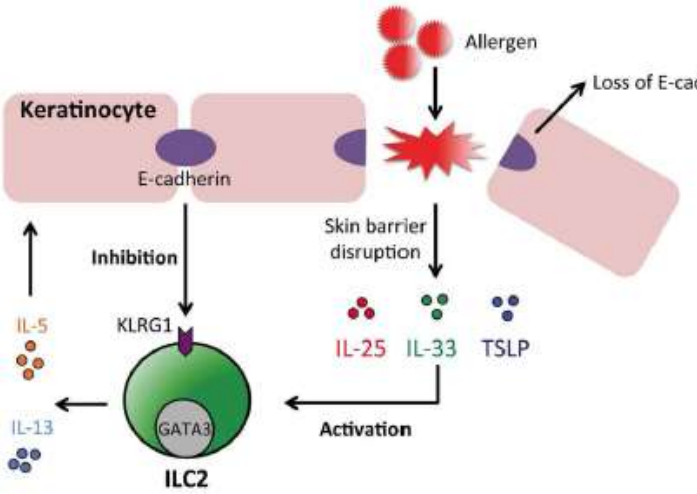
(NK cells)

HHS Public Access
Author manuscript
J Invest Dermatol. Author manuscript; available in PMC 2015 September 01.

Published in final edited form as:
J Invest Dermatol. 2015 March ; 135(3): 673–678. doi:10.1038/jid.2014.401.

Innate Lymphoid Cells in the Skin

Brian S. Kim[1]
[1]Division of Dermatology, Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA. Telephone: (314) 362-8187

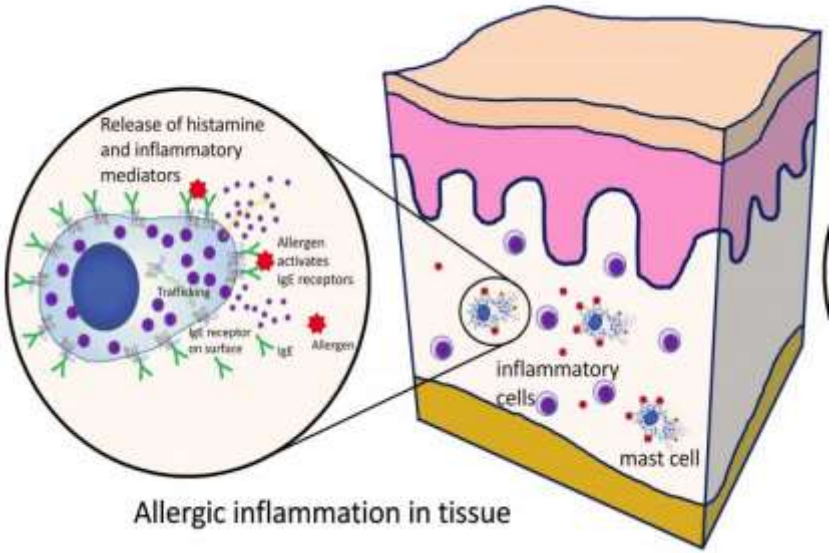


Human skin ILC2s are activated by keratinocyte-derived cytokines IL-25, IL-33 and/or TSLP to produce IL-5 and IL-13. In contrast, the keratinocyte cell adhesion molecule E-cadherin has been shown to inhibit the activation of skin ILC2s, possibly via KLRG1.

Mast cells

PRECLINICAL SCIENCE

- Particularly frequent in skin
- Major effector cells in innate and adaptive immune response
- Variety of cell surface receptors
  - Toll-like receptor
- Activated by IgE, IgG, complement, proteases, hormones, neuropeptides, etc.
- Produce a plethora of pro-inflammatory mediators

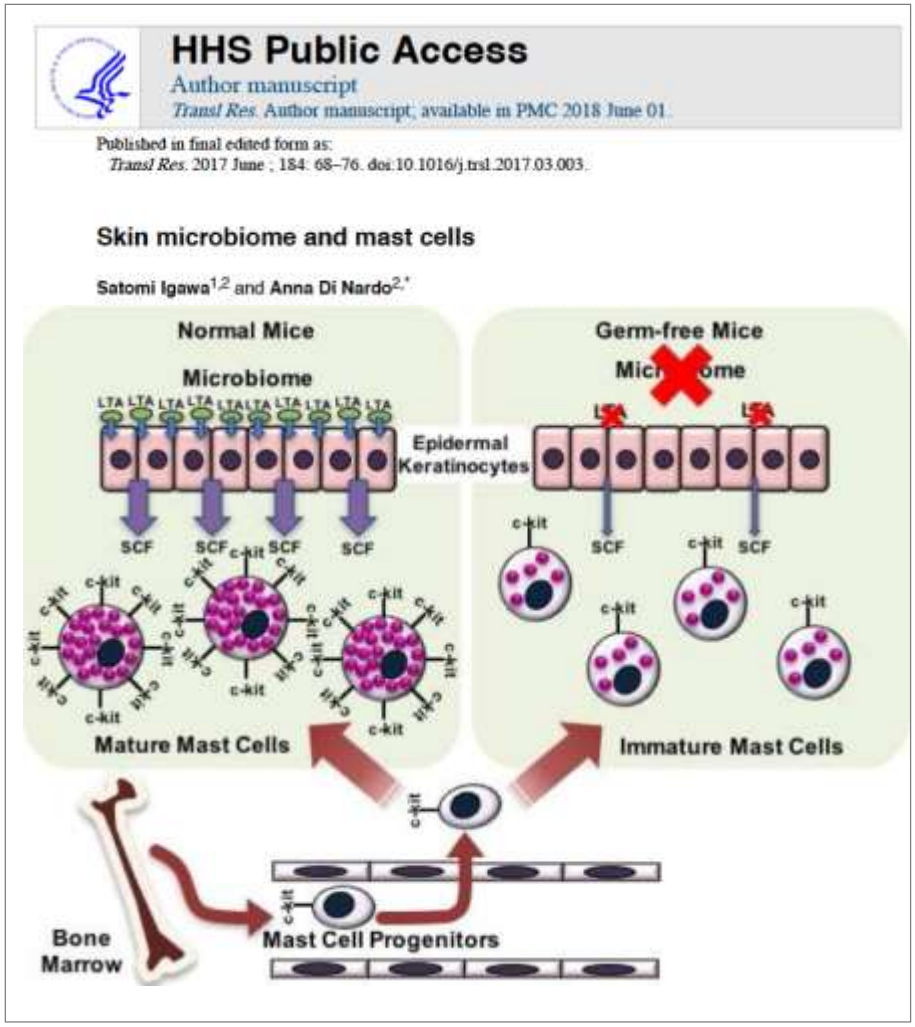


Allergic inflammation in tissue

Mast cells

PRECLINICAL SCIENCE

- Hematopoietic origin
- Migrate as immature progenitor cells
- Complete maturation in peripheral tissues
- Skin microbiome is important for mast cell maturation
- LTA (lipoteichoic acid; major constituent of bacterial cell wall) from the skin microbiome induces keratinocytes to produce sufficient SCF, which results in proper mast cell maturation



Skin microbiome

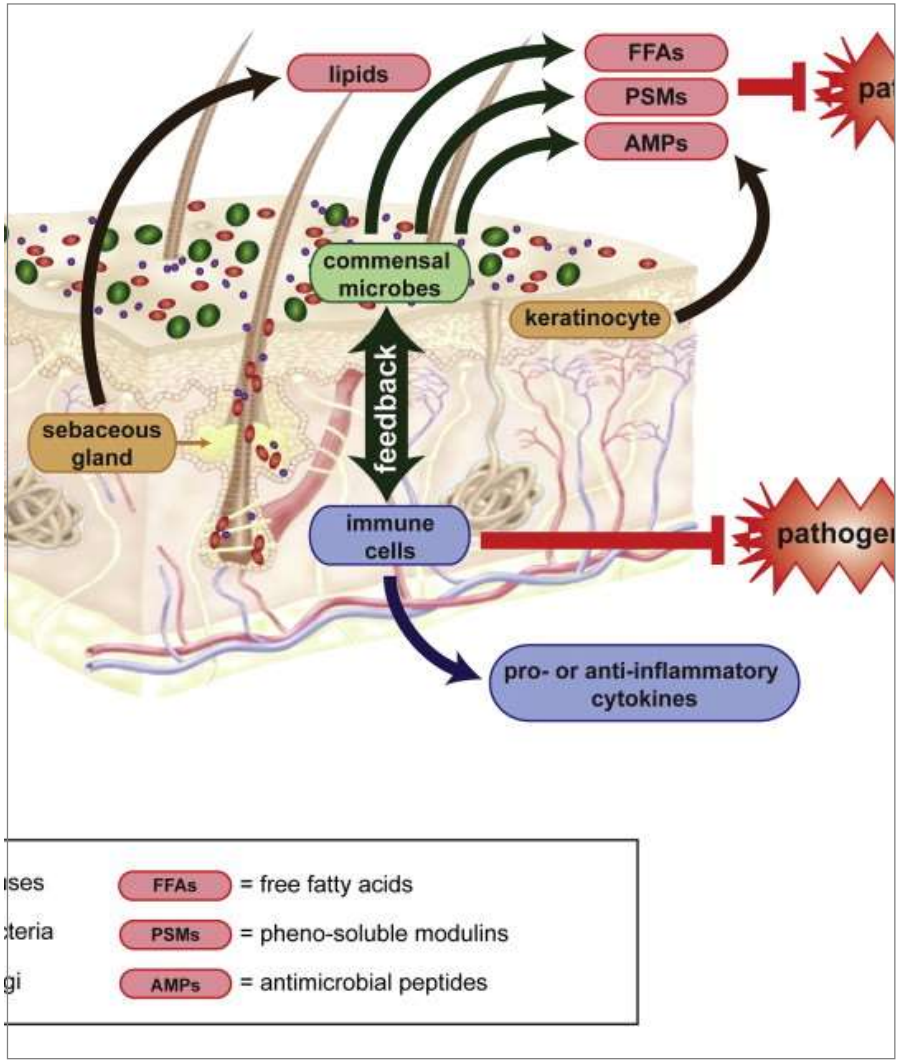
PRECLINICAL SCIENCE

- Diverse commensal organisms that inhabit the skin, hair, and glands
- Bacteria, fungi (*Malassezia spp.*), arthropods (*Demodex spp*.)
- High level of diversity at the species level but low diversity at phylum level
- Human skin: predominantly Gram-positive bacteria
- Bacterial products such as LTA permeate skin
- Diet, environment, genetics, and anatomic location contribute to the microbiome
- Usually without evidence of clinical disease
- Microbiome is deranged as a result of many skin diseases

Skin microbiome

PRECLINICAL SCIENCE

- Homeostasis of microbiome controlled by
  - Lipids (sebaceous glands)
  - Free fatty acids (keratinocytes)
  - Antimicrobial peptides (keratinocytes)



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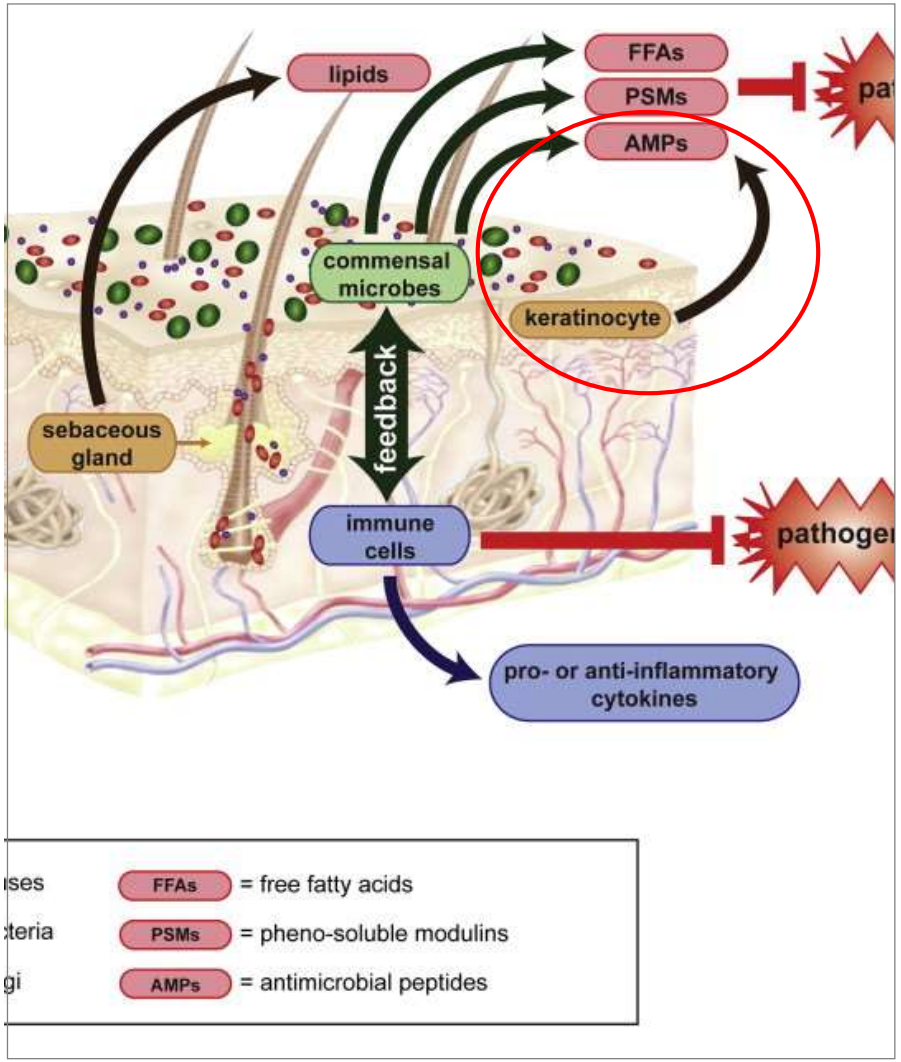
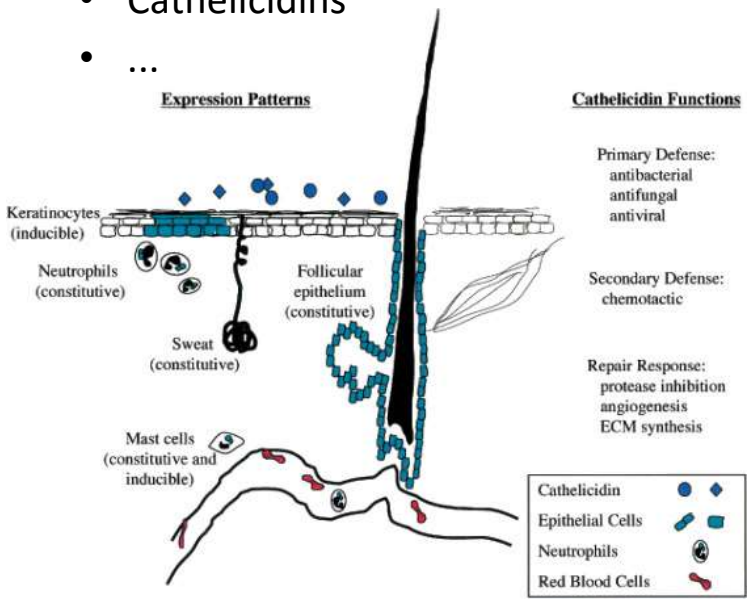


Antimicrobial peptides

PRECLINICAL SCIENCE

- AMPs in resident skin cells:
  - Cathelicidins
  - …



- Direct antimicrobial activity
- Initiation of a host response resulting in **cytokine release from T cells and keratinocytes**

Published in final edited form as:
J Allergy Clin Immunol. 2008 August ; 122(2): 261–266. doi:10.1016/j.jaci.2008.03.027.

Antimicrobial peptides and the skin immune defense system

Jürgen Schauber, MD[a] and **Richard L. Gallo, MD, PhD**[b]

[a]the Department of Dermatology and Allergology, Ludwig-Maximilians-University, Munich, Germany

[b]the Division of Dermatology, University of California, and VA San Diego Healthcare System, San Diego, California

TABLE I
Mammalian peptides with antimicrobial activity in skin (AMPs)*

AMP	Reference
AMPs identified in resident cells	
Cathelicidins	Frohm et al (1997)[9]
	Marchini et al (2002)[10]
β-Defensins	Harder et al (1997)[11]
	Liu et al (1998)[12]
Bactericidal/permeability-increasing protein (BPI)	Takahashi et al (2004)[13]
Lactoferrin	Cumberbatch et al (2000)[14]
Lysozyme	Marchini et al (2002)[10]
Dermcidin	Schittek et al (2001)[15]
	Murakami et al (2002)[6]
Histones	Rose et al (1998)[16]
S100A15	Büchau et al (2007)[17]
RNase 7	Harder et al (2002)[18]
AMPs identified in infiltrating cells	
Cathelicidins	Gallo et al (1994)[19]
	Marchini et al (2002)[10]
α-Defensins	Harwig et al (1993)[20]

IL-17 and resistance to mucocutaneous infections

PRECLINICAL SCIENCE

- IL-17 KO mice display a broad vulnerability to various infectious agents at diverse mucocutaneous surfaces
- In humans, IL-17A/F and/or IL-22 are essential for mucocutaneous immunity to *Candida albicans*
- Dual neutralization of IL-1β/IL-17A leads to sponaneous skin infections in non-human primates

The Journal of Pharmacology and Experimental Therapeutics
J Pharmacol Exp Ther 364:431–441, March 2018

Dual Blockade of Interleukin-1*b* and Interleukin-17A Reduces Murine Arthritis Pathogenesis but Also Leads to Spontaneous Skin Infections in Nonhuman Primates

Melanie C. Ruzek, Lili Huang, Ting- Ting Zhang, Shaughn Bryant, Peter F. Slivka, Carolyn A. Cuff, Catherine Tripp, and Guenter Blaich

AbbVie Bioresearch Center, Worcester, Massachusetts (M.C.R., L.H., T.T.Z., S.B., P.F.S., C.A.C., C.T.); and AbbVie Deutschland, Ludwigshafen, Germany (G.B.)

Received July 19, 2017; accepted December 12, 2017

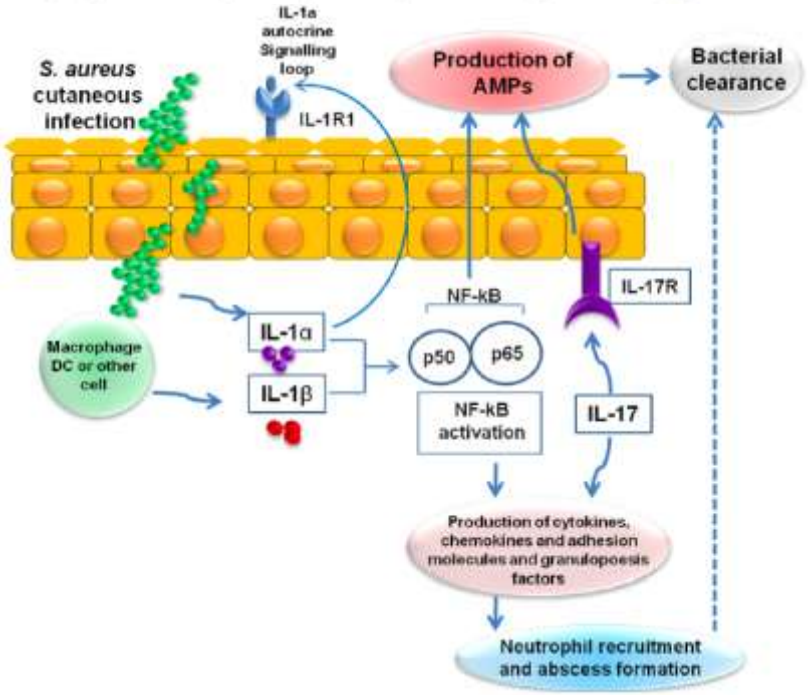
Int. J. Mol. Sci. **2014**, *15*, 8753-8772; doi:10.3390/ijms15058753

OPEN ACCESS
International Journal of
Molecular Sciences
ISSN 1422-0067
www.mdpi.com/journal/ijms

Review

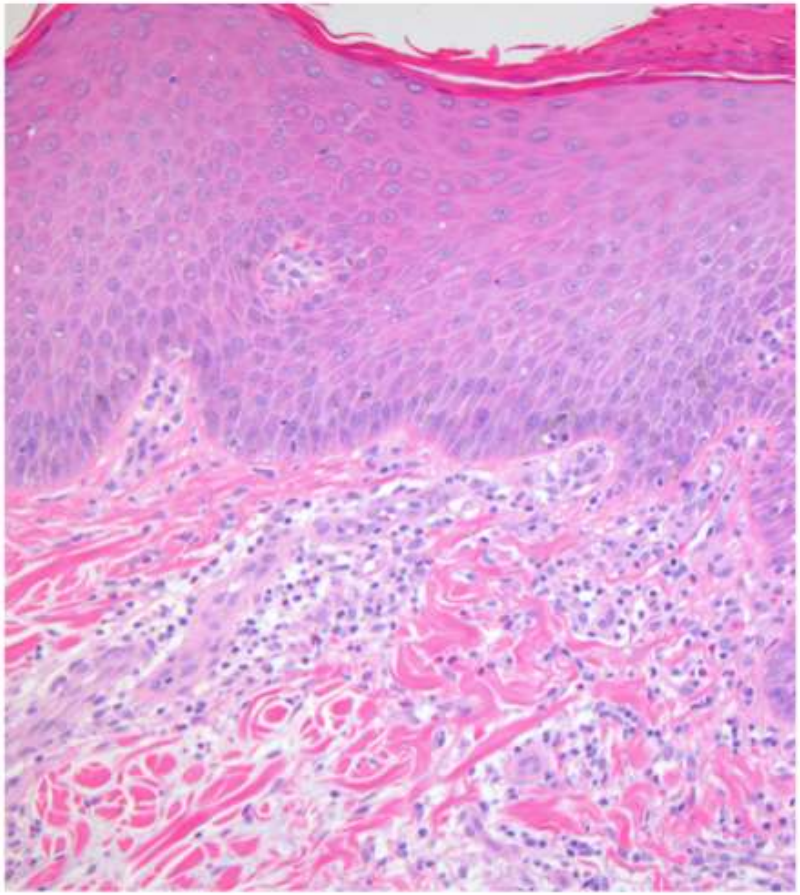
Colonization and Infection of the Skin by *S. aureus*: Immune System Evasion and the Response to Cationic Antimicrobial Peptides

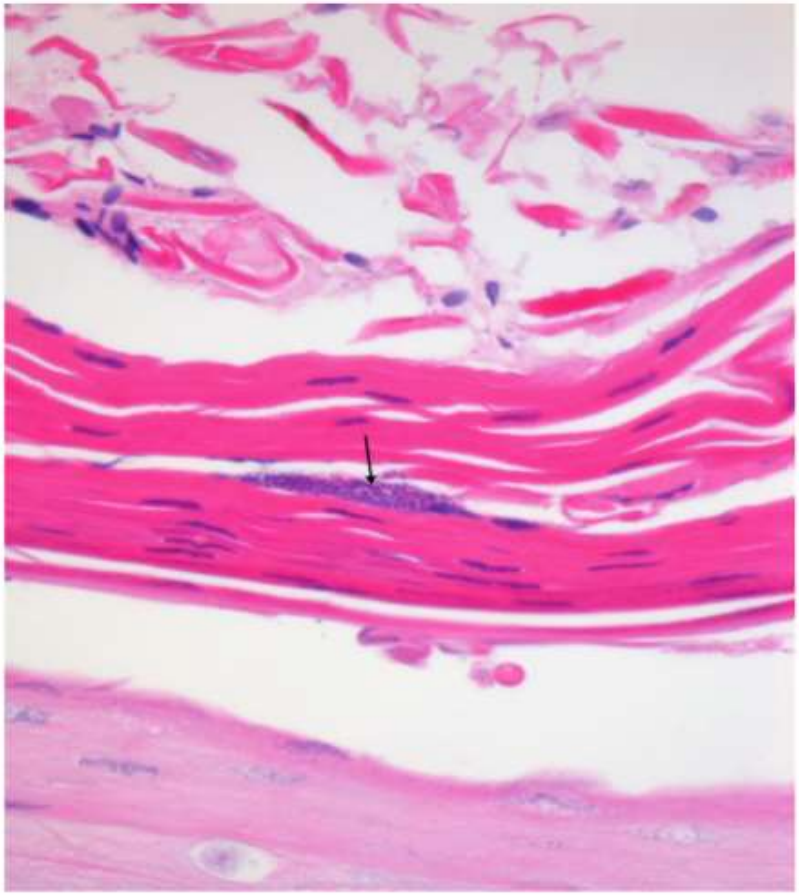
Sunhyo Ryu [1], Peter I. Song [2], Chang Ho Seo [3], Hyeonsook Cheong [1] and Yoonkyung Park [1,*]



Neutralization of IL-1β and IL-17

PRECLINICAL SCIENCE





Skin from cynomolgus macaque

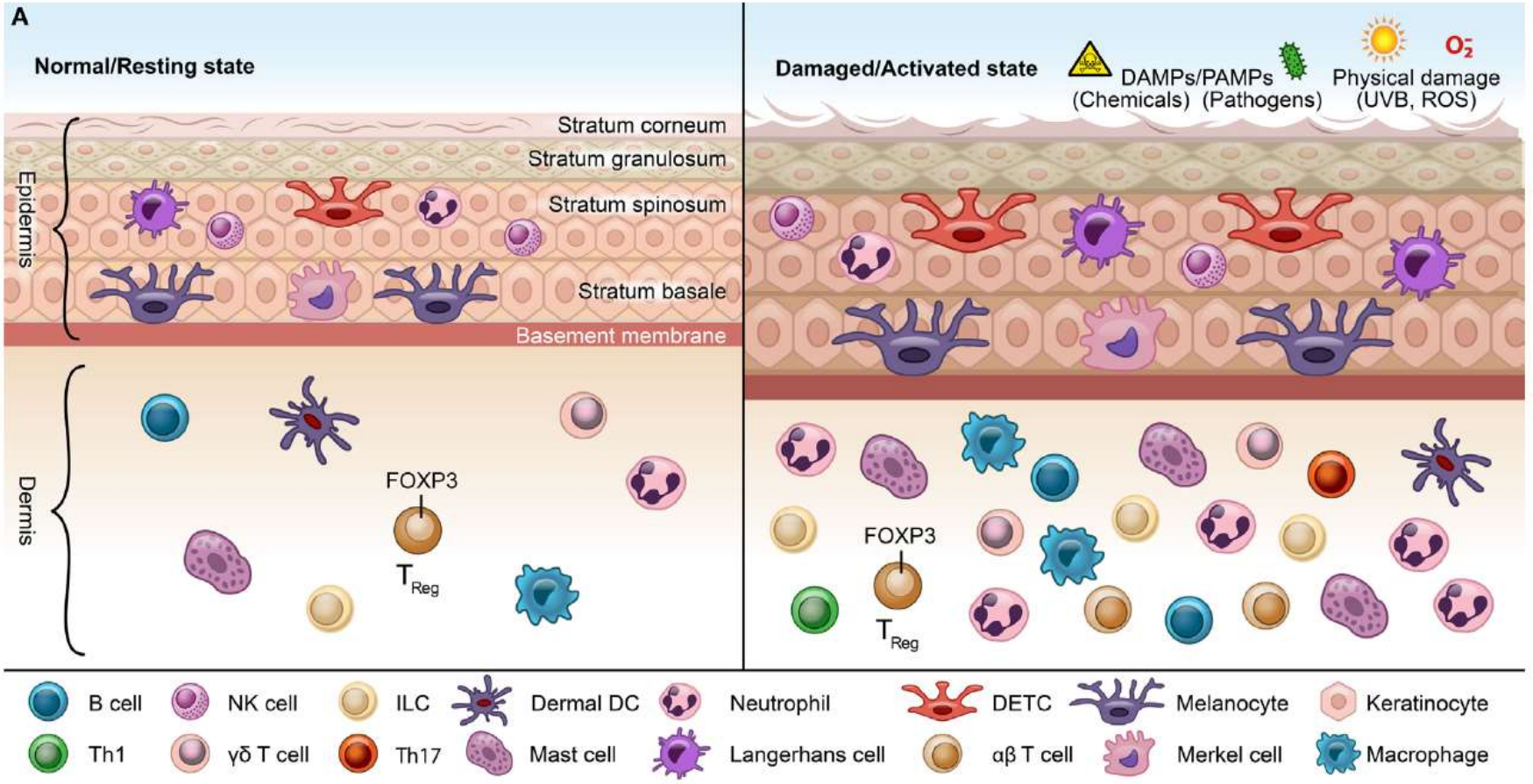
Skin immune response

PRECLINICAL SCIENCE

frontiers in Immunology

More Than Skin Deep: Autophagy Is Vital for Skin Barrier Function

Payel Sil[1*], Sing-Wai Wong[1,2] and Jennifer Martinez[1]



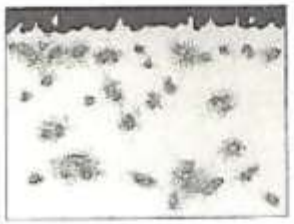
Patterns of skin inflammation

PRECLINICAL SCIENCE

A Superficial perivascular

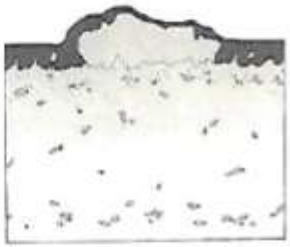
B Superficial and deep perivascular

C Nodular

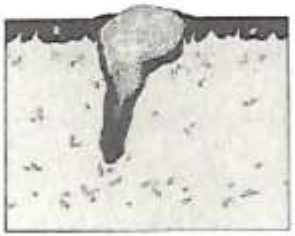


D Vascular

E Intraepidermal vesicular

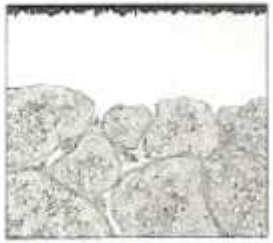


F Subepidermal vesicular

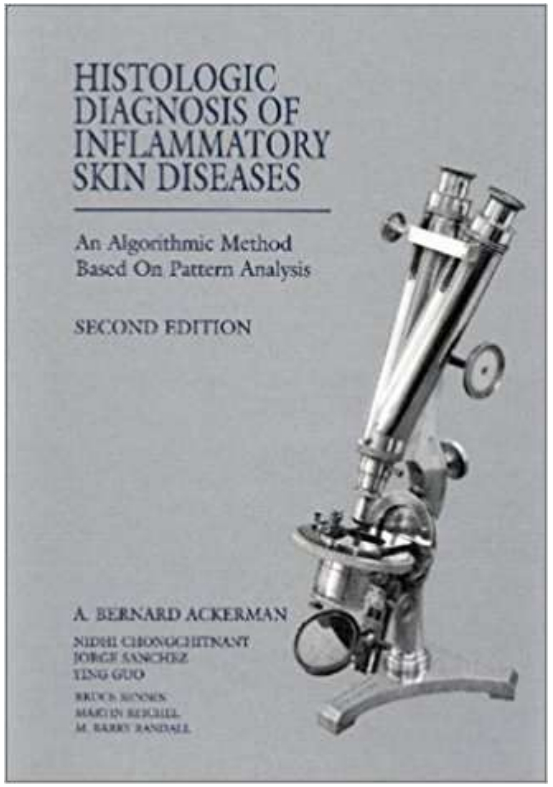


G Follicular

H Fibrosing



I Subcutaneous/ Pannicular



Patterns of skin inflammation

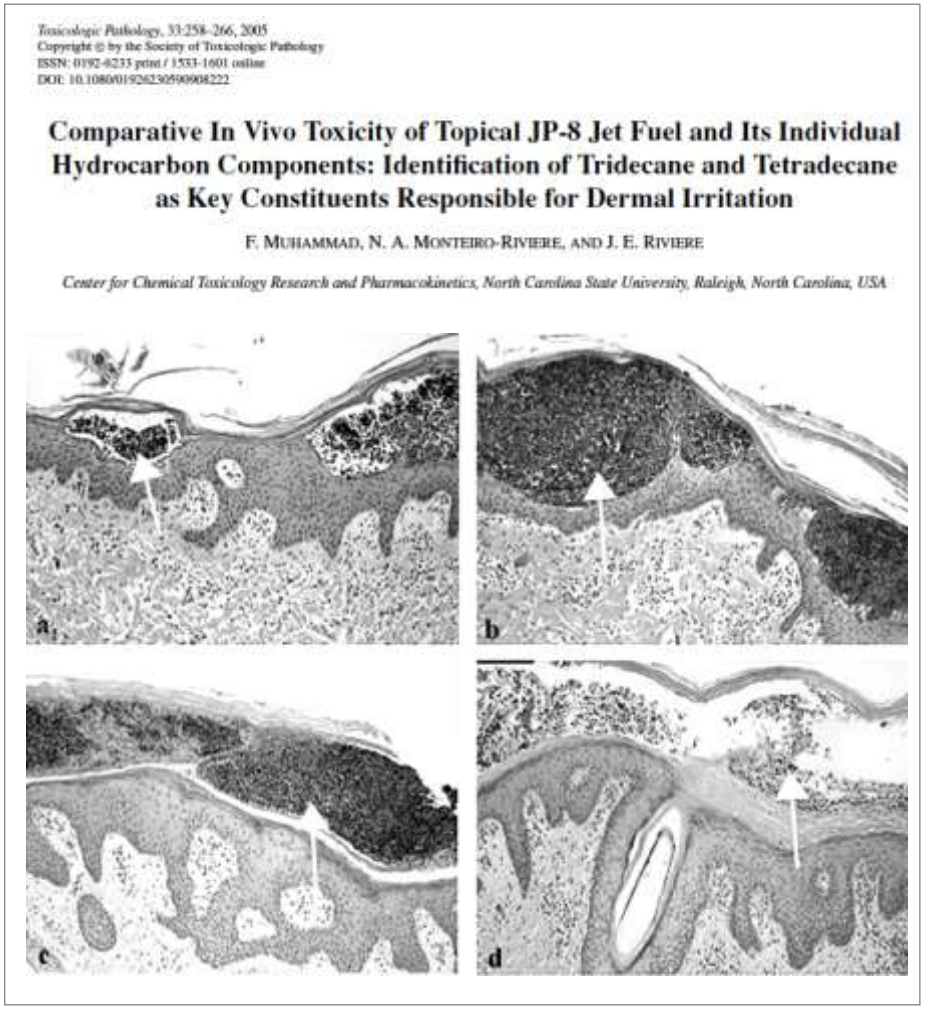
PRECLINICAL SCIENCE

Pattern	Description	Main Diseases
Inflammation, superficial perivascular	Inflammation in the superficial dermis only	• **Irritant contact dermatitis** • **Allergic contact dermatitis** • Urticaria • Atopic dermatitis • Photoirritation / photoallergy
Inflammation, vesicular / pustular	Formation of clear spaces (vesicles) or spaces filled with inflammatory cells (pustules) within the epidermis	• Pemphigus • Superficial bacterial infection • **Allergic contact dermatitis**
Inflammation, lichenoid	Inflammation at the interface between epidermis and dermis, with or without evidence of keratinocyte necrosis	• Systemic lupus erythematosus • **Erythema multiforme** • **Stevens-Johnson Syndrome** • **Toxic epidermal necrolysis**
…	…	• …

Irritant contact dermatitis

PRECLINICAL SCIENCE

- Topical administration of JP-8 jet fuel (hydrocarbon constituents)
- Clinical observations: Erythema
- Microscopic findings
  - Superficial inflammation
  - Epidermal hyperplasia
  - Intracellular and intercellular edema
  - Pustules
  - Parakeratotic hyperkeratosis



Toxicologic Pathology, 33:258–266, 2005

ISSN: 0192-0233 print / 1533-1601 online
DOI: 10.1080/01926230590908222

Comparative In Vivo Toxicity of Topical JP-8 Jet Fuel and Its Individual Hydrocarbon Components: Identification of Tridecane and Tetradecane as Key Constituents Responsible for Dermal Irritation

F. MUHAMMAD, N. A. MONTEIRO-RIVIERE, AND J. E. RIVIERE

Center for Chemical Toxicology Research and Pharmacokinetics, North Carolina State University, Raleigh, North Carolina, USA

Allergic contact dermatitis

PRECLINICAL SCIENCE

- 2-yr-old cynomolgus macaque
- Blisters, papules, crusts at hands, wrists, feet, face, ear

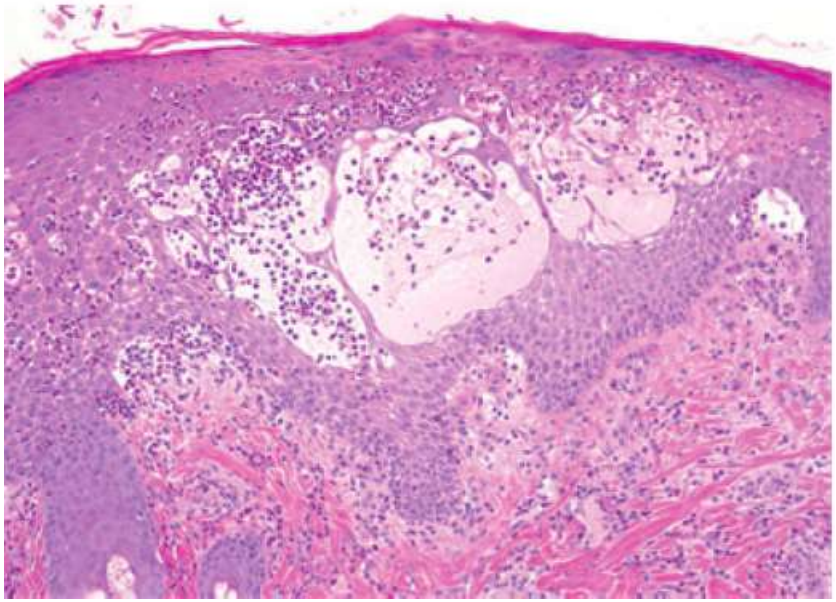
J Med Primatol doi:10.1111/j.1600-0684.2007.00256.x

ORIGINAL ARTICLE

A case of suspected contact dermatitis in a juvenile cynomolgus monkey (*Macaca fascicularis*)

Joanne Morris & Marcia Etheridge

Department of Laboratory Animal Science, GlaxoSmithKline, PA, USA



Irritant contact dermatitis

PRECLINICAL SCIENCE

- Arises **locally** on **initial contact** with chemicals or physical agents that damage the surface of the skin
- Clinically and morphologically similar to allergic contact dermatitis, **but activation of innate skin immunity by release of mediators from injured epidermal cells**
- T-cell activation by **antigen-independent** pathways

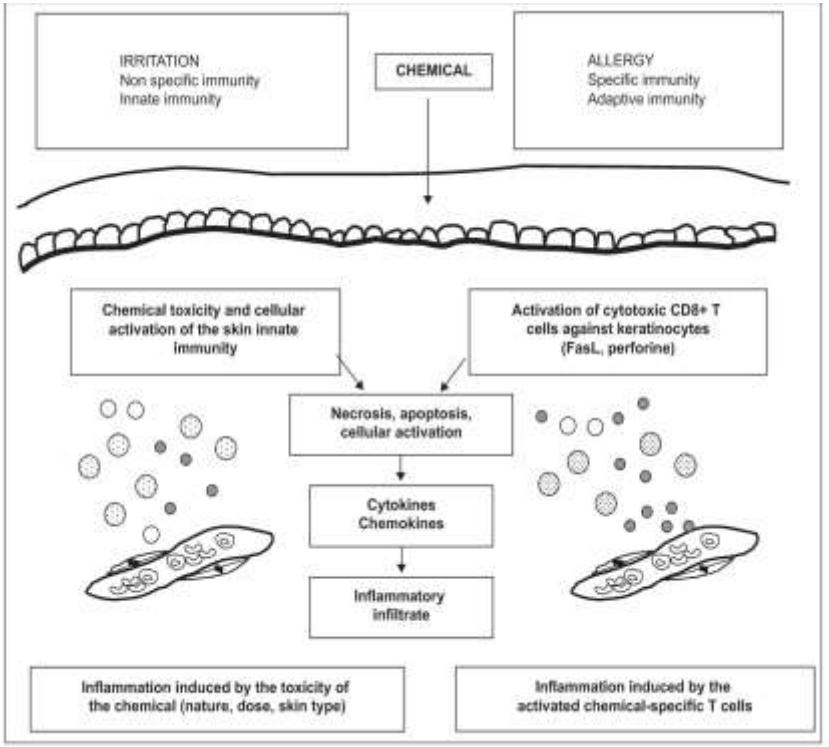
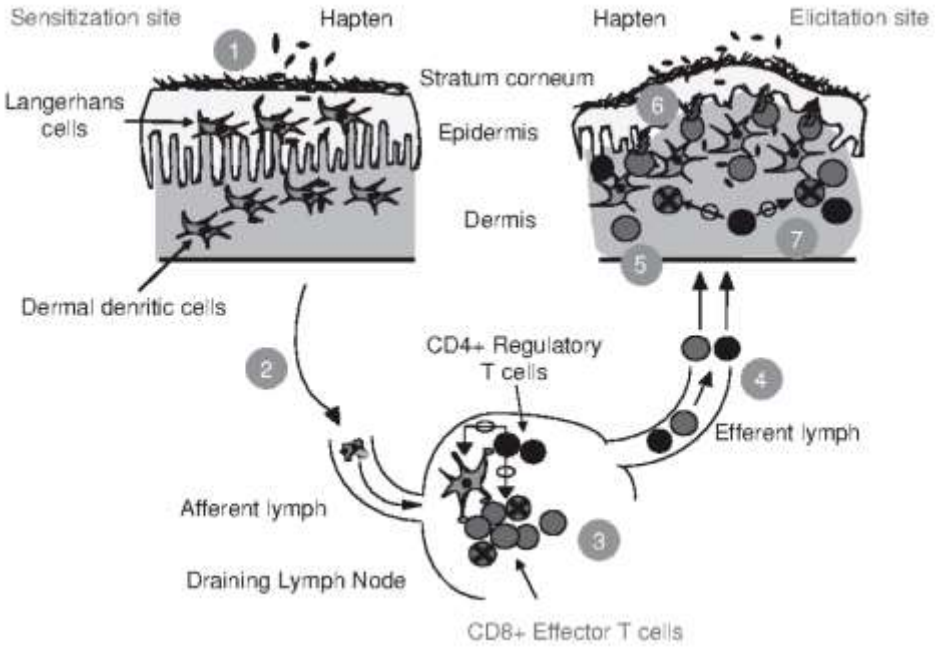


Figure 1. Immune mechanisms in ICD and ACD. ICD and ACD are induced by skin contact with chemicals. The early stage

Allergic contact dermatitis

PRECLINICAL SCIENCE

- **Local (cutaneous) disease**
- Topical allergens
- Arises following **more than one skin contact** with an allergic chemical (induction – elicitation)
- Skin response is delayed
- Immunologically mediated (type IV)
  - Required activation of antigen-specific acquired immunity leading to the activation and clonal expansion of specific allergen-responsive effector T-cells



Hypersensitivity

PRECLINICAL SCIENCE

- Exaggerated (inappropriate) immune response against allergens
- Classification according to Coombs and Gell 1963

Category	Pathomechanism	Main diseases associated with this pattern
Category I	IgE-mediated mast cell degranulation	- Urticaria / Angioedema - Atopic dermatitis
Category II	Antibody-mediated cytotoxicity	- Pemphigus
Category III	Deposition of circulating antigen-antibody complexes	- Systemic lupus erythematosus - Cutaneous vasculitis
Category IV	Antigen-dependent activation of effector T cells	- **Allergic contact dermatitis** - Maculopapular exanthem - Drug-induced rash with eosinophilia and systemic symptoms - Acute generalized exanthematic pustulosis - Lichenoid / Fixed drug eruption - Erythema multiforme (minor/major) - Stevens-Johnson syndrome - Toxic epidermal necrolysis

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Cutaneous Adverse Drug Reactions in Man

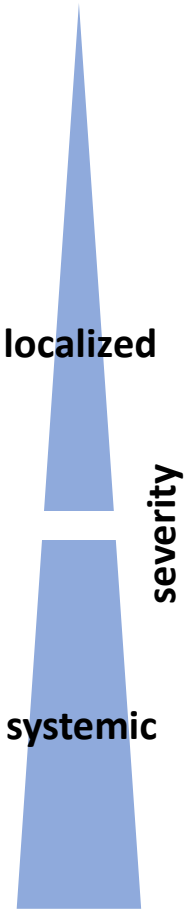
PRECLINICAL SCIENCE

Immediate

- Contact Urticaria (CU)
- Atopic dermatitis (AD)

Delayed

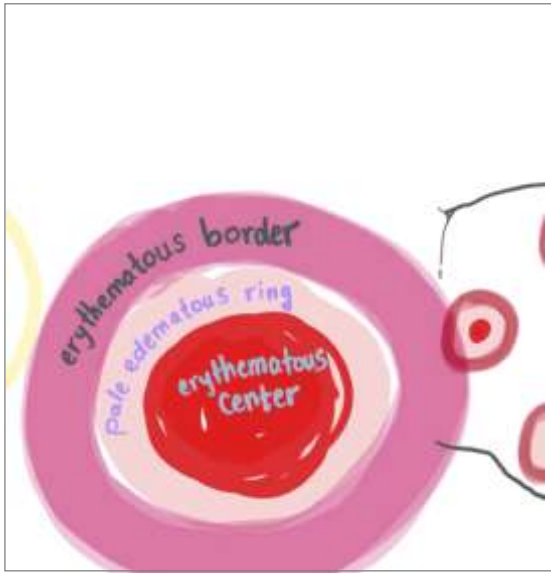
- Allergic Contact Dermatitis (ACD)
- Maculopapular exanthema (MPE)
- Drug-induced rash with eosinophilia and systemic syptoms (DRESS)
- Acute generalized exanthematic pustulosis (AGEP)
- Erythema multiforme (EM)/ Fixed drug eruption (FDE)
- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)

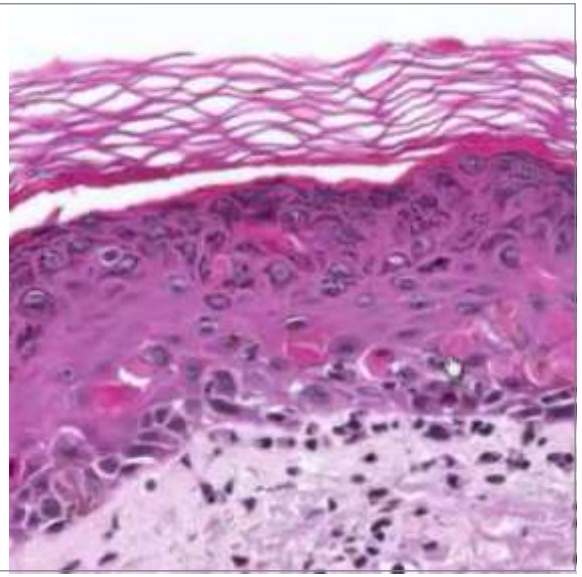


Erythema multiforme

PRECLINICAL SCIENCE

- Acute inflammatory condition with numerous etiologies (infections, drugs)

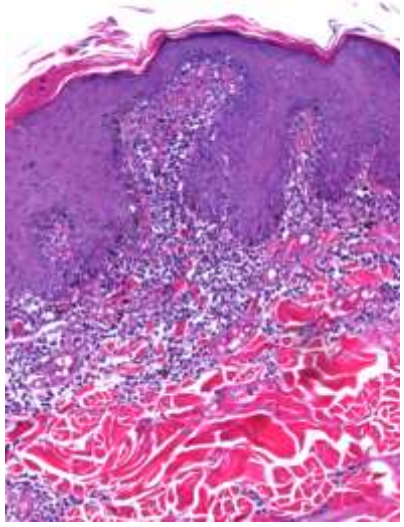
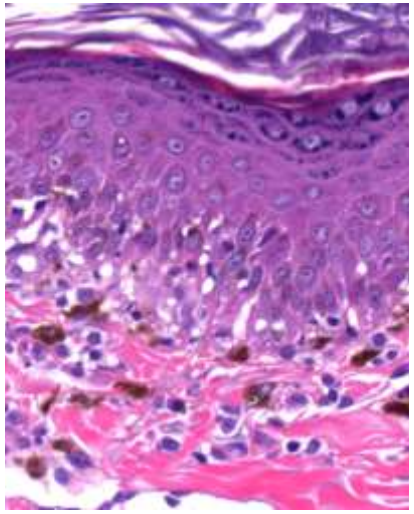
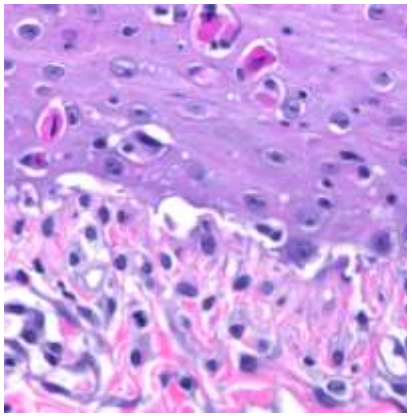
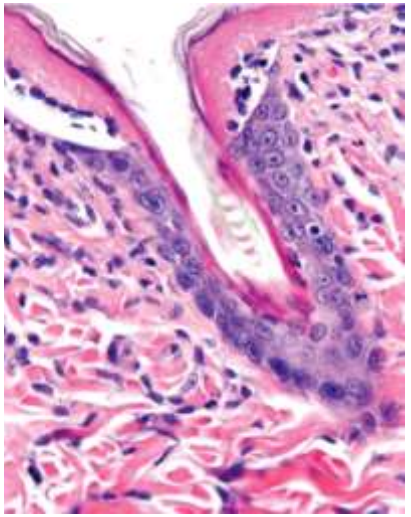




Interface dermatitis

PRECLINICAL SCIENCE

- Lichenoid inflammatory cell infiltrate (mononuclear) at the dermo-epidermal interface
- Keratinocyte necrosis
  - Single cell type
  - Full thickness type

Interface dermatitis in rats treated with nevirapine

PRECLINICAL SCIENCE

- Female Brown Norway rats *(Shenton et al. 2003; 2005)*
- Nevirapine
  - used to treat and prevent HIV/AIDS
  - most common adverse effect is mild or moderate rash; severe or life-threatening skin reactions have been observed in 1.5% of patients (Stevens–Johnson syndrome, toxic epidermal necrolysis)
- Repeated daily oral administration
- Clinical observations
  - Erythema on ear pinnae on study day 7
  - Erythema on back on study day 21
  - (if treatment was stopped and the rash was allowed to resolve, then the rechallenge resulted in a rapid recurrence of the rash within 24 hours)
- Microscopic findings
  - Superficial dermal lymphohistiocytic inflammation
  - Interface dermatitis with epidermal single-cell necrosis
- Pathogenesis
  - Disease can be transferred with isolated CD4 + T cells from sensitized animals

Drug-induced Interface Dermatitis in Cynomolgus macaques

PRECLINICAL SCIENCE

Toxicologic Pathology, 43: 995-1003, 2015
Copyright © 2015 by The Author(s)
ISSN: 0192-6233 print / 1533-1601 online
DOI: 10.1177/0192623315588114

Drug-induced Skin Lesions in Cynomolgus Macaques Treated with Metabotropic Glutamate Receptor 5 (mGluR5) Negative Allosteric Modulators

Gopinath S. Palanisamy[1], John M. Marcek[2], Gregg D. Capps[2], Jessica Whitehouse[2], Christopher L. Shaffer[3], Joseph T. Brady[2], and Christopher Houle[2]

Session: Case Studies of Cutaneous Toxicity, Direct and Systemic

Toxicologic Pathology
2016, Vol. 44(8) 601-606
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DOI: 10.1177/0192623316677710
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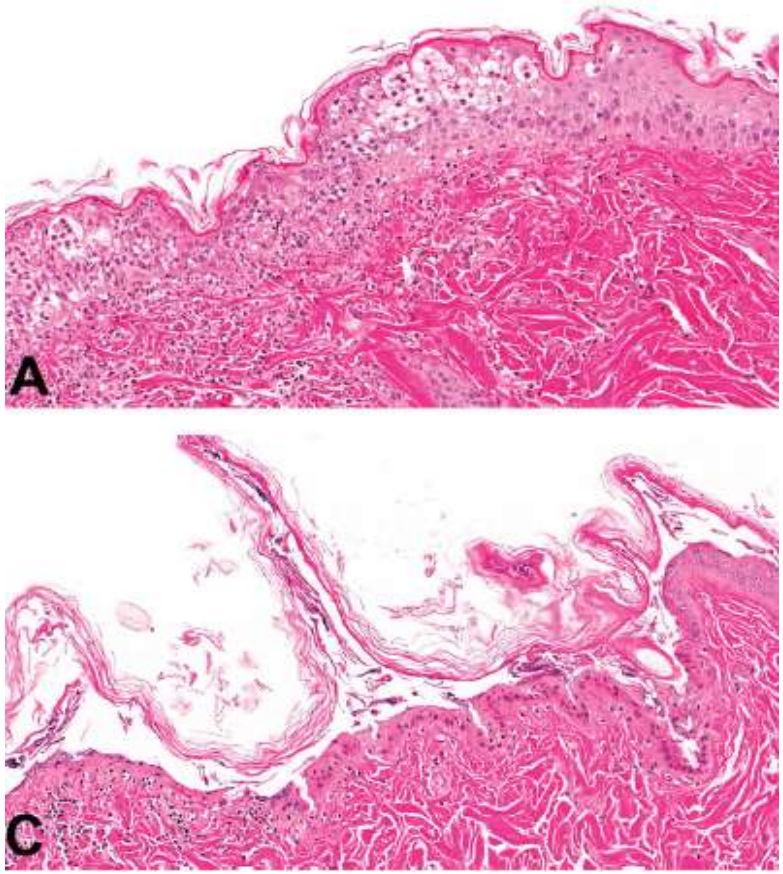
A Case of Drug-induced Cutaneous Toxicity Observed in Cynomolgus Monkeys

Rie Kikkawa[1]



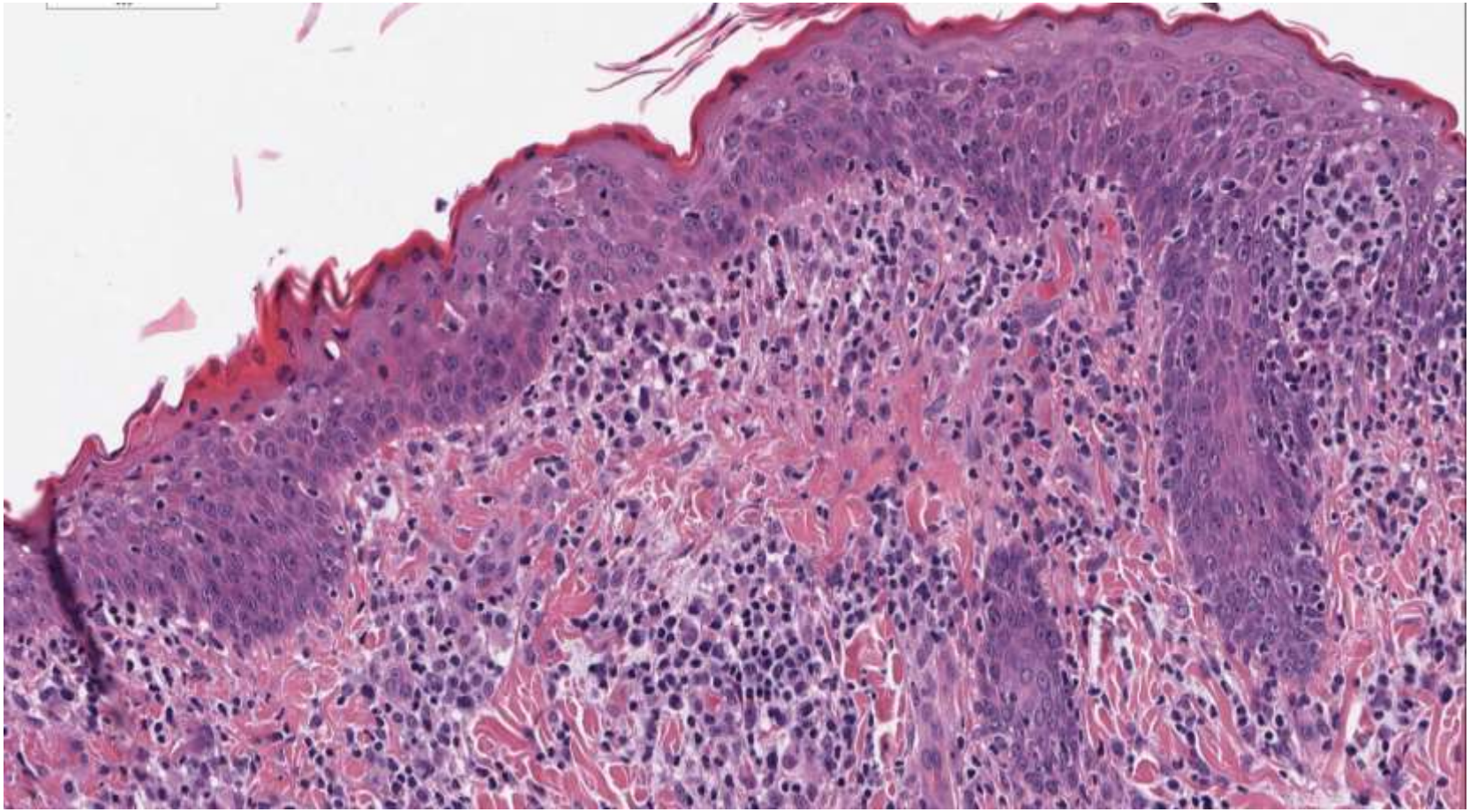
Drug-induced interface dermatitis in cynomolgus macaques

PRECLINICAL SCIENCE

- 28-day oral toxicity study with a NCE
- Day 33 (recovery)**: Focal skin ulceration** and scaling **on face** (cheek); systemic treatment with amoxicillin and metacam; animal separated from cagemate; slight **body weigth decrease** (10%)
- Day 34 (recovery): Focally extensive skin ulceration/ inflammation / scaling on face (cheek), **extending to lips** (cheilitis)
- Day 36 (recovery): **Extensive ulcerative/crusting dermatitis** on the face (affecting the cheeks, chin, perioral skin, upper and lower lips, and forehead), and marked erythema with multifocal ulceration and scaling on the medial aspect of both **forelimbs** (extending from the upper forelimb to the carpal joint region); additional lesions **on ears, vulva and tail**
- The animal was euthanized and several skin samples were collected for histopathology

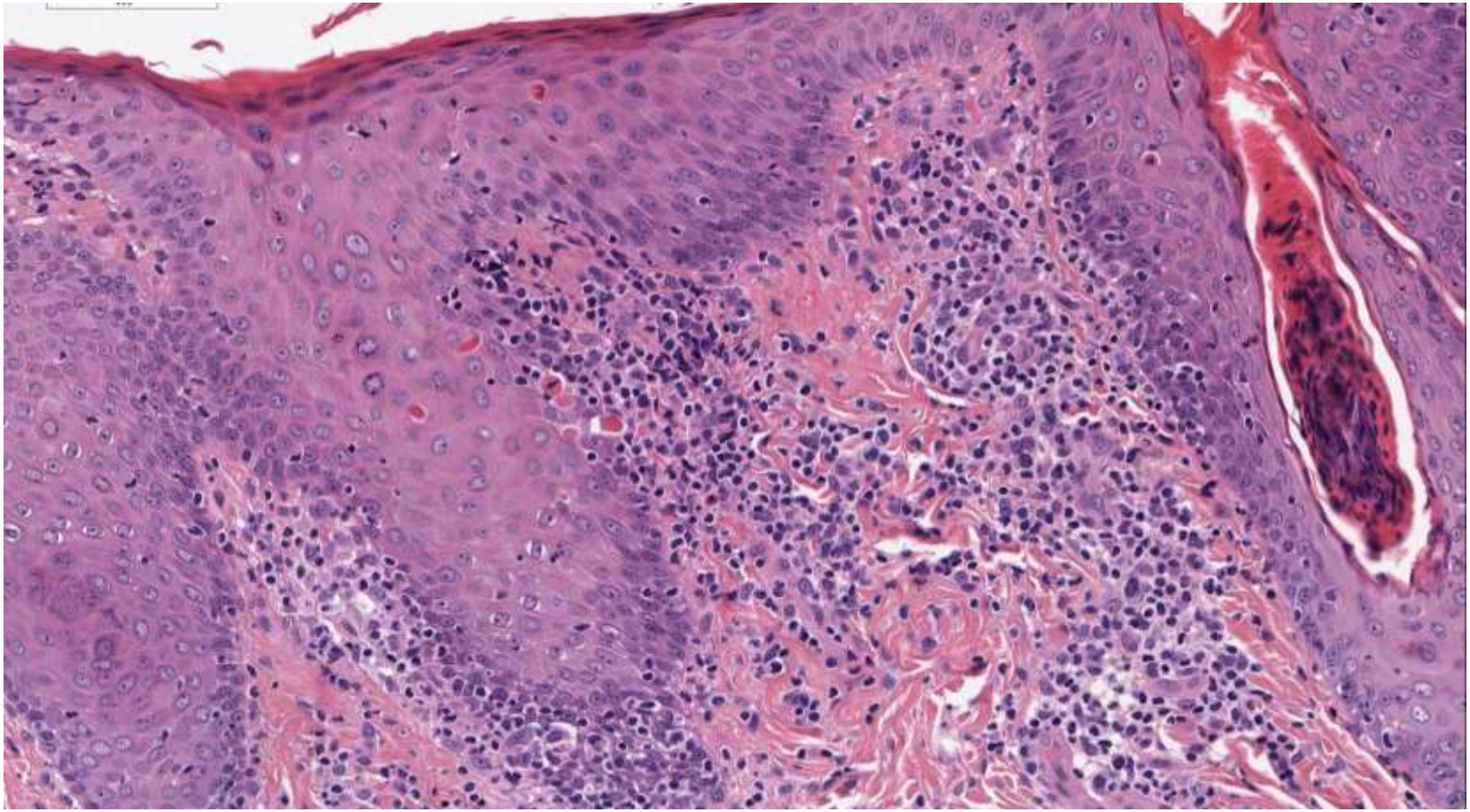
Drug-induced interface dermatitis in cynomolgus macaques

PRECLINICAL SCIENCE



Drug-induced interface dermatitis in cynomolgus macaques

PRECLINICAL SCIENCE



Drug-induced interface dermatitis

PRECLINICAL SCIENCE

- Very rare but histopathologically distinct entity (interface dermatitis) in rats, dogs, cynomolgus macaques
- Delayed onset of clinical signs
- Rapidly progressing to ulceration and several secondary findings
- Commonly affecting mucous membranes or mucocutaneous junctions
- Often in high dose animals

Thank you !

PRECLINICAL SCIENCE

Föll, Mecklenburg & Partner GmbH

www.preclinical-science.com

Althausweg 158 | 48159 Münster | Germany

Phone: +49 (251) 265 26 41

eMail: office@preclinical-science.com

Dr. Roman Föll, Dr. Lars Mecklenburg,
Dr. Geertje Lewin