What is our bread and butter disease?

1

Zeus

1 yr MN

French bull

2

3

Thank you to our Residents Review sponsors!

ZOETIS PETCARE

STALLERGENES GREER

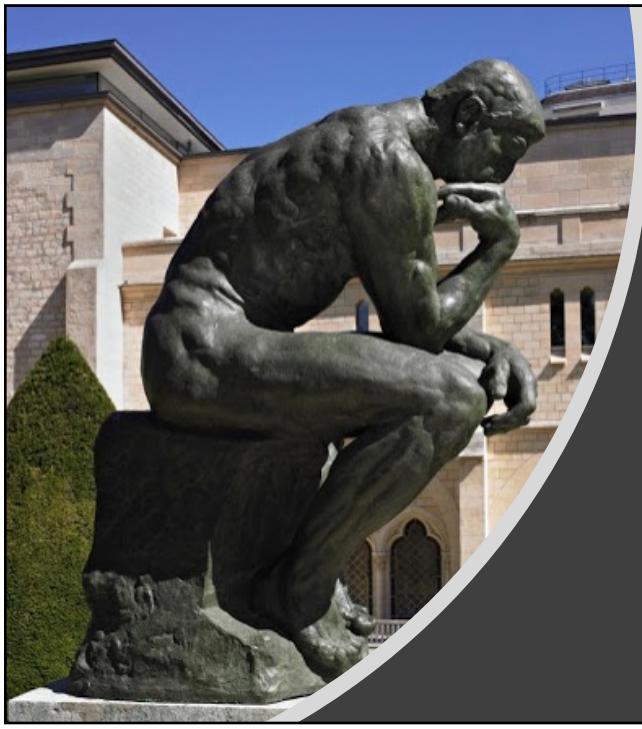
Life beyond allergy

4

Questions?

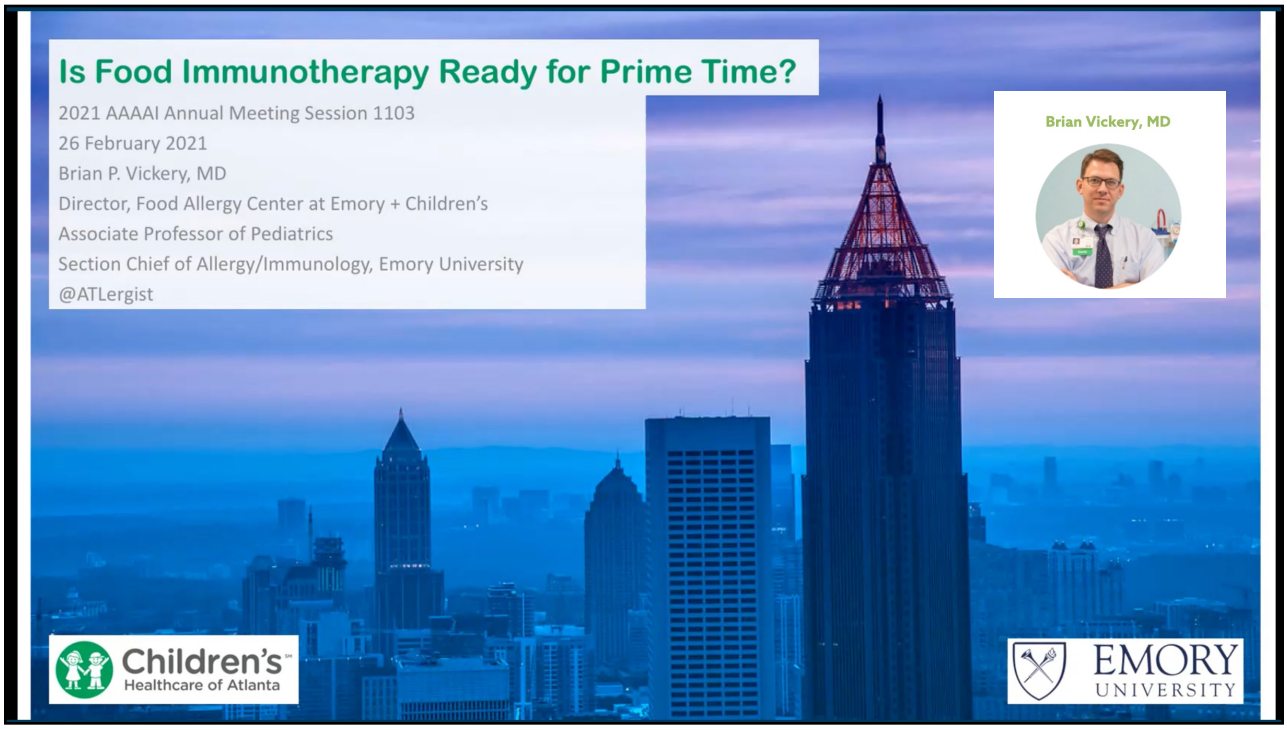
- Ask during the live portion of this session.
- Email me at fadokv@gmail.com OR valerie.fadok@zoetis.com
- Focus on applied/translational allergology!
  - What causes the disease?
  - What allows the disease to progress?
  - How do you diagnose the disease?
  - What interventions can you use to treat/ameliorate this disease?
  - And yes, what might we see in future?

5

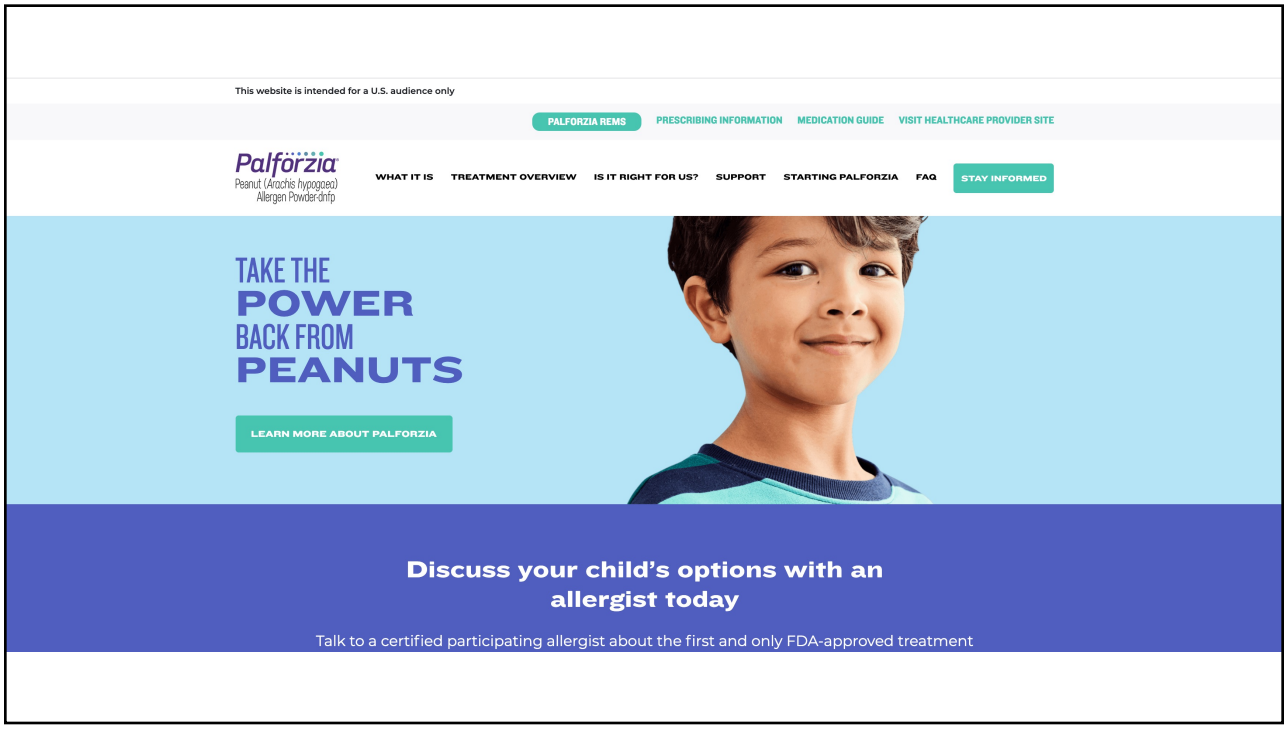


Be a critical thinker

6


Is Food Immunotherapy Ready for Prime Time?
2021 AAAAI Annual Meeting Session 1103
26 February 2021
Brian P. Vickery, MD
Director, Food Allergy Center at Emory + Children's
Associate Professor of Pediatrics
Section Chief of Allergy/Immunology, Emory University
@ATLergist
Brian Vickery, MD
Children's Healthcare of Atlanta
EMORY UNIVERSITY

7


This website is intended for a U.S. audience only
PALFORZIA REMS
PRESCRIBING INFORMATION
MEDICATION GUIDE
VISIT HEALTHCARE PROVIDER SITE
Palforzia
Peanut (Arachis hypogaea) Allergen Powder-dnfp
WHAT IT IS
TREATMENT OVERVIEW
IS IT RIGHT FOR US?
SUPPORT
STARTING PALFORZIA
FAQ
STAY INFORMED
TAKE THE POWER BACK FROM PEANUTS
LEARN MORE ABOUT PALFORZIA
Discuss your child's options with an allergist today
Talk to a certified participating allergist about the first and only FDA-approved treatment

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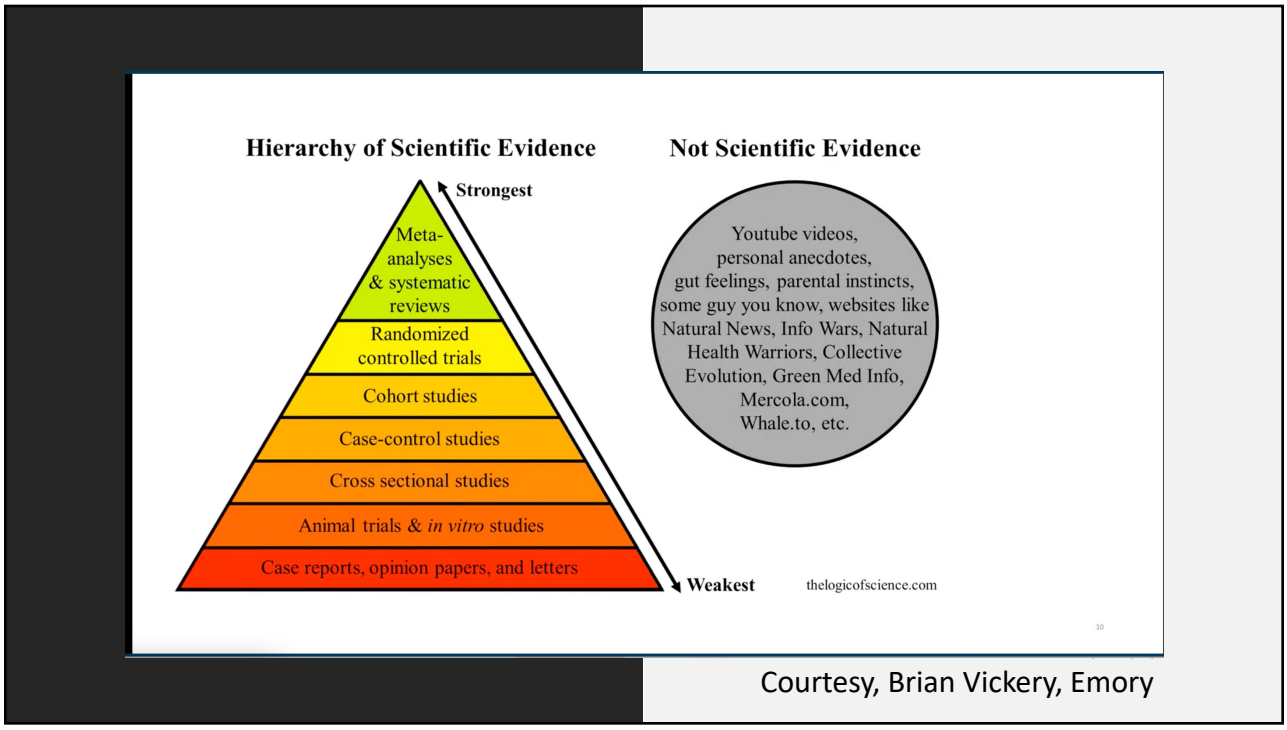


Courtesy, Brian Vickery, Emory

9

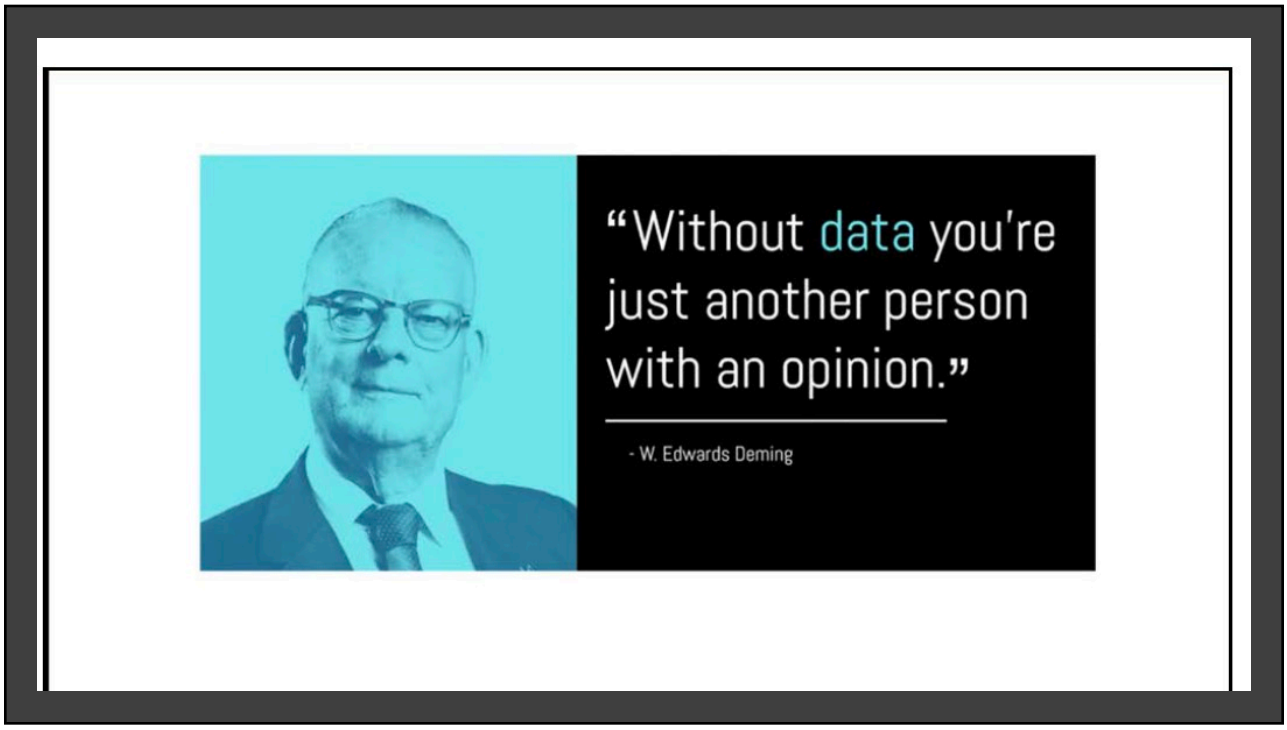
Table 4. PPV of Research Findings for Various Combinations of Power (1 – β), Ratio of True to Not-True Relationships *(R)*, and Bias *(u)*

1 – β	*R*	*u*	Practical Example	PPV
0.80	1:1	0.10	Adequately powered RCT with little bias and 1:1 pre-study odds	0.85
0.95	2:1	0.30	Confirmatory meta-analysis of good-quality RCTs	0.85
0.80	1:3	0.40	Meta-analysis of small inconclusive studies	0.41
0.20	1:5	0.20	Underpowered, but well-performed phase I/II RCT	0.23
0.20	1:5	0.80	Underpowered, poorly performed phase I/II RCT	0.17
0.80	1:10	0.30	Adequately powered exploratory epidemiological study	0.20
0.20	1:10	0.30	Underpowered exploratory epidemiological study	0.12
0.20	1:1,000	0.80	Discovery-oriented exploratory research with massive testing	0.0010
0.20	1:1,000	0.20	As in previous example, but with more limited bias (more standardized)	0.0015

The estimated PPVs (positive predictive values) are derived assuming $\alpha = 0.05$ for a single study.
RCT, randomized controlled trial.
DOI: 10.1371/journal.pmed.0020124.t004

Ioannidis JPA *PLoS Med* 2005 2(8): e124.

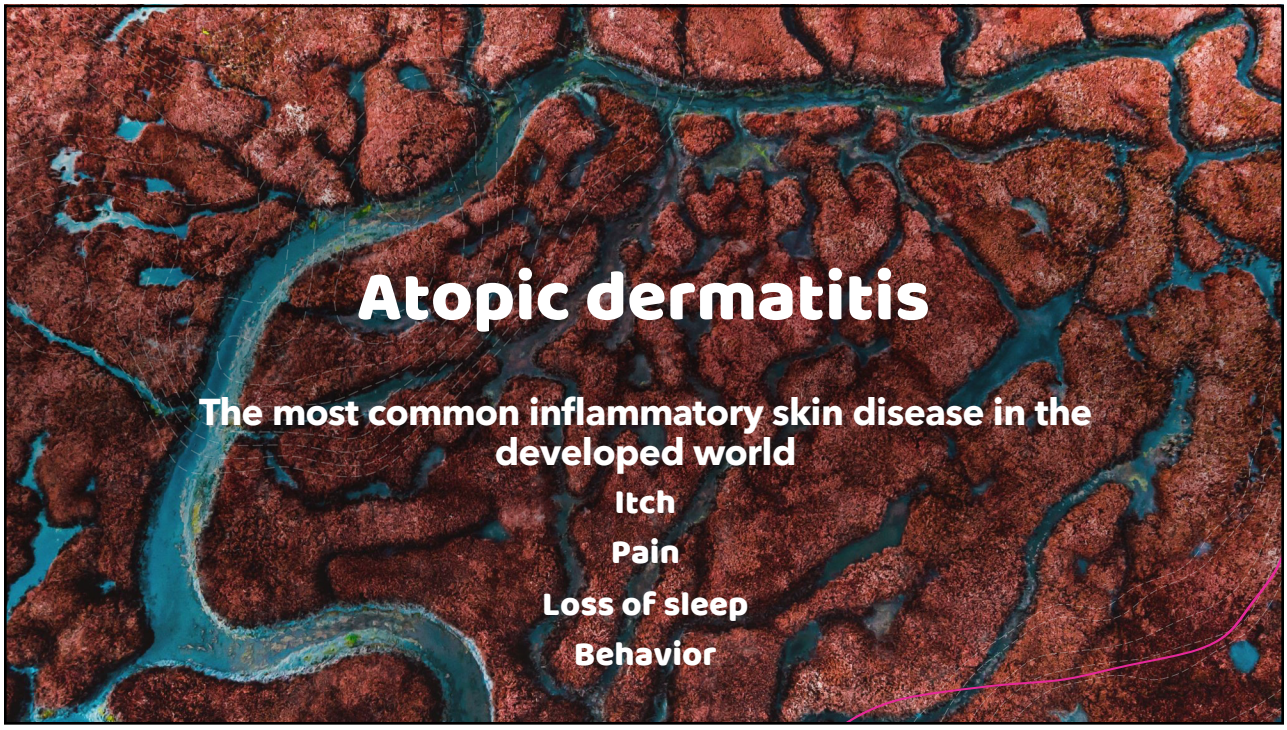
10


"Without data you're just another person with an opinion."
- W. Edwards Deming

11


"Drink deep or taste not the Pierian spring . . ."

12



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Given how common atopic diseases are in multiple species: take the comparative approach

veterinary sciences

MDPI

Review

Atopic Dermatitis in Animals and People: An Update and Comparative Review

Rosanna Marsella [1,2,*] and Anna De Benedetto [1]

Vet Sci 2017: 4, 37

POSITION PAPER

WILEY Allergy

Allergen immunotherapy in people, dogs, cats and horses – differences, similarities and research needs

R. S. Mueller[1] | E. Jensen-Jarolim[2,3] | F. Roth-Walter[2] | E. Marti[4] | J. Janda[5] | A. A. Seida[6] | D. DeBoer[7]

Allergy 2018; 73:1989

14

From your study guide:

Atopy and Hypersensitivity

- Origin and physiology of cells that play a role in atopic dermatitis and other hypersensitivities (e.g., keratinocytes, dendritic cells, mast cells, basophils, eosinophils, lymphocytes)
- Origin and physiology of antibodies that play a role in atopic dermatitis and other hypersensitivities
- Role of inflammatory mediators in atopic dermatitis and other hypersensitivities (e.g., biogenic amines, granule proteins, lipid mediators, cytokines, chemokines)
- Pathophysiology of atopic dermatitis (e.g., barrier function, flare factors, pruritus, immune imbalance, superantigens, microbiome alterations, genetics)
- Pathophysiology of other hypersensitivity disorders that affect the skin (e.g., parasite, microbial, adverse food reaction, contact versus irritant reaction, adverse drug reaction, eosinophilic skin disorders)

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Good Resources!

- Revolutionizing Atopic Dermatitis
- Veterinary Dermatology and beyond!
  - Type "canine atopic dermatitis" or "pathogenesis of canine atopic dermatitis" into PubMed
  - Read more than Vet Derm because some great articles are published elsewhere
- J Allergy Clin Immunol
  - updates every year!
  - Great pictures!
- Don't forget J Invest Dermatol
  - Check out Research Techniques Made Simple
  - Brand new review on atopic dermatitis (Patrick GJ et al, J Invest Dermatol 2021; 141:274)

16

Watch the Zoetis PreCongress at WCVD

Our Speakers

Dr. Donald Leung
Professor and Head of Pediatric Allergy and Immunology
National Jewish Health
Denver, Colorado

Dr. Andrea Gonzales
Senior Director of Companion Animal Research
Global Therapeutics Research
Zoetis
Kalamazoo, Michigan

Dr. Jennifer Schissler
Assistant Professor of Dermatology
College of Veterinary Medicine and Biomedical Sciences
Colorado State University
Fort Collins, Colorado

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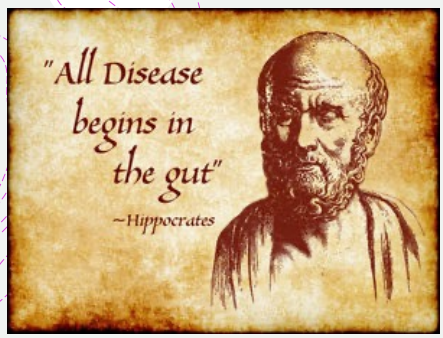
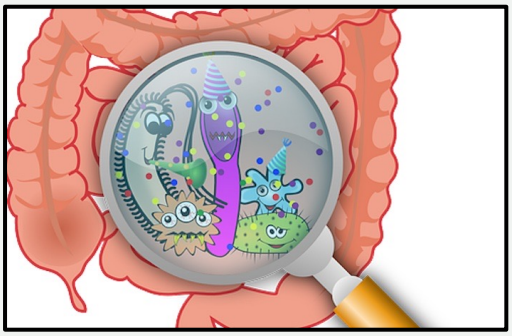




Dysbiosis and the skin-gut connection

A bit of history

Hippocrates (460-370 BC) and food allergy: "let food be thy medicine" unless it makes you sick!

Lucretius 1 AD: "what is food to one man is bitter poison to others"

1819: John Bostock and hay fever

1859: Charles Harrison Blackley summer colds and pollens

18

Veterinary Allergy

- Schnelle GB. Eczema in dogs-an allergy. North American Vet, 1933.
- Pomeroy BS. Allergy and allergic skin reactions in the dog. Cornell Vet, 1934.
- Wittich FW. Spontaneous allergy (atopy) in the lower animal: seasonal hay fever (fall type) in a dog. J Allergy 1941.
- R Patterson. Multiple studies 1959-1963.

19

The canine IgE masters!

20

Clin. exp. Immunol. (1971) **9,** 549–569.

CANINE REAGINIC ANTIBODY

CHARACTERIZATION OF THE SPONTANEOUS ANTI-RAGWEED AND INDUCED ANTI-DINITROPHENYL REAGINIC ANTIBODIES OF THE ATOPIC DOG

R. M. SCHWARTZMAN, J. H. ROCKEY AND R. E. HALLIWELL

Clin. exp. Immunol. (1972) **10,** 399–407.

ANTIGENIC RELATIONSHIP BETWEEN HUMAN IgE AND CANINE IgE

R. E. W. HALLIWELL, R. M. SCHWARTZMAN AND J. H. ROCKEY

The Localization of IgE in Canine Skin: An Immunofluorescent Study

R. E. W. Halliwell

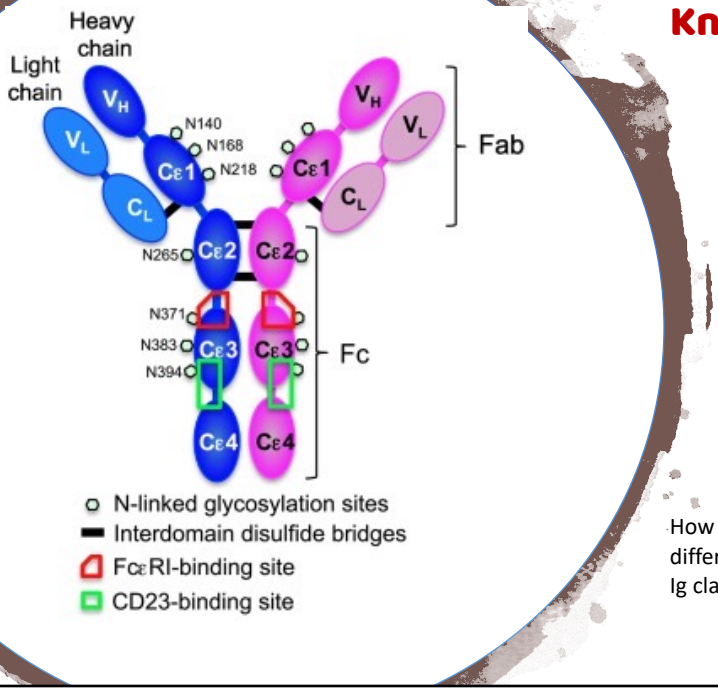
J Immunol February 1, 1973, 110 (2) 422-430;

21

What are the biophysical properties of IgE ?

Heat inactivation at 56°C due to differences in Fc portion

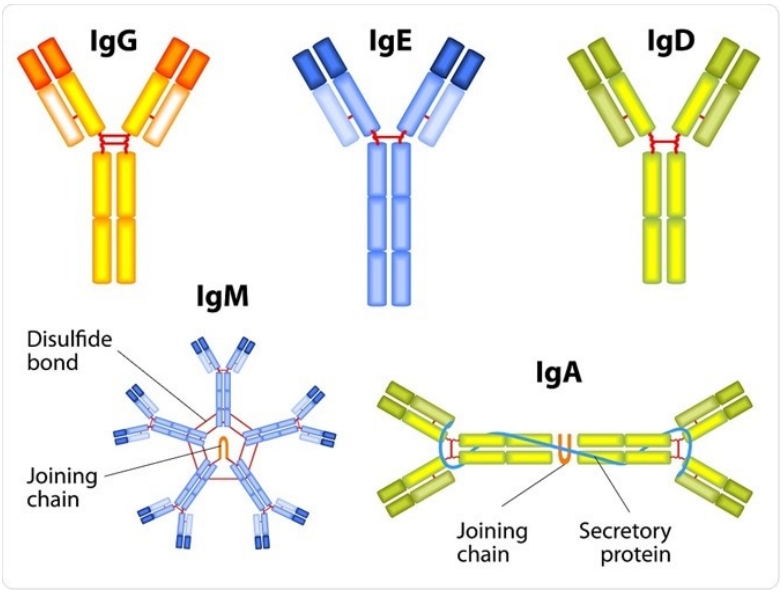
"Blocking antibodies" fall into what class?



Know IgE

How does IgE differ from other Ig classes?

22



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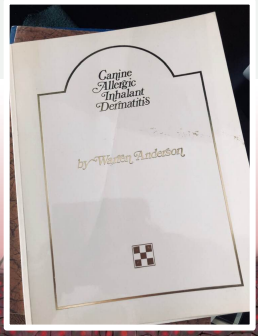
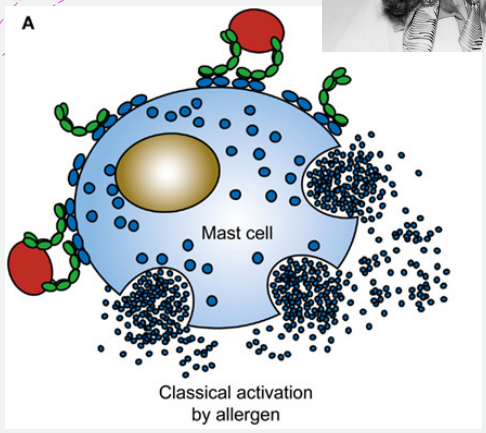
Atopic disease in the skin

24

In the old days . . .





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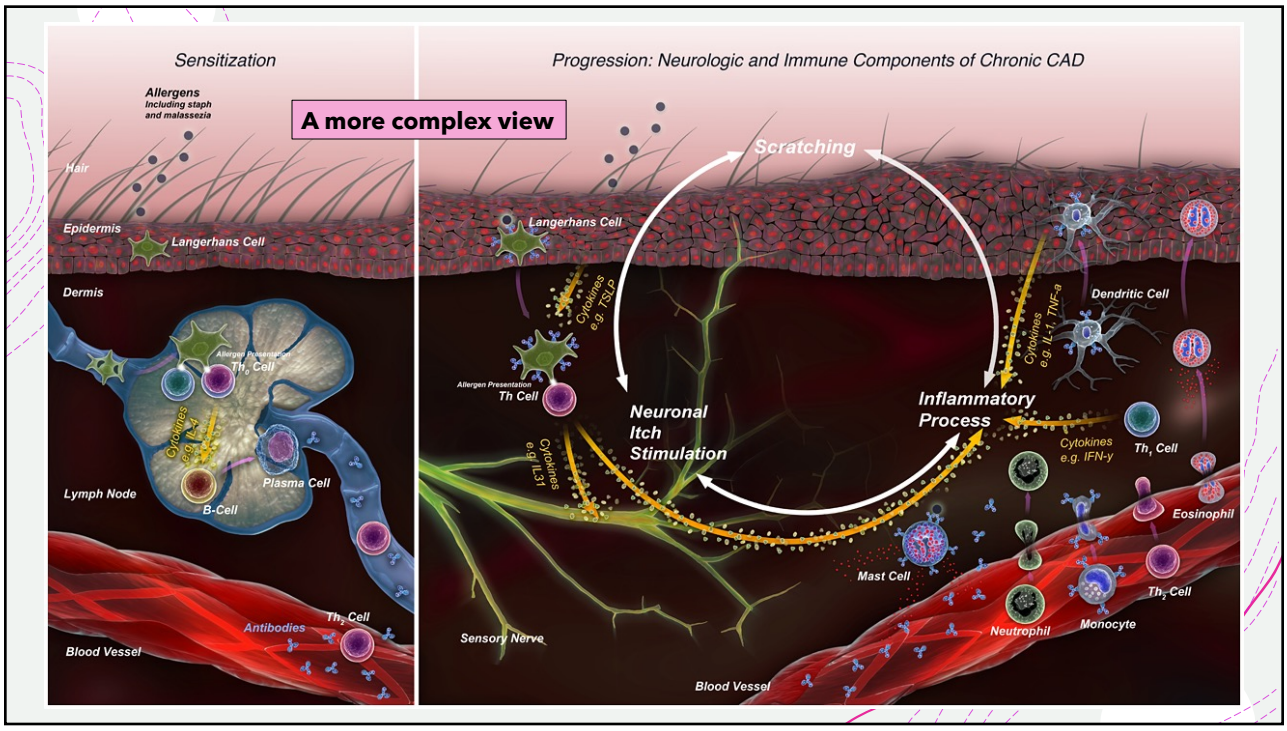

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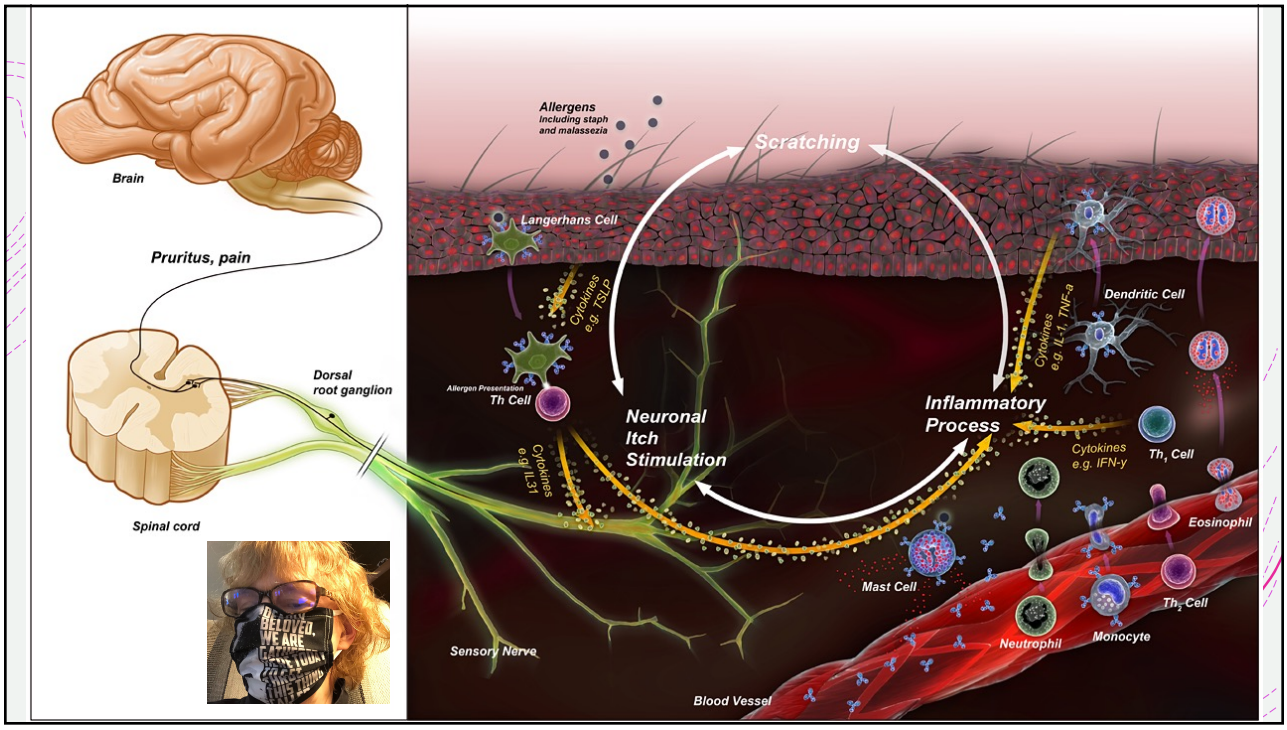

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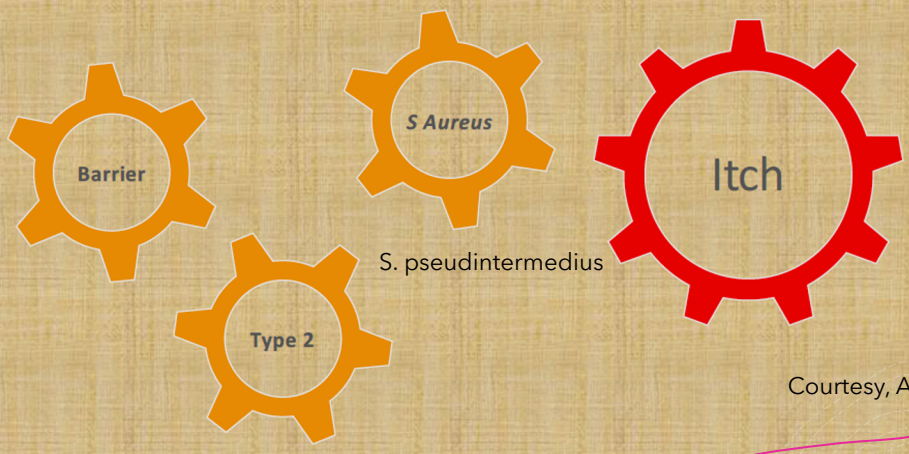
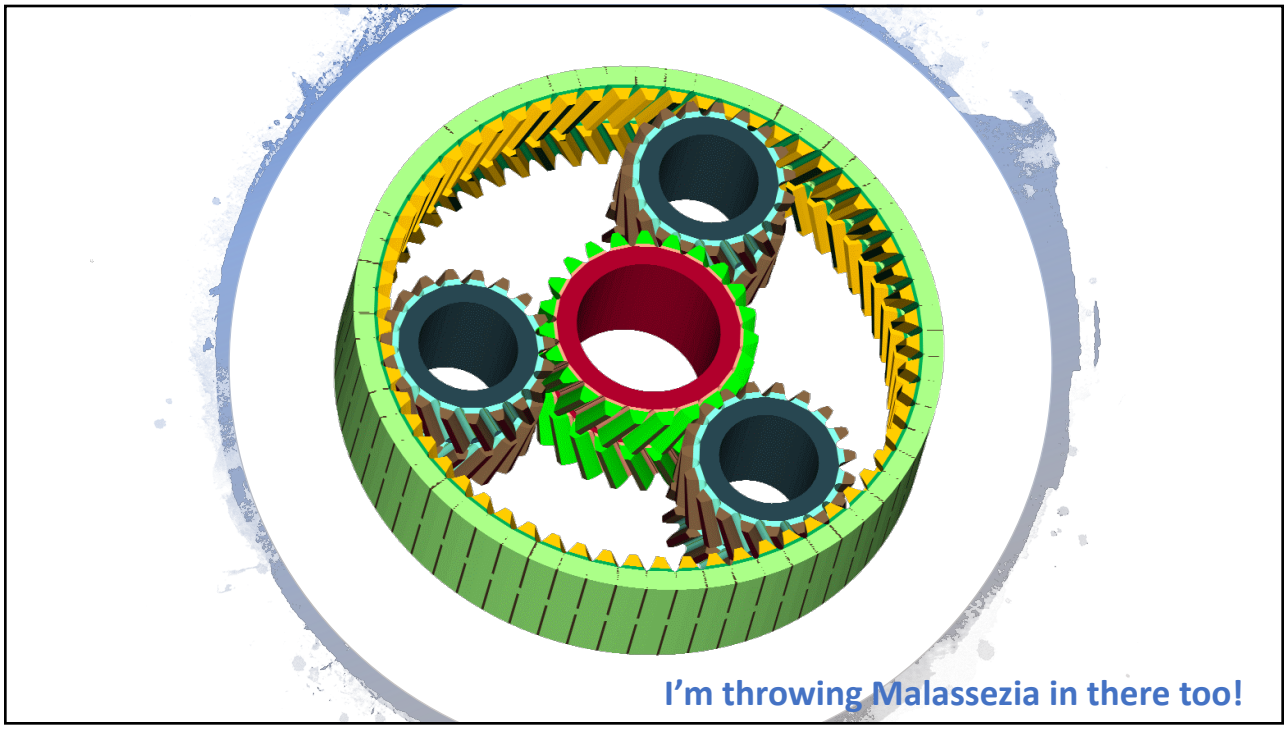
The Integrated View

AD: Complex and interacting pathogenesis



Courtesy, Alan Irvine

28



29

Atopic diseases

Hereditary predisposition to develop hypersensitivity to environmental triggers

- As veterinary dermatologists, we focus on canine atopic dermatitis
- **BUT**
- Allergic rhinitis (dogs, cats, cattle, others?)
- Asthma (cats, dogs)
  - Reactive airway disease in horses
- Food allergies
- And those weird eosinophilic skin syndromes in cats and horses
- Immunologic mechanisms likely shared, but data are sparse
  - For horses, best data is with insect bite (Culicoides) hypersensitivity

30

31

The players

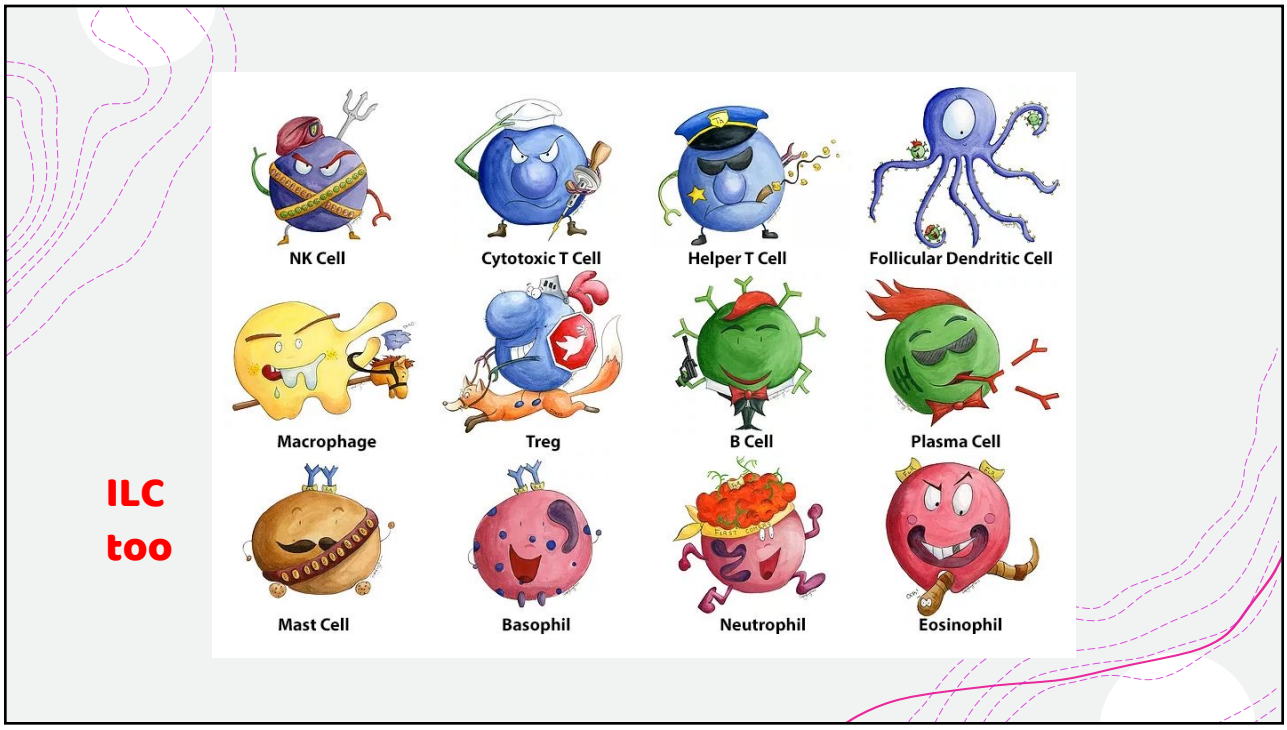
Cells

- Lymphocytes
  - T, B, NK, ILC, NK
- Granulocytes
  - Eosinophils, neutrophils, basophils
- Antigen Presenting Cells
  - Dendritic cells
  - Macrophages
- Mast cells
- Keratinocytes

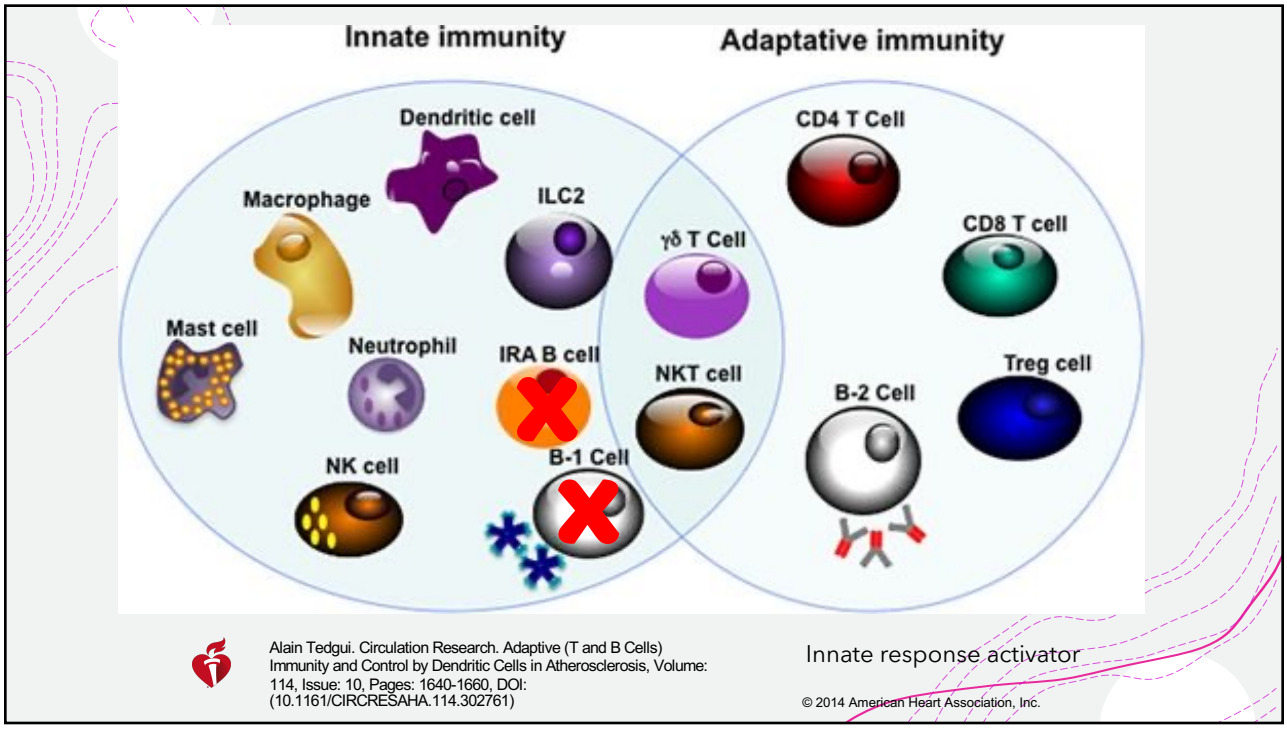
Cytokines, Adhesion Molecules

- Type 2 cytokines are present throughout the disease
- Involvement of other cytokines (e.g. Type 1, Type 17, Type 22) determined by endotype
  - do we have endotypes in dogs? Probably!
- Don't forget adhesion molecules
  - That promote migration into the skin
  - That allow breakdown of barrier

32


NK Cell
Cytotoxic T Cell
Helper T Cell
Follicular Dendritic Cell
Macrophage
Treg
B Cell
Plasma Cell
Mast Cell
Basophil
Neutrophil
Eosinophil
ILC too

33


Innate immunity
Adaptative immunity
Dendritic cell
Macrophage
ILC2
γδ T Cell
CD4 T Cell
CD8 T cell
Mast cell
Neutrophil
IRA B cell
NKT cell
Treg cell
B-2 Cell
NK cell
B-1 Cell
Innate response activator
Alain Tedgui. Circulation Research. Adaptive (T and B Cells) Immunity and Control by Dendritic Cells in Atherosclerosis, Volume: 114, Issue: 10, Pages: 1640-1660, DOI: (10.1161/CIRCRESAHA.114.302761)
© 2014 American Heart Association, Inc.

34

A blending of mechanisms

Innate

+ NK cells
+ Eosinophils
+ Basophils
+ Neutrophils
+ Mast cells
+ Dendritic cell hyperplasia
  + LC
  + Dermal DC
  + **Olivry et al. Arch Dermatol Res1996; 288(10):579-85.**

Skin resident NKT

- Induced by allergen
- Express CXCR4 as do skin memory T cells
- Cluster around fibroblasts producing CXCL12/SDF 1α
- Promote inflammation
- J Allergy Clin Immunol ;2021 Jan 28;S0091-6749(21)00097-X

No info on dogs

γδ T cells

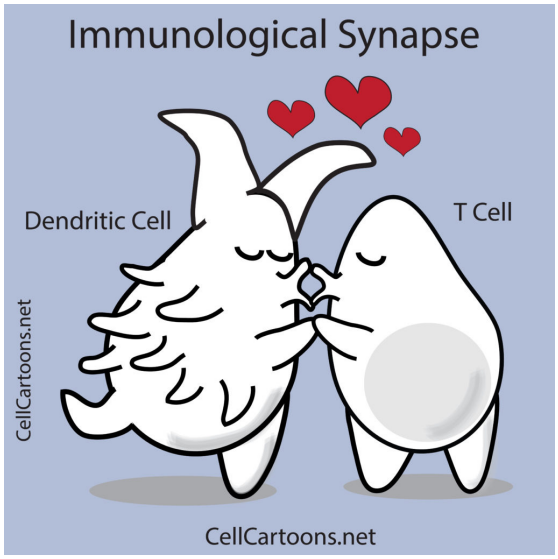
- A source of IL-22 to limit staphylococcal growth
- A source of IL-17A as well to call in neutrophils
- May help control dysbiosis
- Decreased in adult humans with AD; increased in kids and **dogs**
- J Allergy Clin Immunol 2016; 138(4):1098-1107. J Allergy Clin Immunol 2020; Nov 28;S0091-6749(20)31641-9. **Am J Dermatopathol 1997;19(5):477-86.**

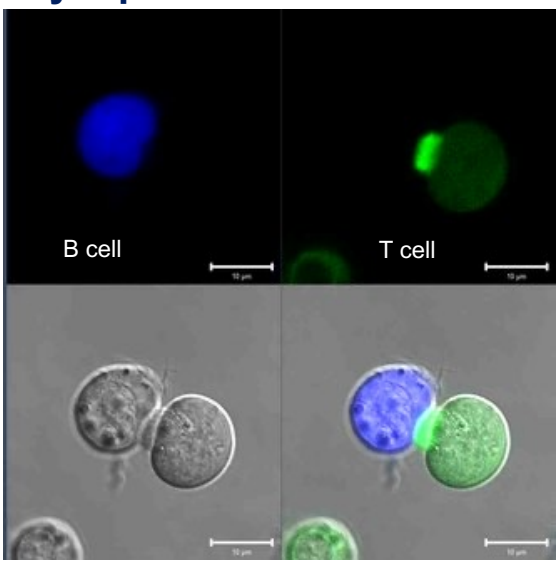
Adaptive

+ CD4+ T cells
+ CD8+ T cells
+ Treg
+ B cells

35

How do T cells know what to do? The immunologic synapse





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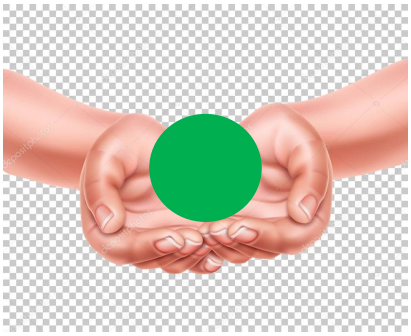
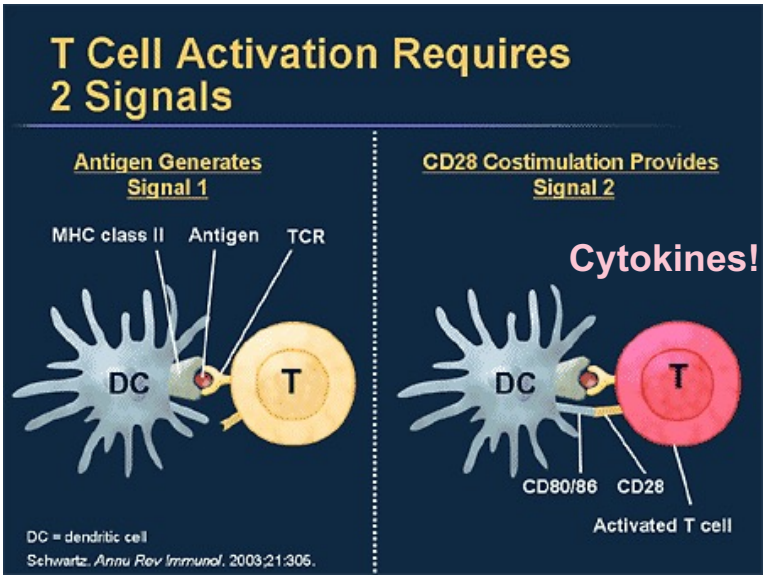
How do T cells know what to do?





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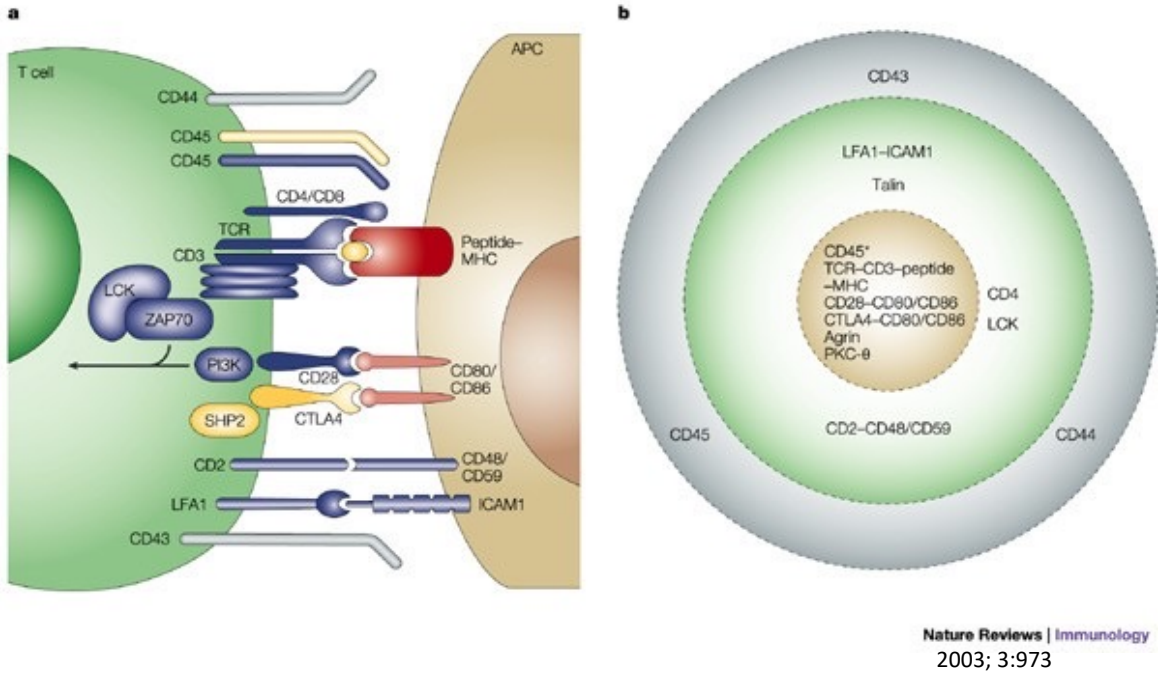

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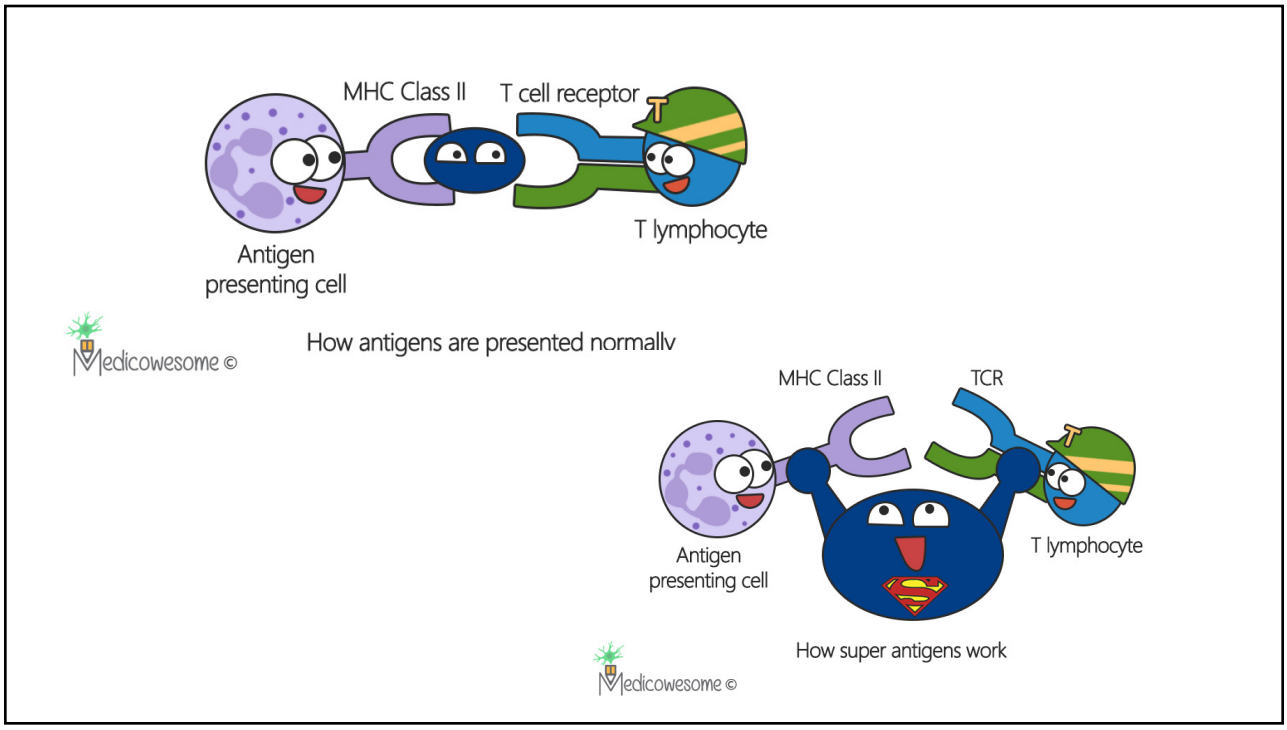

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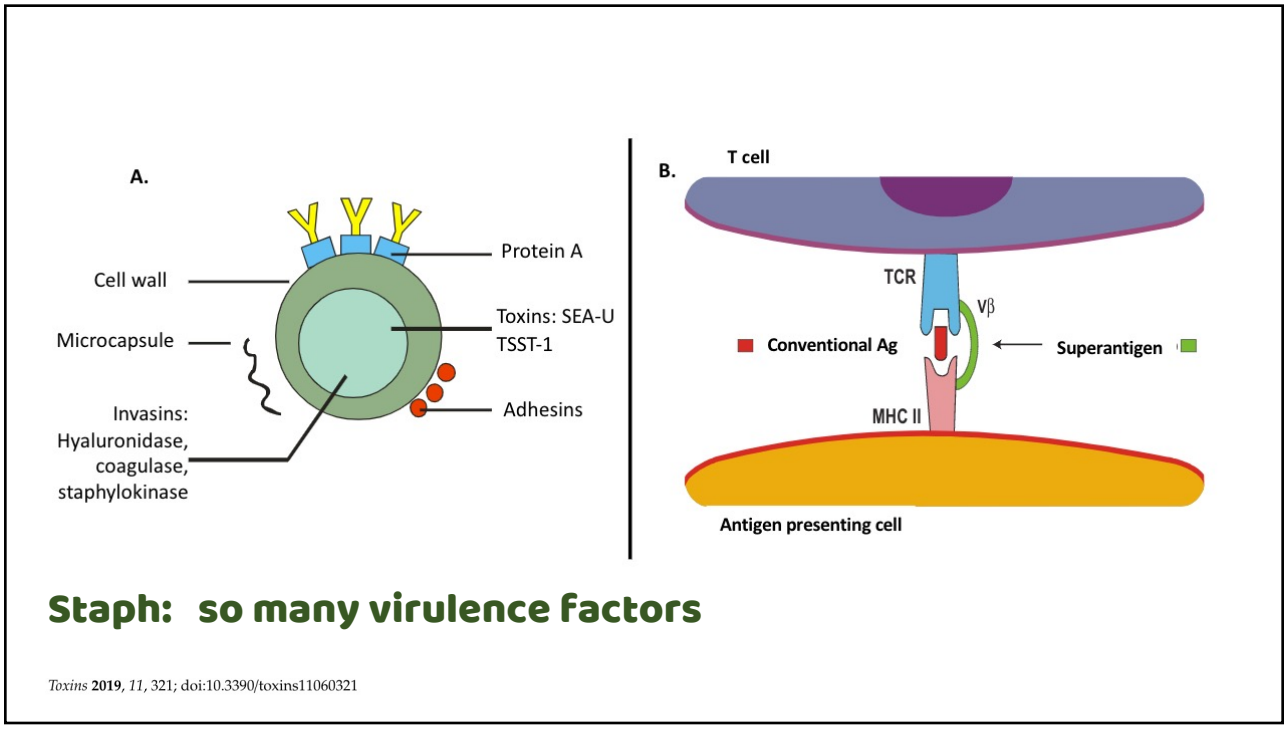

Staph: so many virulence factors

Toxins **2019**, *11*, 321; doi:10.3390/toxins11060321

40

Why do we care about Staph and superantigens?

Allergy Asthma Immunol Res. 2019 Sep;11(5):593-603
https://doi.org/10.4168/aair.2019.11.5.593
pISSN 2092-7355·eISSN 2092-7363

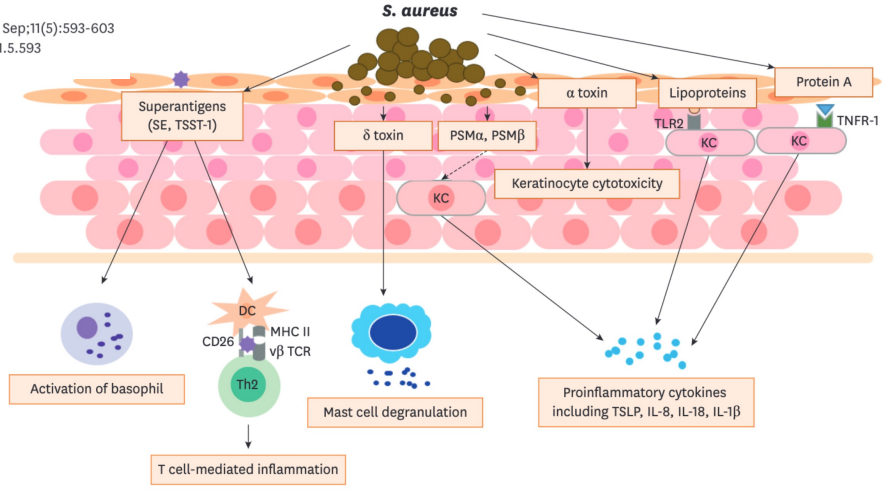

Fig. 2. The pathogenic effects of *Staphylococcus aureus* on atopic dermatitis. *S. aureus* expresses superantigens, such as SE and TSST-1, which activate basophils and cause T-cell-mediated inflammation. PSMα and PSMβ families stimulate the release of proinflammatory cytokines from keratinocytes. *S. aureus* α-toxin and δ-toxin induce keratinocyte cytotoxicity and mast cell degranulation, respectively. Protein A and lipoproteins of *S. aureus* lead to proinflammatory responses by activating TNFR-1 and TLR2 on keratinocytes, respectively.
SE, staphylococcal enterotoxin; TSST-1, toxic shock syndrome toxin-1, DC, dendritic cell; MHC II, major histocompatibility complex class II; TCR, T cell receptor; PSM, phenol-soluble modulins; TNFR-1, tumor necrosis factor receptor-1; TLR2, toll-like receptor 2; TSLP, thymic stromal lymphopoietin; IL, interleukin; KC, keratinocyte.

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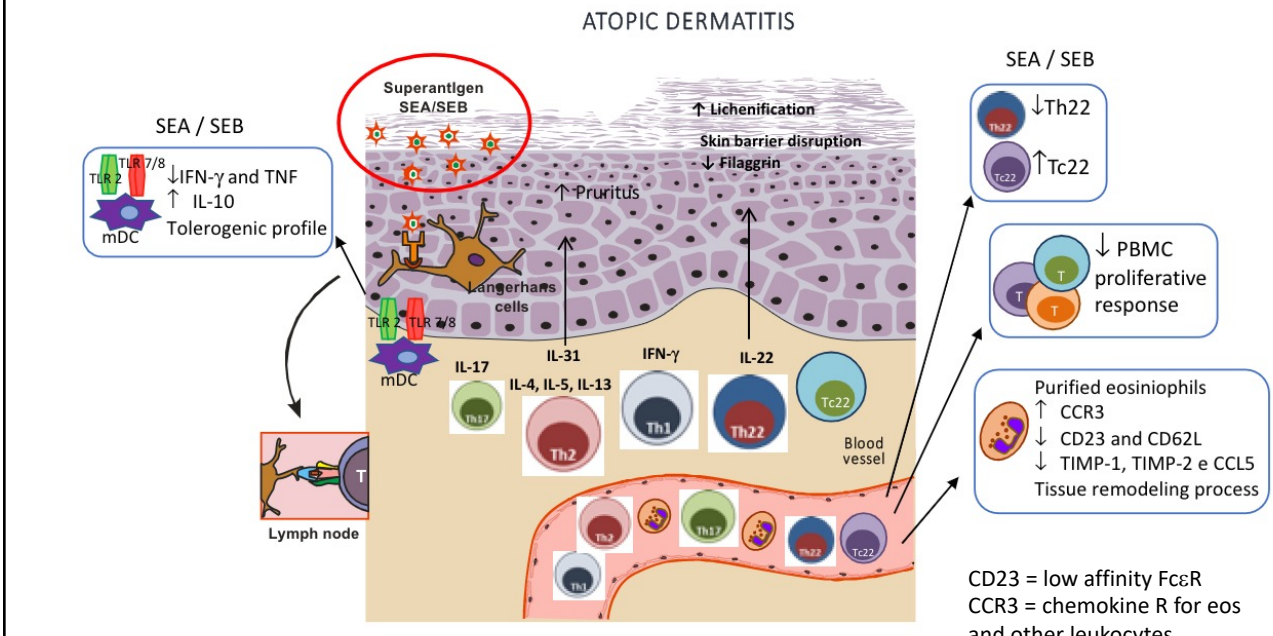

Toxins **2019**, *11*, 321; doi:10.3390/toxins11060321

Chronic activation profile with superantigens in AD

42

Superantigens promote Type 2 polarization

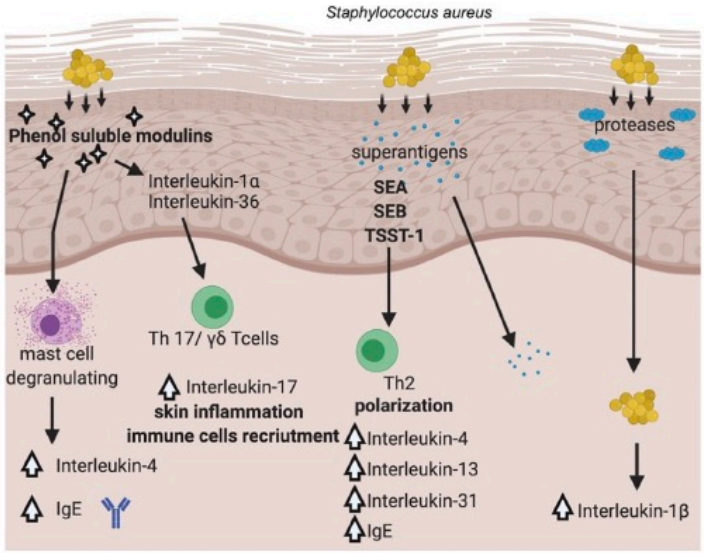

FIGURE 3 | Pathways involved in *S. aureus*' virulence factors contribution to AD. (Created with BioRender).

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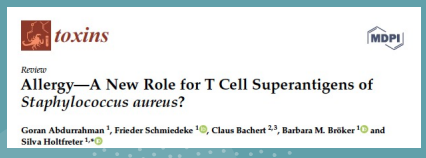
Why do we care about superantigens?


toxins

MDPI

Review

Allergy—A New Role for T Cell Superantigens of *Staphylococcus aureus*?

Goran Abdurrahman [1], Frieder Schmiedeke [1], Claus Bachert [2,3], Barbara M. Bröker [1] and Silva Holtfreter [1,*]

- Production of IgE against Staph Sag MAKES DISEASE WORSE
- Atopic dermatitis
- Allergic rhinitis
- Asthma

Respir Med 2019; 155:66

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45

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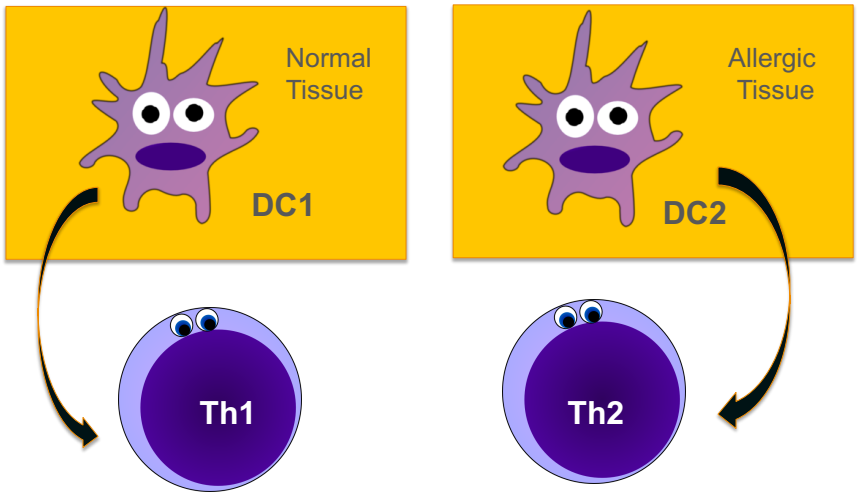
The atopic's skin drives the allergic response

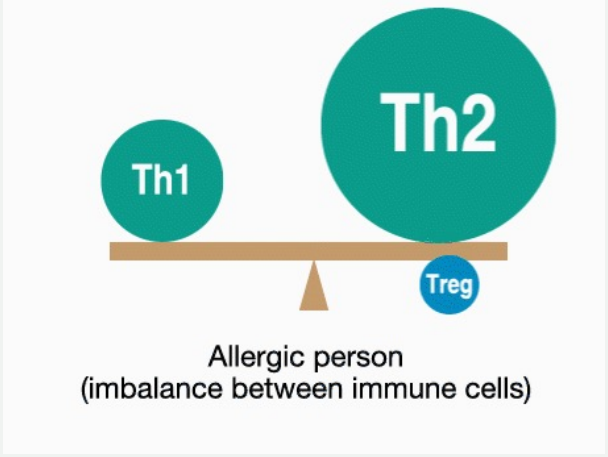


46 |

46

The simple model is too simple

HOWEVER, Th2 cytokines remain important throughout the disease process



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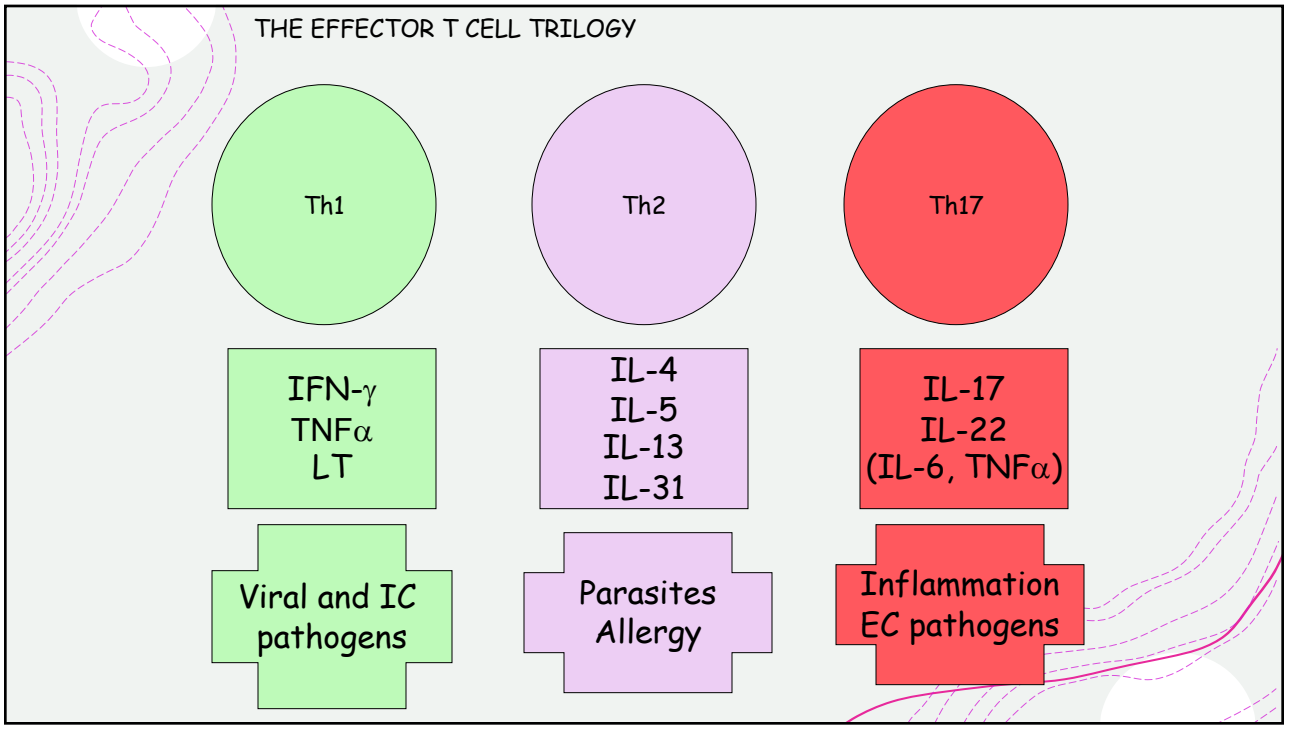
THE EFFECTOR T CELL TRILOGY
Th1
Th2
Th17
IFN-γ
TNFα
LT
IL-4
IL-5
IL-13
IL-31
IL-17
IL-22
(IL-6, TNFα)
Viral and IC pathogens
Parasites
Allergy
Inflammation
EC pathogens

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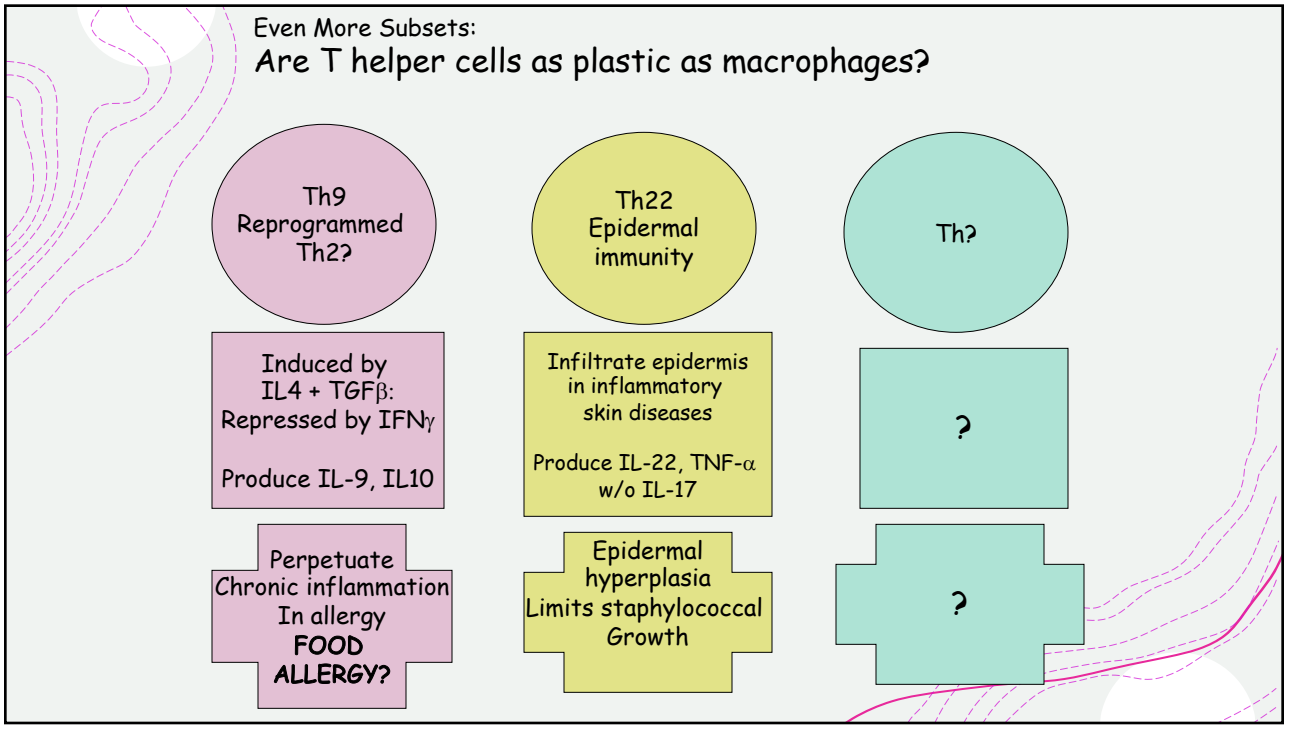
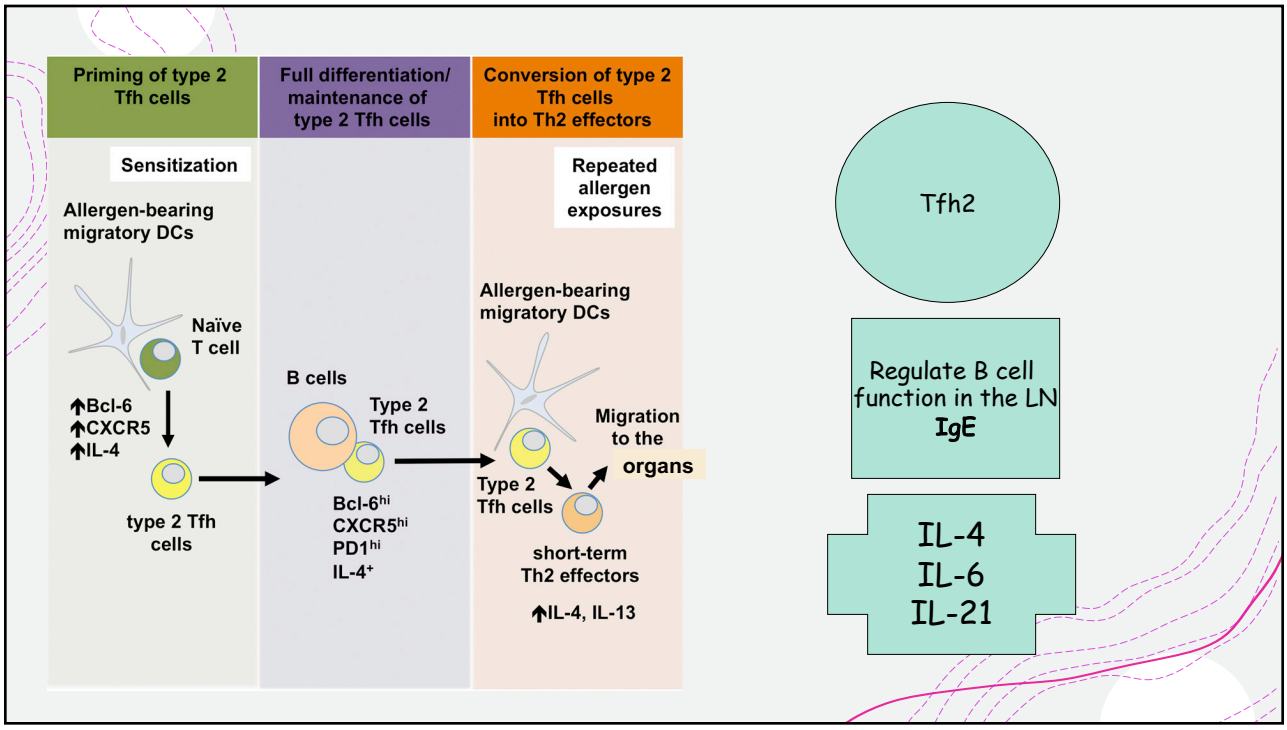

Even More Subsets:
Are T helper cells as plastic as macrophages?
Th9
Reprogrammed
Th2?
Th22
Epidermal
immunity
Th?
Induced by
IL4 + TGFβ:
Repressed by IFNγ
Produce IL-9, IL10
Infiltrate epidermis
in inflammatory
skin diseases
Produce IL-22, TNF-α
w/o IL-17
?
Perpetuate
Chronic inflammation
In allergy
FOOD
ALLERGY?
Epidermal
hyperplasia
Limits staphylococcal
Growth
?

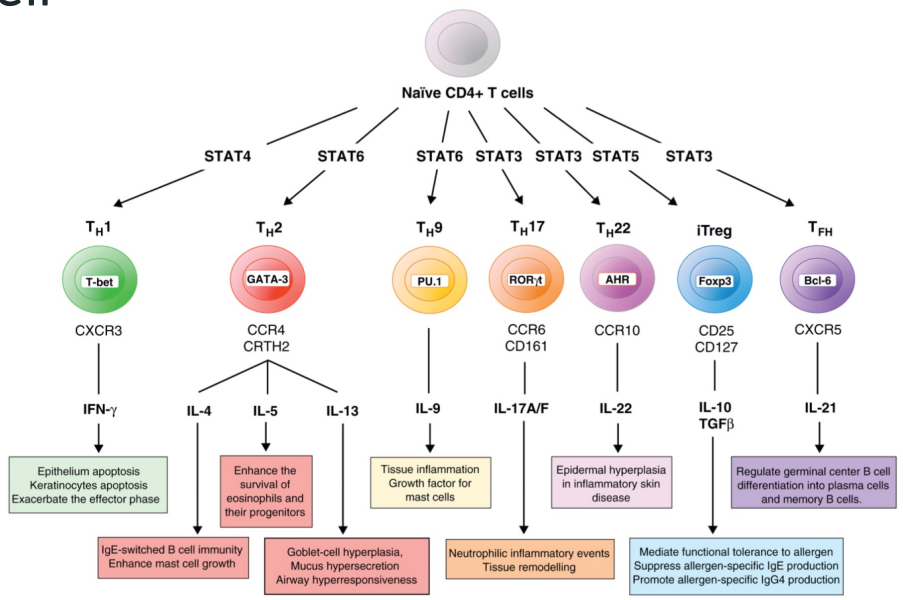
50



51

T helper cell subsets

Curr Opin Immunol 2012; 24:700-706



52

For every Th there is a Tc in atopic patients

Th – CD4+
- Th1
- Th2
- Th17
- Th22

Tc – CD8+
- Tc1
- Tc2
- Tc17
- Tc22

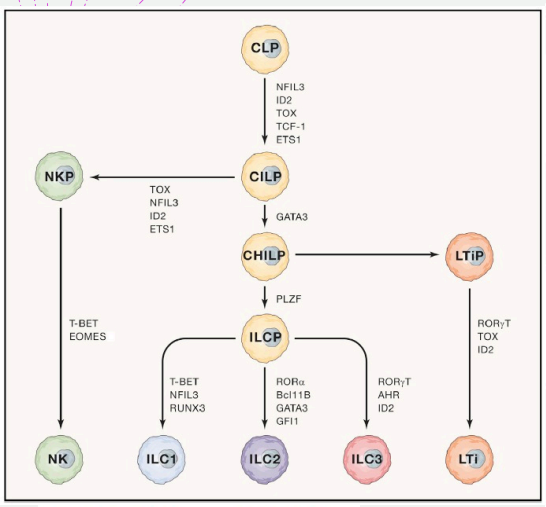
53

It's more than just T cell subsets

Amplification of the Type 2 response

54

Innate Lymphoid Cells In The Tissue



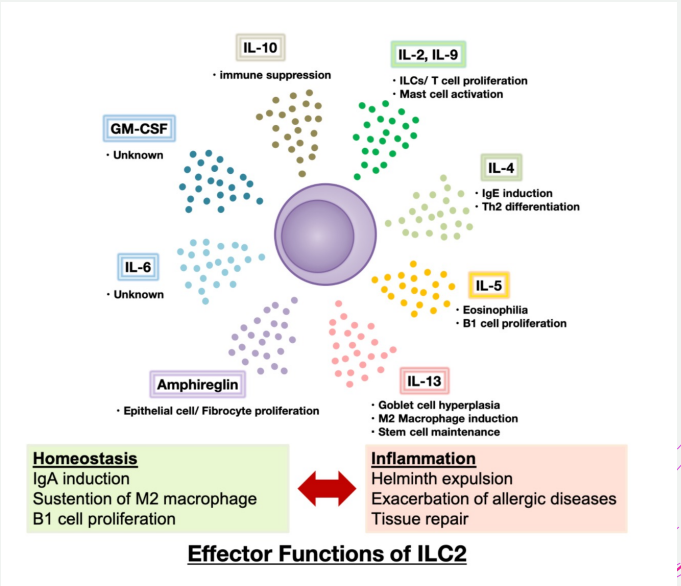
Stimuli		Mediators	Immune function
Tumors, intracellular microbes (Virus, bacteria, parasites)	NK, ILC1	IFN-γ Granzymes Perforin	Type 1 immunity (Macrophage activation, cytotoxicity)
Large extracellular parasites and allergens	ILC2	IL-4 IL-5 IL-13 IL-9 AREG	Type 2 immunity (Alternative macrophage activation)
Mesenchymal organizer cells (Retinoic acid, CXCL13, RANK-L)	LTi	RANK Lymphotoxin TNF IL-17 IL-22	Formation of secondary lymphoid structures
Extracellular microbes (Bacteria, fungi)	ILC3	IL-22 IL-17 GM-CSF Lymphotoxin	Type 3 immunity (Phagocytosis, antimicrobial peptides)

Cell *174*, August 23, 2018

55

ILC2

- Stimulated by epidermal alarmins (TSLP, IL-25, IL-33)
- Make Type 2 cytokines
  - IL-4, IL-5,IL-13
- Make IL-9 too
- Enhance Type 2 allergic response in atopic dermatitis



https://www.ims.riken.jp/labo/56/index.html

56

57

Veterinary Immunology and Immunopathology 221 (2020) 110015

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

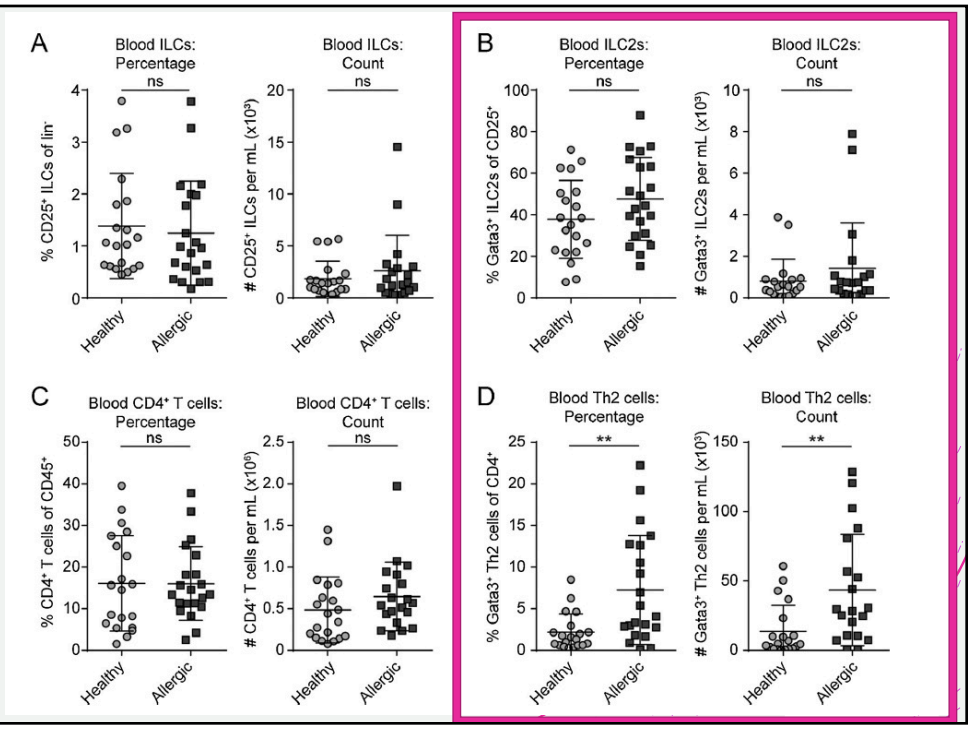
Elevated circulating Th2 but not group 2 innate lymphoid cell responses characterize canine atopic dermatitis

Simon P. Früh[a], Mridusmita Saikia[b], Jeremy Eule[a], Christina A. Mazulis[c], Julia E. Miller[c], Joby M. Cowulich[c], Oyebola O. Oyesola[a,d], Lauren M. Webb[a,d], Seth A. Peng[a], Rebecca L. Cubitt[a], Charles G. Danko[b], William H. Miller[c], Elia D. Tait Wojno[a,d,*]

- ✓ ILC2 function in the tissue not the blood
- ✓ All dogs tested had chronic disease
- ✓ Small numbers

58

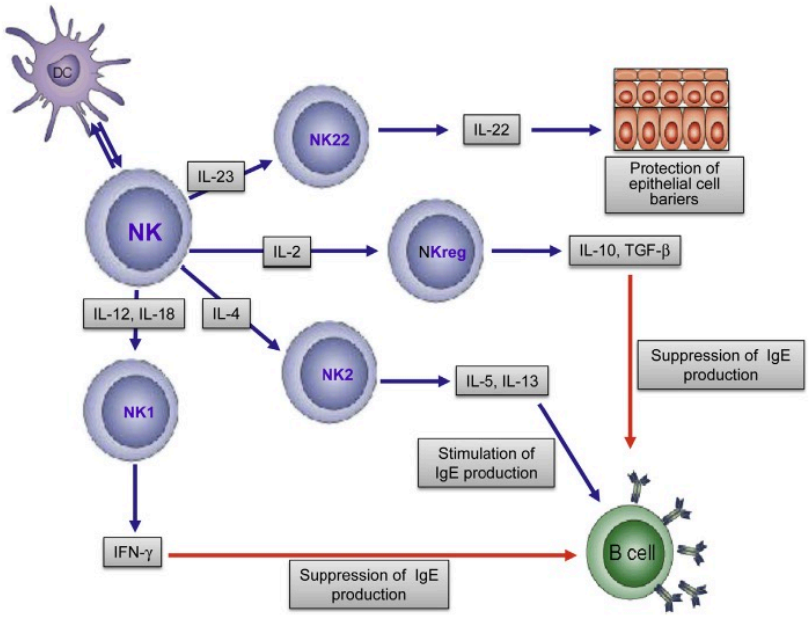
20 healthy dogs
21 allergic dogs



59

NK cell subsets also are players

JACI 2013; 132:527



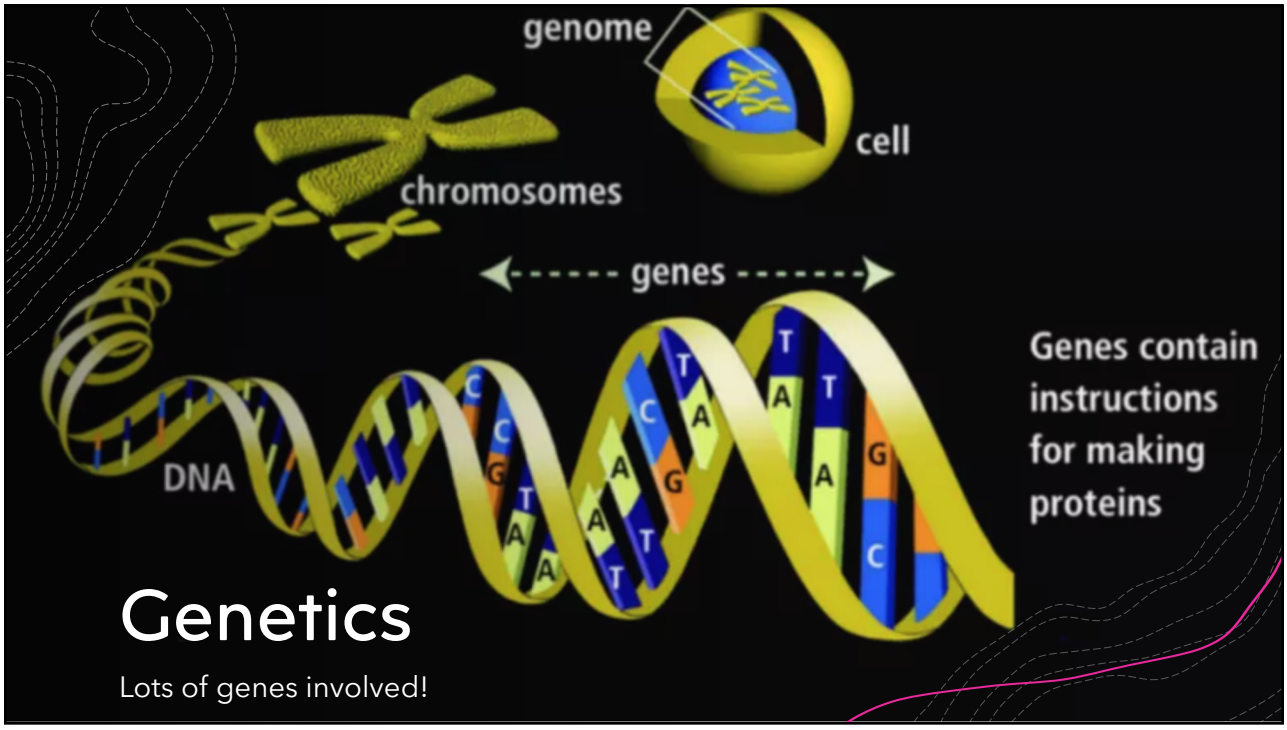
60

What have we learned?

Type 2 responses are not just restricted to T cells

61

62



63

Table 1. Main groups of genes associated with atopic dermatitis (AD) pathogenesis [5–7,9,10,12,23–32].

Pathological Process in AD	Example of Genes Involved
Epidermal barrier genes	*Filaggrin, filaggrin 2, hornerin* Corneodesmosomal genes (*desmoglein, desmocollin*) and tight junction genes (*claudins, ocludins*) Epidermal protease genes (*kallikreins, cathepsins, caspase 14*), and their inhibitors (*SPINK5, Cystatin A*) *OVOL1* (ovo like transcriptional repressor)—transcription factor that regulates FLG expression
Genes of the innate immune mechanisms	*TLR1, TLR2, TLR4, TLR6, TLR9, TLR10, CD14, NOD1* and defensins (*DEFB1*)
Genes of the adaptive immune mechanism	Genes of receptor subunits for IgE (*FcεRI α i FCεRI-¥*) Genes of Th2 response: *IL-4, IL-5, IL-13, IL2RA, IL-13RA IL-5RA, TSLPR, IL-4R, IL-18, IL-31* Other genes of Th bias *IL17A, TNFα, IL-22* Treg genes: *STAT-6, FOXP3, LRRC32*
Genes encoding alarmins produced by keratinocytes	*IL-25, TSLP, IL-33*
Genes regulating DNA methylation	*KIF3A*
Genes regulating vitamin D pathways	*CYP27A1, CYP2R1, VDR*

From: Nedozytko B et al. Genetic and Epigenetic Aspects of Atopic Dermatitis. Int J Mol Sci 2020

64

Why the fuss over filaggrin?

One Remarkable Molecule: Filaggrin

Sara J. Brown[1] and W.H. Irwin McLean[1]

J Invest Dermatol 2012; 132:751

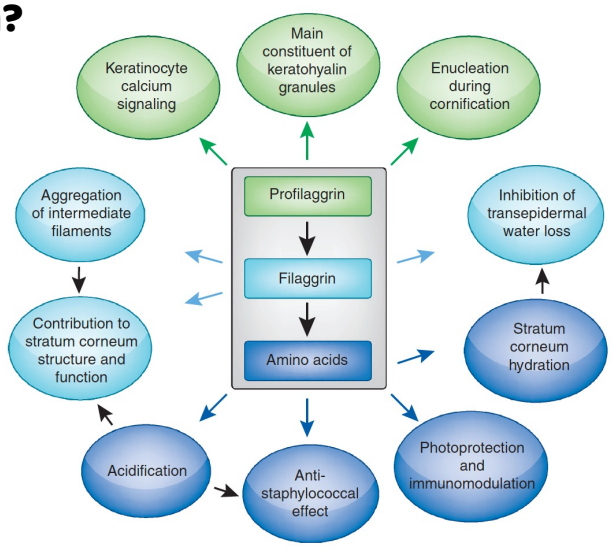


Figure 3. Profilaggrin, filaggrin, and their constituent amino acids are multifunctional proteins contributing to the formation and function of the skin barrier. Diagram summarizing the known and possible functions of profilaggrin, filaggrin, and amino acids released by filaggrin proteolysis.

65

VETERINARY QUARTERLY
2020, VOL. 40, NO. 1, 162–168
https://doi.org/10.1080/01652176.2020.1758357

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS Check for updates

Update on canine filaggrin: a review

Daniel Combarros[a,b], Marie-Christine Cadiergues[a,b] and Michel Simon[a]

[a]UDEAR, Université de Toulouse, INSERM UPS, Toulouse, France; [b]Université de Toulouse, ENVT, Toulouse, France

"Many questions remain about the involvement of filaggrin in canine atopic dermatitis."

66

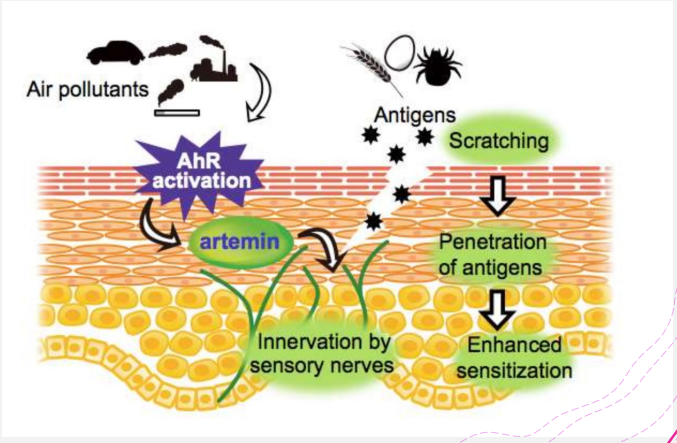
Filaggrin mutations alone neither necessary nor sufficient for AD

67

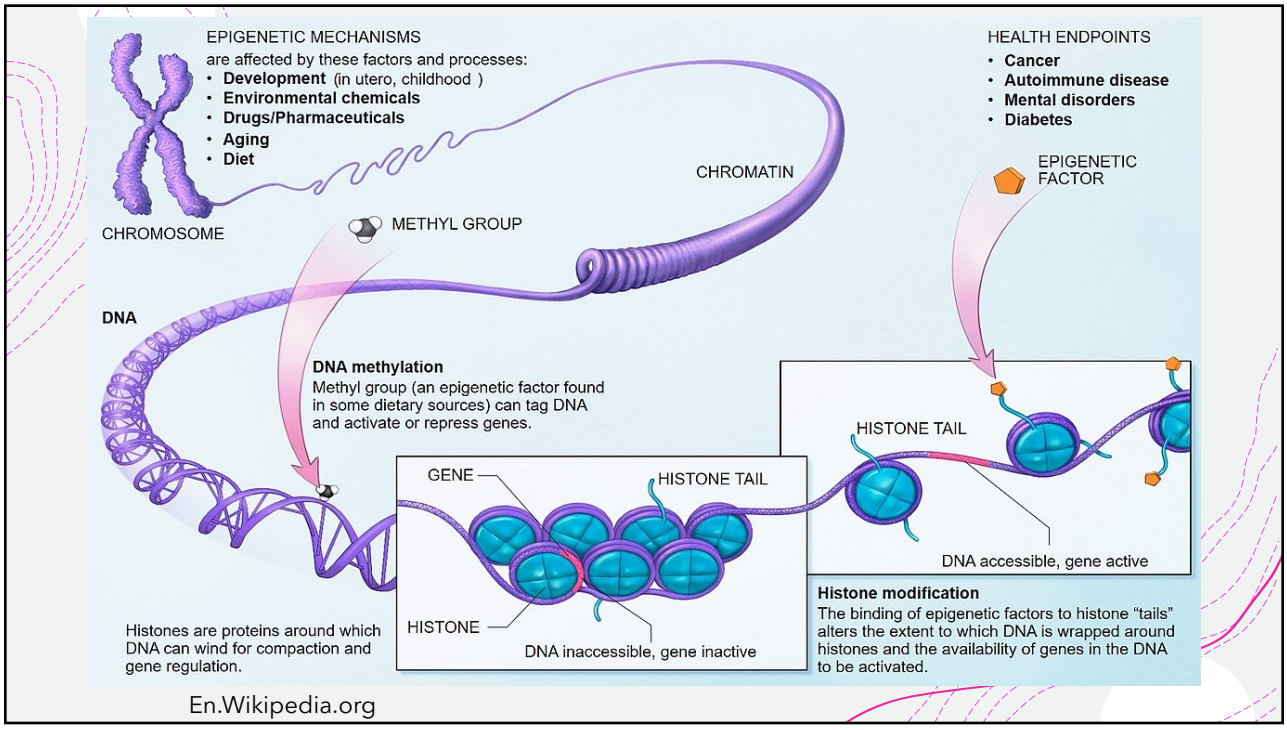
68

Epigenetics

- How the environment alters gene expression
  - Pollutants
  - Chemicals
  - Drugs
  - Diet
- Mechanisms
  - DNA methylation
    - E.g. methylation of a promotor can repress transcription
  - Histone acetylation and methylation
    - Alters wrapping of DNA around histones and therefore whether a gene is active or not
  - microRNA's

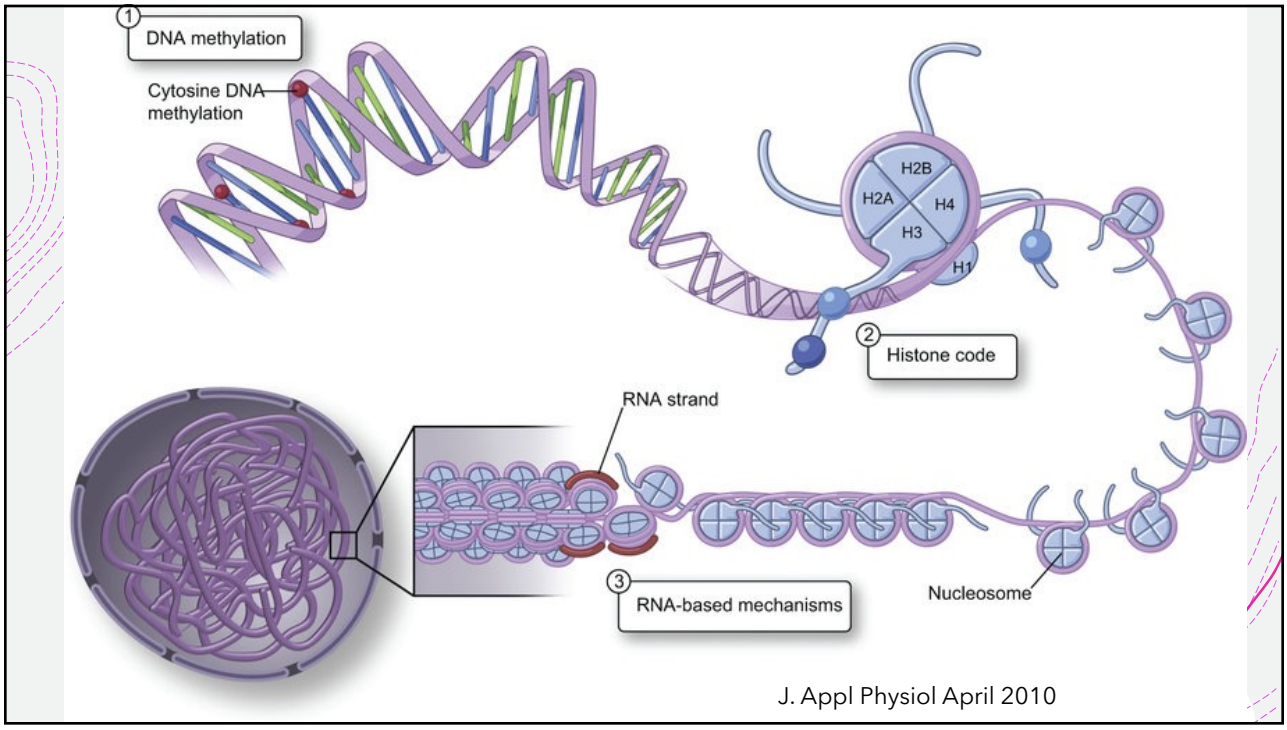


69

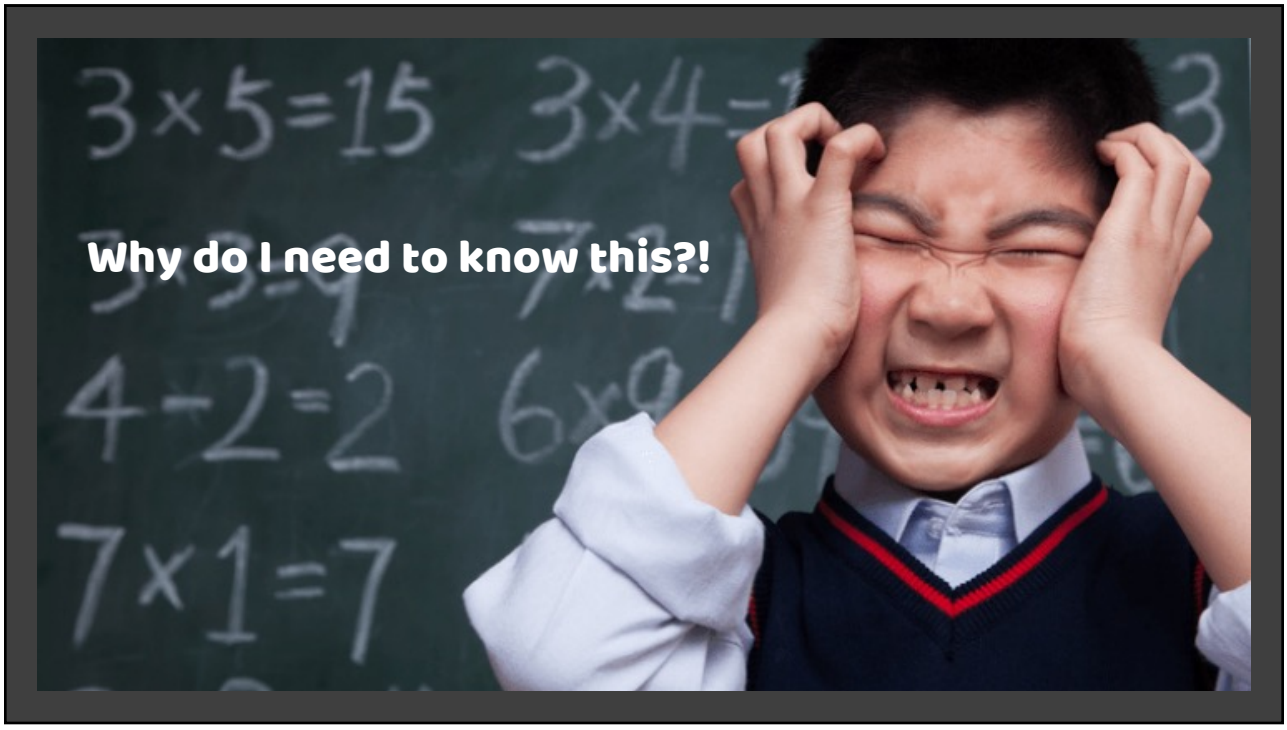


En.Wikipedia.org

70


1
DNA methylation
Cytosine DNA methylation
H2B
H2A
H4
H3
H1
2
Histone code
RNA strand
3
RNA-based mechanisms
Nucleosome
J. Appl Physiol April 2010

71


Why do I need to know this?!

72

Immunogenetics. 2020 May;72(4):241-250. doi: 10.1007/s00251-020-01162-w. Epub 2020 Mar 26.

Identification of differentially expressed microRNAs in the skin of experimentally sensitized naturally affected atopic beagles by next-generation sequencing

Domenico Santoro [1], Antonio Di Loria [2], Teresa Mirante [3], Duarte Mendes Oliveira [3], Carmelo Laudanna [3 4], Donatella Malanga [3 5], Vincenzo Dattilo [6], Enrico Iaccino [3], Rosanna Marsella [7], Paolo Ciaramella [2]

73

Initiation and progression of disease

74

Lennie,
Dr. Alan Irvine's dog

PRIMER

Atopic dermatitis

Stephan Weidinger[1], Lisa A. Beck[2], Thomas Bieber[3,4], Kenji Kabashima[5] and Alan D. Irvine[6,7,8]**

Nature Reviews Disease Primers 2018; 4:1

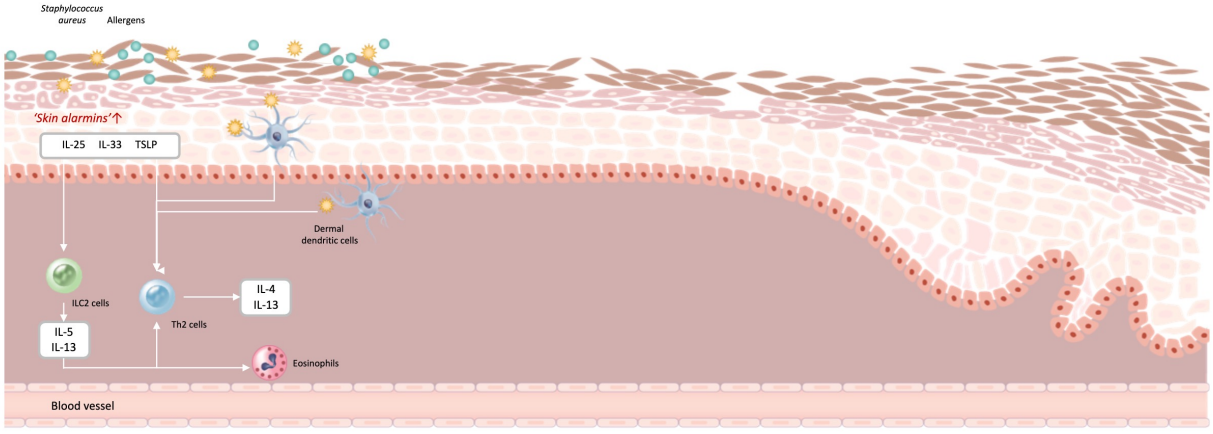
75

Nonlesional skin

Xerosis

- Immune dysregulation
- Skin barrier dysfunction
- Subclinical inflammation

Courtesy, Alan Irvine



AD, atopic dermatitis; IL, interleukin; ILC2, type 2 innate lymphoid cell; Th, helper T cell; TSLP, thymic stromal lymphopoietin.
Adapted from Weidinger S et al. Nat Rev Dis Primers 2018;4:1, with permission from Springer Nature Publishing AG.

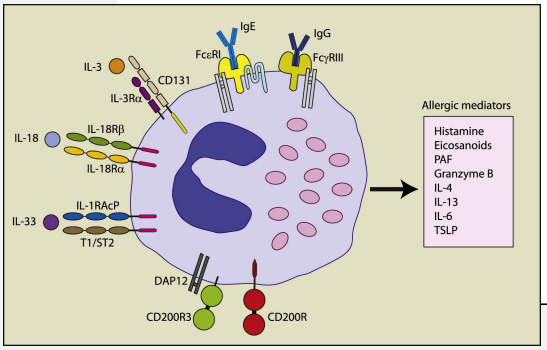
Courtesy, Alan Irvine

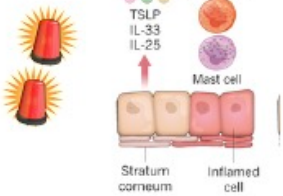
76

Enter the basophil

Staphylococcal enterotoxins stimulate basophils to make IL-4 too!

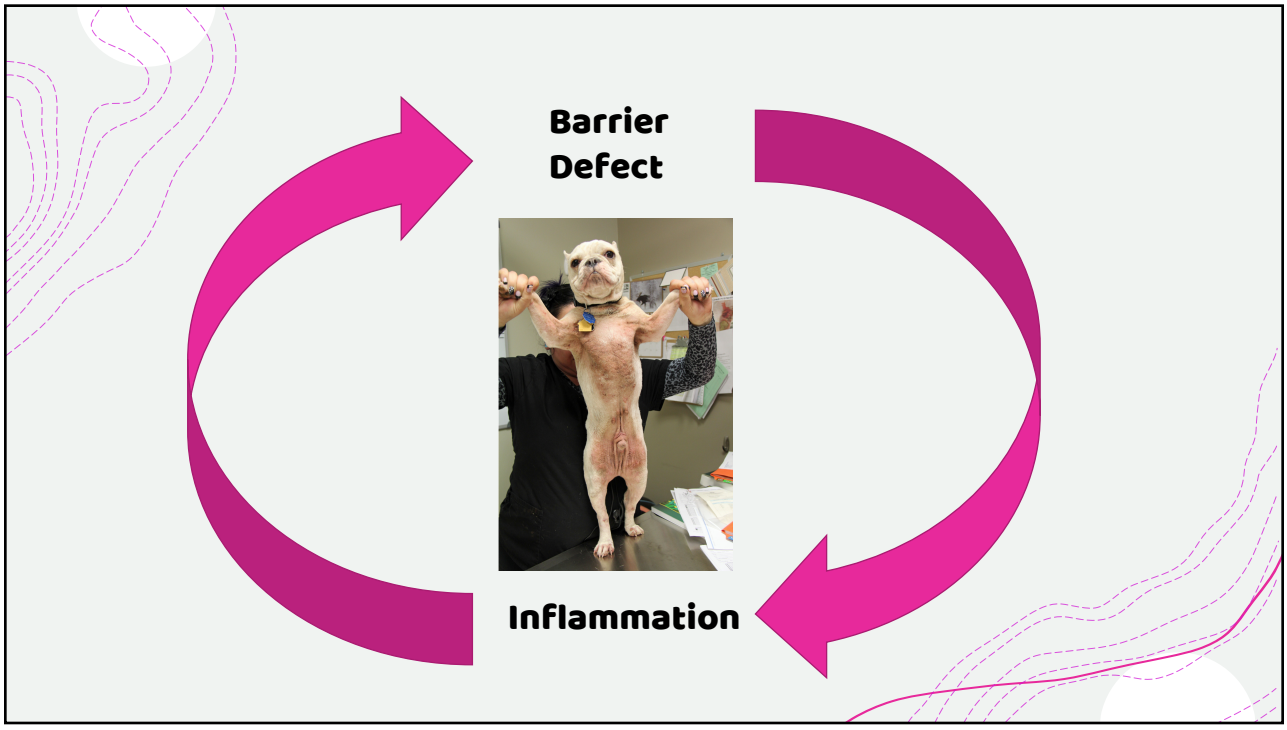
A stressed barrier drives
Immediate Th2 immune responses





David Artis

77



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Changes that contribute to barrier dysfunction

Reduced expression of structural proteins → Imbalances in protease/protease inhibitors → Altered composition and organization of lamellar layers

Altered lipid metabolism → Reduced expression of tight junction proteins → Dysbiosis with increased pathogenic staphylococci

79

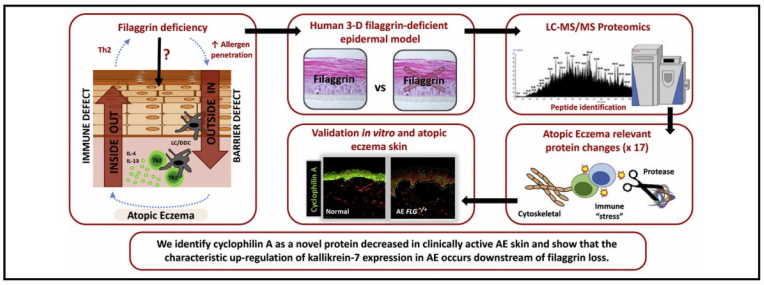
Loss of filaggrin is sufficient to induce inflammatory and immune changes similar to atopic dermatitis

Atopic dermatitis and inflammatory skin disease

Proteomic analysis of filaggrin deficiency identifies molecular signatures characteristic of atopic eczema

Martina S. Elias, BSc,[a] Heather A. Long, PhD,[a,c*] Carla F. Newman, BSc,[b] Paul A. Wilson, MSc,[b] Andrew West, PhD,[b] Paul J. McGill, BSc,[b] Keith C. Wu, MRes, BM, BCh, PhD,[a] Michael J. Donaldson, PhD,[c] and Nick J. Reynolds, BSc, MBBS, MD, FRCP[a,d] *Newcastle upon Tyne and Stevenage, United Kingdom*

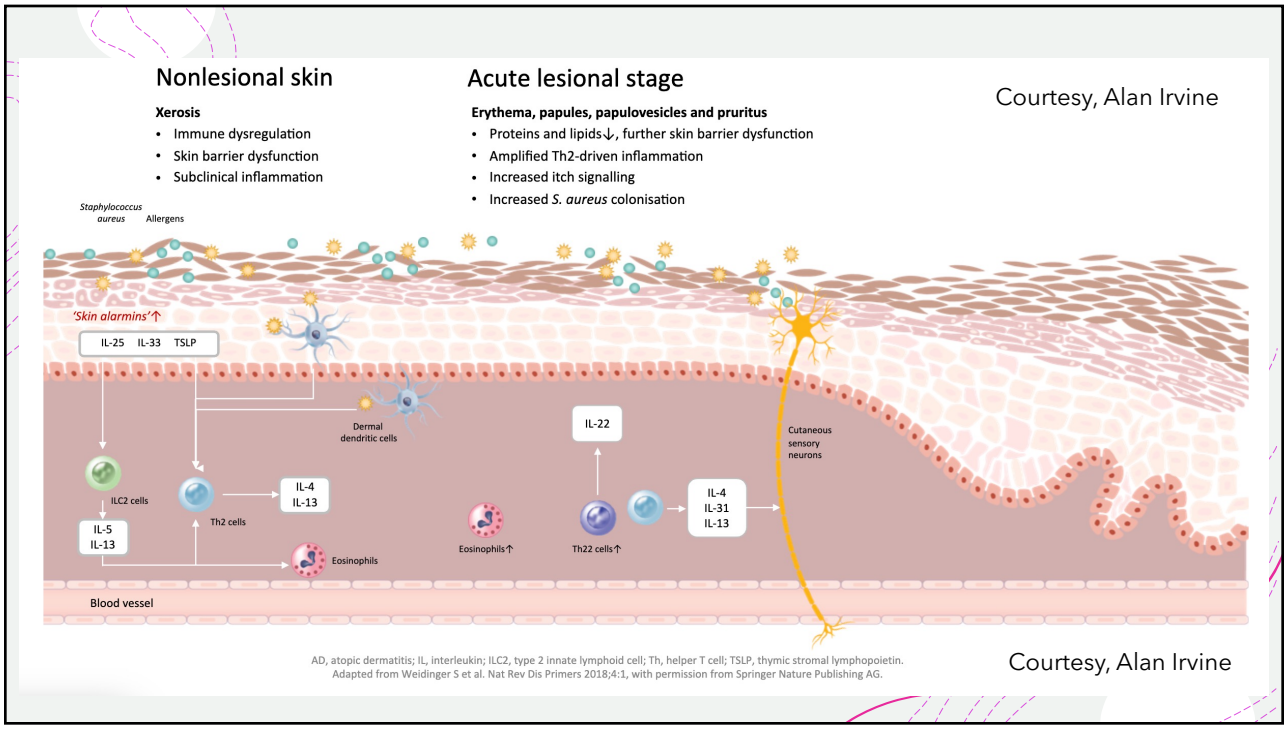
GRAPHICAL ABSTRACT



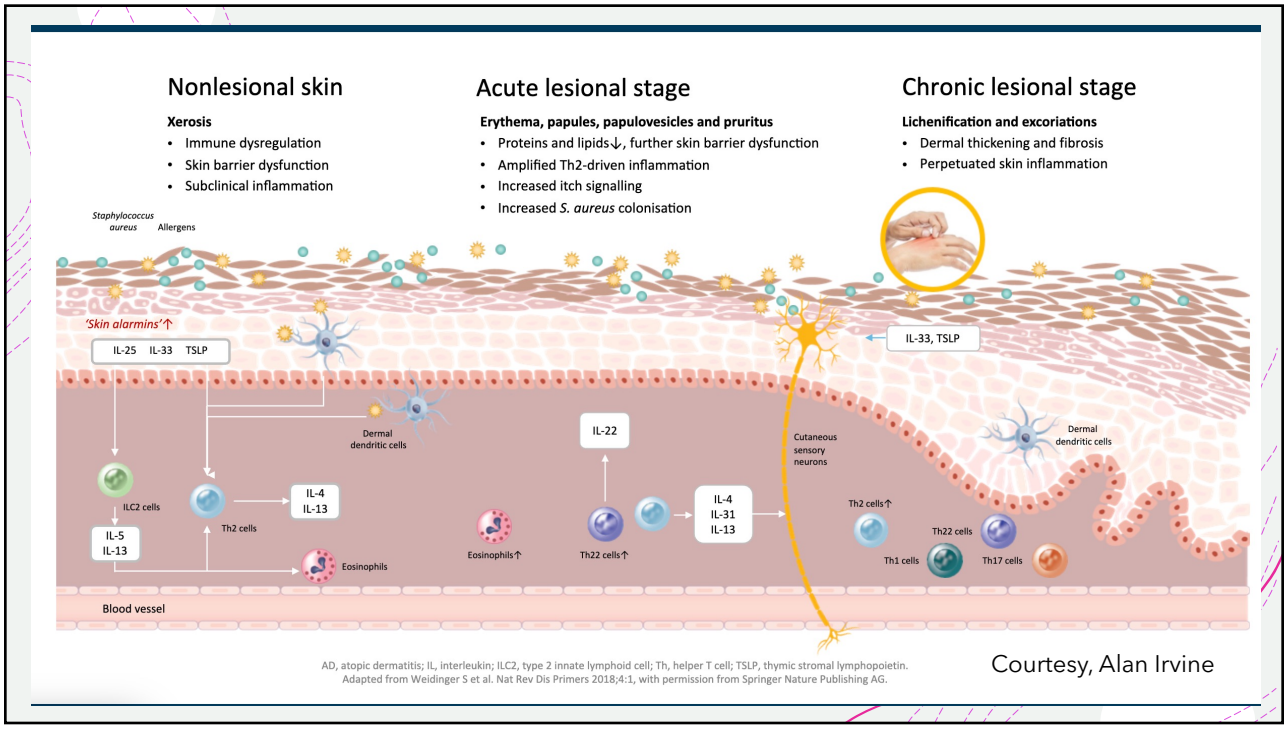
Disconnect occurs between the epidermal proteome and transcriptome

JACI 2017; 140:1299

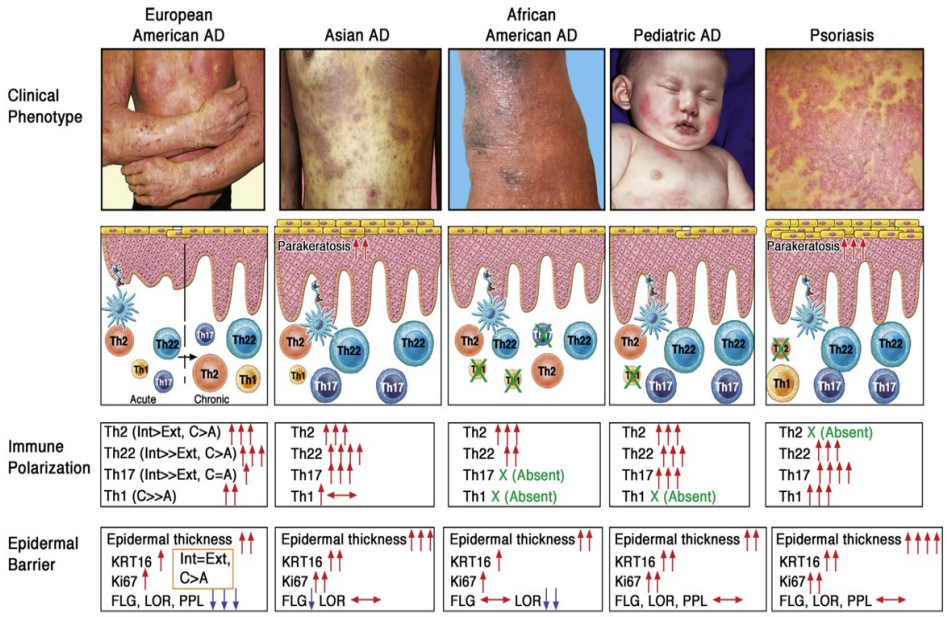
80


Nonlesional skin
Xerosis
• Immune dysregulation
• Skin barrier dysfunction
• Subclinical inflammation
Acute lesional stage
Erythema, papules, papulovesicles and pruritus
• Proteins and lipids↓, further skin barrier dysfunction
• Amplified Th2-driven inflammation
• Increased itch signalling
• Increased S. aureus colonisation
Courtesy, Alan Irvine
Staphylococcus aureus
Allergens
'Skin alarmins'↑
IL-25 IL-33 TSLP
Dermal dendritic cells
IL-22
Cutaneous sensory neurons
ILC2 cells
IL-5 IL-13
Th2 cells
IL-4 IL-13
Eosinophils
Eosinophils↑
Th22 cells↑
IL-4 IL-31 IL-13
Blood vessel
AD, atopic dermatitis; IL, interleukin; ILC2, type 2 innate lymphoid cell; Th, helper T cell; TSLP, thymic stromal lymphopoietin.
Adapted from Weidinger S et al. Nat Rev Dis Primers 2018;4:1, with permission from Springer Nature Publishing AG.
Courtesy, Alan Irvine

81


Nonlesional skin
Xerosis
• Immune dysregulation
• Skin barrier dysfunction
• Subclinical inflammation
Acute lesional stage
Erythema, papules, papulovesicles and pruritus
• Proteins and lipids↓, further skin barrier dysfunction
• Amplified Th2-driven inflammation
• Increased itch signalling
• Increased S. aureus colonisation
Chronic lesional stage
Lichenification and excoriations
• Dermal thickening and fibrosis
• Perpetuated skin inflammation
Staphylococcus aureus
Allergens
'Skin alarmins'↑
IL-25 IL-33 TSLP
IL-33, TSLP
Dermal dendritic cells
IL-22
Cutaneous sensory neurons
ILC2 cells
IL-5 IL-13
Th2 cells
IL-4 IL-13
Eosinophils
Eosinophils↑
Th22 cells↑
IL-4 IL-31 IL-13
Th2 cells↑
Th22 cells
Th1 cells
Th17 cells
Blood vessel
AD, atopic dermatitis; IL, interleukin; ILC2, type 2 innate lymphoid cell; Th, helper T cell; TSLP, thymic stromal lymphopoietin.
Adapted from Weidinger S et al. Nat Rev Dis Primers 2018;4:1, with permission from Springer Nature Publishing AG.
Courtesy, Alan Irvine

82

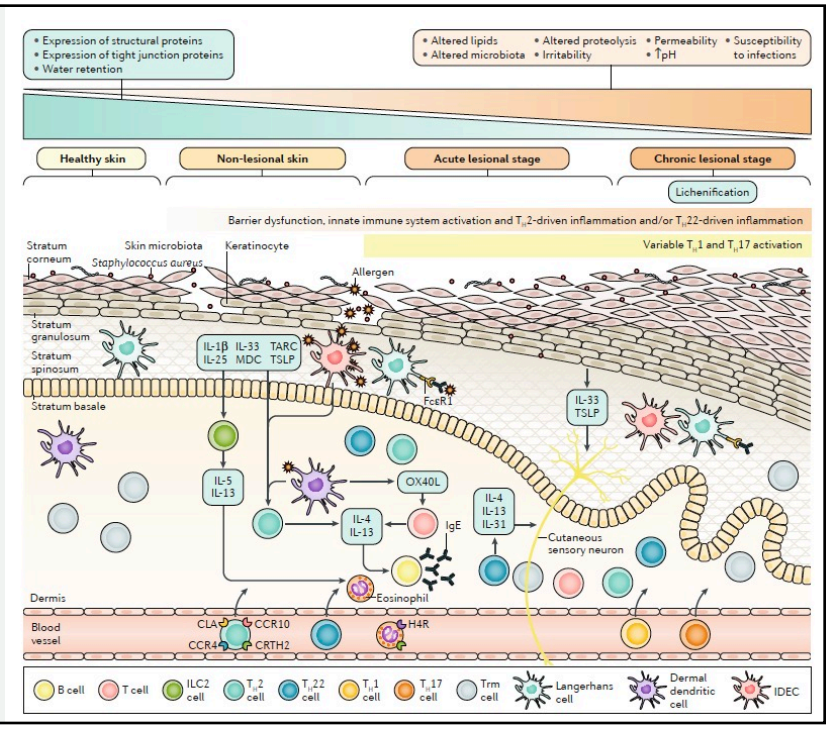


Does this occur in dogs?

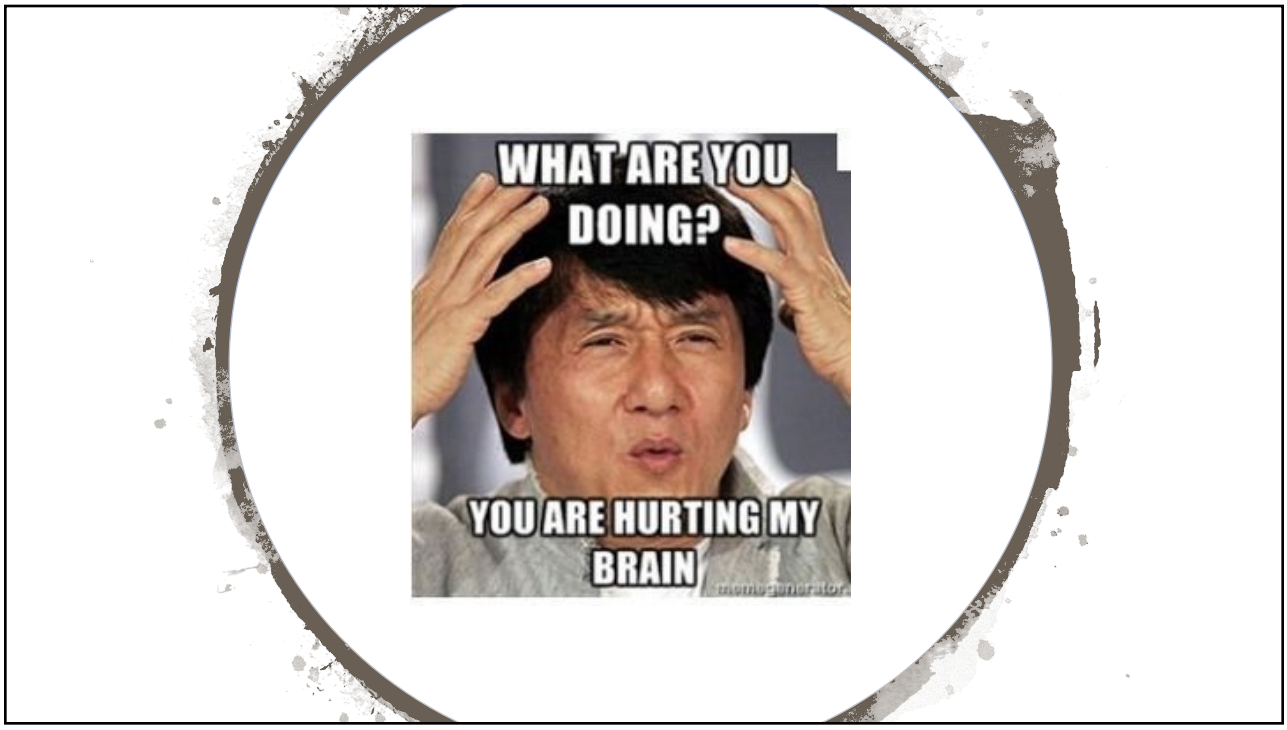
Czarnowicki et al. J Allergy Clin Immunol 2019: 143

83

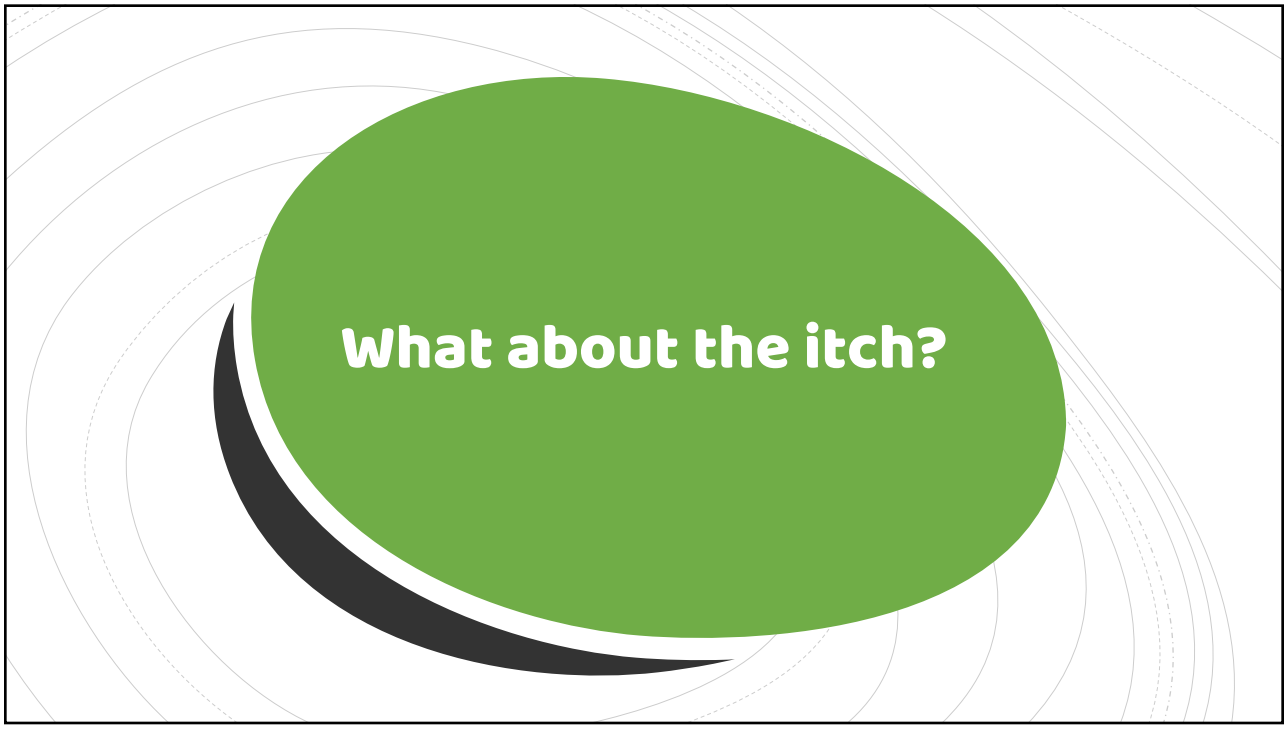
Weidinger S et al. Atopic dermatitis Nature Reviews Disease Primers 2018 Jun 21: 4(1)



84


WHAT ARE YOU DOING?
YOU ARE HURTING MY BRAIN

85


What about the itch?

86

Neuron 98, May 2, 2018 © 2018 Elsevier Inc.

Peripheral and Central Mechanisms of Itch

Xintong Dong[1,2,*] and Xinzhong Dong[1,2,*]
[1]The Solomon H. Snyder Department of Neuroscience and the Center for Sensory Biology, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
[2]Howard Hughes Medical Institute, Johns Hopkins University School of Medicine, Baltimore, MD 21205, USA
*Correspondence: xdong11@jhmi.edu (X.D.), xdong2@jhmi.edu (X.D.)
https://doi.org/10.1016/j.neuron.2018.03.023

Table 1. Peripheral Mediators and Neuronal Receptors of Itch

Molecular Mediator	Main Cellular Source	Neuronal Receptor	Ion Channel	DRG Neuron Subtypes	Cause of Itch
Histamine	mast cells	H1R, H4R	TRPV1, TRPV4	NP2, NP3	insect bites, dermatitis
Serotonin (5-HT)	mast cells, keratinocytes	HTR7, HTR2	TRPA1, TRPV1, TRPV4	NP3	atopic dermatitis
Proteases	mast cells, plants	PAR2, MrgprC11	TRPA1, TRPV1	NP2	cowhage, dermatitis
TSLP	keratinocytes	TSLP receptor (IL-7Rα + TSLPR)	TRPA1		atopic dermatitis
IL-31	Th2 T helper cells	IL-31 receptor (IL-31Rα+ OSMR)	TRPA1, TRPV1	NP3	atopic dermatitis, T cell lymphoma
IL-33	keratinocytes	IL-33 receptor (IL-1RAcP + ST2)	TRPA1, TRPV1	NP2	allergic contact dermatitis atopic dermatitis
IL-4 and IL-13	Th2 cells, ILC2s, basophils	Il-4Rα, IL-13Rα1	TRPA1, TRPV1	NP1, NP2, NP3	atopic dermatitis, chronic idiopathic pruritus
Poly I:C, Imiquimod	pathogens, drug	TLR3, TLR7			psoriasis, xerosis (dry skin)
BAM8-22 peptide	keratinocytes	MrgprC11	TRPA1, TRPV1	NP2	xerosis (dry skin)
Chloroquine	medicine in circulation	MrgprA3	TRPA1, CNO1	NP2	drug-induced itch
β-alanine	medicine in circulation	MrgprD		NP1	drug-induced itch

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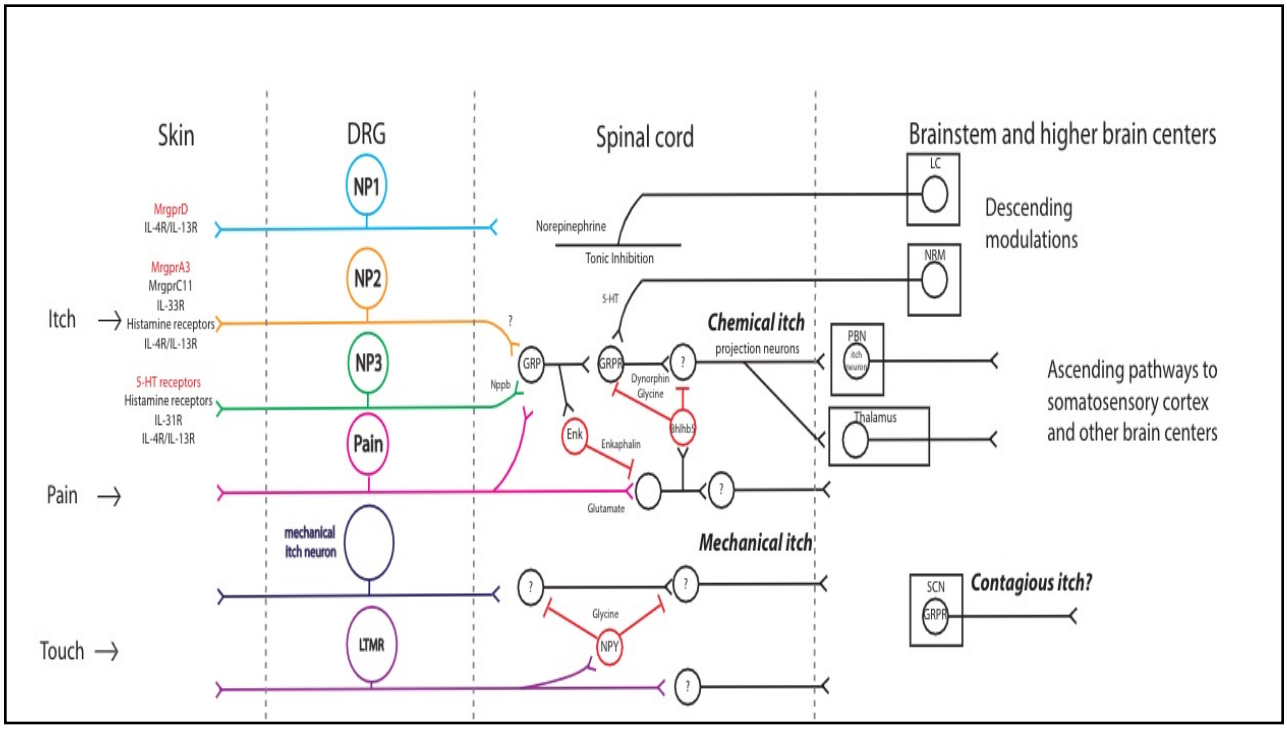


88

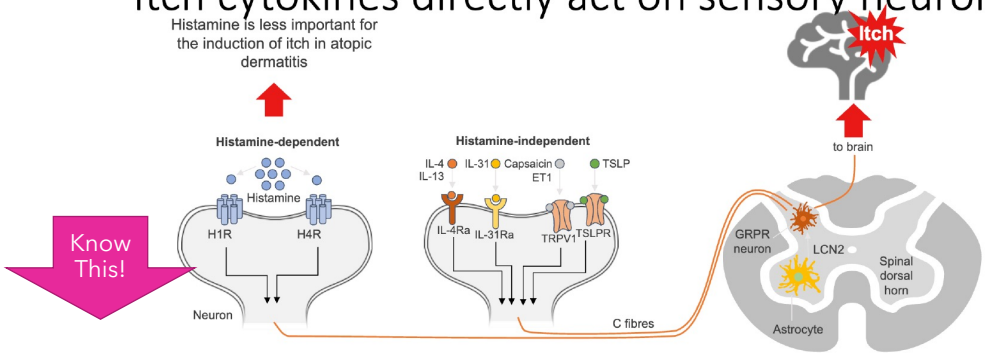
?

That's complicated! What do I really need to know?

89

Itch cytokines directly act on sensory neurons

Histamine is less important for the induction of itch in atopic dermatitis



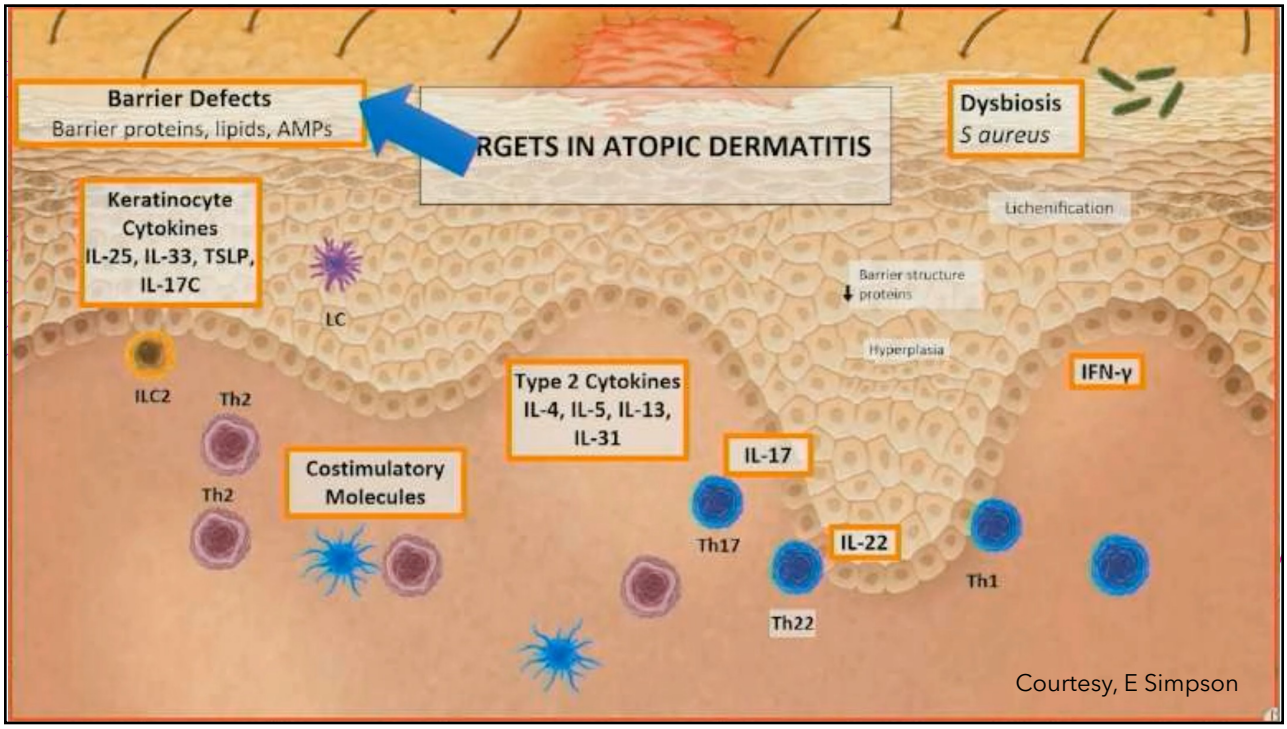
The increased expression of pruritogens including TSLP, IL-4, IL-13 and IL-31 which signal via histamine-independent molecular pathways is most important for induction of itch in atopic dermatitis

ET=endothelin 1; GPRP=gastrin-releasing peptide receptor; H1R/H4R=histamine H1/H4 receptor; IL=interleukin; LCN=lipocalin; TRPV=transient receptor potential cation channel subfamily V member; TSLP= thymic stromal lymphopoietin; TSLPR= thymic stromal lymphopoietin receptor.
Weidinger S, et al. Nat Rev Dis Primers 2018;4(1):1

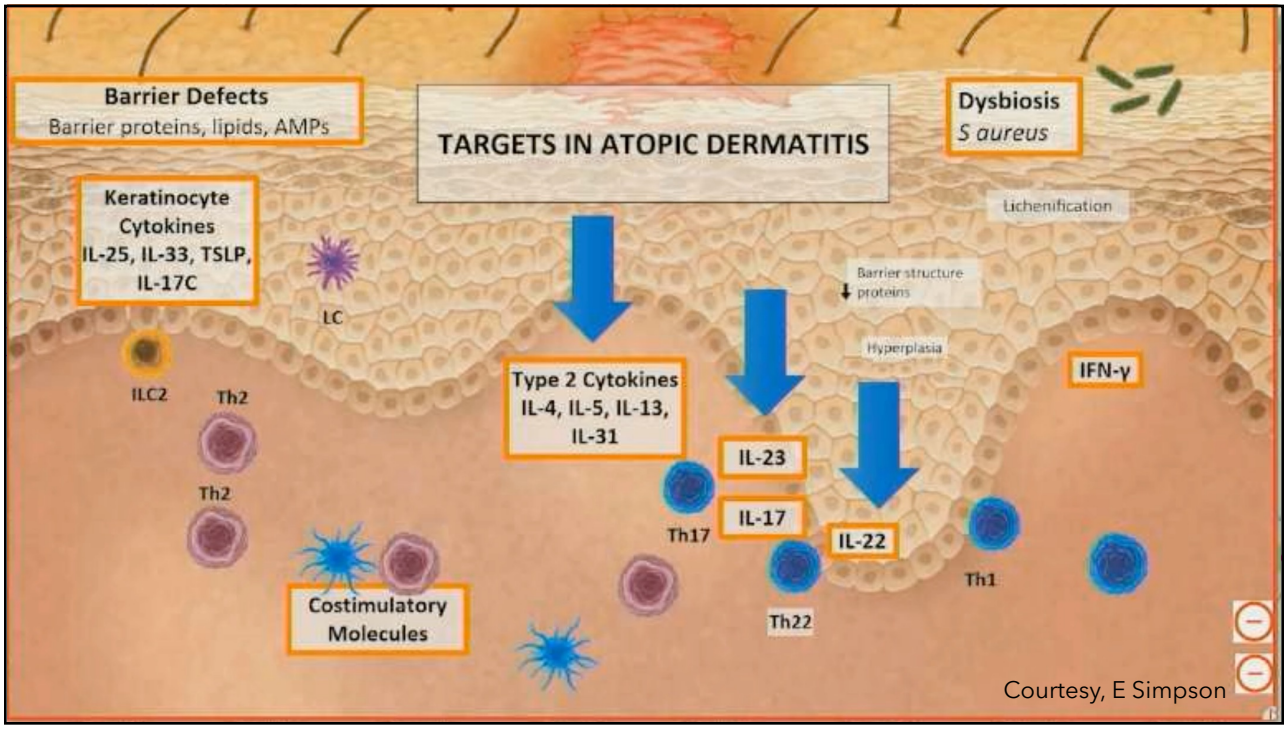
90


How can we test what we believe about immunopathogenesis of AD?
Monoclonal antibodies!
Monoclonal Antibody
Cytokine IL-31

91


Barrier Defects
Barrier proteins, lipids, AMPs
RGETS IN ATOPIC DERMATITIS
Dysbiosis
S aureus
Keratinocyte Cytokines IL-25, IL-33, TSLP, IL-17C
Lichenification
LC
Barrier structure proteins
Hyperplasia
IFN-γ
ILC2
Th2
Th2
Type 2 Cytokines IL-4, IL-5, IL-13, IL-31
Costimulatory Molecules
IL-17
Th17
IL-22
Th1
Th22
Courtesy, E Simpson

92



93

The immune system is more druggable!

94

A very interesting paper!

F1000Research F1000Research 2019, 8(F1000 Faculty Rev):132 Last updated: 01 FEB 2019

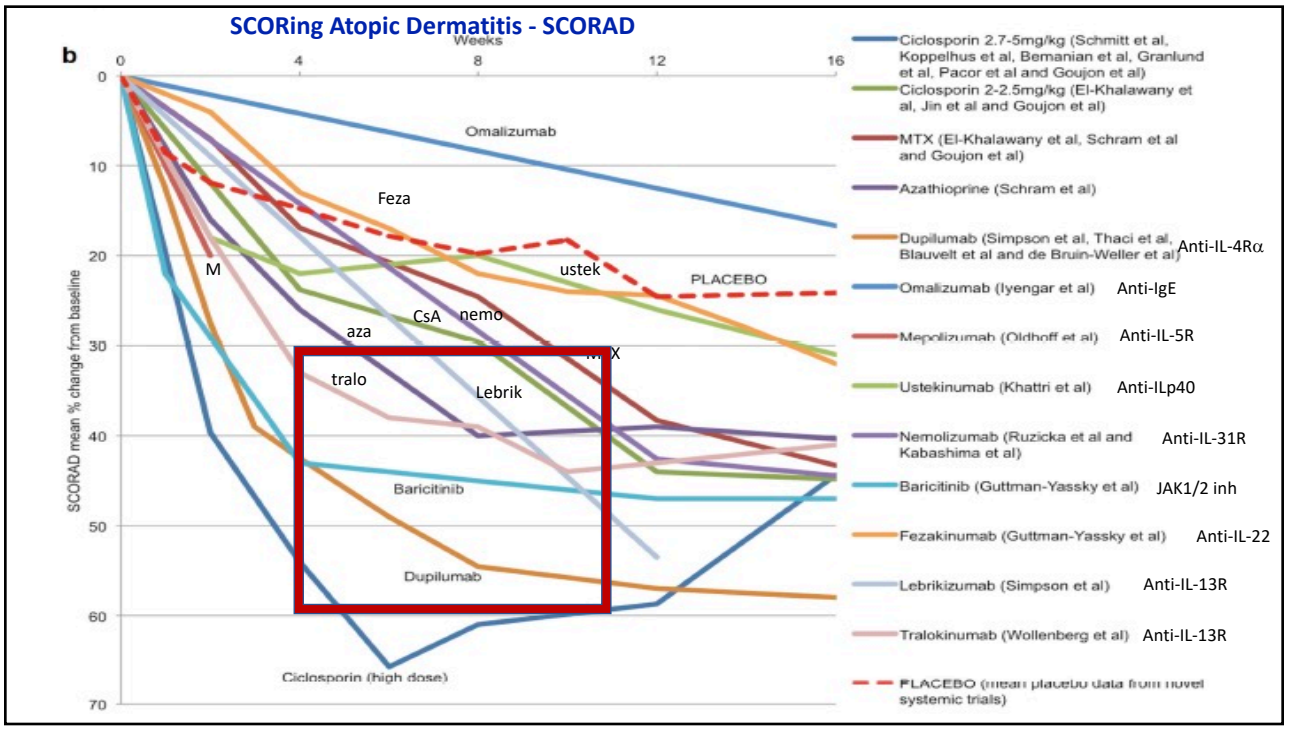
Check for updates

REVIEW

Novel systemic therapies in atopic dermatitis: what do we need to fulfil the promise of a treatment revolution? [version 1; referees: 3 approved]

Helen Alexander [1], Thomas Patton[2], Zarif K. Jabbar-Lopez[1], Andrea Manca[2], Carsten Flohr[1]

95



96

SCORAD ("SCORing Atopic Dermatitis") is a clinical tool for assessing the severity (i.e., extent, intensity) of atopic dermatitis as objectively as possible.

This **free** online application helps physicians and patients in the computation of the SCORAD.
If you find this application useful you can help with the costs of hosting with a small contribution. Donate

Area

Head and neck	(9% BSA)	○0% ○25% ○50% ○75% ○100%
Upper limbs (left)	(9% BSA)	○0% ○25% ○50% ○75% ○100%
Upper limbs (right)	(9% BSA)	○0% ○25% ○50% ○75% ○100%
Lower limbs (left)	(18% BSA)	○0% ○25% ○50% ○75% ○100%
Lower limbs (right)	(18% BSA)	○0% ○25% ○50% ○75% ○100%
Anterior trunk	(18% BSA)	○0% ○25% ○50% ○75% ○100%
Back	(18% BSA)	○0% ○25% ○50% ○75% ○100%
Genitals	(1% BSA)	○0% ○25% ○50% ○75% ○100%

Intensity

A representative area of eczema is selected. In this area, the intensity of each of the following signs is assessed as none (0), mild (1), moderate (2) or severe (3) (see [1]).

Redness	○0 ○1 ○2 ○3
Swelling	○0 ○1 ○2 ○3
Oozing / Crusting	○0 ○1 ○2 ○3
Scratch marks	○0 ○1 ○2 ○3
Skin thickening (lichenification)	○0 ○1 ○2 ○3
Dryness	○0 ○1 ○2 ○3

Subjective symptoms

Using a visual analogue scale where 0 is no itch (or no sleeplessness) and 10 is the worst imaginable itch (or sleeplessness).

Itch	○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10
Sleeplessness	○0 ○1 ○2 ○3 ○4 ○5 ○6 ○7 ○8 ○9 ○10

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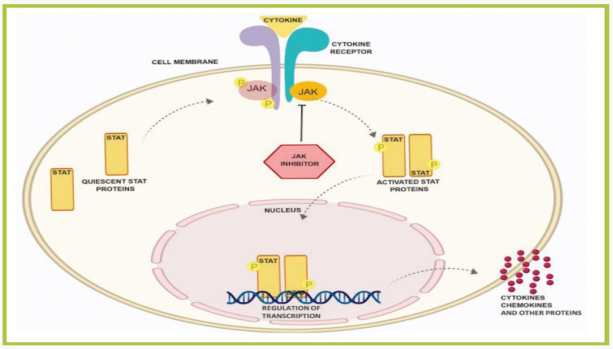
National Eczema Association

ABOUT ECZEMA ∨ LIVING WITH ECZEMA ∨ NEWS & STORIES ∨ GET INVOLVED ∨ RESEARCH ∨ PROFESSIONALS ∨

Jan 4, 2021

JAK Inhibitors Are Coming and They Are the Biggest Eczema Development in Years



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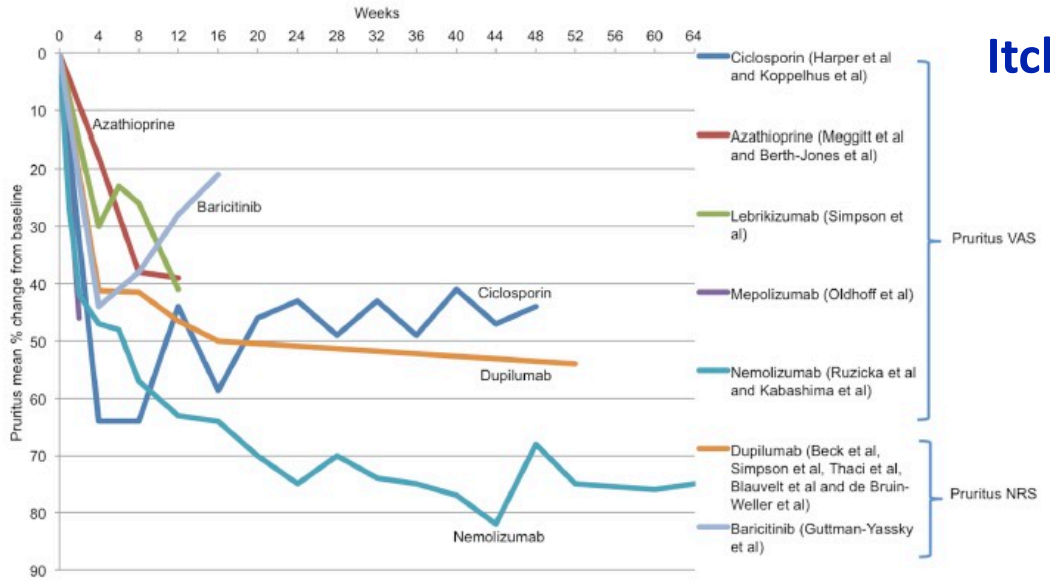

Itch

Figure 4. Treatment effectiveness: patient-reported severity measures. Mean percentage change from baseline in pruritus visual analogue score (VAS) and pruritus numerical rating scale (NRS) for systemic agents for which these data were reported.

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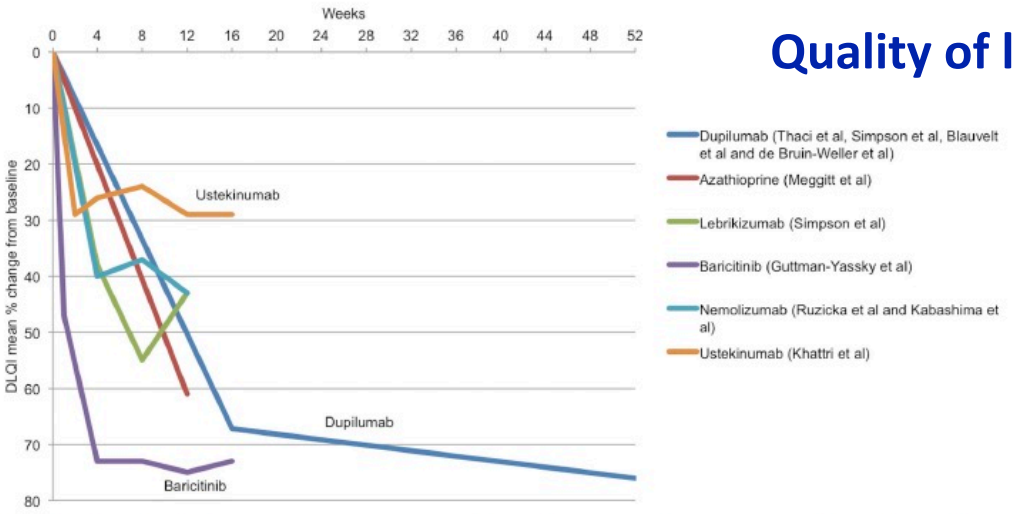

Quality of life

Figure 5. Treatment effectiveness: quality of life. Dermatology Life Quality Index (DLQI) mean percentage change from baseline for systemic agents for which these data were reported.

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Summary of efficacy in human AD

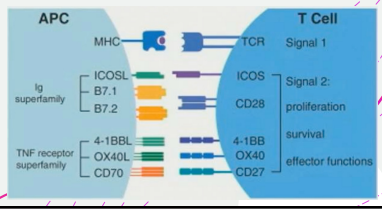
(Courtesy, Eric Simpson, RAD Dec 2020)

Things that worked well

- Blocking IL-4 and IL-13
  - Dupilumab
- Blocking IL-13
  - Tralokinumab
  - Lebrikizumab
- Blocking IL-31
  - Anti-IL31Ralpha (nemolizumab)
    - Except Japanese adolescents and adults
  - Anti-OSMRbeta (KPL-716)

Things that didn't work well

- Blocking IL-33
  - etokimab
- Blocking TSLP
  - tezepelumab
- Blocking IL-17C
  - MOR106
- Blocking adhesion molecule OX40
  - KHK4083



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How does allergy immunotherapy work?

It's complicated ☺

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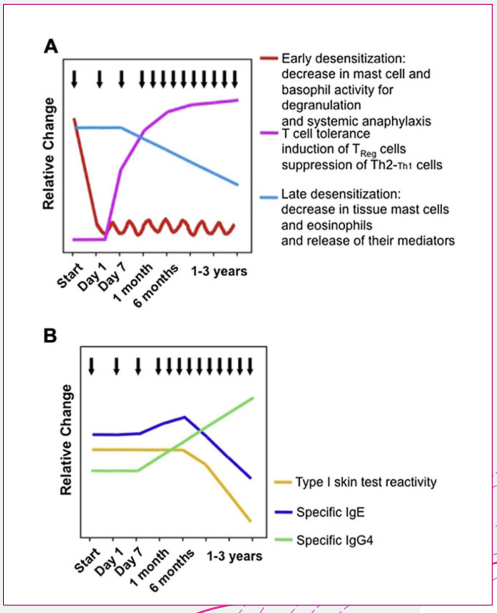
Proposed mechanisms: which comes first?

- Very early
  - desensitization of mast cells and basophils to degranulation
- Days to months, T cell tolerance:
  - T regulatory cells
  - Altered ratio Th2:Th1 and cytokines
- Months to years
  - Increase in blocking antibodies (allergen specific IgG4 and IgG1)
  - Decrease in allergen-specific IgE
- Decreased number of inflammatory cells (eosinophils, basophils, mast cells)



J Allergy Clin Immunol 2013; 131:1288

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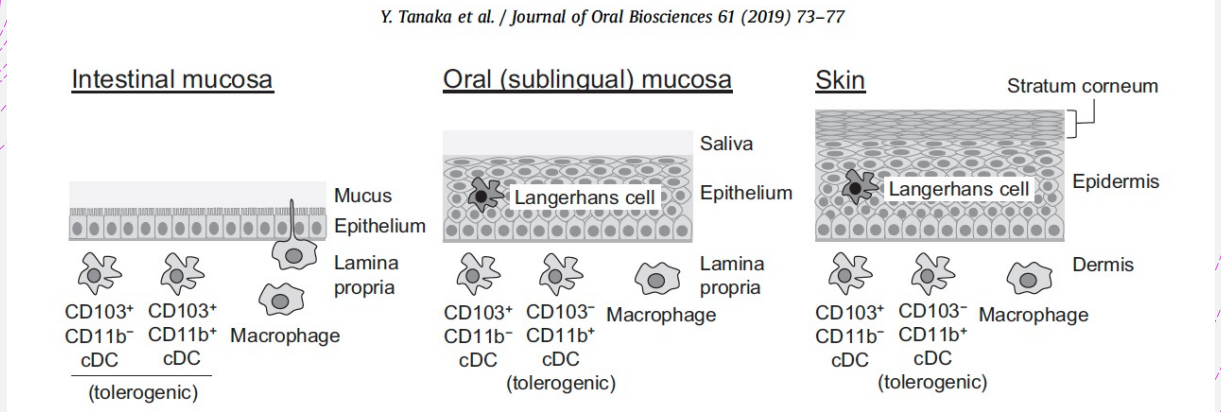
To understand allergy immunotherapy we need to understand the mechanisms of immunological tolerance

105

Sublingual mucosa is more like skin



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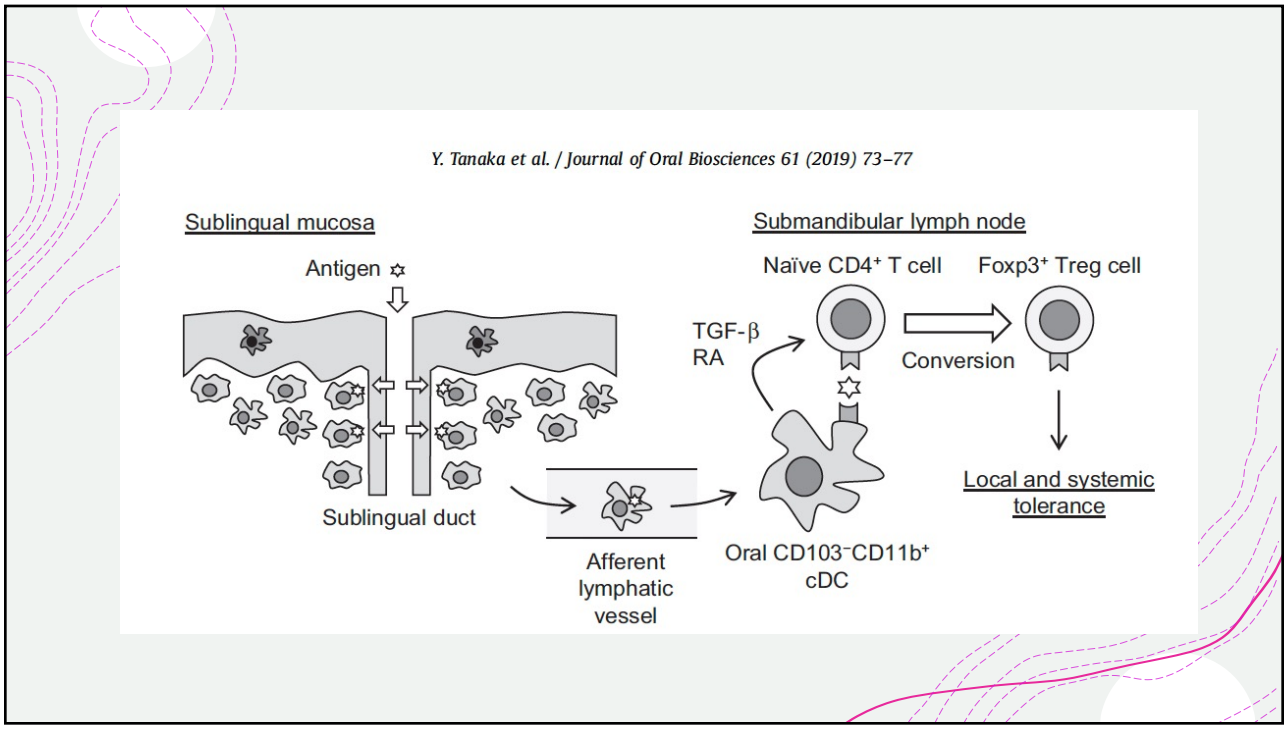
Y. Tanaka et al. / Journal of Oral Biosciences 61 (2019) 73–77
Sublingual mucosa
Antigen
Sublingual duct
Afferent lymphatic vessel
Submandibular lymph node
Naïve CD4⁺ T cell
Foxp3⁺ Treg cell
TGF-β
RA
Conversion
Local and systemic tolerance
Oral CD103⁻CD11b⁺ cDC

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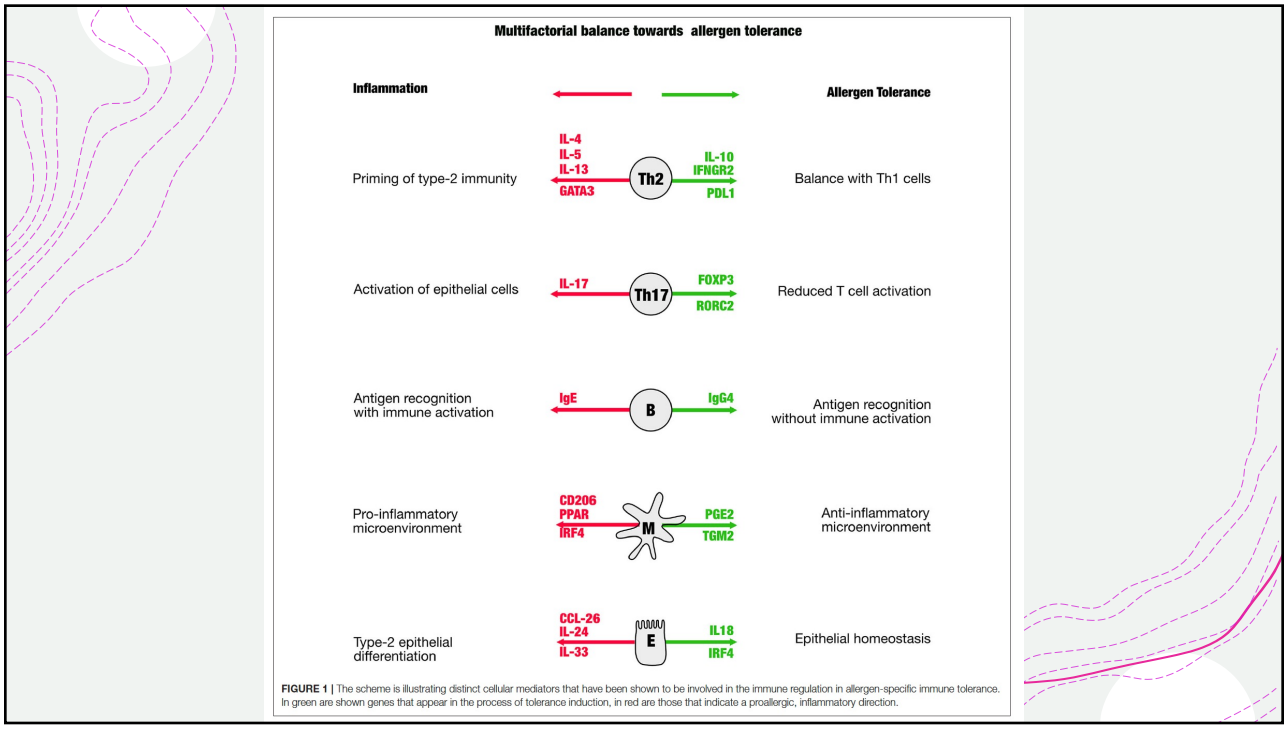
Multifactorial balance towards allergen tolerance
Inflammation
Allergen Tolerance
Priming of type-2 immunity
IL-4
IL-5
IL-13
GATA3
Th2
IL-10
IFNGR2
PDL1
Balance with Th1 cells
Activation of epithelial cells
IL-17
Th17
FOXP3
RORC2
Reduced T cell activation
Antigen recognition with immune activation
IgE
B
IgG4
Antigen recognition without immune activation
Pro-inflammatory microenvironment
CD206
PPAR
IRF4
M
PGE2
TGM2
Anti-inflammatory microenvironment
Type-2 epithelial differentiation
CCL-26
IL-24
IL-33
E
IL18
IRF4
Epithelial homeostasis
FIGURE 1 | The scheme is illustrating distinct cellular mediators that have been shown to be involved in the immune regulation in allergen-specific immune tolerance. In green are shown genes that appear in the process of tolerance induction, in red are those that indicate a proallergic, inflammatory direction.

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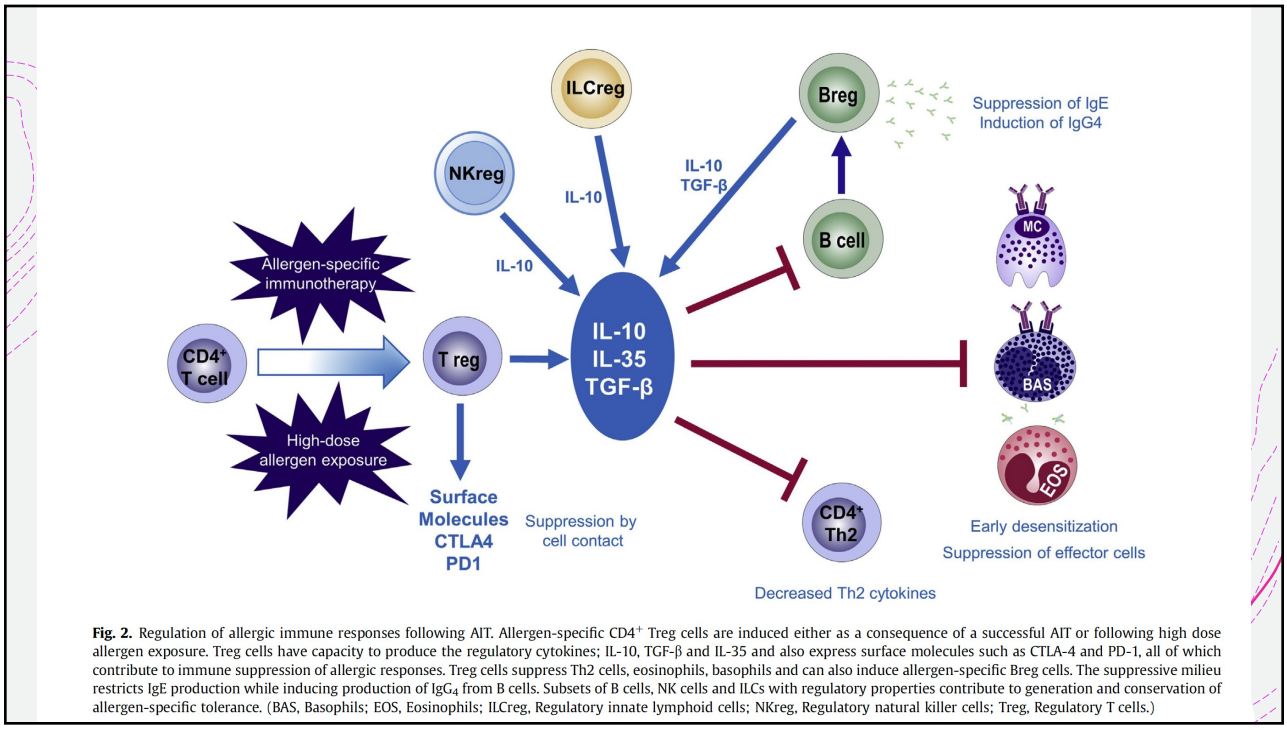

Fig. 2. Regulation of allergic immune responses following AIT. Allergen-specific $CD4^+$ Treg cells are induced either as a consequence of a successful AIT or following high dose allergen exposure. Treg cells have capacity to produce the regulatory cytokines; IL-10, TGF-β and IL-35 and also express surface molecules such as CTLA-4 and PD-1, all of which contribute to immune suppression of allergic responses. Treg cells suppress Th2 cells, eosinophils, basophils and can also induce allergen-specific Breg cells. The suppressive milieu restricts IgE production while inducing production of IgG_4 from B cells. Subsets of B cells, NK cells and ILCs with regulatory properties contribute to generation and conservation of allergen-specific tolerance. (BAS, Basophils; EOS, Eosinophils; ILCreg, Regulatory innate lymphoid cells; NKreg, Regulatory natural killer cells; Treg, Regulatory T cells.)

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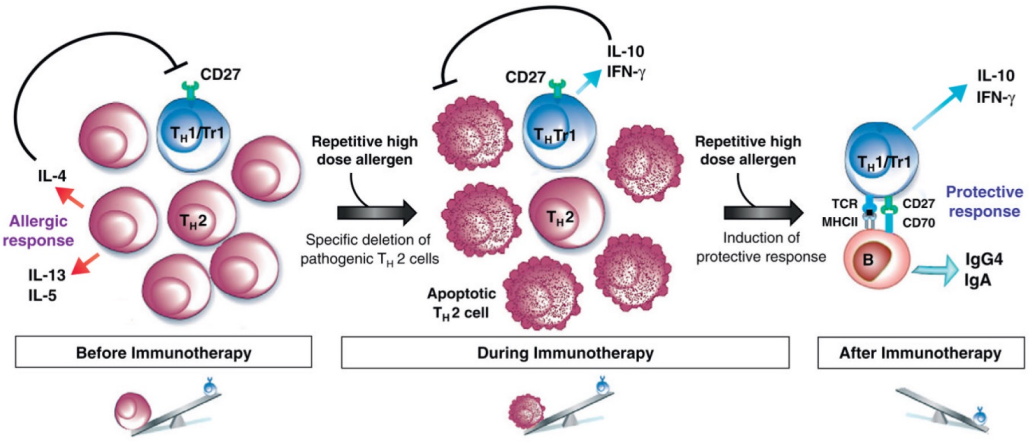
Current Opinion Immunology 2012; 24:700-706

Page 10



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Methods – is any one superior?

WE DON'T KNOW

Methods

- Subcutaneous (SCIT)
  - Rush
- Sublingual (SLIT)
- Intralymphatic (ILIT)
- Oral (OIT)
- Epicutaneous (EPIT)

Problems

- Too many variables
  - How the IT is prepared
  - Allergens selected
  - Geographic variation
  - Variable severity
  - Other?
- Very low #'s patients
- Hi drop-out rates

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Selection criteria

"‘when is it appropriate to use AIT?

To my knowledge, we have no guidelines

For me:

- Committed owners
- Dogs with signs occurring when they are young
- An allergy test that allows for rational selection of allergens

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Impact of medications on allergy immunotherapy

What is the evidence? Not much!

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Glucocorticoids

Article

Concomitant Use Of Glucocorticoids During Allergen Immunotherapy Upregulates Il10 Production By Peripheral Blood Mononuclear Cells (pbmc)

January 2007 · Journal of Allergy and Clinical Immunology 119(1)

DOI: 10.1016/j.jaci.2006.11.211

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Cyclosporine

I can't find much!
Effects on induction of Treg are mixed

115

JAK inhibitors

> Allergy. 2019 Sep;74(9):1814-1816. doi: 10.1111/all.13808. Epub 2019 May 20.

Supporting allergen-specific immunotherapy by inhibition of Janus kinases

Jan Gutermuth [1], Carsten B Schmidt-Weber [2], Simon Blank [2]

Affiliations + expand

PMID: 30953592 DOI: 10.1111/all.13808

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Biologics

Review

Allergologie select, Vol. 5/2021 (108-118)

Use of biologics in allergen immunotherapy

Wolfgang Pfützner and Mathias Schuppe

Department of Dermatology and Allergology, Clinical-Experimental Allergology, Allergy Center Hessen, University Hospital Marburg, Philipps-University Marburg

ISSN 2512-8957

DOI 10.5414/ALX02206E
e-pub: February 19, 2021

Omalizumab (anti-IgE) seems to improve efficacy and safety of AIT

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Other types of immunotherapy?

- Anti-cytokine mAbs
- Vaccination against cytokines

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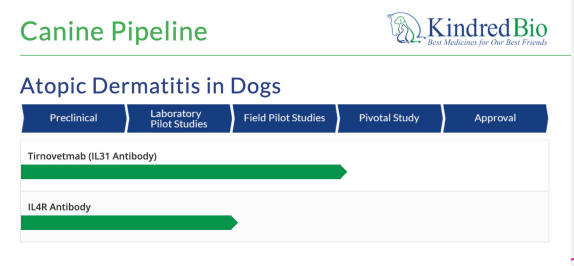
Anti-cytokine mAb in dogs

+Lokivetmab – caninized anti-canine IL-31

+You are using it!

+Review the literature by typing lokivetmab into PubMed

+Anything more coming? Probably!



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Active vaccination against cytokines

A new approach for allergic skin disease

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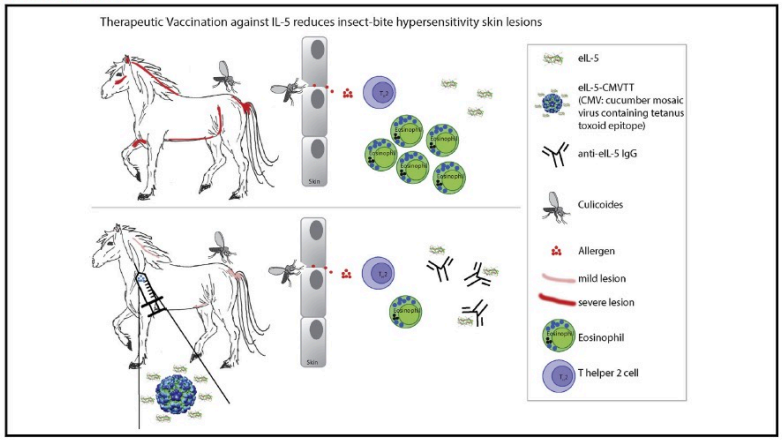
Treating insect-bite hypersensitivity in horses with active vaccination against IL-5

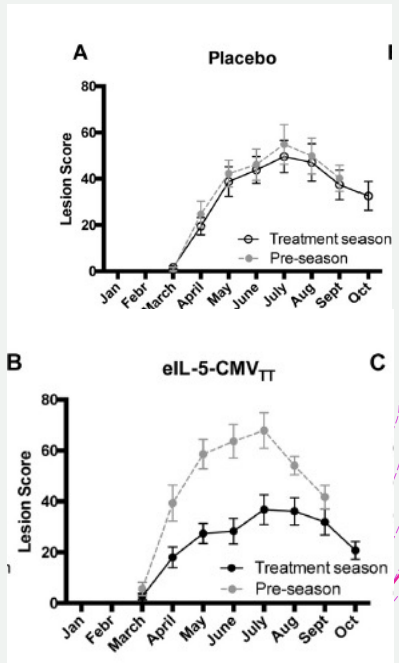
Antonia Fettelschoss-Gabriel, PhD,[a,b] Victoria Fettelschoss, MSc,[a,b] Franziska Thoms, PhD,[a] Christoph Giese, PhD,[c] Michelle Daniel, BSc,[a] Florian Olomski, MSc,[a] Jivko Kamarachev, MD,[d] Katharina Birkmann, DVM,[e] Maya Bühler, DVM,[e] Martin Kummer, DVM,[e] Andris Zeltins, PhD,[f] Eliane Marti, DVM,[g] Thomas M. Kündig, MD,[d] and Martin F. Bachmann, PhD[h,i]

Schlieren, Münchwilen, Zurich, Niederuzwil, and Bern, Switzerland; Riga, Latvia; and Oxford, United Kingdom

J Allergy Clin Immunol 2018: 142:1194

GRAPHICAL ABSTRACT





121

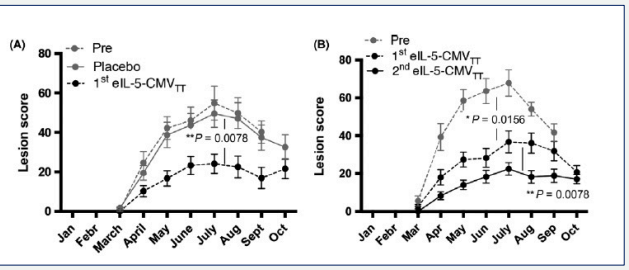
Received: 27 June 2018 | Revised: 3 October 2018 | Accepted: 8 October 2018
DOI: 10.1111/all13659

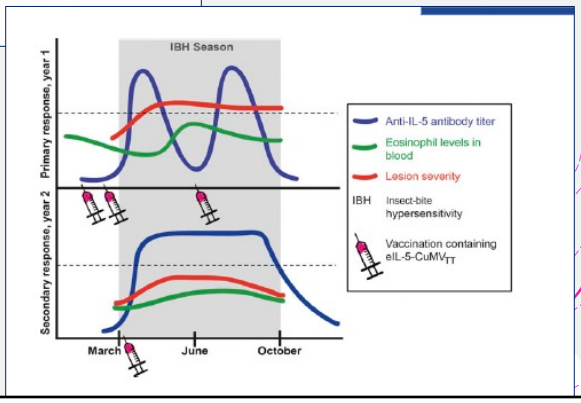
ORIGINAL ARTICLE

Drug Allergy, Insect Sting Allergy, and Anaphylaxis

Active vaccination against interleukin-5 as long-term treatment for insect-bite hypersensitivity in horses

Antonia Fettelschoss-Gabriel[1,2,3] | Victoria Fettelschoss[1,2,3] | Florian Olomski[1,2] | Katharina Birkmann[3] | Franziska Thoms[1,2] | Maya Bühler[4] | Martin Kummer[4] | Andris Zeltins[5] | Thomas M. Kündig[2,6] | Martin F. Bachmann[7,8]





122

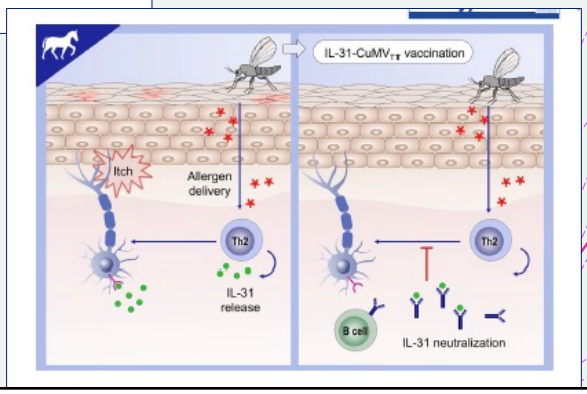
Received: 21 June 2019 | Revised: 15 August 2019 | Accepted: 2 September 2019
DOI: 10.1111/all.14145

ORIGINAL ARTICLE
Atopic Dermatitis, Urticaria and Skin Disease

Allergy WILEY

Interleukin 31 in insect bite hypersensitivity—Alleviating clinical symptoms by active vaccination against itch

Florian Olomski[1,2] | Victoria Fettelschoss[1,2,3] | Sigridur Jonsdottir[4] | Katharina Birkmann[3] | Franziska Thoms[1,2] | Eliane Marti[4] | Martin F. Bachmann[5,6] | Thomas M. Kündig[2,7] | Antonia Fettelschoss-Gabriel[1,2,3]



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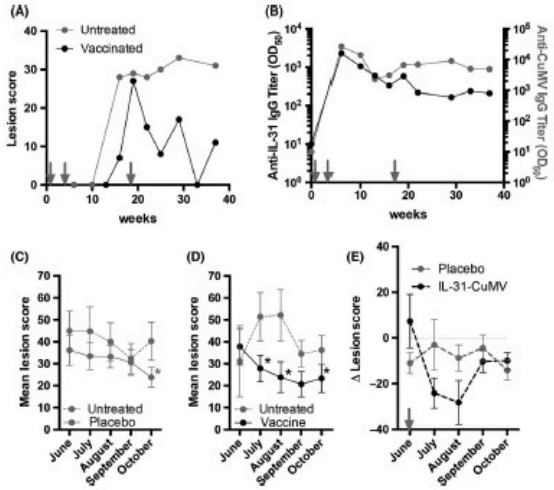

FIGURE 4 Efficacy of eIL-31-CuMV$_{TT}$ vaccine by reduction of lesion scores. A & B, Case report. A, IBH lesion scores of single horse during untreated previous season (gray) and vaccination season (black). B, Antibody titer against eIL-31 (left y-axis, black) and CuMV$_{TT}$ (right y-axis, gray) of single horse. Vaccinations are indicated by arrows. C-E, Double-blind placebo-controlled randomized clinical study. C, Monthly lesion score of placebo group during untreated (dotted gray line) and placebo-treated (continuous gray line) season. Statistics is only indicated when significant. D, Monthly lesion score of vaccinated group during untreated (dotted gray line) and eIL-31-CuMV$_{TT}$ vaccinated (continuous black line) season. Statistics is only indicated when significant. E, Delta of monthly lesion scores after booster vaccination from previous IBH season subtracted by placebo- or vaccine-treated season. Mid-season booster indicated by arrow

Itch Not Assessed

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Thanks for listening
Reach out if I can help
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fadokv@gmail.com

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