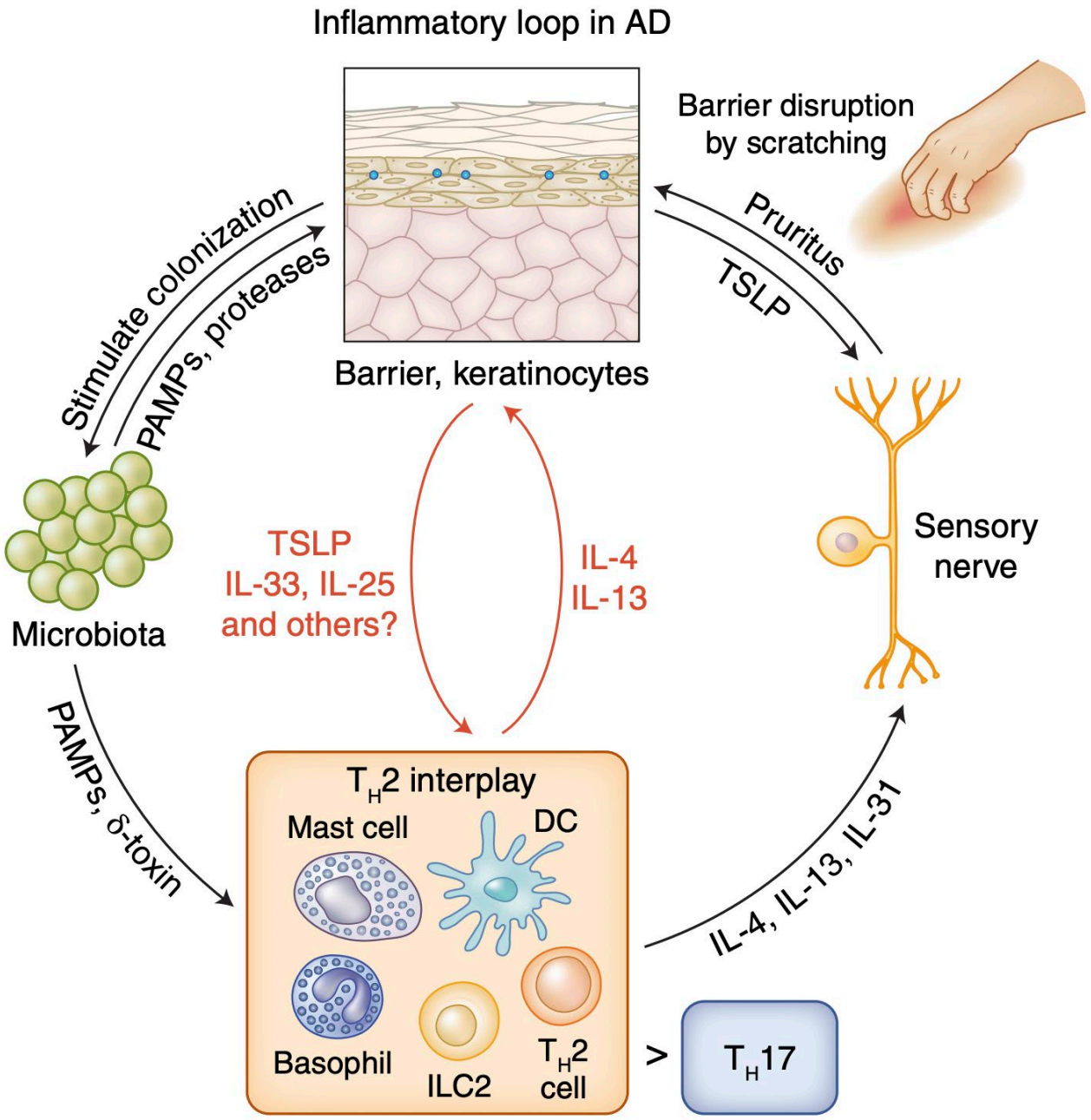
Environmental Impact on Atopy

Peter Lio, MD

DISCLOSURES FOR PETER LIO, MD

Relationship	Manufacturer
Speaker	AbbVie, Arcutis, Eli Lilly, Galderma, Hyphens Pharma, Incyte, La Roche-Posay/L'Oreal, MyOR Diagnostics, ParentMD, Pfizer, Pierre-Fabre Dermatologie, Regeneron/Sanofi Genzyme, Verrica
Advisory Board	Alphyn Biologics, AbbVie, Almirall, Amyris, Arcutis, ASLAN, Boston Skin Science, Bristol-Myers Squibb, Burt's Bees, Castle Biosciences, Codex Labs, Concerto Biosci, Dermavant, Eli Lilly, Galderma, LEO Pharma, Lipidor, L'Oreal, Merck, Micreos, MyOR Diagnostics, Pelthos Therapeutics, Regeneron/Sanofi Genzyme, Sibel Health, Skinfix, Sonica, Soteri Skin, Suneco Technologies, Theraplex, Thimble Health, UCB, Unilever, Verdant Scientific, Verrica, Yobee Care
Research	AbbVie, AOBiome
Patent Holder	Theraplex AIM (Patent Pending)
Stock Options	Alphyn Labs, Codex Labs, Concerto Biosci, LearnSkin/Learn Health, Medable, Modernizing Medicine, Soteri Skin, Suneco Technologies, Thimble, Yobee Care, Verdant Scientific

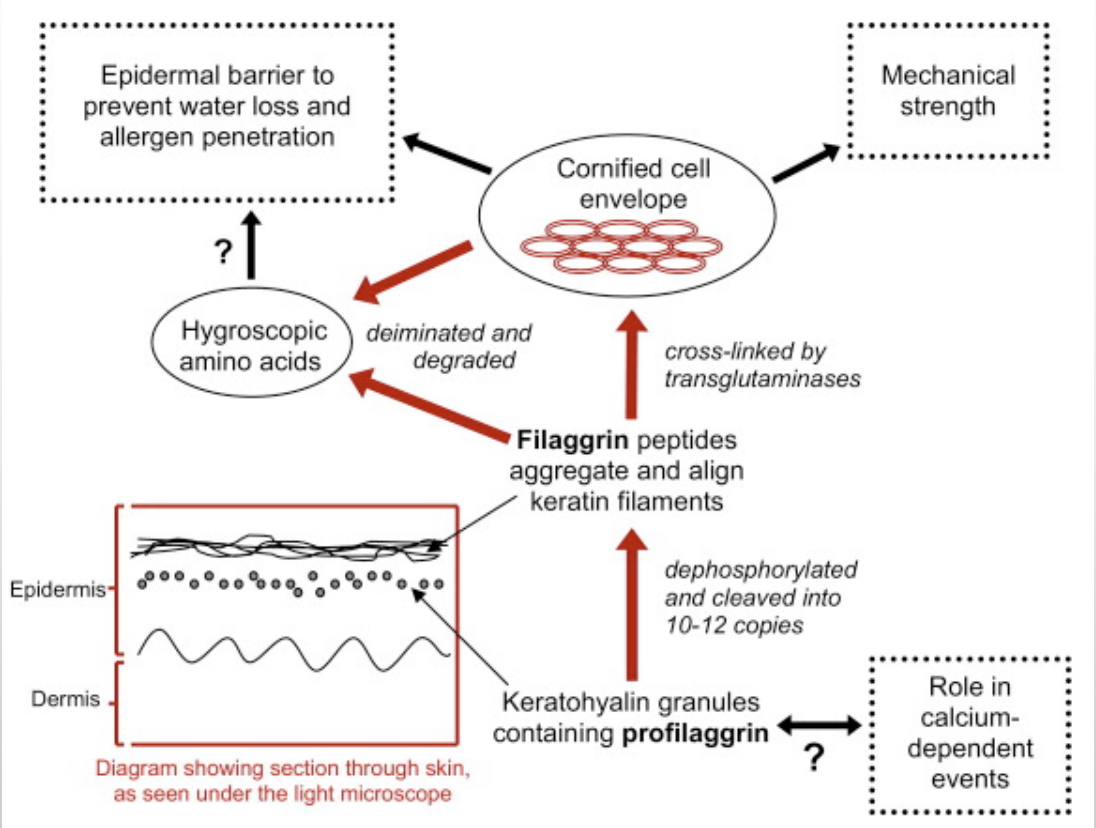
LOOPS



- THE EPITHELIAL IMMUNE MICROENVIRONMENT (EIME) IN ATOPIC DERMATITIS AND PSORIASIS. DAINICHI T, KITOH A, OTSUKA A, NAKAJIMA S, NOMURA T, KAPLAN DH, KABASHIMA K. NAT IMMUNOL. 2018 DEC;19(12):1286-1298.

FILAGGRIN

*FIL*AMENT-*AGG*REGATING PROTE*IN*



Brown SJ, Irvine AD. Atopic eczema and the filaggrin story. Semin Cutan Med Surg. 2008 Jun;27(2):128-37.

FILAGGRIN

- MUTATIONS CAUSE ICHTHYOSIS VULGARIS (IV)
- 8% OF ECZEMA PATIENTS HAVE FEATURES OF IV
- 14-56% OF ECZEMA PATIENTS HAVE 1 OR MORE FILAGGRIN NULL MUTATIONS
- SO: ~15% OF ECZEMA MAY BE DUE TO FILAGGRIN MUTATIONS ON A POPULATIONS SCALE

Dennin M, Lio PA. Filaggrin and childhood eczema. Archives of disease in childhood. 2017 Dec 1;102(12):1101-2.

BARRIER DEVELOPMENT

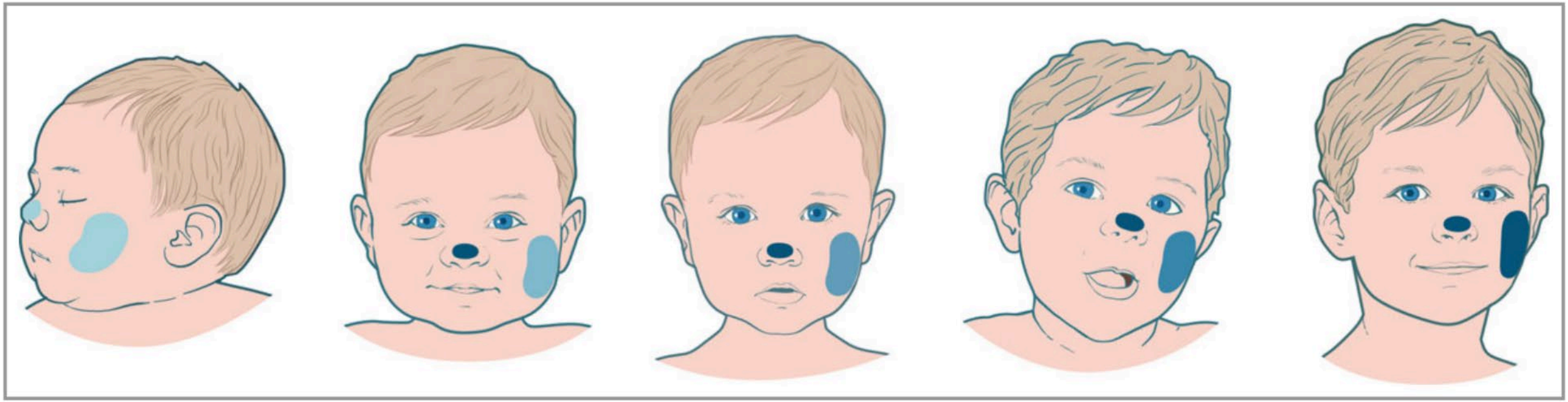
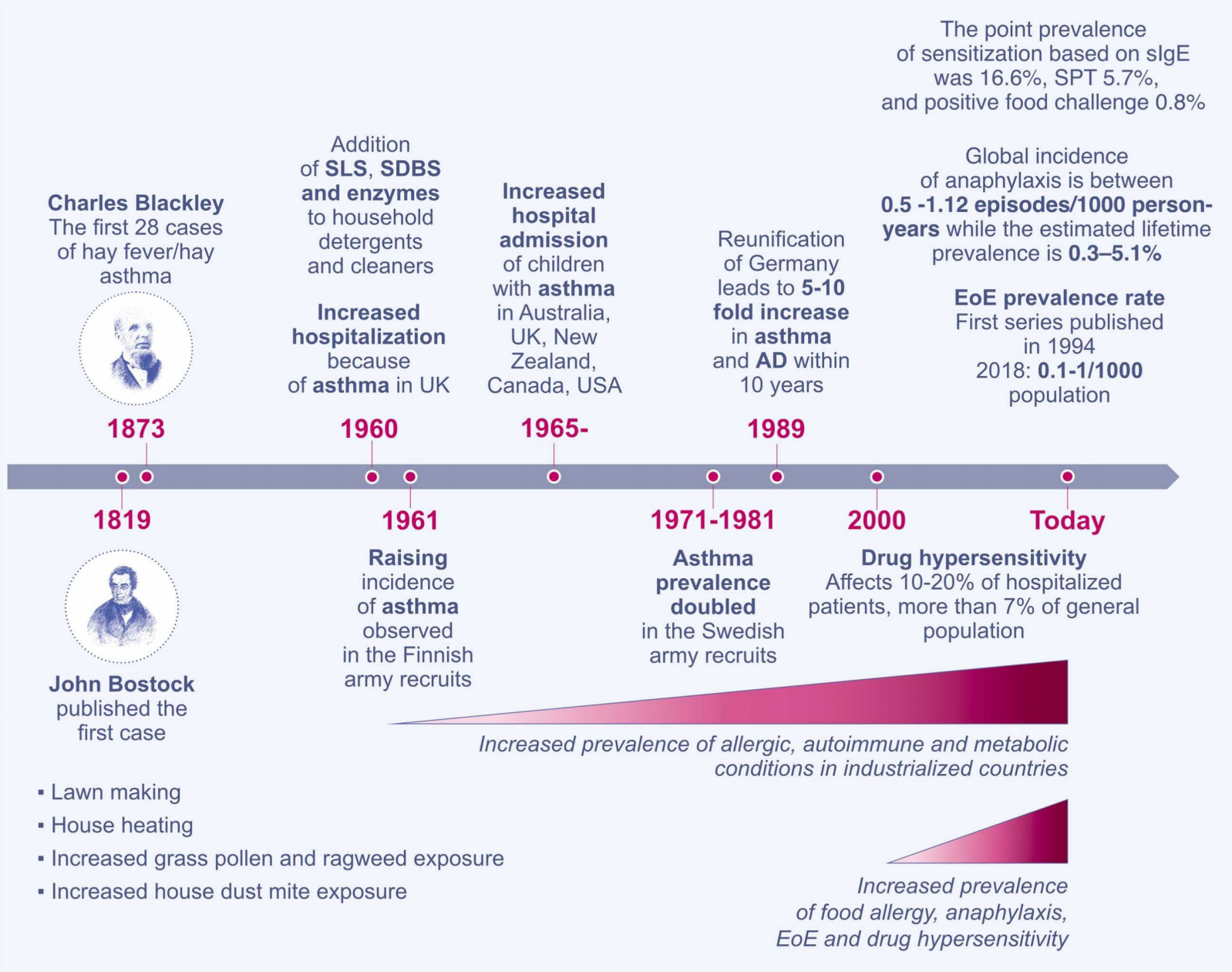


Fig 7. Cheek skin is slow to mature with respect to natural moisturzing factor (NMF) levels and corneocyte maturity. While other exposed sites, such as the nasal tip, rapidly reach steady-state maturity in the early months of life, the cheek skin starts life with the lowest NMF and only reaches steady-state NMF levels at approximately 7 years of age. NMF levels are graphically represented by depth of blue colour.

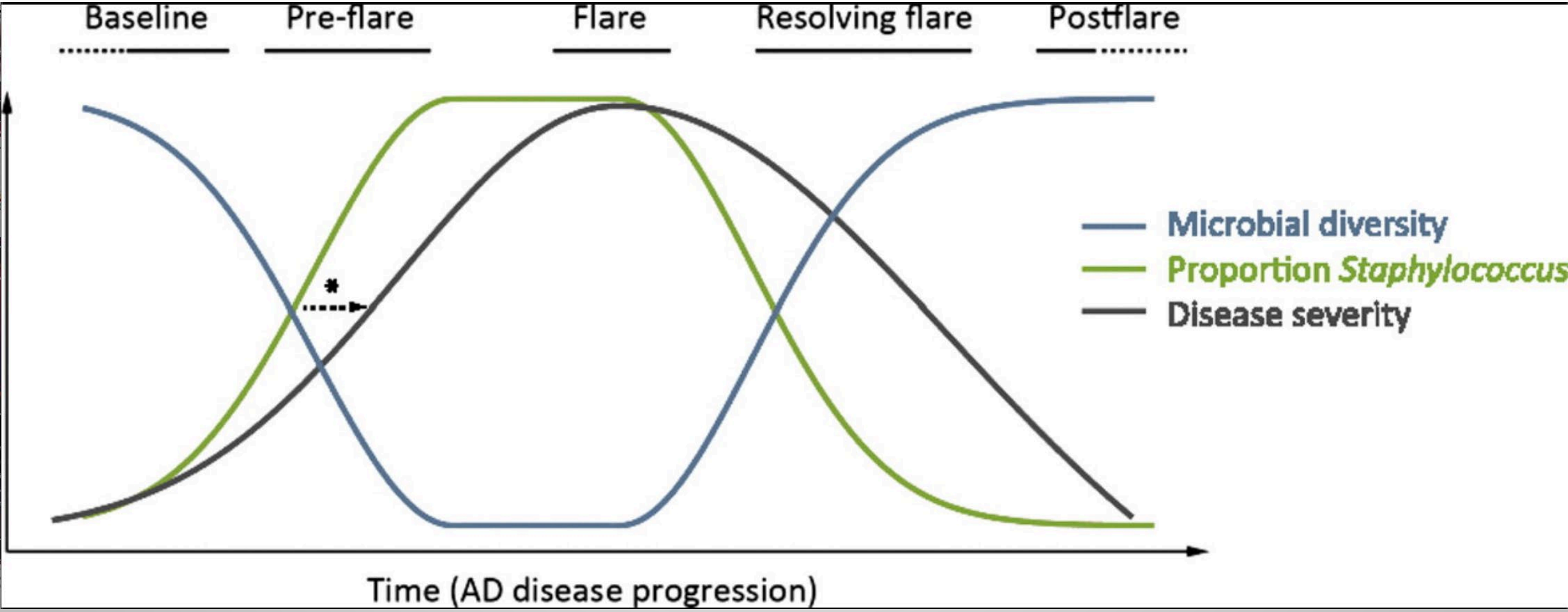
McAleer MA, Jakasa I, Raj N, O'Donnell CPF, Lane ME, Rawlings AV, Voegeli R, McLean WHI, Kezic S, Irvine AD. Early-life regional and temporal variation in filaggrin-derived natural moisturizing factor, filaggrin-processing enzyme activity, corneocyte phenotypes and plasmin activity: implications for atopic dermatitis. Br J Dermatol. 2018 Aug;179(2):431-441.

THE RISE OF ALLERGY



Yazici D, Ogulur I, Pat Y, Babayev H, Barletta E, Ardicli S, Huang M, Koch J, Li M, Maurer D, Radzikowska U. The epithelial barrier: The gateway to allergic, autoimmune, and metabolic diseases and chronic neuropsychiatric conditions. InSeminars in Immunology 2023 Nov 1 (Vol. 70, p. 101846). Academic Press.

Staph



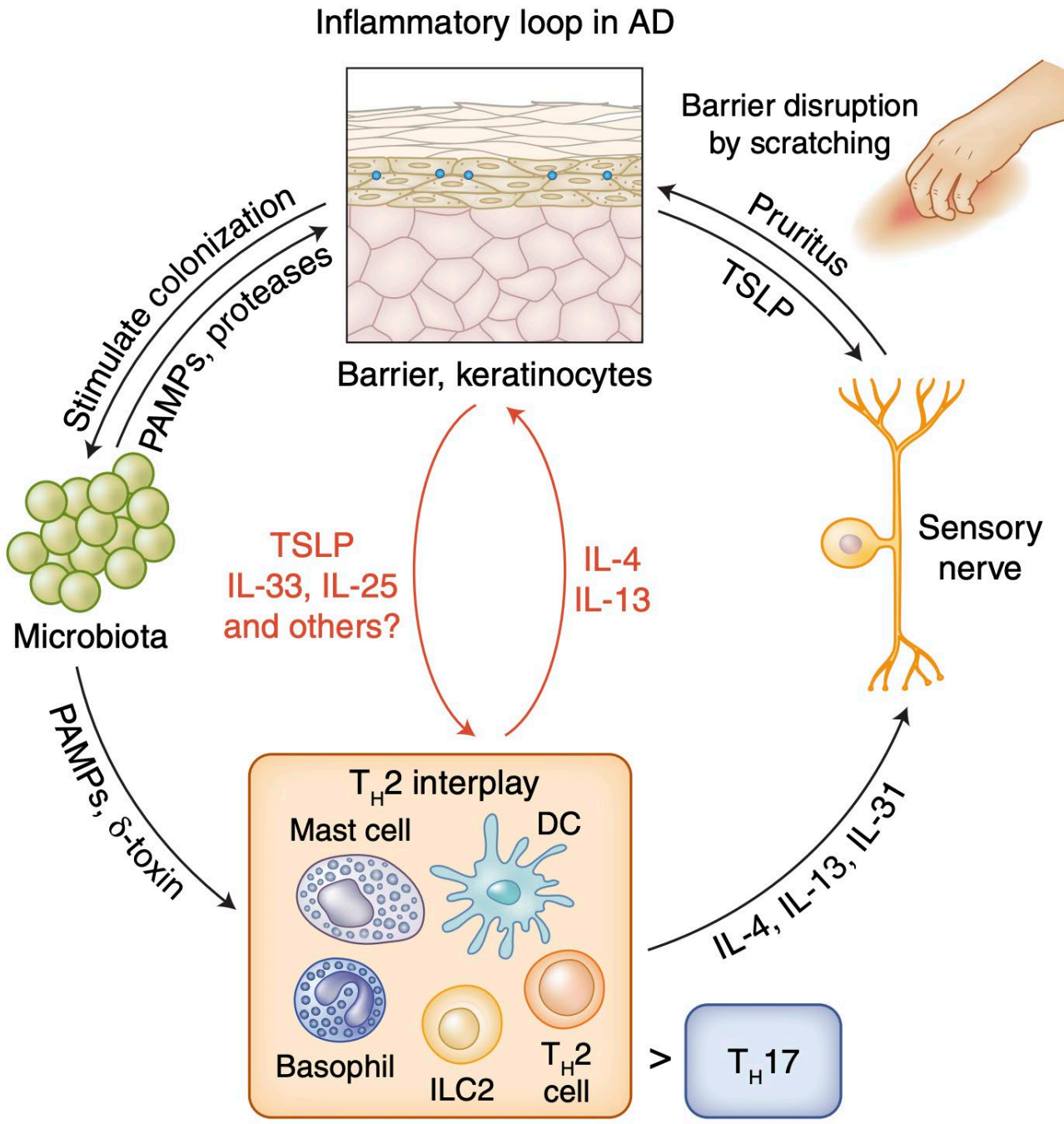
Heidi H. Kong et al. Genome Res. 2012;22:850-859

Table 1. *Staphylococcus aureus* Proteins That Contribute to Atopic Dermatitis

S. aureus proteins	Possible role in AD
Clumping factor B	Adhesion to corneocytes in stratum corneum via loricrin or other ligands
Fibronectin-binding proteins	Adhesion to fibronectin that is present at high levels in the upper strata of epidermis and stratum corneum of AD skin
Protein A	Proinflammatory. Binds to TNFR-1 on keratinocytes
Lipoproteins	Proinflammatory. Activate TLR-2 on keratinocytes
α-Toxin	Membrane damage/lysis of keratinocytes
δ-Toxin	Mast cell degranulation. Synergy with IgE. Allergic skin inflammation
Phenol-soluble modulins	Trigger proinflammatory responses associated with AD in keratinocytes at sublytic concentrations
Enterotoxins and TSST-1	Excessive T cell cytokine production and toxicity. Allergens. Enterotoxins might trigger mast cell degranulation directly
Staphopain Aureolysin	Inactivation of antimicrobial peptides
V8 serine protease	Epidermal barrier dysfunction in hairless mice
Serine protease-like proteins	Potent allergens in idiopathic asthma following *S. aureus* colonization. Similar role in AD?

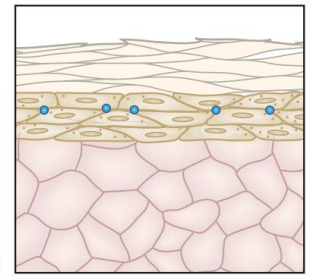
Staphylococcus aureus and Atopic Dermatitis: A Complex and Evolving Relationship. Geoghegan JA, Irvine AD, Foster TJ. Trends Microbiol. 2018 Jun;26(6):484-497.

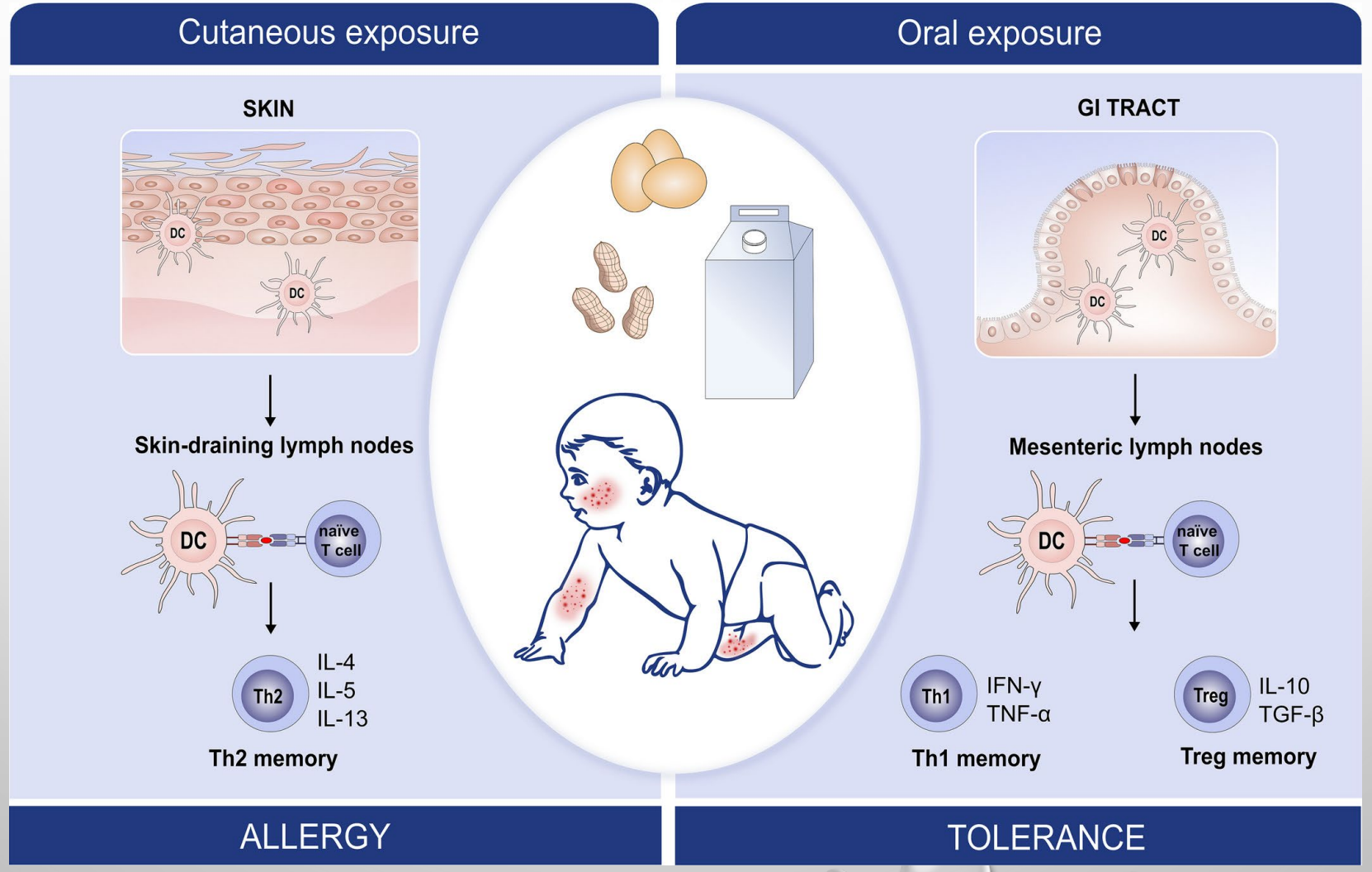
ETIOPATHOGENESIS



The epithelial immune microenvironment (EIME) in atopic dermatitis and psoriasis. Dainichi T, Kitoh A, Otsuka A, Nakajima S, Nomura T, Kaplan DH, Kabashima K. *Nat Immunol*. 2018 Dec;19(12):1286-1298.

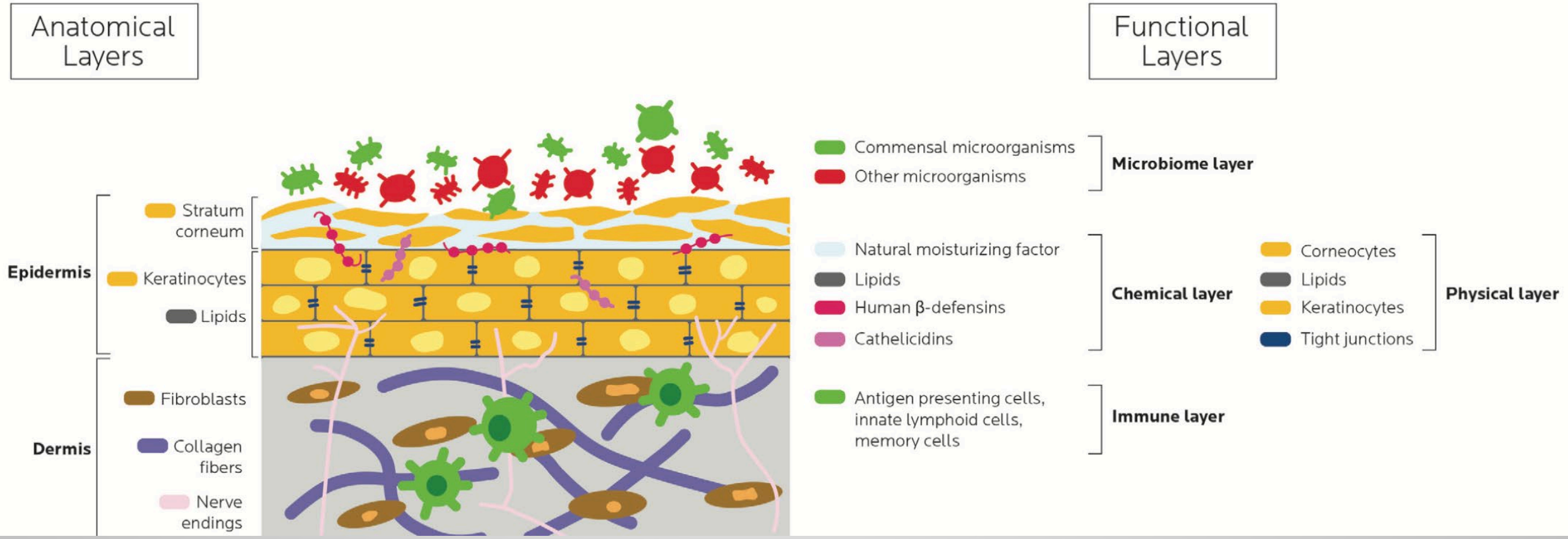
EPICUTANEOUS SENSITIZATION





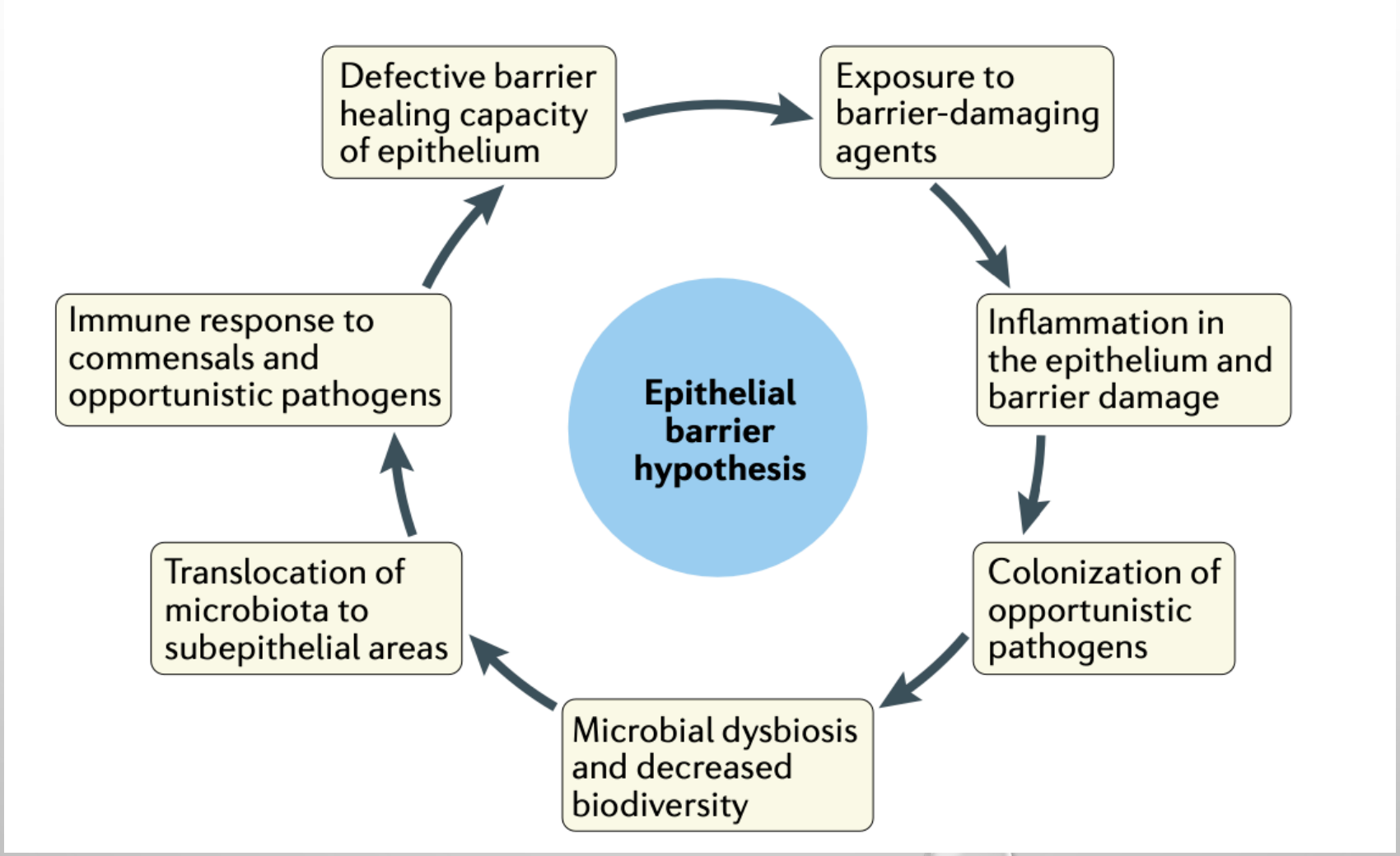
Allergy. 2020;75(9):2185-2205. doi: 10.1111/all.14304.

BARRIER



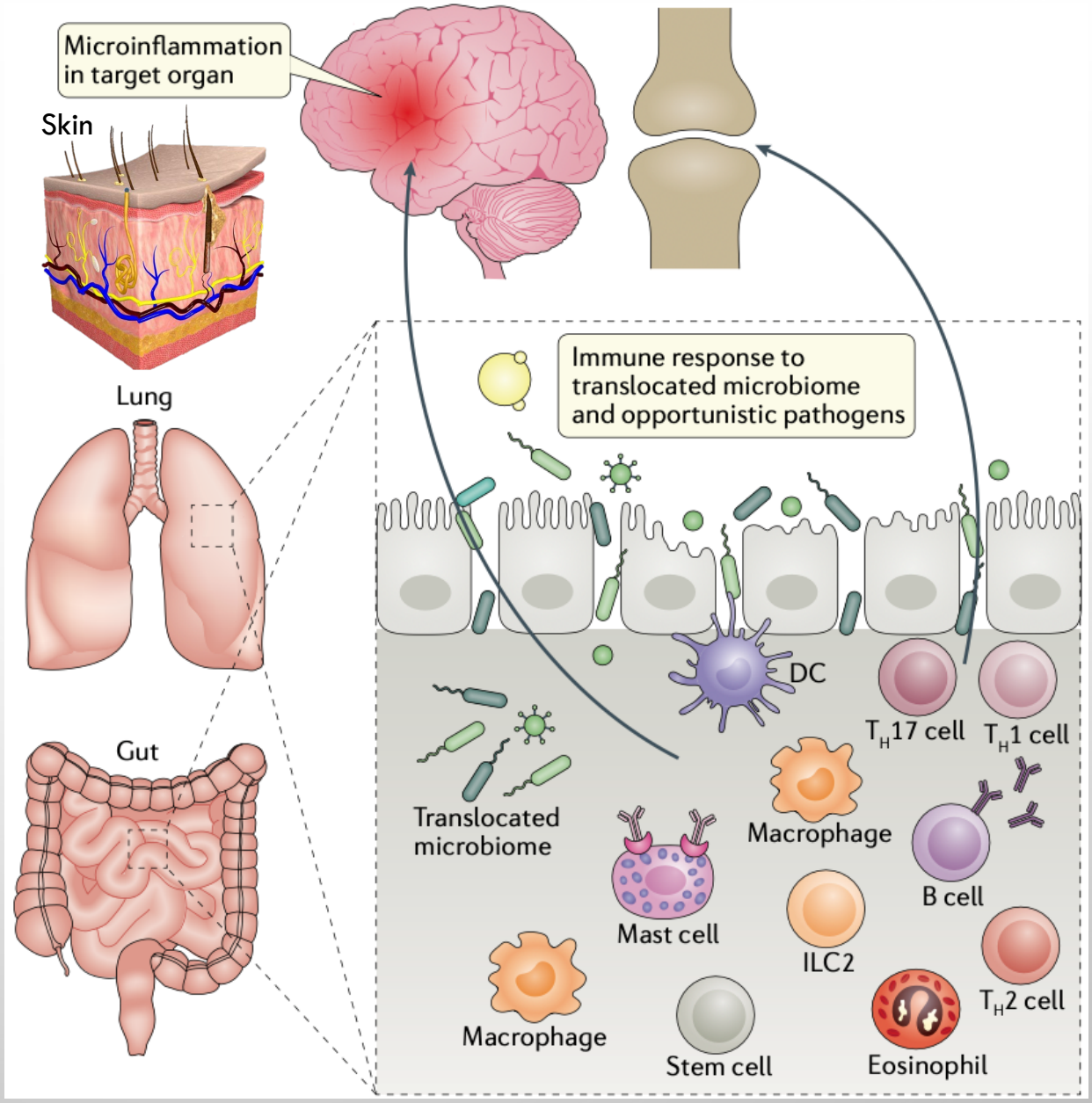
Strugar TL, Kuo A, Seité S, Lin M, Lio P. Connecting the Dots: From Skin Barrier Dysfunction to Allergic Sensitization, and the Role of Moisturizers in Repairing the Skin Barrier. Journal of drugs in dermatology: JDD. 2019 Jun;18(6):581-.

BARRIER HYPOTHESIS



Akdis, C.A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?. *Nat Rev Immunol* (2021). https://doi.org/10.1038/s41577-021-00538-7

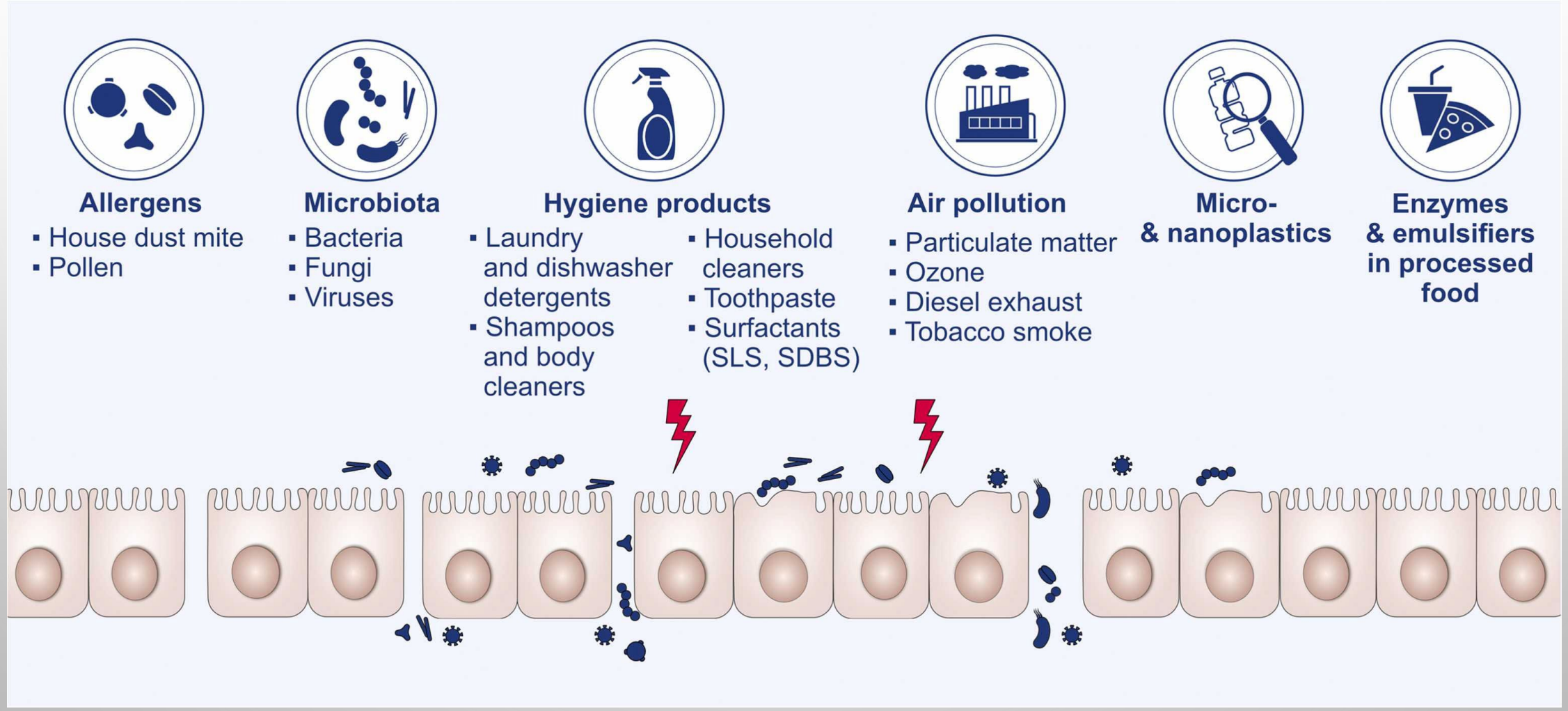
FAR-REACHING EFFECTS OF LEAKY EPITHELIA



Akdis, C.A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?. *Nat Rev Immunol*. 2021. https://doi.org/10.1038/s41577-021-00538-7

EPITHELIAL BARRIER HYPOTHESIS

Industrialization, urbanization and Westernized lifestyle have a devastating impact on the epithelial barriers of the skin, airways and gut mucosa as proposed by "The Epithelial Barrier Theory"



Yazici D, Ogulur I, Pat Y, Babayev H, Barletta E, Ardicli S, Huang M, Koch J, Li M, Maurer D, Radzikowska U. The epithelial barrier: The gateway to allergic, autoimmune, and metabolic diseases and chronic neuropsychiatric conditions. InSeminars in Immunology 2023 Nov 1 (Vol. 70, p. 101846). Academic Press.

SELECTED BARRIER DISRUPTORS

Substance	Evidence
Polystyrene microplastic	Mouse models show effect of polystyrene microplastics on gut barrier
Ozone	Mouse models show respiratory barrier injury through ozone
Cigarette smoke	Mouse models show that cigarette smoke causes acute lung injury
Particulate matter	Ex vivo experiments with human and rat alveolar epithelial cells show that particulate matter affects the distribution of occludin and the alveolar barrier; PM2.5 causes defects in the nasal epithelial barrier in non-inflamed nasal biopsy samples of patients with sinusitis; PM10 stimulates myeloid dendritic cells to induce T_H17 cells with brain-homing property in vitro
Diesel exhaust particulates	Human and rat alveolar epithelial cells exposed to diesel exhaust particulates show low occludin expression and barrier leakiness
Nanoparticles	Human cell cultures show that nanoparticles disrupt intestinal barrier homeostasis
Anionic surfactants and commercial detergents	Human skin keratinocyte cultures show that anionic surfactants and commercial detergents decrease tight junction barrier integrity
Detergent residue	Human bronchial epithelial cell air–liquid interface cultures show that detergent residues disrupt tight junction barrier integrity in human bronchial epithelial cells even at low concentrations
Emulsifiers in processed food	Emulsifiers increased damage to the structure of hamster small intestine in vivo and the translocation of *Escherichia coli* across M-cells in vitro

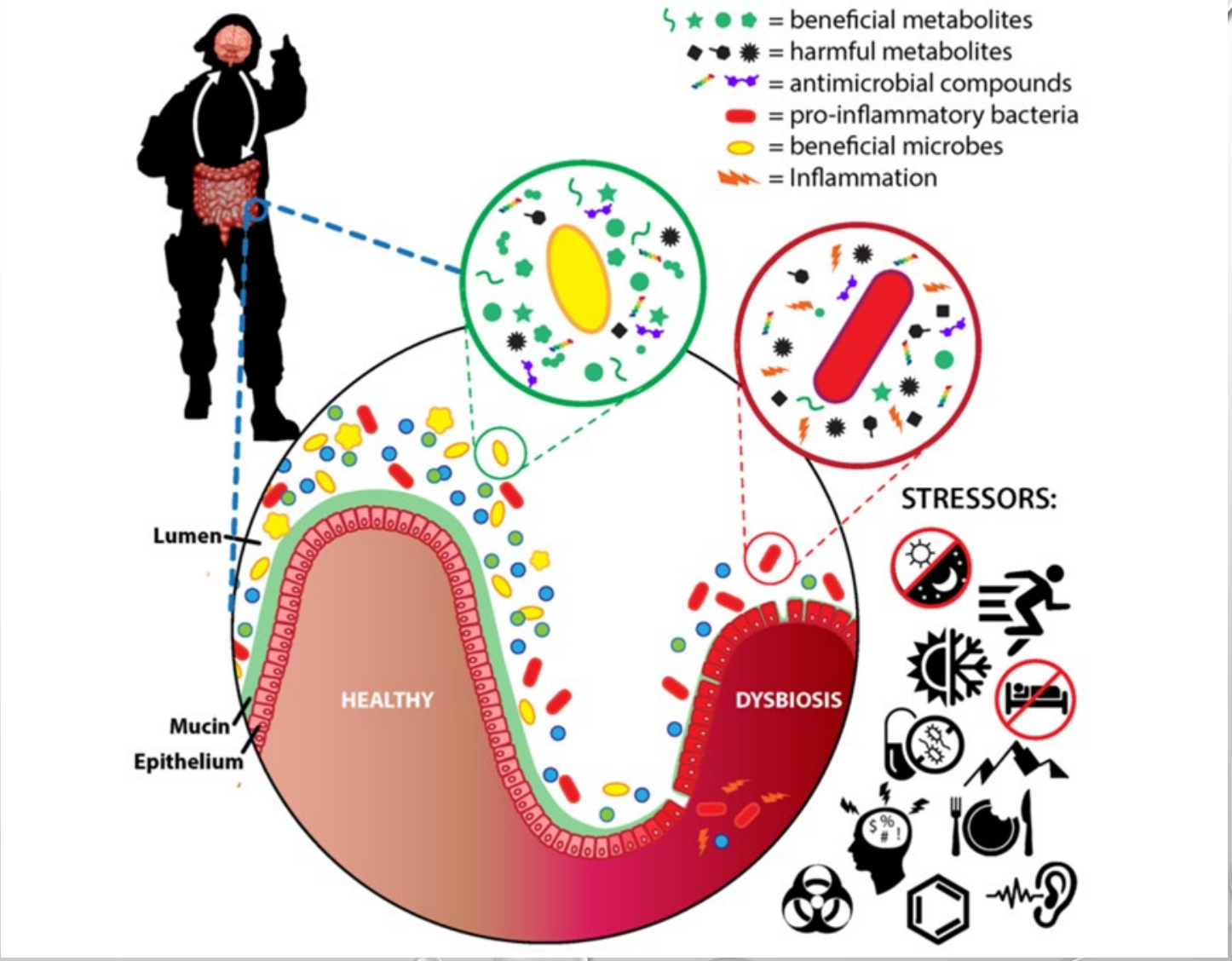
PM2.5, particulate pollutant that is 2.5 μm or smaller in size; PM10, particulate pollutant that is 10 μm or smaller in size; T_H17, T helper 17.

Akdis, C.A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?. *Nat Rev Immunol* (2021). https://doi.org/10.1038/s41577-021-00538-7

Human Microbiome

Stressors and the Microbiota

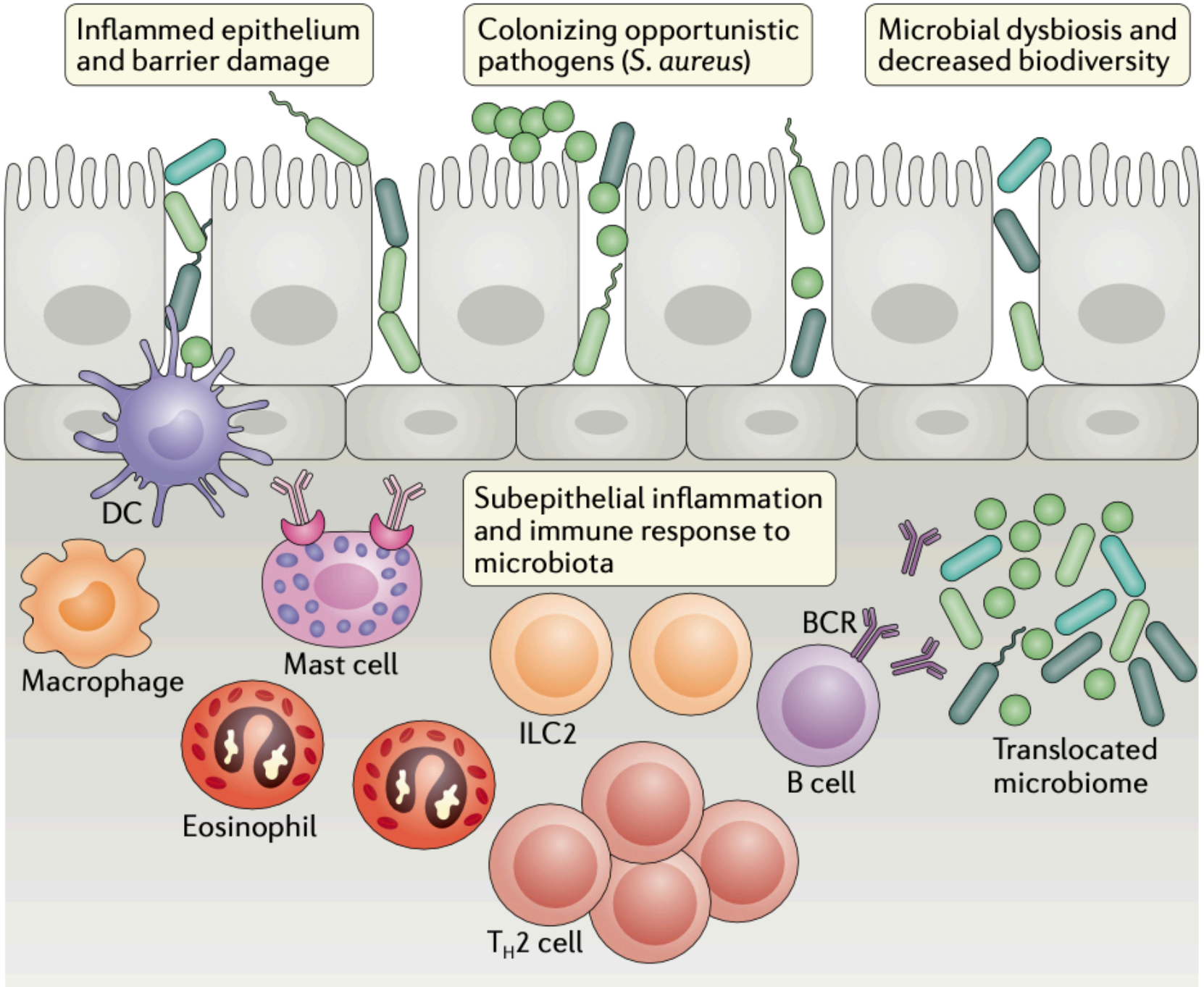
- Psychological stress
- Circadian disruption
- Sleep deprivation
- Environmental extremes
- Environmental pathogens
- Toxins/pollutants
- Noise
- Physical activity
- Diet (nutrient composition and food restriction)



Karl JP, Hatch AM, Arcidiacono SM, Pearce SC, Pantoja-Feliciano IG, Doherty LA, Soares JW. Effects of psychological, environmental and physical stressors on the gut microbiota. Frontiers in microbiology. 2018 Sep 11;9:2013.

BARRIER DAMAGE

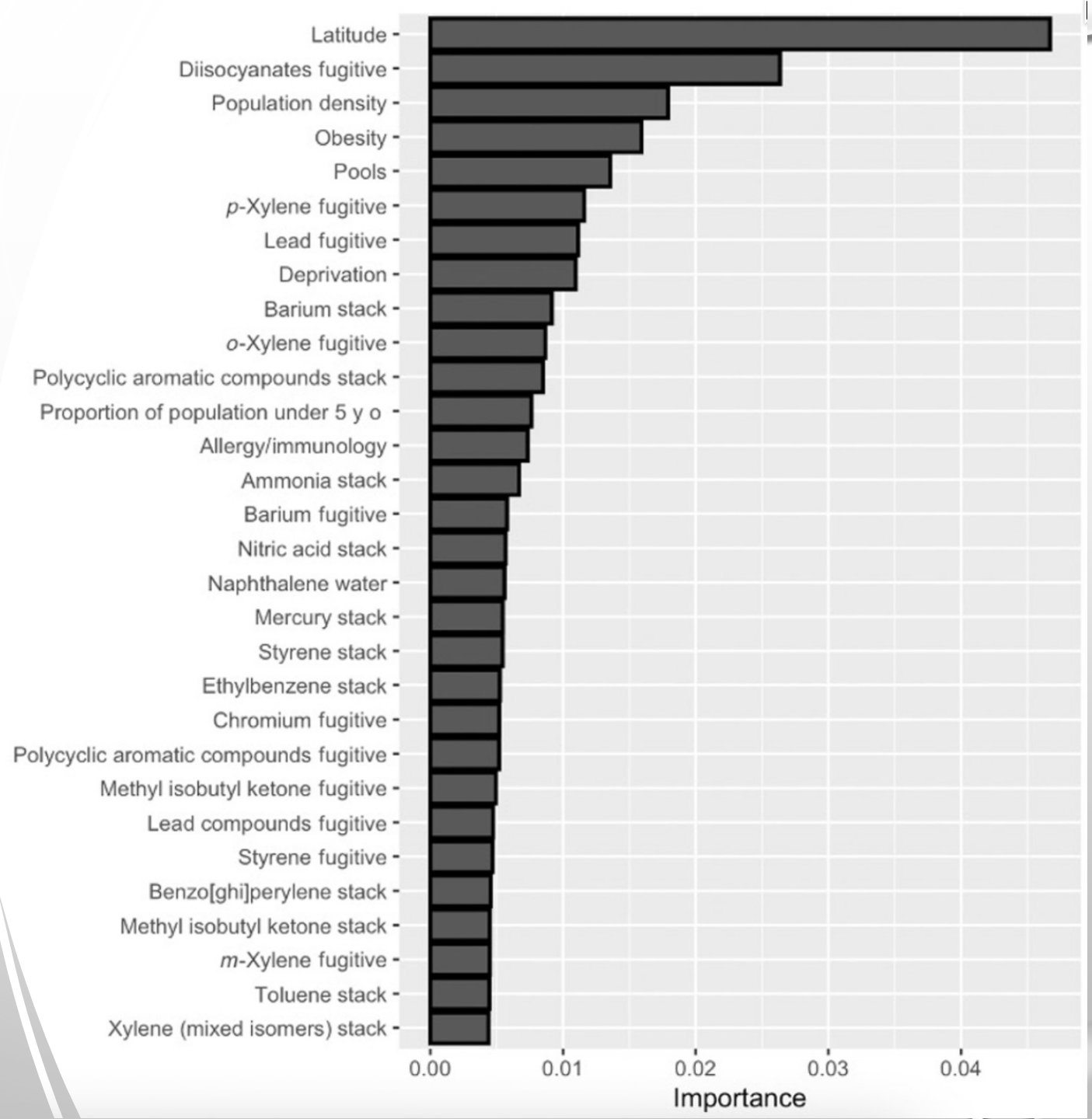
→ colonization of opportunistic pathogens and inflammation



Akdis, C.A. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions?. *Nat Rev Immunol* (2021). https://doi.org/10.1038/s41577-021-00538-7

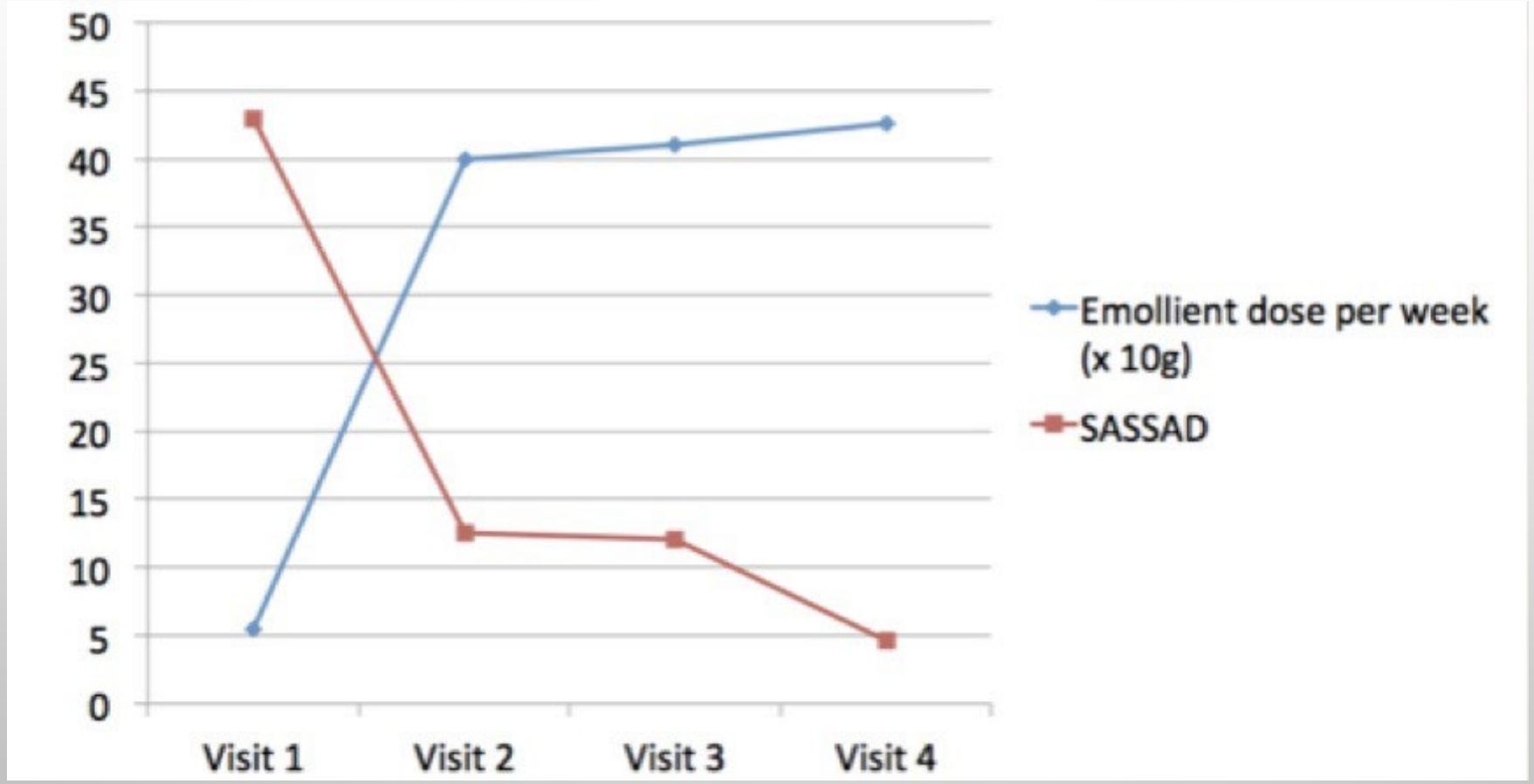
POLLUTION?

Zeldin J, Chaudhary PP, Spathies J, Yadav M, D'Souza BN, Alishahedani ME, Gough P, Matriz J, Ghio AJ, Li Y, Sun AA. Exposure to isocyanates predicts atopic dermatitis prevalence and disrupts therapeutic pathways in commensal bacteria. Science Advances. 2023 Jan 6;9(1):eade8898.



What can we do?

MORE MOISTURIZER = LESS ECZEMA!



Cork, et al. BJD 2003; 149: 582-589.

MOISTURIZER TIPS

- IF THEY FIND IT TOO COLD: HAVE THEM "FLOAT" THE JAR IN THE TUB WHILE THE PATIENT TAKES A BATH TO WARM IT UP
- IF THE SKIN IS HOT AND IT MAKES IT FEEL HOTTER/ITCHIER: KEEP IT IN THE REFRIGERATOR (NOT FREEZER)
- IF INFECTION IS A PROBLEM: USE A CLEAN SPOON TO DISPENSE THE CREAM (INSTEAD OF FINGERS)

Journal of Drugs in Dermatology

A Comparison of Physicochemical Properties of a Selection of Modern Moisturizers: Hydrophilic Index and pH

Vivian Y. Shi BS,[a] Khiem Tran PhD,[b] and Peter A. Lio MD[c]

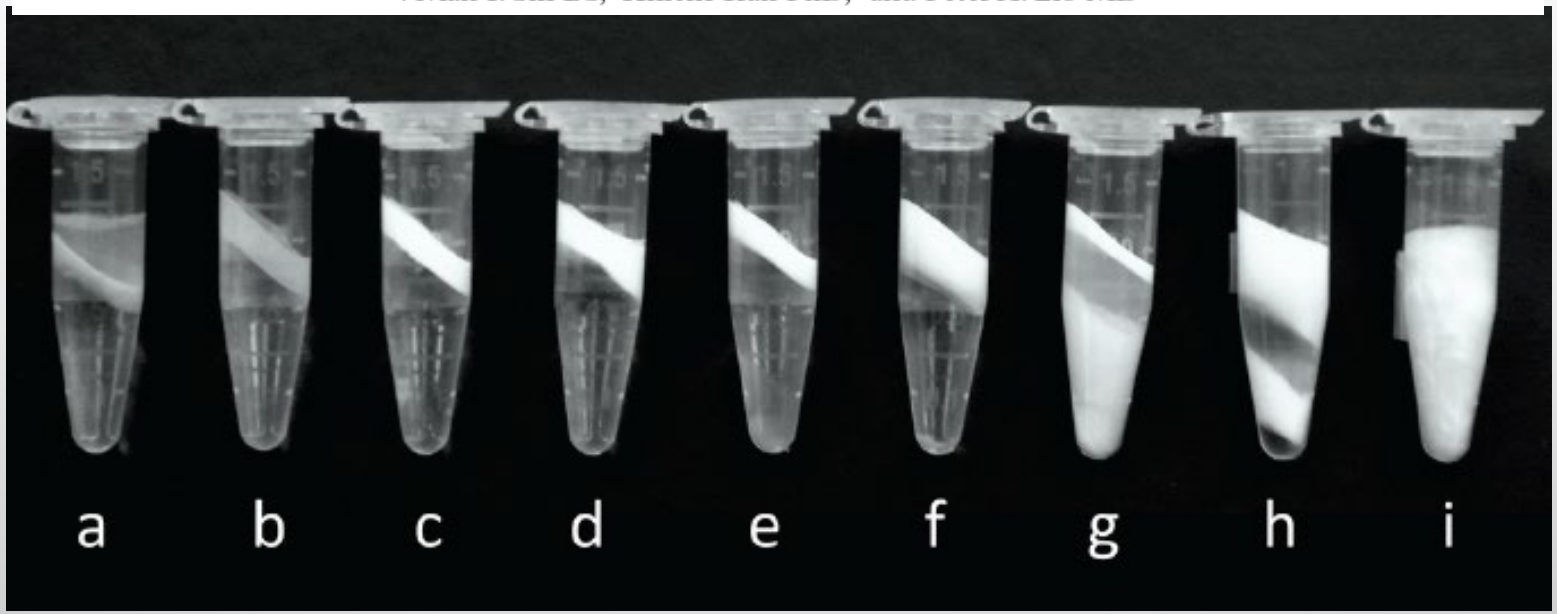


FIGURE 1. Separation of hydrophobic and hydrophilic layers after centrifugation. The most translucent (aqueous) layer is extracted. **a)** Motor Oil; **b)** Aquaphor® Ointment; **c)** Eucerin® Original Dry Skin Therapy Cream; **d)** Eucerin® Original Dry Skin Therapy Lotion; **e)** Cetaphil® Restoraderm Skin Restoring Moisturizer; **f)** Aveeno® Advanced Care Moisturizing Cream; **g)** Dove® Day Lotion (SPF15); **h)** CeraVe® Moisturizing Cream; **i)** Neosalus® Cream.

Shi VY, Tran K, Lio PA. A comparison of physicochemical properties of a selection of modern moisturizers: hydrophilic index and pH. Journal of drugs in dermatology: JDD. 2012 May 1;11(5):633-6.

SELECT BIOACTIVE INGREDIENTS OF MOISTURIZERS AND THEIR INTENDED FUNCTION

Bioactive ingredients	Intended functions
Cannabinoids	Mitigate itch and inflammation, stimulate lipid production
Petroleum	Occlusion, decreasing TEWL; strengthen lipid lattice, stimulate AMP production
Ceramides	Restore SC lipid matrix, water permeability and barrier function
Antioxidants	Prevent oxidative damage by decreasing ROS
Niacinamide	Improve epidermal barrier function by decreasing TEWL, increasing ceramides, and thickening the stratum corneum. Anti-inflammatory
Pre/Probiotics	Improve skin barrier by decreasing TEWL and increasing ceramide levels

Chandan N, Rajkumar JR, Shi VY, Lio PA. A New Era of Moisturizers. Journal of Cosmetic Dermatology. 2021 May 12.

CERAMIDES PLAY A KEY ROLE IN BARRIER FUNCTION

- CERAMIDES ARE THE MOST COMMON CONSTITUENT AMONG SC LIPIDS
- CERAMIDE LEVELS IN THE SC ARE REGULATED BY A BALANCE OF ENZYMES, CERAMIDASE, SPHINGOMYELINASE AND B-GLUCOSCEREBROSIDASE
- CERAMIDE 1 AND 3* LEVELS ARE REDUCED AND THE QUANTITY OF CERAMIDE 3 WERE SIGNIFICANTLY CORRELATED WITH TEWL IMPAIRMENT IN AD SUBJECTS

**There is a new nomenclature for ceramides… but it's a bit cumbersome and most of the original landmark studies used these older terms…*

Choi MJ, Maibach HI. *Am J Clin Dermatol*. 2005;6:215-223. Pilgram GS et al. *J Invest Dermatol*. 2001;117:710-717. Di Nardo A, et al. *Acta Derm Venereol*. 1998;78:27-30. Chamlin S, et al. *J Am Acad Dermatol*. 2002;47:198-208.

HELIANTHUS ANNUUS (SUNFLOWER SEED OIL)

- SUNFLOWER SEED OIL LIPIDS HAVE BEEN SHOWN TO BE SIMILAR IN AMOUNT AND PROPORTION TO THOSE CONSTITUTING THE EPIDERMAL BARRIER AND TO INCREASE THEIR SYNTHESIS
- A SUNFLOWER DISTILLATE HAS BEEN SHOWN TO ACTIVATE PPAR-A *IN VITRO*
- PPAR-A AGONISTS STIMULATE KERATINOCYTE DIFFERENTIATION AND IMPROVE BARRIER FUNCTION

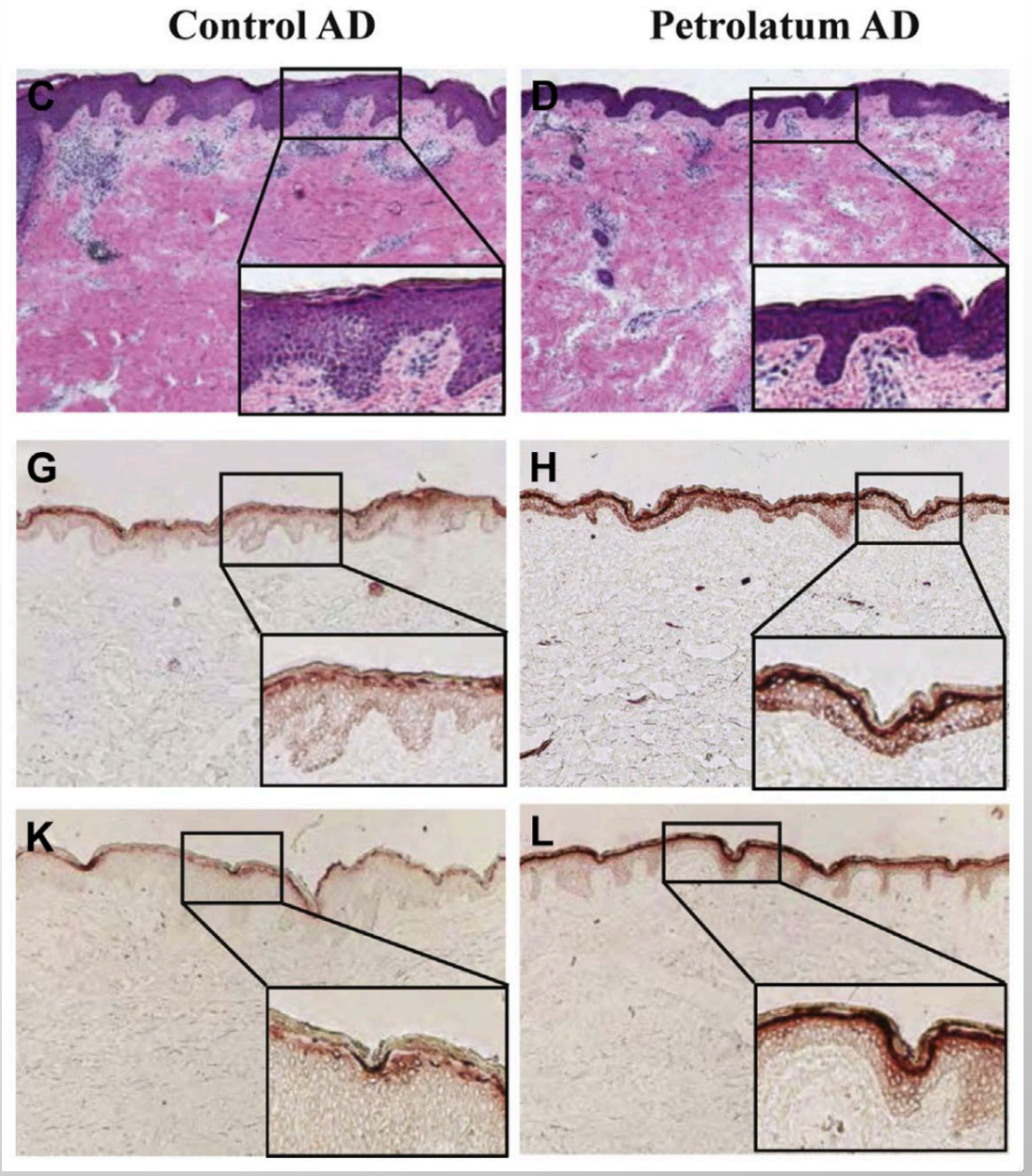
Eichenfield L, *Pediatr Derm*. 2009;26:669-675; Hanley K et al. *J Invest Dermatol*. 1999;113:788-795. Msika P, et al. *Pediatr Derm* . 2008;25:606-612. Piccardi N. *J Invest Dermatol*. 2001;117:390-423; Imokawa G. *J Am Acad Dermatol*. 2001;45 (1 Suppl): S29-32.

GOOD OLD PETROLATUM

- “PETROLATUM ROBUSTLY MODULATES ANTIMICROBIALS AND EPIDERMAL DIFFERENTIATION BARRIER MEASURES.”

- “AD SKIN SHOWS PARAKERATOSIS AND FOCAL DISRUPTIONS OF THE GRANULAR LAYER…WITH RESTORATION OF ORTHOKERATOSIS WITH PETROLATUM…”

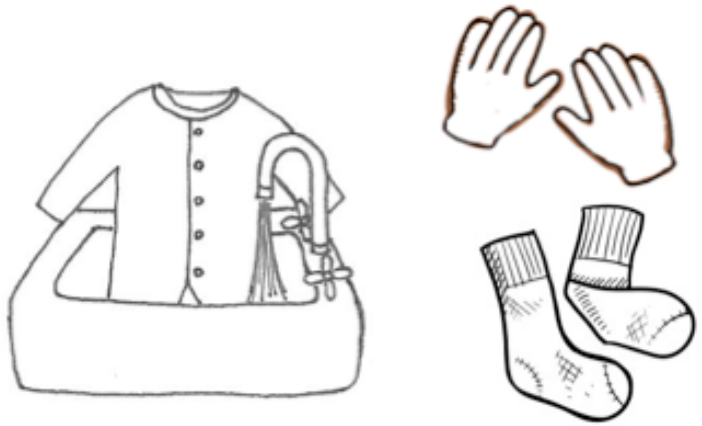
- “WEAK AND DISCONTINUOUS LOR (G) AND FLG (K) STAINING WAS OBSERVED IN CONTROL AD SKIN, WITH INCREASED INTENSITY AND RESTORATION OF CONTINUOUS EXPRESSION OF BOTH MARKERS AFTER OCCLUSION WITH PETROLATUM.” (HISTOLOGIC MAGNIFICATION X10)



Czarnowicki T, Malajian D, Khattri S, da Rosa JC, Dutt R, Finney R, Dhingra N, Xiangyu P, Xu H, Estrada YD, Zheng X. Petrolatum: barrier repair and antimicrobial responses underlying this “inert” moisturizer. Journal of Allergy and Clinical Immunology. 2016 Apr 1;137(4):1091-102.

Follow these 4 steps:

1. Take one pair of onesies, pajamas, gloves, and/or socks and soak it in warm water.



2. Wring out the onesies, pajamas, glov socks until they are only slightly dam

3. Put the damp onesies, pajamas, gloves, or socks on. Then put the dry onesies, pajamas, gloves, or socks on top of the damp layer.

4. Make sure the room is warm enough go to sleep.

MAXIMIZING THINGS WITH WET WRAPS

Image courtesy of Peter Lio, MD. (www.chicagoeczema.com)

"SOAK AND SEAL"

- Randomized crossover trial: frequent versus infrequent baths
- Children 6m-11y with moderate-to-severe AD
- Randomized 1:1 into 2 groups:
  - Group 1 underwent twice-weekly SS baths for 10-minutes or less over 2-weeks ("dry method" - DM) followed by twice-daily Soak and Seal (SS) baths, for 15-20 minutes, over 2- 56 weeks ("wet method" - WM)
  - Group 2 did the inverse
- Primary outcome: SCORAD
- Of the 63 children screened, 42 fulfilled inclusion criteria and were randomized
- WM decreased SCORAD significantly more than DM ($p<0.0001$)

Cardona ID, Kempe EE, Lary C, Ginder JH, Jain N. Frequent Versus Infrequent Bathing in Pediatric Atopic Dermatitis: A Randomized Clinical Trial. The Journal of Allergy and Clinical Immunology: In Practice. 2020 Mar 1;8(3):1014-21.

STUDY

Soak and Smear

A Standard Technique Revisited

Ari Benjamin Gutman, MD; Albert M. Kligman, MD, PhD; Joslyn Sciacca, MD; William D. James, MD

"Hydration for 20 minutes before bedtime followed by ointment application to wet skin and alteration of cleansing habits is an effective method for caring for several common skin conditions."

Figure 1. A patient with psoriatic hand involvement before treatment (A and B). The patient was using clobetasol ointment at night with vinyl glove occlusion and frequent moisturization and cream in the morning.

Figure 2. Same patient as in Figure 1 four weeks after treatment. The only change to the patient's regimen was to add a 20-minute plain water soak before the nighttime ointment application.

Gutman AB, Kligman AM, Sciacca J, James WD. Soak and smear: a standard technique revisited. Archives of dermatology. 2005 Dec 1;141(12):1556-9.

“SLUGGING”

- “Slugging” is a viral beauty trend on TikTok™ that entails slathering a petrolatum-based ointment on the skin as a last step in evening skincare routine

- HCPs had more views and followers than other creators

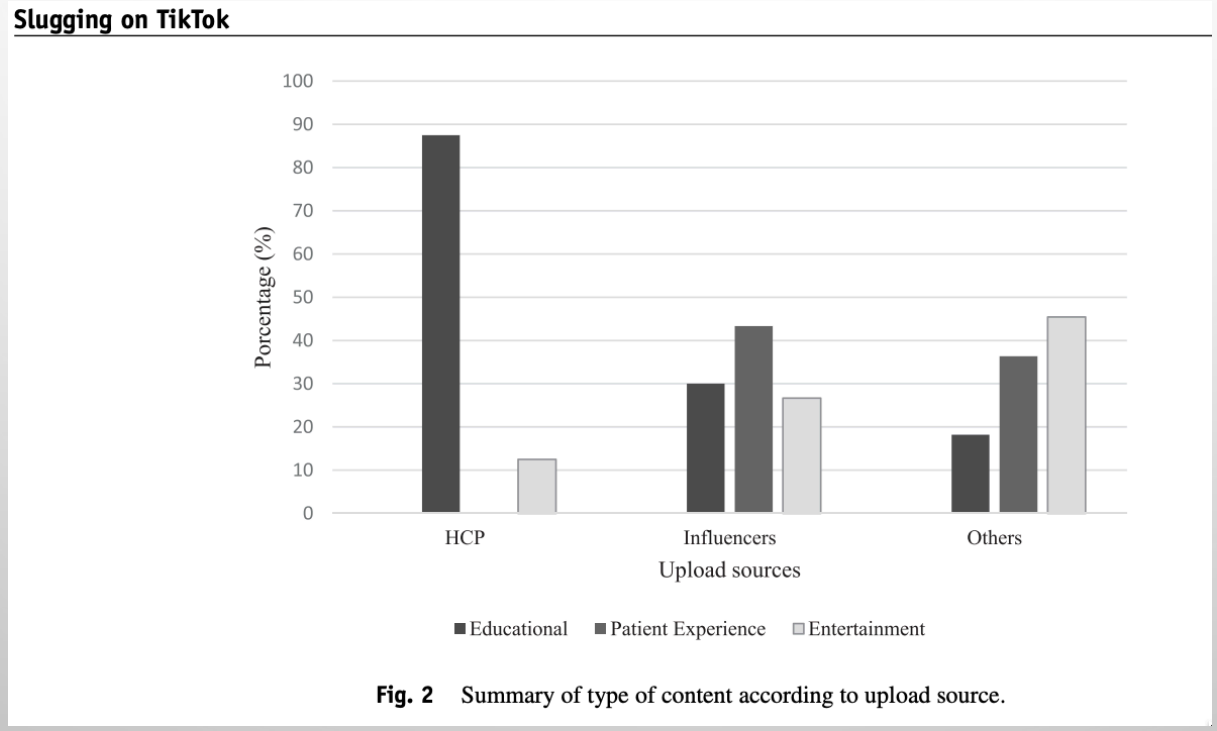


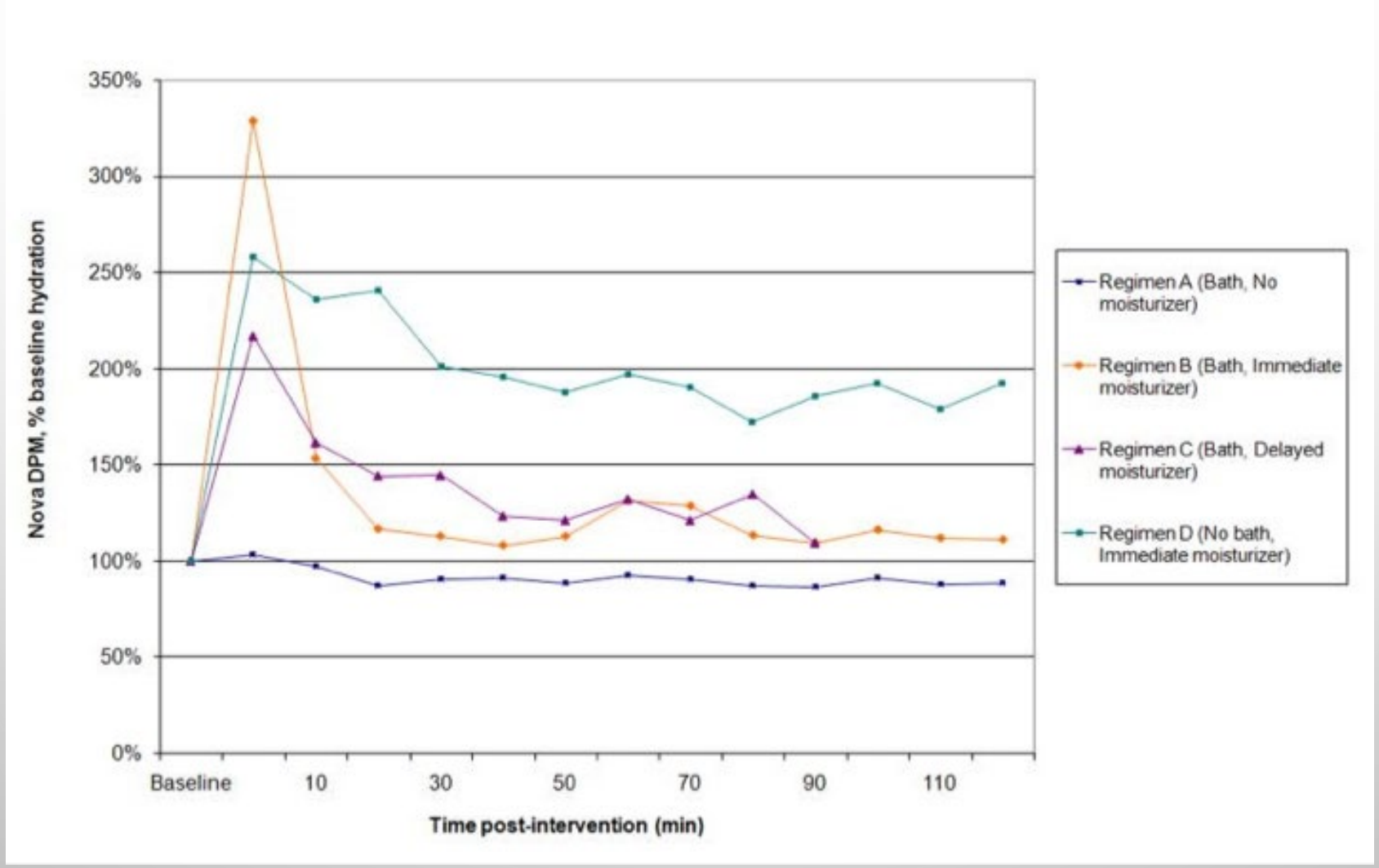
Fig. 2 Summary of type of content according to upload source.

Pagani K, Lukac D, Martinez R, Jablon K, McGee JS. Slugging: TikTokTM as a source of a viral “harmless” beauty trend. Clinics in Dermatology. 2022 Aug 9.

WHAT ABOUT BATHING?

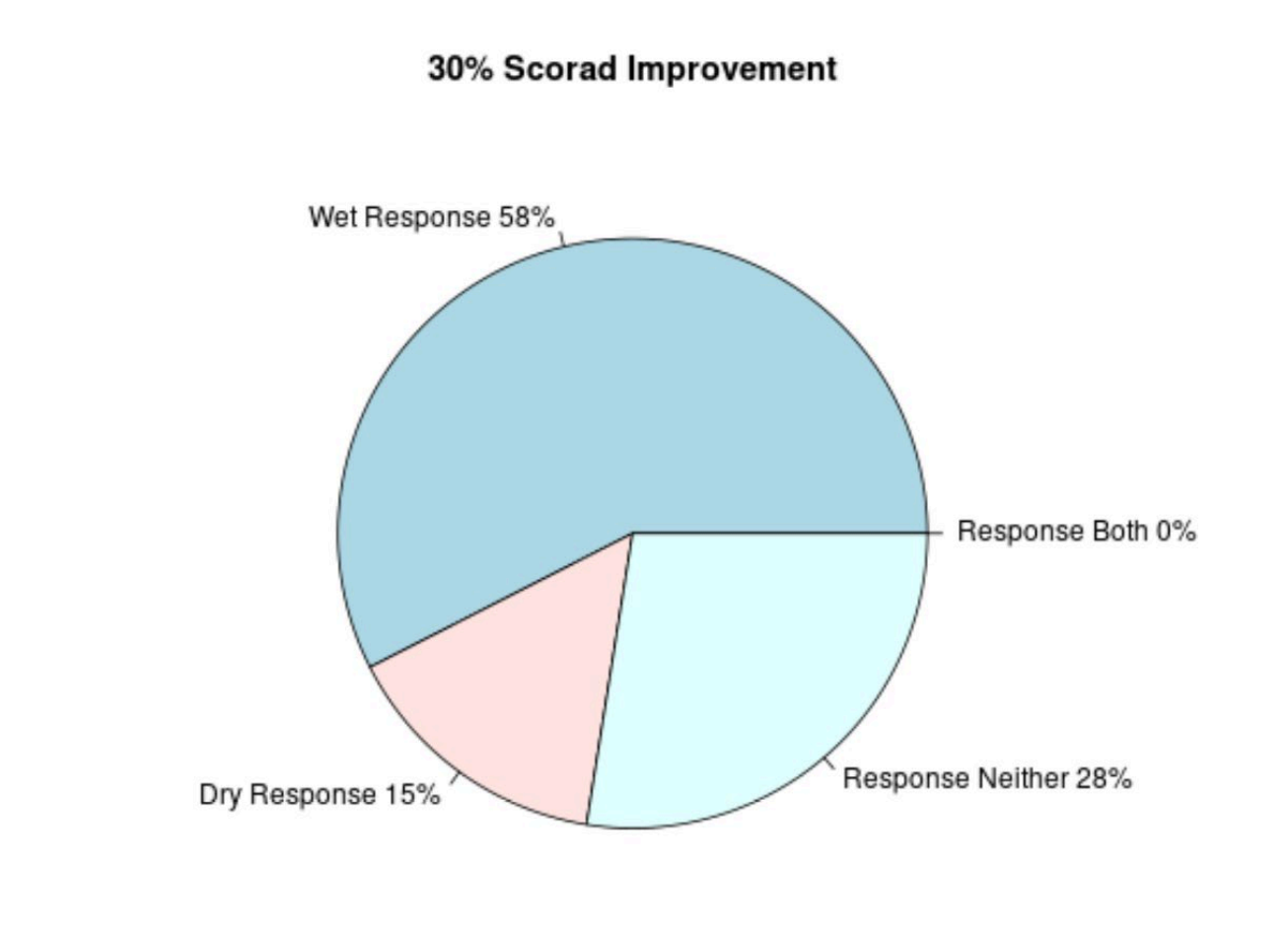
- WATER LOSS IS FUNDAMENTAL, SO BATHING SHOULD BE IMPORTANT
- BALNEOTHERAPY IS ANCIENT, BUT MODERN PRACTICES BEGAN IN EUROPE IN THE 1800S

BATHTUBS



Chiang C, Eichenfield LF. Quantitative assessment of combination bathing and moisturizing regimens on skin hydration in atopic dermatitis. Pediatr Dermatol. 2009 May-Jun;26(3):273-8.

MORE FREQUENT BATHING IS BETTER!



Cardona ID, Kempe EE, Lary C, Ginder JH, Jain N. Frequent Versus Infrequent Bathing in Pediatric Atopic Dermatitis: A Randomized Clinical Trial. The Journal of Allergy and Clinical Immunology: In Practice. 2020 Mar 1;8(3):1014-21.

WHAT ABOUT SPA THERAPY?

- DATA CAN BE A BIT MESSY SINCE MINERAL WATER BATHS ALSO INVOLVE:
  - WARM WEATHER (CLIMATOTHERAPY)
  - SUNSHINE (HELIOTHERAPY)
  - A VACATION SETTING (RELAXATION)

BALNEOTHERAPY

THERE IS SOLID DATA THAT CHILDREN AND ADULTS WITH MODERATE-TO-SEVERE AD GENERALLY IMPROVE WITH BALNEOTHERAPY/SPA THERAPY

BUT IT'S:

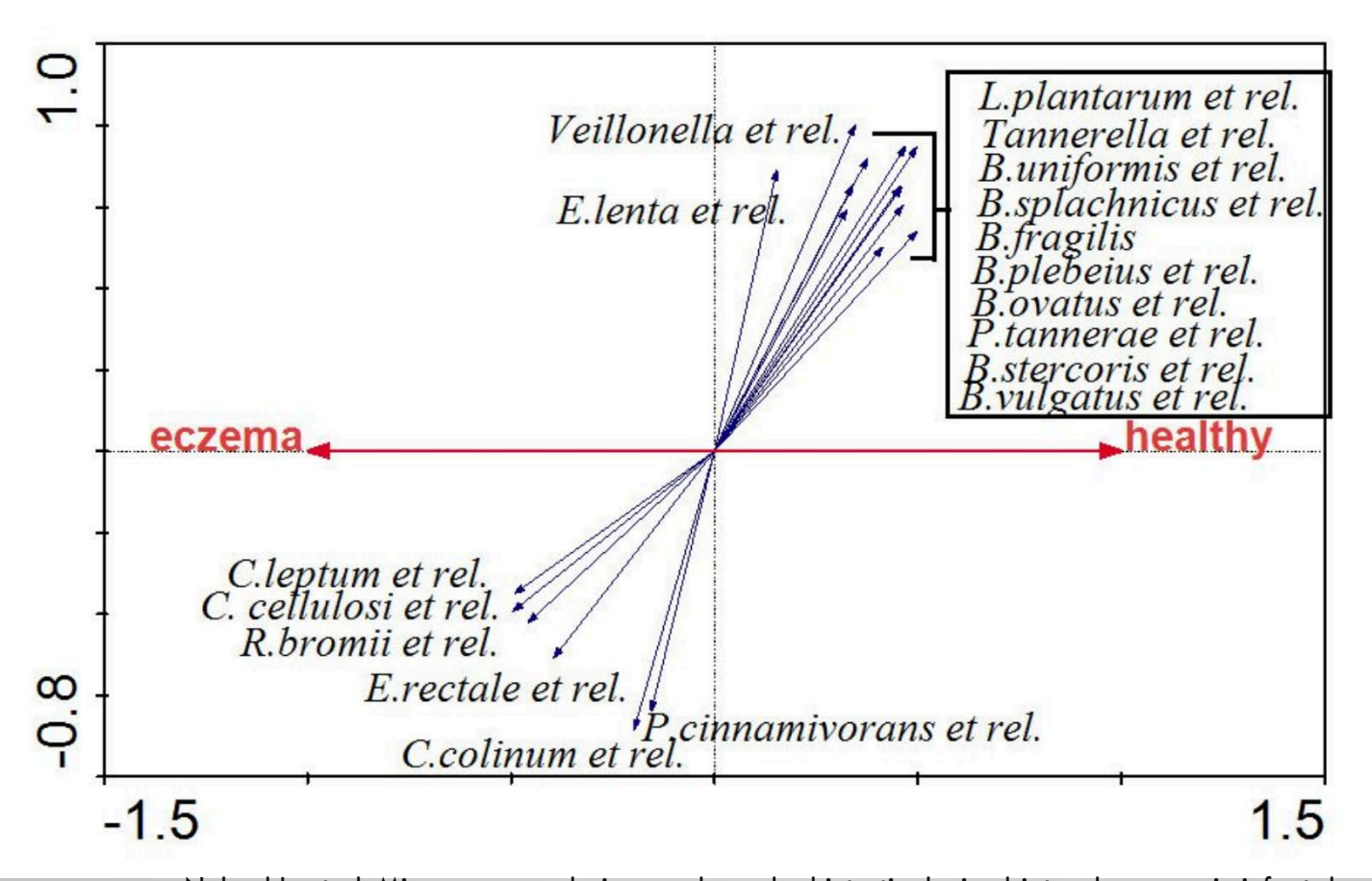
- EXPENSIVE
- TIME-CONSUMING
- TEMPORARY

WATER SOFTENER?

- PARADOX: BALENTHERAPY STUDIES SHOW IMPROVEMENT WITH MINERAL-RICH WATER = "HARD" WATER
- RANDOMIZED TRIAL OF 336 CHILDREN FOUND, AT 12 WEEKS, NO SIGNIFICANT DIFFERENCE IN ECZEMA IMPROVEMENT WITH AND WITHOUT A WATER "SOFTENER" (REMOVES MINERALS)

Thomas KS, Dean T, O'Leary C, Sach TH, Koller K, Frost A, et al. A randomised controlled trial of ion-exchange water soft- eners for the treatment of eczema in children. PLoS Med. 2011;8:e1000395.

DIVERSITY MATTERS

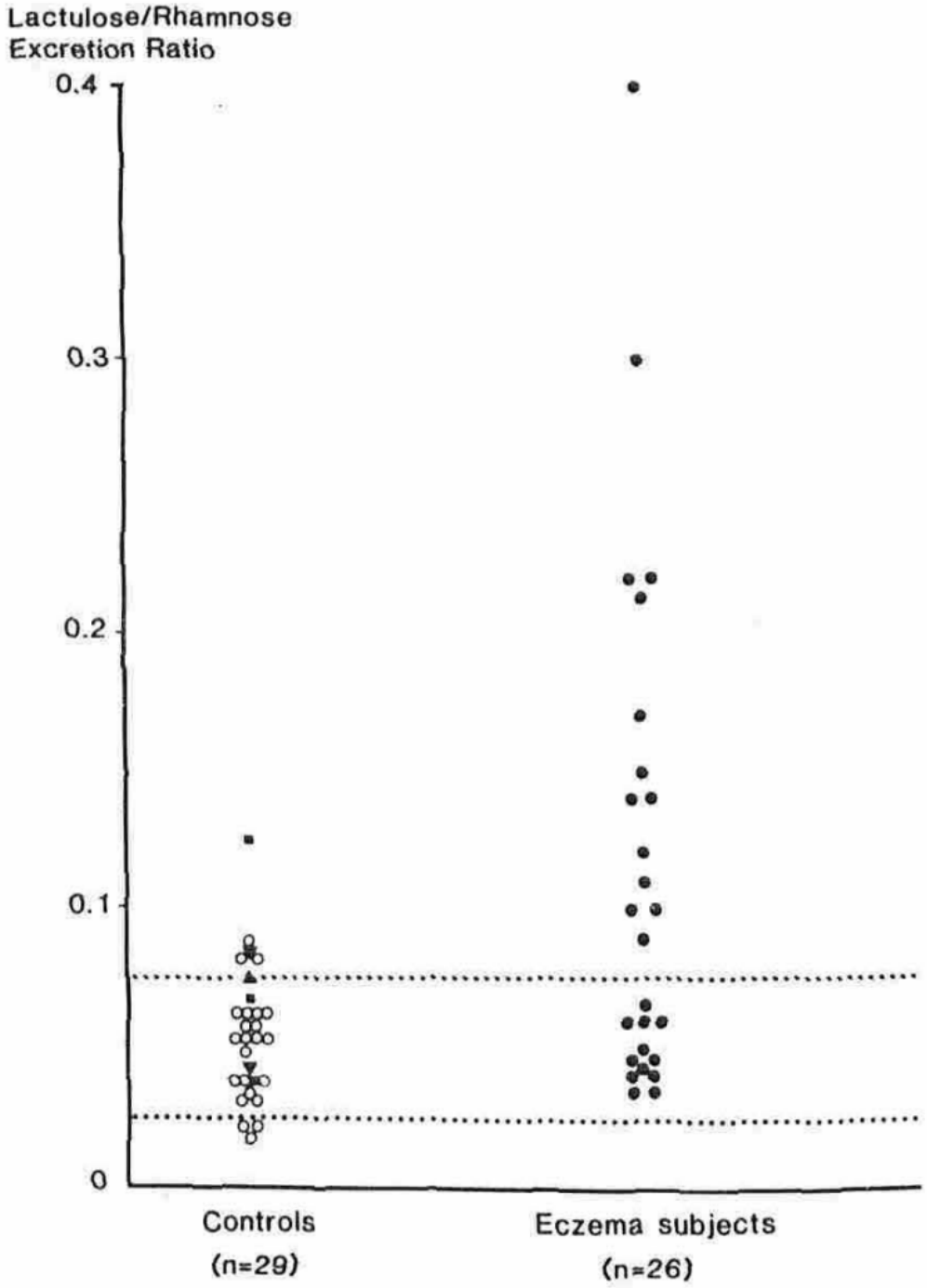


Nylund L, et al. Microarray analysis reveals marked intestinal microbiota aberrancy in infants having eczema compared to healthy children in at-risk for atopic disease. BMC Microbiol. 2013 Jan 23;13:12. doi: 10.1186/1471-2180-13-12.

…BUT SO IS GUT BARRIER!

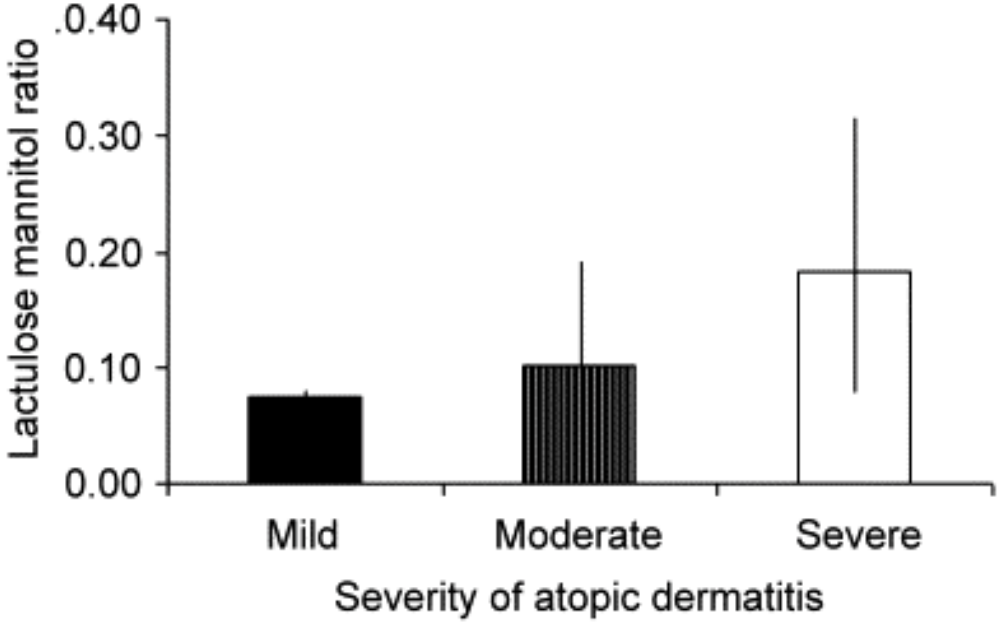
- SMALL INTESTINAL PERMEABILITY WAS FOUND TO BE IMPAIRED IN CHILDREN WITH ATOPIC DERMATITIS AND IMPROVED WITH LACTOBACILLUS SUPPLEMENTATION (P=.001 ON LACTULOSE-MANNITOL TEST RESULTS)

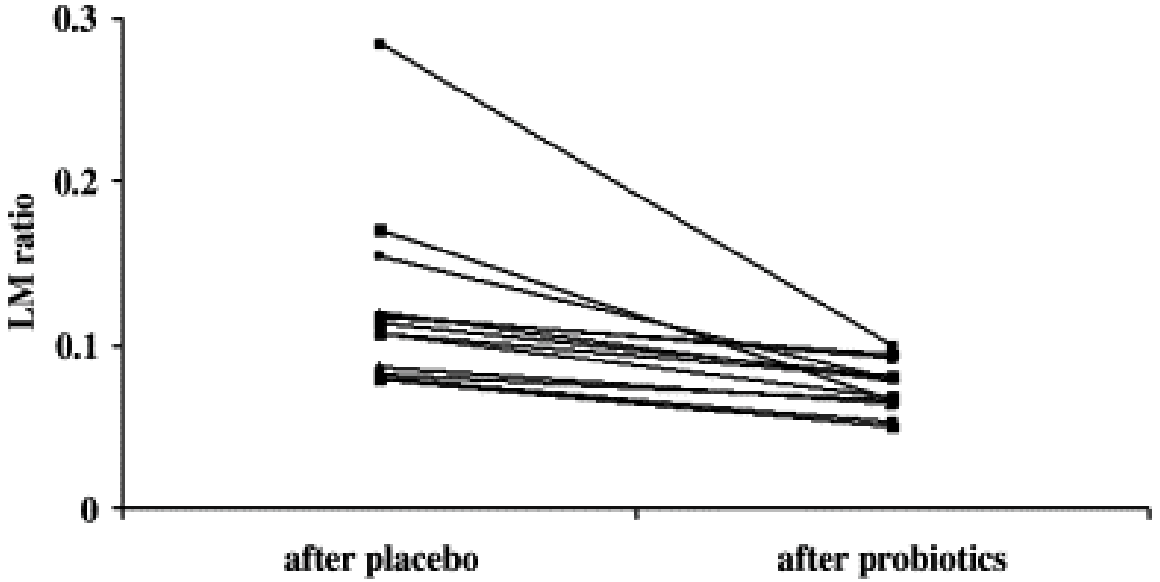
Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. Rosenfeldt V, Benfeldt E, Valerius NH, Paerregaard A, Michaelsen KF. J Pediatr. 2004 Nov;145(5):612-6.



Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. Rosenfeldt V, Benfeldt E, Valerius NH, Paerregaard A, Michaelsen KF. J Pediatr. 2004 Nov;145(5):612-6.

LEAKY





Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. Rosenfeldt V, Benfeldt E, Valerius NH, Paerregaard A, Michaelsen KF. J Pediatr. 2004 Nov;145(5):612-6.

EFFECT OF PROBIOTICS ON PREVENTION

- 21 STUDIES ANALYZED
- BEST EVIDENCE: PROBIOTICS IN MOTHERS AND INFANTS FOR PREVENTING DEVELOPMENT/REDUCING SEVERITY OF AD
- LACTOBACILLUS RHAMNOSUS GG

Foolad N, Brezinski EA, Chase EP, Armstrong AW. Effect of nutrient supplementation on atopic dermatitis in children: a systematic review of probiotics, prebiotics, formula, and fatty acids. JAMA Dermatol. 2013 Mar;149(3):350-5.

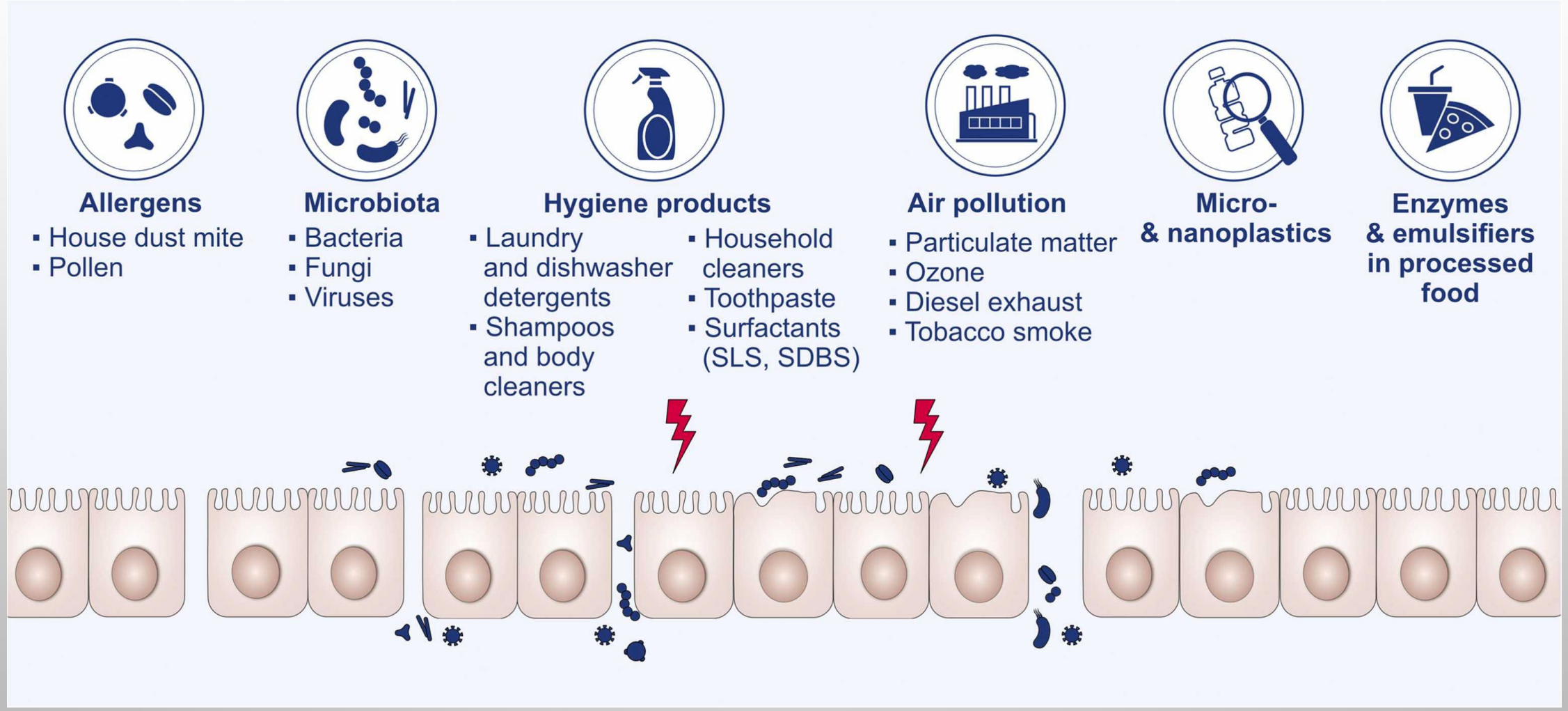
LONGER TERM?

- 171 CHILDREN WERE GIVEN LACTOBACILLUS PARACASEI OR PLACEBO
- INITIALLY FOUND REDUCTION OF INCIDENCE IN INFANT ECZEMA
- FOLLOW UP AT 8-9 YEARS OF AGE REVEALED NO DIFFERENCE, SUGGESTING PERHAPS ONLY DELAYED ONSET OF ECZEMA

West CE, Hammarström ML, Hernell O. Probiotics in primary prevention of allergic disease - follow-up at 8-9 years of age. Allergy. 2013 Jul 30.

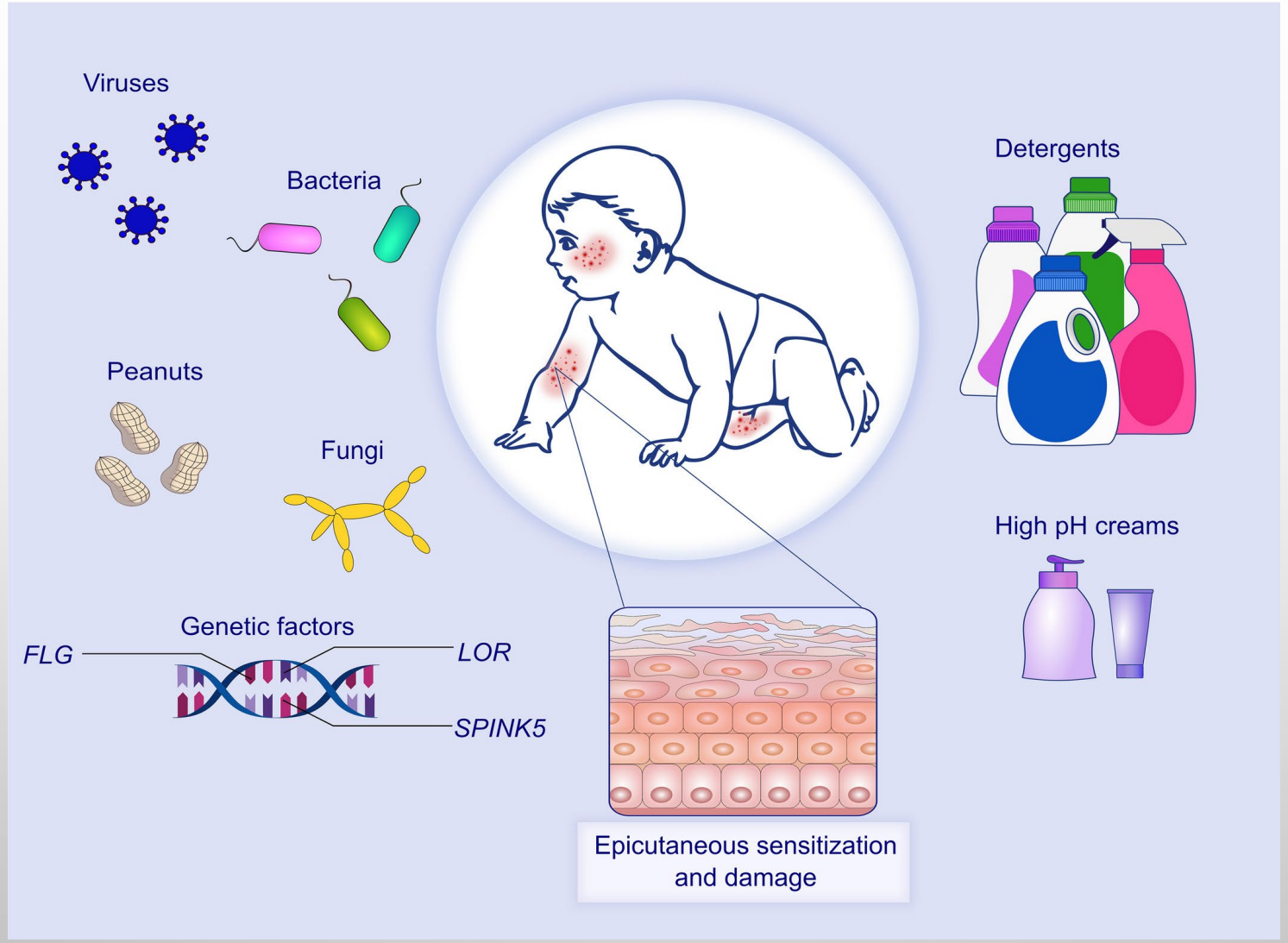
EPITHELIAL BARRIER HYPOTHESIS

Industrialization, urbanization and Westernized lifestyle have a devastating impact on the epithelial barriers of the skin, airways and gut mucosa as proposed by "The Epithelial Barrier Theory"



Yazici D, Ogulur I, Pat Y, Babayev H, Barletta E, Ardicli S, Huang M, Koch J, Li M, Maurer D, Radzikowska U. The epithelial barrier: The gateway to allergic, autoimmune, and metabolic diseases and chronic neuropsychiatric conditions. InSeminars in Immunology 2023 Nov 1 (Vol. 70, p. 101846). Academic Press.

Environmental and genetic factors leading to epicutaneous damage



Allergy, Volume: 75, Issue: 9, Pages: 2185-2205, First published: 06 April 2020, DOI: (10.1111/all.14304)

WE MIGHT NEED TO CHANGE THE ENVIRONMENT.