# Immunology and Pathophysiology of Atopic Dermatitis

Michael Nevid, MD
National Jewish Health

# Outline

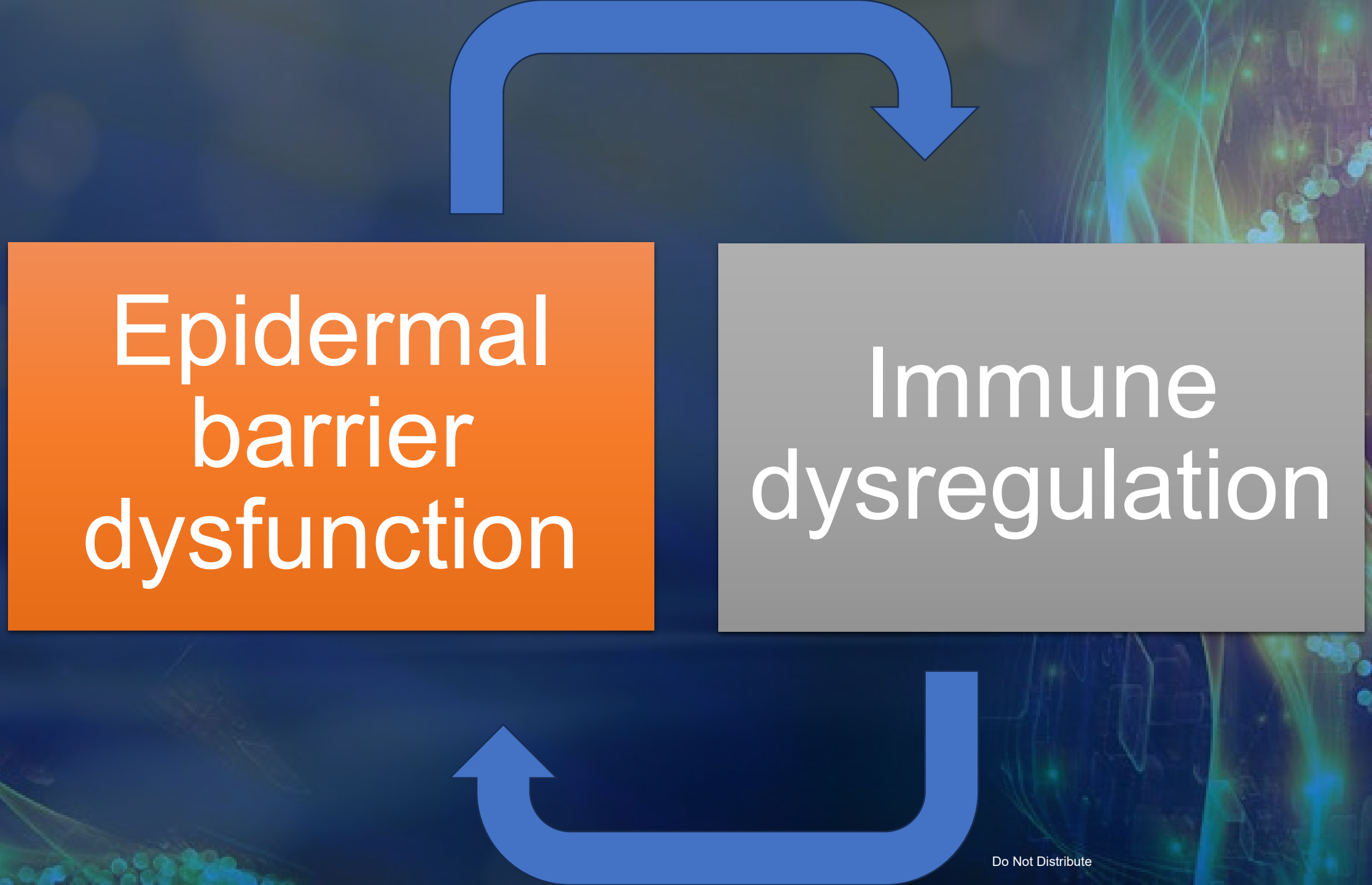
- Skin anatomy
- Immunology 101
- Pathophysiology
  - Immune dysregulation
  - Skin barrier dysfunction
  - Genetic predisposition
  - Microbial dysbiosis
- Intracellular signaling and therapeutic targets
- Atopic march

# AD Pathophysiology is Complex

# Key Features

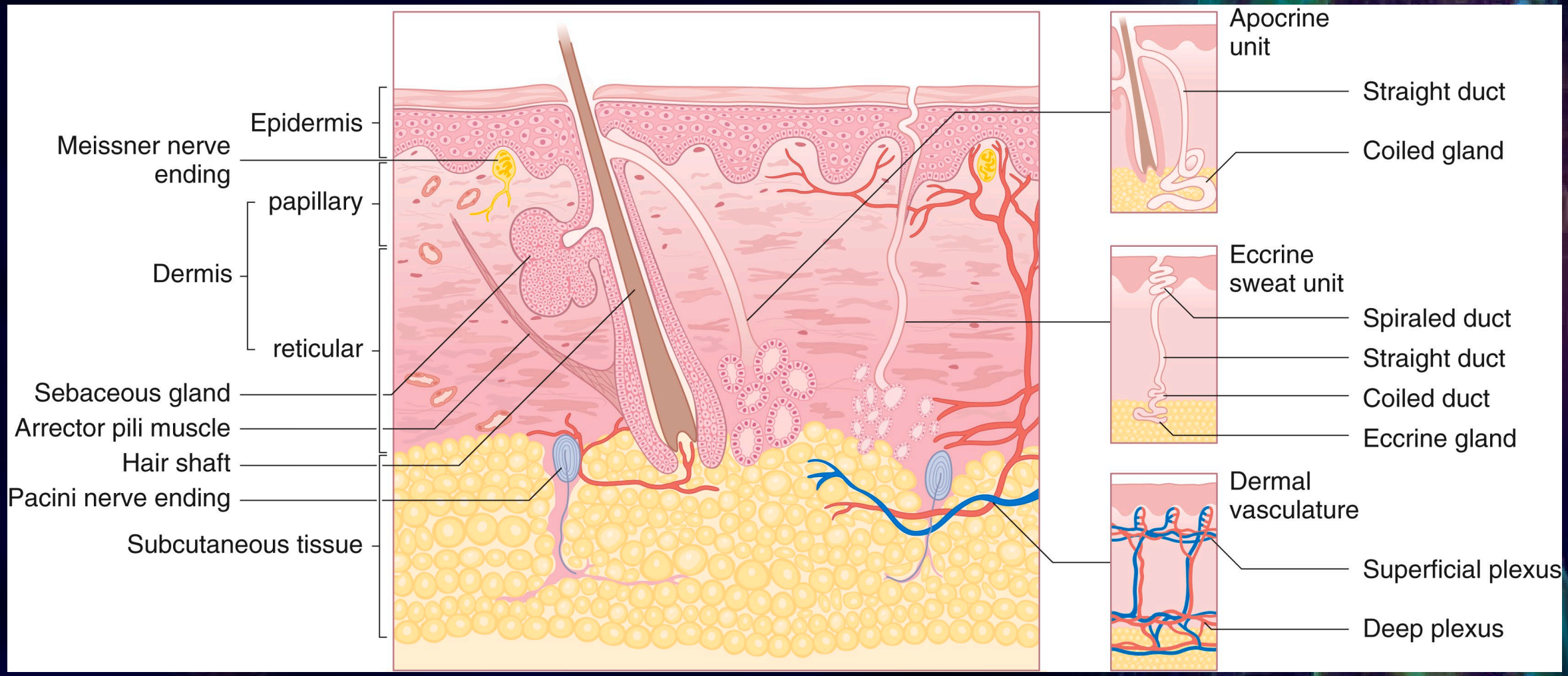
Epidermal barrier dysfunction

Immune dysregulation



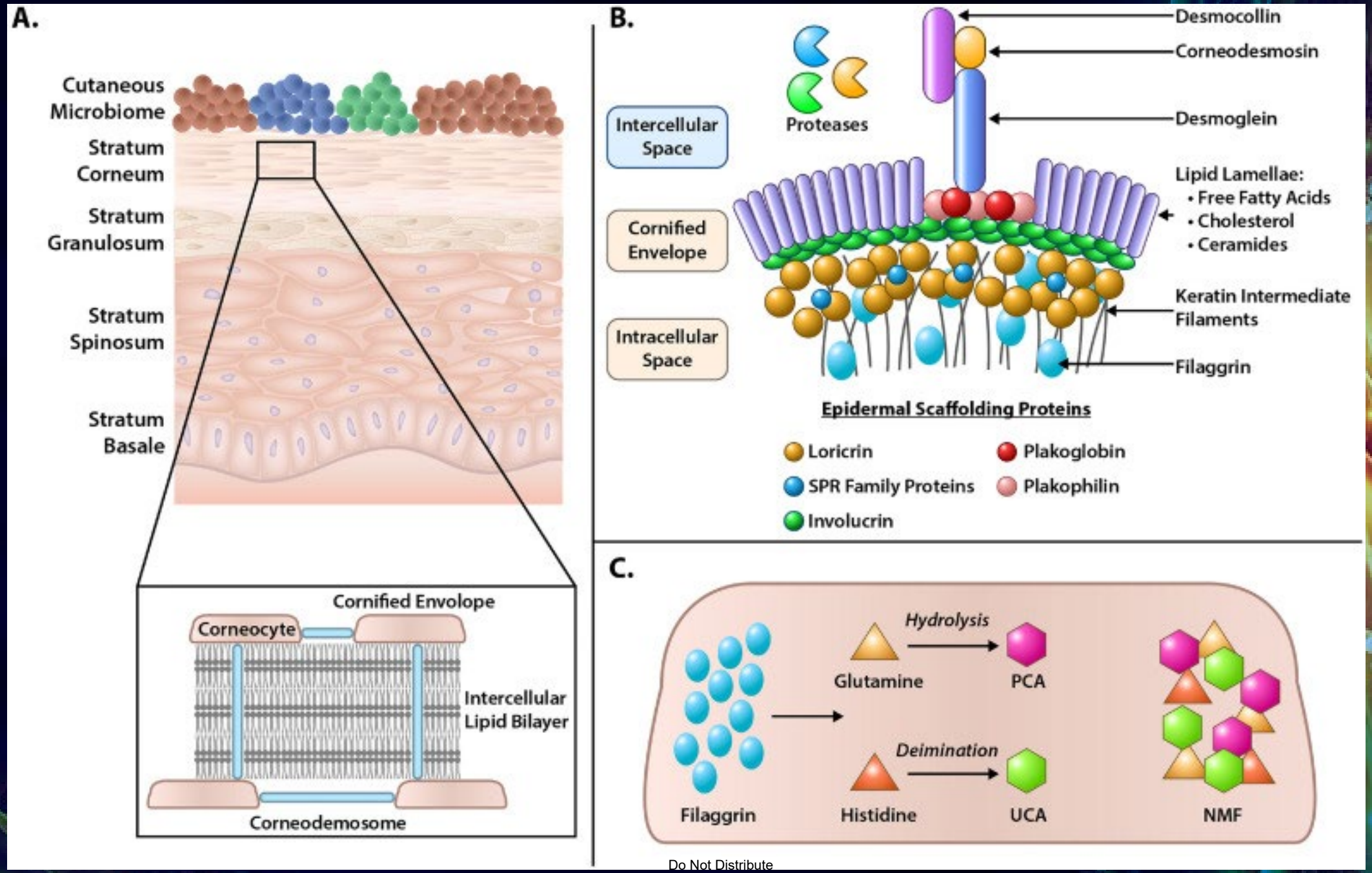
# Skin anatomy and immunology

# Physical barrier






Dhossche and Chiu in Nelson's Textbook of Pediatrics

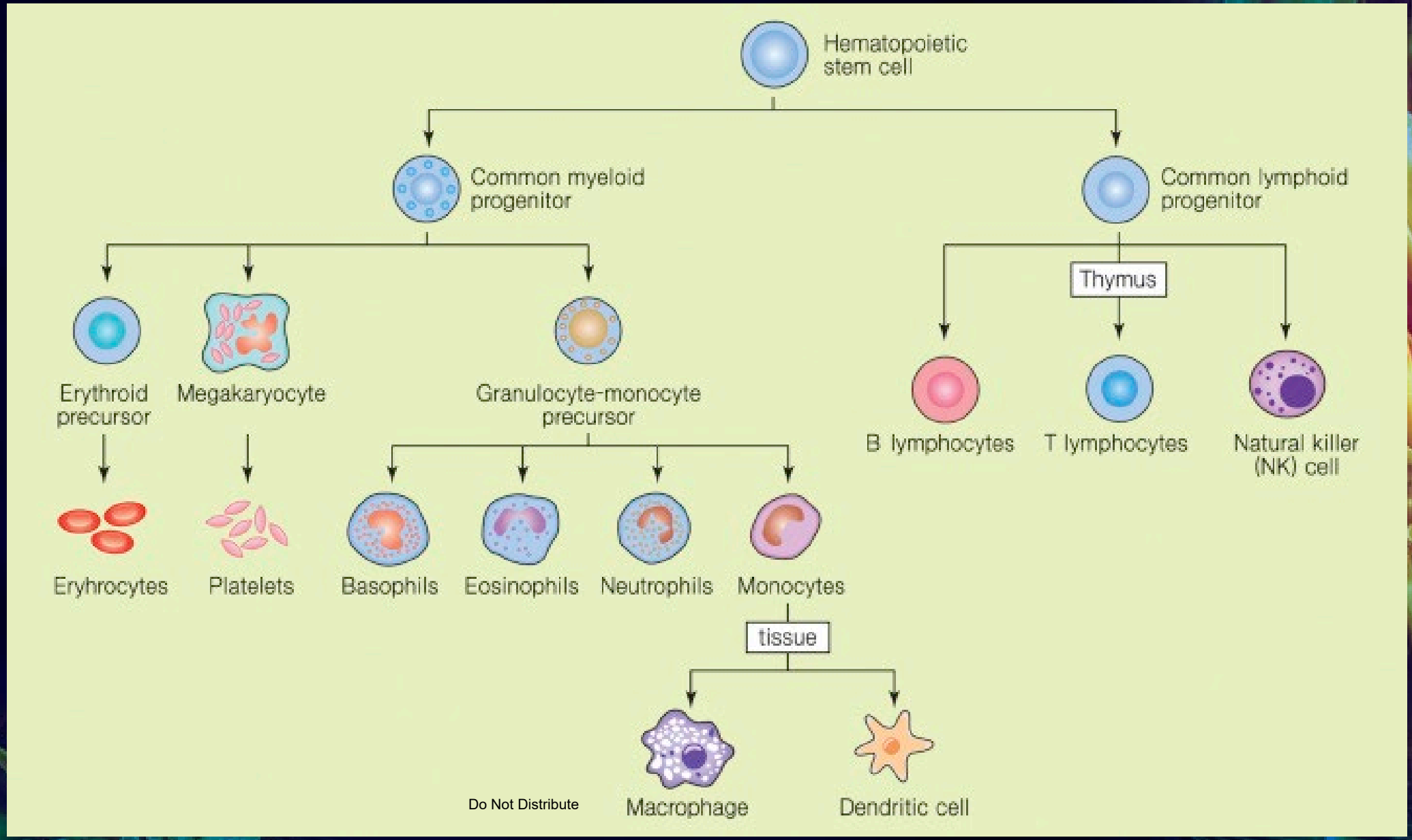





Stefanovic & Irvine 2024

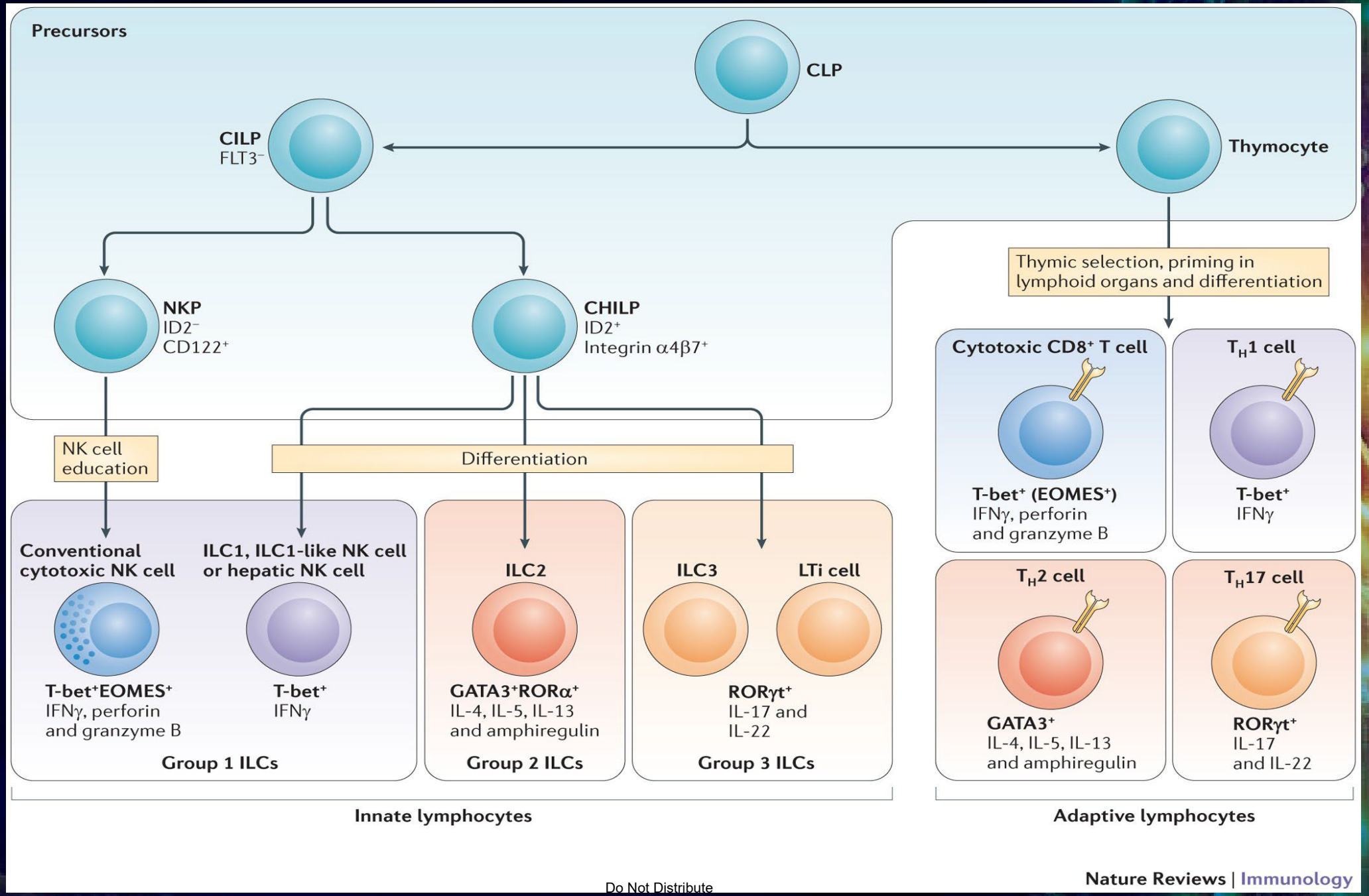
# Immunological barrier

# Immunology 101



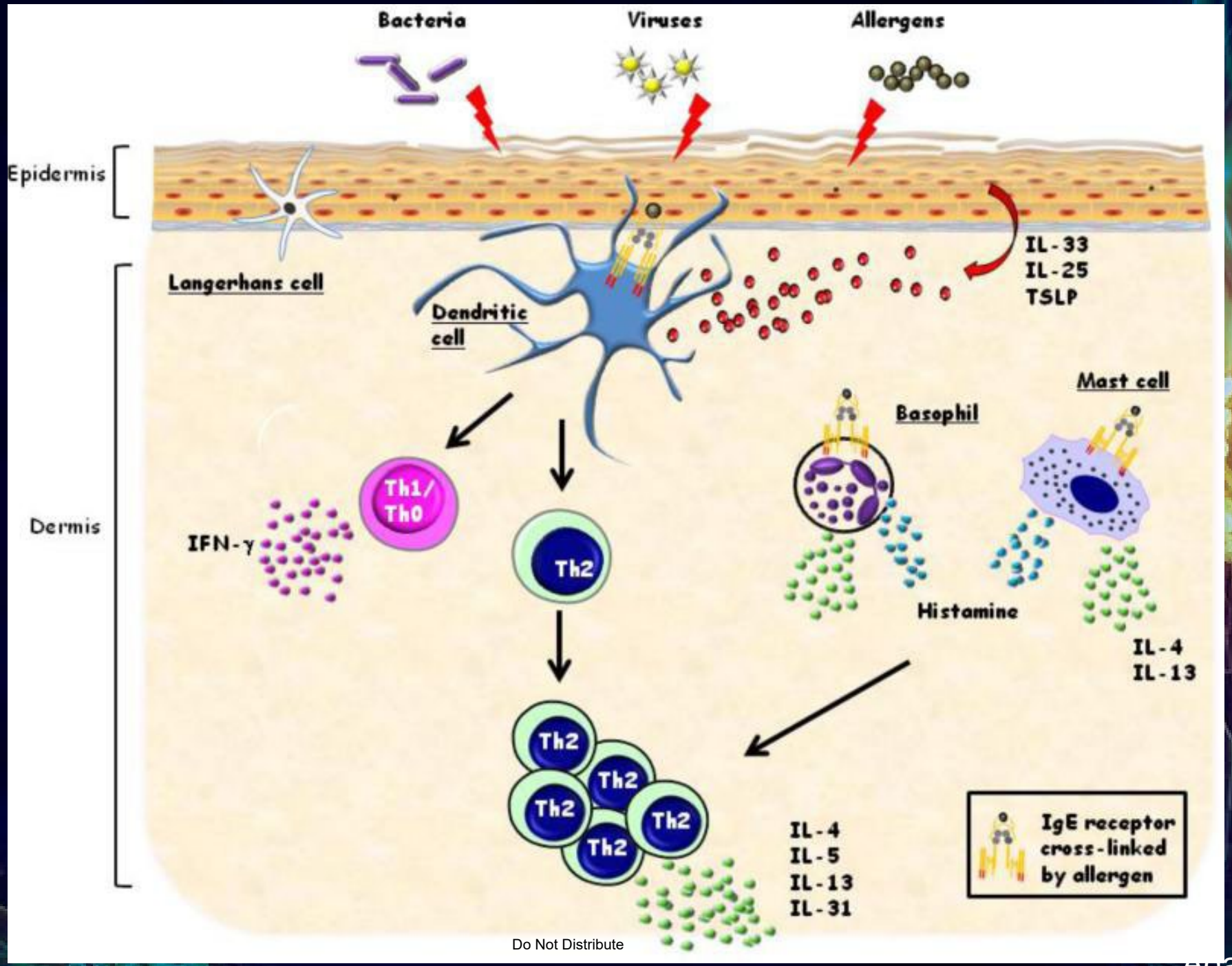



Ryu 2017



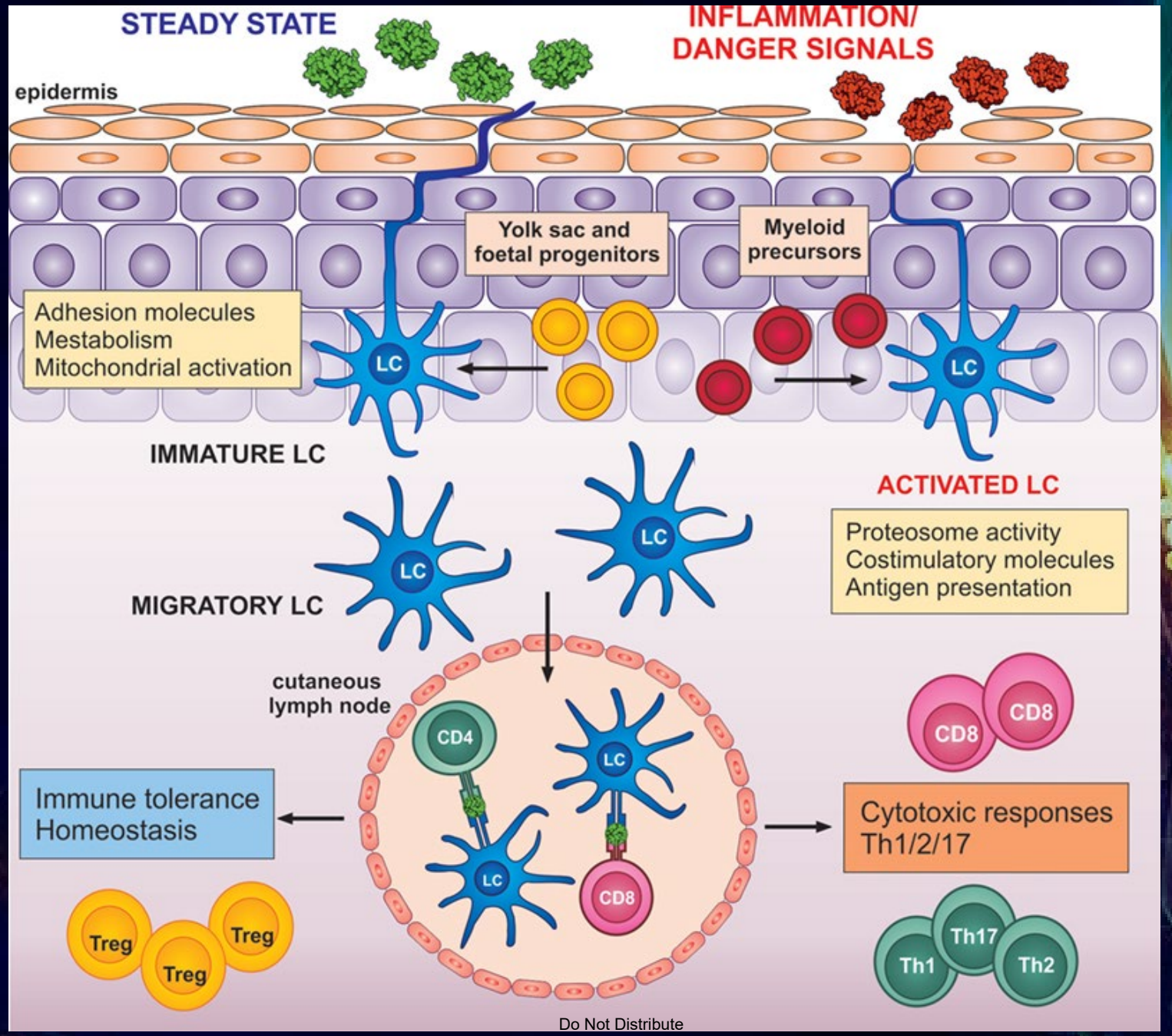



Gasteiger & Rudensky 201

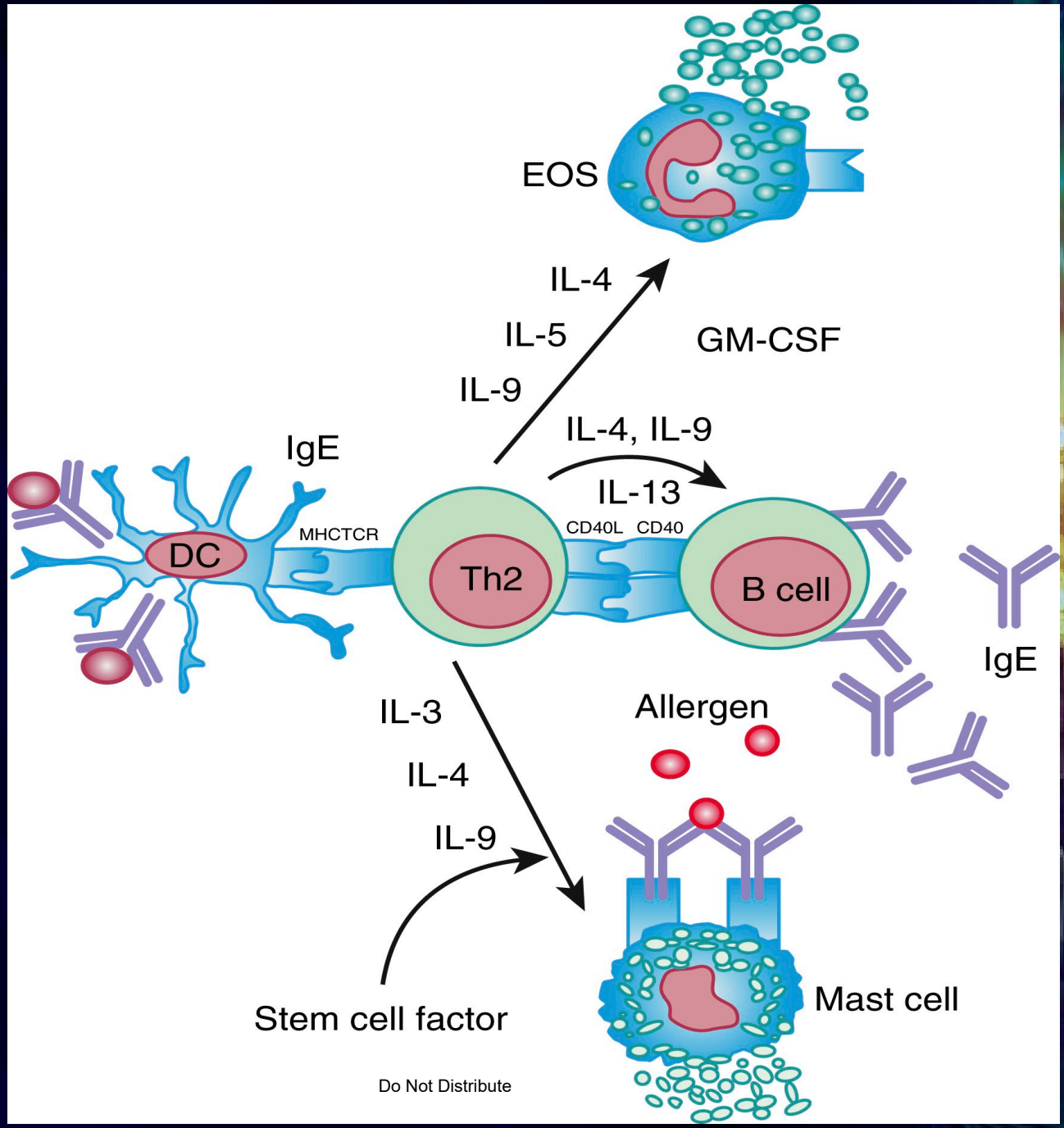





Agarwal and Woodfolk 2014




Clayton et al. 2017

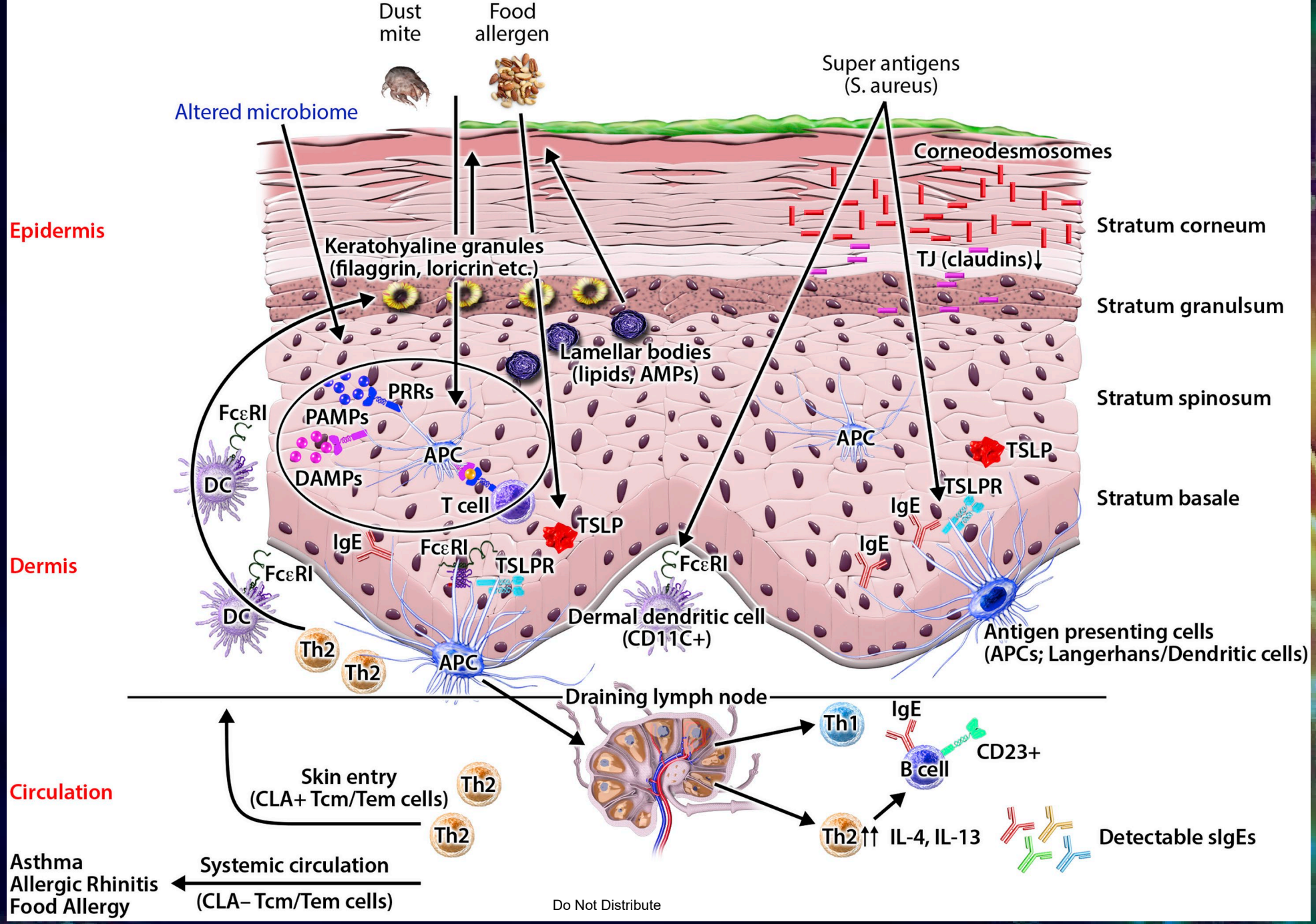



Akdis and Sicherer in Nelson's Textbook of Pediatrics

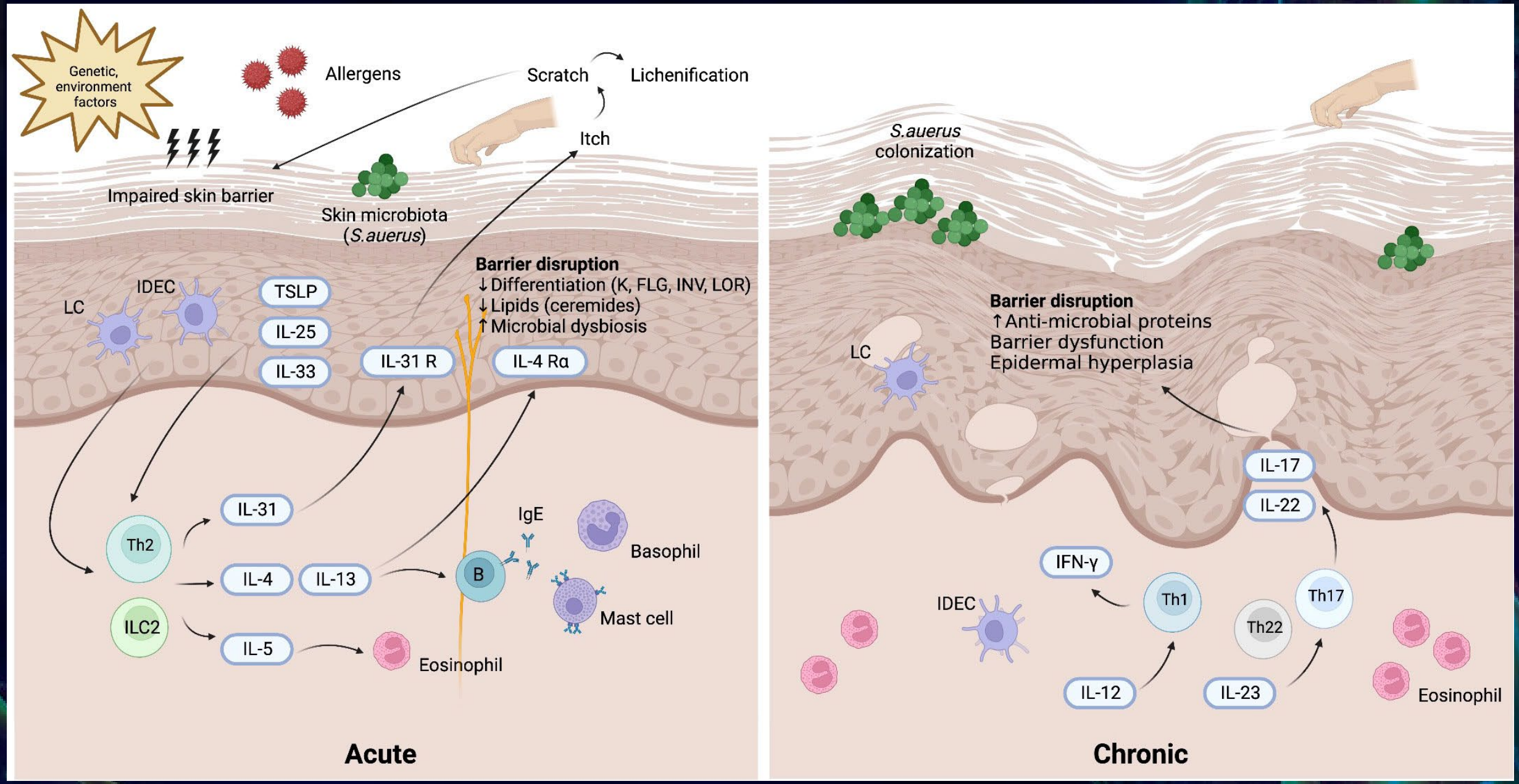
# Key Features

Epidermal barrier dysfunction

Immune dysregulation

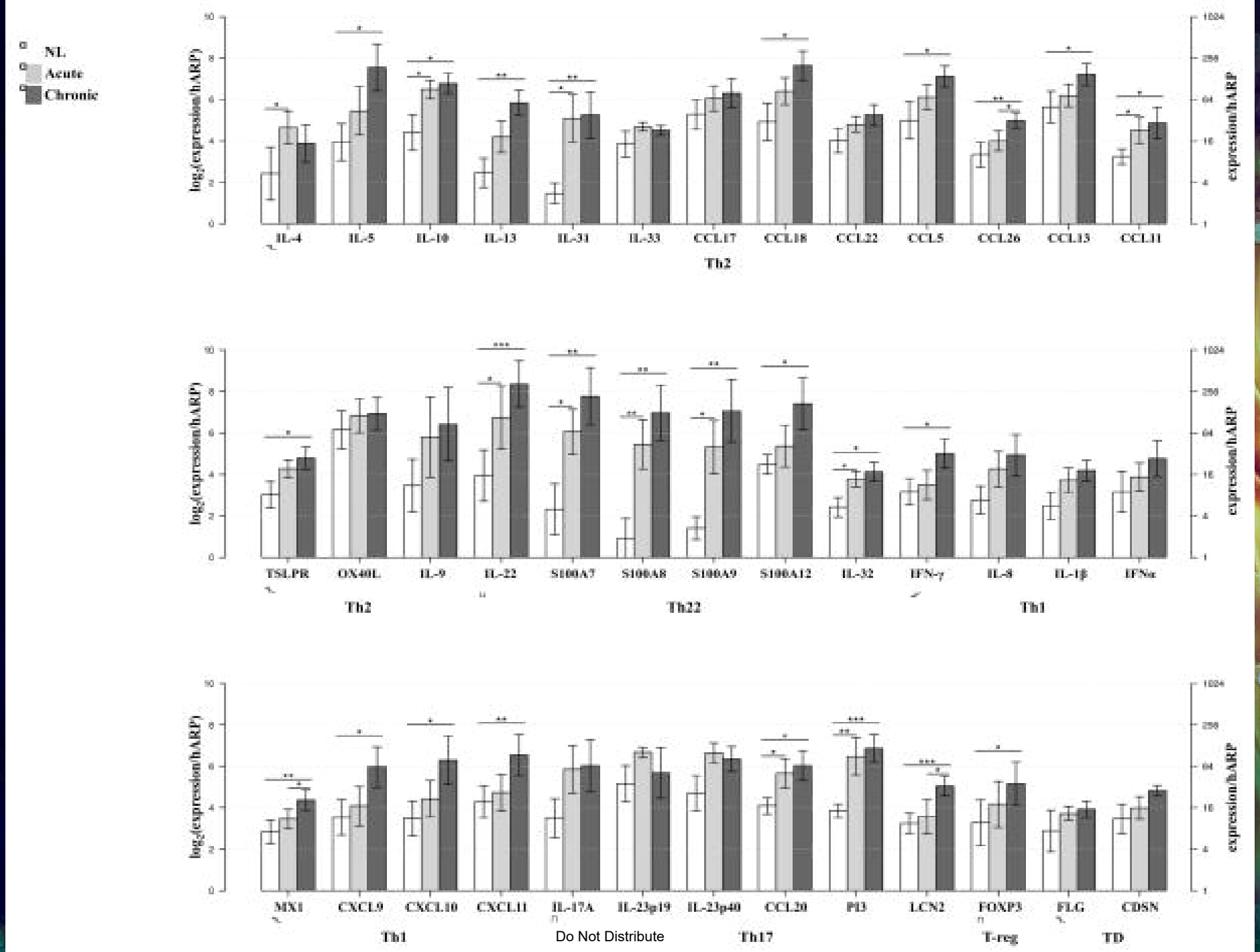



Czarnowicki et al. 2017






Huang et al. 2022




Gittler et al. 2012

# Differential In Situ Cytokine Gene Expression in Acute versus Chronic Atopic Dermatitis

**Qutayba Hamid,* Mark Boguniewicz,‡§ and Donald Y. M. Leung‡§**

**Meakins–Christie Laboratories and Department of Pathology, McGill University, Montreal, Quebec, Canada H2X 2P2, ‡Department of Pediatrics, The National Jewish Center for Immunology and Respiratory Medicine, Denver, Colorado 80206, and §Department of Pediatrics, University of Colorado Health Sciences Center, Denver, Colorado 80262*

## Abstract

**The mechanisms involved in the initiation and maintenance of skin inflammation in atopic dermatitis (AD) are poorly understood. Recent data suggest that the pattern of cytokines expressed locally plays a critical role in modulating the nature of tissue inflammation. In this study, we used in situ hybridization to investigate the expression of interleukin 4 (IL-4), IL-5, and interferon-gamma (IFN-γ) messenger RNA (mRNA) in skin biopsies from acute and chronic skin lesions of patients with AD. As compared with normal control skin or uninvolved skin of patients with AD, acute and chronic skin lesions had significantly greater numbers of cells that were positive for mRNA, IL-4 ($P < 0.01$), and IL-5 ($P < 0.01$), but not for IFN-γ mRNA expressing cells. However, as compared with acute AD skin lesions, chronic AD skin lesions had significantly fewer IL-4 mRNA-expressing cells ($P < 0.01$), but significantly greater IL-5 mRNA ($P < 0.01$). T cells constituted the majority of IL-5-expressing cells in acute and chronic AD lesions. Chronic lesions also expressed significantly greater numbers of activated EG2+ eosinophils than acute lesions ($P < 0.01$). These data indicate that although acute and chronic AD lesions are associated with increased activation of IL-4 and IL-5 genes, initiation of acute skin inflammation in AD is associated with a predominance of IL-4 expression whereas maintenance of chronic inflammation is predominantly associated with increased IL-5 expression and eosinophil infiltration. (*J. Clin. Invest.* 1994. 94:870–876.) Key words: atopic dermatitis • inflammation • cytokines • eosinophils • T cells**

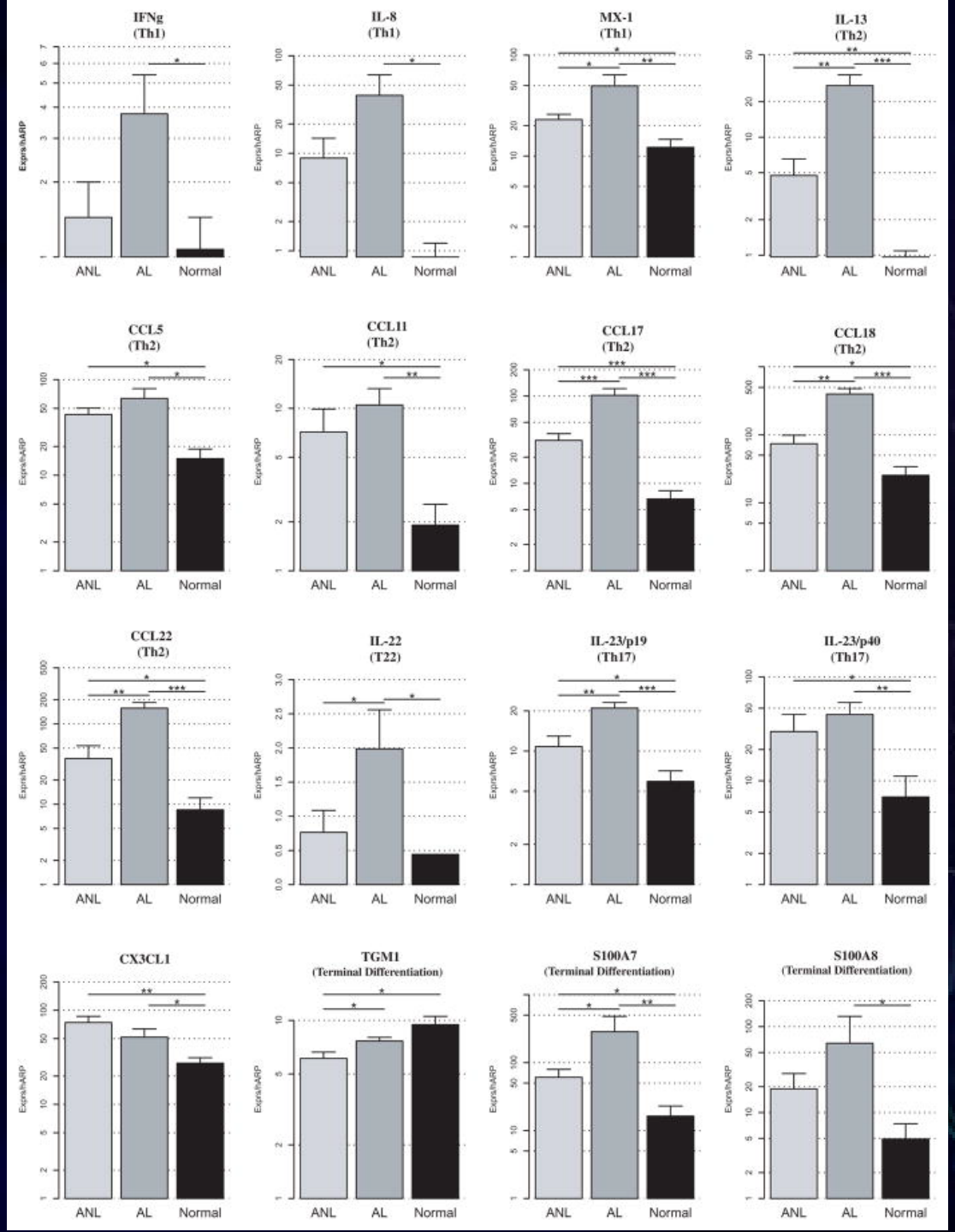
## Introduction

Atopic dermatitis (AD)[1] is a chronic skin disease affecting up to 10% of children and is the major cause of occupation-related disability caused by skin disease. It is associated with intense pruritus, increased serum IgE levels, and peripheral blood eosinophilia (1, 2). The actual events that result in this inflammatory skin condition are poorly understood. However, it is thought that genetic susceptibility, environmental trigger factors such as allergens, and altered immune responses contribute to its pathogenesis (3). Acute and chronic skin lesions in AD are characterized by the infiltration of activated T cells and monocyte-macrophages (4, 5). Although eosinophils are not prevalent by routine histology, chronic AD is associated with extensive dermal deposition of eosinophil-granule major basic protein (6). In this regard, serum levels of sIL2R and eosinophil cationic protein have been reported to correlate with severity of skin disease (7, 8). Favorable clinical responses of AD patients to cyclosporin A also implicate immune activation as an important mechanism in the pathogenesis of AD (9, 10).

Identification of the immunologic elements that play a role in initiating and maintaining skin inflammation in AD is critical for the development of new approaches to treat this common and often debilitating skin disease. Studies of T cell clones support the concept that activation of a subpopulation of helper cells leads to the release of cytokines important in the pathogenesis of allergic diseases. In mice, two types of CD4+ T cell clones have been described on the basis of their cytokine gene transcription and secretion (11). T helper type 1 (Th1) cells express mRNA and secrete IL-2 and interferon-gamma (IFN-γ) but not IL-4 or IL-5. In contrast, Th2 cells elaborate IL-4 and IL-5 but not IFN-γ. Both subpopulations of T cells produce IL-3, GM-CSF, and TNF-α. IL-4 acts as an IgE isotype-specific switch factor (reviewed in reference 12), promotes mast cell growth (13), and induces the expression of vascular cell adhesion molecule (VCAM-1), an adhesion molecule involved in the migration of mononuclear cells and eosinophils into sites of tissue inflammation (14). IL-5 promotes the differentiation, vascular endothelial adhesion and survival of eosinophils as well as enhances histamine release from basophils (reviewed in reference 15). In contrast, IFN-γ inhibits IgE synthesis as well as the proliferation of IL-4 and IL-5-producing Th2 lymphocytes (16, 17). The lack of IFN-γ production, as well as the concomitant activation of IL-4 and IL-5, is thought to play a critical role in the pathogenesis of AD and asthma (17–19).

Address correspondence to Donald Y. M. Leung, M.D., Ph.D., Department of Pediatrics, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson Street, Denver, CO 80206.

*Received for publication 11 January 1994 and in revised form 7 April 1994.*



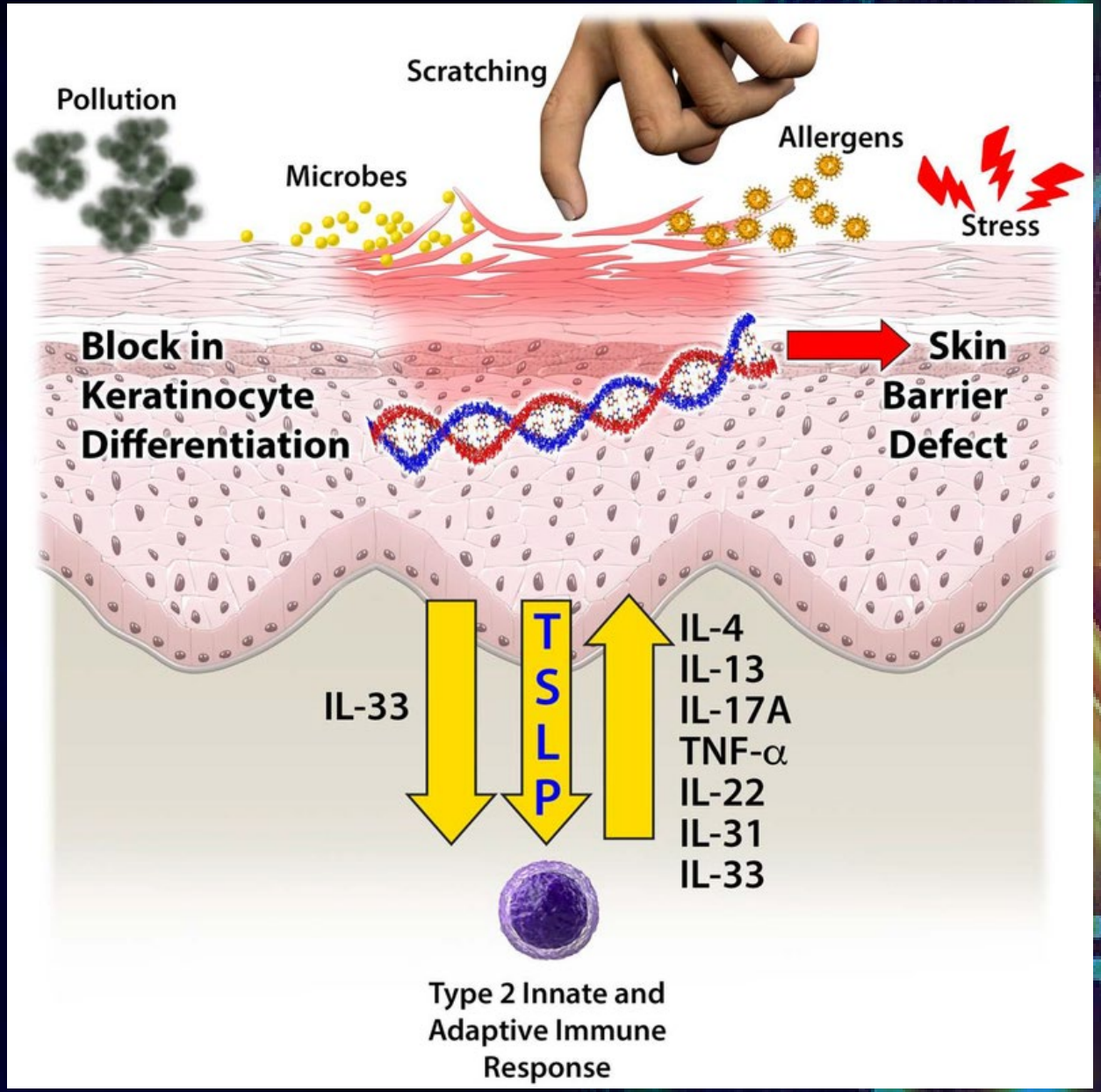



Suarez Farinas et al. 2011

# Systemic Immune Activation

- Peripheral blood in pediatric severe AD shows proteomic Th2 and Th17 signature (Brunner et al. 2019)
- Peripheral blood in adult severe AD shows increases in Th2 and Th22 (Czarnowicki et al. 2015)
- Systemic agents such as biologics, small molecules, and immunosuppressives have been used therapeutically

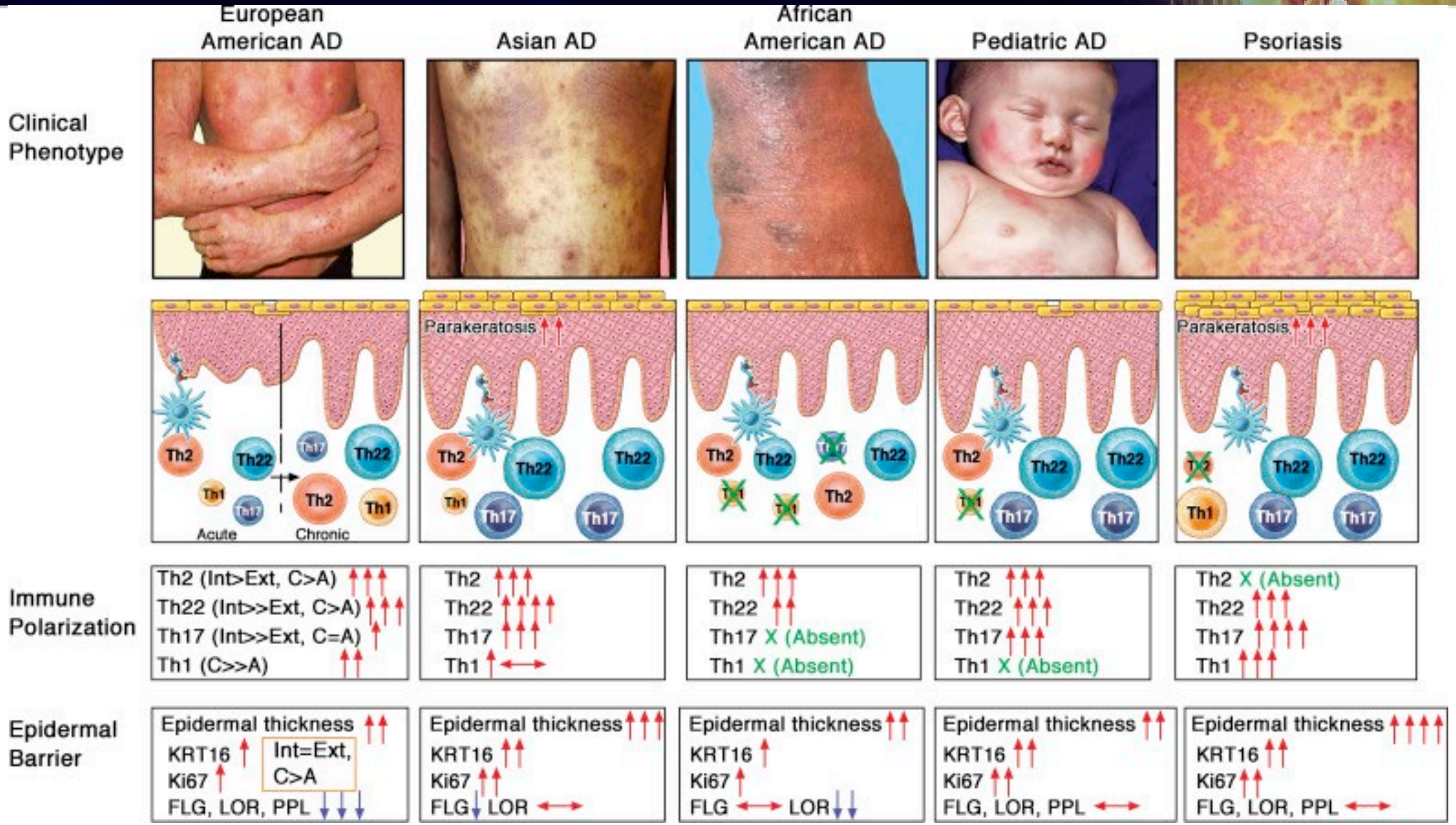
# Epidermal barrier dysfunction






Leung et al 2020

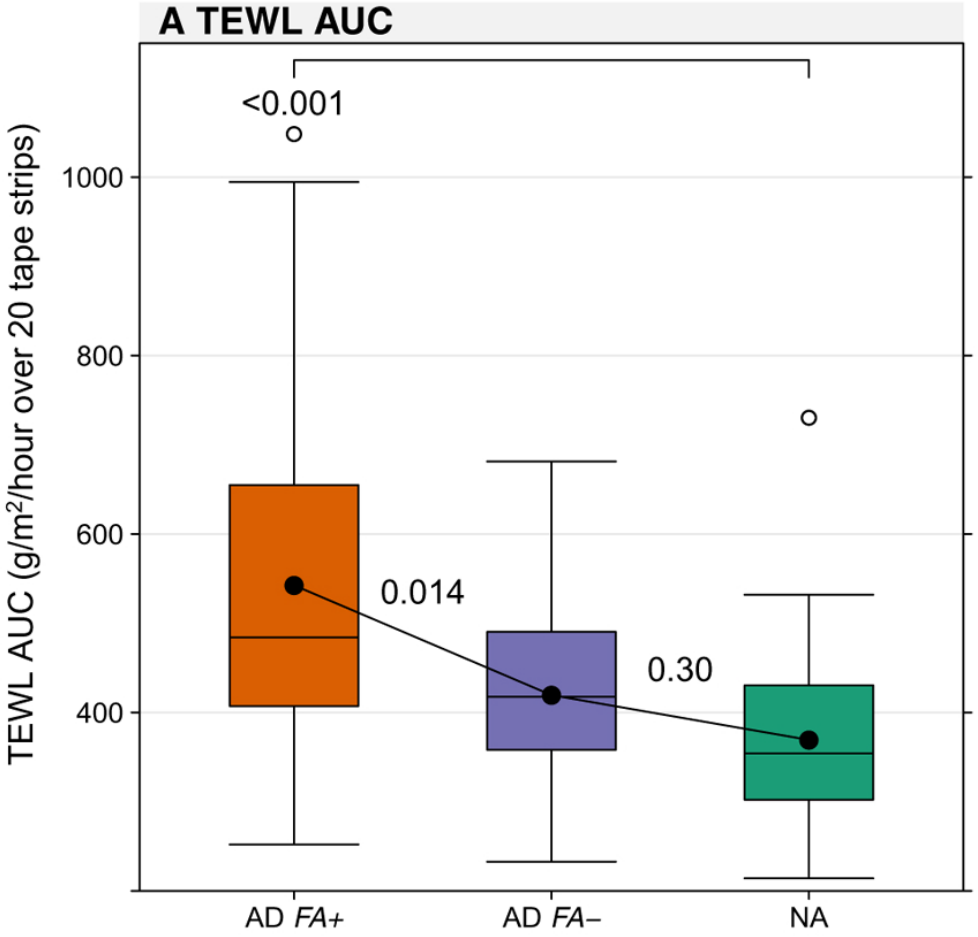
# AD Phenotypes and Endotypes

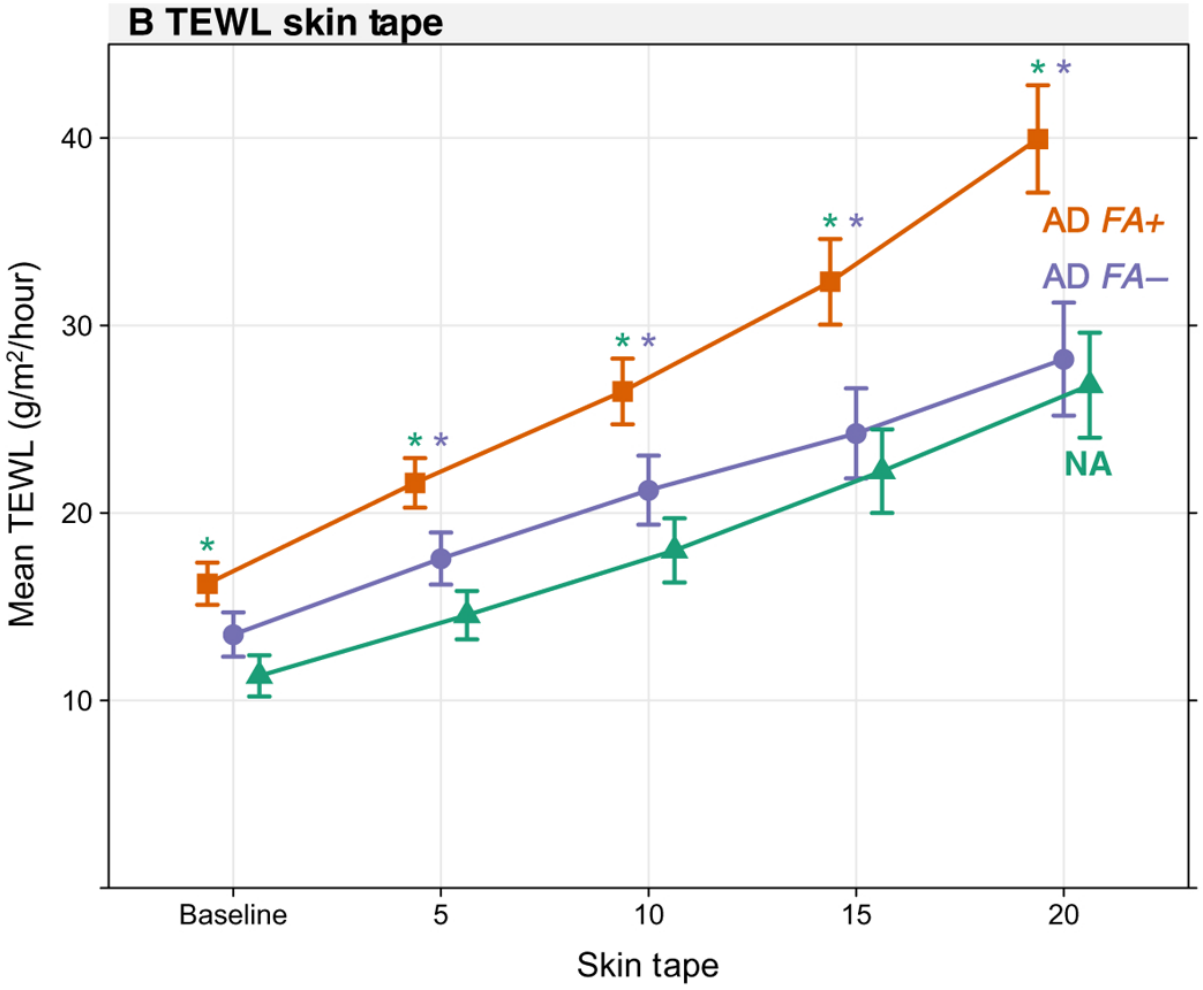





Czarnowicki et al 2019

# AD Endotypes

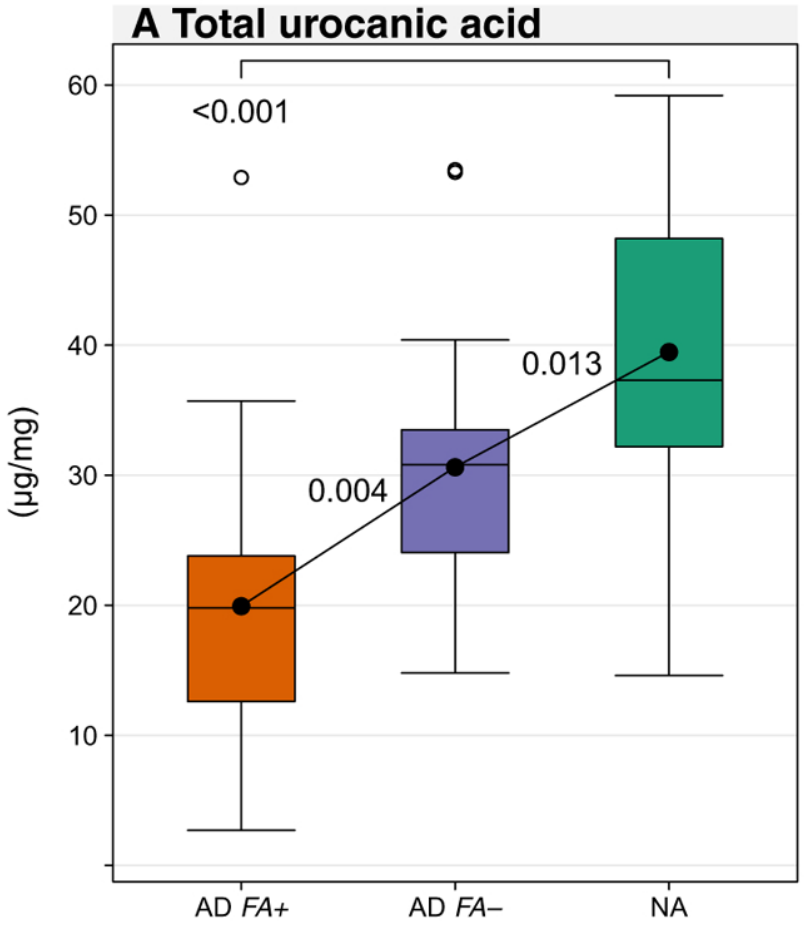


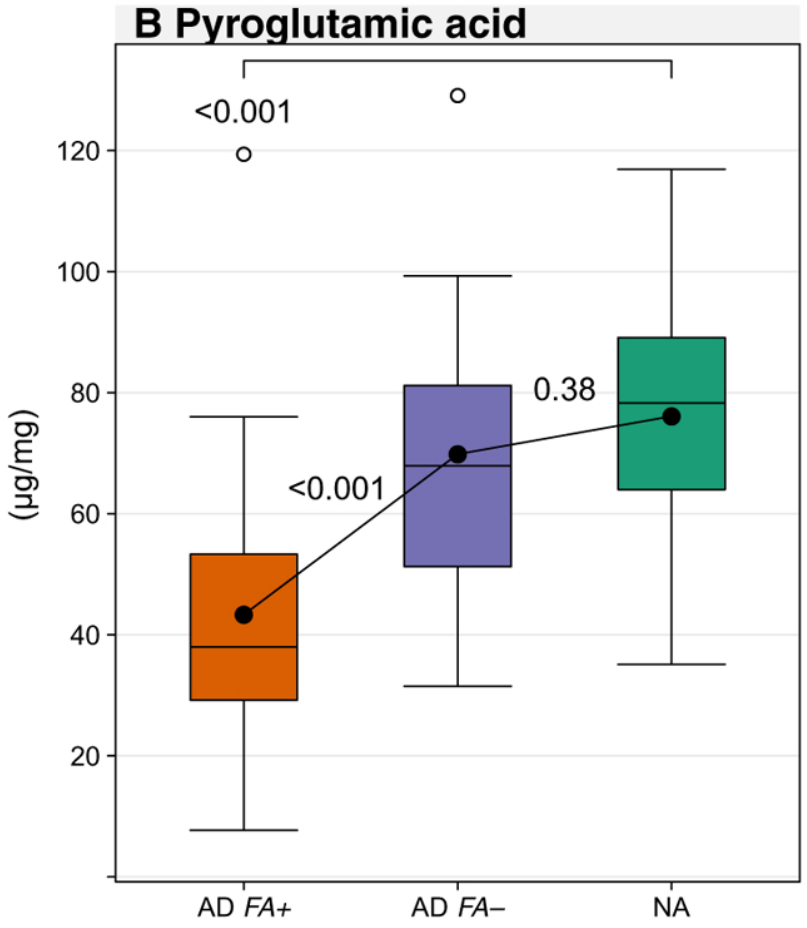



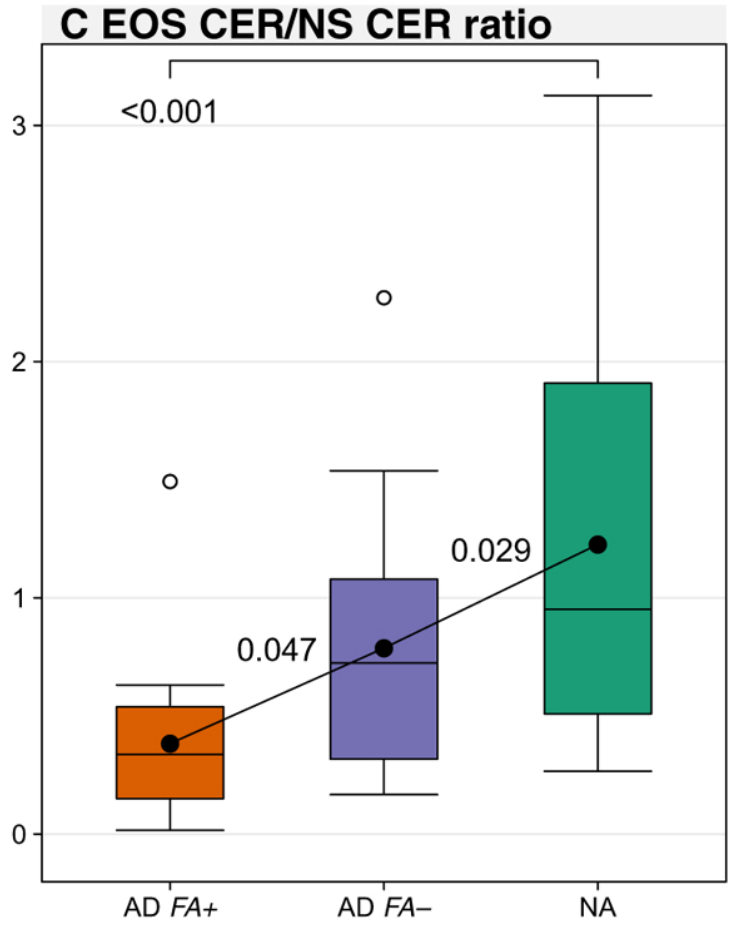



Leung et al. 2019

# AD Endotypes



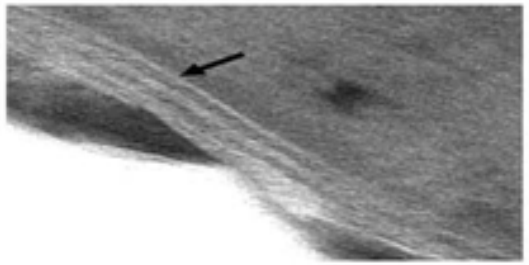



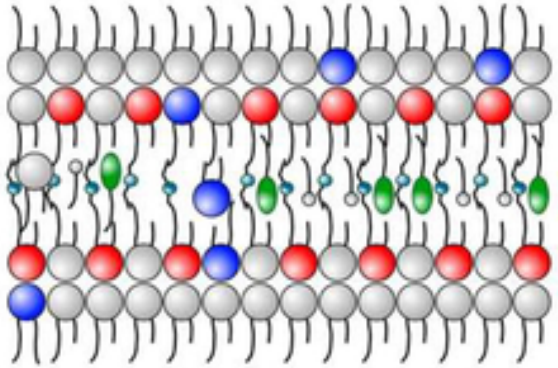






Leung et al. 2019

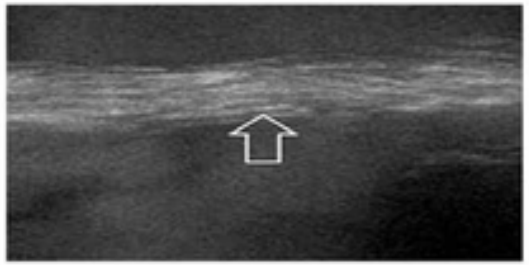
NA

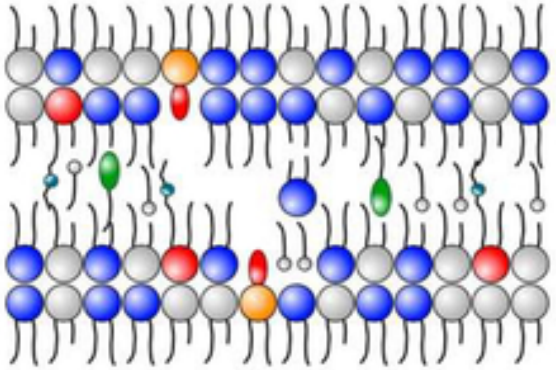




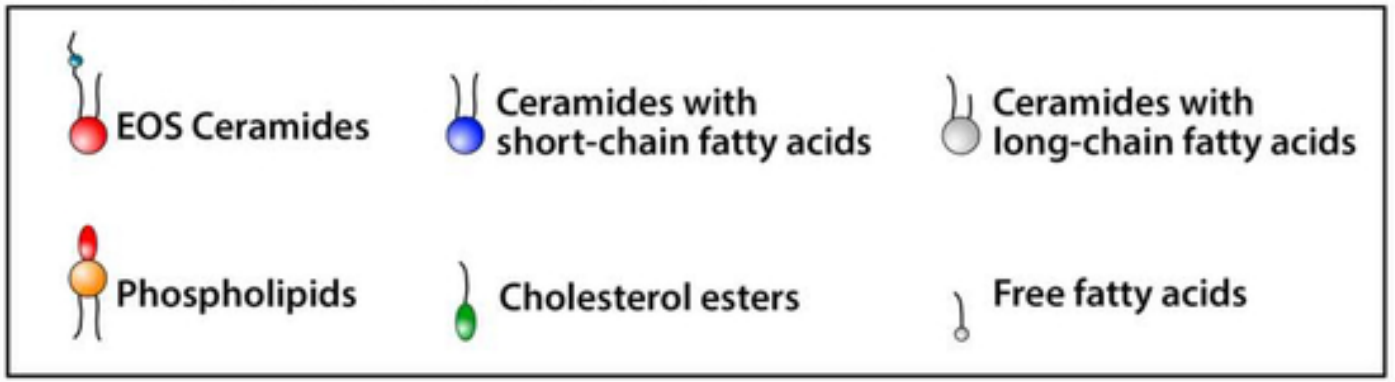
- Well-organized periodic lamellar membrane structures
- Prevalence of ultra long chain hydrophobic fatty acids in ceramides

AD+
FA+





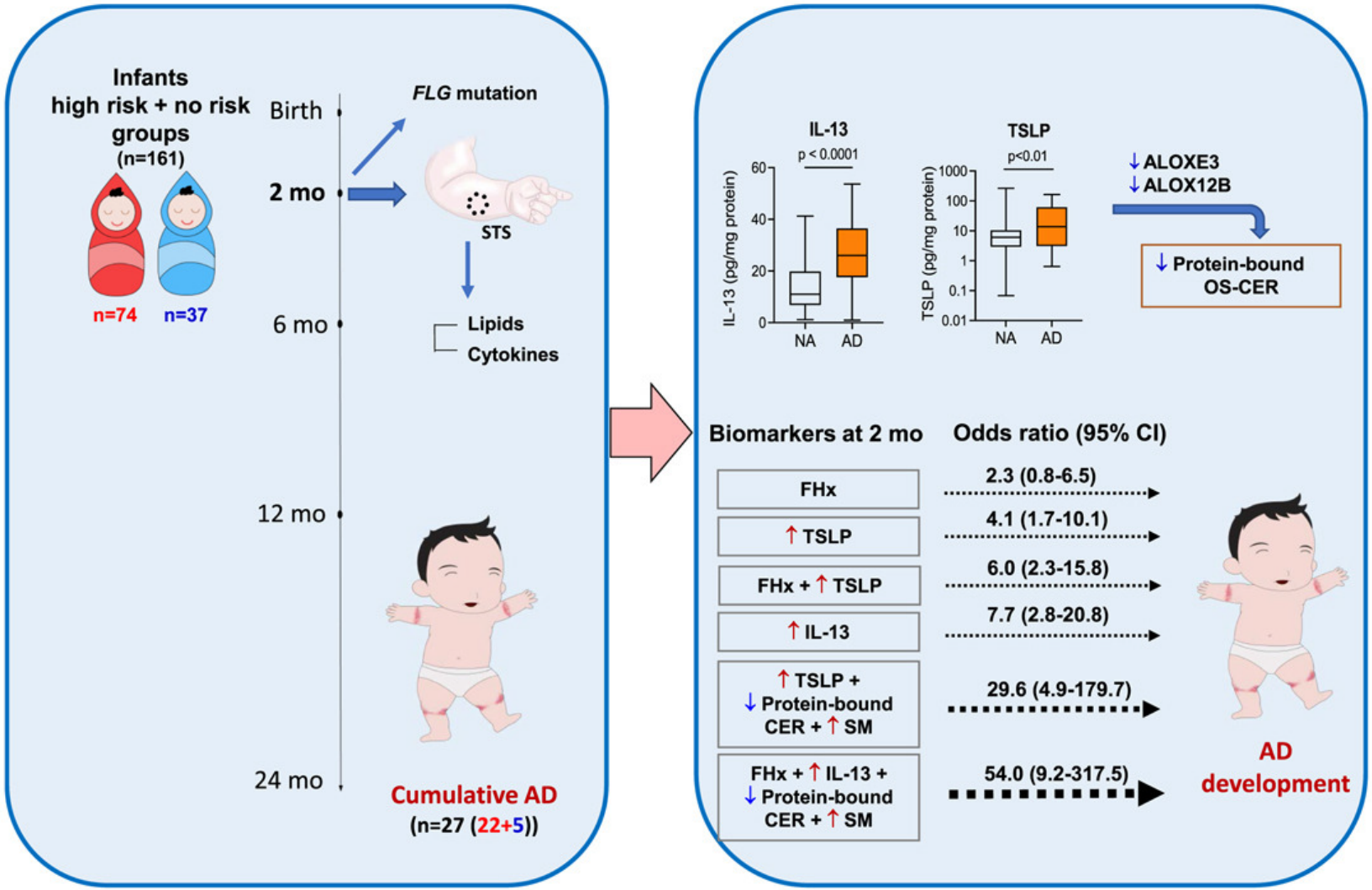
- Disorganized lamellar bilayers
- Change in ceramide classes composition
- Reduced fatty acid chain length in ceramides
- Presence of polar phospholipids






Leung et al 2020

# Stratum Corneum Lipid and Cytokine Biomarkers at Two Months of Age Predict the Future Onset of Atopic Dermatitis




**Abbreviations: ALOXE3:** arachidonate lipoxygenase 3; **ALOX12B:** arachidonate 12-lipoxygenase, **CI:** confidence interval; **CER:** ceramides; **FHx:** family history; **mo:** months; **OS-CER:** omega-hydroxy fatty acid sphingosine ceramides; **SM:** unsaturated sphingomyelins; **STS:** skin tape strip; **TSLP:** thymic stromal lymphopoietin

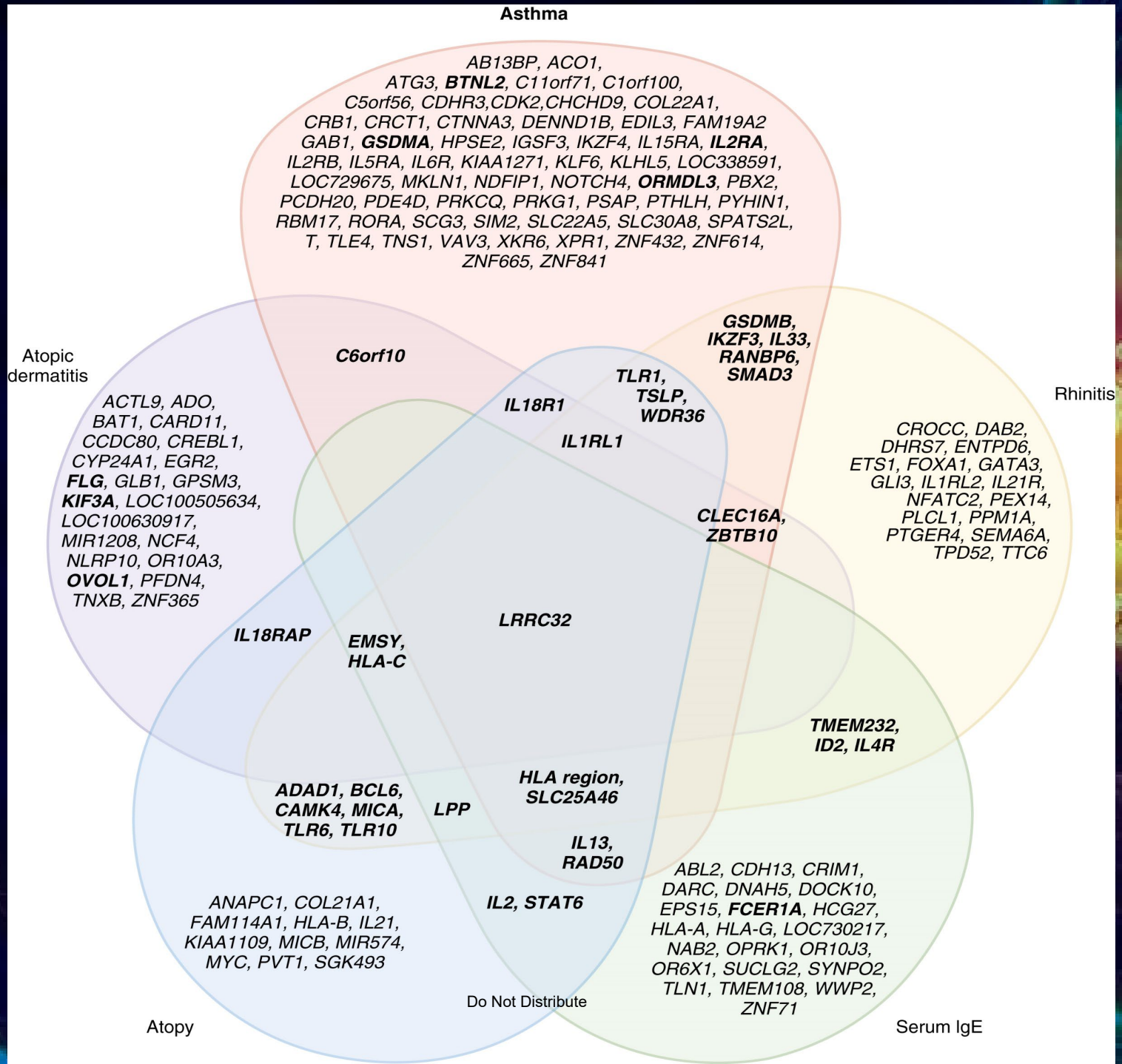


Berdyshev et al. 2023

# Additional Key Features

Genetic predisposition

Microbial dysbiosis





Holloway 2021 In Pediatric Allergy Principles and Practice

# Genetic predisposition

- Filaggrin (FLG) is a major structural component of the stratum corneum
  - Loss of function is most common genetic link to AD
- FLG expression is reduced in AD lesional skin (Howell et al. 2007)
- IL-4 and IL-13 lowers FLG expression (Howell et al. 2007)
- FLG is not everything

# Microbial Dysbiosis

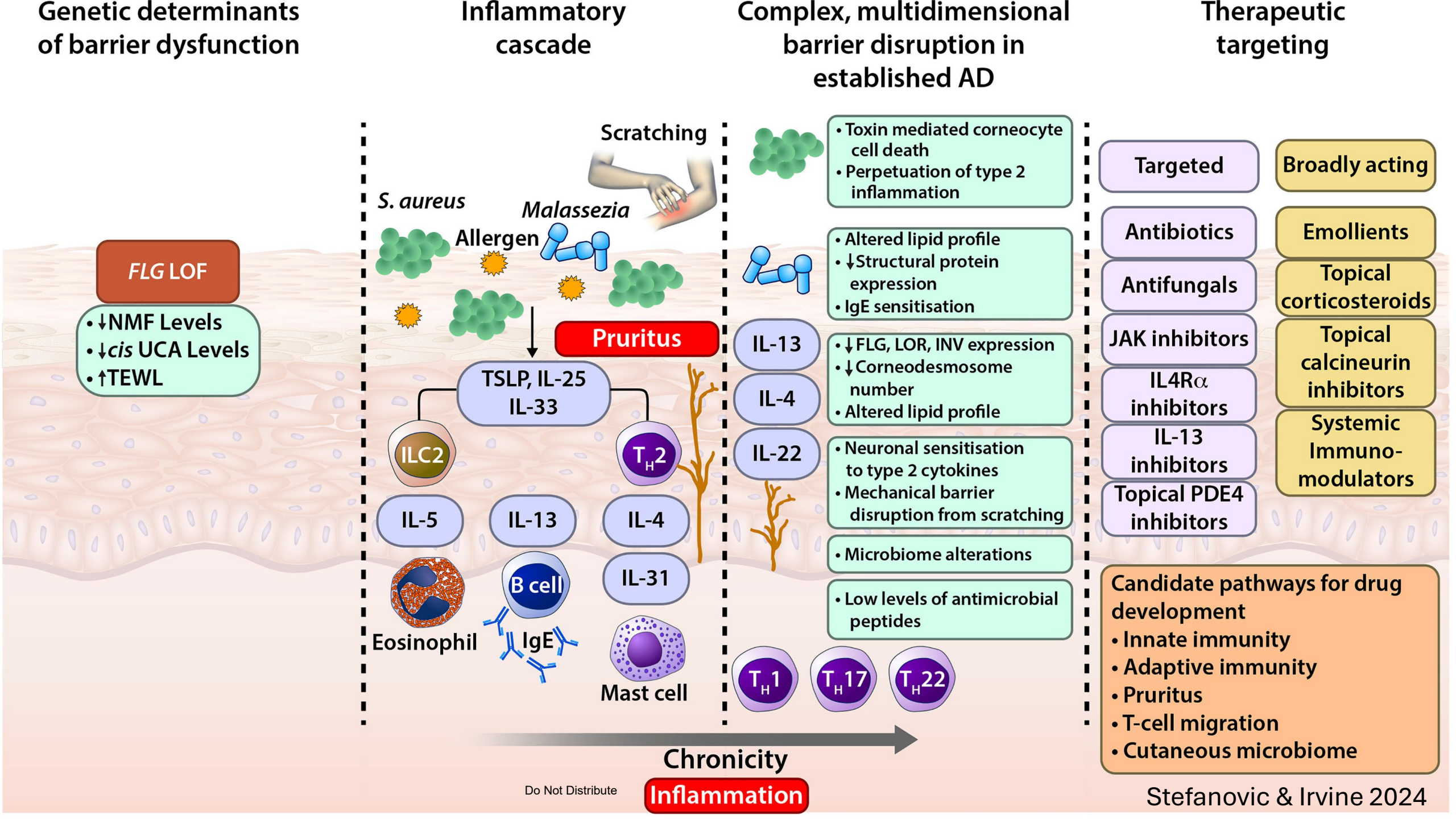
- Decreased bacterial diversity in AD (Kong et al. 2012, Callewaert et al. 2020)
- Increase *staphylococcus aureus* in severe AD (Gong et al. 2006)
- *S. aureus* roles in pathogenesis
  - Enhanced protease activity and downregulation of skin barrier proteins
  - Upregulation of proinflammatory cytokines (TSLP, IL-4, IL-12, IL-22)
  - Stimulate mast cell degranulation
  - Induced t cell independent B cell expansion
  - Decrease in more protective bacteria
  - Superantigens induce cytokine production and IgE production (Niebuhr et al. 2010)
- Treatment with dupilumab increases microbial diversity and decreases *S. aureus* (Callewaert et al. 2020)
- *Malassezia* implicated in skin barrier dysfunction, inflammation, and head and neck AD (Glatz et al. 2015)

## Genetic determinants of barrier dysfunction

## Inflammatory cascade

## Complex, multidimensional barrier disruption in established AD

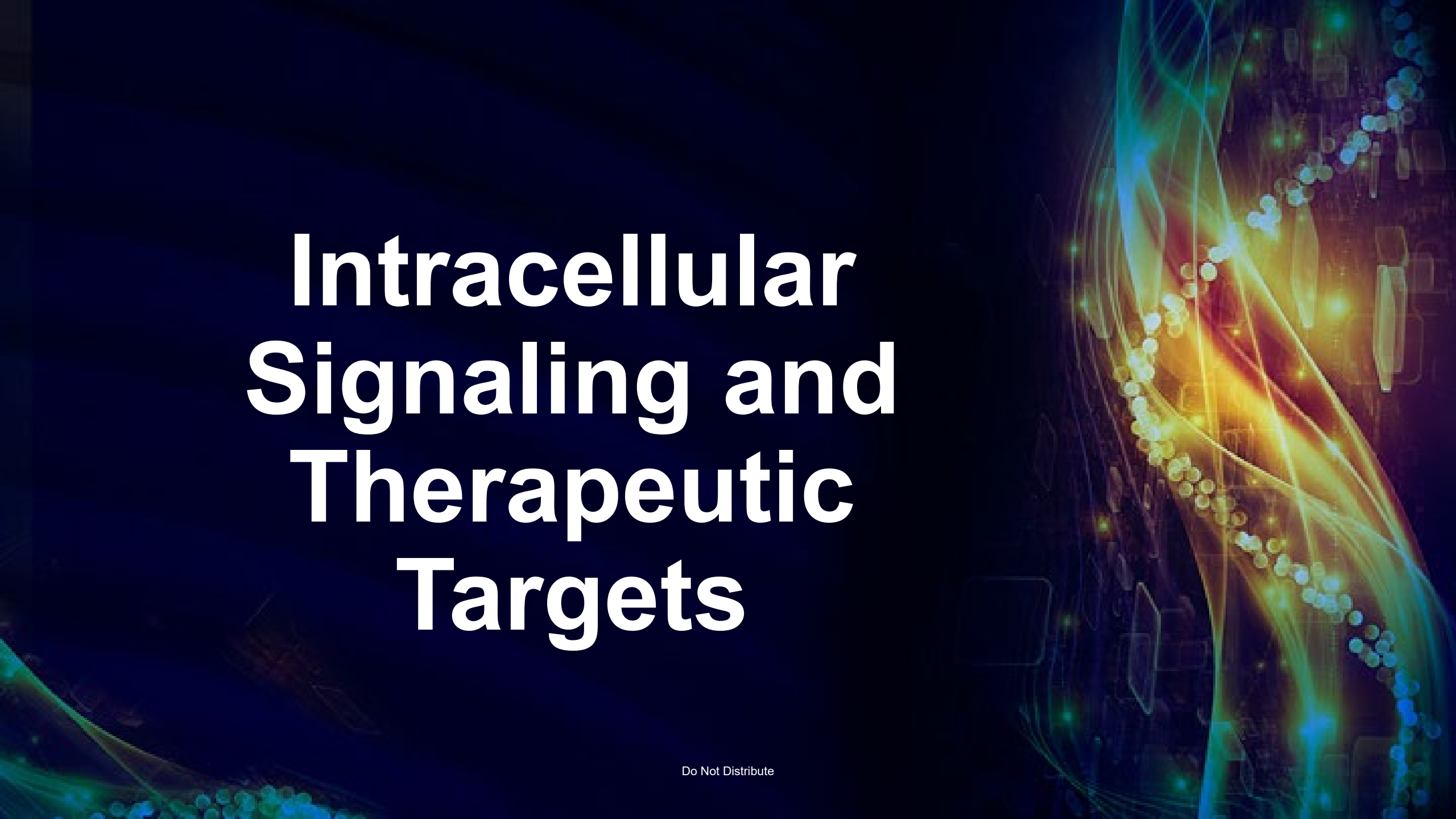
## Therapeutic targeting

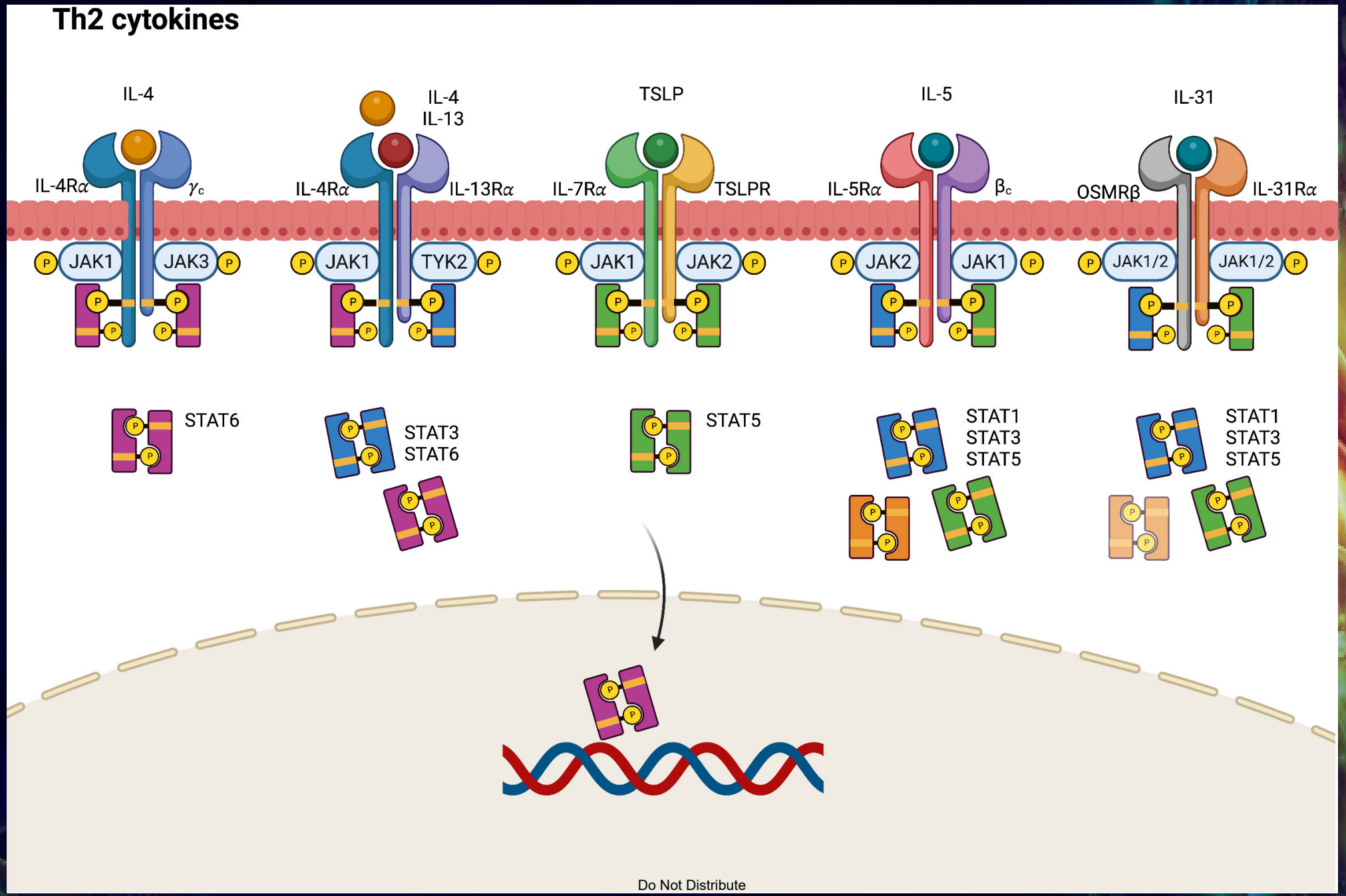




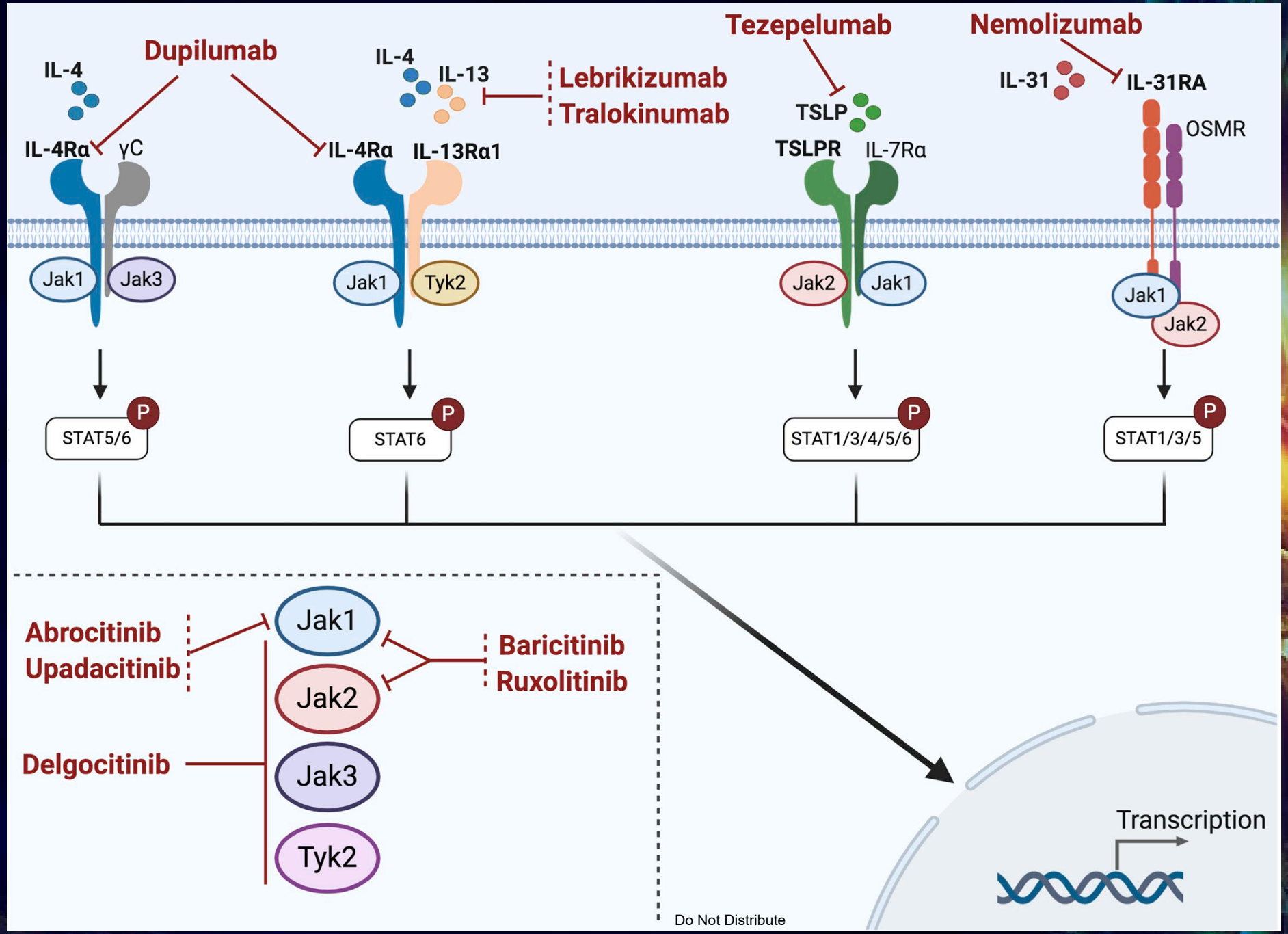

Stefanovic & Irvine 2024

# Intracellular Signaling and Therapeutic Targets





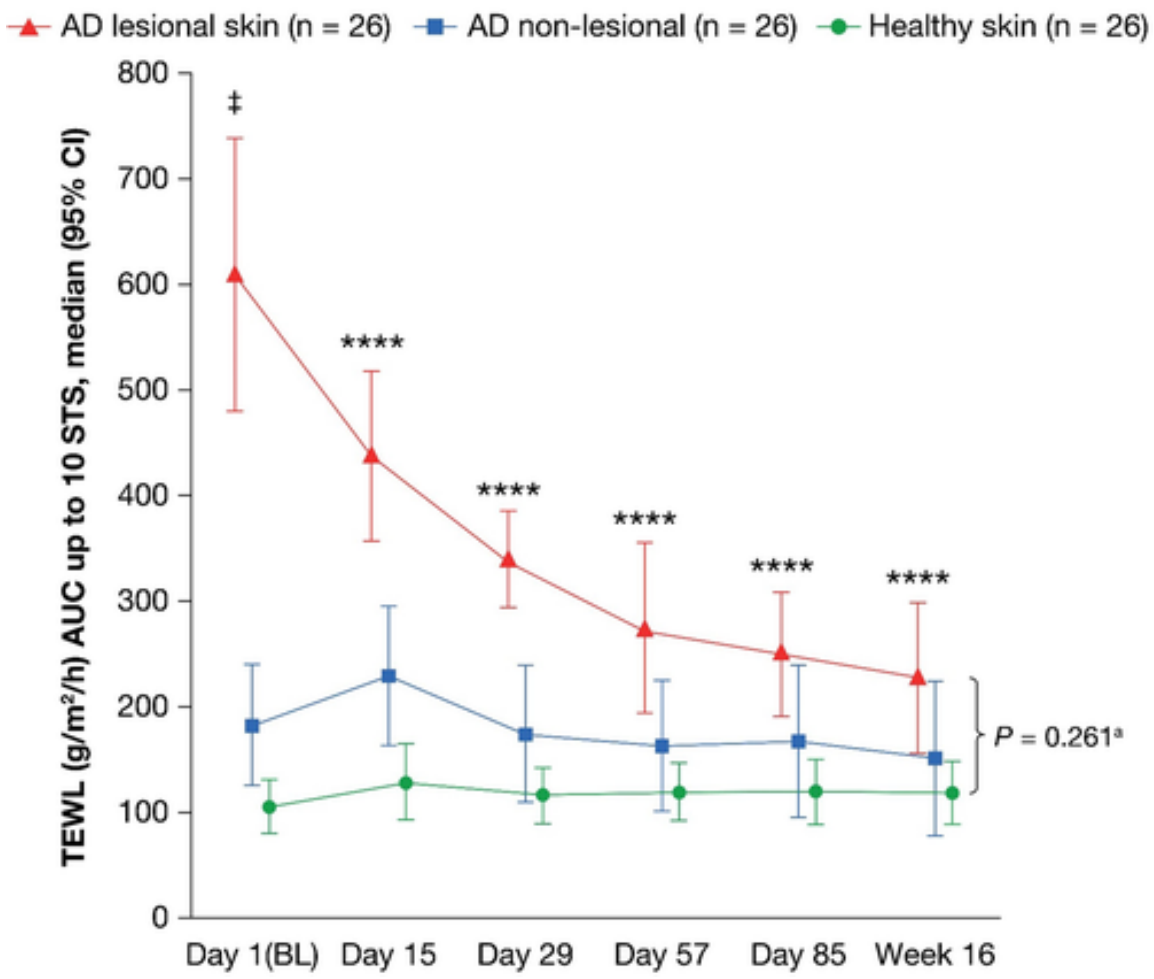

Huang et al. 2022




Abreu and Kim 2021

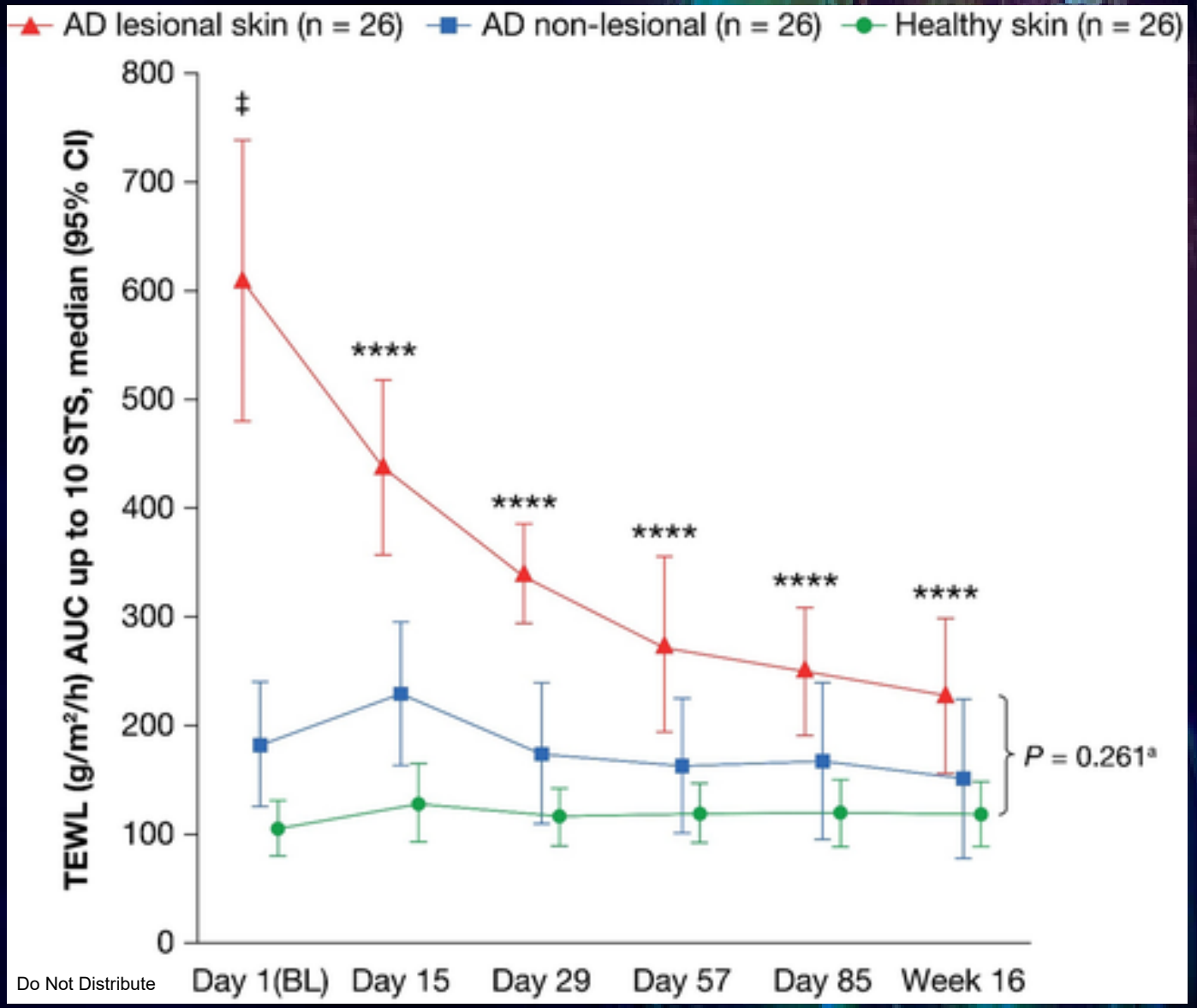
# Effect of Biologics on Skin Barrier

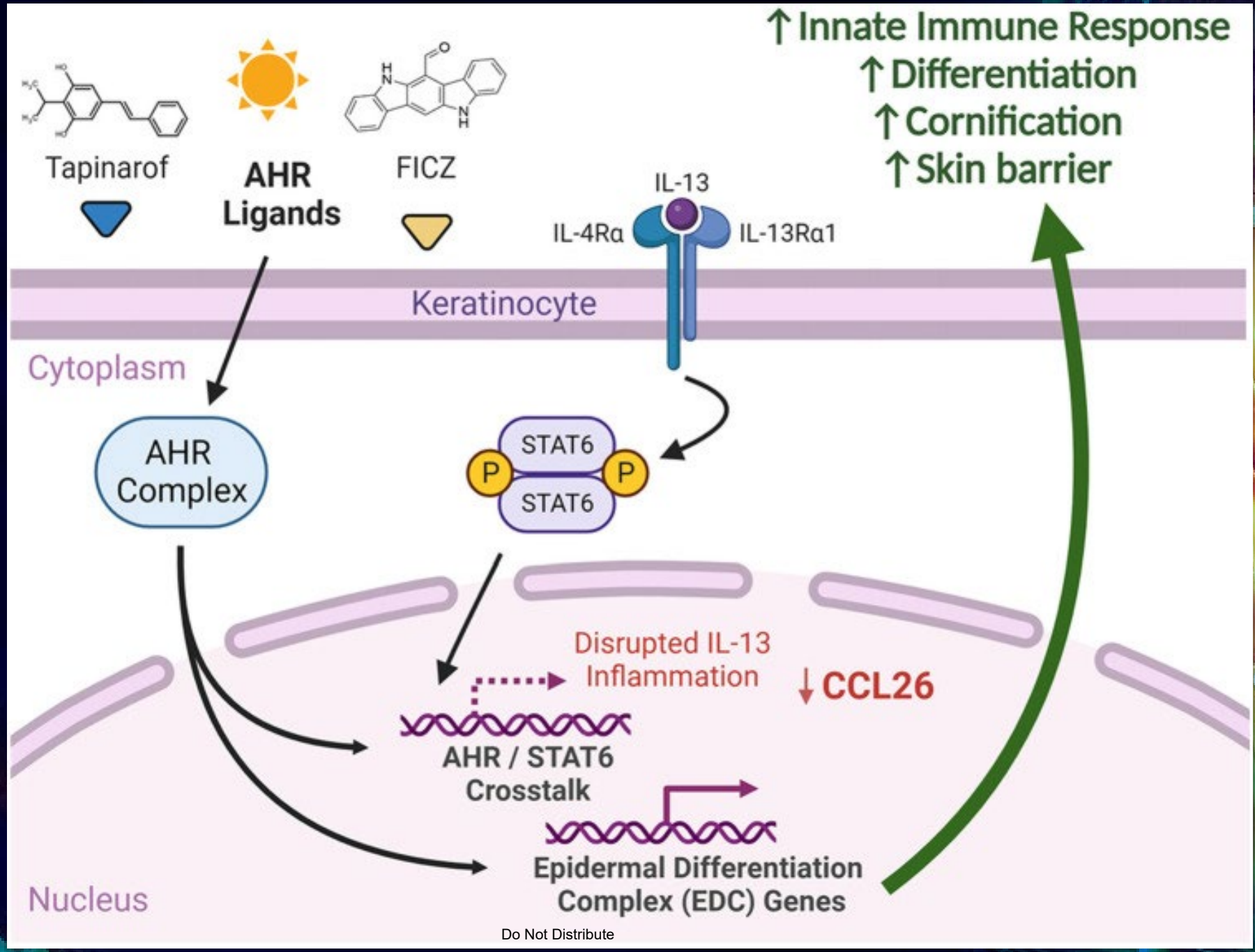
- In adolescents and adults with AD, Dupilumab decreased TEWL, normalized lipid composition, and increased ceramide chain length (Berdyshev et al. 2022)



# Effect of Biologics on Skin Barrier

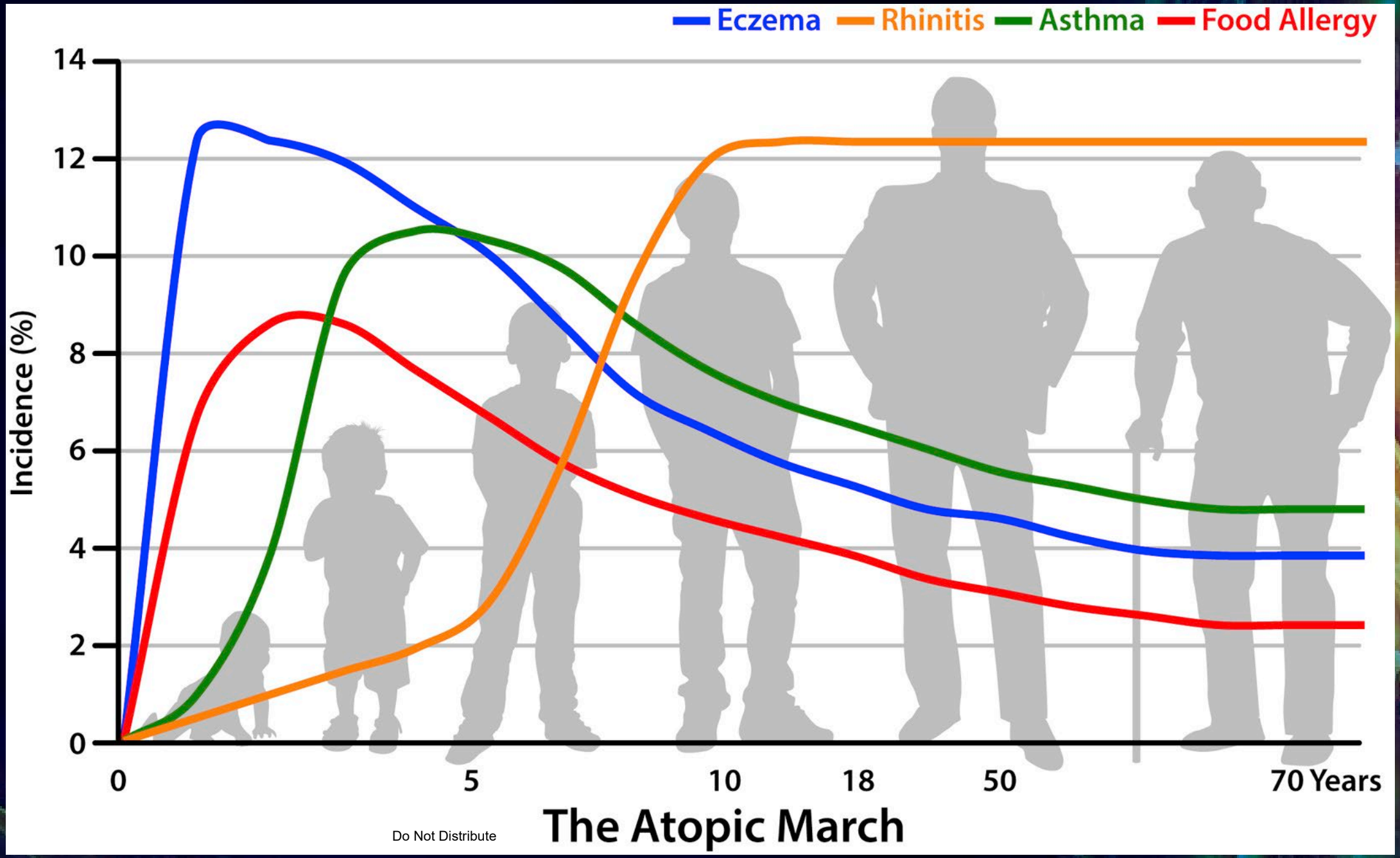
- In adolescents and adults with AD, Dupilumab decreased TEWL, normalized lipid composition, and increased ceramide chain length (Berdyshev et al. 2022)






Proper et al. 2024

# Atopic March



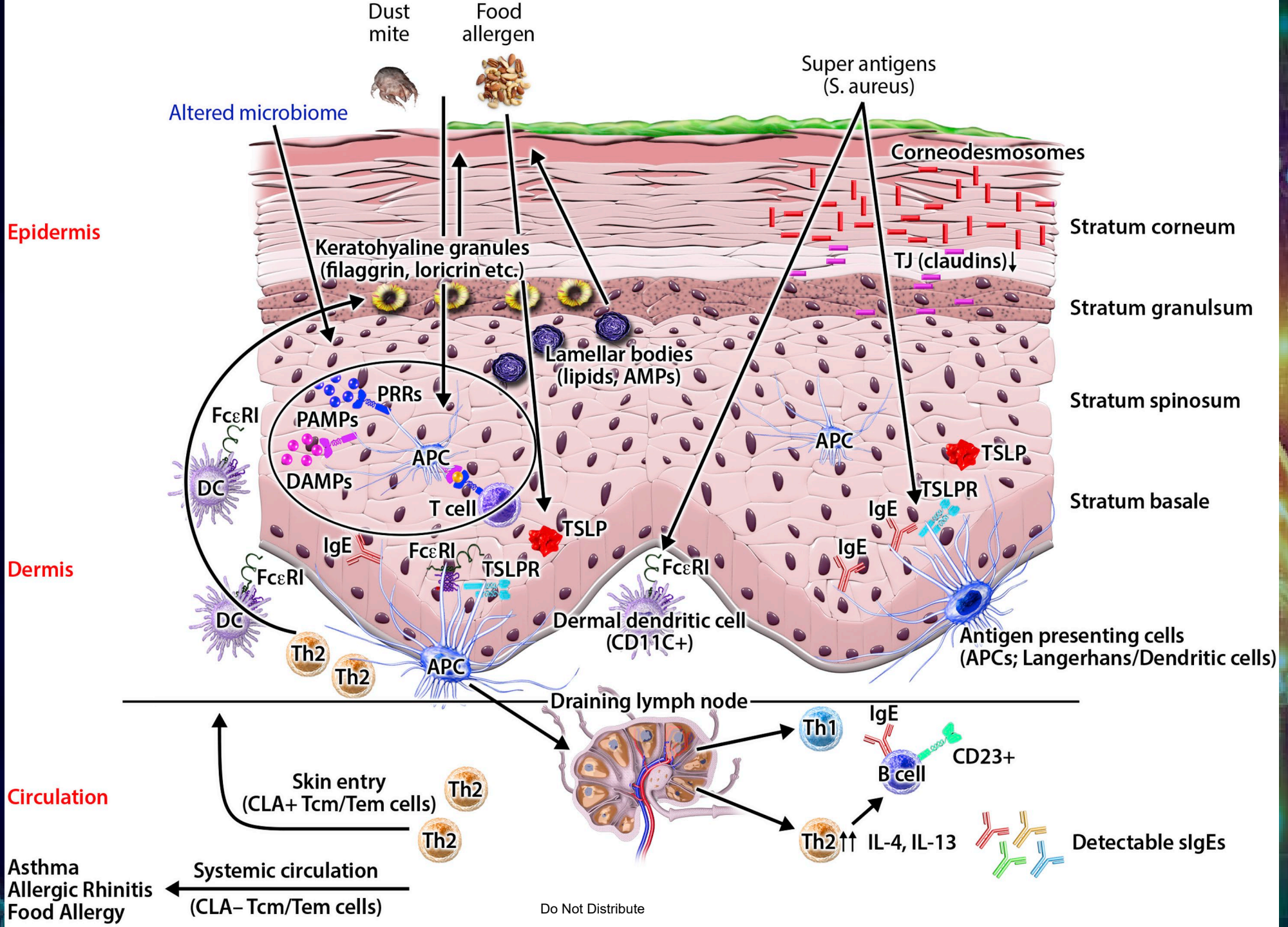

Czarnowicki et al. 2017

# Atopic March Evidence

- Clinical evidence
  - Overall prevalences from birth cohort studies (Rhodes et al. 2002, Gustafsson et al. 2000)
  - Correlation between AD severity and risk of other atopic disease (FA, asthma, allergic rhinitis)
  - Association between peanut allergy and FLG mutations (Brown et al. 2011, Brough et. A 2014)
- Experimental evidence
  - Peanut exposure initiates Th2 responses in mice (Strid et al. 2005)

# Atopic March Mechanism

Impaired skin barrier→ increased allergic sensitization and skewing towards Th2 responses




Czarnowicki et al. 2017

# Key Points

- Atopic dermatitis pathophysiology is complex
- Atopic dermatitis is characterized by epidermal barrier dysfunction and immune dysregulation
- A primary function of skin is to be a barrier from the external environment
- This barrier includes the physical structure of the epidermis and the connection to the immune system
- Skin barrier dysfunction can predispose to type 2 inflammation and atopic dermatitis
- Type 2 inflammation can decrease skin barrier function
- AD pathogenesis includes skewed Th2/Th22 axis but Th1 and Th17 are also implicated

# Key Points Continued

- Genetic predisposition, including FLG deficiency, can increase risk of atopic dermatitis and atopic disease
- There are differing endotypes of AD
- Microbial dysbiosis contributes to AD by inducing inflammatory response and decreasing skin barrier function
- Pathophysiology informs therapeutic interventions
- Therapeutic success helps us to understand pathophysiology
- AD might be the “window” into the development of other atopic conditions and a small subset follow the prototypical atopic march

# References


- Abreu D, Kim BS. Innate Immune Regulation of Dermatitis. Immunol Allergy Clin North Am. 2021 Aug;41(3):347-359. doi: 10.1016/j.iac.2021.04.011. Epub 2021 Jun 5. PMID: 34225893.
- Bantz SK, Zhu Z, Zheng T. The Atopic March: Progression from Atopic Dermatitis to Allergic Rhinitis and Asthma. J Clin Cell Immunol. 2014;5(2):202. doi:10.4172/2155-9899.1000202
- Berdyshev E, Kim J, Kim BE, et al. Stratum corneum lipid and cytokine biomarkers at age 2 months predict the future onset of atopic dermatitis. J Allergy Clin Immunol. 2023;151(5):1307-1316. doi:10.1016/j.jaci.2023.02.013
- Berdyshev E, Goleva E, Bissonnette R, et al. Dupilumab significantly improves skin barrier function in patients with moderate-to-severe atopic dermatitis. *Allergy*. 2022;77(11):3388-3397. doi:10.1111/all.15432
- Bissonnette R, Goleva E, Berdyshev E, et al. Dupilumab treatment restores lesional and non-lesional skin barrier function in adults and adolescents with atopic dermatitis irrespective of the filaggrin genotype: Results from an open-label, healthy-control-matched, phase 4 clinical study (BALISTAD). J Am Acad Dermatol. Published online January 22, 2025. doi:10.1016/j.jaad.2024.11.079
- Brough HA, Simpson A, Makinson K, et al. Peanut allergy: effect of environmental peanut exposure in children with filaggrin loss-of-function mutations [published correction appears in J Allergy Clin Immunol. 2014 Dec;134(6):1468. doi: 10.1016/j.jaci.2014.10.024.]. J Allergy Clin Immunol. 2014;134(4):867-875.e1. doi:10.1016/j.jaci.2014.08.011
- Brown SJ, Asai Y, Cordell HJ, et al. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. J Allergy Clin Immunol. 2011;127(3):661-667. doi:10.1016/j.jaci.2011.01.031
- Brunner PM, He H, Pavel AB, et al. The blood proteomic signature of early-onset pediatric atopic dermatitis shows systemic inflammation and is distinct from adult long-standing disease. J Am Acad Dermatol. 2019;81(2):510-519. doi:10.1016/j.jaad.2019.04.036
- Callewaert C, Nakatsuji T, Knight R, et al. IL-4Rα Blockade by Dupilumab Decreases Staphylococcus aureus Colonization and Increases Microbial Diversity in Atopic Dermatitis. J Invest Dermatol. 2020;140(1):191-202.e7. doi:10.1016/j.jid.2019.05.024
- Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. J Allergy Clin Immunol. 2017 Jun;139(6):1723-1734. doi: 10.1016/j.jaci.2017.04.004. PMID: 28583445.
- Czarnowicki T, Gonzalez J, Shemer A, et al. Severe atopic dermatitis is characterized by selective expansion of circulating TH2/TC2 and TH22/TC22, but not TH17/TC17, cells within the skin-homing T-cell population. J Allergy Clin Immunol. 2015;136(1):104-115.e7. doi:10.1016/j.jaci.2015.01.020
- Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143(1):1-11. doi:10.1016/j.jaci.2018.10.032
- Danso MO, van Drongelen V, Mulder A, et al. TNF-α and Th2 cytokines induce atopic dermatitis-like features on epidermal differentiation proteins and stratum corneum lipids in human skin equivalents. J Invest Dermatol. 2014;134(7):1941-1950. doi:10.1038/jid.2014.83
- De Benedetto A, Rafaels NM, McGirt LY, et al. Tight junction defects in patients with atopic dermatitis. J Allergy Clin Immunol. 2011;127(3):773-86.e867. doi:10.1016/j.jaci.2010.10.018
- Gasteiger G, Rudensky AY. Interactions between innate and adaptive lymphocytes. Nat Rev Immunol. 2014 Sep;14(9):631-9. doi: 10.1038/nri3726. Epub 2014 Aug 18. PMID: 25132095; PMCID: PMC4504695.
- Glatz M, Bosshard PP, Hoetzenecker W, Schmid-Grendelmeier P. The Role of Malassezia spp. in Atopic Dermatitis. J Clin Med. 2015;4(6):1217-1228. Published 2015 May 29. doi:10.3390/jcm4061217

# References


- Gittler JK, Shemer A, Suárez-Fariñas M, et al. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. J Allergy Clin Immunol. 2012;130(6):1344-1354. doi:10.1016/j.jaci.2012.07.012
- Gong JQ, Lin L, Lin T, et al. Skin colonization by Staphylococcus aureus in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial. Br J Dermatol. 2006;155(4):680-687. doi:10.1111/j.1365-2133.2006.07410.x
- Gustafsson D, Sjöberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis--a prospective follow-up to 7 years of age. Allergy. 2000;55(3):240-245. doi:10.1034/j.1398-9995.2000.00391.x
- Guttman-Yassky E, Suárez-Fariñas M, Chiricozzi A, Nograles KE, Shemer A, Fuentes-Duculan J, Cardinale I, Lin P, Bergman R, Bowcock AM, Krueger JG. Broad defects in epidermal cornification in atopic dermatitis identified through genomic analysis. J Allergy Clin Immunol. 2009 Dec;124(6):1235-1244.e58. doi: 10.1016/j.jaci.2009.09.031. PMID: 20004782.
- Hamid Q, Boguniewicz M, Leung DY. Differential in situ cytokine gene expression in acute versus chronic atopic dermatitis. J Clin Invest. 1994;94(2):870-876. doi:10.1172/JCI117408
- Hönzke S, Wallmeyer L, Ostrowski A, et al. Influence of Th2 Cytokines on the Cornified Envelope, Tight Junction Proteins, and ß-Defensins in Filaggrin-Deficient Skin Equivalents. J Invest Dermatol. 2016;136(3):631-639. doi:10.1016/j.jid.2015.11.007
- Huang IH, Chung WH, Wu PC, Chen CB. JAK-STAT signaling pathway in the pathogenesis of atopic dermatitis: An updated review. Front Immunol. 2022 Dec 8;13:1068260. doi: 10.3389/fimmu.2022.1068260. PMID: 36569854; PMCID: PMC9773077.
- Holloway JW. The genetics of allergic disease and asthma. In: Leung DYM, Akdis CA, Bacharier LB, et al., eds. Pediatric Allergy Principles and Practice. 4th ed. Philadelphia: Elsevier; 2021. Fig. 3.3, p 22
- Howell MD, Kim BE, Gao P, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. J Allergy Clin Immunol. 2007;120(1):150-155. doi:10.1016/j.jaci.2007.04.031
- Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases. N Engl J Med. 2011;365(14):1315-1327.

# References


- Kabashima K, Honda T, Ginhoux F, Egawa G. The immunological anatomy of the skin. Nat Rev Immunol. 2019;19(1):19-30.
- Kong HH, Oh J, Deming C, et al. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. Genome Res. 2012;22(5):850-859. doi:10.1101/gr.131029.111
- Leung DYM, Calatroni A, Zaramela LS, et al. The nonlesional skin surface distinguishes atopic dermatitis with food allergy as a unique endotype. Sci Transl Med. 2019;11(480):eaav2685. doi:10.1126/scitranslmed.aav2685
- Leung DYM, Berdyshev E, Goleva E. Cutaneous barrier dysfunction in allergic diseases [published correction appears in J Allergy Clin Immunol. 2021 Sep;148(3):905. doi: 10.1016/j.jaci.2021.06.014.]. J Allergy Clin Immunol. 2020;145(6):1485-1497. doi:10.1016/j.jaci.2020.02.021
- Niebuhr M, Scharonow H, Gathmann M, Mamerow D, Werfel T. Staphylococcal exotoxins are strong inducers of IL-22: A potential role in atopic dermatitis. J Allergy Clin Immunol. 2010;126(6):1176-83.e4. doi:10.1016/j.jaci.2010.07.041
- Proper SP, Dwyer AT, Appiagyei A, et al. Aryl hydrocarbon receptor and IL-13 signaling crosstalk in human keratinocytes and atopic dermatitis. Front Allergy. 2024;5:1323405.
- Rhodes HL, Sporik R, Thomas P, Holgate ST, Cogswell JJ. Early life risk factors for adult asthma: a birth cohort study of subjects at risk. J Allergy Clin Immunol. 2001;108(5):720-725. doi:10.1067/mai.2001.119151
- Stefanovic N, Irvine AD. Filaggrin and beyond: New insights into the skin barrier in atopic dermatitis and allergic diseases, from genetics to therapeutic perspectives. Ann Allergy Asthma Immunol. 2024;132(2):187-195.
- Smits JPH, van den Brink NJM, Meesters LD, et al. Investigations into the FLG Null Phenotype: Showcasing the Methodology for CRISPR/Cas9 Editing of Human Keratinocytes. J Invest Dermatol. 2023;143(8):1520-1528.e5.
- Suárez-Fariñas M, Tintle SJ, Shemer A, et al. Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities. J Allergy Clin Immunol. 2011;127(4):954-64.e644. doi:10.1016/j.jaci.2010.12.1124
- Sander N, Stölzl D, Fonfara M, et al. Blockade of interleukin-13 signalling improves skin barrier function and biology in patients with moderate-to-severe atopic dermatitis. Br J Dermatol. 2024;191(3):344-350. doi:10.1093/bjd/ljae138
- Strid J, Hourihane J, Kimber I, Callard R, Strobel S. Epicutaneous exposure to peanut protein prevents oral tolerance and enhances allergic sensitization. Clin Exp Allergy. 2005;35(6):757-766. doi:10.1111/j.1365-2222.2005.02260.x