



Signaling Pathways in the Pathophysiology of Atopic Dermatitis

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Disclosures

- › Investigator, Regeneron, Incyte
- › Advisory Boards, Regeneron, Sanofi-Genzyme, Abbvie, Leo, Lilly, Pfizer, Janssen

Learning Objectives

Upon completion of this learning activity, participants should be able to:

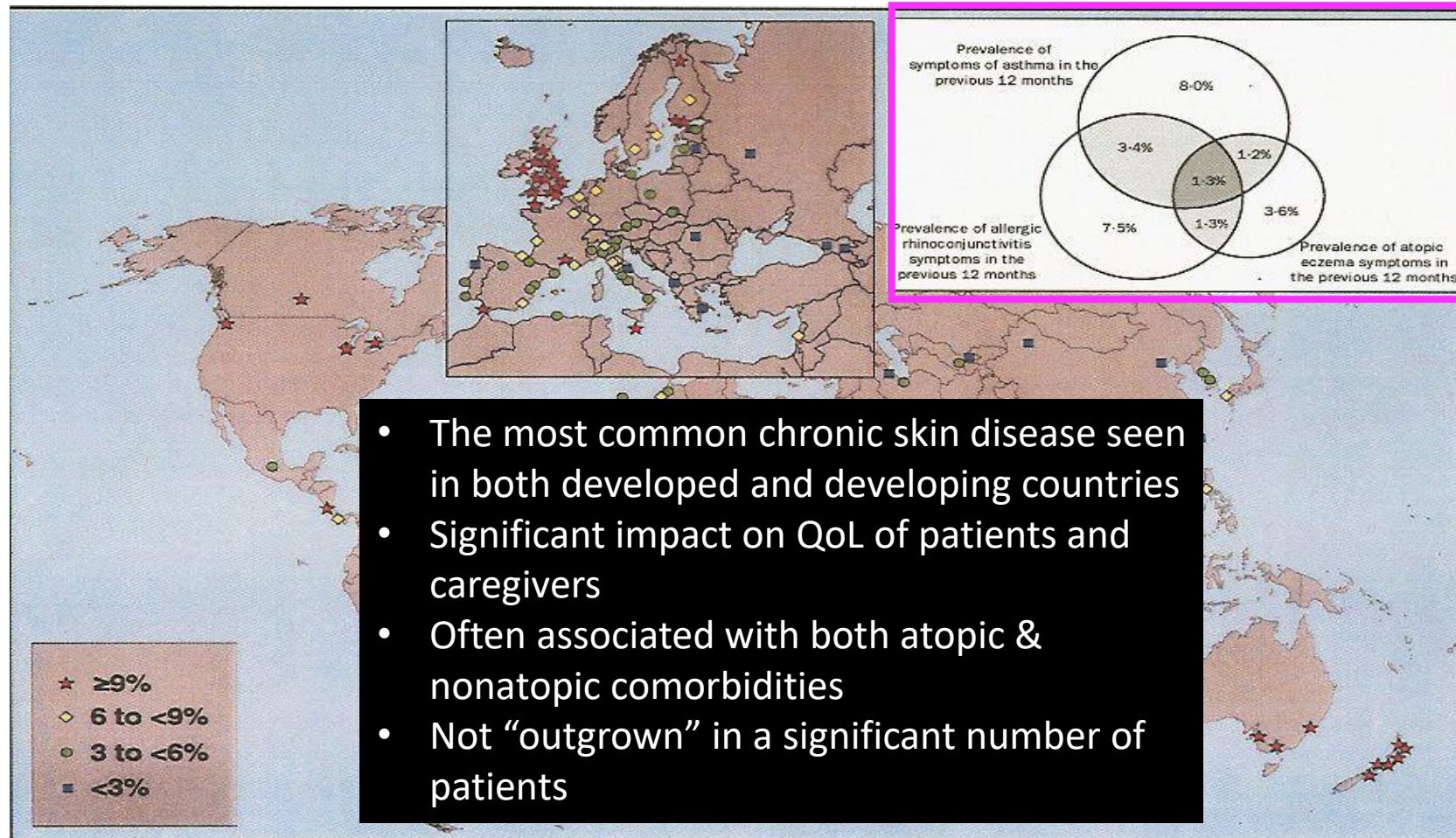
1. Describe skin barrier and immune abnormalities implicated in the pathophysiology of atopic dermatitis
2. Recognize therapeutic implications of key research insights for targeted therapies in atopic dermatitis

Clinical vignette

- › You are asked to see Noel, a 22 year old college student with a history of chronic pruritic eczematous rash present since infancy involves his face, trunk and all 4 extremities including flexural aspects
- › Course complicated by superficial skin infections including with MRSA as well as past history of localized HSV infection, but no recurrence; no history of deep seated abscesses or PNAs, no warts or molluscum
- › Intermittent asthma treated with prn ICS & SABA and SAR treated with prn antihistamines
- › He wants to understand his illness...what lies beneath, not just here for another Rx!



Global variations in prevalence of eczema symptoms in children from ISAAC Phase



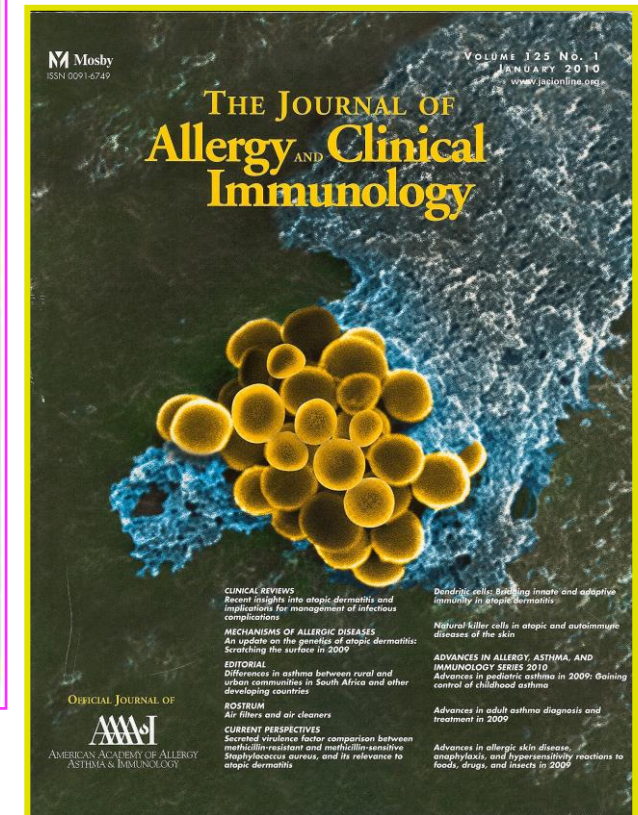
Recent insights into atopic dermatitis and implications for management of infectious complications

Increased susceptibility to infection or colonization with microbial organisms: *S. aureus**, Herpes simplex

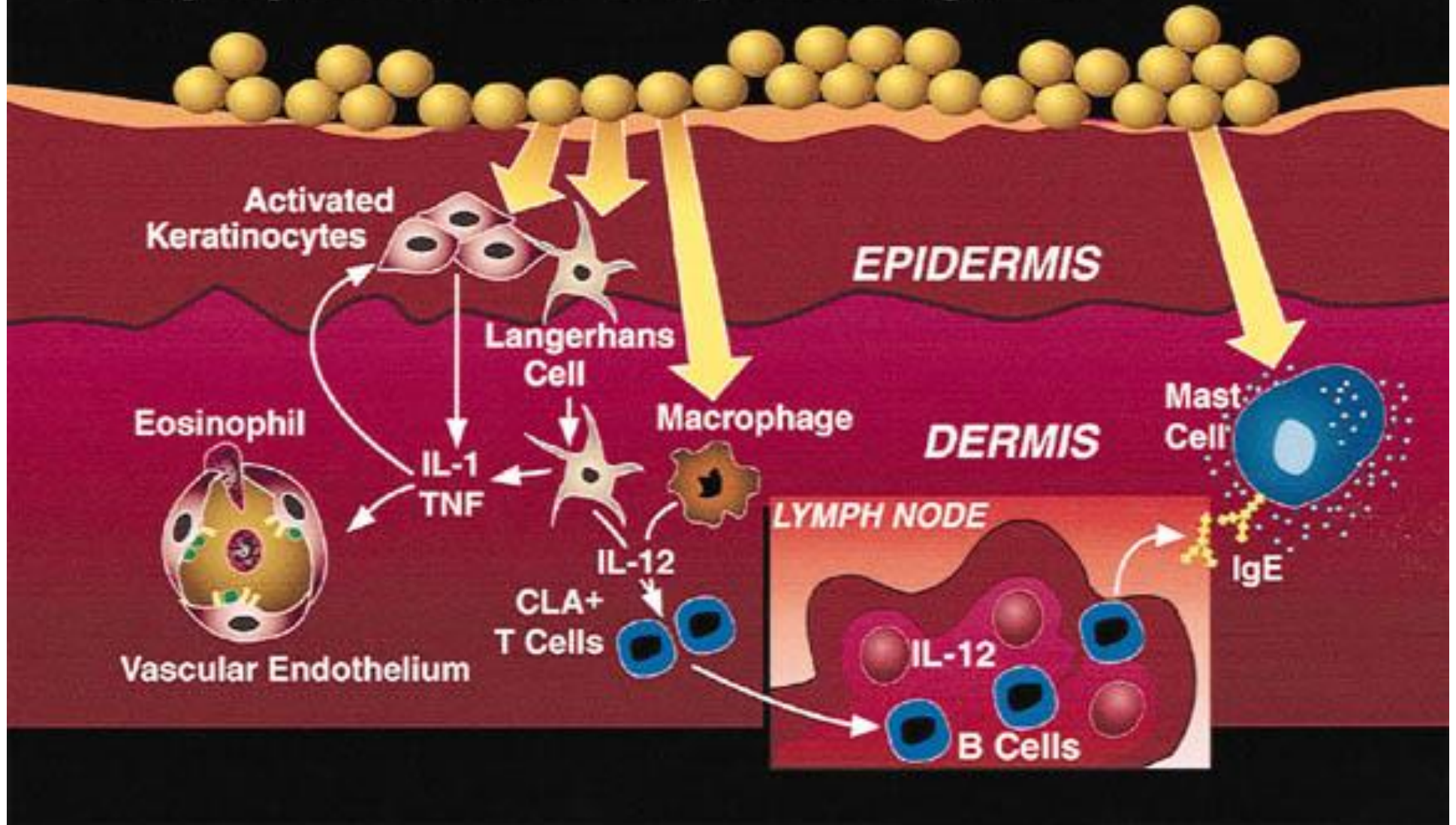


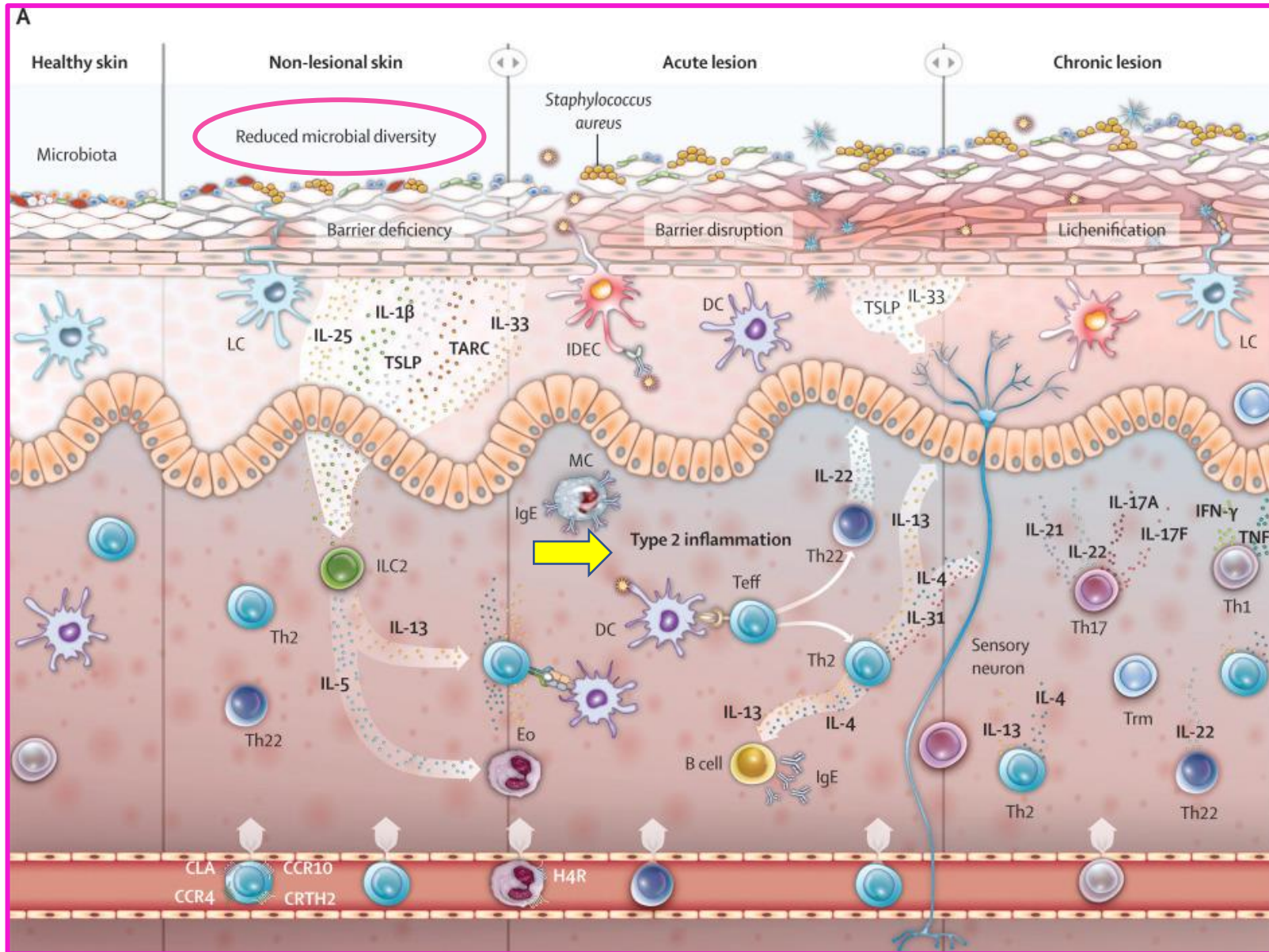
*epidemic of CA-MRSA in US

Boguniewicz M, et al. J Allergy Clin Immunol 2010;125:4

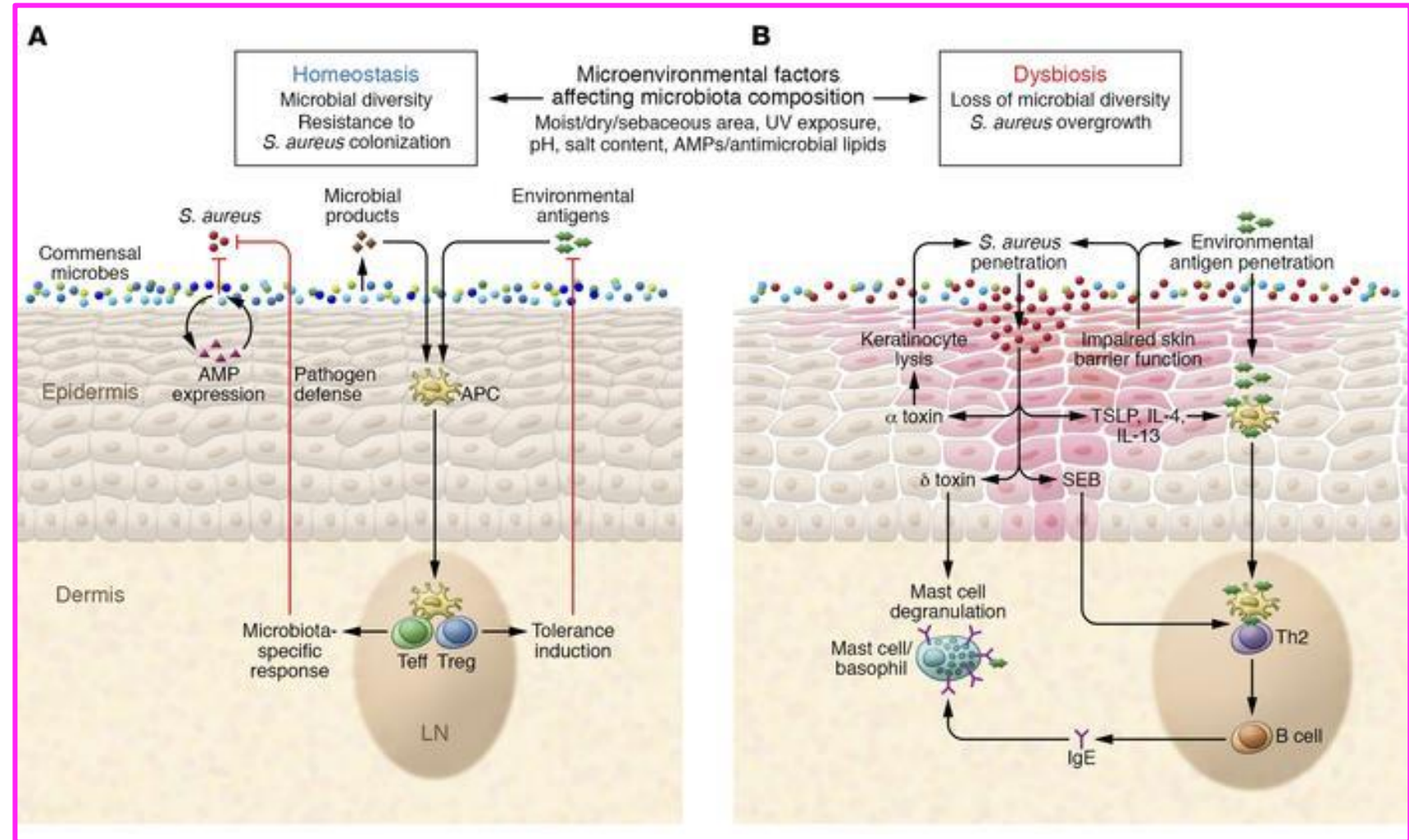


Staphylococcal Superantigens





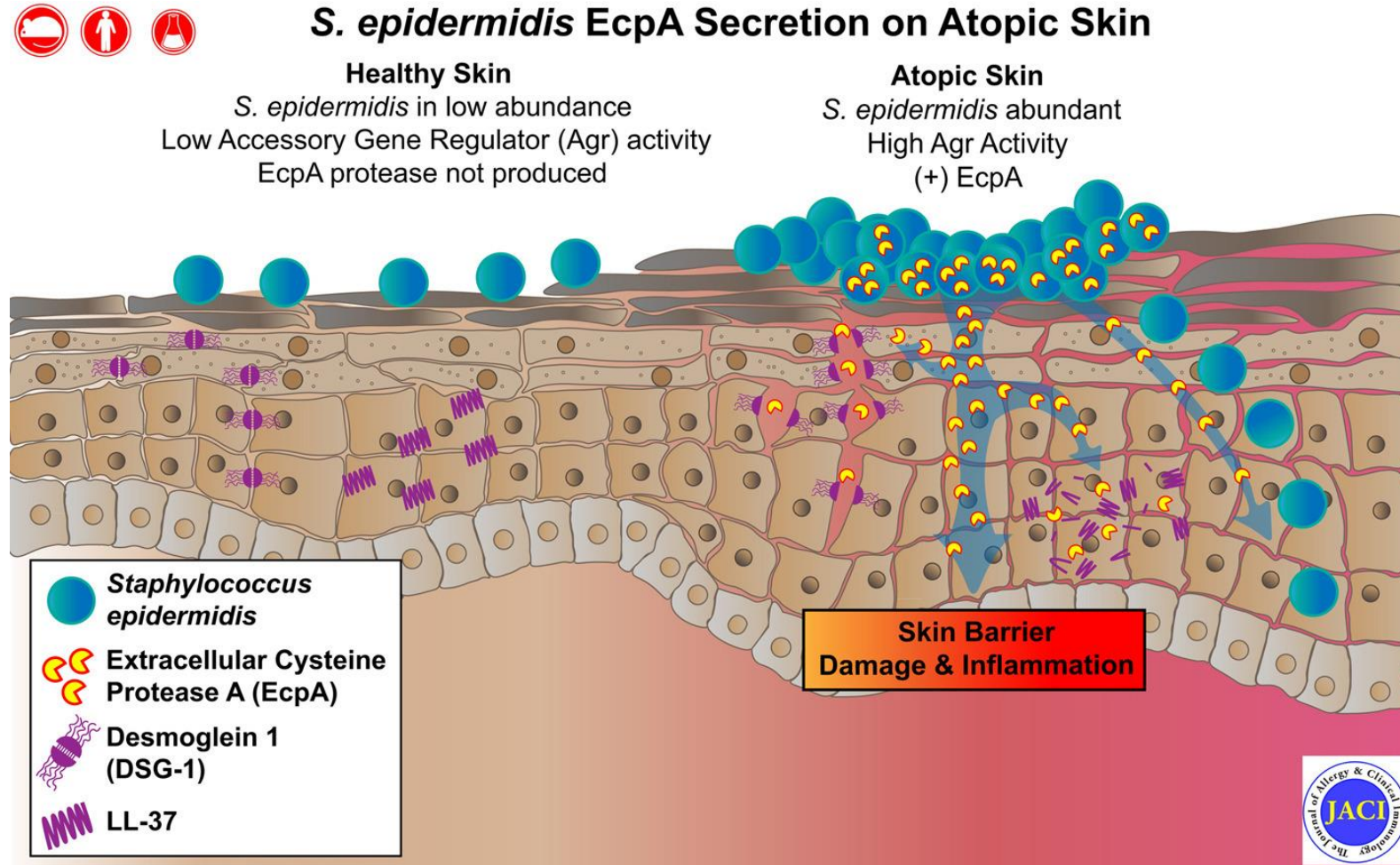
Skin commensals and intact skin barrier promote tolerance induction, while skin barrier impairment and dysbiosis can drive type 2 inflammation



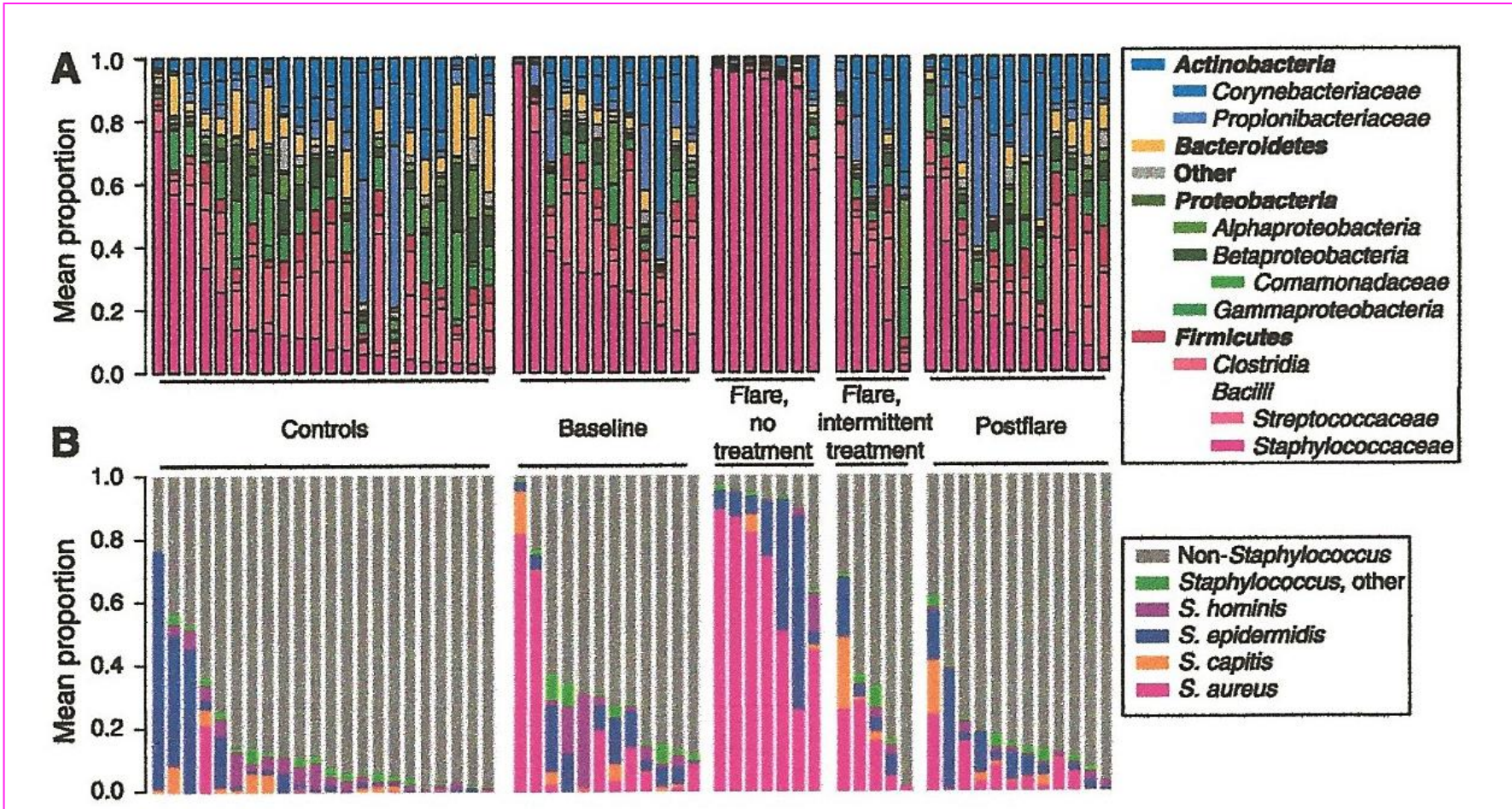
Atopic dermatitis subjects colonized with *S. aureus* have a distinct phenotype and endotype

- › Compared to *S. aureus* (-) AD pts, *S. aureus* (+) AD pts had more severe disease based on all scoring systems except itch (NRS)
 - › higher levels of type 2 biomarkers (eosinophil count, tlgE, CCL17, and periostin)
 - › significantly greater allergen sensitization (Phadiatop and tlgE)
 - › greater barrier dysfunction (TEWL and SC integrity) and higher serum LDH
- › *FLG* mutations did not associate with *S. aureus* (+) colonization
- › Adult AD pts colonized with *S. aureus* have more severe disease, greater type 2 immune deviation, allergen sensitization, barrier disruption, and LDH elevation than noncolonized AD subjects

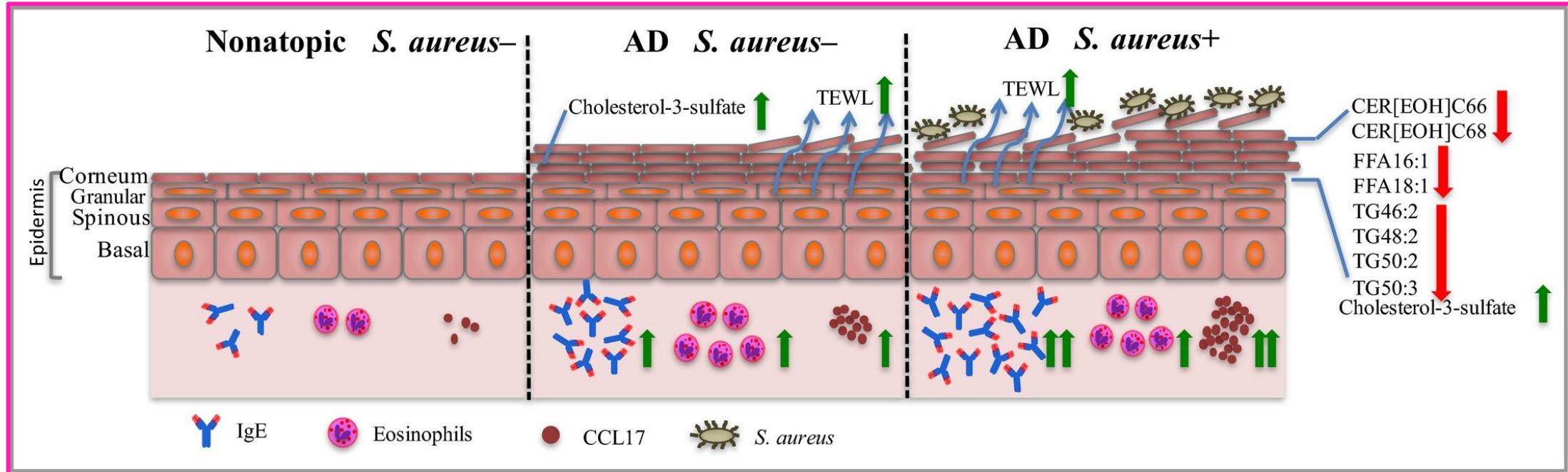
Staphylococcus epidermidis protease EcpA can be a deleterious component of the skin microbiome in atopic dermatitis



Microbiome in AD

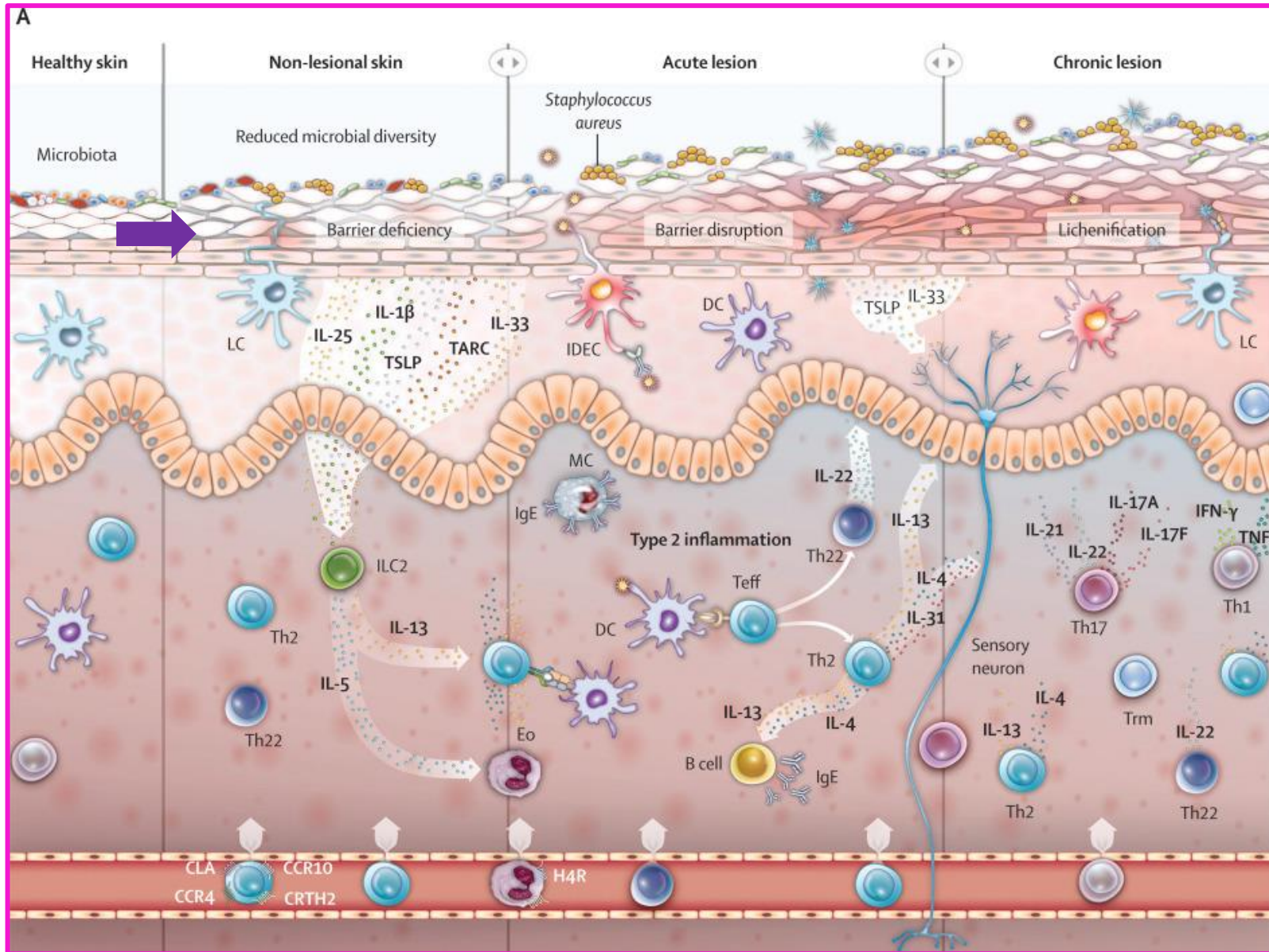


Altered composition of epidermal lipids correlates with *Staphylococcus aureus* colonization status in atopic dermatitis

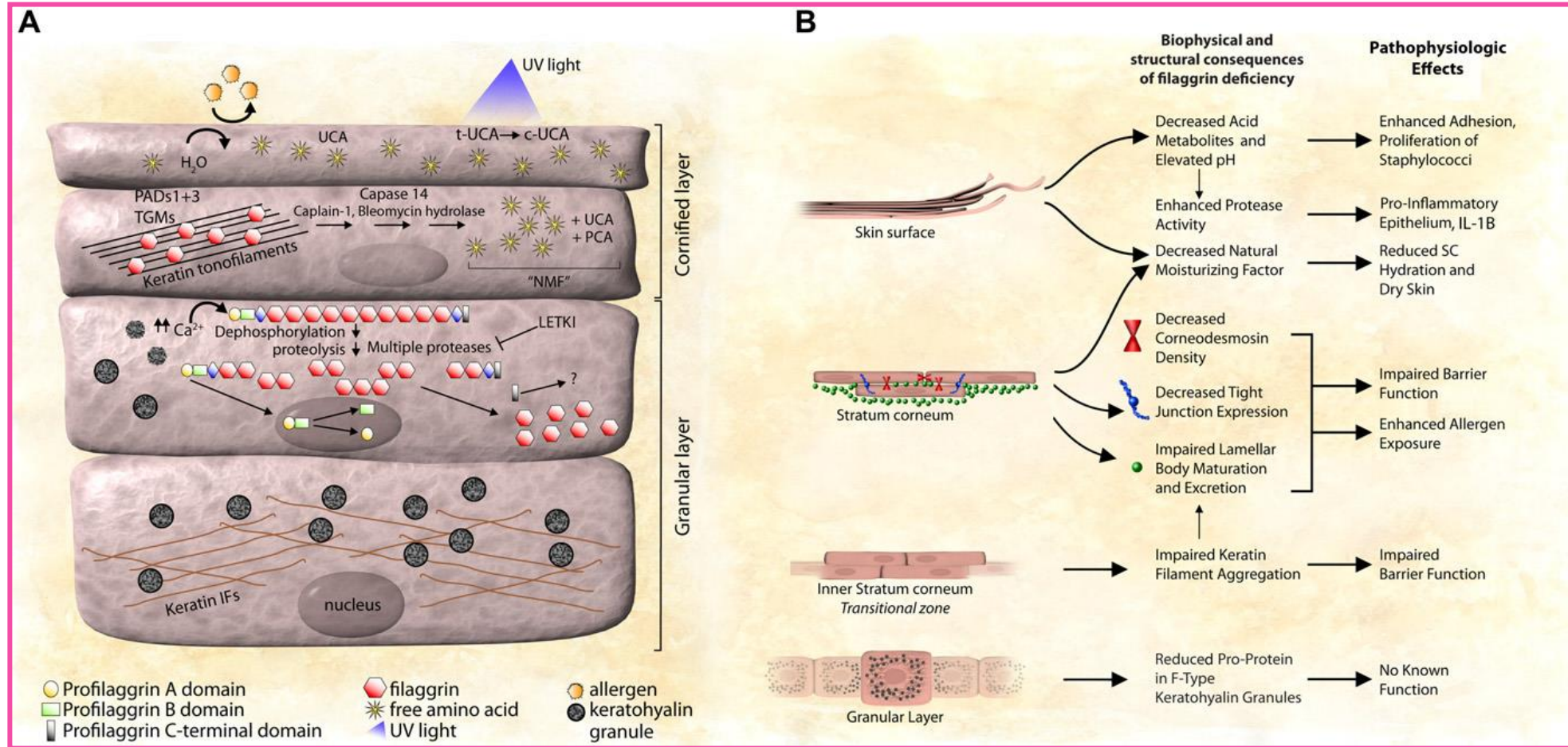


Lipid abnormalities in atopic skin are driven by type 2 cytokines

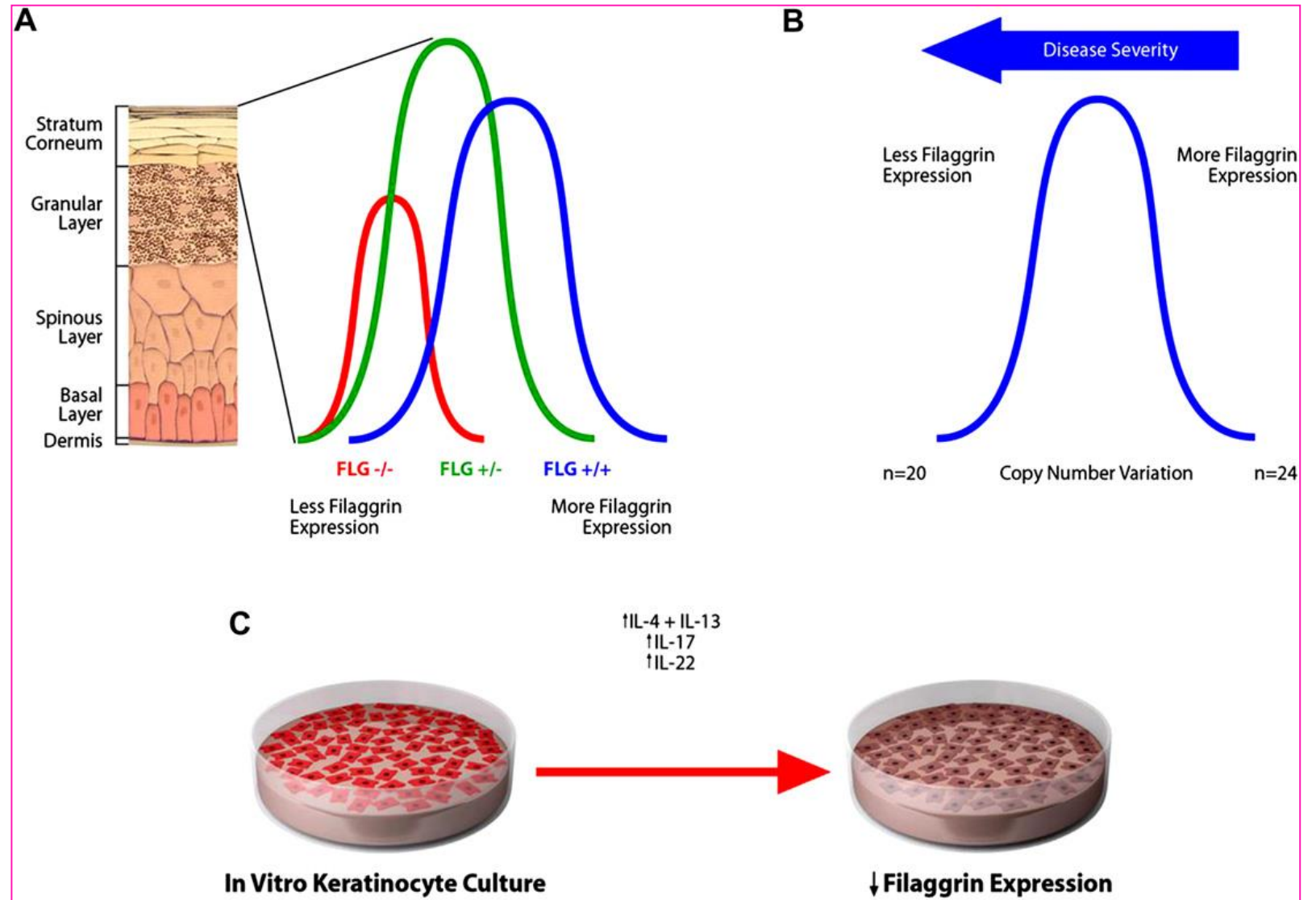
- › Lipids in the stratum corneum of AD patients differ substantially in composition from healthy subjects
- › RNA sequencing analysis performed on stratum corneum of AD as compared with healthy subjects identified decreased expression of fatty acid elongases ELOVL3 and ELOVL6 that contributed to observed changes in atopic skin lipids
- › IL-4/IL-13 inhibited ELOVL3 and ELOVL6 expression in keratinocyte cultures in a STAT6-dependent manner
- › Data strongly support the pathogenic role of type 2 immune activation in AD skin lipid metabolism

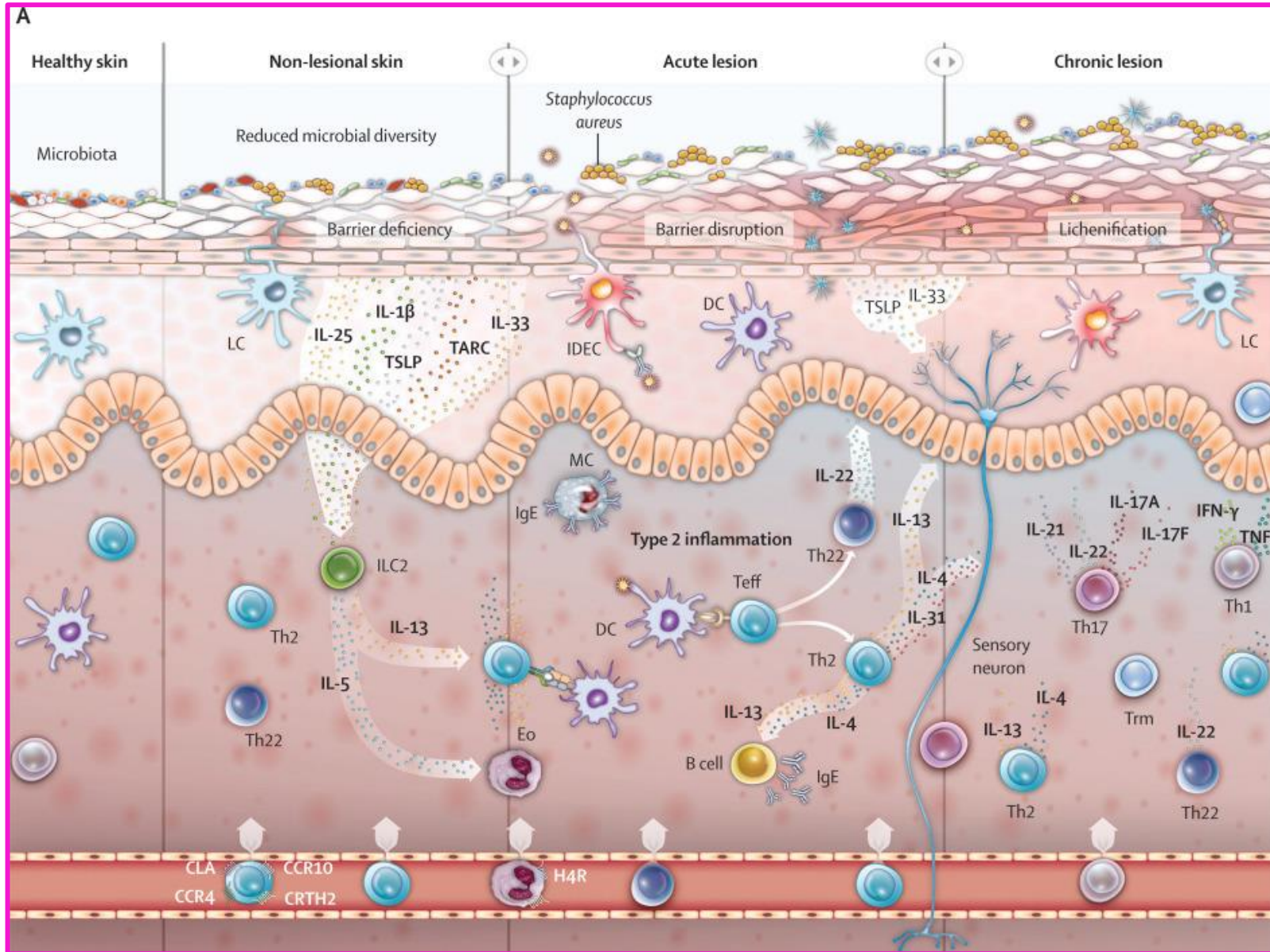


Role of filaggrin in the skin and structural and biophysical consequences of filaggrin deficiency

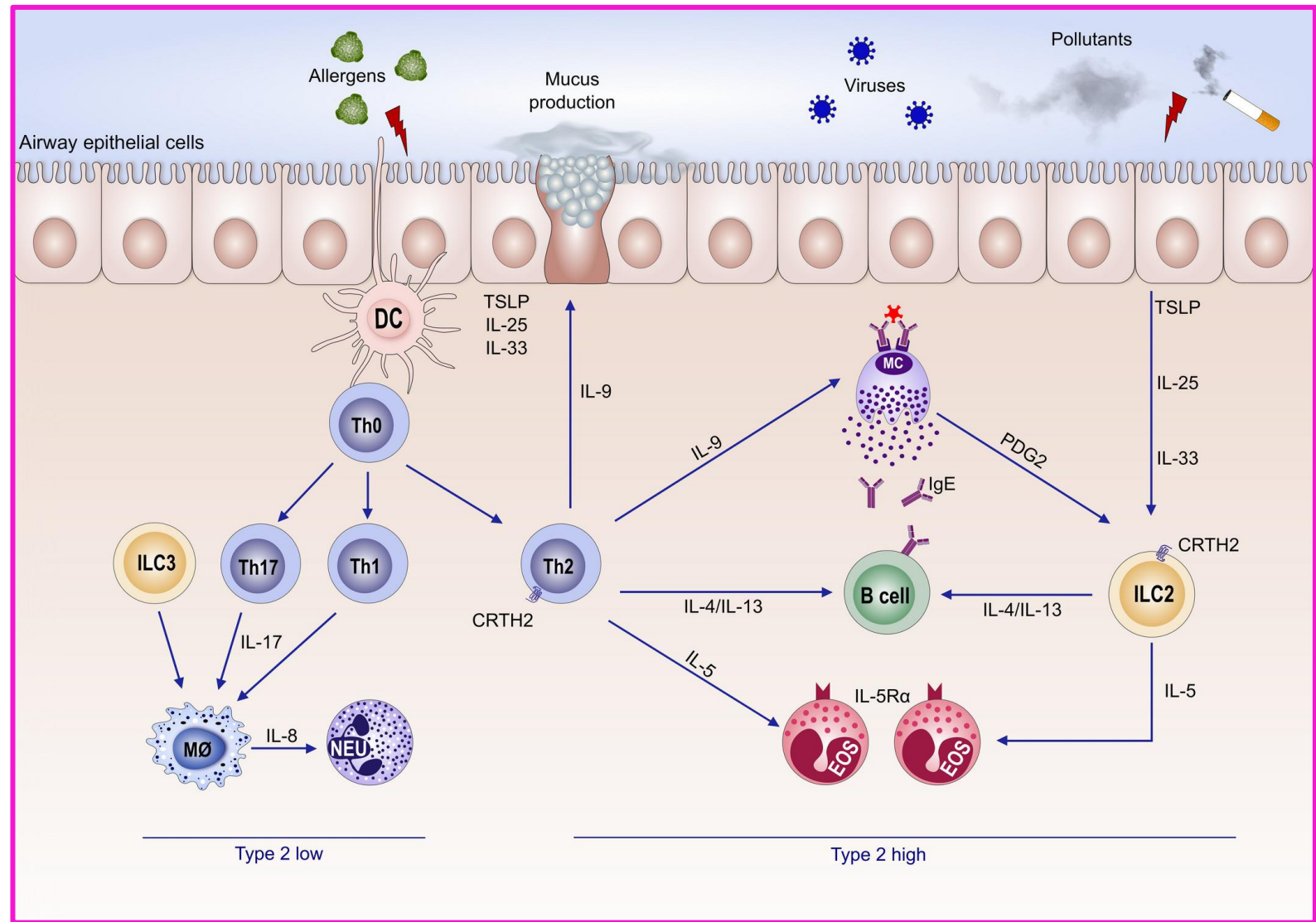


Genetic and immunologic influences on filaggrin expression

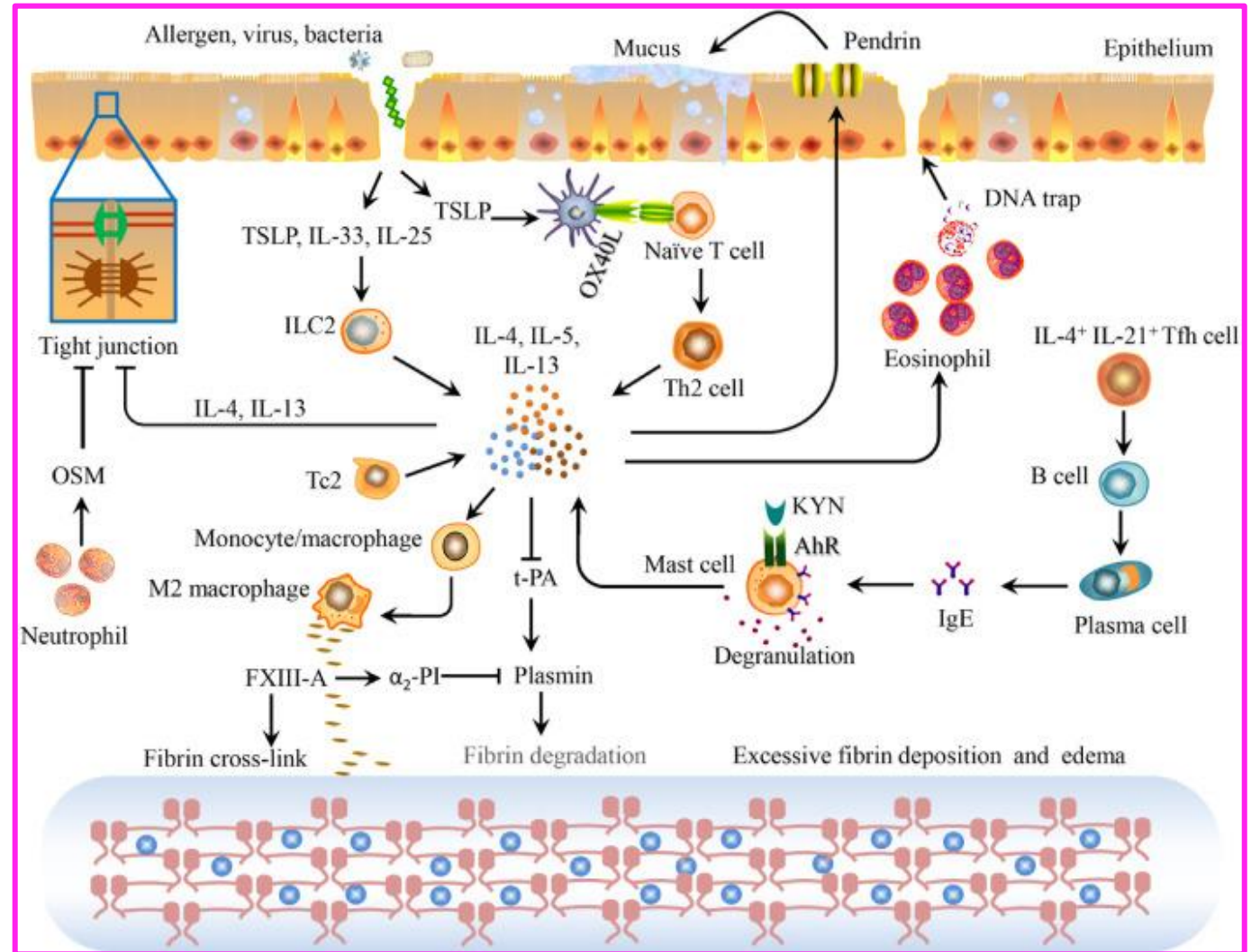




Asthma pathogenesis and type 2 high & low inflammation



Type 2 immune responses in human chronic rhinosinusitis



Role of type 2 cytokines in Atopic Dermatitis

Rapid Publication

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

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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

Rapid communication

In vivo expression of IL-12 and IL-13 in atopic dermatitis

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Eleanor M. Minshall, PhD,^a Yan L. Song, MD,^a Mark Boguniewicz, MD,^b
and Donald Y. M. Leung, MD, PhD^b *Montreal, Quebec, Canada,
and Denver, Colo.*

In vivo expression of cytokine receptor mRNA in atopic dermatitis

Rame A. Taha, MD,^a Donald Y. M. Leung, MD, PhD,^b Omar Ghaffar, BSc,^a Mark Boguniewicz, MD,^b and Qutayba Hamid, MD, PhD^a *Montreal, Canada, and Denver, Colo.*

Type 2 cytokines & AD...

[The Journal of Immunology]

Cytokine Milieu of Atopic Dermatitis, as Compared to Psoriasis, Skin Prevents Induction of Innate Immune Response Genes¹

Ichiro Nomura,^{*} Elena Goleva,^{*} Michael D. Howell,^{*} Quatyba A. Hamid,[†] Peck Y. Ong,^{*} Clifton F. Hall,^{*} Marc A. Darst,[‡] Bifeng Gao,[§] Mark Boguniewicz,^{*} Jeffrey B. Travers,[‡] and Donald Y. M. Leung^{2*}

Clinical Immunology (2006) 121, 332–338



available at www.sciencedirect.com



www.elsevier.com/locate/jclim



Mechanism of HBD-3 deficiency in atopic dermatitis

Michael D. Howell^{a,b}, Mark Boguniewicz^{a,b}, Saveria Pastore^c,
Thomas Bieber^e, Giampiero Girolomoni^d, Donald Y.M. Leung^a

Clinical Immunology (2008) 124, 332–337



available at www.sciencedirect.com



www.elsevier.com/locate/jclim



Loricrin and involucrin expression is down-regulated by Th2 cytokines through STAT-6

Byung Eui Kim^{a,b}, Donald Y.M. Leung^{a,*},
Mark Boguniewicz^a, Michael D. Howell^a

Defective killing of *Staphylococcus aureus* in atopic dermatitis is associated with reduced mobilization of human β -defensin-3

Kevin O. Kisich, PhD,^{a,b} Charles W. Carspecken, BS,^{a,b} Stephanie Fiéve, BS,^a Mark Boguniewicz, MD,^{a,b}
and Donald Y. M. Leung, MD, PhD^{a,b} *Denver, Colo*

ENDOGENOUS ANTIMICROBIAL PEPTIDES AND SKIN INFECTIONS IN ATOPIC DERMATITIS

PECK Y. ONG, M.D., TAKA AKI OHTAKE, M.D., PH.D., CORINNE BRANDT, B.S., IAN STRICKLAND, PH.D.,
MARK BOGUNIEWICZ, M.D., TOMAS GANZ, M.D., PH.D., RICHARD L. GALLO, M.D., PH.D.,
AND DONALD Y.M. LEUNG, M.D., PH.D.

Immunity 24, 341–348, March 2006 © 2006 Elsevier Inc. DOI 10.1016/j.immuni.2006.02.006

Cytokine Milieu of Atopic Dermatitis Skin Subverts the Innate Immune Response to Vaccinia Virus

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Mark Boguniewicz,³ James F. Jones,² Cathy Wong,²
Joanne E. Streib,¹ and Donald Y.M. Leung^{1,4}
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2002. This possibility has led to a debate over reinstating voluntary vaccinations against smallpox (Bicknell, 2002; Fauci, 2002; Drzen, 2002).
Individuals with atopic dermatitis (AD) are excluded from voluntary smallpox vaccination due to their predisposition to develop eczema vaccinatum (EV). The potential impact of this recommendation was seen recently as up to 34% of military personnel deferred voluntary smallpox vaccination, with various contraindications with skin conditions being the main cause for deferral (Grabenstein and Winkler, 2003).
Approximately 17% of children are diagnosed with AD (Leung et al., 2004; Leung and Bieber, 2003), and, according to the current Centers for Disease Control guidelines, these children and those in close contact with them should not be vaccinated (Rotz et al., 2001). It is not understood why AD patients are susceptible to

Th2 Cytokines Act on S100/A11 to Downregulate Keratinocyte Differentiation

Michael D. Howell¹, Heather R. Fairchild¹, Byung Eui Kim¹, Lianghua Bin¹, Mark Boguniewicz^{1,2},
Jasmina S. Redzic³, Kirk C. Hansen³ and Donald Y.M. Leung^{1,2}

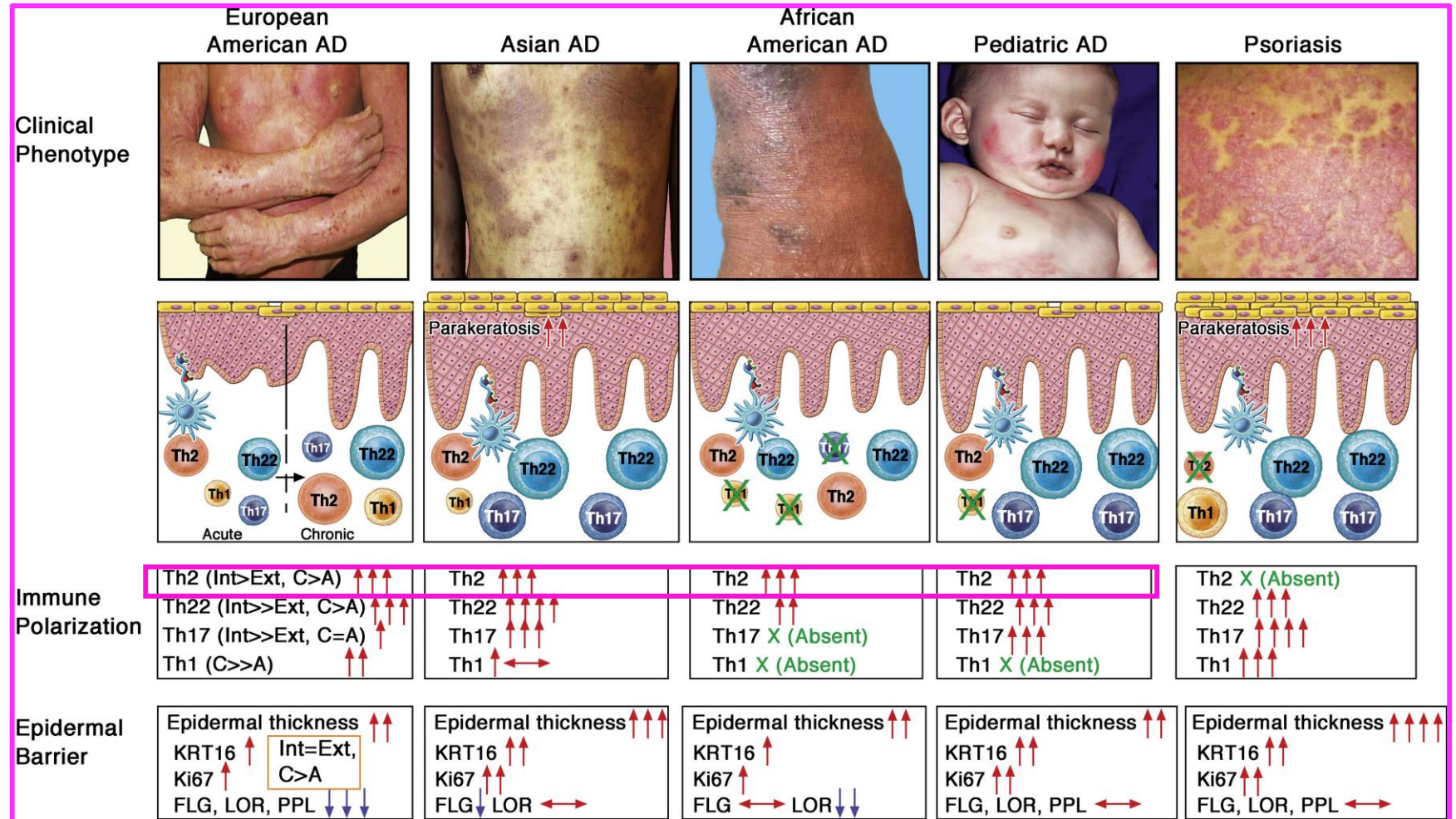
Food allergy, anaphylaxis, dermatology, and drug allergy

Rapid publication

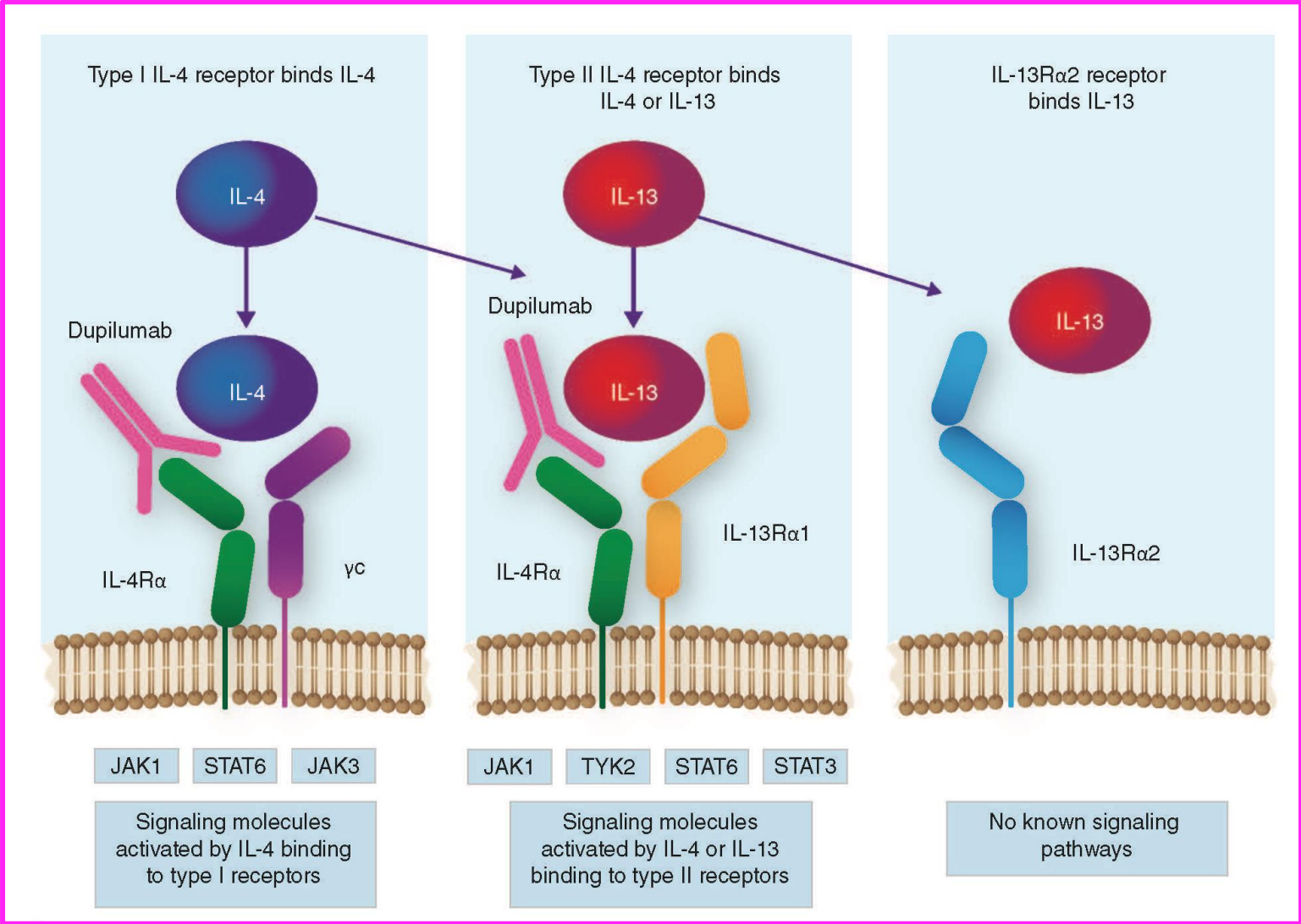
Cytokine modulation of atopic dermatitis filaggrin skin expression

Michael D. Howell, PhD,^{a,*} Byung Eui Kim, MD, PhD,^{a,b,*} Peisong Gao, PhD,^c Audrey V. Grant, ScM,^c Mark Boguniewicz, MD,^a Anna DeBenedetto, PhD,^d Lynda Schneider, MD,^a Lisa A. Beck, MD,^d Kathleen C. Barnes, PhD,^e and Donald Y. M. Leung, MD, PhD^a
Denver, Colo, Seoul, Korea, Baltimore, Md, Rochester, NY, and Boston, Mass

AD phenotypes and related endotypes

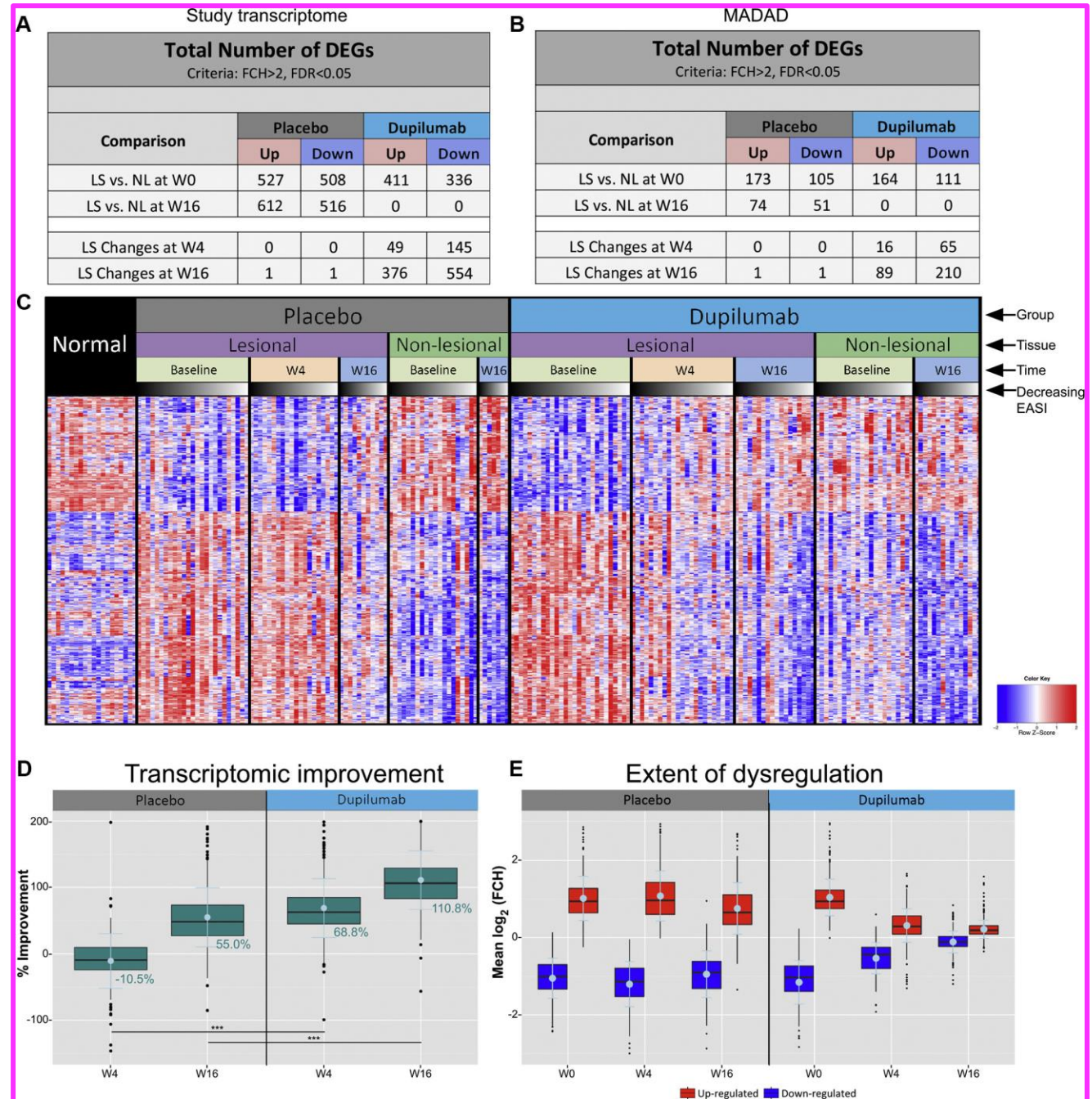


Dupilumab, a fully human monoclonal antibody targeting IL-4 receptor-alpha



Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis

Guttman-Yassky E, et al.
 J Allergy Clin Immunol 2019;143:155

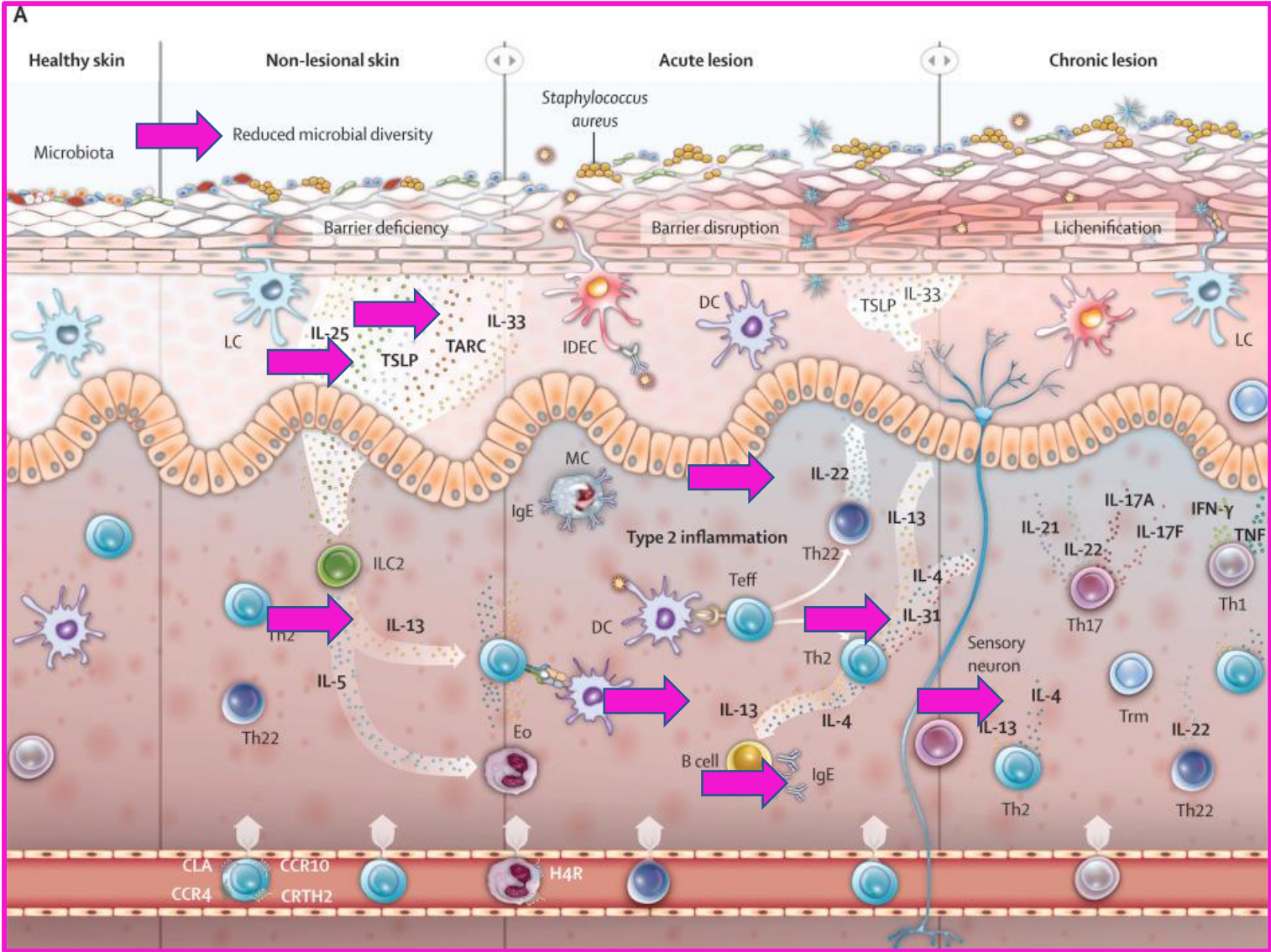


AD patients from phase 2 & 3 trials pre-/post-dupilumab



Photos courtesy of Dr E Guttman-Yassky

Therapeutic targets



NIAID Atopic Dermatitis Research Network

