Atopic Dermatitis, Pathophysiology: New Insights and Therapeutic Implications

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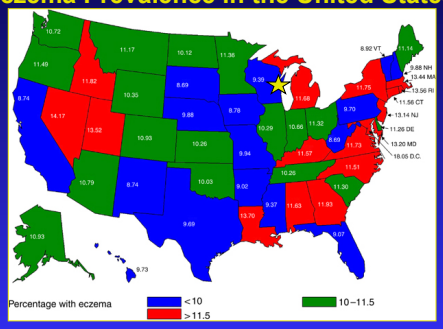
Objectives

At the end of this session, participants will be able to:

- Discuss new insights into the pathophysiology of atopic dermatitis including skin barrier and immune abnormalities
- Understand implications of skin barrier abnormalities for allergic diseases

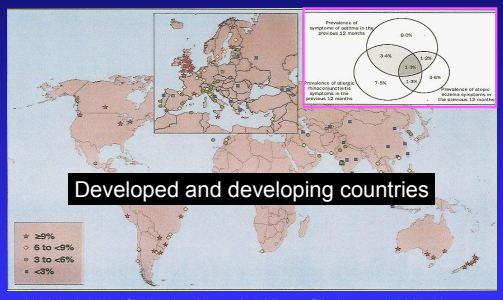
Eczema Prevalence in the United States*



*data from 2003 National Survey of Children's Health

Shaw TE, et al. J Invest Dermatol 2011;131:67

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



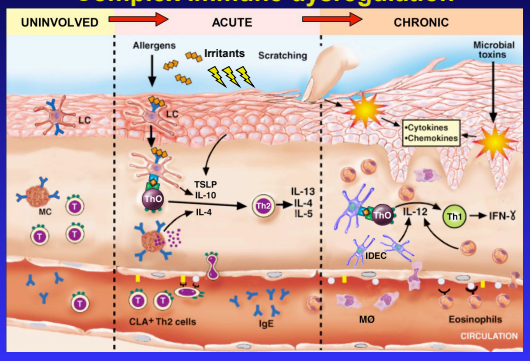
Lancet 1998;351:1225; Odhiambo JA, et al. J Allergy Clin Immunol 2009;124

Atopic March and beyond: The prevalence of atopic triad in children with physician-confirmed atopic dermatitis

- In the largest cross-sectional study of a cohort of 2270 children with diagnosis of AD confirmed by physician and treated for a minimum of 6 wks with topical prescription product for their AD:
  - nearly 66% had symptoms of asthma or allergic rhinitis and 38% had both associated with their AD
  - nearly 80% reported some additional allergic illness (asthma, allergic rhinitis, seasonal allergy, food allergy, animal allergy, or drug allergy) by the third year of life
- Results differ from previous studies in that prevalence rates of asthma and allergic rhinitis are higher and the onset is earlier i.e., if an additional illness is to be noted, it will be by the age of 3 years

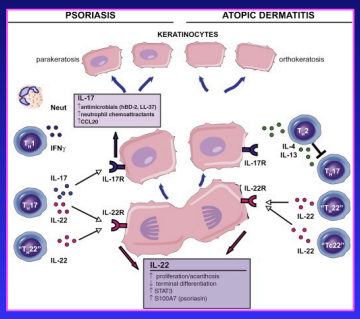
Kapoor R, et al. J Am Acad Dermatol 2008;58:68

Complex immune dysregulation



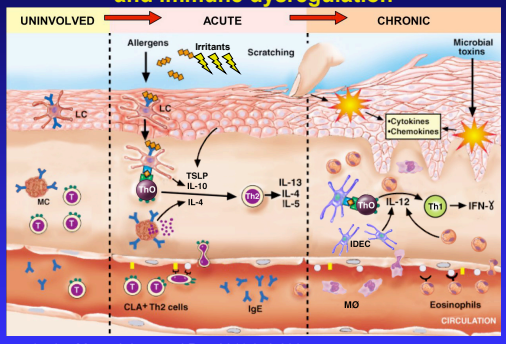
Modified from Leung DY, Boguniewicz M, et al. J Clin Invest 2004

IL-22-producing "T22" T cells account for upregulated IL-22 in atopic dermatitis despite reduced IL-17-producing TH17 T cells



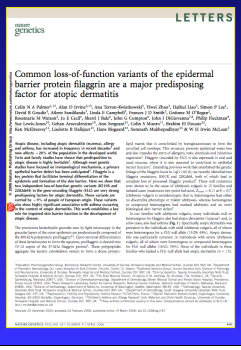
Nograles KE, et al. J Allergy Clin Immunol 2009;123:1244

Atopic dermatitis: a disease of altered skin barrier and immune dysregulation



Boguniewicz M, et al. Immunol Rev 2011;242:233

A milestone in the genetics of complex allergic disorders…


LETTERS

nature genetics

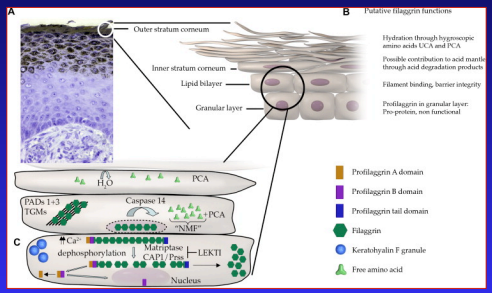
Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis

Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for AD

- Filaggrin (filament-aggregating protein) is a key protein that facilitates terminal differentiation of the epidermis and formation of the skin barrier
- *FLG* gene located on chromosome 1q21 in the EDC
- 2 loss-of-function genetic variants (R510X and 2282del4) in *FLG* shown to be very strong predisposing factors for AD
- These variants also show highly significant association with asthma occurring in the context of AD
- This data suggests a key role for impaired skin barrier function in development of atopic disease

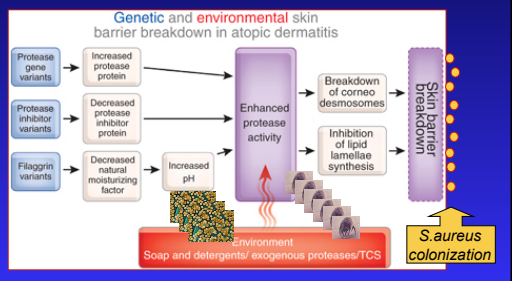
Palmer CNA, et al. Nature Genetics 2006;38:441

Filaggrin in atopic dermatitis



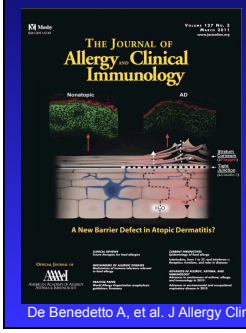
O'Regan GM, et al. J Allergy Clin Immunol 2008;122:689

Genes contributing to skin barrier breakdown



Cork MJ, et al. J Invest Dermatol 2009;129:1892

Tight junctions and claudin-1: A new barrier defect in atopic dermatitis?



- Reduced expression of TJ protein claudin-1 in AD pts validated at mRNA & protein levels
- Claudin-1 expression inversely correlated with Th2 biomarkers
- Functional relevance associated with impairment of bioelectric barrier function in AD
- *CLDN1* SNPs associated with AD

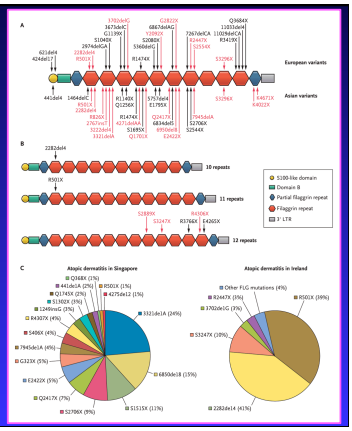
De Benedetto A, et al. J Allergy Clin Immunol 2011;127:773

FILAGGRIN

- *FLG* null alleles occur in up to 50% of patients with moderate-severe AD suggesting a fundamental role for barrier homeostasis in this disease
- Patients with *FLG* mutations more likely to have early-onset, severe, persistent AD
- *FLG* mutations are the strongest and most widely replicated genetic risk factors for AD identified to date

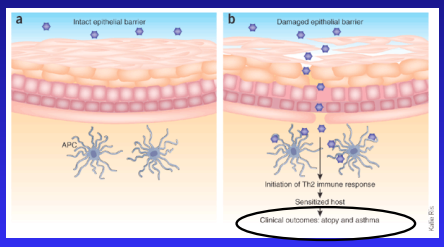
O'Regan GM, et al. J Allergy Clin Immunol 2010;126:574

Variation in filaggrin mutations among ethnic groups and other populations



Irvine AD, et al. N Engl J Med 2011;365:1315

Skin barrier function and allergic risk



Hudson TJ. Nature Genetics 2006;38:399

The burden of disease associated with filaggrin mutations: a population based, longitudinal birth cohort study

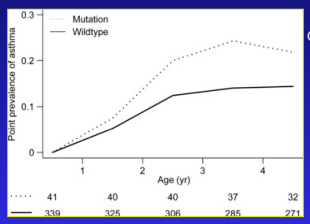
- To determine the natural history and burden of atopic disease conferred by the 2 most common *FLG* mutations in a large, population-based birth cohort study
- Analyzed the effect of the most common null alleles (R501X and 2282del4) on several atopic phenotypes in a cohort of approximately 7000 English children born in 1990-1991
- *FLG* null alleles associated strongly with eczema; eczema associated with these mutations presents in early life and is more persistent (hazard ratio for eczema resolution for those with *FLG* mutations to *FLG* wild type, 0.67; 95% CI, 0.58-0.77; P = 5 x10^{-8})

Henderson J, et al. J Allergy Clin Immunol 2008;121:872-7

- *FLG* mutations conferred a population asthma risk of 1.80 (95% CI, 1.34-2.41; P = .00019); asthma risk was especially high in the context of eczema (odds ratio, 3.16; 95% CI, 2.25-4.43; P = 1.4 x 10^{-11})
- Strong associations were identified with sensitization to grass, house dust mite, and cat dander and sensitization to multiple allergens (odds ratio, 2.12; 95% CI, 1.03-4.37; P = 5.42 x 10^{-27})
- *FLG* mutations confer risk of a particular trajectory for eczema, with increased duration of disease and greater risk of asthma and multiple allergic sensitizations
- *FLG* alleles help define the risk profile of children with eczema and help define the "eczema plus early wheeze" and "eczema plus asthma" phenotypes

Henderson J, et al. J Allergy Clin Immunol 2008;121:872-7

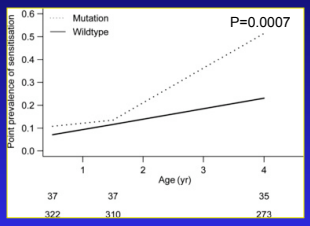
Asthma point prevalence



OR for asthma by age 5 yr for *FLG* vs wild-type was 2.62 (1.12;6.11), p=0.03

Bønnelykke K, et al. Pediatr Allergy Immunol 2010 Sep;21:954

Sensitization point prevalence



Bønnelykke K, et al. Pediatr Allergy Immunol 2010 Sep;21:954

Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy

- Case-control study of 71 English, Dutch, and Irish oral food challenge–positive pts with peanut allergy and 1000 non peanut-sensitized English population controls
- Replication tested in 390 white Canadian pts with peanut allergy (defined by food challenge or clinical history and skin prick test wheal to peanut ≥8 mm and/or peanut-specific IgE ≥15 kUL^{-1}) and 891 white Canadian population controls
- Most prevalent filaggrin loss-of-function mutations assayed in each population: R501X and 2282del4 in Europeans, and R501X, 2282del4, R2447X, and S3247X in Canadians

Brown SJ, et al. J Allergy Clin Immunol 2011;127:661

- *FLG* loss-of-function mutations showed a strong and significant association with peanut allergy in the food challenge–positive patients ($P = 3.0 \times 10^{-6}$; odds ratio, 5.3; 95% CI, 2.8-10.2) and this association was replicated in the Canadian study ($P = 5.4 \times 10^{-5}$; odds ratio, 1.9; 95% CI, 1.4-2.6)
- The association of *FLG* mutations with peanut allergy remains significant (P = .0008) after controlling for coexistent atopic dermatitis
- *FLG* mutations represent a significant risk factor for IgE-mediated peanut allergy, indicating a role for epithelial barrier dysfunction in the pathogenesis of this disease

Brown SJ, et al. J Allergy Clin Immunol 2011;127:661

Meta-analysis of filaggrin polymorphisms in eczema and asthma: robust risk factors in atopic disease

- *FLG* mutations significantly increase risk of
  - AD, odds ratio 3.12; 95% CI 2.57-3.79
  - Asthma, odds ratio 3.29; 95% CI 2.84-3.82
- Associated with more severe AD

Rodriguez E, et al. J Allergy Clin Immunol 2009;123:1361

Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis

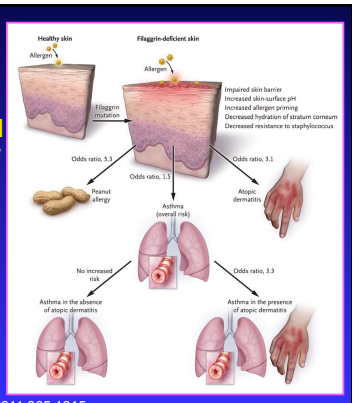
- 24 studies
- Odds of developing allergic sensitization was 1.91 (95% CI 1.44 to 2.54) in family studies and 1.57 (1.20 to 2.07) in case-control studies

Filaggrin is a robust biomarker for allergic conditions

Data supports an Atopic March

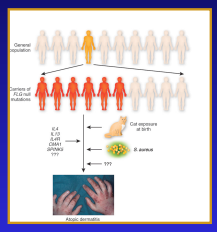
Van den Oord RA, et al. BMJ 2009;339:b2433

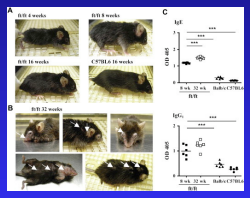
Filaggrin haplo-insufficiency and increased risk of several complex traits



Irvine AD, et al. N Engl J Med 2011;365:1315

Of flaky tails and itchy skin…

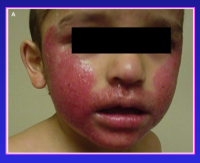


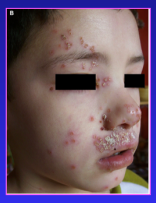


Vercelli D. Nature Genetics 2009;41:512;
Oyoshi M, et al. J Allergy Clin Immunol 2009;124:485

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

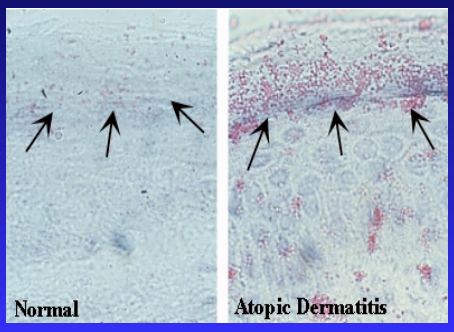
Increased susceptibility to infections or colonization with microbial organisms: *Staphylococcus aureus*, *Herpes simplex*



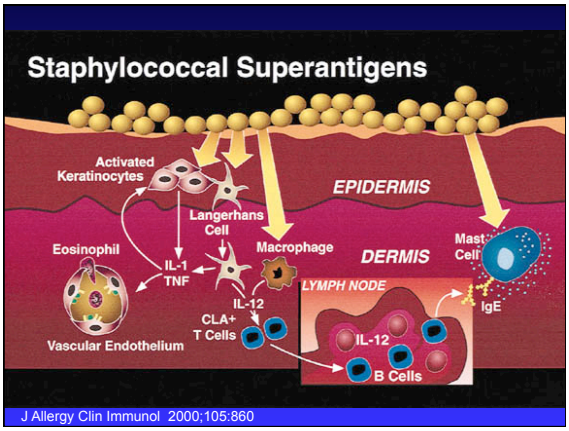


Boguniewicz M, et al. J Allergy Clin Immunol 2010;125:4

S. aureus adherence to normal healthy skin and uninvolved AD skin



Cho S-H et al. J Allergy Clin Immunol 2001;108:269



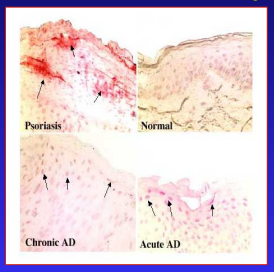
J Allergy Clin Immunol 2000;105:860

S. aureus, toxins & AD

- Most AD pts colonized by toxin-secreting *S. aureus*
- ~ 25% isolates from AD pts MRSA (higher [>50%] in Southern states)
- Both MSSA & MRSA produce alpha-toxin critical for enhanced survival on skin
- ~ 10% of *S. aureus* isolates from AD pts shown to produce 2 superantigenic toxins (SEB & TSST) (co-production not seen in isolates from >5000 pts with TSS)
- Use of topical steroids and TCIs may select for *S. aureus* strains that adapt to their "new" skin surface niche by increasing virulence capabilities
- AD pts make serve as an important reservoir for evolving *S. aureus* strains

Schlievert PM, et al. J Allergy Clin Immunol 2010;125:39

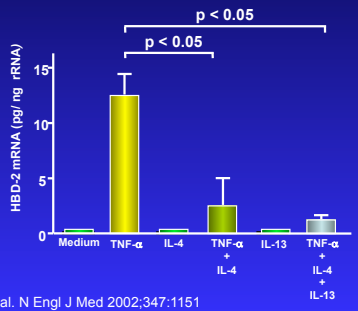
A deficiency in antimicrobial peptide* (H-β-defensin-2) expression may allow *S. aureus* to colonize and infect skin of AD patients



**** keratinocytes are the major source of AMPs in the skin***

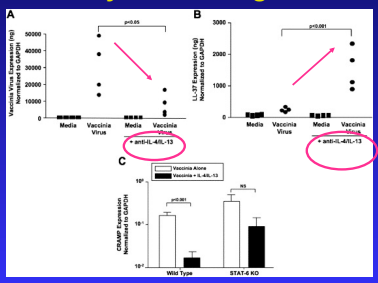
Ong PY, et al. N Engl J Med 2002;347:1151

Effects of IL-4 and IL-13 on TNF-α-induced H-β-defensin-2 expression in HaCat cells



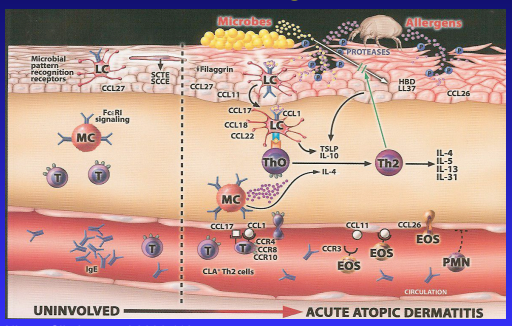
Ong PY, et al. N Engl J Med 2002;347:1151

IL-4 and IL-13 inhibit cathelicidin expression through STAT-6 and can be reversed by neutralizing antibodies



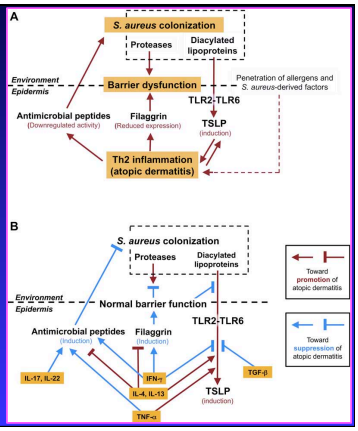
Howell MD, et al. Immunity 2006;24:341

Thymic stromal lymphopoietin: Master switch for allergic inflammation



J Allergy Clin Immunol 2006;118

Staphylococcus aureus membrane and diacylated lipopeptide induce thymic stromal lymphopoietin in keratinocytes through the Toll-like receptor 2–Toll-like receptor 6 pathway



Vu AT, et al. J Allergy Clin Immunol 2010;126:985

Phenotype of atopic dermatitis subjects with a history of eczema herpeticum

- AD patients with more polarized Th2-type disease with allergies and asthma and increased biomarkers including serum IgE, TSLP and cutaneous T cell-attracting chemokine more likely to have severe skin disease complicated by eczema herpeticum, *S. aureus* or molluscum infections

Beck LA, et al. J Allergy Clin Immunol 2009;124:260

FLG mutations and Th2 polarization
(Genetic variants in thymic stromal lymphopoietin are assocated with AD & EH)

- A critical link between barrier defect in AD patients with *FLG* mutations and Th2 polarization could be explained in part by enhanced allergen penetration through the damaged epidermis accompanied by increased production of TSLP* by keratinocytes leading to a Th2-type milieu

* significant associations for TSLP and IL7R tagging SNPs and AD and ADEH in European Americans with replication of associations between TSLP and IL7R SNPs in an independent African American sample

Gao P-S, et al. J Allergy Clin Immunol 2010;125:1403

Filaggrin mutations that confer risk of atopic dermatitis confer greater risk for eczema herpeticum

- 2 common loss-of-function mutations plus 9 FLG single nucleotide polymorphisms genotyped in 278 European American patients with AD, of whom 112 had ADEH, and 157 nonatopic controls; replication performed on 339 African American subjects
- Significant associations observed for both the R501X and 2282del4 mutations and AD among European American subjects (P = 1.46 x 10(-5), 3.87 x 10(-5), respectively), but the frequency of the R501X mutation was 3 times higher (25% vs 9%) for ADEH than for AD without EH (OR, 3.4; 1.7-6.8; P = .0002)
- Associations with ADEH stronger with the combined null mutations (OR, 10.1; 4.7-22.1; P = 1.99 x 10(-11))

Gao PS, et al. J Allergy Clin Immunol 2009;124:507

- Associations with the R501X mutation were replicated in the African American population; the null mutation was absent among healthy African American subjects, but present among patients with AD (3.2%; P = .035) and common among patients with ADEH (9.4%; P = .0049)
- The 2282del4 mutation was absent among African American patients with ADEH and rare (<1%) among healthy individuals
- The R501X mutation in the gene encoding filaggrin, one of the strongest genetic predictors of AD, confers an even greater risk for ADEH in both European and African ancestry populations, suggesting a role for defective skin barrier in this devastating condition

Gao PS, et al. J Allergy Clin Immunol 2009;124:507

NIAID Atopic Dermatitis Research Network

ADRN *S. aureus* related research

Research area 2: Susceptibility to staphylococcal colonization and infections, including MRSA

- Clinical Mechanistic Studies:
  - Identification of genetic determinants for bacterial dissemination in ethnically diverse patients with AD
  - Identification of epidermal barrier defects that predispose AD subjects to colonization with *S. aureus*
  - Exploratory studies on PBMC immunoprofiles in AD subjects with and without bacterial colonization
- Clinical Trial:
  - AD, innate immunity and vitamin D
- Animal Mechanistic Study:
  - *S. aureus*, innate immunity and vitamin D in mouse models

Research area 3: Susceptibility to colonization and/or infection with other commensal organisms

- Clinical Mechanistic Study of the skin microbiome in AD patients to understand the susceptibility to colonization and/or infection with other commensal organisms

Registry & Repository of Biological Specimens

- *S. aureus* repository

Translating lessons from research to patient care

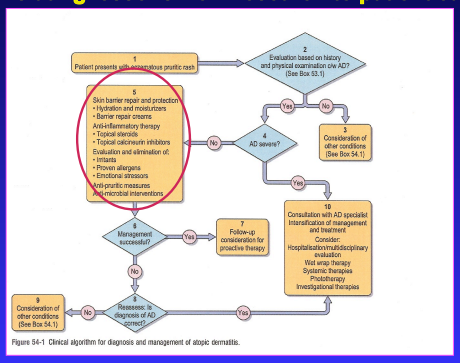
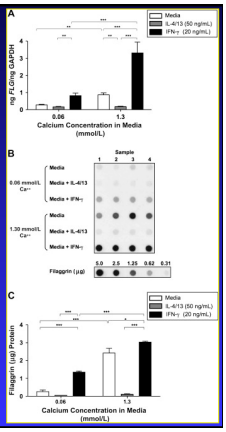


Figure 54-1 Clinical algorithm for diagnosis and management of atopic dermatitis.

Boguniewicz M, et al. In Pediatric Allergy 2010; 566

TH2 cytokines downregulate filaggrin gene expression

Immune Modulation?



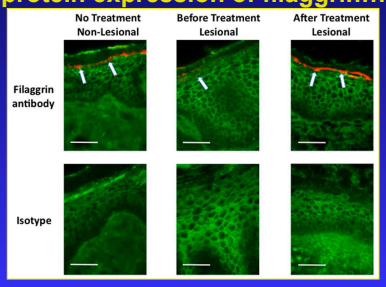
Howell MD, et al.
J Allergy Clin Immunol 2007;120:150

Different effects of pimecrolimus and betamethasone on the skin barrier in patients with atopic dermatitis

- 15 AD pts randomized to pimecrolimus (P) to one upper limb and betamethasone (B) to other 2x/day for 3 wks
- Stratum corneum (SC) hydration and TEWL improved and dye penetration reduced with both treatments
- EM evaluation of barrier structure showed prevalently ordered SC lipid layers and regular lamellar body extrusion in P-treated skin but inconsistent extracellular lipid bilayers and only partially filled lamellar bodies with B treatment
- Both drugs normalized epidermal differentiation and reduced epidermal hyperproliferation
- Decreased filaggrin restored with both treatments
- B was superior in reducing clinical symptoms and epidermal proliferation; however, it led to epidermal thinning

Jensen JM, et al. J Allergy Clin Immunol 2009;123:1124

Psoriasis patients treated with a TNF-alpha antagonist* showed increased protein expression of filaggrin…



Kim BE, et al. J Invest Dermatol 2011;131:1272

*etanercept

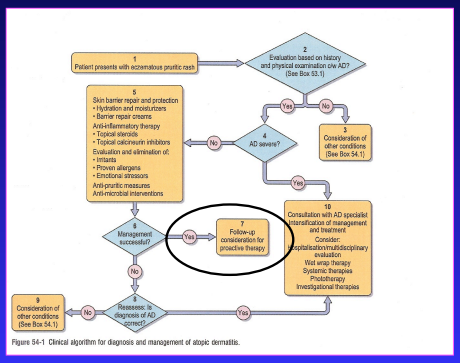
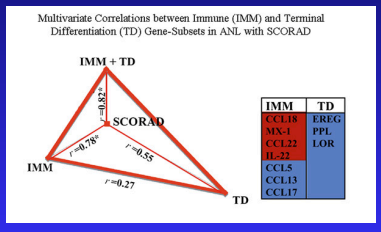


Figure 54-1 Clinical algorithm for diagnosis and management of atopic dermatitis.

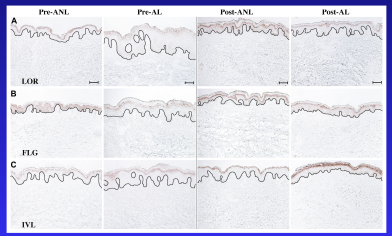
Boguniewicz M, et al. In Pediatric Allergy 2010; 566

Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities



Suarez-Farinas M, et al. J Allergy Clin Immunol 2011;127:954

Reversal of atopic dermatitis with narrow-band UVB phototherapy and biomarkers for therapeutic response



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