Atopic Dermatitis

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1 Introduction

Atopic dermatitis (AD) is the most common chronic and relapsing, **pruritic**, inflammatory skin disease that affects both children and adults with a prevalence of up to 18% and 7%, respectively. The atopic dermatitis pathogenesis is multifactorial: **epidermal barrier dysfunction**, immunological abnormalities as **antimicrobial peptides deficiency**, host genetics as null mutations in the gene encoding the epidermal structural protein filaggrin (FLG) and missense variants in genes encoding the T_H2 signature cytokine IL-13 and IL-6R, altered skin microbiota, and environmental factors. AD patients have an increased risk of bacterial, viral, and fungal infections, such as ***S. aureus, Herpes simplex, Molluscum, and Malassezia***. Some endotypes are associated with a higher risk for the **atopic march**: early onset AD, those with polysensitization, with an atopic parent, with a persistent or severe endotype, and those with a **filaggrin** mutation.

Cases 1

A 3-year-old child presents to your office with a severe, itchy, rash, involving his chest, back, upper and lower extremities, including the flexural areas, not relieved with sporadic topical (corticosteroid) CS medications given by his primary care provider (PCP). On physical exam, some lesions are frankly red and with crusts, and his nares are crusted.

Question 1

What criteria is compatible with an atopic dermatitis diagnosis?

A. Posterior subcapsular cataracts
B. Unilateral keratoconjunctivitis
C. Lesional skin with spongiosis in the epidermis
D. Parakeratosis with neutrophilic collections, spongiform pustules with neutrophils

The answer is C

The Hanfin and Rajka criteria for diagnosis AD include (Table 1).

The minor criteria for diagnosing include: (Table 2).

Table 1 Criteria for diagnosis of atopic dermatitis

Pruritus
Facial and extensor involvement in infants and children
Flexural lichenification in older children and adults
Scratching-related: Lichenification, prurigo nodularis
Chronic or relapsing dermatitis
Personal or family history of atopic disease (asthma, rhinitis, conjunctivitis, food allergy)

Table 2 Minor criteria for diagnosing AD

Xerosis
Keratosis pilaris
Hyperlinear palms
Ichthyosis
Pityriasis alba
Allergic shiners
Dennie-Morgan folds
Cheilitis
Keratoconus (conical deformity of the cornea from persistent rubbing of the eyes)
Immediate skin test reactivity
Elevated serum IgE
Food intolerance
Tendency towards cutaneous infections—*S. aureus*, *HSV*, *Molluscum*, dermatophytosis
Tendency towards nonspecific hand or foot dermatitis (especially in adults)
Nipple eczema
Itch when sweating
White dermatographism and delayed blanch response
Anterior subcapsular cataracts (may develop during adolescence or early adult life)
Intolerance to wool and lipid solvents
Course influenced by environmental/emotional factors

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Other related conditions are: quality of life impairment (sleep disturbance, anxiety, depression, suicidality).

Atopic keratoconjunctivitis is always bilateral and symptoms include itching, burning, tearing, and copious mucoid discharge. It is frequently associated with eyelid dermatitis and chronic blepharitis and may result in visual impairment from corneal scarring. The Hertoghe's sign is a rarefaction of the lateral eyebrow.

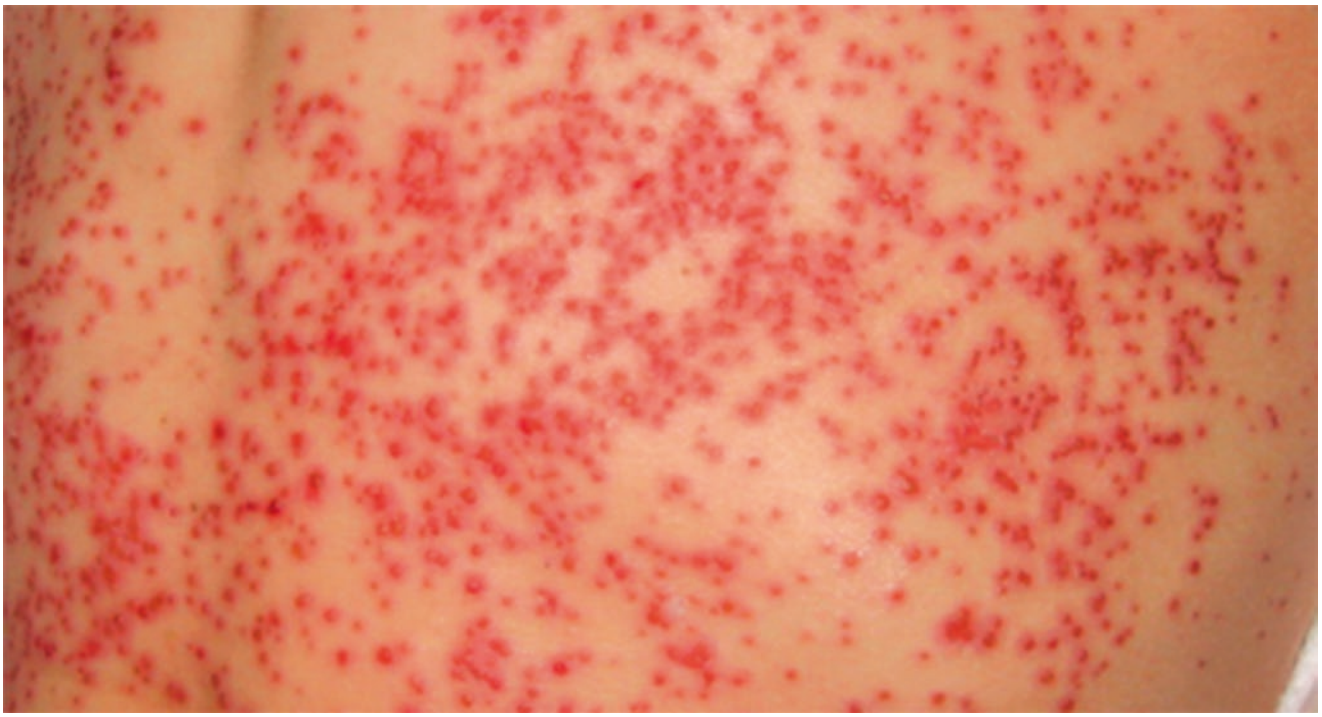
Acute AD skin lesions are characterized by spongiosis, or marked intercellular edema, of the epidermis. Dendritic antigen-presenting cells in the epidermis, such as Langerhans cells, with surface-bound immunoglobulin (Ig) E molecule, present allergen to Th2 cells. Perivenular T cells with occasional monocyte-macrophages are also present. Lymphocytes are CD3, CD4, CD45RO memory T cells and also CD25, HLA-DR, and CLA+ T cells (attracted by CCL27). Mast cells are found in normal numbers but in different stages of degranulation. Innate lymphocyte cells 2 (ILC2) and basophils are an important source of T2 cytokines.

The C-C chemokines RANTES (regulated on activation, normal T cell expressed and secreted), MCP-4 (monocyte chemotactic protein-4), and eotaxin are increased in AD skin lesions, resulting in chemotaxis of eosinophils, macrophages, and Th2 lymphocytes expressing their receptor (CCR3). $COL6A5^{+}$ fibroblasts are found in the dermal-epidermal junction.

Parakeratosis with neutrophilic collections and spongiform pustules with neutrophils refer to psoriasis.

Question 2

He develops this rash, as shown in figure below



What predisposed him to this rash?

A. Filaggrin (FLG) loss-of-function mutation
B. Presence of MRSA on his nares
C. Smallpox vaccine given to his active military dad
D. STAT3 deficiency

The answer is A

The odds ratio of eczema herpeticum (EH) is more than 10 in patients with FLG mutations.

Loss-of-function (LoF) mutations in the gene encoding filaggrin, the epidermal barrier protein, are also associated strongly with early and persistent AD, asthma, and peanut allergy. FLG heterozygotes outgrow their disease, slower than those without the mutation. Th2 cytokines such as interleukins 4 and 13 (IL-4, IL-13), which are upregulated in AD, can downregulate *FLG* expression.

FLG LoF leads to decreased expression of filaggrin protein and its metabolites, urocanic acid, and pyrrolidone carboxylic acid, increasing the ph of skin, and the expression of

two staphylococcal surface proteins, clumping factor B and fibronectin-binding protein, allowing *Staphylococcus aureus* to proliferate. Patients with AD with FLG LoF have a higher risk for four or more episodes of skin infections requiring antibiotics within a year than patients with AD without FLG LoF. African Americans have a 1.7 risk of having AD, and the odds of having an FLG loss-of-function variant is 2.44-fold greater in white children compared with African American children.

EH is caused by infection with herpes simplex virus (HSV-1). Patients may complain of pruritus or pain. The lesions can be vesicles, punched-out erosions, or hemorrhagic crusts.

AD patients with EH have more severe disease based on scoring systems, body surface area affected, and biomarkers (e.g., circulating eosinophil counts, serum IgE, TARC, CTACK) They also have more cutaneous infections with *Staphylococcus aureus* or molluscum contagiosum virus, and they are more likely to have a history of asthma and food and inhalant allergies.

AD patients with EH have reduced interferon γ (IFN-γ) production, and IFN-γ and receptor (IFN-γR1) single-nucleotide polymorphisms (SNPs) are significantly associated with AD and EH.

A leaky barrier in both lesional and nonlesional skin allows the entrance of irritants and allergens and increased transepidermal water loss. (TEWL).

S. aureus is the main organism isolated in patients with AD, causing impetigo, cellulitis, and skin abscesses. If warmth, edema, erythema, and tenderness in an extensive skin area are present, the patient may have erysipelas or cellulitis. Pustules or impetigo may also be due to *Streptococcus pyogenes*, which may cause infections by itself or in combination with *S. aureus*, and sometimes it may cause some lesions resembling eczema herpeticum.

STAT3 deficiency, autosomal dominant Hyper IgE syndrome (HIES), is characterized by eczema, recurrent staphylococcal skin abscesses, recurrent lung infections (resulting in the formation of cavitary lesions in the lungs or pneumatoceles), eosinophilia, and elevated serum IgE. Other frequent findings of STAT3 deficiency include a newborn rash, mucocutaneous candidiasis, connective tissue and skeletal abnormalities such as a typical facial appearance, hyperextensibility of their joints, retained primary teeth, and recurrent bone fractures secondary to even minimal trauma.

Autosomal recessive Hyper IgE syndrome (AR-HIES) with DOCK8 deficiency, presents with eczema, skin abscesses, recurrent respiratory infections, candidiasis, and other fungal infections, and severe, recurrent viral infections from *Herpes simplex, Herpes zoster, and Molluscum contagiosum.* They are also susceptible to allergic and autoimmune manifestations, including food allergy, hemolytic anemia, and vasculitis. They also may develop encephalitis and vascular brain lesions. Patients with AR-HIES do not have connective tissue or skeletal abnormalities.

A history of atopic dermatitis in the household contacts is a contraindication for smallpox vaccine in the military. The exanthem of smallpox appears 2–4 days after the onset of fever in the proximal extremities and spreads distally; lesions are vesicles with central depression, or homogeneous pustules raised, embedded in the skin.

Question 3

What correlates with disease severity?

A. Peanut and egg allergy
B. IgE against superantigens
C. Filaggrin deficiency
D. Decrease in commensal organisms *S. hominis* and *Roseomonas mucosa*

The answer is B

Ninety percent of patients with AD are colonized with *S. aureus*, and most produce enterotoxins A, B, and toxic shock syndrome toxin-1. Staphylococcal toxins can activate T cells as superantigen, a biopsy shows expansion of the T cell receptor (TCR) variable-domain β chain (Vb) in skin lesions and in CLA+ T cells, consistent with superantigen stimulation. The toxins may also induce specific IgE. Basophils from patients with antitoxin IgE release histamine on exposure to the relevant toxin.

Staph superantigens can induce glucocorticoid resistance, and can exacerbate itch by inducing IL-31 mRNA. Even though CD4+ CD25+ (Tregs) are increased in patients with AD, their function is decreased after activation of T cells by superantigens.

Disease severity is dependent on the colonization of *Staph aureus* and production of superantigens, the amount of house dust mite (HDM) IgE, a decrease in microbiome diversity, and the degree of sensitization to aeroallergens.

Beyond 3 years of age, inhalation and intranasal challenge of HDM can induce skin lesions, and T cells specific to Dpter are isolated from lesional skin.

Respiratory route is an important factor in exacerbations-inhalant allergens such as mites, animal danders, and pollens.

A decrease in microbiome diversity correlates with increased colonization of *S. aureus*; topical application of commensal organisms (*S. hominis* or *Roseomonas mucosa*) reduces AD severity, S. hominis produces antimicrobial peptides that reduce *S. aureus* colonization. Staph epidermidis found in some atopic patients damage the skin barrier by expression of a cysteine protease.

Question 4

Staph aureus is found on his nares and on his skin culture. What predisposes patients with AD to *Staph aureus?*

A. Low CD86B cells
B. Antimicrobial peptides deficiency
C. Increase IFN-g
D. Low CCL18 expressed in DC, LC, IDECS

The answer is B

AD patients are predisposed to *S. aureus*, and disseminated infections with *herpes simplex*, *molluscum human papillomavirus (HPV),* and/or *smallpox*.

Antimicrobial peptides—Cathelicidin LL-37 and B-defensins—are part of the innate immune system responsible for the rapid response against bacteria, fungi, and viruses. Toll-like receptors-2(TLR-2)-sensing of *S. aureus* by Langerhans cells are impaired. *S. aureus* can induce release of IL-33 from human keratinocytes independent of the Toll-like receptor.

The costimulatory molecule CD86 is expressed on Langerhans cells in both the epidermis and the dermis in AD patients, and in B cells; and CD86+ B cells correlate with the amount of IgE.

CCL18 is expressed by DCs in the dermis and LCs and IDECs in the epidermis; it binds to CLA+ T cells in peripheral blood. Expression of CCL18 is induced by exposure to allergens and *S. aureus* enterotoxin B (SEB).

Low IFN-g is associated with EH. The production of IFN-g is inhibited by IL-4 and by PGE2. Keratinocytes from AD patients exhibit increased IFN-g-induced apoptosis.

Deficient NK cells and absence of Tregs may also contribute to the immune deficiency in patients with atopic dermatitis. Both myeloid and plasmacytoid dendritic cells in patients with AD produced less interferon-A.

Question 5

He develops hypopigmented areas in all the sites where her mother was applying topical corticosteroids, and you switch to non-steroidal crisaborole

What is the mechanism of action of crisaborole?

A. Phosphodiesterase (PDE4) inhibitors reduce cAMP
B. Phosphodiesterase (PDE4) inhibitors prevent the degradation of cAMP
C. Calcineurin inhibitor, blocking the dephosphorylation of NFAT
D. Inhibits intracellular signaling of IL-4, IL-13, IL-5, IL-31 IFN-g, and TSLP

The answer is B

Phosphodiesterase inhibitors increase the reduced levels of cyclic adenosine monophosphate (cAMP)of AD, suppressing the activity of NF-kB and NFAT thus inhibiting inflammatory cytokines, IFN-g, TNF-a, IL-2, and IL-5. Crisaborole is approved from 3 months of age and older. Epidermal thickness is significantly decreased compared with baseline only in crisaborole-treated lesions, improved TEWL and pruritus. Significant reductions in numbers of CD3 T cells and CD11c DCs are also seen.

Pimecrolimus and tacrolimus are topical calcineurin inhibitors that block NFAT. JAK inhibitors prevent STAT recruitment and thus inhibit the intracellular signaling of multiple cytokines—IL-4, IL-13, IL-5, IL-31, IFN-g, and TSLP.

Case 2 AD

A 23-year-old female with a history of allergic rhinitis and atopic dermatitis in the past, presents with generalized, severe dermatitis on her chest, eyelids, and lichenified flexural areas in her extremities. Her primary physician prescribed her a midpotency topical corticosteroid (CS) to the chest and extremities, which did not improve her rash.

Question 1

What will you do next?

A. Skin biopsy to r/o Sezary syndrome
B. Patch test to r/o contact allergen
C. Skin test to r/o food and/or inhalant allergy
D. Prescribe an oral CS

The answer is B

A contactant should be considered in patients whose AD does not respond to appropriate therapy, especially those with eyelid, hand, or foot dermatitis or with a history of worsening eczema after application of topical corticosteroids. Sensitizing chemicals, such as parabens and lanolin, can be irritants for patients with AD and are commonly found as vehicles in therapeutic topical agents. This patient may be reacting to the propylene glycol present in the CS preparation; to allergens from the nails that were carried to the eyelids; to sylamide, formaldehyde, methacrylate; or to fragrance/Balsam of Peru.

Eczematous dermatitis has also been reported with HIV infection and scabies. Other conditions that can be confused with AD include psoriasis, ichthyoses, and seborrheic dermatitis.

Only 33–40% of infants and young children (not adults) with moderate-severe atopic dermatitis may have an immediate IgE-mediated reaction to milk, egg, peanut, soy, wheat, fish, and nuts. The immunological reactions include immediate reactions, within 2 h; late-onset IgE reactions, within 6–10 h; and delayed reactions, 6–48 h (T cell-mediated)

Pruritic, morbilliform, or macular eruptions in the predilection sites for AD, or GI/respiratory reactions after inges-

tion of the food allergen is seen; and there are food-specific T cells from peripheral blood and lesional skin.

An adult who has eczematous dermatitis with no history of childhood eczema (Most cases of AD, 95% approximately, are diagnosed prior to 5 years of age) and without other atopic features may have contact dermatitis, but more importantly, cutaneous T cell lymphoma needs to be ruled out. A red, pruritic rash with adenopathy and increased atypical lymphocytes on the blood smear may be Sezary syndrome**,** if the rash in her chest does not improve, she needs a biopsy from three separate sites to increase the yield to identify Sezary cells, also need to r/o HIV dermatitis.

Question 2

You start her on pimecrolimus, a calcineurin inhibitor, inhibiting the activation of NFAT (nuclear factor of activated T cells), inhibits activation of helper lymphocytes and production of IL-2, to treat her eyelids with good response. Her dermatitis in the chest and extremities however do not respond to a short course of oral CS, and you start her on dupilumab

Dupilumab:

A. Improves EASI-90 score by 50%
B. It inhibits the IL-4R and the IL-13R through JAK2/STAT3 signaling
C. Most common adverse event is conjunctivitis and blepharitis in 26% of patients
D. It improves itch by 30% in patients older than 6 years of age

The answer is C

A humanized monoclonal antibody, dupilumab inhibits interleukin-4 (IL-4) and IL-13 signaling by specifically binding to the IL-4R-alpha subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab reduces the expression of genes involved in type 2 inflammation, epidermal hyperplasia, T cells, DCs.

The IL-4R and IL-13 R signal through Jak1, Jak3, Tyk2, STAT5/6.

Lower levels of IL4RA and IL13 and high IL36A expression were related to a stronger clinical response to dupilumab.

Seventy-eight percent improved EASI-50 score after 16 weeks of treatment; 33% EASI-90 score after 16 weeks of treatment.

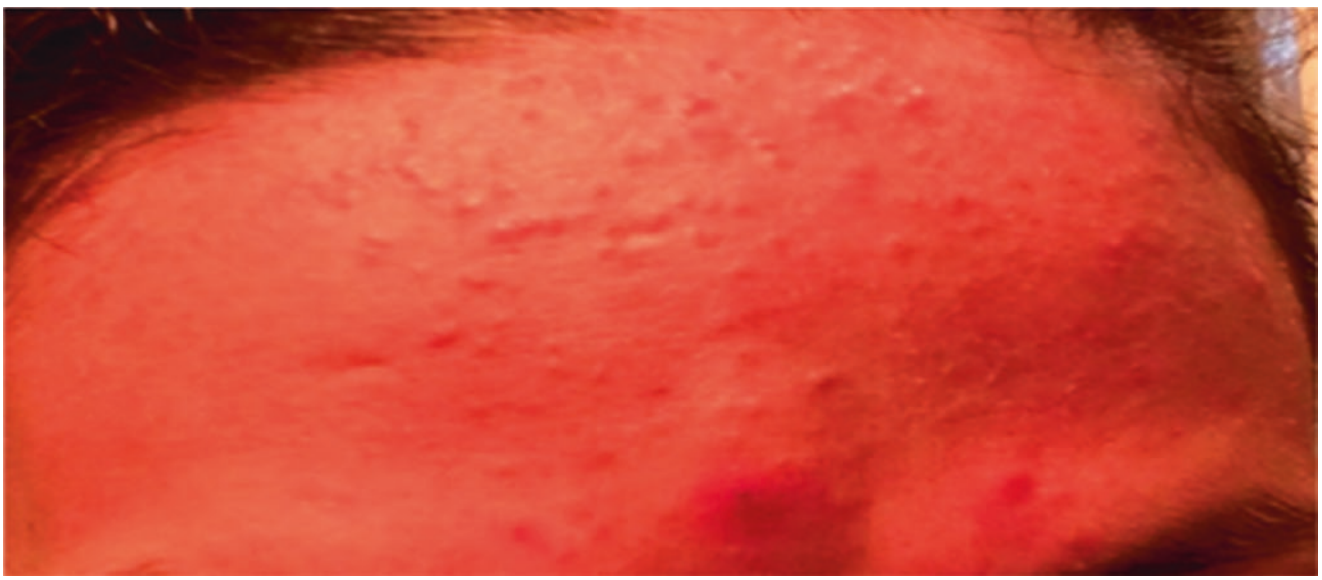
Dupilumab improves itch by 48–57% in patients 6 years of age and older, taking 300 mg dose, every 4 weeks, by day 2–5. Both IL-4 and IL-13 interact with the itch sensory neurons. IL-4 promotes neural hypersensitivity to many pruritogens: histamine, IL-31, TSLP, and thus an inhibitor to IL-4 and IL-13 ameliorates itch.

Some patients taking dupilumab experience facial erythema. Most common adverse event seen in 26% of 908 patients with AD (14 studies) was conjunctivitis and blepharitis, seen bilaterally, and most patients did not discontinue the medication.

Biomarkers to follow AD severity and disease improvement with treatment are CTACK (CCL27) and the chemokine C-C motif ligand 17/thymus and activation-regulated chemokine(TARC), a chemoattractant of T_H2 cells.

Question 3

Her dermatitis improved but then she presents with head and neck acneiform-looking lesions and/or hypopigmented lesions. What does the picture show? How will you treat her now?



A. *Malassezia sympodialis*, treat with itraconazole 100 mg qd for 1 week, then 200 mg qd
B. Comedonal acne, treat her with benzoyl peroxide/clindamycin gel.
C. Pityriasis alba, low potency topical CS or pimecrolimus with moisturizer
D. Contact dermatitis, pimecrolimus

The answer is A

Dermatophytosis may cause AD to flare. The opportunistic yeast *Malassezia sympodialis* (formerly *Pityrosporum ovale*) has been associated with a predominantly head and neck distribution of AD, one can order IgE to *Malassezia*. The autoantigen that may cross-react with *Malassezia*, seen in chronic AD patients is Human manganese superoxide dismutase. The superficial dermatophyte *Trichophyton rubrum* has also been associated with elevated allergen-specific IgE levels.

Question 4

What will the skin biopsy of a chronic, lichenified lesion show?

A. Degranulated mast cells
B. CD4+ Th2 cells only
C. Activated eosinophils
D. CD4+ Th1 cells only

The answer is C, activated eosinophils, releasing BMP (basic major protein)

Barrier dysfunction leads to the secretion of IL-33 and TSLP from keratinocytes, promoting type 2 inflammation activating basophils, group2 innate lymphoid cells, and Th2 cells. These cells, in turn, produce the effector cytokines IL-4, IL-5, IL-13, and IL-31. The acute inflammation in the skin is mostly due to IL-4 and chronic inflammation is mostly due to IL-5 and eosinophils. Chronic atopic dermatitis involves Th2, Th22, Th1, and Th17 cells. The biopsy will also show epidermal hyperkeratosis, increased epidermal Langerhans, monocytes, macrophages in dermis, and mast cells (intact, not degranulated) with minimal spongiosis.

The old paradigm that acute atopic dermatitis activated Th2 and chronic AD activated Th1 is changing to a range of AD endotypes with mixed T_H1, T_H2, T_H17, and T_H22 characteristics.

There are many cells responsible for the inflammation in AD: Th1, Th2, ILC2, IDECs, eosinophils, and CD8+ T cells. According to ethnicity, the immune signal differs. The African American patients are predominately Th2, Th22; the pediatric patients are Th2, Th22, Th17; the Asian Th2, Th 22, Th17, Th1, with parakeratosis(more typical for psoriasis); and the European American Th2, Th22, Th1.

Question 5

Which one of the following is true about IL-31:

A. Is the only pruritogen expressed in lesional skin
B. Induced by enterotoxin B from *S. aureus*
C. Produced mostly by keratinocytes
D. IL-31 receptor is expressed constitutively on mast cells

The answer is B

IL-31 is produced mainly by activated CD4Th2 cells, and skin homing CD45RO+CLA+T cells, basophils, ILC2, but also by keratinocytes, mast cells, eosinophils, fibroblasts, DC's, macrophages. IL-31 expression occurs in lesional and nonlesional skin of patients with AD; and its serum levels correlate with the severity of AD. The IL-31 receptors are expressed constitutively on keratinocytes, eosinophils, and neurons. The signaling involves four pathways: JAK-STAT, NF-KB, MAPK, and AKT-PI3K. *Staph aureus* colonization increases IL-31 expression.

The pruritogens (IL-4, IL-13, IL-31, TSLP, histamine, proteases, neuropeptides) are released by inflammation and by scratching, and they are released by keratinocytes, mast cells, and immune cells (T cells and eosinophils). The pruritogens bind to receptors on the sensory C-nerve fibers and A delta-nerve fibers in the epidermis and dermis, which trigger pruritus and pain. Only a small group (<5%) of skin C-nerve fibers are histamine sensitive.

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