

Allergic skin diseases

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The skin is one of the largest immunologic organs and is affected by both external and internal factors, as well as innate and adaptive immune responses. Many skin disorders, such as atopic dermatitis, contact dermatitis, urticaria, angioedema, psoriasis, and autoimmune blistering disorders, are immune mediated. Most of these diseases are chronic, inflammatory, and proliferative, in which both genetic and environmental factors play important roles. These immunologic mechanisms might have implications for potential targets of future therapeutic interventions. (J Allergy Clin Immunol 2010;125:S138-49.)

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The skin is one of the largest immunologic organs and is often a target for allergic and immunologic responses. Many skin disorders, such as atopic dermatitis (AD), contact dermatitis (CD), urticaria, angioedema, psoriasis, and autoimmune blistering disorders, are immune mediated, with abnormalities in innate and adaptive immunity. Most of these diseases are chronic, inflammatory, and proliferative, in which both genetic and environmental factors play important roles. These immunologic mechanisms might have implications for potential targets of future therapeutic interventions. This review will examine some recent research advances in allergic and immunologic skin diseases.

CONTACT DERMATITIS

Allergists and clinical immunologists are seeing increasing numbers of patients with eczema and CD and are performing more patch testing. Cohort population-based studies in Europe showed point prevalence rates of 0.7% to 18.6% for allergic contact dermatitis (ACD).^{1,2} Allergists trained in patch testing are more confident about the clinical relevance of such testing, especially for the differential diagnosis of the common eczematous diseases.³

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Abbreviations used

ACD:	Allergic contact dermatitis
AD:	Atopic dermatitis
AMP:	Antimicrobial peptide
ASST:	Autologous serum skin test
BHR:	Basophil histamine release
BP:	Bullous pemphigoid
CAPB:	Cocoamidopropyl betaine
CD:	Contact dermatitis
CIU:	Chronic idiopathic urticaria
CU:	Chronic urticaria
DC:	Dendritic cell
EH:	Eczema herpeticum
FDA:	US Food and Drug Administration
HBD:	Human β -defensin
ICD:	Irritant contact dermatitis
IDEC:	Inflammatory dendritic epidermal cell
IVIG:	Intravenous immunoglobulin
LC:	Langerhans cell
NACDG:	North American Contact Dermatitis Group
PDC:	Plasmacytoid dendritic cell
PPD:	Paraphenylenediamine
PV:	Pemphigus vulgaris
ROAT:	Repeat open application test
SCD:	Systemic contact dermatitis
TLR:	Toll-like receptor
T.R.U.E. TEST:	Thin layer rapid use epicutaneous test
TSLP:	Thymic stromal lymphopoietin

Pathophysiology

CD can be allergic (20%) or irritant (80%). The morphology, severity, and location of CD is affected by the innate allergenicity or irritancy of the allergen, the site and degree of contact, the thickness and integrity of the skin involved, exposure time, environmental conditions, the immunocompetency of the patient, and even genetics.

ACD is the prototype of the type IV cell-mediated hypersensitivity reaction. The allergens in ACD are usually small-molecular-weight molecules or haptens that conjugate with proteins in the skin and induce activated epidermal keratinocytes to release proinflammatory cytokines. The Langerhans cells endocytose, process, and combine specific hapten peptides with HLA class I molecules and then migrate to the draining regional lymph nodes, where they activate and sensitize naive CD4⁺ T cells (T_H0 cells). Activated T_H cells then proliferate and generate clones of hapten-specific CD4⁺CD25⁺ regulatory and CD8⁺ effector cells, which become either memory or effector cells. This is known as the afferent limb of the immune reaction. The CD4⁺ regulatory/effector and CD8⁺ effector cells then “home” to the original skin site and there function as the efferent limb of the immune response. Both CD4⁺ and CD8⁺ sensitized effector cells release proinflammatory cytokines/cytotoxins (INF- γ , TNF- α , GM-CSF, IL-2, perforin, and granzyme), which cause an intense perivascular inflammatory

infiltrate and spongiosis. CD4⁺ CCR10 chemokine-expressing memory lymphocytes are retained for long periods of time in the original ACD sites, accounting for the shortened latent period (anamnesis) on subsequent exposure. In mice mast cells at the site of ACD have been shown to recruit polymorphonuclear leukocytes to the site through the release of the mediators TNF- α and IL-8.

Irritant contact dermatitis (ICD) is the result of nonimmunologic, multifactorial, direct tissue reaction. T cells activated by means of nonimmune, irritant, or innate mechanisms release inflammatory cytokines (TNF- α , IL-1, IL-8, and GM-CSF) that contribute to the dose-dependent inflammation seen in patients with ICD.⁴ There is usually a higher concentration of offending agents, such as solvents, detergents, chemicals, and alcohol. Lesions with erythema, edema, desquamation, and fissures are sharply demarcated typically and limited to the area in direct contact with the offending agent. They can burn or sting. Scratching, scrubbing, washing, excessive wetness, improper drying, perspiration, and extremes of temperature contribute to the reaction (Table I).

ACD and ICD frequently overlap because many allergens at high enough concentrations can also act as irritants. Impairment of the epidermal barrier layer, such as fissuring, can increase allergen entry into the epidermis.

Clinical evaluation

The diagnosis of ACD is suspected from the clinical presentation of the rash and the possible exposure to a contact allergen.

Face and eyelid. Fifty-five percent to 63.5% of eyelid dermatitis might be from ACD, 15% from ICD, less than 10% from AD, and 4% from seborrheic dermatitis.⁵ Data collected by the North American Contact Dermatitis Group (NACD) showed that in 193 (72%) of 268 patients with only eyelid dermatitis, gold was the most common allergen. Fragrances, preservatives, nickel, thiuram (rubber), cocamidopropyl betaine (CAPB) and amidoamine (shampoos), and tosylamide formaldehyde resins (nail polish) are other allergens to consider in the evaluation of eyelid dermatitis.⁶ In patients with mixed facial and eyelid dermatitis, nickel, Kathon, and fragrance had the most positive patch test responses.^{7,8}

Hands and feet. Hand dermatitis can be due to ICD, ACD, AD, dyshidrosis, or psoriasis. It can be extremely difficult to distinguish the cause of hand dermatitis, particularly because of tremendous overlap. Neither ACD nor ICD has pathognomonic clinical or histologic features. A thorough medical, work, and recreational history, together with a physical examination, ancillary laboratory tests, and patch tests, is critical in the evaluation of patients with hand eczema. Patch tests in patients with hand eczema showed that the relevant allergens include nickel sulfate (17.6%), potassium dichromate (7.2%), rubber elements (19.6%, including thiuram mix, carba mix, paraphenylenediamine [PPD], and mercaptobenzothiazole), and cobalt chloride (6.4%).⁹ A Swedish study of 5700 patients showed that patients whose entire hands were involved were more likely to react to thiuram mix, PPD, chromate, and balsam of Peru. Patients with involvement of the fingers and interdigital spaces and those with palm involvement reacted more to nickel, cobalt, and 5-chloro-2-methyl-4-isothiazolin-3-one/2-methyl-4-isothiazolin-3-one.¹⁰

The prevalence of hand eczema in patients with AD is 2- to 10-fold higher than that seen in nonatopic subjects, and 16% had nail dystrophy. The increasing prevalence of hand involvement with increasing age is probably due to increased water exposure and

TABLE I. Differentiation between ICD and ACD

Criteria	ICD	ACD
At risk	Anyone, especially if repeated exposure and occupational exposure	Previously sensitized and genetically predisposed
Mechanism	Nonimmunologic, direct tissue damage	Immunologic, delayed-type hypersensitivity reaction
Concentration of offending agent	Usually high, dose effect	Might be low threshold dose, all or nothing
Common causative agents	Water, soaps, solvents, detergents, acids, bases, saliva, urine, stool	Poison ivy, poison oak, poison sumac, metals, cosmetics, medications, rubber, resins, adhesives
Risk if atopic	Increased	Decreased
Symptoms	Burning, stinging, soreness	Itching
Morphology	Erythema, edema, desquamation, fissures	Erythema, edema, vesicles, papules, lichenification
Demarcation	Usually sharp, limited to area in contact with agent	Sometimes sharp
Typical onset	Minutes to hour	Hours to days
Histology	Spongiosis, primarily neutrophilic infiltrates	Spongiosis, primarily lymphocytic infiltrates

occupational insults, along with coexisting irritant dermatitis. Certain morphologic features can help distinguish the different contributing factors to hand eczema. Involvement of the dorsal hand and finger combined with the volar wrist suggest AD as a contributing causative factor.¹¹ ICD commonly presents as a localized dermatitis without vesicles in the webs of fingers; it extends onto the dorsal and ventral surfaces ("apron" pattern; Fig 1), dorsum of the hands, palms, and ball of the thumb. On the other hand, ACD often has vesicles and favors the fingertips, nail folds, and dorsum of the hands and less commonly involves the palms. ICD often precedes ACD, and therefore some pattern changes, such as increasing dermatitis from web spaces to fingertips or from palms to dorsal surfaces, should prompt patch testing or a repeat of it.¹²

Although ICD can cause dermatitis of the feet, ACD seem to be more common. ACD of the feet is usually located on the dorsum of the feet and toes (especially the hallux) but can also involve the sole and calcaneus. The interdigital areas are rarely involved. Humidity, heat, friction, and AD can contribute to or facilitate the development of CD of the feet. The most common positive patch test reactions in patients with ACD exclusively on the feet are rubber compounds (mercaptobenzothiazole mix, thiuram mix, carba mix, and PPD mix), with some patients sensitive to more than 1 of the agents. Other chemicals in footwear (eg, leather, adhesives, glues, and dyes) or in topical agents used for treatment (eg, creams, ointments, and antiperspirants) can cause ACD. Chemical agents used in the tanning and dyeing processes of leather (chrome), glues (colophony) used in soles and insoles, and nickel sulfate used in footwear buckles, eyelets, and ornaments¹³ can be sensitizing agents.

Systemic contact dermatitis

Systemic contact dermatitis (SCD) is a systemic disease that demonstrates the inherent role of the skin as an immunologic organ. In the event that the suppressor function is inadequate, systemic administration of an allergen can lead to a full-blown effector



FIG 1. Irritant contact dermatitis of the hands: localized dermatitis without vesicles of webs of fingers extending onto the dorsal and ventral surfaces ("apron" pattern).

response. SCD is a localized or generalized inflammatory skin disease in contact-sensitized individuals exposed to the hapten orally, transcutaneously, intravenously, or by means of inhalation. It manifests as dermatitis at the cutaneous site of exposure, at previously sensitized sites (eg, an old lesion or the site of a previously positive patch test response), or in previously unaffected areas.¹⁴ A variety of metals (cobalt, copper, chromium, gold, mercury, nickel, and zinc) have been found to cause SCD. The exposure type, duration, and environmental conditions (sweat and oxygen) in proximity to the metal are critical for mobilization of the ions inducing immune reactions. Medications reported to cause SCD include corticosteroids, antihistamines (diphenhydramine, ethylenediamine, hydroxyzine, and doxepin), miconazole, terbinafine, neomycin, gentamicin, erythromycin, pseudoephedrine, cinchocaine, benzocaine, tetracaine, oxycodone, intravenous immunoglobulin (IVIG), aminopenicillins, 5-aminosalicylic acid, naproxen, allopurinol, mitomycin C, 5-fluorouracil, and suxamethonium. In drug-induced SCD the clinical picture is frequently that of symmetric drug-related intertriginous and flexural exanthema. The criteria for the diagnosis of symmetric drug-related intertriginous and flexural exanthema include the following:

- 1 exposure to a systemic drug at first or repeated dosing (contact allergens excluded);
- 2 erythema of the gluteal/perianal area, V-shaped erythema of the inguinal/perianal area, or both;
- 3 involvement of at least 1 other intertriginous/flexural localization;
- 4 symmetry of affected areas; and
- 5 absence of systemic signs and symptoms.¹⁵

With alternative medicine's increasing popularity, more patients are using herbal preparations, homeopathy, and herbs in food, spices, and cosmetics that might contain plants and botanical extracts. Ragweed, chamomile, feverfew (*Tanacetum parthenium*), *Arnica* species, marigold, *Echinacea* species, mugwort, cinnamon oil, vanilla oil, and balsam of Peru have been reported to cause SCD.

Occupational exposure

CD in the occupational setting can be benign and short lived or lead to severe disabling dermatitis. Patients with severe cases have poorer prognosis despite improvements in general working conditions, better availability of diagnostic patch testing, improved understanding of cutaneous biology, and treatment with topical and systemic steroids. ACD to nickel or chromium, a history of chronic dermatitis, delay of adequate treatment, a history of AD, and poor understanding by the worker of his or her disease is associated with a worse prognosis. Treatment of ACD in the workplace includes a timely diagnosis, identification of allergens or irritants, elimination of causal exposures, patient education, and use of therapeutic agents. AD is an important factor in susceptibility to persistent postoccupational dermatitis, and potential involvement of genetic predisposition to chemicals is observed. Two genomic screens^{16,17} showed areas of genetic linkage on several chromosomes.

Patch testing. Patch testing is the only practical, scientific, and objective method for the diagnosis of ACD. It is indicated in patients with a chronic, pruritic, eczematous, or lichenified dermatitis in whom ACD is suspected. Patch test reactions are affected by oral corticosteroids (>20 mg of prednisone per day or its equivalent), cancer chemotherapy, or immunosuppressive drugs but not by antihistamines. Topical corticosteroids on the patch test site should be discontinued for 5 to 7 days before patch testing.

Sources of allergens. Commercially available, standardized patch testing allergens have been calibrated with respect to nonirritant concentrations and compatibility with the test vehicle. Test systems currently available are the thin-layer rapid-use epicutaneous test (T.R.U.E. TEST) and certain screening panels that are not US Food and Drug Administration (FDA) approved but conform to the standards of care recommended by CD experts. Commercial sources of customized patch testing materials include Smart Practice Canada (Calgary, Alberta, Canada); Hermal Pharmaceutical Laboratories, Inc (Hawthorne, NY); Dormer Laboratories, Inc (Rexdale, Ontario, Canada); and Trolab

Allergens (Omniderm Pharma Canada, Inc, Vaudreuil-Dorion, Quebec, Canada). The standardized allergens are loaded in Finn chambers or AllergEaze patch testing chambers (Haye's Service B.V., Alphen aan den Rijn, The Netherlands).

Number of allergens. Although the usefulness of patch testing is enhanced with the number of allergens tested, the ideal number of patch tests to be applied remains controversial. The T.R.U.E. Test contains 29 allergens, and the NACDG series ranges from 65 to 70 allergens. Studies show that the T.R.U.E. Test has higher false-negative reactions to neomycin, thiuram mix, balsam of Peru, fragrance mix, cobalt, and lanolin. Also, gold, bacitracin, methylidibromoglutaronitrile/ phenoxyethanol, propylene glycol, bromonitropropane, cinnamic aldehyde, DMDM hydantoin, and ethylene urea/melamine formaldehyde have a prevalence of more than 2% in the NACDG 2004 but are not included in the current T.R.U.E. Test. Allergens not found on commercially available screening series in the United States frequently result in relevant reactions, and personal products are a useful supplement, especially in facial or periorbital dermatitis. The T.R.U.E. Test might serve as a triage or screening tool in an allergists' practice, but occupational exposures can benefit from early referral for supplemental testing.

Patch test technique. Patches are applied to upper or middle back areas (2.5 cm lateral to a midspinal reference point) free of dermatitis and hair and kept in place for 48 hours. Test results are read 30 minutes after removal of the patches to allow resolution of erythema caused by the tape, chamber, or both if present. A second reading should be done 3 to 5 days after the initial application. Thirty percent of relevant allergens eliciting negative reactions at the 48-hour reading elicit positive reactions in 96 hours. Irritant reactions tend to disappear by 96 hours. Metals (gold, potassium dichromate, nickel, and cobalt), topical antibiotics (neomycin and bacitracin), topical corticosteroids, and PPD can elicit positive reactions after 7 days. More than 50% of positive gold test results are delayed for about 1 week.

Nonstandardized patch tests, such as with the patient's personal products, allergens from cosmetics, or industrial allergens, might be needed. Leave-on cosmetics (makeup, perfume, moisturizer, and nail polish), clothing, and most foods are tested "as is," whereas wash-off cosmetics (soap and shampoo) are tested at 1:10 to 1:100 dilutions. Household and industrial products should only be tested after ascertaining their safety and patch test concentrations in the MSDS information.

Determining clinical relevance. The relevance of positive reactions to clinical ACD can only be established by carefully correlating the history, including sources of antigen in the patient's environment. A positive patch test reaction might be relevant to present or previous dermatitis, multiple true-positive results can occur, and mild responses can still represent an allergic reaction. A positive patch test reaction is considered to be a "definite" reaction of ACD if the result of a "use test" with the suspected item was positive or the reaction to patch testing with the object or product was positive, "probable" if the antigen could be verified as present in known skin contactants and the clinical presentation was consistent, and "possible" if skin contact with materials known to contain allergen was likely. Multiple sensitivities can occur when different allergens are present in different products used simultaneously. Likewise, concomitant sensitization of allergens can occur when multiple allergens are present in

TABLE II. Nickel content of certain foods

>50 µg	Soybean, boiled, ~1 cup: 895 µg Cocoa, 1 tbsp: 147 µg Cashew, ~18 nuts: 143 µg	Figs, ~5: 85 µg Lentils, ½ cup cooked: 61 µg Raspberry: 56 µg
20-50 µg	Vegetables, canned ½ cup: 40 µg Lobster, 3 oz: 30 µg Peas, frozen ½ cup: 27 µg	Asparagus, 6 spears: 25 µg Oat flakes, ⅔ cup: 25 µg Pistachios, 47 nuts: 23 µg
<20 µg	Strawberries, 7 medium: 9 µg Wheat bread, 1 slice: 5 µg Poultry, 3.5 oz: 5 µg Carrots, 8 sticks: 5 µg Apple, 1 medium: 5 µg	Cheese, 1.5 oz: 3 µg Yogurt, 1 cup: 3 µg Mineral water, 8 fl oz: 3 µg Mushroom, raw ½ cup: 2 µg Corn flakes, 1 cup: 2 µg

the same product; both processes induce sensitization. Cross-sensitization can also occur. Common combinations of positive patch test results are PPD and benzocaine (cross-sensitize); thiuram mix, carba mix, and mercapto mix (rubber products); quaternium 15 and paraben (quaternium-15, a formaldehyde releaser and formaldehyde are frequently combined and cosensitize); and cobalt and nickel (cobalt used in alloys with nickel and chromium and cosensitized). Patients older than 40 years are prone to multiple sensitivities.

The repeat open application test (ROAT) might confirm the presence or absence of ACD. The suspected allergens are applied to the antecubital fossa twice daily for 7 days and observed for dermatitis. The absence of reaction makes CD unlikely. If eyelid dermatitis is considered, ROAT can be performed on the back of the ear.

SELECTED CONTACT ALLERGENS

Metals

Nickel. The prevalence rate of a positive patch test reaction to nickel in North America is consistently increasing. The most recent patch test data from the NACDG¹⁸ reported that 18.7% of patients evaluated for ACD had a positive patch test reaction to nickel. Female subjects' sensitization to nickel is higher because of increased ear piercing. Laws regulating nickel products (eg, limiting the migration limit of nickel, the nickel ion release threshold of nickel-plated objects in prolonged contact with the skin, and the nickel content of post assemblies) in Europe appear to decrease sensitization in the younger population.

Evidence supports the contribution of dietary nickel to vesicular hand eczema.¹⁹ A meta-analysis of SCD estimated that about 1% of patients with nickel allergy would have systemic reactions to the nickel content of a normal diet. Ten percent would react to exposures to 0.55 to 0.89 mg of nickel.²⁰ Foods with higher nickel content include soybean, fig, cocoa, lentil, cashew, nuts, and raspberry (Table II).

Gold. Previous NACDG data reported that 389 (9.5%) of 4101 patients had positive patch test reactions to gold. The most common sites of dermatitis were in the hands (29.6%); the face, with seborrheic distribution (19.3%); and the eyelids (7.5%).²¹ Although mostly used for fashion appeal, gold is also an anti-inflammatory medication, is used in the electroplating industry, and is part of dental appliances. Patients with gold dental appliances (especially if present for more than 10 years) can present with oral symptoms. A subset of patients with facial dermatitis clear

with gold avoidance, mostly women with titanium dioxide in facial cosmetics, which adsorbs gold released from jewelry. Patients with gold allergy and eyelid dermatitis have cleared by not wearing gold jewelry, and therefore a trial of gold avoidance might be warranted with positive patch test reactions to gold. The avoidance period required for demonstrating benefit is long and might only be partially mitigating.²²

Cosmetics

An individual is exposed to more than 100 chemical contactants in a typical day. Common allergens in these products include fragrances, preservatives, excipients, glues, and sun blocks.

Fragrance. Fragrance, the allergen of the year for 2007, is the most common cause of ACD from cosmetics and results in positive patch test reactions in 10.4% of patients. There are more than 2800 fragrance ingredients listed in the database of the Research Institute for Fragrance Materials, Inc.,²³ and more new chemicals and botanical extracts are frequently used as fragrances. A manufacturer's label of "unscented" might erroneously suggest absence of fragrance when, in fact, a masking fragrance is present. "Fragrance-free" products are typically free of classic fragrance ingredients and are generally acceptable for the allergic patient. However, botanical extracts can be added to improve odor characteristics.

Because fragrances are complex substances, a perfume can contain hundreds of different chemicals that are difficult to identify individually. Fragrance mix I contains allergens found in 15% to 100% of cosmetic products²³ and might detect approximately 85% of subjects with fragrance allergy.²⁴ The addition of other commonly used fragrance ingredients (ylang ylang oil, narcissus oil, sandalwood oil, and balsam of Peru) increases the yield to 96%. The actual fragrance mix widely used in cosmetics and household products are seldom used in patch testing by the NACDG. Thus a positive patch test reaction to fragrance must correlate with distribution of the dermatitis and an evaluation of clinical relevance, such as a positive ROAT reaction.

Preservatives and excipients. Lanolin is a common component of consumer products. Unfortunately, its composition has not been fully characterized. Medicaments containing lanolin are more sensitizing than lanolin-containing cosmetics. It is a weak sensitizer on normal skin but a stronger sensitizer on damaged skin. Thus patients with chronic dermatitis, especially stasis dermatitis, are at higher risk of lanolin sensitivity.²⁵

Cosmetic preservatives can be grouped into formaldehyde releasers and non-formaldehyde releasers. Paraben, a non-formaldehyde releaser, is the most commonly used preservative in cosmetics, as well as in pharmaceutical and industrial products, because of its broad spectrum of activity against yeasts, molds, and bacteria. Type I immediate hypersensitivity reactions (contact urticaria) and SCD from ingestion of paraben-containing medications or foods have been reported.²⁶

Hair products. Hair products are second only to skin products as the most common cause of cosmetic allergy.

PPD is currently the most common cause of CD in hairdressers. In hair dye users the dermatitis often spares the scalp and usually involves the face near the hairline, eyelids, and neck. Nevertheless, generalized eruptions can occur. IgE-mediated contact urticaria and anaphylaxis, as well as lymphomatoid reactions, have also been reported. PPD cross-reacts with other chemicals, such as COX-2 inhibitor (celecoxib), sunscreens, and antioxidants used in the manufacture of rubber products (N-isopropyl-N'-

phenyl-*p*-phenylenediamine). Theoretically, once oxidized, the PPD is no longer allergenic, but in reality, it is likely that PPD is never completely oxidized.²⁷ The FDA-required labeling and home-user tests appear to be predictive of PPD sensitization.²⁸ New hair dyes that contain FD&C and D&C dyes have very low levels of cross-reactivity with PPD and its other chemically related oxidative dyes (eg, Elumen Hair Color; Goldwell Cosmetics, Linthicum Heights, Md).

CAPB is an amphoteric surfactant often found in shampoos, bath products, and eye and facial cleaners. CAPB allergy typically presents as eyelid, facial, scalp, and/or neck dermatitis. Contaminants, such as amidoamine and dimethylaminopropylamine, which occur in the manufacture of CAPB, are thought to be allergens causing ACD. Positive patch test reactions to CAPB are often clinically relevant.²⁹

Glycerol thioglycolate is the active ingredient in permanent wave solution. Unlike PPD, the thioglycolates might remain allergenic in the hair long after it has been rinsed out. Thus skin eruptions can continue for weeks after application of the permanent wave solution, and hairdressers allergic to it might be unable to cut permanent waved hair.

Medications

Antibiotics and antiseptics. Neomycin and nitrofurazone are potent sensitizers. Neomycin sulfate can cross-sensitize with gentamicin, kanamycin, streptomycin, spectinomycin, tobramycin, and paromomycin.

Corticosteroids. Although type I hypersensitivity reactions have been observed to corticosteroids, delayed-type hypersensitivity is by far the most common.³⁰ ACD to topical corticosteroids is rarely suspected from the history or from the appearance of the dermatitis, probably because of its anti-inflammatory action. Thus patients with a long-standing nonhealing dermatitis (eg, AD, stasis dermatitis, or chronic hand eczema) and patients with worsening of a previous dermatitis or an initial improvement followed by a deterioration of the dermatitis after application of corticosteroids should be evaluated for corticosteroid allergy. Patch tests for corticosteroid allergy should include the groups of simultaneously or cross-reacting corticosteroids,³¹ as well as the vehicle and preservatives in the preparations. There is a 7-fold increase in frequency of a positive patch test reaction within a corticosteroid group. Cross-reactivity between groups A and D2 and groups B and D2 also has been reported.³²

The optimal patch test concentration has not been worked out for most corticosteroids. A high patch test concentration of a potent corticosteroid might result in a false-negative test result on early readings because of its anti-inflammatory action. In such cases a lower concentration can be used if there is a strong suspicion of ACD, including corticosteroid-treated asthma and rhinitis. Patch tests to corticosteroids should include the patient's own commercial product. Thirty percent of the cases of ACD to corticosteroids might be missed if a delayed 7-day reading is not done.³³

Surgical implant devices

The use of nickel in biomedical devices, especially in joint prostheses and endovascular stents, has led to increasing concern about the safety of permanent or semipermanent metal medical devices in suspected nickel-sensitized patients. Presently, there is high variability of care in terms of testing, recommendations, and, in some cases, selection of more expensive and less optimal

options. Unfortunately, there are no large, evidence-based, prospective case studies or expert panel consensus guidelines on this issue.¹⁹

In patients with ACD to orthodontics, nickel is the most common allergen. Stainless-steel arch wires are thought to release less amounts of nickel compared with flexible titanium-nickel arch wires. In a retrospective study of 131 patients suspected of coronary in-stent restenosis 6 months after 316L stainless-steel stent placement and patch testing 2 months after angioplasty, there were 11 positive patch test reactions in 10 (8%) of the patients. All 10 patients with a positive patch test reaction to metal (7 to nickel and 4 to molybdenum) had in-stent restenosis associated with clinical symptoms and a higher frequency of restenosis than seen in patients without metal allergy, suggesting that allergy to metals, nickel in particular, plays a relevant role in inflammatory fibroproliferative restenosis.³⁴ A prospective study of 174 patients with stents noted that patients with a recurrence of in-stent restenosis, although not after initial stent placement, had significantly greater positive patch test reactions to metals, most commonly nickel and manganese.³⁵ To date, the evidence for complications caused by nickel allergy is weak; proved cases are rare and remain on the case report level. The need for patch testing is controversial, and patch tests are not reliable in predicting or confirming implant reaction. A negative patch test reaction is reassuring for the absence of a delayed hypersensitivity reaction.

CD and patch testing in children

Although ACD is more common in teenagers, children as young as 6 months can be sensitized to contact allergen. The relevant allergens in children are similar to those in adults, with nickel, fragrance, and rubber being common sensitizers. The increasing rate of sensitization might be due to new trends in body piercing, tattooing, and use of cosmetic products. Adolescents constitute a significant portion of the population allergic to nickel. Kütting et al³⁶ recommend that ear piercing be delayed until after 10 years of age, presumably to allow for the development of immune tolerance. Children can tolerate the same patch test concentrations as adults, and polysensitization is common. Children with and without AD have the same rate of positive patch test reactions.

Treatment and prevention

Allergen identification to improve contact avoidance can be challenging, especially in work-related CD. Alternatives and substitutes to cosmetics should be offered to the patient to increase compliance. For patients with nickel allergy, barriers such as gloves and covers for metal buttons and identification of nickel by using the dimethyl-glyoxime test can be prescribed.

For supportive care and relief of pruritus, cold compresses with water or saline, Burrow solution (aluminum subacetate), calamine, and colloidal oatmeal baths might help acute oozing lesions. Excessive handwashing should be discouraged in patients with hand dermatitis, and nonirritating or sensitizing moisturizers must be used after washing.

A topical corticosteroid is the first-line treatment for ACD. For extensive and severe CD, systemic corticosteroids might offer faster relief. Studies on calcineurin inhibitors are limited, and their efficacy in patients with ACD or ICD has not been established. Oral antihistamines can be tried for pruritus, but oral diphenhydramine should not be used in patients with ACD to Caladryl (diphenhydramine in a calamine base) and hydroxyzine

hydrochloride (Atarax) in an ethylenediamine-sensitive patient. Other modes of therapy are UV light treatment and immunomodulating agents, such as methotrexate, azathioprine, and mycophenolate mofetil.

OTHER IMMUNE-MEDIATED SKIN DISORDERS

Psoriasis

Psoriasis and AD have many similarities. They are common, chronic, inflammatory, and proliferative skin disorders in which both genetic and environmental factors play important roles. Psoriasis is primarily T_H1 mediated, whereas AD is generally thought to be T_H2 mediated. T cells in both diseases are triggered by conventional antigens and superantigens. Some studies suggest that group A streptococcus is a superantigen for acute guttate psoriasis, which is often preceded by or concurrent with infection^{37,38} and is associated with an increase in serum antistreptococcal titers. Symptoms in patients with guttate psoriasis and AD frequently improve with systemic antibiotic therapy.

Although both psoriasis and AD have been associated with increased numbers of dendritic cells (DCs) in the skin, differences in DC populations, as well as the chemokine and cytokine environment, might have implications on potential targets for future therapeutic interventions. In patients with AD, myeloid DCs upregulate CCL17 and CCL18, which is in contrast to TNF- α and inducible nitric oxide synthase in patients with psoriasis.³⁹

T_H17 cells have been implicated in the pathogenesis of psoriasis and other autoimmune inflammatory diseases.³⁷ Keratinocytes produce 2 T_H17 cytokines: IL-17A and IL-22. IL-23, which is overproduced by DCs and keratinocytes in patients with psoriasis, stimulates survival and proliferation of T_H17 cells within the dermis and drives keratinocyte hyperproliferation.

Autoimmune bullous diseases

Autoimmune blistering diseases are associated with antibodies against structural components of the skin and mucous membranes that maintain cell-to-cell and cell-to-matrix adhesion. In pemphigus vulgaris (PV), autoantibodies target the desmoglein adhesion molecule in the intercellular junctions and produce intraepithelial blisters. In bullous pemphigoid (BP) and epidermolysis bullosa acquisita, subepidermal blistering is associated with autoantibodies against the anchoring complex at the junction of the dermis and epidermis. Autoantibodies in patients with BP are formed against the basement membrane hemidesmosomal glycoproteins BP230 and BP180 and preferentially recognize phosphoepitopes in collagen XVII. In most subepidermal autoimmune blistering conditions, autoantibodies form deposits that cause the release of proteolytic enzymes through activation of the complement cascade, which destroys the basement membrane.⁴⁰

Drugs containing sulfhydryl groups that cleave epidermal intercellular substances have resulted in the production of antibodies and blistering skin diseases. Penicillamine, furosemide, captopril, penicillin and its derivatives, sulfasalazine, salicylazosulfapyridine, phenacetin, nalidixic acid, and topical fluorouracil have been implicated.

The diagnosis of autoimmune bullous diseases requires the detection of tissue-bound and circulating serum autoantibodies by using various immunofluorescence methods, such as immunoblotting, ELISA, and immunoprecipitation.⁴¹



FIG 2. Urticarial skin lesions.

Treatment of PV includes long-term use of systemic corticosteroids to diminish autoantibody production, and only about 10% of patients achieve complete remission after initial treatment. Azathioprine, cyclophosphamide, methotrexate, mycophenolate, hydroxychloroquine, gold, and dapsone are other potential options. Rituximab, alone or in combination with IVIG, appears to be an effective therapy for patients with refractory PV and pemphigus foliaceus.

The mainstay of therapy in most patients with BP is oral corticosteroids at the lowest maintenance dose that will prevent new lesion formation and allow alternate-day therapy. A randomized trial suggests that patients with BP might have improved outcomes with topical rather than systemic corticosteroids, even in the presence of extensive disease.⁴² Steroid-sparing agents, such as azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate, dapsone, and tetracycline, can be used in combination with prednisone. In patients with cicatricial pemphigoid with involvement of the eyes, esophagus, or larynx, IVIG, etanercept, and infliximab have been used.

URTICARIA

Significant advances have occurred in our understanding of chronic urticaria (CU) since the last publication of the primer in 2003, but our understanding of this challenging illness is still imperfect. This review will cite pertinent recent review articles, and the reader is encouraged to find primary citations within these reviews. During the last 5 years, further evidence has accumulated that quality of life is severely affected in patients with CU, and these patients deserve our unqualified attention.^{43,44} The most significant recent conceptual advances in our understanding of CU have been (1) the deepening appreciation that there is evidence of autoimmunity for a substantial number of patients and (2) a better understanding of the implications of diminished basophil function.⁴⁵⁻⁴⁸ Nevertheless, it is still unclear whether the detected

autoimmune phenomena or defects in basophil signaling contribute to the pathophysiology of CU and, if they do participate, what pathways are involved. Therapy of CU has also advanced, with more evidence supporting the efficacy of immunomodulatory drugs.^{49,50}

Background

Urticarias are pruritic, edematous erythematous lesions of variable size that blanch under pressure (Fig 2). An episode of urticaria is a common phenomenon affecting 15% to 25% of individuals during their lives.⁵¹ Most of these cases are acute in nature and are easily managed, but about 30% of patients continue to have frequent episodes of hives for more than 6 weeks and are considered to have chronic disease.⁴⁴ Approximately 40% of patients also have angioedema, swelling of the subdermis, that accompanies the urticarial lesions. In a smaller number, approximately 10%, angioedema is present without visible urticaria.⁴⁴ CU occurs more often in adults and affects women (75%) more than men. Based on the results of history, physical examination, laboratory testing, and provocative testing, CU has been further divided into IgE-mediated urticaria (approximately 1% to 5%) or the physical urticarias (approximately 20%) and idiopathic urticaria (75% to 80%). The idiopathic cases, chronic idiopathic urticaria (CIU), include 30% to 60% who have an autoimmune phenotype, but the evidence that autoimmunity is pathophysiologic in the same way that physical stimuli are considered directly related to the development of hives is not generally accepted.^{44,47,52} For the purpose of this discussion, patients with autoantibodies will be considered to have idiopathic urticaria with evidence of autoimmunity.

Pathogenesis

The primary effector cells in patients with urticaria are mast cells, which are present in high numbers throughout the body,

including the subcutaneous tissue. Activated mast cells produce a wide variety of proinflammatory and vasodilatory substances, including the immediate (<10 minutes) release of histamine from granules and the production of leukotriene C₄ and prostaglandin D₂ from membrane phospholipids. There is also more delayed (4–8 hours) production and secretion of inflammatory cytokines, such as TNF- α , IL-4, and IL-5. The immediate products are responsible for pruritus, swelling, and erythema, whereas the later products lead to an influx of inflammatory cells.⁴⁷

Lesions of acute urticaria are characterized by subcutaneous edema with widened dermal papillae and rare inflammatory cells. Lesions of CU, in addition to the presence of edema, are characterized by a perivascular inflammatory infiltrate consisting of CD4⁺ and CD8⁺ T lymphocytes, eosinophils, basophils, and neutrophils. A small number of patients with urticarial vasculitis present with atypical clinical features and have histologic evidence of vascular destruction.⁴⁷

In small subgroups of patients, CU is driven by IgE/allergen interactions stimulating the high-affinity receptor for IgE (Fc ϵ RI) or by physical stimuli acting through nonspecific pathways. For CIU, the pathophysiology is still unclear. The earliest observations suggestive of an autoimmune mechanism was by Grattan and Humphreys,⁴³ who reported in 1986 that sera from a subset of patients with CIU could cause a wheal-and-flare reaction when injected intradermally into their own (autologous) skin. The results of this autologous serum skin test (ASST) are positive in approximately 40% of patients with otherwise idiopathic CU and generally in less than 5% of control subjects.⁵² Two other *in vitro* tests of serum-derived activity that activates basophils have been published. Assay of serum-mediated expression of CD63 on donor basophils correlates with the basophil histamine release (BHR) assay and assay of serum-induced expression of the surface marker CD203c, which is correlated with both the BHR assay and the size of the ASST reaction. There is general consensus that these assays detect IgG autoantibodies to the α -chain of Fc ϵ RI (90%) or IgE.^{46,52} These “functional” autoantibodies are distinct from immunochemical detection of IgG recognizing Fc ϵ RI (α -chain) in an ELISA or on immunoblotting because autoantibodies measured in this fashion are found in many healthy subjects.^{45–48,52}

Although at first glance the importance of functional autoantibodies to Fc ϵ RI appears to be a good conceptual framework, there are a number of limitations.^{45,48} The finding that some donor basophils work better than others and that mast cells and basophils do not always work with the same serum is a mystery and undermines the general applicability of these assays.^{45,48} Although *in vitro* tests are dependent on IgG in the serum, some sera that result in a positive ASST response can still produce a positive ASST response after removal of IgG by protein G, suggesting the presence of other histamine-releasing factors.^{45,48} Discrepancies have been reported between *in vivo* ASST and *in vitro* BHR tests. For example, only about 50% of sera from patients with CIU who have a positive ASST response have a positive BHR response with single-donor basophils, whereas the correlation is better if the study is done with those who have the strongest ASST responses and more than 1 donor of basophils/mast cells is used in the assay.⁴⁸ If the autologous test is performed with plasma, 86% of patients have positive responses compared with 40% of those when the test is performed with serum, suggesting that the coagulation pathway might play a role.^{45,48} The importance of autoantibodies has been questioned

because there are only small differences between the clinical course of those with and those without evidence of functional autoantibodies and the autoantibodies can be detected in patients who are in remission.⁴⁷

An entirely different view of the mechanisms underlying CIU comes from the observation that patients with CIU tend to be basopenic and that the basophils that are present are relatively resistant to activation by anti-IgE. This has led Brodell et al⁴⁷ to divide patients with CIU into 2 groups: responders and nonresponders. Although the patients with the responder phenotype complain of more itching, these defects resolve as disease activity lessens, and there are only modest differences in the clinical course of these 2 populations.⁴⁸ An additional interesting finding is that these subgroups do not segregate with the subgroups with and without evidence of autoimmunity.⁴⁸ As in the case of the subpopulation with evidence of autoantibodies, the knowledge of these subgroups has not resulted in changes in therapy.

Diagnosis

This discussion will focus on recently described laboratory tests for patients with CIU that either lead to a specific treatment regimen or allow the physician to reassure the patient that their hives are due to an intrinsic process and not an extrinsic cause. Several general approaches to the workup of patients with CU have been recently published.^{43,44}

Many specialists look for evidence of autoimmunity. The most common tests ordered are those for anti-thyroid antibodies because results on these tests are abnormal in 15% to 20% of patients with otherwise idiopathic urticaria. Other tests for autoimmunity include the ASST and 2 new *in vitro* tests for antibodies that activate target basophils: the BHR test and a test for upregulation of the basophil surface marker CD203c. As mentioned above, patients with evidence of autoantibodies have been reported to have more severe disease, but the effect is small.^{43,44} In patients who are desirous of knowing what might be contributing to their CU, knowledge of these autoantibodies might help them accept that CIU is a skin disease and is not caused by an exogenous trigger.

Yet another area of controversy is the detection of infection with *Helicobacter pylori*. This common infection is found in a minority of patients with CU. A meta-analysis of 10 studies provided evidence that eradicating *H pylori* from patients with CIU who have evidence of this infection is beneficial at resolving the urticaria.⁴³ The pathophysiologic link between infection with *H pylori* and urticaria is uncertain, leaving the general idea that low levels of immune complexes might be causative.⁴⁴

Measurement of the ability of *ex vivo* basophils from patients with CIU to release histamine when triggered with anti-IgE is still a research test that might become clinically useful in the future.⁴⁸

Treatment

For many patients with acute urticaria and for a few patients with CU, a specific trigger can be identified, and avoidance can be an effective approach. This is not the case for some patients with acute urticaria and most with CU. A generally accepted approach for those with acute urticaria is to suppress the hives with H₁-type antihistamines, with preference for low-sedating and nonsedating agents on a daily basis and potentially sedating antihistamines for rescue and at night. For some patients with severe acute urticaria

who are unresponsive to antihistamines, a brief course of oral corticosteroids is warranted.

Treatment of patients with CIU is much more complicated. Low-sedating and nonsedating type 1 antihistamines remain the mainstay of therapy, and their efficacy has been shown to be greater than that of placebo in multiple double-blind, placebo-controlled trials. Many specialists believe that it is important to treat underlying immunologic and infectious conditions that have been detected through a detailed history, a thorough physical examination, and selected laboratory evaluations. If the urticaria is controlled with standard doses of H₁ blockade, it is reasonable to continue this treatment for several months, occasionally stopping it briefly to see whether the hives have spontaneously resolved. For patients whose symptoms are not controlled by H₁ blockade, there are a variety of opinions as to what to do next. A brief course of oral corticosteroids might be warranted, but systemic corticosteroids are not an acceptable long-term treatment. The only treatment beyond antihistamines that has been proved to be effective in a double-blind, placebo-controlled fashion is cyclosporin A.^{43,44,49} Because this is a fairly aggressive treatment, some specialists try a variety of other interventions before prescribing cyclosporine. The most common approach is to push the H₁ blockade by using these agents at 2 to 4 times the FDA-approved dose.⁴⁴ Other approaches include adding an H₂ blocker, a leukotriene pathway modifier, or both. Commonly tried immunomodulatory agents with a better side-effect profile than cyclosporine include hydroxychloroquine, sulfasalazine, colchicines, dapsone, mycophenolate, and omalizumab (anti-IgE); however, none of these have been formally proved to be effective. The decision to treat patients with CIU who have anti-thyroid antibodies and normal thyroid-stimulating hormone levels with L-thyroxine is controversial.^{43,52} Antimetabolites, such as methotrexate, azathioprine, and the anti-B-cell drug rituximab have also been used. Reviews of these treatments and specific guidelines for use of many of these agents and for monitoring risks and side effects have been published recently.^{43,44,49,50}

AD

The reader is referred to a number of excellent recent reviews on the pathophysiology and treatment of AD.^{51,52} This section will therefore primarily focus on advances in our understanding of AD since the last primer was published.

Skin barrier dysfunction

During the past year, it has become well accepted that skin barrier dysfunction plays a critical role in the development of AD. This is largely because loss-of-function null mutations in the skin barrier gene filaggrin have been repeatedly demonstrated to be a major risk factor for the development of AD.⁵³⁻⁵⁶ Filaggrin gene mutations are associated with persistent and more severe eczema, early onset of AD, and an increased risk of asthma in patients with a previous history of eczema.^{57,58} Therefore this mutation contributes to the atopic march by enhancing systemic allergen sensitization through the skin. Defects in skin barrier function, however, likely result from a combination of factors, including a deficiency of skin barrier proteins, increased peptidase activity, the lack of certain protease inhibitors, and lipid abnormalities.⁵⁹⁻⁶¹ Furthermore, T_H2 responses have also been found to reduce filaggrin gene and protein expression.⁶²

Innate immune response

Study of the innate immune response in patients with AD has been an active area of investigation. There is now considerable evidence that a defective innate immune response contributes to increased bacterial and viral infections in patients with AD.⁶³ Pattern-recognition receptors play a critical role in sensing the environment for invading pathogens. Toll-like receptors (TLRs) are prototypic pattern-recognition receptors that discriminate between diverse pathogen-associated molecular patterns. A polymorphism within the *TLR2* gene has been shown to be associated with severe forms of AD prone to recurrent bacterial infections and has been linked to TLR2 dysfunction.⁶⁴

Keratinocytes and DCs in the epidermis represent the key cells involved in the skin innate immune response. AD skin contains an increased number of IgE-bearing Langerhans cells (LCs). Binding of IgE to LCs occurs primarily through high-affinity IgE receptors. In contrast to mast cells and basophils where the FcεRI is a tetrameric structure, the receptor on LCs consists of the α-chain, which binds IgE and γ-chain dimers containing an immunoreceptor tyrosine-based activation motif for downstream signaling, but lacks the classic β-chain.⁶⁵ Allergens that invade the skin are taken up by IgE molecules bound to FcεRI-expressing LCs for allergen presentation to T_H2 cells. The clinical importance of these IgE receptors is supported by the observation that the presence of FcεRI-expressing LCs bearing IgE molecules is required to provoke eczematous skin lesions through application of aeroallergens to uninvolved skin of patients with AD.

Human plasmacytoid dendritic cells (PDCs) are the only professional IFN-producing cells, and their responses to viral antigens are important for effective host defense against viral infections.⁶⁶ Human PDCs bear TLR7 and TLR9 on their cell surfaces. Furthermore, they express FcεRI. Because of a close interaction of FcεRI with TLR9, the amount of IFN-α and IFN-β released in response to TLR9 stimulation is profoundly downregulated in PDCs after FcεRI aggregation and allergen challenge *in vitro*.^{67,68} Compared with psoriasis, CD, or lupus erythematosus, the frequency of PDCs in patients with AD is decreased.^{69,70} This might account for the increased propensity of patients with AD to have disseminated viral skin infections.

Keratinocytes play an important role in the skin innate immune response by producing antimicrobial peptides (AMPs) in response to stimulation by invading pathogens and inflammation or trauma to the skin. Defensins and cathelicidins are broad-spectrum AMPs that act as natural antibiotics to kill a wide variety of bacterial, viral, and fungal pathogens.⁶³ Chronic inflammatory skin diseases, such as psoriasis or CD, demonstrate marked upregulation of cathelicidin and defensin expression in their skin lesions. In contrast, AD skin lesions are associated with very weak upregulation of human β-defensin (HBD) 2 and 3 and LL-37.⁷¹ Expression of T_H2 cytokines, such as IL-4, IL-13, and IL-10, have been shown to downregulate AMP expression *in vitro* and might account for low AMP levels in the skin of patients with AD.^{71,72} Moreover, reduced mobilization of human HBD3 accounts for defective killing of *Staphylococcus aureus* in patients with AD.⁷³ In addition to the propensity for bacterial infections caused by low HBD2, HBD3, and LL-37 expression, cathelicidin and HBD3 deficiency in patients with AD also contributes to severe viral infections, such as eczema vaccinatum caused by orthopoxvirus⁷⁴ and eczema herpeticum (EH).⁷⁵ In support of this concept, lower levels of cathelicidin are detected

in skin lesions of patients with AD with 1 or more episodes of EH in their history compared with patients with those seen in patients with AD without EH.

The adaptive immune response in patients with AD

Systemic immune response. Most patients with AD have peripheral blood eosinophilia and increased serum IgE levels. This is reflected in an increased frequency of peripheral blood skin-homing T_H2 cells producing IL-4, IL-5, and IL-13 but little IFN- γ . This might be due to selective apoptosis of circulating memory/effector T_H1 cells in patients with AD.⁷⁶ The decreased IFN- γ levels produced by T cells from patients with AD might be the result of reduced production of IL-18.⁷⁷ Furthermore, an inverse relationship between skin colonization with *S aureus* and spontaneous T cell–derived IFN- γ production has been observed.⁷⁸

Biphasic T_H2-T_H1 cytokine skin response. Acute AD skin lesions are associated with the infiltration of T_H2 cells expressing increased levels of IL-4, IL-13, and IL-31, a pruritogenic T_H2 cytokine that correlates with severity of AD.⁷⁹ A number of determinants support T_H2 cell development in patients with AD. These include the cytokine milieu in which the T-cell development is taking place, the costimulatory signals used during T-cell activation, and the antigen-presenting cells. IL-4 promotes T_H2 cell development, whereas IL-12 induces T_H1 cells. AD keratinocytes participate in the adaptive immune response by expressing high levels of the IL-7–like cytokine thymic stromal lymphopoietin (TSLP), which activates myeloid DCs to promote T-cell expression of IL-5 and IL-13.⁸⁰ Skin-specific overexpression of TSLP in a transgenic mouse resulted in an AD-like phenotype, with the development of eczematous lesions containing inflammatory dermal cellular infiltrates, an increase in T_H2 CD4⁺ T cells expressing cutaneous homing receptors, and increased serum levels of IgE,⁸¹ suggesting an important role of TSLP in AD. DCs primed by TSLP might convert to strong inducers of T-cell responses of the T_H2 type *in vitro*,⁸² so that enhanced TSLP release triggered by frequent allergen challenge might initiate and microbes might perpetuate T_H2 immune responses in patients with AD.

LCs bearing Fc ϵ RI are the major myeloid DC population present in nonlesional and acute AD skin. After IgE binding and internalization of the allergen, LCs migrate to peripheral lymph nodes, present the processed allergen to naive T cells, and initiate a T_H2 immune response with sensitization to the allergen. Concomitantly, aggregation of Fc ϵ RI on the surface of LCs *in vitro* promotes the release of chemotactic factors, which *in vivo* is thought to contribute to the recruitment of IgE receptor–bearing inflammatory dendritic epidermal cells (IDECs) into the epidermis. IDECs mainly present at inflammatory sites, produce high amounts of proinflammatory cytokines after Fc ϵ RI cross-linking, display a high stimulatory capacity to T cells, and serve as amplifiers of the allergic inflammatory immune response.⁸³ Moreover, stimulation of Fc ϵ RI on the surface of IDECs induces the release of IL-12 and IL-18 and enhances the priming of naive T cells into IFN- γ –producing T_H1 or T_H0 cells. These mechanisms might contribute to the switch from the initial T_H2 immune response in the acute phase to the T_H1 immune responses in the chronic phase of AD.

Regulatory T cells

Other T-cell types can also contribute to the magnitude and persistence of AD-related skin inflammation. Recent studies have

examined the potential role of regulatory T cells. Mice deficient in forkhead box protein 3–positive regulatory T cells spontaneously have eczema.⁸⁴ Although one report found an absence of resident regulatory T cells in AD skin lesions,⁸⁵ another found increased numbers of regulatory T cells in AD skin.⁸⁶ Reefer et al⁸⁷ analyzed the properties of CD25^{hi} T-cell subtypes in patients with AD associated with increased serum IgE levels. CD25^{hi} T cells expressing regulatory T-cell markers (forkhead box protein 3, CCR4, and cutaneous lymphocyte-associated antigen) were increased in patients with AD compared with those seen in control subjects with low serum IgE levels. This phenomenon was linked to disease severity. Two subtypes of CD25^{hi} T cells were identified on the basis of differential expression of the chemokine receptor CCR6. Activated CCR6^{neg} cells secreted T_H2 cytokines, and coculture with effector T cells selectively enhanced IL-5 production. Moreover, induction of a T_H2-dominated cytokine profile on activation with bacterial superantigen was restricted to the CCR6^{neg} subtype. These studies indicate that despite a regulatory phenotype, activated CD25^{hi} T cells that lack expression of CCR6 promote T_H2 responses and might therefore contribute to the atopic immune response.

T_H17 cells

T_H17 cells have also been identified in AD skin lesions and might therefore contribute to skin inflammation in patients with AD.⁸⁸ However, their expression is significantly less than that seen in patients with psoriasis.⁸⁹ Furthermore, T_H2 cytokines, such as IL-4 and IL-13, inhibit IL-17–induced effects on generation of AMPs by keratinocytes.⁹⁰

Management

Recent approaches to the management of AD have focused on the development of improved skin barrier creams, early dietary interventions, and novel immunomodulators that can reduce skin inflammatory responses.^{51,91} There remains interest in treating infants with hydrolyzed infant formulas⁹² or probiotics to control eczema early in life by directing allergic responses.^{93–96} Perhaps the most interesting development is the observation that oral supplementation with vitamin D augments the innate immune response in patients with AD.⁹⁷ There also remains interest in the use of topical calcineurin inhibitors as an anti-inflammatory therapy. Promising novel anti-inflammatory therapies are also gaining attention. Although these require further controlled trials, they include lymphocyte function-associated molecule 3/IgG fusion protein⁹⁸ and anti-CD20.⁹⁹

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