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IgE-dependent histamine-releasing factors

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Atopic dermatitis is a chronic inflammatory skin disorder characterized by extreme pruritus, chronically relapsing course, and specific distribution. It constitutes one of the "allergic triad" (atopic dermatitis, asthma, and allergic rhinitis) and generally begins in early life as an erythematous, papulovesicular eruption which progresses to a scaly, lichenified dermatitis over time [33]. The distribution of the rash typically varies with age [10], involving the cheeks and extensor surfaces of the arms and legs in the young infant, moving to the flexor surfaces, neck, wrists, and ankles in the young child, and then affecting the flexural surfaces, face (especially periorbital), hands, and feet in the teenage patient and young adult.

Although studies of large family kindreds and twin pairs indicate a significant genetic component in atopic dermatitis [40], environmental factors play a major role in the expression of this disorder. Several reasons have been given to implicate a pathogenic role for an IgE-mediated mechanism in atopic dermatitis: transfer of eczema to bone-marrow recipients from atopic transplant donors [1], elevated serum IgE concentrations and positive immediate skin tests and radioallergosorbent tests (RAST) to various dietary and environmental allergens in 80% of patients [11, 12, 32], positive family history of atopy in 70% to 90% of patients [28, 37], and the development of other atopic disorders in most children with atopic dermatitis [30, 46]. The histological appearance of eczematous lesions has suggested a classical type IV, cell-mediated hypersensitivity reaction in the pathogenesis of atopic dermatitis [27]. However, infiltration of lymphocytes and monocytes in the terminal stages of the "late-phase" IgE-mediated response following allergen-induced mast cell activation also have been implicated [18, 44]. During the "immediate" phase of mast cell activation, chemotactic factors are generated which attract neutrophils and eosinophils to the area. Approximately 4 to 8 h later, neutrophils and eosinophils infiltrate the dermis. Biopsies obtained 8 to 10 h after the initiation of a reaction contain 48% lymphocytes, 27% eosinophils, 9% neutrophils, and 7% monocytes [44]. Lymphocytes and monocytes become pre-

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dominant in 1 to 2 days. Eosinophils release "major basic protein" (MBP), a cytolytic protein capable of damaging skin epithelial cells and promoting further mast cell histamine release, eosinophil cationic protein (ECP), eosinophil-derived neurotoxin, and eosinophil peroxidase [43]. Skin biopsies from chronic eczematous lesions of patients with atopic dermatitis contain large quantities of MBP and ECP in the superficial dermis. MBP and ECP are not present in non-eczematous skin, indicating selective deposition of these eosinophil products by infiltrating eosinophils [17].

Mechanisms involving IgE molecules other than direct allergen-IgE activation of cutaneous mast cells also are likely to be responsible for the inflammation in eczematous skin lesions. Langerhans cells containing high-affinity FcE₁ receptors [8, 50] are found in increased numbers in lesional skin of atopic dermatitis patients [49]. Although the cytokine profile from human Langerhans cells is still being investigated, murine cells may be activated through surface-bound IgE molecules to release a variety of cytokines including IL-1, IL-6, and tumor necrosis factor- α (TNF- α) [24], which in turn attract and activate infiltrating CD4⁺ TH2-type lymphocytes. Another mechanism believed to play a pathogenic role in atopic dermatitis involves the generation of novel cytokines termed "histamine-releasing factors" (HRF).

HRF was first described by Theuson and co-workers [47, 48]. They reported that peripheral blood mononuclear cells cultured in the presence of concanavalin A, streptokinase/streptodornase, *Candida albicans*, or Staphylococcal endotoxin B generated a factor, first termed "histamine-releasing activity," which was chemotactic for basophils and which led to the release of histamine from basophils [19]. The release of histamine was rapid (1–5 min) and was shown to be calcium dependent and magnesium dependent. Subsequently Sedgwick et al. [41] demonstrated that the concanavalin A-dependent HRF was synthesized by a monocyte-dependent T cell. Kaplan et al. [13] described an HRF produced by streptokinase/streptodornase-stimulated peripheral blood mononuclear cells. The HRF activity was detected in three fractions; proteins of 10–12 kDa, 15–17 kDa, and 40–41 kDa. A monoclonal antibody was generated to the 10- to 12-kDa fraction which was then affinity-purified and sequenced [7]. It was found to be homologous to "connective tissue-activating peptide" (CTAP III), a member of the chemokine (formally called intercrine) family. Neutrophil-activating peptide (NAP II), a cleavage product of CTAP III also was found to have HRF activity. Later these workers reported that another member of the chemokine family, "monocyte chemotactic and activating factor" (MCAF) was the most potent HRF isolated to date [15]. This was confirmed by Alam et al. [6] who also showed that MCAF was chemotactic for basophils. Other members of the chemokine family have been shown to affect basophil histamine release. "Macrophage inflammatory factor" (MIP_{1 α}) is a direct agonist causing release from the basophils of several normal donors as well as 14 of 20 allergic donors [5]. Two other members of this family, RANTES and IL-8 have controversial effects on histamine release. At high concentrations, White et al. [52] and Grant et al. [4] showed direct histamine release with IL-8. Kuna et al. [14] showed that IL-8 inhibited one form of HRF- as well as inhibiting IL-3- and CTAP III-induced histamine release. Alam and co-workers have stated that both IL-8 and RANTES inhibit basophil histamine release induced by MCAF and one form of mononuclear cell-produced HRF. On the contrary, Kuna et al. [16] have reported

that RANTES is a potent activator of basophil histamine release and that RANTES may function through the same, or a closely related, receptor as MCAF-1 in basophils. All HRF discussed above apparently activate basophils through surface receptors, regardless of their source of origin, i.e., atopic or nonatopic subjects and, thus, can be considered to act on basophils via an IgE-independent mechanism. This is very different from the IgE-dependent HRF which are discussed below. Furthermore, although the IgE-independent HRF have been characterized and cloned, their significance *in vivo* remains to be established.

Schulman et al. [39] at Johns Hopkins first described an HRF secreted by human lung macrophages which could activate lung mast cells and basophils. HRF was also detected in skin blister chamber fluid following antigen-induced late-phase reactions [51] and activated platelets [29]. Investigators at Johns Hopkins [20] later demonstrated that the human lung macrophage HRF was calcium dependent, had intermediate kinetics of histamine release (similar to that of IgE-antigen-induced release) and appeared to be IgE dependent. However, this factor did not seem to induce consistent histamine release from all donor basophils. Utilizing a similar IgE-dependent HRF derived from nasal lavage fluid, and later a U937 macrophage/monocytic cell line, MacDonald et al. [21] first demonstrated heterogeneity of IgE molecules. In a series of experiments, these workers established the IgE dependence of this family of HRF and showed that 50% of atopic individuals possessed surface-bound IgE molecules (IgE⁺) capable of interacting with IgE dependent HRF, whereas the IgE molecules (IgE⁻) of the other 50% of these atopic subjects and all non-atopic controls did not interact with HRF. Not only is this IgE-dependent HRF present *in vitro*, it is also found *in vivo* in nasal lavages [21, 42], late-phase nasal lavages [31], late-phase skin blister fluids [51], and in broncho-alveolar lavages [3, 9]. Later MacDonald et al. [22] showed that IL-3 may play a pro-inflammatory role by inducing histamine release from basophils coated with IgE⁺ or basophils "activated" by other secretagogues.

Another source of an IgE-dependent HRF is found by culturing mononuclear cells from children with atopic dermatitis and food hypersensitivity [38] (see below). In these children and adolescents with atopic dermatitis and food hypersensitivity, both immediate and late-phase effects of ingested food allergens have been documented during double-blind placebo-controlled food challenges (DBPCFC) [17, 35–37]. To investigate the pathogenic role of food hypersensitivity in atopic dermatitis, 320 patients have been evaluated. Patients ranged in age from 6 months to 25 years and were highly atopic, with nearly half exhibiting both asthma and allergic rhinitis at the time of initial evaluation and only 20% presenting with atopic dermatitis alone. Foods suspected by history or the results of prick skin tests or RAST are discontinued for 10 to 14 days prior to the patient's admission to a Clinical Research Unit. Anti-histamines are discontinued for 1 to 2 weeks prior to admission and systemic steroids for at least 2 months. Once hospitalized, patients were treated aggressively for 3 to 4 days to clear cutaneous pruritus and erythema. DBPCFC consisted of administering up to 10 g of dehydrated food or a placebo substitute over a period of 60 to 90 min, starting with 250–500 mg and doubling the dose every 15 min until 10 g was delivered. All challenges were scored on a standardized scoring form [34]. A challenge was considered positive and stopped if objective symptoms developed (e.g., morbilliform rash, vomiting, wheezing, etc). The food challenge was considered negative

if the patient tolerated the full challenge without developing obvious symptoms. Once the blinding was broken, the patient was fed a large portion of all foods which did not elicit symptoms during the challenge to confirm the negative response elicited with a dehydrated food.

DBPCFC provoked a variety of symptoms within minutes to 2 h. Cutaneous reactions developed in 75% of positive challenges, but symptoms were confined to the skin alone in only 30% of positive responses. Skin symptoms provoked by DBPCFC usually consisted of a markedly pruritic, erythematous, morbilliform rash, which developed in patients' predilection sites for atopic dermatitis. Urticarial lesions were rarely seen. The pruritic, erythematous morbilliform rash generally arose abruptly and persisted for 30 to 120 min. Gastrointestinal symptoms developed in 41% of patients (nausea, abdominal cramping, and vomiting and/or diarrhea), upper respiratory symptoms, especially laryngeal edema (sensation of itching and tightness in the throat, persistent throat clearing with dry hacking cough, and hoarseness) in about one-third, and wheezing in about 10% of positive challenges. Relatively few foods were responsible for the majority of food allergic symptoms, despite the wide variety of foods tested. Egg, peanut, and milk accounted for over two-thirds of the reactions documented by DBPCFC.

The continued ingestion of even minute amounts of specific food allergens by atopic dermatitis patients with food hypersensitivity provokes chronic inflammation and pruritus of the skin, which results in frequent scratching and the consequent trauma-induced lichenified, eczematous lesions. As reported by May earlier [25, 26], it was found that children ingesting foods to which they were allergic had high "spontaneous" release of histamine from peripheral blood basophils in vitro. As depicted in Fig. 1, "spontaneous" basophil histamine release (SBHR) from peripheral blood basophils in vitro was elevated significantly compared to atopic dermatitis patients without food hypersensitivity and normal controls (respective

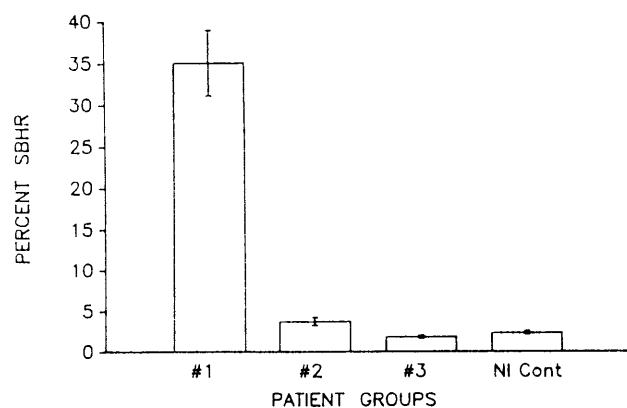


Fig. 1. Mean ($\pm$ SE) rates of spontaneous release of histamine from basophils (SBHR) in three groups of patients with atopic dermatitis and a group of control subjects. Group 1 consists of 25 patients with food hypersensitivity recently diagnosed and not yet started on an allergen-avoidance diet; group 2 included 38 patients with food hypersensitivity who had followed an allergen-avoidance diet for at least 1 year; and group 3 included 20 patients with atopic dermatitis but no food hypersensitivity. The controls consisted of 18 volunteers with no food hypersensitivity. [With permission from *N Engl J Med* (1989) 321:228]

means: $35.1\% \pm 3.9\%$ vs $1.8\% \pm 0.2\%$ vs $2.3\% \pm 0.2\%$, $P < 0.001$) [36]. When these food allergic patients were placed on appropriate elimination diets for at least 1 year, they experienced clearing of their eczema and a significant fall in SBHR ($38.0\% \pm 9.6\%$ to $4.3\% \pm 2.1\%$, $P < 0.01$). Subsequent studies have shown that SBHR returns to normal levels over 4 to 9 months of strict allergen elimination.

The etiology of the high SBHR was unknown. It was postulated that chronic food allergen ingestion might lead to the generation of an HRF in vivo which could be responsible for increased basophil releasability [23] and SBHR. A culture technique similar to that originally described by Thuesen et al. [47, 48] was utilized to determine whether mononuclear cells (lymphocytes or monocytes) might be the source of an HRF. Since patients with atopic dermatitis and food allergy were known to have activated circulating plasma cells "spontaneously" synthesizing large quantities of IgE in vitro, it was postulated that they might also have mononuclear cells "spontaneously" producing an HRF. Peripheral blood mononuclear cells were isolated with Ficoll-Hypaque, resuspended (5×10^6 cells/ml) in RPMI 1640 buffered with 25 mM HEPES and containing penicillin and streptomycin, and cultured at 37°C in a humidified 5% CO_2 environment for 24 h. No fetal calf serum, mitogens, or antigens were added to the culture medium; i.e. HRF was generated "spontaneously." Cell-free supernatants were obtained by centrifugation and dialyzed for 36 to 48 h to remove residual histamine, and stored at -20°C until analyzed. Residual histamine was consistently less than 50 pg/ml.

HRF activities in cell-free supernatants were determined by adding 50 μl of mononuclear cell supernatant to 50 μl of a leukocyte preparation containing 1.5×10^4 – 2×10^4 basophils. After incubating leukocyte preparations at 37°C for 45 min, supernatants were removed by centrifugation and histamine content analyzed [38]. The release of histamine was recorded as a percentage of total cell histamine content and compared to spontaneous histamine release. In 26 atopic dermatitis patients with newly diagnosed food hypersensitivity, mononuclear cell supernatants induced significant BHR compared with SBHR, with a mean rise of $58.0\% \pm 25.6\%$ from $3.0\% \pm 1.3\%$ ($P < 0.01$).

The generation of HRF was found to be associated with the increased spontaneous basophil histamine release in vitro, increased basophil releasability in vitro, and increased cutaneous hyperirritability (a state of increased reactivity of the skin to a variety of minor non-specific stimuli, e.g. heat, cold, detergents, etc). As depicted in Fig. 2, elimination of the responsible allergens from the diet for a 6- to 9-month period led to a decrease in spontaneously generated HRF to normal levels (mean HRF-induced basophil histamine release: $57.1 \pm 9.3\%$ to $2.0 \pm 0.8\%$; $P < 0.001$) [38]. In addition, SBHR returned to normal levels, basophil releasability normalized, and cutaneous hyperirritability diminished. In patients with asthma, Alam et al. [2] reported an association between bronchial hyperreactivity and the spontaneous generation of HRF by peripheral blood mononuclear cells.

The IgE molecules in children with atopic dermatitis and food hypersensitivity were found to differ in their ability to react with HRF compared to IgE from patients with no demonstrable food hypersensitivity. Utilizing lactic acid-stripped basophils from nonatopic donors, passive sensitization with IgE from food allergic children (IgE^+) rendered basophils capable of secreting histamine in response

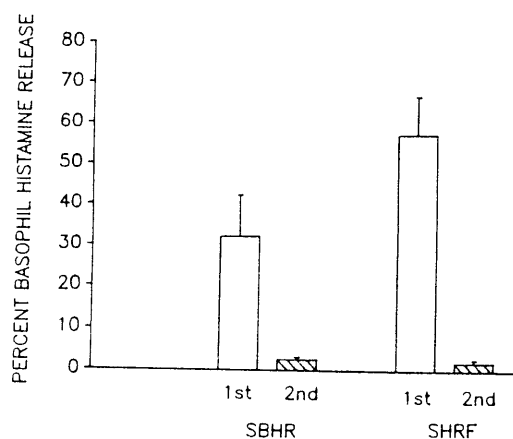


Fig. 2. Rates of SBHR and histamine-releasing factor (HRF)-induced histamine release in 10 patients. The rates shown were determined at diagnosis and after 1 year of an appropriate allergen-avoidance diet

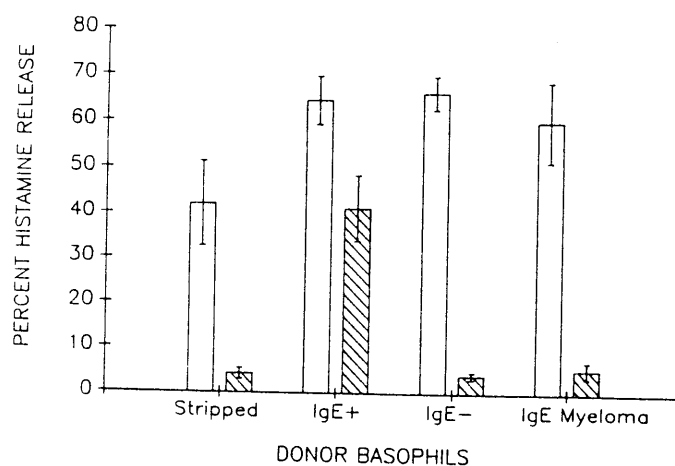


Fig. 3. Mean rates of histamine release from basophils induced by HRF after passive sensitization. Basophils not responsive to HRF were passively sensitized with serum samples from five patients with atopic dermatitis and food allergies (containing IgE⁺), serum samples from six subjects without food allergies (containing IgE⁻), and three IgE myeloma proteins. [With permission from N Engl J Med (1989) 321:228]. □ Anti-IgE; ▨ HRF

to histamine-releasing factor [38], whereas passive sensitization with IgE from nonallergic individuals or three different IgE myeloma proteins [IgE⁻] was incapable of mediating HRF-induced histamine release (Fig. 3). These studies supported the hypothesis that different post-translational events (e.g., glycosylation) may occur to account for the heterogeneity seen in IgE molecules.

Over the last several years we have been attempting to isolate and characterize an IgE-dependent HRF. Three sources of HRF have been utilized for these studies: nasal lavage fluid from unstimulated donors (nHRF) [21], supernatants from the U937 macrophage/monocyte-like cell line (uHRF), and supernatants from unstimulated mononuclear cells of patients with atopic dermatitis and food hypersensitivity (pHRF) [38]. Nasal lavage fluid was partially purified by anion exchange chromatography prior to use in basophil experiments. pHRF was ob-

tained from supernatants of unstimulated patient mononuclear cells, which were dialyzed to remove potential contaminating histamine. uHRF was isolated from supernatants of the U937 cell line which were concentrated and then run over a Sephadex G75 column in TRIS buffer with a physiological salt concentration. The peak uHRF activity, which appeared in a broad band between 50 and 30 kDa, was chromatographed on a Mono Q, anion exchange column with an increasing salt concentration, 0 to 1 M NaCl. Although three distinct regions of activity were found, only the middle fraction (from 0.4 to 0.6 M NaCl), which was IgE dependent, was used in these studies. When subjected to SDS-PAGE under reducing and denaturing conditions, the three different preparations of HRF are comprised of multiple protein fractions ranging in size from 10 to 70 kDa. Of note, only four bands were found to be identical in all three preparations: one at 66 kDa, one at 29 kDa, and a doublet at 23 kDa. Efforts to sequence these four bands are ongoing (see below).

Two lines of evidence suggest that the three factors are similar, but not identical. Basophil cross-desensitization experiments with each of the three sources of HRF demonstrated that each factor was capable of desensitizing basophils to the other two factors, e.g., nHRF blocked response to uHRF and pHRF. In experiments where each HRF was added separately to basophils from food allergic patients, histamine release was provoked in all patients, but the degree of response to the various HRF differed among individual patients. From these studies it can be concluded that nHRF, uHRF, and pHRF bind IgE ($\pm$ basophil membrane) at the same, or a closely located site, but vary in their ability to activate basophils from different IgE⁺ patients.

Several attempts have been made to characterize the IgE-dependent HRF. Utilizing the middle fraction of uHRF from the Mono Q column, two sets of monoclonal antibodies were generated by intrasplenic injection of BALB/c mice. The first injection protocol resulted in several IgM monoclonal antibodies. Antibody from one clone, D119, was capable of inhibiting HRF activity. Using immunoblots of the three HRF, D119 bound a fraction at 29 kDa and a fraction at 66 kDa. Sequencing of the 66-kDa band indicated that the band was bovine serum albumin and sequencing of the 29-kDa band revealed a blocked end terminus. Efforts to produce sufficient amounts of D119 for generation of an affinity column to purify sufficient quantities of the 29-kDa fraction for characterization are now under way. A second injection protocol resulted in several IgG₁ monoclonal antibodies with high affinity to a 24-kDa fraction. This monoclonal antibody bound nHRF, uHRF, and pHRF but could not block HRF-induced BHR. Sufficient quantities of this 24-kDa fraction were obtained for sequencing which showed it to be homologous to nucleolin, a nucleolar phosphoprotein which is important in the synthesis and maturation of ribosomes. The human nucleolin gene has been localized by Srivastava et al. [45]. The protein product for this gene has been elusive but an antibody to the nucleolin gene was kindly provided and proved not to inhibit the IgE-dependent HRF activity, and, therefore, is not the protein of interest.

A small quantity of a single fraction containing uHRF activity was obtained by placing the Mono Q fraction on a reverse-phase C4 column and eluting with 65% acetonitrile. However, initial attempts at sequencing this protein failed when it was found to possess a blocked end terminus. Purification has been scaled up to preparative levels in an attempt to circumvent this problem. Based on kinetics

of release (classified as "intermediate") and cross-desensitization experiments, the IgE-dependent HRF are not known cytokines nor any of the chemokines described to date.

The role of the IgE-dependent HRF in atopic disorders remains to be fully delineated. Studies in children with atopic dermatitis suggest it may be important in initiating the IgE-dependent late-phase reaction and play a central role in the chronic cutaneous inflammation seen in these patients. Similarly, a study in patients with asthma suggest HRF may be related to chronic airway inflammation and increased bronchial hyperreactivity. Isolation and characterization of the IgE-dependent HRF should lead to a major breakthrough in our understanding of chronic allergic disorders.

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