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Allergic rhinitis and the phenomenon of entopy

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ABSTRACT

This article provides a review of the phenomenon of entopy or local atopy from the viewpoint of allergic phenotypes and endotypes. A clinical form of the entopy endotype is local allergic rhinitis, which is still a fertile area for research. The exact mechanisms in the breakdown of allergen tolerance in entopy remain unclear. The review focuses on the pathogenesis, diagnostic algorithm, and the choice of treatment strategies in local allergic rhinitis.

Key words: allergens, atopy, entopy, allergen tolerance, allergic rhinitis, local allergic rhinitis, phenotypes, endotypes, biomarkers, type 2 helper T-cells, T-regulatory cells.

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Аллергический ринит и феномен энтопии

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РЕЗЮМЕ

Представлен обзор современных исследований, посвященных недавно открытому явлению – феномену энтопии (локальной атопии), с точки зрения его фенотипов и эндотипов. Клиническим вариантом эндотипа энтопии является локальный аллергический ринит, новая патология, – объект исследований в современной иммунологии, аллергологии и оториноларингологии. Точные механизмы срыва толерантности к аллергенам при энтопии остаются неясными. Между тем феномен энтопии может стать ключом для расшифровки нерешенных вопросов срыва аллергической толерантности в разных анатомических сайтах. Обзор посвя-

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щен патогенезу, диагностическому алгоритму и проблеме выбора терапевтических подходов при локальном аллергическом рините.

Ключевые слова: аллергены, атопия, энтопия, толерантность к аллергенам, аллергический ринит, локальный аллергический ринит, фенотипы, эндотипы, биомаркеры, Т-хелперы 2-го типа, Т-регуляторные клетки.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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ATOPY AND ENTOPY (LOCAL ATOPY): HISTORY, MECHANISMS, BIOMARKERS, AND CLINICAL VALUE

Initially, the term “atopy” was denoted as “out of place” and “strange disease” by Coca and Cooke in 1923 in their seminal work [1, 2], when IgE was not discovered yet by Ishizaka et al. [3]. In 1963, Gell and Coombs [4] proposed an updated classification of known allergic phenomena where atopy was classified as type 1 hypersensitivity (immediate hypersensitivity). This classification is still used today. Taking into account the rising prevalence of many types of allergies in modern human populations, the hygiene and toxic hypotheses were proposed [5]. In particular, allergic reactions may be considered as maladaptive IgE immune responses towards environmental antigens [6]. Intriguingly, these mechanisms appeared to be very similar to those implicated in the acquisition of immunity against helminths and arthropods in human bodies. Based on the hypothesis that IgE-mediated immune responses evolved in humans and other mammals to provide extra protection against metazoan parasites rather than to cause allergy, the environmental allergens might share some properties with the metazoan parasite antigens, which are specifically targeted by IgE in infected human populations [6].

On the other hand, immediate hypersensitivity, or atopy, occurs in selected populations of *Homo sapiens*. It appears to be a polygeneously inherited disorder, as genome-wide association studies have convincingly detected a large number of loci associated with allergic diseases [7]. However, there are so-called primary atopic disorders based on monogenic inheritance [8]. In addition to that, epigenetic changes have been recently considered as a potential mechanism involved in the development of many disorders, including atopic diseases [9]. Atopy appears to show a strong hereditary component as a consequence of evolution (Fig. 1). From an evolutionary point of view, house dust mites, *Dermatophagoides pteronyssinus* (European species), and *Dermatophagoides farinae* (American species) are the “kings of allergens,” or panallergens [10, 11]. Likely, they used to be skin parasites in ancient humans in the Stone Age [12].

Nowadays, the term “atopy” is used by allergists and scientists for any hyper-IgE-mediated reaction induced by B-cell mediated Th2-dependent response to various allergens [12], such as household dust, house dust mites, animal hair and skin scales, pollens, flour, food proteins, insect venoms, molds, latex, penicillin, etc. There are also oligomeric components of allergen molecules and allergen-associated molecular patterns (AAMP), which may be responsible for effective cross-linking of allergen with the B cell receptor (BCR)/IgE [13]. Supposedly, a deficit of the AAMP leads to tolerance maintenance, whereas an AAMP excess results in tolerance breakdown. Exposure to allergens may occur during inhalation, ingestion, injection, or direct contact. In the course of B-cell-mediated immune response, plasma cells are stimulated by type 2 helper CD4+T cells to produce IgE antibodies specific to one allergen or allergen group. The difference between a normal B-cell-mediated response and a type 1 hypersensitivity response is that in type 1 hypersensitivity, the IgE antibodies predominate instead of IgM, IgG, or IgA immunoglobulins. The IgE antibodies bind to type 1 Fcε receptors (FcεRI) on the surface of mast cells and circulating basophils. After exposure to the same allergen, the allergen cross-links the bound IgE on target cells that result in degranulation and secretion of inflammatory mediators.

Type 1 hypersensitivity reactions may consequently be divided into two phases, the early phase reaction

and the late phase reaction. The early phase typically occurs within 10–20 minutes, or even seconds after the penetration of the allergen, which is associated with the release of preformed mediators, such as histamine, serotonin, chemotactic peptides for neutrophils and eosinophils, enzymes, etc. These mediators affect the nerve cells causing itching, smooth muscle contraction (e.g. asthmatic attack), mucus production by goblet cells, an increase in capillary permeability, and subsequent tissue edema with further recruitment of neutrophils and eosinophils in the focus. Mast cells located in the skin and lining epithelium of the respiratory, gastrointestinal, and genitourinary tracts are involved in recognizing signals coming from the external environment. Once activated, mast cells trigger the early phase of the atopic response, promote the recruitment of other inflammatory cells, such as eosinophils and neutrophils, and take part in the regulation of IgE adaptive immune response [14, 15]. Activated mast cells with their mediators, including tryptase and histamine, are the main biomarkers of the early phase.

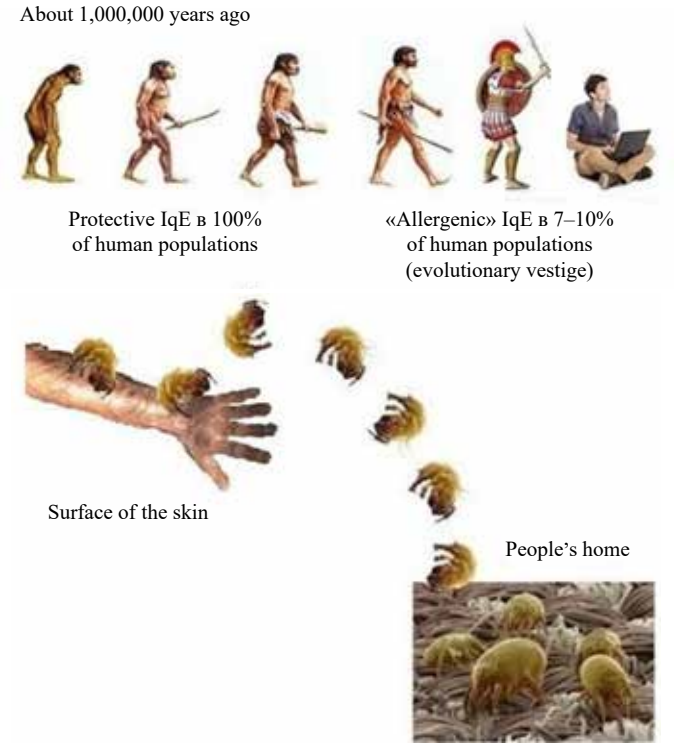

Fig. 1. Atopy as a vestige of evolution [12]

The **late phase** develops over 6–12 hours by the generation of newly formed mediators, such as thromboxane, leukotriene C4, leukotriene B4, prostaglandin D2, and platelet-, cytokine-, and chemokine-activating factors, which affect the surrounding tissues enhancing the inflammatory process. Endothelial cells express the adhesion molecules which facilitate the recruitment and activation of neutrophils, eosinophils, and type 2 innate lymphoid cells (ILC2) from the blood and other biological fluids into the site of the allergic inflammation. Commonly, the infiltrating cells contain a high proportion of eosinophils. The activated eosinophils release a variety of inflammatory molecules, including eosinophil cationic protein, major basic proteins, IL-5, etc. [14, 16]. The involved type 2 helper T cells secrete IL-4, IL-5, IL-6, IL-13, IL-33, etc. and affect plasma cells, which promote IgE isotype switching. The inflammatory process becomes chronic. Therefore, these cytokines, eosinophil mediators, and eosinophil surface molecules are the main biomarkers of the late phase.

Type 1 hypersensitivity is responsible for atopic dermatitis, perennial and seasonal allergic rhinitis, bronchial asthma, food allergies, insect allergies, anaphylactic shock, etc. In predisposed individuals, the term "atopic march" denotes a subsequent change of target organs in the following order: the skin, nose/conjunctiva, and bronchi, whereas some individuals may simultaneously develop all atopic disorders [12, 17]. Allergic skin tests and investigation of blood IgE are preferential methods for diagnosing atopic allergic conditions.

Recently, entopy, a new allergy-like phenomenon, has been identified [18], and the term came from the Spanish expression "*en topo*" that means "on-site." Interestingly, entopy sounds almost like ENT (Ear, Nose, and Throat). Initially, entopy was not related to atopy. Currently, the phenomenon is referred to an endotype of the atopic disorder which can develop local allergic rhinitis [19, 20], local allergic conjunctivitis [21], and local allergic asthma [22]. Among all entopic phenomena, the biggest number of investigations are performed in patients with local allergic rhinitis [19, 20; 23–26]. Patients with severe asthma having dramatic beneficial effects from Omalizumab treatment prove that the concept of local allergy (entopy) is worth discussing in severe asthma [27].

Detailed mechanisms of entopy remain unclear, and the phenomenon is a fertile area for further research. We suppose that, like any form of atopy, entopy is associated with allergen tolerance breakdown. Allergen tolerance is an active process which can be considered as a non-pathogenic immune response to the allergen. The development of allergen tolerance reflects immunoregulatory networks that recruit multiple secreted mediators, such as IL-10, IL-35, and

TGFβ, surface molecules, Treg, and other regulatory cell types. Allergen tolerance also occurs upon natural exposure to high levels of allergen in the environment, as typified by the modified type 2 helper CD4+ T cell-regulated response to this allergen [28]. Historically, there is classical differentiation of tolerance into central and peripheral mechanisms of tolerance induction [12]. The systemic (in the bloodstream) and local (in specific tissues) allergen tolerance is not the same differentiation. For understanding the mechanisms of tolerance induction and breakdown, it should be considered according to "systemic" and "local, or entopic" forms of atopy (Table) to clarify what factors of tissue microenvironment prevail. Specific anatomic sites, e.g., the mouth and respiratory tract, may provide favorable conditions for tolerance induction [28]. This point is open for debate, particularly due to the entopy phenomenon and sublingual allergen-specific immunotherapy.

Table

Forms of tolerance breakdown to allergens

Systemic forms	Local forms (entopy)
Dermal Oral (gastrointestinal) Genitourinary? Combined (may include conjunctival, nasal, and bronchial forms as a part of systemic forms)	Conjunctival Nasal Bronchial

ALLERGIC RHINITIS: PHENOTYPES, ENDOTYPES, AND BIOMARKERS

Allergic rhinitis is a global health problem [29, 30]. Allergic rhinitis (rhinoconjunctivitis) develops in predisposed individuals in two phenotypes: (1) perennial and/or (2) seasonal rhinitis (rhinoconjunctivitis) [25, 31]. Nowadays, both phenotypes of allergic rhinitis, in particular perennial rhinitis, cause considerable asthma prevalence in atopic individuals, impact on the quality of life, performance, sleep, exercise tolerance, and social functioning, and create a significant financial burden on healthcare systems throughout the world [29, 31].

In allergic rhinitis, patients complain of chronic symptoms of nasal obstruction, itching, rhinorhea, paroxysmal sneezing, and sometimes loss of smell, snoring and conjunctival redness and swelling [29, 32]. Clinically, phenotypes of "non-allergic rhinitis" almost do not differ from phenotypes of allergic rhinitis [33]. Perennial rhinitis commonly starts at the age of 3–5 years. It manifests itself through the mentioned symptoms all year round and sometimes throughout the life, being persistent and complicated by nasal polyps, sinusitis, and asthma. Sometimes the course of rhinitis can be mild and subtle. Allergens of *Dermatophagoides* house dust mites, cats, and other pets, feathers, cockroaches, and mold are the main responsible proteins for IgE dependent sensitization in persons with perennial allergic rhinitis [12, 34]. In seasonal rhinitis or "pollinosis", symptoms occur during certain periods of the year when trees, shrubs, and herbs pollinate, but the pathology may commence at any age, in any geographical location. Hypersensitivity is caused by allergens of birch, hazel tree, oak, fescue, ryegrass, timothy, ragweed, artemisia, and a wide variety of plants [12, 35, 36].

An initial diagnosis of allergic rhinitis is more likely when rhinitis is seasonal, or with a family history of atopy [37]. As a rule, examination and investigations include patient's history (family, past medical, social, occupational, etc.), allergic skin tests, serum/nasal secretion IgE assays, nasal secretion cytology, video rhinoscopy, acoustic rhinometry, tests for asthma, etc. [37, 38].

Cluster analysis for allergic rhinitis in adults identified 4 clusters [39]: (1) moderate childhood-onset rhinitis, (2) mild adolescence-onset female rhinitis, (3) severe early-onset rhinitis with asthma, and (4) moderate childhood-onset male rhinitis with asthma. The characteristics that distinguished patients with rhinitis and separated them into clusters were sex, the presence of asthma, and the severity and age of rhinitis onset. Seasonal allergic rhinitis predominated in all clusters. Several other clinical phenotypes and endotypes were subsequently described in various studies [40], whereas endotyping and confirmatory biomarkers showed a more significant impact on management and personalized therapy for patients with allergic rhinitis [41, 42].

The term "local allergic rhinitis" (LAR) was first proposed by Rondón et al. [19]. One group of researchers [43] just supposed that LAR did not fit into the systemic allergic (atopic) rhinitis vs. non-allergic rhinitis classification, and LAR was hence differentiated as a new rhinitis phenotype. However, the other group of researchers [20, 44, 45] substantiated LAR as an endotype of allergic rhinitis, since it displays all atopic biomarkers not at the systemic level but in the nasal mucosa, i.e. at the local level. Furthermore, recent evidence supports the existence of a bronchial counterpart of LAR named local allergic asthma [22], and its conjunctival counterpart defined as local allergic conjunctivitis [21].

Patients with LAR have the same classic symptoms typical of allergic rhinitis, such as nasal obstruction, sneezing, itching, and rhinorrhea. A study comparing patients with allergic rhinitis and LAR also showed that both groups of patients share a similar clinical phenotype. LAR is caused by sensitization to *Dermatophagoides* house dust mites, occurs mostly in nonsmokers, and displays a severe and persistent clinical picture, often with conjunctival and asthma symptoms, developed in both children and adults [44]. LAR can be verified by (1) detection of specific IgE house dust mite allergens and other aeroallergens in nasal secretion and (2) positive response to the nasal provocation test with the same allergens, whereas skin prick tests, intracutaneous tests, and serum IgE assay may be negative [25, 46, 47]. Incorvaia et al. [20] recommend a double nasal provocation test to diagnose LAR accurately. The algorithm for LAR diagnosis [45, 47] is shown in Fig.2.

Unfortunately, due to high cost and complexity, nasal provocation tests with house dust mite allergens and detection of specific IgE in nasal secretion are not yet recommended in everyday clinical practice. As a consequence, patients with LAR, including elderly persons [48], are still classified as individuals with non-allergic rhinitis in most hospitals [49].

As a result of a 7-year retrospective follow-up study, Sennekamp et al. [46] demonstrated conversion of LAR to conventional systemic respiratory allergic reactions in almost half of the observed patients. The conversion rate was higher in children and adolescents than in adults. On the other hand, following the results of a 10-year follow-up study of a cohort of 176 patients with LAR, Rondón et al. [50] insist on low conversion of entopy to systemic atopy and natural evolution of the disease towards allergic asthma.

Treatment for LAR is similar to that of conventional allergic rhinitis. It includes allergen avoidance/environmental controls, corticosteroid nasal sprays, antihistamines, leukotriene receptor antagonists, intranasal Cromolyn, medications containing immunosuppressive monoclonal antibodies like Omalizumab, and allergen-specific immunotherapy [45, 51, 52]. However, the problem of choice between subcutaneous or sublingual administration of allergens for allergen-specific immunotherapy or development of the other routes of their administration remains open for research and discussion [52].

In accordance with the concept of a single unified airway [52, 53], the upper and lower respiratory tracts are connected anatomically, functionally, and

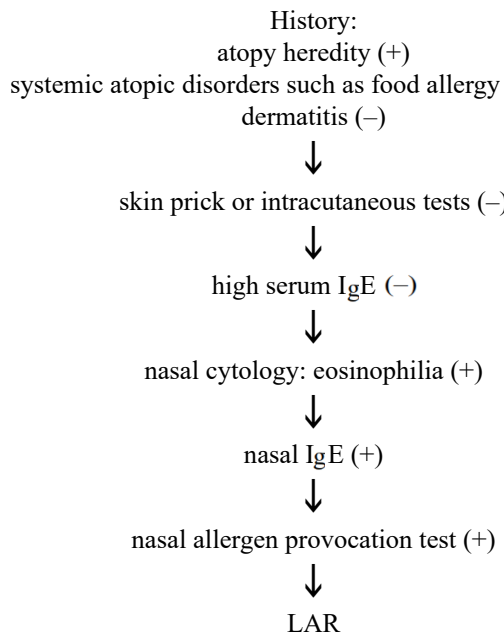

Fig.2. Diagnostic algorithm for local allergic rhinitis [45, 47]

immunologically, which is essential for the formation of a generalized inflammatory process. Disruption of systemic allergen tolerance often leads to the development of all forms of atopy and its complications (allergic rhinitis, rhinosinusitis, polyps, asthma) in the respiratory tract in combination with atopy in non-respiratory target organs. At present, it remains unclear how to relate the concept of a single unified airway and the phenomenon of entopy, its clinical manifestations, possible complications, dynamics of development, and the optimal choice of treatment strategies.

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