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THE EVOLUTION OF ATOPIC DISORDERS: INSIGHTS INTO THR ATOPIC MARCH

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Abstract. The atopic march encompasses a sequence of allergic conditions, including atopic dermatitis, food allergy, allergic rhinitis, and asthma, that frequently develop in a sequential pattern within the same individual. It was introduced as a conceptual framework aimed at elucidating the developmental trajectory of allergic conditions during childhood. Following the introduction of this concept, it was initially believed that the atopic march represented the sole and definitive trajectory of the development of allergic diseases. This review outlines epidemiologic evidence for the existence of allergic march trajectories (distinct paths of atopy development in individuals); reviews the roles that genetics, environment, and disease endotypes play in determining trajectory outcomes; and discusses the clinical utility of the trajectory model. A systemic immune response to cutaneous inflammation may drive or amplify the development of atopic comorbidities in genetically or immunologically susceptible individuals. However, these observed associations could instead reflect the influence of shared genetic loci and environmental exposures – such as microbiome dysregulation – rather than a true sequential progression of disease. The apparent temporal order of disease onset may simply correspond to the tissue-specific peak incidence of each condition, suggesting a clustering of atopic disorders rather than a unidirectional "march." Prospective longitudinal cohort studies offer a valuable framework for researching the post-dermatitis emergence of additional atopic conditions, while also identifying predictive phenotypic, genotypic, and environmental factors. Recent research has identified several risk factors for the development of multiple atopic comorbidities in young children with atopic dermatitis, including disease severity and chronicity, early age of onset, parental history of atopy, filaggrin mutations, polysensitization, and living in nonrural environments. Early intervention trials—targeting epidermal barrier restoration, modulation of microbiome composition, or altered exposure to allergens – may help to clarify the relative contributions of skin barrier dysfunction, genetic predisposition, and environmental exposures to the risk, timing, and progression of Th2-mediated disorders.

This evolution calls for a shift from viewing allergic diseases as a linear progression of comorbidities to recognizing them as components of an overlapping multimorbidity model. Such an approach enables proactive patient monitoring based on their predisposition to develop concurrent allergic disorders. Importantly, early onset of atopic disease has been linked to a heightened risk of persistent multimorbidity. Current data also indicate that allergic conditions often co-occur without following a fixed sequence of symptom development. Effective control and timely treatment of allergic diseases may influence the trajectory of the atopic march and potentially prevent its advancement. The application of systems medicine – including integration of clinical data, multi-omics, epidemiology, and mechanistic modeling – will be key to understanding the underlying pathophysiological pathways that drive divergent allergic trajectories. This approach promises to transform diagnosis, treatment, and prognostic accuracy, ultimately enabling the prevention of allergic disease onset.

Keywords. atopic march, allergic diseases, pathogenetic links, atopic dermatitis, food allergy, allergic rhinitis, bronchial asthma, early childhood.

Introduction. Allergic diseases are the greatest prevalent chronic immunological diseases, including athopic dermatatis (AD), asthma, and allergic rhinitis (AR), which are estimated to affect more than 230 million, 330 million, and 400 million people worldwide, respectively. Currently, the issue of diagnosing and treating allergic diseases is extremely relevant worldwide, as up to 40% of the general population and 10–15% of the pediatric population suffer from allergic conditions. The prevalence of allergic diseases is increasing in both industrial and developing countries, making it a global epidemic. Notably, people with allergic diseases are more likely to have a family disposition known as atopy. Many studies show that the progression of allergic diseases occurs in a predictable time sequence and

is widely distributed to various organs, which is referred to as the atopic march. It is known that AD in infancy gradually develop into asthma and AR in childhood. However, the mechanism of the atopic march remains unclear. Some studies have shown that the atopic march does not progress completely in a temporal pattern with genes and the environment [2]. The way symptoms manifest across various organs or systems, such as the skin, lungs, and nasal passages, can offer insights into the underlying pathophysiological processes. Understanding pathophysiological mechanisms could offer a mode of intervention for disease prevention as well as treatment [3].

Many risk factors (and some protective factors) for atopic diseases have been identified. Although most of these concern the development of asthma, some factors are also associated with the development of atopic dermatitis and hay fever. Risk factors must be distinguished from triggering factors, which are elicitors of acute allergic or asthmatic reactions in atopic patients, for example, allergens, tobacco smoke, and occupational agents. Nevertheless, there is an overlap between these since, for example, exposure to tobacco smoke and allergens may also be risk factors for development of allergic disease and asthma in the long run. No single risk factor sufficiently explains these alterations in global atopic disease prevalence. Because substantive, rapid changes during only 5 to 10 years were observed in some countries, environmental factors likely have a dominant role. Differences in prevalence between urban and rural populations or farming communities have been attributed to the risk of atopy, including diet, hygiene, infections, allergens, and air pollution, in combination with genetic factors. Exposure to household pets, livestock, unpasteurized milk, and endotoxins during childhood are associated with a reduced incidence of allergic manifestations, although the data are inconsistently reported overall. Nevertheless, there is convincing evidence that demonstrates a clear correlation between increased microbial exposure and reduced allergic sensitization [4].

Classic Allergic March Trajectory: From Atopic Dermatitis to Other Allergic Conditions

The classic atopic march typically begins with AD and progresses to IgE-mediated food allergy FA, and/or asthma and AR [4]. It is important to note that each of these conditions has a complex pathophysiology involving multiple immune system responses. For instance, AD was once considered a primary manifestation of atopy, but it is now understood to result from a combination of a primary skin barrier defect and a genetic or environmental predisposition to type 2 inflammation. Although non–type 2 inflammation may also play a role in the pathophysiology of AD, this article will focus on type 2 inflammation, as it represents a central mechanism in the atopic march. The impaired skin barrier in AD serves as a portal of entry for allergens, triggering a systemic Th2-driven inflammatory response.

It is believed that allergen exposure through inflamed skin is the primary route by which allergens influence the human body within the framework of the atopic march. This hypothesis is supported by data from animal models, which demonstrate that transcutaneous exposure to allergens promotes the development of specific T-cell and B-cell responses, ultimately leading to allergic disease.

Over the past decade, there has been a notable increase in the incidence of food allergy-related anaphylaxis, indicating a broader rise in food allergy prevalence. AD and food allergy frequently co-occur, especially in individuals with early-onset, severe, and persistent atopic eczema. Food allergy is recognized as a contributing factor in the development or exacerbation of AD, with approximately 35% of children with AD exhibiting IgE-mediated food allergies. However, whether children with IgE-mediated food allergy are at heightened risk for subsequent allergic conditions such as asthma and allergic rhinitis remains uncertain. One study demonstrated that early food sensitization and the presence of filaggrin gene mutations in infants with early-onset eczema independently increased the risk for persistent eczema and the later development of asthma. Nonetheless, the predictive sensitivity of combining these two factors for identifying at-risk children was low. Another prospective study followed 118 children with confirmed cow's milk allergy (CMA) from infancy to school age. It found that children with IgE-positive CMA diagnosed at an average age of seven months – not those with IgE-negative CMA-exhibited greater airway inflammation and increased bronchial responsiveness to histamine at eight years of age.

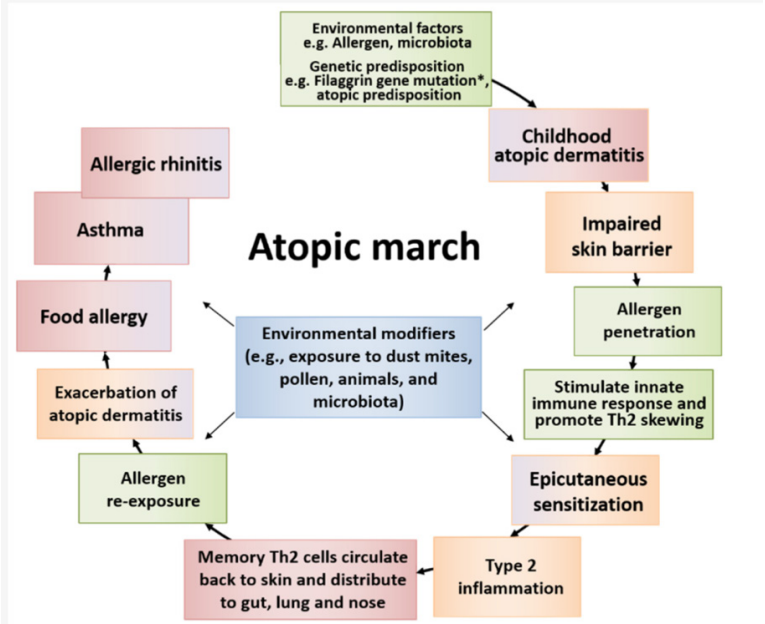
It remains unclear whether the progression from IgE-mediated food allergy to asthma in children without eczema is due to a causal relationship or reflects shared environmental or genetic factors. Given that eczema and food allergy often coexist in infancy, it is also uncertain whether the observed associations reflect co-manifesting allergic conditions – such as eczema and allergic rhinitis – that are known predictors of asthma, or whether food allergy independently contributes to disease progression.

To clarify this, large-scale, population-based prospective cohort studies are needed. These should include food allergy as a baseline variable to better assess whether it represents an initiating step in the atopic march in infants with shared environmental and genetic susceptibilities, or whether it acts as an independent risk factor.

The skin barrier function is impaired in AD due to multiple abnormalities that contribute to the barrier defect. These include a reduction in essential lipids such as ceramides and sphingosine, as well as abnormal keratinization resulting from filaggrin (FLG) dysfunction. FLG is a critical component in the formation of the cornified envelope and serves as a key mediator in interactions with environmental allergens and other external agents, such as toxins, irritants, and pollutants. This pathway is now considered a major mechanism in the pathogenesis of AD [5].

After an allergen penetrates the skin, it gains the opportunity to interact with the immune system. The skin is functionally divided into two immunological compartments: the epidermis, which primarily contains Langerhans cells and $CD8^+$ cytotoxic T lymphocytes, and the dermis, which houses dendritic cells, macrophages, mast

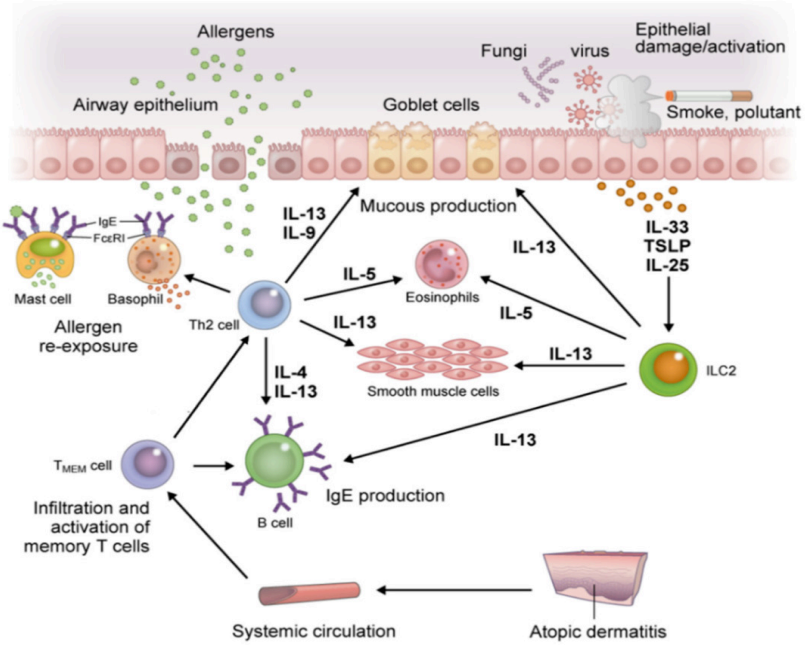
cells, and both innate and adaptive lymphocyte subsets. Keratinocytes are capable of producing a unique cytokine profile, including IL-13, TSLP (thymic stromal lymphopoietin), IL-33, IL-25, and various chemokines, all of which promote a type 2 (Th2) inflammatory response. TSLP, in particular, plays a critical role in activating dendritic cells (DCs), which then migrate to the draining lymph nodes where they prime T- and B-cells, initiating a Th2-skewed immune response [6] (pic.1).



Pic. 1. The general course of atopic march [7]

These same cytokines also attract and activate innate immune cells, including innate lymphoid cells (ILCs) and basophils, which produce type 2 cytokines (e.g., IL-4) that further enhance dendritic cell activation. Activated DCs process allergens and present peptides via MHC class II molecules, traveling to lymph nodes where they interact with T- and B-lymphocytes, leading to the development of allergen-specific adaptive immune responses.

The inflammation observed in atopic dermatitis (AD) is associated with elevated production of IL-4, IL-25, IL-33, and TSLP, which in turn stimulate type 2 helper T cells (Th2) to secrete IL-5 and IL-13 (pic. 2).



Pic. 2. Pathogenesis of athopic march [7]

These cytokines promote the differentiation of B-cells into plasma cells, which subsequently produce allergen-specific immunoglobulin E (IgE). Th2 cells circulate in the bloodstream, exerting systemic immunological effects. Studies in murine models have demonstrated that epicutaneous sensitization can elicit allergen-specific IgE responses, leading to allergic inflammation in the lungs, esophagus, gastrointestinal tract, and even anaphylaxis. The prevailing concept suggests that individuals who develop the atopic march predominantly exhibit a systemic Th2-skewed immune response. Allergen-specific Th2 cells subsequently back to the skin through the expression of CCR4 (C-C chemokine receptor type 4), CLA (cutaneous lymphocyte-associated antigen), and other homing molecules. Concurrently, B cells differentiate into plasma cells, producing allergen-specific IgE, a hallmark of allergic sensitization and a central element of the atopic march.

Filaggrin, a barrier protein, has important roles in the integrity of the stratum corneum in terms of structure and composition. Mutations in the filaggrin gene (FLG) can impair the barrier function of the skin and induce an allergic response. The interior of keratinocytes is primarily composed of keratin filaments aggregated by FLG, which also contributes to anchoring these structures to the extracellular lipid layer. FLG degradation products play an essential role in maintaining skin hydration and acidic pH levels. Exogenous factors contributing to pH elevation include metabolites produced by the skin microbiota and sweat gland activity. A shift in skin pH from its natural acidic state toward alkalinity facilitates colonization by pathogenic microorganisms, most commonly *Staphylococcus aureus* and *Candida albicans*. These alterations collectively lead to reduced FLG aggregation, thereby compromising the skin barrier and enabling the penetration of allergens and pathogens.

Th2 cytokines such as IL-4, IL-13, and IL-25, as well as cytokines from other T-cell subtypes, can suppress the expression of filaggrin (FLG) in keratinocytes, thereby worsening the skin barrier defect through a positive feedback mechanism. This indicates that a FLG defect can be both genetically determined and acquired. A reduced amount of loricrin and involucrin has also been found in patients with atopic dermatitis (AD), and their expression is similarly regulated by Th2 cytokines.

Mutations and deficiencies in FLG are also associated with various skin diseases, such as ichthyosis, herpetic eczema, AD, recurrent *Staphylococcus aureus* infections, nickel allergy, allergic contact dermatitis in combination with AD, eczema, and others.

As previously mentioned, AD often precedes asthma and allergic rhinitis in the atopic march, indicating that epicutaneous sensitization to allergens may play a significant role in triggering allergic reactions on other barrier surfaces. TSLP and IL-33 are two cytokines that can initiate type 2 responses in the skin; both are potential targets for the treatment of allergic diseases.

Several studies have explored the functional role of *IL-33* and its interaction with TSLP in mouse models of the atopic march and gastrointestinal allergy. In conclusion, IL-33-induced allergy developed independently of TSLP. In contrast, mice lacking IL-33 signaling were protected from allergic diarrhea caused by TSLP-driven disease. Epithelial-derived IL-33 was essential in this model, as the specific loss of IL-33 expression in the epithelium reduced skin inflammation and the subsequent progression to allergic airway disease. Thus, IL-33 plays a crucial role in both the early and late phases of skin inflammation and the development of the atopic march. Even after sensitization has occurred, therapeutic blockade of IL-33 can improve disease outcomes in this model [8].

IL-33 alone can influence the development of the atopic march independently of TSLP. This research identifies IL-33 as a key factor that may be common to numerous events initiating Th2-type inflammation during the atopic march. These findings provide further insight into the interaction between TSLP and IL-33 and suggest new approaches for preventing the development of the atopic march and treating allergic diseases.

Special attention should also be paid to *TSLP*, which belongs to the type 1 interleukin family. As previously mentioned, it is produced by keratinocytes in the skin through a protease-activated receptor-2 (PAR-2)/nuclear factor kappa B (NF-κB) pathway and promotes the development of a Th2-type immune response. TSLP activates Langerhans cells, which influence the differentiation of T-cells into Th2 cells in lymph nodes. Additionally, TSLP reduces the expression of FLG in the skin and acts as a sensorineural activator, contributing to pruritus.

It was previously demonstrated that sensitization of the skin with TSLP and ovalbumin (OVA) can lead to the development of AD in a model of the atopic march. TSLP likely is not required during sensitization, as disease still developed in TSLP-deficient mice. Further studies showed that IL-33 is necessary for both local skin inflammation after sensitization with OVA combined with TSLP, and for diarrhea following oral exposure to OVA in this model [8].

Similarly to TSLP, intradermal administration of IL-33 and OVA induces local skin inflammation and systemic sensitization to the antigen, as well as the development of food allergy following intragastric exposure to OVA. However, the severity of the disease and the induction of type 2 cytokines mediated by IL-33 remained unchanged in the absence of TSLP signaling.

It has been shown that TSLP expression is significantly upregulated in the keratinocytes of AD skin in IL-13 transgenic mice using immunohistochemistry and enzyme-linked immunosorbent assay (ELISA), and that topical application of vitamin D3 induces TSLP expression in murine keratinocytes and triggers AD. When overexpressed by skin keratinocytes, TSLP acts as a systemic driver of bronchial hyperresponsiveness, and its deletion prevents the development of the atopic march. This suggests that keratinocyte-derived TSLP may be implicated in the link between AD and asthma [9]. Some authors propose that circulating TSLP may serve as a biomarker of pulmonary allergic responses [5]. TSLP is considered an important therapeutic target for reducing asthma and aller-

gic rhinitis in children with AD.

Patients with AD have a unique predisposition to colonization or infection with *Staphylococcus aureus*. Approximately 70 % of isolated *S. aureus* strains produce bacterial exotoxins with superantigen (SAg) properties. As a result, there is a positive correlation between the severity of AD and staphylococcal SAgs, including staphylococcal enterotoxin B (SEB). Superantigens secreted by *S. aureus* in the skin of patients with AD further stimulate keratinocytes to produce TSLP and induce polyclonal activation of T cells by directly binding to the variable β (vβ) chains of T-cell receptors. This leads to an enhanced Th2 inflammatory response and exacerbation of AD. It may also contribute to a systemic Th2 response and allergic lung inflammation through an IL-17A–dependent mechanism. The possible role of IL-17 in the atopic march is supported by studies showing that inhalation of OVA in previously transcutaneously sensitized mice triggered IL-17 expression and bronchial hyperresponsiveness, which was abrogated by IL-17 blockade [10].

Impaired Antiviral Immunity in AD. While much is understood about the inflammatory pathways, our knowledge of how AD predisposes children to asthma remains incomplete. Emerging evidence suggests that cytokine dysregulation in AD may impair antiviral interferon (IFN) production. Reduced IFN responses in AD patients allow respiratory viruses, such as rhinovirus or respiratory syncytial virus (RSV), to reach the lower airways, causing necrosis and releasing IL-33, which in turn triggers Th2-mediated inflammation and wheezing. IFNs also directly suppress Th2 proliferation and cytokine production (IL-4, IL-13), as well as ILC2 activation. A key factor in this impaired antiviral response is the presence of IgE on plasmacytoid dendritic cells (pDCs), which are major IFN-α producers during viral infections. This deficiency may explain why adults with AD experience more frequent systemic infections beyond the skin.

Environmental Exposure and the Exposome Hypothesis. The "exposome" hypothesis posits that modern environmental factors—such as cleaning agents, microplastics, air pollutants, smoke, and food additives—can compromise epithelial barriers across the skin, gut, and lungs. Chronic exposure to even low doses of microplastics can damage intestinal epithelial cells and alter barrier function. Similarly, inhalation of polystyrene microplastics has been shown to induce inflammation, oxidative stress, and degradation of lung epithelial junctions.

Genetic and Epigenetic Contributions. Genetic predisposition also shapes the atopic march. A genome-wide association study (GWAS) by Marenholz et al. identified seven susceptibility loci, including FLG, IL4, KIF3A, and others, linked to AD and asthma [11]. Additional genes (e.g., TSLP, FOXP3, CD4) have been implicated through bioinformatic analyses, although further validation is required [12]. Epigenetic mechanisms, particularly DNA methylation, are increasingly recognized as modifiers of gene expression in atopic disease. Studies have linked differential methylation patterns in cord and peripheral blood with FA and asthma risk, highlighting their potential role in long-term allergic sensitization.

Potential Role of Elevated Oxidative Stress in the Atopic March. Oxidative stress refers to an imbalance between the generation of reactive oxygen species (ROS) and the biological system's capacity to neutralize these reactive intermediates or repair the resulting cellular damage. ROS include a range of oxygen-containing reactive molecules, such as superoxide ($O^{2-}\cdot$), hydroxyl (OH·), alkoxyl (RO·), peroxyl (ROO·) radicals, hydrogen peroxide (H2O2), nitric oxide (NO·), and peroxynitrite (ONOO−). These species are produced by various cell types – neutrophils, eosinophils, monocytes, macrophages, cytotoxic lymphocytes, epithelial and endothelial cells, among others. ROS generation involves multiple enzymatic processes, and their accumulation is normally controlled by intrinsic antioxidant defense systems composed of enzymes, proteins, and small molecules [13]. When redox balance is disrupted, it can result in cellular toxicity and structural damage to lipids, proteins, and DNA. Some ROS also act as signaling molecules in redox pathways, and oxidative stress can therefore disrupt redox-dependent processes such as enzyme regulation, membrane signaling, gene expression, cellular proliferation or apoptosis, and the development of precursor cells.

The development of atopic march is complex and multifactorial, involving immune dysregulation as well as genetic predisposition and environmental influences [14]. Given that ROS contribute to inflammation, compromise barrier integrity, and upregulate proinflammatory genes, oxidative stress likely plays a significant role in advancing the atopic march [15]. The assessment of oxidative damage markers and antioxidant levels has been instrumental in clarifying the contribution of oxidative stress in various pediatric allergic conditions.

Conclusion. AD is widely recognized as the initial manifestation in the progression of the atopic march. However, emerging evidence suggests that allergic disease development follows diverse trajectories influenced by both environmental exposures and individual patient factors. Multiple hypotheses have been proposed to unravel the complexities of AD and its role in the atopic march. These theories are shaped by the sequence of disease onset – specifically whether epidermal barrier dysfunction facilitates the transcutaneous entry of microbes and allergens, thereby initiating an immune response ("outside-in" hypothesis), or whether a skewed immune response inherently contributes to barrier disruption ("inside-out" hypothesis). From a clinical standpoint, both pathways warrant consideration in disease management. Nevertheless, in preventive strategies, comparing primary barrier defects with immunologic dysfunction may be critical .

The integration of precision medicine into the atopic march framework holds promise for refining endophenotypes of allergic diseases and identifying specific risk factors for progression along the allergic spectrum. The concept of the atopic march has recently broadened to include additional T2-inflammatory conditions beyond AD, asthma, and food allergy, such as eosinophilic esophagitis. In the near future, this paradigm may extend further to en-

compass upper airway diseases like chronic rhinosinusitis with nasal polyps.

This evolution calls for a shift from viewing allergic diseases as a linear progression of comorbidities to recognizing them as components of an overlapping multimorbidity model. Such an approach enables proactive patient monitoring based on their predisposition to develop concurrent allergic disorders. Importantly, early onset of atopic disease has been linked to a heightened risk of persistent multimorbidity. Current data also indicate that allergic conditions often co-occur without following a fixed sequence of symptom development. Effective control and timely treatment of allergic diseases may influence the trajectory of the atopic march and potentially prevent its advancement. To achieve this, early intervention strategies must be guided by robust research that identifies target populations and minimizes delayed or inappropriate treatments Future research must address critical questions regarding the timing, patient selection, and optimal modalities of intervention. Meeting these goals will require accurate early identification of allergic trajectories, reliable biomarkers for endotyping, and the initiation of prompt and intensive therapeutic approaches. The application of systems medicine – including integration of clinical data, multi-omics, epidemiology, and mechanistic modeling – will be key to understanding the underlying pathophysiological pathways that drive divergent allergic trajectories. This approach promises to transform diagnosis, treatment, and prognostic accuracy, ultimately enabling the prevention of allergic disease onset.

Prospects for Future Research. Future research must address critical questions regarding the timing, patient selection, and optimal modalities of intervention.

Conflicts of Interest. The authors declare that they have no conflicts of interest related to this study, including financial, personal, authorship, or any other types of conflicts that could have influenced the research and its results presented in this article.

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ЕВОЛЮЦІЯ АТОПІЧНИХ ЗАХВОРЮВАНЬ: НОВІ ПОГЛЯДИ НА АТОПІЧНИЙ МАРШ

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Резюме. Атопічний марш охоплює послідовність алергічних захворювань, таких як атопічний дерматит, харчова алергія, алергічний риніт і бронхіальна астма, які часто розвиваються в певній послідовності в одного й того самого індивіда. Цей термін було запропоновано як концептуальна модель, що покликана пояснити траєкторію розвитку алергічних захворювань у дитячому віці. Спочатку вважалося, що атопічний марш є єдиною та визначальною траєкторією розвитку алергії. У цьому огляді розглядаються епідеміологічні докази існування різних траєкторій алергічного маршу (тобто відмінних шляхів розвитку атопії у різних людей), аналізується роль генетичних факторів, навколишнього середовища та ендотипів захворювання у формуванні цих траєкторій, а також обговорюється клінічна цінність цієї моделі. Системна імунна відповідь на шкірне запалення може запускати або посилювати розвиток атопічних коморбідностей у генетично чи імунологічно схильних осіб. Однак дані зв'язки можуть відображати не стільки послідовний розвиток хвороб, скільки наявність спільних генетичних локусів і зовнішніх факторів, таких як дисбіоз мікробіоти. Удаване тимчасове співпадіння виникнення захворювань може насправді свідчити про пікову частоту кожної хвороби у певних тканинах, що більше вказує на кластеризацію порушень, а не на послідовний «марш».

Перспективні довготривалі когортні дослідження є цінним інструментом для вивчення виникнення додаткових атопічних станів після розвитку дерматиту, а також для виявлення фенотипових, генотипових та екологічних факторів ризику. Нещодавні дослідження визначили низку факторів ризику розвитку множинних атопічних коморбідностей у дітей раннього віку з атопічним дерматитом. До них належать: тяжкість і хронічність перебігу захворювання, ранній вік початку, наявність атопії у батьків, мутації гена філаггріну, полісенсибілізація тощо. Ранні дослідження, спрямовані на відновлення епідермального бар'єра, модифікацію складу мікробіому або зміну впливу алергенів, можуть допомогти з'ясувати відносний внесок дефектів бар'єра, генетичних змін і впливу навколишнього середовища у ризик, час виникнення та перебіг Th2-опосередкованих порушень.

Ця еволюція вимагає переходу від розгляду алергічних захворювань як лінійної прогресії супутніх захворювань до визнання їх компонентами моделі мультиморбідності, що перекривається. Такий підхід дозволяє проводити проактивний моніторинг пацієнтів на основі їхньої схильності до розвитку супутніх алергічних розладів. Важливо, що ранній початок атопічного захворювання пов'язаний з підвищеним ризиком стійкої мультиморбідності. Сучасні дані також вказують на те, що алергічні стани часто супроводжуються без дотримання фіксованої послідовності розвитку симптомів. Ефективний контроль та своєчасне лікування алергічних захворювань можуть впливати на траєкторію атопічного маршу та потенційно запобігати його прогресуванню. Для досягнення цієї мети стратегії раннього втручання повинні керуватися надійними дослідженнями, які визначають цільові групи населення та мінімізують затримки або невідповідне лікування. Застосування системної медицини, включаючи інтеграцію клінічних даних, мультиоміку, епідеміологію та механістичне моделювання, буде ключем до розуміння основних патофізіологічних шляхів, які рухають розбіжними алергічними траєкторіями. Цей підхід обіцяє змінити діагностику, лікування та прогностичну точність, що зрештою дозволить запобігти виникненню алергічних захворювань.

Ключові слова. атопічний марш, алергічні захворювання, патогенетичні зв'язки, атопічний дерматит, харчова алергія, алергічний риніт, бронхіальна астма, дитячий ранній вік.

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