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Current understanding of allergic march and the role of eczema in its development

Aktualne spojrzenie na marsz alergiczny i rolę atopowego zapalenia skóry w jego rozwoju

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Summary

An increasing morbidity of atopic diseases (atopic dermatitis, food allergy, asthma and allergic rhinitis) documented in large cohort epidemiological studies is at least partially determined by high hygienic standards of living. Over the last 40 years, the accepted concept of pathogenesis of atopic diseases, the so-called atopic march, was proposed by Fouchard in 1973. It referred to the natural history of atopy manifestation, with a typical sequence of symptoms presented as atopic dermatitis in early childhood for subsequent development of allergic respiratory symptoms in late childhood and adolescence. New data suggests that the leading role of atopic dermatitis in atopic march might be less pronounced than previously expected, indicating coexistence rather than succession of atopic symptoms. The objective of this paper is to present the currently discussed concepts of atopic dermatitis – its pathogenesis, etiology, course and role in the development of other allergic diseases. More widely, we will present: 1. The genetic factors involved in skin barrier disruption with the leading role of loss-of-function gene for filaggrin mutation, 2. Genetic defects and epigenetic regulation of the immune system 3. Epidermal changes with physical barrier dysfunction as well as 4. Skin microbiome disturbances with Staphylococcus aureus colonization leading to abnormalities of the epidermal protective barrier.

Keywords: **atopic dermatitis • asthma • allergic rhinitis • epicutaneous sensitization • filaggrin**

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Abbreviations: **AD** – atopic dermatitis, **ALSPAC** – Avon Longitudinal Study of Parents and Children, **AMPs** – antimicrobial peptides, **AR** – allergic rhinitis, **CLDNs** – claudins-encoding genes, **ECAP** – Epidemiology of Allergic Diseases in Poland, **ECRHS II** – European Community Respiratory Health Survey II**, EDC** – epidermal differentiation complex, **EPI** – epicutaneous immunotherapy, **FcεRI** – high affinity IgE receptor, **FLG** – filaggrin, **HBD** – human beta-defensin, **HSV** – Herpes simplex viruses, **ISAAC** – The International Study of Asthma and Allergy in Childhood, **IVL** – involucrin, **LOR** – loricrin, **LPS** – bacterial lipopolysaccharides, MAAS – Manchester Asthma and Allergy Study**, MRSA** – methicillin-resistant *S. aureus,* **MSSA** – methicillin-sensitive *S. aureus,* **NMF** – natural moisturizing

factor, **ORCA study** – Observatory of Respiratory risks linked with Cutaneous Atopy study, **PRRs** – pattern recognition receptors**, S**. – *Staphylococcus,* **SC** – stratum corneum, **SEB** – staphylococcal enterotoxin B, **SPINK5/LEKTI** – serine protease inhibitor Kazal-type 5/lympho-epithelial Kazal-type-related inhibitor, **TCR** – T Cell Receptor, **TEWL** – transepithelial water loss, **TJs** – tight junctions, **TSLP** – thymic stromal lymphopoietin

Introduction

Allergic diseases belong to the most common chronic diseases of childhood and adolescence and are therefore becoming an ever-increasing challenge for modern medicine. An increasing morbidity of atopic diseases as atopic dermatitis (AD), food allergy, asthma and allergic rhinitis (AR) are at least partially determined by high hygienic standards of living and modern life-style [58,66]. The most extensive epidemiological study evaluating the allergic disease incidence in the Polish population is ECAP (Epidemiology of Allergic Diseases in Poland; www.ecap.pl). The study was based on the same methodology as the International Study of Asthma and Allergy in Childhood (ISAAC) and European Community Respiratory Health Survey II (ECRHS II) [55]. The incidence of allergic diseases following verification by medical examinations in children aged 6-7 years, adolescents aged 13-14 years and adults aged 22-40 years was 40%, 43% and 39%, respectively [4]. Although in the studied population, the AD prevalence was lower than the mean European incidence (3.91% vs. 20%), the profile of risk factors (female sex, high social-economic status, parental history of atopy, living in a city) was similar to the data originating from other European countries [19,60]. A high allergic diseases morbidity was also reflected in the data from two longitudinal prospective epidemiological studies performed in large cohorts of British children: Avon Longitudinal Study of Parents and Children (ALSPAC – 8665 children) and Manchester Asthma and Allergy Study (MAAS – 1136 children) [12], where, in the group of children investigated from birth to 11 years of age, 48.7% reported one of the following symptoms: eczema, expiratory wheeze or rhinitis. Such a common occurrence of allergic diseases necessitates a search for their causes, a determination of their natural course and possible preventive measures.

Over the last 40 years, the predominating concept explaining this phenomenon focused on the so-called atopic march, based on the evolution of organ-related manifestations of allergy in children. The term was proposed by Fouchard in 1973 and referred to the natural history of atopic diseases, with a typical sequence of serial symptoms presented from early to late childhood and adolescence: food allergy→atopic dermatitis→asthma→allergic rhinitis. In keeping with the hypothesis, AD symptoms in early childhood (up to 2 years of age) constituted a triggering factor and predictor of asthma and AR in later childhood. The validity of the atopic march idea was suggested by the results of numerous population studies based on correct methodology (prospective studies) and large cohorts [22,50]. The data based on joint results of MAAS and ALSPAC studies throw a new light on the current concept [12]. Authors selected eight possible phenotypes of sequential AD – eczema, wheezing and rhinitis. The classic sequence of atopic march was followed only by 3.1% of the respondents [12]. Even when a separate analysis of MAAS data included only children with moderate to severe AD symptoms, the percentage of those manifesting symptoms chronology typical for the atopic march increased only to 7%. Currently, four clinical phenotypes of AD are identified: 1. Early onset and low atopy grade, 2. Early onset, high atopy grade and high eosinophilia, 3. Late onset and low atopy grade, and 4. Late onset, high atopy grade and normal eosinophil count. Only the second phenotype shows an association with the atopic march, manifested as bronchial hyperreactivity and asthma [41]. Early AD onset (below 6 months of age) seems to be familial (parental atopy), while late AD development (above 12 months of age) is affected by antibiotic therapy administered before the end of 6 months of life [45]. In the cohort of prospective ORCA (Observatory of Respiratory risks linked with Cutaneous Atopy) study conducted in 2002-2012, children with early-onset AD were grouped in two phenotypes: 39% demonstrated multiple sensitization to different food and inhalant allergens, in 17%, symptoms were strongly associated with familial asthma history, while 44% presented no atopic disease in later life [3].

The above reports prompt an analysis of AD anew from a broader perspective. The objective of the paper is to present the currently discussed concepts of AD pathogenesis and etiology, its course and role in development of other allergic diseases.

AD pathogenesis

In light of contemporary knowledge, the etiology and pathogenesis of AD result from genetic and environmental factors. Both groups of factors determine epidermal lesions and affect the immune system balance, initiating the vicious circle of negative phenomena initially located in the skin, which, under favorable conditions, may also involve remote tissues and organs (Figure 1) [28].

Genetic factors involved in skin barrier disruption

Genetic factors involved in the disruption of skin barrier function are associated with the locus on chromosome 1q21, the so-called epidermal differentiation complex (EDC) [18]. It includes a gene family that encodes proteins, such as loricrin (LOR), involucrin (IVL) and the most significant – filaggrin (FLG) [7]. In the Caucasian

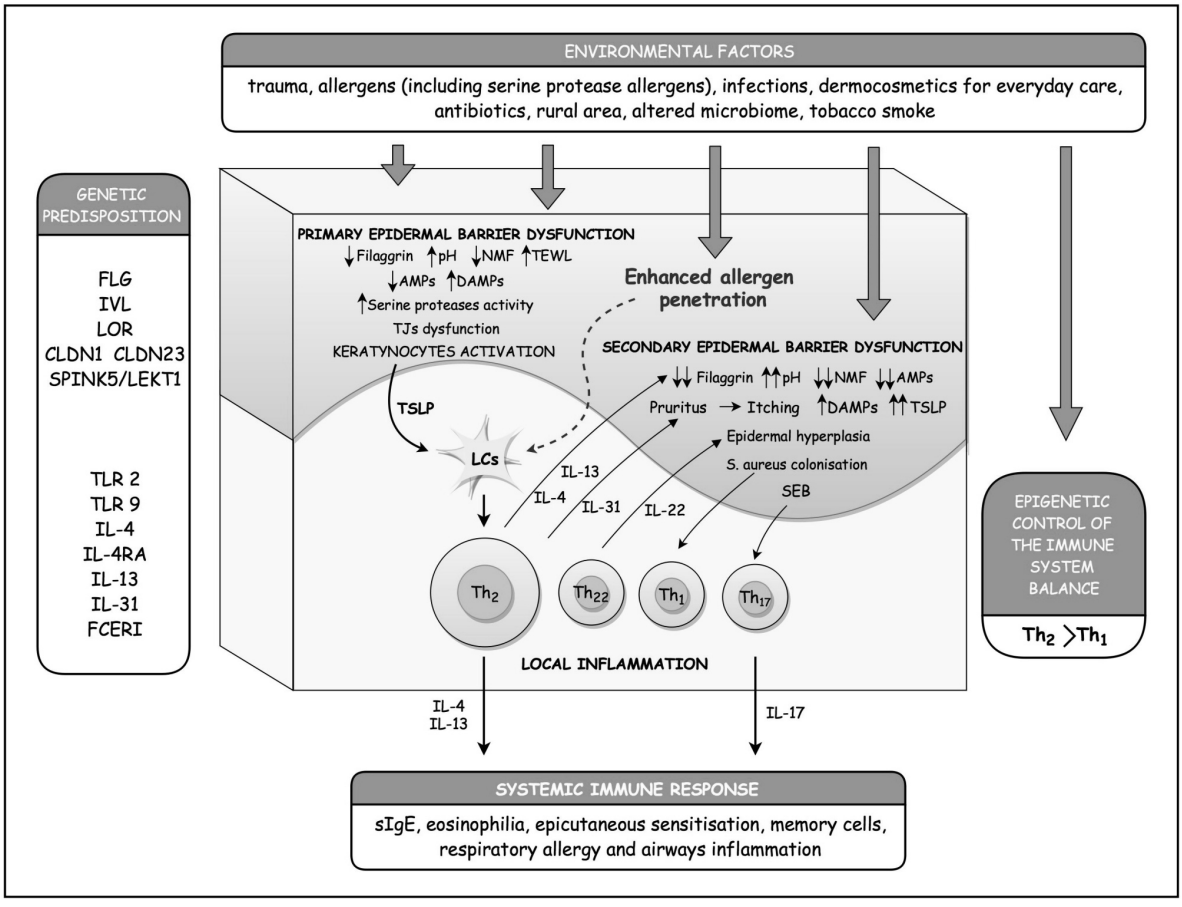

Fig. 1. A scheme of pathophysiological reactions observed in acute and chronic AD (own modification based on [28]);FLG – filaggrin; IVL – involucrin; LOR – loricrin; CLDN – claudin; SPINK5/LEKTI – serine protease inhibitor Kazal-type 5; TLR – Toll-like receptor; IL4RA – interleukin-4 receptor alfa chain; FcεRI – the high-affinity receptor for the Fc region of immunoglobulin E; NMF – natural moisturizing factor; TEWL – transepidermal water loss; AMPs – antimicrobial peptides; DAMPs – damage-associated molecular patterns; TJs – tight junctions; TSLP – thymic stromal lymphopoietin; LCs – Langerhans cells; SEB – Staphylococcal enterotoxin B

population, approximately 1/3 of AD patients carry two most common FLG loss-of-function mutations – R501X and 2282del4 [9], in the general European population, the above variants are found in 9% of the investigated subjects [52]. According to ECAP, in the Polish general population, the incidence of the mutations is low (0.8% and 3.67%, respectively) [53]. FLG mutation causes more than a three-fold increase of AD risk [5]. In FLG loss-of-function mutation carriers, AD is characterized by early onset and a severe, chronic course (Table 1) [25, 47]. Also, according to ECAP, carrying FLG mutation increases the risk of AD, AR and atopic asthma [53].

Other genes associated with epidermal dysfunctions are the serine protease inhibitor Kazal-type 5/lympho-epithelial Kazal-type-related inhibitor (SPINK5/LEKTI) encoding gene (defective in Netherton syndrome with an autosomal recessive pattern of inheritance) [32] and claudins-encoding genes (such as CLDN 1, CLDN 4) – tight junction adhesion proteins in epidermal cells [7].

Genetic factors in immune skin barrier

The most important candidates include genes associated with the Toll-like receptor 2 (TLR2), Toll-like receptor 9 (TLR9), IL4, IL13 and IL31 cytokines, alpha chain of the IL-4 receptor (IL4RA) and high affinity IgE receptor (FcεRI) [7,13]. The TLR are a link between the allergic march concept and the so-called hygienic theory, since transcutaneous exposure to bacterial lipopolysaccharides (LPS) shifts the Th1/Th2 balance towards Th1, stimulates INF-gamma synthesis and supports the protective role of the skin microbiome in allergic diseases development [30]. Restricting the exposure to LPS resulting from high hygiene standards shifts the balance towards the Th2 phenotype and favors atopic disease manifestation [67].

Regardless of the well-defined genetic defects, an increasing role is ascribed to the epigenetic regulation of the immune system activity, affected by environmental factors [31]. The so-called cofactors affect the

Table 1. Comparison of the clinical and biochemical features of patients with AD_{FLG} and patients with $AD_{NON-FLG}$ (based on [48])

	Features	AD_{FLG}	$AD_{NON-FLG}$
Clinical	Palmar hyperlinearity	Present	Absent
	Durability and intensity	More severe and persistent	Less persistent
	Risk of asthma	High	Low
	Allergic sensitization	Often present	Rarely or not
	Eczema herpeticum	Often present	Rarely or no
Biophysical	NMF	↓↓	↓
	pH	↑	lower compared to AD_{FLG}
	IL–1β	↑	lower compared to AD_{FLG}

NMF (natural moisturising factor)

"silencing" gene mechanisms and thus may affect their unblocking and activation. The best known epigenetic processes include DNA methylation, usually leading to gene silencing via transcription inhibition [31] and post-translational histone modifications, resulting in chromatin loosening (active euchromatin) or condensing (inactive heterochromatin), and thus respectively affecting upregulated or downregulated gene expression [11]. Although each cell expresses the identical DNA sequence, from the epigenetic viewpoint, further differentiation and cell activation is possible due to the above mechanisms [31]. For example, a shift in the balance towards Th2 lymphocytes results from a simultaneous activation of the T Cell Receptor (TCR) and IL-4 receptor, while the IL-4 gene expression in case of allergen-specific T lymphocytes results from IL-4 promoter demethylation [39]. Numerous environmental factors have been identified – allergens, microorganisms and LPSs, tobacco smoke, folic acid supplementation, that determine development of a given atopic disease via epigenetic activity (Table 2). Moreover, increasing evidence indicates the inheritance of epigenetic changes and their persistence in subsequent generations [11].

Epidermal changes – physical barrier defects – role of filaggrin and tight junctions

The stratum corneum (SC) is the site where normally differentiated keratinocytes are responsible for producing a lipid-protein matrix playing the role of a physical protective barrier, preventing water loss and protecting against allergens and microorganisms [43]. The main protein produced by keratinocytes is FLG, the role of which consists in aggregating the keratin cytoskeleton, determining keratinocyte flattening in the outermost skin layer [43]. FLG decomposition products together with chloride and sodium ions, lactic acid and urea form a natural moisturizing factor (NMF) for SC and maintain low pH with its antibacterial function and beneficial effect on ceramide-metabolizing enzymes [15]. AD skin is characterized by intensified transepithelial water loss (TEWL) and abnormal final keratinocyte differentiation process, which leads to decreased contents of ceramides, FLG and antimicrobial peptides (AMPs) [43]. Another significant element determining the physical integrity of the epidermal barrier are protein-formed (the major types are the claudins and the occludins) so-called tight junctions (TJs), situated in the epidermal layers below SC [43]. Their role is to stabilize intercellular junctions, to maintain cell polarization and to control solute flow through intercellular space [20]. AD patients manifest decreased levels of claudine-1 (CLDN1) and claudine-23 (CLDN23) [8, 20]. In an animal model, CLDN1-deficient mice died at approximately 24 days of life due to severe dehydration resulting from intensified transepithelial water loss (TEWL) [26]. In infants, intensified TEWL on the second day and in the second month of life is of a prognostic value for AD occurrence at 12 months of age [34], and its degree is correlated with the degree of allergy to inhalant allergens [21]. Also, decreased expression of occludins was identified in the nasal epithelium of patients with allergic rhinitis allergic to house dust mites [59].

Immune disturbances in AD – the vicious circle mechanism

The skin barrier plays a significant protective role. It is the first line of defense, the site where the immune system comes in contact with the external environment.

Table 2. Examples of environmental exposure on occurrence of particular atopic disorder mediated through epigenetic modifications (based on [31])

Environmental Factor	Epigenetic Regulation	Clinical phenotype
Allergens (ovalbumin)	Histone deacetylation Histone acetylation	Allergic asthma, COPD Allergic asthma
Microbes/farm environment	DNA methylation	Allergic asthma
Tobacco smoke	DNA methylation Histone de- and acetylation	COPD COPD
Folic acid	DNA methylation Histone acetylation	Allergic asthma Allergic asthma
Lifestyle (obesity)	DNA methylation	Allergic asthma

COPD – chronic obstructive pulmonary disease

In AD patients, allergens, binding with keratinocyte pattern recognition receptors (PRRs), affect an increased release of thymic stromal lymphopoietin (TSLP), IL-25 and IL-33. They, in turn, induce the release of IL-5 and IL-13 by innate lymphoid cells (ILC), intensifying Th2 type skin inflammation [25, 44, 67]. Additionally, TSLP activates dendritic cells, which play the role of antigen presenting cells and are responsible for Th2 lymphocyte maturation [44]. In keeping with the Th1/Th2 paradigm, the key role in allergy development is believed to lie in upsetting the balance between the two helper lymphocyte populations. Th1-type lymphocytes produce IL-2, IL-12 and IFN-γ cytokines, responsible for immunity to infectious factors, while Th2 lymphocytes are a source of cytokines capable of inducing IgE class antibodies production (IL-4 and IL-13) and promoting the development of allergic inflammation (interleukins: IL-3, IL-5, IL-6, IL-9, IL-13) [36]. Keratinocytes that differentiate in the presence of IL-4 and IL-13 demonstrate a decreased FLG expression, which suggests that the allergic inflammatory response leads to a (acquired) dysfunction of the epidermal protective barrier with a decreased FLG function [33]. Mechanical trauma, infectious factors and exposure to certain allergens also facilitate intensified expression of TSLP, IL-25 and IL-33 [46,49] and a shift in the balance in favor of Th2-type response [43]. Some protease allergens (e.g. house dust mite allergens) penetrate deeper into the epidermal and dermal layers and, thanks to their proteolytic effect on occludins, impair TJs function [67].

According to the current view, there are three main phenotypes of AD: nonlesional skin, acute disease flares, and chronic remitting relapsing AD, which correspond to certain types of inflammation, with type 2 immune response present in all 3 phenotypes, peaking in acute disease flares. TH22-and TH17-driven inflammation adds to the type 2 immune response and is present in nonlesional skin, whereas TH22 – and TH1-driven inflammation is prominent in patients with the chronic form of AD. [28,49].

Skin microbiome disturbances in AD

The term microbiome includes the total of microorganisms that occasionally or permanently colonize the superficial skin layers. The composition of skin-colonizing microorganisms depends on its current condition and maturity [10]. In seborrheic regions, Propionibacterium and Staphylococcus sp. bacteria predominate, regions with increased humidity abound in Corynebacterium sp., while in dry skin areas, the flora is the most diversified [29]. A different skin microbiome is seen in an infant, which results from skin structural and functional immaturity and becomes similar to that of an adult when the child is one year old [10]. In the case of Cesarean deliveries, from the beginning, the neonatal skin becomes colonized with microorganisms bacteria living on maternal skin (i.e. Staphylococcus, Propionibacterium and Corynebacterium sp.) [23]. Staphylococcus (S.) epidermidis is the dominant commensal bacterium permanently colonizing the human skin, having the ability to release proteins with activity similar to that of AMPs produced by keratinocytes and thus inhibiting skin colonization by such pathogens as Staphylococcus aureus, group A streptococci and Escherichia coli [27]. Moreover, S. epidermidis affects the Toll-like keratinocyte receptors, exerting a beneficial effect on maintaining the integrity of the skin's protective barrier, including the intensification of TJs expression and proinflammatory cytokine production [10]. AD patients manifest a typical skin microbiome abnormality – in more than 90% of cases, the skin is colonized by S. aureus, while in the healthy population, the percentage is close 5% [35]. Polish authors also draw attention to this problem [54]. S. aureus colonization and secondary loss of skin microbiome versatility in AD patients are facili-

tated by abnormalities of the epidermal protective barrier [10]. Under physiological conditions, FLG decomposition products inhibit Staphylococcus colonization. In AD patients, who manifest decreased levels of FLG, increased adhesion and propagation of S. aureus occurs more easily [48]. Moreover, AD patients demonstrate a relatively low level of AMPs produced by keratinocytes (IL–37 – cathelicidin, human beta-defensin – HBD1, HBD2, HBD3), which constitute the chemical defense line against skin pathogens, especially S. aureus and Herpes simplex viruses (HSV [37]. An additional aspect of local inflammatory potentiation by S. aureus is its ability to release toxins, e.g. staphylococcal enterotoxin B (SEB), which is noted in approximately 50% of AD patients [47]. Since SEB acts as a superantigen, directly activating Th2 lymphocytes without the contribution of antigen-presenting cells, it thus intensifies inflammation and IgE synthesis [47]. In an animal model [68], with mice transepidermally exposed to SEB, systemic Th17/IL-17 reaction and intensified Th2 reaction were achieved, with secondary inflammatory state and respiratory hyperactivity. Also, recent results indicate an association between poorer asthma control in adults and the presence of staphylococcal enterotoxin sIgE [57,61]. A significant clinical problem is a linear increase in the percentage of AD children colonized by methicillin-resistant S. aureus (MRSA). A longitudinal study (1999-2014) performed in AD children (0-18 years) showed a 24-fold increase of MRSA-positive vs. methicillin-sensitive (MSSA) S. aureus and Streptococcus sp. results [17].

Current views on and role in the development of other atopic diseases

Though AD is a common atopic disease of childhood and the most common skin disease in children, it may not precede respiratory allergy symptoms [19,24]. The results of large cohort MAAS and ALSPAC studies indicate that the sequence of the allergic march diseases is followed by much less than it was previously evaluated. Additionally, more than one-half of AD children do not develop any subsequent allergic disease [12]. Thus, we are faced with the necessity of developing precision medicine which would allow us to better define the disease endotypes associated with a higher risk of developing asthma and allergic rhinitis. Potential candidates may include FLG, TSLP, IL-31, IL-33 [24,42,49]. Though opposite to respiratory allergies, in AD, due to pathogenetic diversity, its phenotypes, endotypes and corresponding biomarkers are far less defined, causing the diagnosis to remain clinically-based [38]. In the natural course of AD, there are two phenotypes that differ in the probability of developing coexisting allergic diseases: the decidedly more common exogenous type, also called "allergic", associated with an elevated total IgE and the presence of specific IgE for environmental and food allergens, and the endogenous type, non-allergic, without the presence of a specific IgE and with normal total IgE [62] (Table 3). The exogenous type is associated with the impairment of the protective skin barrier and increased allergen penetration, which may lead to the so-called transcutaneous allergy [22]. The phenomenon was confirmed in individuals with FLG loss-of-function mutation, in whom early transcutaneous exposure to peanut allergens increased the risk of becoming allergic and, in consequence, developing an symptomatic allergy to peanuts [14]. A similar phenomenon is seen in other food allergies [63,65]. Therefore, the development of allergic diseases in distant organs most likely results from a systemic response of the immune system to intensified allergen penetration through the FLG mutation-impaired

Table 3. Features of the extrinsic and intrinsic types of atopic dermatitis (based on [62])

Features	Extrinsic AD	Intrinsic AD
Frequency	80%	20%
Specific IgE	Present (especially against house dust mites)	Absent
Sensitization	Confirmed	Absent
Men : Women	1 : 1	1 : 3-4
Onset	Early	Late
Remission	Early	Late or not
FLG mutation	Yes	No
Disrupted skin barrier	Yes	No
T-cell polarisation	Th1 < Th2	Th1 > Th2
Others:	Severe itching Eosinophilia	Metal allergy (contact allergy)
	An increased risk for asthma and allergic rhinitis	Lower risk for asthma and allergic rhinitis

skin barrier [47]. Hypersensitivity and the production of specific IgE to inhalant and food allergens in the mechanism of transcutaneous sensitization may lead to IgE-involving chronic inflammatory diseases, especially asthma and AR [6]. In the case of the same allergen, the allergy at the skin level precedes the allergy at the respiratory tract level [22], which may be associated with immune methods-confirmed FLG presence solely in the skin epithelial tissue, oral and nasal vestibule, with FLG being not detected in bronchial biopsy specimens of the respiratory epithelium [47]. Impaired skin barrier by FLG-loss of function leads to innate immunity mediated inflammation with subsequent progression and acquired (secondary) immunological response manifested by allergic respiratory symptoms [56]. The above phenomena confirm the hypothesis of a "double exposure to allergens", where consumption of food allergens induces their tolerance, while transcutaneous exposure via damaged skin leads to allergy development [40]. This view remains in line with the concept of atopic march.

Contrary to the role of an impaired skin barrier in AD, a healthy, intact skin barrier allows for treating some allergic diseases via epicutaneous immunotherapy (EPI), predominantly in the case of food allergens (milk, hen egg-white, peanuts) [2,46]. Under normal conditions, interactions between the healthy skin barrier allows for the proper maturation of the immune system, inducing immune tolerance via the transcutaneous route [46].

The concept of the allergic march is not confirmed by running results of intervention studies aimed at preventing atopic diseases. At the current stage of research, no evidence supports the idea that AD prevention simultaneously prevents respiratory tract atopy, while the recommended primary prevention methods seem to be organ-specific – different for the skin, gastrointestinal and respiratory tract. [16,64].

Summarizing the current views on immunopathophysiology of AD, we can state that it is a complex disease with various phenotypes giving rise to variations underlying genetic and immunologic patomechanisms, as well as an individualized response to pharmacologic treatment, which allows us to distinguish subclasses of phenotypes termed endotypes. The leading role of AD in atopic march might be less pronounced than previously expected, as less than 10% of children follow this scenario. Currently, it seems rather to be the coexistance of skin and respiratory symptoms, while a cause-and-effect relationship seems to be uncertain.

Constantly up-dated guidelines on the treatment of AD, endotype-addressed therapeutic intervention, according to modern precision medicine, may give AD children a greater potential for both better outcome and prevention with respect to respiratory symptoms [1,49,51].

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