

## EDITORIAL

# Recurrent airway inflammations in children – allergy or immune deficiency?

Aleksandra Szczawińska-Popłonyk, Anna Bręborowicz

Department of Pediatric Pneumonology, Allergology and Clinical Immunology,  
III Chair of Pediatrics, Medical University of Poznań

### SUMMARY

*Recurrent airway inflammations in children – allergy or immune deficiency?*

Szczawińska-Popłonyk A., Bręborowicz A.

Department of Pediatric Pneumonology, Allergology and Clinical Immunology, III Chair of Pediatrics, Medical University of Poznań, Poland

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*Recurrent airway inflammations in children are an important diagnostic problem and result in difficulties in differentiation between allergic background and primary immune deficiencies. In the paper issues related to maturation of innate and adaptive immunity in newborns, infants and young children as well as resulting dysregulation of the immune response and predisposition to development of allergy have been presented. Connections between primary immune deficiencies and allergic background have been discussed, with particular emphasis on the role of T regulatory lymphocytes. In the context of presented associations between allergy and defects of the immune response, these phenomena should be considered not as pathogenetically precluding, but as a specific “overlapping syndrome”.*

**Key words:** allergy, immune deficiency, children, hypogammaglobulinemia, regulatory T lymphocytes

Recurrent airway inflammations in children are an important diagnostic and therapeutic problem in pediatric practice. They localize on different stages of the respiratory tract and manifest as chronic rhinitis and paranasal sinusitis, recurrent otitis media, hypertrophy of the lymphatic tissue of the upper airways, recurrent laryngitis, recurrent bronchitis and pneumonia with obstruction of the lower airways. Considering possibility of common clinical manifestation as well as coexisting of pathogenetically heterogeneous disorders, a differential diagnosis is an essential challenge and requires specialistic multidirectional tests. The purpose of these diagnostic procedures is to exclude / to confirm such

### STRESZCZENIE

*Nawracające zapalenia dróg oddechowych u dzieci – alergja czy niedobór immunologiczny?*

Szczawińska-Popłonyk A., Bręborowicz A.

Klinika Pneumonologii, Alergologii Dziecięcej i Immunologii Klinicznej, Uniwersytetu Medycznego w Poznaniu

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*Nawracające zapalenia dróg oddechowych u dzieci stanowią istotny problem diagnostyczny i są źródłem trudności w różnicowaniu pomiędzy podłożem alergicznym i pierwotnymi niedoborami odporności. W pracy przedstawiono zagadnienia związane z dojrzewaniem odporności wrodzonej i adaptatywnej u noworodków, niemowląt i małych dzieci oraz wynikającą stąd dysregulację odpowiedzi immunologicznej i predyspozycję do rozwoju alergii. Omówiono powiązania między pierwotnymi niedoborami odporności i podłożem alergicznym, ze szczególnym zwróceniem uwagi na rolę limfocytów T regulatorowych. W kontekście przedstawionych asocjacji alergii i defektów układu odpornościowego należy je rozpatrywać nie jako wykluczające się patogenetycznie zjawiska, ale szczególnie „zespół nakładania”.*

**Słowa kluczowe:** alergja, niedobór odporności, dzieci, hypogammaglobulinemia, regulatorowe limfocyty T

diagnoses as asthma, primary immune deficiency, cystic fibrosis, gastroesophageal reflux, and immotile cilia syndrome. Major questions regard diagnostic difficulties appearing in conjunction with differentiation between allergic background of the symptoms in the respiratory tract and disturbances within the immune system.

### RECOMMENDATIONS CONCERNING DIAGNOSIS OF PRIMARY IMMUNE DEFICIENCIES

Principles of establishing diagnosis of primary immune deficiencies had been initiated and worked out

by World Health Organization and then have been published in the form of broad elaborations, systematically introducing current elements. These recommendations, in the modified form as “10 warning signs of primary immunodeficiencies”, addressed above all to general practitioners and pediatricians, have been launched and propagated by the Jeffrey Modell Foundation in the USA for the purpose to improve the detectability of this group of disorders [1].

In the aspect of considered problem of recurrent airway inflammations in children, these recommendations are characterized by usefulness and substantial limitations as well. Respiratory symptoms are mentioned as clinical situations which require diagnostic procedures towards primary immune deficiencies. Likewise, attention is paid to clinical manifestations from other organs and systems, as gastrointestinal tract and skin changes as well as general symptoms, eg. malnutrition. In differentiation also the response to administered treatment, particularly to antibiotic therapy must be taken into account. Nevertheless, diagnosis of infections of severe and life threatening clinical course is mostly stressed, hence these recommendations are first of all helpful in detection of severe immune deficiency diseases in children. Moreover, these above mentioned principles do not define or not exclude the role of allergy, they either are not a source of any diagnostic algorithms for the clinical problem of recurrent airway inflammations in children. Diagnostic criteria issued by the European Society for Immunodeficiencies (ESID) comprise, in turn, directions concerning application and precise interpretation of highly specialistic immunological diagnostics tests, hence they are very detailed and oriented in their character, resulting in limitations in considering clinical problems [2, 3].

## **MATURATION OF THE IMMUNE SYSTEM**

Physiological phenomenon of maturation of the immune system contributes to the difficulties in interpretation of the results of the immunodiagnostic tests, evaluating functions of the immune system in children. This process, initiated within the fetal period, is dynamic in its character and is expanding in time through the first months and even years of child's life. Hence, within the neonatal period, infancy and early childhood dysfunction of numerous components of the immune system is observed.

Within the neonatal period considerable immaturity characterizes the system of monocytes-macrophages. It consists in decreased expression of costimulatory molecules and diminished ability to

differentiation into dendritic cells as well as weak production of IL-12 by monocytes [4]. Macrophages exhibit diminished response to  $\text{IFN}\gamma$ , decreased activity upon phagocytosis [4] and impairment of intracellular killing [5].

In neonates the immaturity concerns function of dendritic cells. This consists in downregulated expression of costimulatory molecules by myeloid (mDC) and of plasmacytoid (pDC) dendritic cells, defective maturation and synthesis of cytokines –  $\text{IFN}\gamma$  and IL-12 as the response to signaling pathways downstream of Toll-like receptors engagement, particularly TLR4 and TLR9 and CD40 molecule as well as impaired ability to stimulate the immune response by pDC. The proposed mechanisms to explain the dysfunction of neonatal DC comprise intrinsic immaturity, defective interaction between dendritic cells and T lymphocytes as well as modulatory effect of natural regulatory T cells (nTreg). These cells, playing an important role during pregnancy and maintaining maternal tolerance to the fetus, are present in high numbers in neonates and are critical in maintaining homeostasis, immunological tolerance and preventing autoimmunity. Neonatal nTregs exert their immunosuppressive function by the mechanism of interaction between molecules CTLA-4 and CD80 / CD86 on antigen-presenting cells and by secretion of L-10 and  $\text{TGF}\beta$  [4].

Functional alterations of neonatal antigen-presenting cells may in turn lead to secondary defects of adaptive T cell response. In neonates occurs a T cell functional deficiency manifesting as downregulated expression of TCR / CD3 complex, adhesion molecules and CD40 ligand (CD40L, CD154), impaired cytotoxic activity of CD8+ T cells as well as decreased cytokine synthesis. Expression of a range of cytokines playing an essential role in the immune response, such as IL-4, IL-5,  $\text{IFN}\gamma$ ,  $\text{TNF}\alpha$ , and IL-12 is a dynamic process and their production increases with child's age [6]. *Hodge* et al. demonstrated a diminished number of neonatal T lymph cells and NK cells exhibiting expression of  $\beta$  chain of the IL-2 receptor. Moreover, the production level of cytokines such as IL-1 $\alpha$ , IL-1 $\beta$  and  $\text{TNF}\alpha$  was lower compared to adults, pointing to decreased capacity to mount effective inflammatory response. In contrary, the level and kinetics of expression of other functional molecules – CD71, HLA-DR and CD152 was comparable to that in adults [7].

Predominance of the Th2-dependant immune response prevailing within the fetal period and expanding through the neonatal period and infancy [8, 9,10] may be among others a result of exerted activity of regulatory T cells, suppressing the proinflammatory Th1-mediated response [11]. Moreover, mechanisms

of the innate immune response profiling development of the adaptive response towards advantageous Th1 or Th2 mediated immunity, contribute to the predisposition or to the protection from asthma and allergy. Dose, settings, and timing of exposure to antigens are of crucial importance in modulating the immune response profile within the early child's life [12, 13].

Immaturity of the effector mechanisms and suppressive activity of the transplacentally transmitted maternal IgG antibodies contribute to the consequent deficiency of specific humoral response [8]. In neonates rapid increase of the immunoglobulin M active in primary immune response to antigens, relatively high concentration of IgG of maternal origin and weak production of child's own immunoglobulins IgG and IgA manifests as dysgammaglobulinemia and reflects distinct dynamics of different isotype synthesis. In infants between the second and sixth months of life hypogammaglobulinemia continues as a result of still weak production of own and the breakdown of maternal immunoglobulin G. At the end of the first year of life still IgG amounts 60%, IgA – 25%, and IgM – 75% of total concentration in adults. Delayed maturation of the humoral response manifests frequently as transient hypogammaglobulinemia of infancy (THI), which abates typically until the end of the second year of life [14], but may be prolonged even up to the fifth or sixth year of life [15]. Hitherto the evaluation if the immune defect in a child is transient or is signaling a permanent primary immune deficiency, may be difficult. Hence, elaboration of wide population-based standards, taking into consideration a dynamic and variable process of maturation of different elements of the immune response, as well as development and broadening of spectrum of investigations on the field of immunogenetics are of crucial importance.

## ALLERGIC DISEASES COEXISTING WITH IMMUNE DEFICIENCIES

To the clinical problem of concomitant occurrence of allergic diseases and primary immune deficiencies in children drew attention *Klemola*, who reported symptoms of atopic diseases in 50% of children with selective IgA deficiency (sIgAD) [16]. Interestingly, it was noted a better correlation between the prevalence and severity of the clinical course of allergic diseases in children within the first two years of life and a low normal IgA concentration in serum than a concentration of IgE increased above the normal value for age [17]. In the prospective study evaluating the same group of children at the age of four years it was observed an association between occurrence of allergic diseases and asthma and decreased IgA

and IgG4 subclass in serum as well as secretory salivary IgA [18]. The *Papadopoulou* study revealed not solely a higher prevalence of atopy in a group of children with selective IgA deficiency compared to a control group, but also pointed to the more frequent coexisting bronchial hyperreactivity and hypersensitivity to *Dermatophagoides pteronyssinus* in children with sIgAD [19]. The results of the study performed by *Kutukculer* et al [20] indicated that partial IgA deficiency and IgG subclass deficiency are transient in 52% and 51% children, respectively and that increases in serum immunoglobulins to age-related normal levels occur up to the sixth year of life. Exactly in this group of children atopic diseases proved to occur more frequently than among children with complete selective IgA deficiency (in 41% and 24% patients, respectively). An analysis of correlation between clinical and immunological phenotypes was done in the recent report of Iranian authors [21] on the group of patients aged 4-32 years, showing IgA concentration below 6 mg/dl. Recurrent airway inflammations were the most frequent clinical problems, referring to 94% of patients. Allergic diseases – asthma, atopic dermatitis, allergic rhinitis and conjunctivitis were diagnosed in 84% of patients, indicating the fact, that not a predisposition to infections resulting from an immunodeficiency solely, but also an allergic background considerably affects the clinical manifestation of the disease. Interestingly, an asthmatic phenotype was present exclusively in patients with selective IgA deficiency amounting 62% of the study group. On the contrary, in 38% of patients, who suffered from a complex immunodeficiency consisting in IgA deficiency, IgG subclass deficiency, and deficiency of specific antibodies against polysaccharide antigens (sAbD), infections of the respiratory tract predominated as clinical manifestations and exclusively in this group of patients occurrence of bronchiectases was observed. *Moraes* et al [22] in the study on the group of 41 severe asthmatic children showed an association between the degree of asthma control and recurrent airway infections as well as deficiencies within the immune system. In children with poor asthma control more frequently than in children with sufficiently controlled asthma (66% vs 55% of children) a deficiency of one or more IgG subclasses (IgG3, IgG4, IgG1, IgG3-IgG4, IgG1-IgG3, IgG1-IgG3-IgG4), and IgG3 or IgG4 deficiency were diagnosed as well as solely in this group of children a combined IgA and IgG subclass deficiency was revealed.

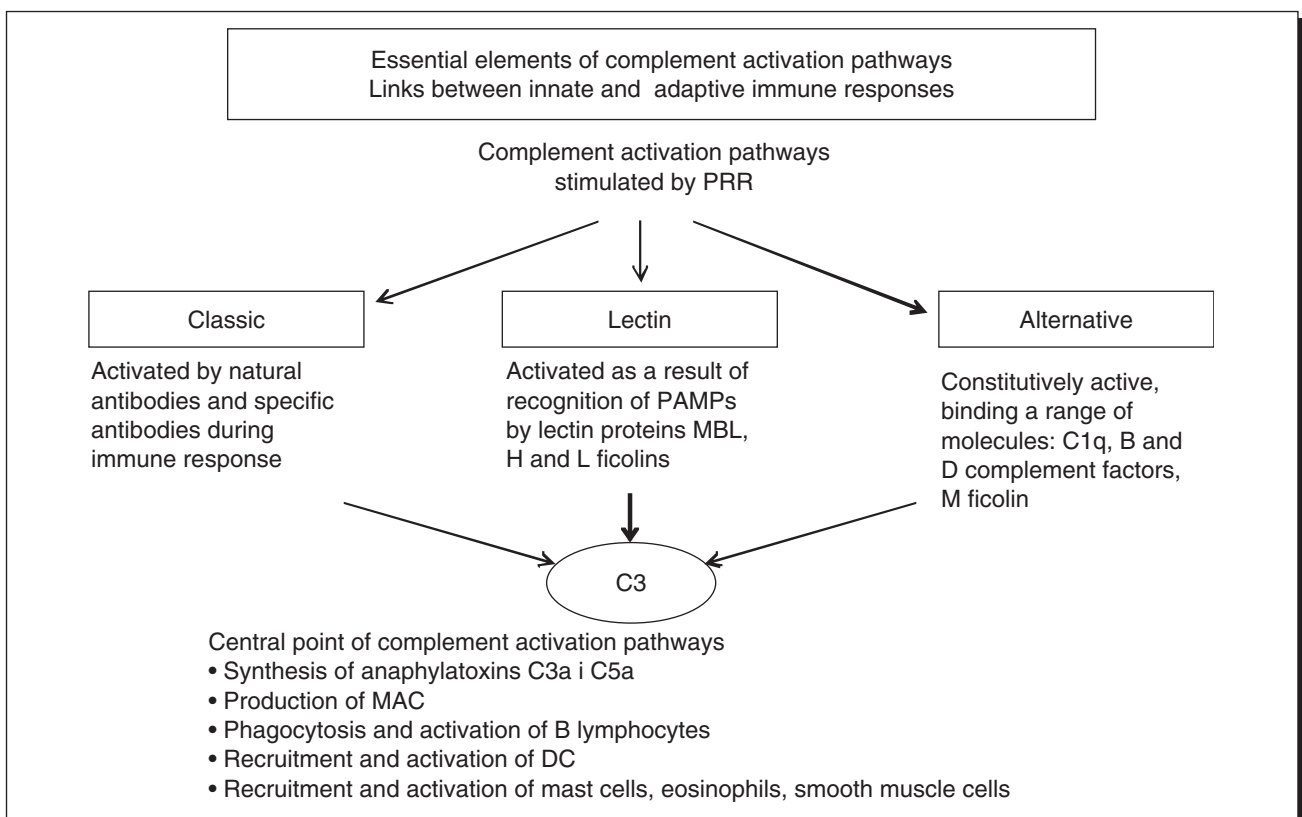
Single reports in the literature concerning selective immunoglobulin M deficiency (sIgMD) in pediatric population and in adults point to the recurrent respiratory tract infections as the predominant clinical fea-

ture. Allergic diseases and asthma coexist with this immune deficiency in 7,8% of affected children [23] and as much as 33% of adult patients [24].

Interestingly, an association between allergic diseases and immune deficiencies was observed in patients manifesting profound defects of antibody production. *Shabestari et al* [25] reported a case of a boy with Bruton's agammaglobulinemia in whom concentrations of main classes of immunoglobulins were decreased within all isotypes, including IgE (<0,1IU/ml), B lymph cells bearing antigens CD19 and CD20 amounted less than 1% of normal value for age and the disease was confirmed by BTK gene mutation. Recurrent episodes of respiratory infections with obstruction of the lower airways were the most important clinical symptoms, and in additional diagnostic examinations – positive skin prick tests with alimentary and airborne allergens as well as bronchial hyperreactivity in spirometry were noted. A bias towards Th2-mediated immune response was also documented in patients with common variable immunodeficiency (CVID) through investigation of cytokine levels and demonstration of increased IL-4 and IL-10 production [26].

Associations between allergic background of respiratory symptoms and immune defects are not exclusively confined to a dysregulation of immunoglobulin production and impaired balance between Th1 and Th2 lymph cells compartments. These phenomena are also determined by the activity of complement

pathway components, establishing links between innate and adaptive immune responses (figure 1). Although each pathway is activated by distinct pathway recognition receptors (PRRs), they all culminate in activation of C3 component, a central step in complement activation. Activation of C3 leads to the generation of anaphylatoxins C3a and C5a, which through binding their receptors on inflammatory cells proved to induce pathophysiological features of allergic inflammation. In support of this proallergic role of C3, its deficiency was shown on an animal model to have a protective effect against antigen-induced bronchial hyperreactivity [27, 28]. C5a, in turn, in allergic inflammation plays a dual role, both promoting and protective, depending on the inflammatory cells and cytokine environment upon its activation. Immunological role of C5a component consists principally in modulation of the adaptive immune response through altering the phenotype and function of antigen-presenting dendritic cells [29]. A deficiency in C5a leads to a shift of the proportion of the myeloid dendritic cells (mDC) to plasmacytoid dendritic cells (pDC), being a source of IL-12 and IFN $\gamma$  and to the consequent development of Th2-dependant effector phase. In this condition of a lack of C5a also an increase of the production of Th2-specific chemokines, CCL17 and CCL22 by pulmonary mDCs occurs, enhancing homing of Th2 lymph cells [30]. Impairment of the immune tolerance results from a defective



**Fig. 1.** Complement activation pathways – a link between innate and adaptive immune responses

stimulation of pDCs and absence of regulatory T cell induction, corroborating a concept of a tolerogenic role of C5a. A recognition of pattern-associated molecular patterns (PAMPs) leads to the activation of complement pathway by lectin proteins. A decreased level of a mannose-binding lectin (MBL), playing an important role in opsonization was found in a group of asthmatic children [31]. Moreover, an association was shown between an allelic variant of MBL2 gene leading to decreased MBL concentration in serum and higher risk of asthma in children presenting with recurrent and chronic *Chlamydia pneumonia* infection [32]. In adults an allelic MBL variant was not only associated with predisposing effect to asthma, but also correlated with a decrease in lung function [33].

Ficolins M, L, and H (1,2, and 3, respectively), structurally similar to collectins, MBL, and surfactant protein A and D initiate the lectin pathway of complement activation through serin proteases MASPs [34]. *Cedzynski* et al reported an association between relative L-ficolin deficiency and recurrent respiratory infections coexisting with asthma in children [35].

Interestingly, *Fitzpatrick* et al [36] demonstrated impaired alveolar macrophage phagocytosis in children with poorly controlled asthma. These findings suggest, that a functional deficiency of innate immunity contributes to a defective antimicrobial response and recurrent airway inflammation resulting in exacerbations of asthma. This phenomenon of impaired phagocytosis may be explained by an alternative mechanism of macrophage activation potentiated by IL-4 in the Th2 microenvironment where inhibition of phagocytosis associated with defective phagosome formation and concomitant increased proinflammatory cytokine secretion was observed by *Varin* et al [37].

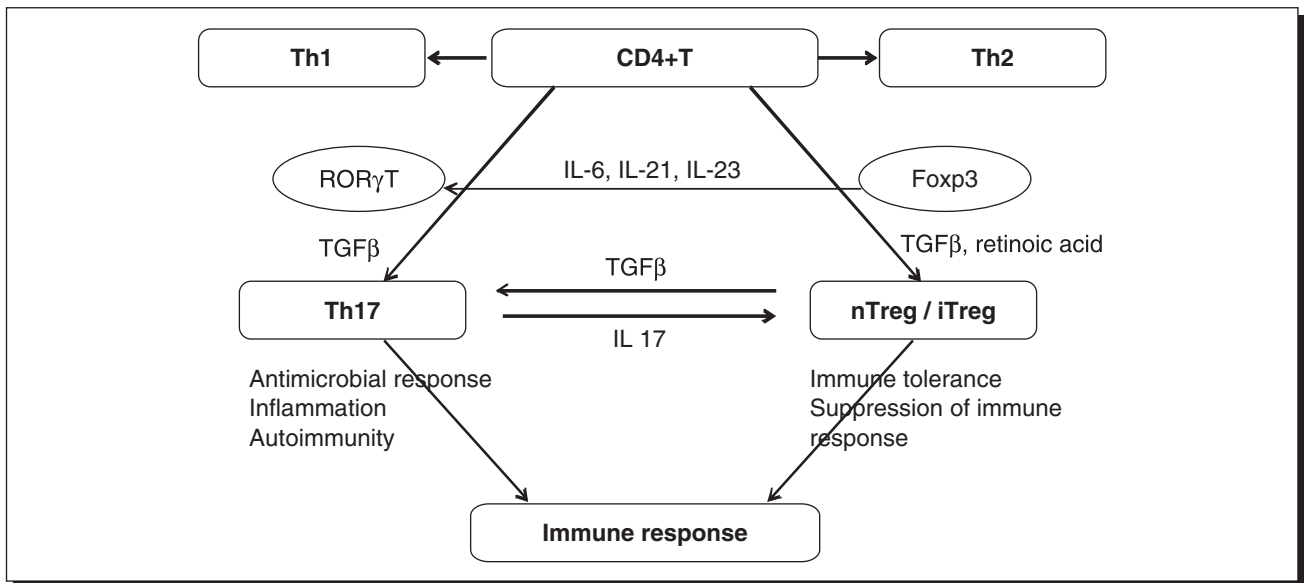
The above mentioned findings point to the pathogenetic relationship between allergy and immune deficiencies which better than mechanisms of atopy correlate with symptomatology of the allergic diseases in children. These observations regarding mainly young children and infants presenting transient deficiencies of the immune response indicate a delayed maturation of immunological components as a phenomenon of crucial importance. A dysregulation of the immune response contributing to the defective antigen elimination in the early childhood of the predisposed individual may be considered as the critical risk factor preceding development of allergy.

## ROLE OF REGULATORY T LYMPHOCYTES

Regulatory T lymphocytes of thymic origin (nTreg) constitute 5-10% of the peripheral T CD4+ lymph cells

population, are characterized by expression of such molecular markers as:  $\alpha$  chain of IL-2 receptor (CD25),  $\alpha$  chain of IL-7 receptor (CD127), GITR (glucocorticoid-induced tumor necrosis factor receptor-related protein), OX40 (CD134), L-selectin (CD62L), and CTLA-4 (cytotoxic T lymphocyte – associated antigen, CD152). It is worth of note that any of these antigens is not specific solely for regulatory T lymphocytes, they may be expressed in different degree on activated T lymphocytes and on antigen-presenting cells [38]. Natural Treg cells of a CD4+CD25+ phenotype are best characterized by an intracellular marker – a transcription factor Foxp3, playing an essential role in development and activity of these cells [39, 40, 41]. Inducible regulatory T lymph cells (iTreg, Tr1) arise as a result of activation of mature T cells in the settings lacking an optimal exposure to antigen or costimulation as well as in the environment of inhibitory cytokines and are characterized by IL-10 and TGF $\beta$  production. Naïve CD4+ T cells may also develop into Tr1 cells in the presence of chronic stimulation with allergens, infectious and tumor antigens. However, the suppressive function is not strictly Treg-specific and all CD4+ T cells exhibit suppressive activity in different degree. Lymph cells of Th1 subset secrete IFN $\gamma$ , inhibiting proliferation of Th2 lymph cells; the latter, in turn, are the source of IL-4 suppressing development of Th1 population and IFN $\gamma$  synthesis. Collectively, IFN $\gamma$  and IL-4 inhibit differentiation of Th17 cells and secretion of IL-17 by effector Th17 cells; IL-17, in contrast, suppresses differentiation of Th1 lymph cells [39]. Besides, expression of transcription factors essential for differentiation of CD4+ T cell lineage is the subject of several regulatory factors. Foxp3 expression is induced in nTreg cells during their thymic stage of development and in iTregs as an effect of TGF $\beta$  and retinoic acid in the periphery. Moreover, ROR $\gamma$ T, a transcription factor critical for development of Th17 cells subset is induced by TGF $\beta$ , connecting differentiation pathways of Treg and Th17 cells lineages [42]. In the settings lacking proinflammatory cytokines signals, Foxp3 suppresses function of ROR $\gamma$ T and stimulates differentiation of Tregs; Th17 development, in turn, occurs in the environment of IL-6 and IL-21, where the Foxp3 function is downregulated [43, 44, 45]. Mechanisms determining types of immune response as a result of transcription factors ROR $\gamma$ T and Foxp3 activity towards CD4+ T cell subsets is displayed on figure 2.

For T regulatory lymphocytes the following non-exclusive functions are proposed: prevention of autoimmunity by establishing and maintaining immunological tolerance to self antigens, induction of maternal tolerance to the fetus, induction of tolerance



**Fig. 2.** Mechanisms of lymph cell differentiation towards Treg and Th17 determining type of the immune response

against alimentary antigens and suppression of pathogen-induced immunopathology [39, 40, 46].

In allergic diseases and asthma activation of CD4+ T cells plays a key role and allergic inflammation in the airways is mediated by subpopulations of effector Th2 and Th17 cells. Regulatory T cells, both nTregs having CD4+CD25+ phenotype and antigen-induced IL-10 secreting Tr1 cells achieve their regulatory effect by different pathways, inhibiting dendritic cells activity, suppressing effector Th2 and Th17 cells, suppressing mast cells and basophils, as well as decreasing migration of inflammatory cells to target tissues [47, 48, 49]. They also downregulate IgE synthesis and stimulate class switching towards anti-inflammatory isotypes – IgG4 subclass and, in a lesser extent, to IgA. Induction of IgA synthesis is first of all determined by activation of B lymphocytes through Toll-like receptors TLR9 and TLR7 pathway [49]. *Hartl*

*et al* [51] reported significantly decreased number of CD4+CD25+ T cells and lower concentration of cytokines IL-10 and TGFβ in bronchoalveolar lavage fluid of asthmatic as compared to healthy children. Likewise, in patients manifesting symptoms of atopic diseases *Saito* [52] demonstrated a smaller proportion of cells Foxp3+CD4+ than in asymptomatic individuals in the control group, having similar concentrations of IFNγ and IgE in serum as well as blood eosinophil count. These above mentioned findings suggest that development of symptoms of allergic diseases is determined by mutual relationship between proinflammatory Th2 and Th17 lymph cells subsets and and regulatory T cells.

A deficiency of regulatory T cells resulting from FOXP3 gene mutation is an essential factor in pathogenesis of IPEX syndrome (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) [53]. In a range of pri-

<b>Table 1.</b> Genetic background of primary immune deficiencies associated with regulatory T cells dysfunction	
CD4+CD25+Foxp3+Treg ↓ CD4+Th2 ↑	
Primary immune deficiency syndromes	Genetic defects
immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)	forkhead box protein 3 (Foxp3), Signal transducer and activator of transcription (STAT5b), CD25
Wiskott-Aldrich syndrome (WAS)	Wiskott-Aldrich syndrome protein (WASP)
Omenn syndrome (OS)	Recombination activation genes (RAG1 /RAG2)
Comel-Netherton syndrome (CNS)	serin protease inhibitor Kazal type (SPINK) /lymphoepithelial Kazal type inhibitor (LEKTI)
polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED) / autoimmune polyglandular syndrome type II (APS II)	Autoimmune regulator (AIRE)
DiGeorge syndrome (DGS) – incomplete form	Microdeletion 22q11

mary immune deficiency diseases an immunological dysregulation may be consequent to functional regulatory T cells impairment and predominating Th2-dependent immune response, as it was demonstrated in patients with common variable immunodeficiency, a disorder predisposing to autoimmunity [54, 55].

Primary immune deficiencies of different genetic background, associated with regulatory T cells dysfunction are displayed in table 1.

## CONCLUDING REMARKS

Multidirectional interactions and precise control of elements of the immune response determine homeostasis between effector mechanisms and tolerance. Above mentioned associations between numerous elements of the immune system, the innate as well as adaptive immune response and mechanisms predisposing to the development of allergy suggest complex considering of the clinical problem of recurrent airway inflammations in children. The immune deficiencies and allergy are thus not precluding phenomena, but should be considered as a specific "overlapping syndrome".

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**Correspondence:** Aleksandra Szczawińska-Popłonyk  
Department of Pediatric Pneumology, Allergy and Clinical Immunology  
III Chair of Pediatrics, Medical University  
60-572 Poznań, Szpitalna Street 27/33  
Tel/fax +48-61-848 01 11  
email: ola@malwa.com.pl

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