

EDITORIAL

Immune responses to allergens early in life: when and why do allergies arise?

Introduction

The prevalence of atopic diseases such as bronchial asthma, atopic dermatitis and allergic rhinitis (SAR) [1] has increased over the last decades in industrialized countries [2–4], making allergies a very serious public health problem [5]. This is especially true in children [6], where asthma has become the most common chronic illness overall [7]. Therefore, valid predictions of predisposing factors for the development of allergic diseases are highly desirable to enable early preventive or interventional treatments of patients on high-risk. One possible way to investigate the ‘when and why’ of atopic disorders is to prospectively study immune responses of cord and peripheral blood mononuclear cells (CBMC, PBMC) from newborns and infants in order to delineate the parameters associated with subsequent development of childhood atopy. The study by Böttcher and colleagues in this issue of *Clinical and Experimental Allergy* is a further example of such a cohort and extends our present knowledge by looking at immune reactivity towards birch pollen allergen in the first seven years of life [8].

CBMC/PBMC immune responses associated with the development of atopic diseases

There is little doubt about the postulate that increased T helper cell type 2 (Th2) responses to allergens are the main underlying mechanism leading to the development of allergic diseases [9]. Increased numbers of Th2 cells and Th2 cytokines are found in bronchial biopsies and bronchoalveolar lavage fluid of patients suffering from asthma and tend to correlate with diseases severity [10, 11]. Predominant production of Th2 cytokines induces increased total and allergen-specific IgE serum levels, regulated by IL-4 and IL-13, and leucocytic and eosinophilic tissue inflammation, regulated by IL-5, hallmarks of the allergic immune reaction [12]. In animal models of allergic diseases, antagonization of Th2 responses by monoclonal anti-cytokine/-receptor antibodies [13, 14] or by treatment with Th1 cytokines (IL-12, IFN- γ) [15, 16] effectively abrogates allergen-mediated sensitization and/or disease. Thus, the balance between Th1/Th2 immune responses upon activation with allergen is considered to be crucial for the onset and persistence of atopic diseases.

There are good reasons to believe that prenatal influences may effect the development of postnatal allergies and/or atopy [17]. Allergen exposure may already occur *in utero*, thus stimulating an allergen-specific immune response in the fetus. Indeed, prenatal sensitization has been demonstrated for environmental and food allergens by several groups [18, 19]. Still, it remains controversial if the amount of allergen exposure of the mother during pregnancy is closely associated with the magnitude of the fetal immune response as reported by some groups [20],

or if maternal exposure to allergens is rather unrelated to fetal CBMC proliferative responses, as demonstrated by Szepefalusi et al. [18] and others [21, 22]. The latter observations support the evidence that allergen avoidance during pregnancy is not a useful instrument for primary allergy prevention [23]. Another setback regarding the use of proliferative responses as predictor for allergen sensitization is the possibility that this method, especially in the case of prolonged culture conditions of up to 6 days, detects (also) primary *in vitro* T cell responses or cross-reactivity rather than specific activation of previously sensitized T cells [24]. Moreover, the dissociation between allergen-specific CBMC responsiveness and subsequent development of atopy/allergy found in some studies [21, 25] suggests that prenatal (*in utero*) sensitization may just be one, but not necessarily the main, risk factor for immune deviation towards the allergic phenotype.

This assumption is supported by studies investigating T cell cytokine responses to allergen and/or mitogen from subsequent atopic and non-atopic infants. They provide some insights about the plasticity of the immune system and the changes occurring during manifestation of allergic diseases. Initial immune responses from all neonates, regardless of their subsequent atopic state, are rather dominated by Th2 cytokine production reflecting the Th2 milieu of the pregnancy [26]. Kondo et al. were the first to describe CBMC responses to food allergens as prediction for atopy [27] and extended this observation by showing that infants who later developed allergic diseases showed decreased Th1 (IFN- γ) responses compared to later non-atopic children [28]. Since then, the association of impaired Th1 responses at birth or delayed Th1 maturation in the postnatal period with atopy is one of the most concordantly observed differences between atopic and non-atopic individuals [29–33]. In a very elegant longitudinal study on infants over 2 years, Prescott et al. demonstrated that continuation of Th2 responses (IL-4, IL-13) and decreased capacity for Th1 responses (IFN- γ) to house dust mite allergen was associated with the development of allergy, whereas non-atopic patients showed strong Th2 responses only at birth, but declining Th2 and increasing Th1 responses later on in life (> 6 months) [25]. The present study by Böttcher et al. [8] adds to this observation by investigating responses to seasonal inhalant allergens (birch pollen) and extending the cohort to 7 years. Again, proliferative responses to allergen were inconsistently associated with atopic state and did not change significantly during the course of the study or in correlation to the magnitude of allergen exposure, making this method questionably reliable as a predictor for allergy/atopy. In concordance with the study by Prescott et al. those patients who developed allergy (birch-related SAR, $n = 2$) were the only ones to show persistent and increased Th2 responses (IL-5, IL-4, partly IL-13) and birch-specific IgE

production over the whole length of the study, indicating a postnatal deficiency to down-regulate neonatal Th2 immunity. In non-allergic patients, a transient Th2 response to allergen was down-regulated after the fourth pollen season. Interestingly, both atopic (defined by allergic symptoms other than birch-related SAR, $n=8$) and non-atopic patients (no allergic symptoms, $n=13$) had similar and, after the fifth season, increasing birch-induced IFN- γ production, with high IFN- γ levels during the whole study also in the group of birch-allergic patients ($n=2$). Similarly, all patients, regardless of allergic or atopic state, produced detectable and increasing levels of birch-specific IgG₁, which is considered to be a Th1-related Ig, whereas only the two birch-allergic patients had high and persistent birch-specific IgG₄ serum levels. The results of this study are notable since they suggest that: (1) elevated allergen-specific Th1 responses and IgG1 production are found in allergic patients, and (2) allergen sensitization and development of allergic diseases by shift of Th1/Th2 immune reactivity may occur beyond the first year of life. If this observation from a single cohort with only two allergic patients sensitized to a seasonal allergen holds true for a wider population and a variety of allergens, it would allow to extend preventive means to the first three or four years of life.

Risk factors for the development of allergy

The main risk factor for the development of allergic diseases is heritage. Family and twin analyses clearly show a genetic basis for atopic traits, without identifying a single or major gene for the different diseases, which rather follow complex multifactorial inheritance patterns [34]. For the shortness of time, however, genetic shift or variations are unlikely to be the reason for the significant increase in prevalence rates of allergic diseases observed in the last two decades. Therefore, environmental factors have been studied and associated with the increased development of atopy/allergies [35]. The 'hygiene hypothesis' was formulated as the result of these studies stating that the lack of 'danger signals' during early infancy prevents the down-regulation of neonatal Th2 responsiveness, thus favouring the development of allergen-mediated Th2-driven immune responses later in life [36, 37]. These signals may be provided by a variety of bacterial or viral compounds or dietary factors, with the common mechanism of enhanced induction of Th1 responses by engagement of receptors or cells of innate immunity. T cell proliferative and cytokine responses of CBMC/PBMC from infants and children to allergens are merely the result of the complex interaction of the host with diverse stimuli prior to and during the first and subsequent encounter of allergen. They will allow us to determine the 'when' of an allergic sensitization, but will be unlikely to tell us why one person becomes atopic and the other remains non-atopic. Thorough studies of gene-environment interactions are required to further delineate the molecular mechanisms leading to the development of allergic immune reactions. Newborn cohorts of high-risk patients investigating gene expression profiles during the natural course of disease and alterations of these patterns by environmental factors or interventional means are underway and will hopefully lead the way to effective primary prevention of allergic diseases.

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