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Brief report

A role for Waldeyer's ring in immunological response to allergens

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Abstract

Objective:

Adenoids, tubal tonsil, palatine tonsil, and lingual tonsil are immunological organs included in the Waldeyer's ring, the basic function of which is the antibody production to common environmental antigens. Adenoidal hypertrophy (AH) is a major medical issue in children, and adenoidectomy is still the most used treatment worldwide. The response of adenoids to allergens is a good model to evaluate their immunological function. This report assessed the immunological changes in adenoid tissues from children with allergic rhinitis (AR) undergoing sublingual immunotherapy (SLIT).

Methods:

Adenoid samples from 16 children (seven males, nine females, mean age 7.12 years) with AH and clinical indication to adenoidectomy were collected. Of them, five children were not allergic and 11 had house dust mite and grass pollen-induced AR. Among allergic children, in four AR was treated by antihistamines while in seven AR was treated by high-dose SLIT during 4–6 months. The evaluation addressed the T helper 1 (Th1), Th2, and Th3 cells by performing a PCR array on mRNA extracted from adenoid samples.

Results:

In non-allergic children, a typical Th1 pattern was found. SLIT induced a strong down-regulation of genes involved in Th2 and Th1 activation and function. In particular, in SLIT-treated allergic children IL-4, CCR2, CCR3, and PTGDR2 (Th2 related genes) and CD28, IL-2, and INHA (Th1 related genes) expression was reduced, compared with children treated with antihistamines.

Conclusions:

These preliminary findings warrant investigation in trials including larger numbers of patients, but indicate that hypertrophic adenoids of allergic children have the typical response to the specific allergen administered by SLIT. This should suggest that one should reconsider the immunological role of adenoids.

Introduction

Adenoids are part of the Waldeyer's ring, the basic function of which is the antibody production to common antigens^{1,2}. Adenoidal hypertrophy (AH) is a major medical issue in children, and adenoidectomy is still the most used treatment worldwide. However, the rationale of such an approach seems quite convincing in obstructive sleep apnoea³, but it is a matter of discussion for other indications, as showed by a recent meta-analysis concluding that 'current evidence on the effect of adenoidectomy on recurrent or chronic nasal symptoms or nasal obstruction alone is sparse, inconclusive, and has a significant risk of bias'⁴. In fact, it is true that almost all hypertrophic adenoids contain bacteria (mostly aerobic, but also anaerobic organisms), but appropriate antibiotic treatment is able to eliminate the bacteria⁵. The response of adenoids to environmental allergens is a good model to evaluate their immunological function. Indeed,

there is evidence of a pathophysiologic relationship between AH and allergy^{6,7}, and a recent study showed that the role of allergic inflammation in children with adenotonsillar hypertrophy may be overlooked because, in subjects with a negative result to common allergy tests, specific IgE may be detected only locally⁸. This suggests a role for anti-inflammatory treatments, including allergen immunotherapy. We evaluated the effects on adenoid tissues of sublingual immunotherapy (SLIT), that is effective on inflammation by modifying the immunological response to the causative allergen⁹.

Patients and methods

Patients

Children with allergic rhinitis (AR) undergoing SLIT with standardized allergen extracts were included in the study. Adenoid samples from 16 children (mean age = 7.12 years, range = 5–9 years, seven males, nine females) with AH of 4th grade, i.e., the highest, and clinical indication to adenoidectomy were collected. Of them, five children were not allergic and 11 suffered from house dust mite (HDM) and grass pollen-induced AR. Among allergic children, in four AR was treated by antihistamines, while in seven AR was treated by high-dose HDM and grass pollen SLIT (Staloral 300) (Stallergenes, Antony, France) during 4–6 months. The daily maintenance dose assumed by patients was 16.8 µg of the major allergen Phl p 5 for grass pollen and 24 µg of the major allergen Der p 1 for HDM.

RNA extraction from adenoid samples

Adenoid tissues were homogenized till complete disruption in 1 ml of RNAzol reagent (Duotech). Total RNA was isolated from adenoid tissue following the standard method of phenol-chloroform extraction for nucleic acid. RNA was dissolved in RNase-free water and purified from genomic DNA with RNase-free DNase (New England Biolabs, Ipswich, MA). One microliter of RNA was used for quantification and assessed for quality evaluating the ratios 260/280 and 260/230 by a Nanodrop Spectrophotometer (Thermo Scientific, Waltham, MA).

Quantification of gene expression level

One mM of RNA was reverse transcribed into first-strand cDNA using 1 mM random hexanucleotide primers, 1 mM oligonucleotide, and 200 U Moloney murine leukemia virus reverse transcriptase (Promega, Madison, WI). The reactions were incubated for 60 min at 37°C and 5 min at 95°C. Quantification of the housekeeping gene GAPDH (Glyceraldehyde 3-phosphate dehydrogenase) was performed by real-time PCR in order to analyze the quality

of the samples and subsequently cDNAs were pooled according to the different patients groups. Pooled cDNAs were used to perform the real-time PCR Arrays 'Human Th1-Th2-Th3 PCR Array' (SA Biosciences Corporation, Frederick, MD) that included a set of optimized real-time PCR primers in 96-well plates. A RealMasterMix SYBR ROX (5 prime, Gaithersburg, MD) was used following the procedures suggested by the manufacturer and the reactions were incubated for 2 min at 95°C, 40 cycles of 15 s at 92°C, 20 s at 62°C, 20 s at 68°C, and 5 min at 68°C in the DNA Engine Opticon 2 (MJ Research, Ramsey, NJ). The analyses were conducted using the PCR Array Data Analysis Web Portal from SA Biosciences; results were expressed as Ct and presented as fold-change between the SLIT-treated allergic children and the antihistamines-treated allergic children. GAPDH and beta-actin, included in the array plate, were used as housekeeping genes for normalization.

Results

In non-allergic children, a typical T-helper 1 (Th1) pattern was found. In allergic children, SLIT induced a strong down-regulation of genes involved in T-helper 2 (Th2) and Th1 activation and function. In particular, in SLIT-treated allergic children IL-4, CCR2, CCR3, and PTGDR2 (Th2 related genes) and CD28, IL-2, and INHA (Th1 related genes) expression was reduced, compared with children treated with antihistamines. Figure 1 shows the mRNA expression profile of Th1-Th2-Th3 related genes in the SLIT-treated allergic children group in comparison to the antihistamines-treated allergic children group. The expression of 96 genes involved in the Th1-Th2-Th3 response was assessed by real-time quantitative RT-PCR and shown as fold-change expression from the antihistamines-treated allergic children group (SLIT/antihistamines). Only the targets showing an N-Fold bigger than 2.5 or lower than –2.5 are presented.

Discussion

The mucosal-associated lymphoid tissue (MALT) provides both innate and adaptive immunological responses to foreign antigens, with an important role for toll-like receptors, which are very important in the clearance of pathogens and also in orientation of the adaptive response to antigens (towards sensitization or tolerance)¹⁰. In the first tract of the digestive system MALT is represented by the Waldeyer's ring, that includes the adenoids. This localization is strategic to ensure that noxious agents are eliminated, while innocuous agents (including allergens) are tolerated. The breakage of oral tolerance is one of the mechanisms underlying the development of allergy that

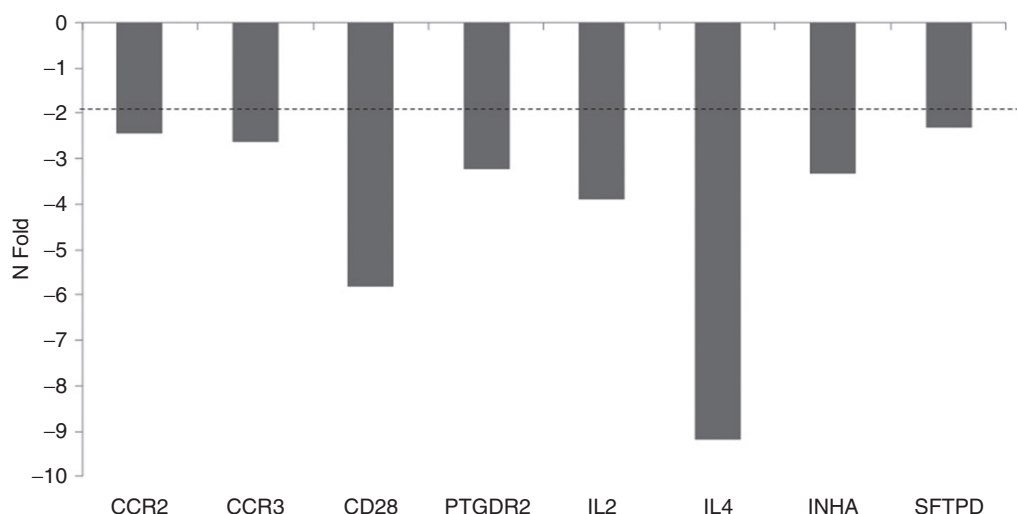


Figure 1. Down-regulation of both Th1-related genes (CD28, IL2, INHA) and Th2-related genes (CCR2, CCR3, PTGDR2, IL4) in SLIT-treated allergic children.

usually starts with sensitization to food allergens and then continues with sensitization to inhalant allergens¹¹. Once established, allergy is maintained by exaggerated responses of lymphocytes Th2 and by defective activity of regulatory T cells (Tregs)¹². The immunologic role of the Waldeyer's ring organ was long recognized for the tonsils, and had led to a huge reduction in the number of tonsillectomies over time¹³, while the fact that adenoids play the same role was, thus far, not taken into account.

In the present study, we found that the adenoids from allergic children showed the immunologic profile of Th2 prevalence, and that SLIT treatment was able to modify such a profile. Our preliminary findings warrant investigation in trials including larger numbers of patients, but indicate that hypertrophic adenoids of allergic children have a response to the specific allergen administered by SLIT similar to that commonly described by studying T-cells and the cytokine profile in blood or in biopsies from concerned tissues, particularly regarding the changes in T-cell sub-populations⁹. This should lead one to reconsider on the one hand the immunological function of adenoids and on the other hand the role of allergic inflammation in the pathophysiology of adenoidal hypertrophy and its modification by sublingual immunotherapy¹⁴.

Transparency

Declaration of funding

No funding was secured for this study.

Declaration of financial/other relationships

FF and ID'A are employees of Stallergenes Italy. CI is a scientific consultant for Stallergenes Italy. The other authors don't have any conflict of interests to declare relating to this work. CMRO peer reviewers may have received honoraria for their

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