Introduction

Asthma is the most common noncommunicable disease among children. The main risk factors for developing asthma are a combination of genetic predisposition with environmental exposure. An understanding of the cellular and cytokine interaction during allergic inflammation, especially leading to Th2-dominated immune response is necessary for predicting the risk of asthma developing, identification of new prophylactic and treatment goals.

Differentiation of effector T cell requires the multiple environmental factors and simultaneous cytokine signals interaction, that provide stimulation of the T cell receptor (TCR) and as a consequence significant morphological and functional changes of naive T cells. The mammalian target of rapamycin (mTOR, also known as FRAP, RAFT, or RAPT) is an evolutionarily conserved serine/threonine kinase that regulates cell metabolism, growth and proliferation according to environmental factors – energy or nutrient available, cytokine signaling. The mechanism of nutrient sensing function of mTOR is unclear, however it has been suggested, that mTOR may be regulated by intracellular amino acids, or their metabolites, or by amino acid-activated second messengers. Researches demonstrate the significant role of mTOR in regulation of cytokine signals, differentiation and development of effector Th cells, maturation and degranulation of mast cells, regulation of the process of antigen presentation via autophagy, that subsequently lead to formation of Th2 cell polarized effector phenotype. The aim of this study was to determine whether single-nucleotide polymorphisms in mTOR gene and ATG5 gene are associated with development of allergic phenotype in children. SNPs rs11121704 in mTOR and rs510432 in ATG5 were selected for genotyping, as they hypothetically can affect development of Th2 phenotype and are reported to be common in European populations. To test this hypothesis, we examined differences in the frequency of these SNPs between children without allergic pathology (control group) and children with atopic diseases (eczema plus asthma).
Materials and methods

Genotyping for mTOR (rs11121704) was performed in the following populations: patients with atopic diseases, N = 91; ages 5-18 years (7 ± 2.1) and control group, N = 87; ages 5–18 years (13 ± 2.1), using Real-time PCR. Genotyping for ATG5 (rs510432) was performed in the following populations: patients with atopic diseases, N = 98; ages 5-18 years (7 ± 2.1) and control group, N = 97; ages 5–18 years (13 ± 2.1)

All children had symptoms of asthma, eczema or allergic rhinitis, at least one positive skin prick test result to a panel of 15 aeroallergens. Testing for asthma was performed; the definition included a parental report of persistent wheezing (≥2 wheezing episodes not associated with a cold or upper respiratory tract infection), spirometry (a reduced FEV1 and FEV1/FVC ratio, positive test with β-2 agonists), increased IgE level.

Results

We found that 50 (54.9%) of patients and 43 (49.4%) of control group had major allele of rs11121704 in mTOR (TT), 36 (39.6%) and 32 (36.8%) of patients and control group, respectively, had heterozygous allele, (TC) and 5 (5.5%) and 12 (13.8%) had minor allele (CC). 51 (52%) of patients and 43 (44.3%) of control group had heterozygous allele (CT) of rs510432 in ATG5 gene, 29 (29.6%) and 21 (21.6%) of patients and control group, respectively, had minor allele (TT), and 18 (18.4%) and 33 (34%) had major allele. TT genotype of rs510432 in ATG5 gene was associated with increased risk of early manifestation of the asthma (until 3 years of life).

Discussion

Based on significant functions of mTOR in cell development and survival, it was hypothesized that mTOR in naïve T cells may determine antigen recognition outcome and T cells differentiation.

Stimulation of mTORC1 reduces the autophagy – process of intracellular lysosomal degradation of proteins, cytoplasmic components, organelles, that provides mechanism of protein quality control. Beside this, autophagy serves as
delivering pathogen-derived antigens for MHC class II loading. Autophagy plays role in T- and B- cells proliferation, maintaining intracellular homeostasis, maturation and release secretory granules in mast cells, induce airway remodeling via increasing collagen releases from fibroblasts. These data demonstrate the significant role of mTOR in regulation of cytokine signals, differentiation and development of effector Th cells, maturation and degranulation of mast cells, regulation of the process of antigen presentation via autophagy, that subsequently lead to formation of Th2 cell polarized effector phenotype.

In this article, we determined the frequency of the rs11121704 in mTOR gene and showed that minor allele occurs 2.5 times more frequently among control group, although there was no statistical significance. Association of genotype with clinical parameters also was not established previously. Some researchers demonstrated association of an increased risk of cancer in particular polymorphism rs11121704 (T> C), widely studied in populations of European, US and China.

Recent studies have demonstrated the association between gene polymorphisms ATG5 (rs12201458 and rs510432) and asthma in children in the US population. Minor allele (T) of rs51032 in ATG5 is associated with an increased risk of asthma in children. In addition, as shown in the research, rs510432 increases the activity of the gene promoter, and allele C led to an increase of promoter activity by 23% compared with the allele T. The next study confirmed the predicted increase gene expression of ATG5 in patients with bronchial asthma in the stage exacerbation. There was also found the dependence of spirography parameters (FEV1) and polymorphism of the ATG5 gene (rs 12212740) in patients with asthma in the US and Canadian populations. In our study we demonstrated, that TT genotype of rs510432 in ATG5 gene was associated with increased risk of early manifestation of the asthma (until 3 years of life).
Conclusions

We propose that single-nucleotide polymorphisms in mTOR gene and ATG5 gene may serve as important predictive markers for estimation risk of developing allergic diseases in children.