RESEARCH HIGHLIGHT

Beta-2-adrenergic receptor methylation influences asthma phenotype in the school inner city asthma study

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Asthma is the most common chronic illness of childhood and inner city residents suffer a disproportionately high rate of asthma diagnosis and asthma morbidity. The School Inner City Asthma Study investigates the school classroom based environmental exposures that may lead to asthma morbidity in inner city school children with asthma. Within this cohort, we investigated the role of methylation at the promoter region of the beta-2-adrenergic receptor in relation to asthma morbidity. We found that high levels of methylation in the region studied was significantly associated with decreased report of dyspnea and trended towards significance for lower levels of asthma symptoms and airway obstruction. This Research Highlight discusses the findings of the recent study and the investigators' active research endeavors.

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Asthma is the most common chronic disease of childhood [1] with a rise in prevalence over the past few decades [2]. It is largely accepted that gene by environ-ment interactions are responsible for the development of asthma. In light of the rapid increase in the prevalence of asthma and asthma morbidity, a large focus of attention has been paid to the environment as a source more rapidly changing than that of the human genome [3]. However, an aspect of genetic variation that may be both influenced by the human-environment interaction and affect gene expression is that of epigenetic variation. Epigenetics describes the molecular factors and processes around DNA that regulate genome activity independent of DNA sequence. Methylation of cytosine of the CG dinucleotide can be the result of environmental [4] or endogenous stimuli. DNA methyla-tion is mitotically and meiotically conserved and, thereby tissue specific and heritable [5]. In a complex disease process, such as asthma, DNA methylation offers a potential mechanism for differential gene expression directly influenced by environ-mental exposure. Hence, these processes may explain a temporally relevant gene by environment interaction to elicit a particular asthma trait.

The beta-2 adrenergic receptor (Human Genome Organization name, ADRB2) is a g-protein coupled receptor present in the airway smooth muscle and lymphocytes. The beta-2-adrenergic receptor has been central to the understanding of asthma for over 50 years and

is the primary target for rescue therapy, such as albuterol, during asthma exacerbations. Despite this, the beta-2-adrenergic receptor (ADRB2) gene has had inconsistent results when evaluated for relationships to asthma susceptibility [6], severity and lung function [7, 8].

In our recent study entitled "beta-2 adrenergic receptor gene methylation is associated with decreased asthma severity in Inner-City School Children" [9] we undertake an epigenetic approach to the question of whether the ADRB2 gene is associated with asthma symptom severity in a cohort of highly phenotyped children with asthma in the School Inner City Asthma Study [10] (NIAID R01AI073964; PI Phipatanakul). Over a 2 year period, 177 school aged children provided DNA samples at the time of phenotypic assessment of their asthma and enrollment in the School Inner City Asthma Study.

There was relatively low percent methylation of the ADRB2 over the region investigated, ranging from 1-6%. However, even with the small range of percent methylation, we found that the average methylation at the promoter region of the ADRB2 gene was inversely associated with asthma symptom severity. This asso-ciation was statistically significant for a measure of reported shortness of breath over the previous 4 weeks and trended toward significance for multiple measures of asthma symptoms and lung function.

These findings are an important step in understanding how epigenetic changes to the ADRB2 gene may influence asthma symptoms in children. Moreover, these findings present tangible evidence that epigenetic changes may influence clinically relevant phenotypic variation.

Our research group is vigorously working to understand the role of the environment in the development [3,11,12], exacerbation and control of asthma in children. Inner city children suffer a dispropor-tionately high level of asthma prevalence and asthma morbidity [13-15]. In addition to known variation based on race, ethnicity and socioeconomic factors, environ-mental exposures specific to the inner city are likely to play a critical role in asthma prevalence and morbidity [16]. Through major efforts from NIAID the effect of inner city-specific allergen exposures on asthma morbidity in children have been well described [17-19], however there is relatively little information on the effect of the indoor classroom environment on the respiratory health of children with asthma. This is an important source of exposure given that children spend 6-10 hours of their day in this environment. The School Inner City Asthma Study (R01 AI 073964 and R01 AI 073964-02S1; PI Phipatanakul) is an epidemiologic study of the effect of environmental exposures in school classrooms and asthma morbidity in inner city school children [20]. Students with asthma are screened and recruited from entire urban elementary schools. Eligible students with asthma undergo extensive phenotyping at a baseline visit and then report on their health quarterly through the academic year. During the study period, one home visit and two classroom visits collect air and dust samples for each enrolled child to evaluate their personal exposure to environmental allergens, endo-toxin, mold, and air pollutants. In this manner, the child's personal environment to the level of the school classroom can be related to their asthma morbidity.

To date, our group has demonstrated significant exposures to mouse [21,22] dog, and cat allergens [23], mold [22], endotoxin [24] and air pollution [25] in the classrooms. We have begun to explore genetic and epigenetic [9] predisposition to asthma morbidity and the environment-host interaction in relation to disease. We look forward to reporting our health outcome results in the near future.

Conflicting interests

The authors have declared that no competing interests exist.

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