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Asthma, allergy, and responses to methyl donor supplements and nutrients

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After a brief period of stabilization, recent data have shown that the prevalence of asthma and allergic diseases continues to increase. Atopic diseases are major public health problems resulting in significant disability and resource use globally. Although environmental factors influence the development of atopic disease, dietary changes might partially explain the high burden of atopic disease. Potential mechanisms through which diet is suspected to effect asthma and allergy susceptibility are through epigenetic changes, including DNA methylation. Dietary methyl donors are important in the one-carbon metabolic pathway that is essential for DNA methylation. Findings from both observational studies and interventional trials of dietary methyl donor supplementation on the development and treatment of asthma and allergy have produced mixed results. Although issues related to the differences in study design partially explain the heterogeneous results, 2 other issues have been largely overlooked in these studies. First, these nutrients affect one of many pathways and occur in many of the same foods. Second, it is now becoming clear that the human intestinal microbiome is involved in the metabolism and production of the B vitamins and other methyl donor nutrients. Future studies will need to account for both the interrelationships between these nutrients and the effects of the microbiome. (J Allergy Clin Immunol 2014;133:1246-54.)

Key words: *Allergy, asthma, betaine, choline, vitamin B2, vitamin B6, vitamin B12, folate, methyl donor, microbiome*

Abbreviations used
LINE-1: Long interspersed element-1
MTHFR: Methylenetetrahydrofolate reductase
SAM: S-adenosyl-methionine

Asthma and allergic diseases, including allergic rhinitis and atopic dermatitis, continue to be major public health problems resulting in significant disability and resource use globally.[1,2] Although the trend in asthma prevalence in the United States had initially stabilized, since 2003, the prevalence of asthma and allergic disease in the United States and abroad has been increasing.[3-7] There is substantial evidence for the genetic predisposition to complex diseases, such as asthma and allergy, with multiple genetic loci demonstrating reproducible associations with these diseases, but genetics alone is unable to explain the overall burden of atopic disease.

Although the cause of the increasing prevalence is not definitively known, several factors have been proposed to account for this increase, including environmental causes.[8,9] Environmental exposures, such as tobacco smoke, have been shown to influence the incidence of both asthma and allergy in children[10-12] and adults.[13,14] Other environmental exposures, including traffic-related air pollution, have also shown modest associations with atopic diseases in children.[15-17] However, even the contribution of these environmental exposures to asthma and allergy susceptibility is unlikely to fully explain the increasing prevalence of asthma and allergic diseases worldwide.

Epidemiologic data suggest that changes in dietary patterns might also partially explain the increasing prevalence of asthma and allergy in industrialized countries.[18-20] However, the role of certain dietary nutrients in the development of atopic diseases has been conflicting in part because of the fact that the role of diet in the development of atopy is complex, difficult to measure, and limited by a dearth of interventional trials investigating the effect of diet on atopic disease susceptibility.

METHYL DONORS

One of the proposed mechanisms by which diet is suspected to affect asthma and allergy susceptibility is through ***epigenetic*** mechanisms, including DNA ***methylation***, which results in heritable changes in gene expression without alteration of the original DNA sequence.[21] Methylation of CpG islands within regulatory regions of DNA is an important mechanism for the control of gene expression and has been shown to be transmissible across generations.[22] DNA methylation results from the transfer of methyl groups to the cytosine in the CpG dinucleotide, resulting in a reversible modification that can alter both chromosome stability and suppress gene transcription. Environmental exposures, including air pollution and dietary factors, have been shown to

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Terms in boldface and italics are defined in the glossary on page 1247.

influence the epigenome.[23] Furthermore, recent evidence from the ***Normative Aging Study*** suggests that prior allergen sensitization is associated with increased methylation of the retrotransposon-derived element Alu, which is a proxy for global DNA methylation ($\beta = 0.32$ for sensitized vs nonsensitized patients, $P = .003$), even after adjustment for smoking status and air pollutants.[24]

Dietary methyl donors, including folate and choline, are necessary for the one-carbon metabolic pathway that produces S-adenosyl-methionine (SAM), which is the universal methyl donor that is essential for the DNA methylation process to occur (Fig 1). Vitamin B12 and betaine, which are additional agents derived from the diet, are also necessary for methionine synthesis, which is another important step in DNA methylation. Therefore differential intake of these nutrients might lead to differences in DNA methylation and ultimately alter gene expression. In an agouti mouse model, mothers receiving a diet supplemented with methyl donors resulted in hypermethylation of the ***metastable epiallele*** in the progeny, resulting in a brown coat color, lower incidence of obesity, and increased longevity.[25] In a mouse model of allergic airway disease, *in utero* supplementation of a diet that is high in methyl donors (including folic acid, choline, and vitamin B12) resulted in increased atopy (IgE and eosinophils) and airway responsiveness in the exposed progeny.[26] In addition, *in utero* exposure to a high methyl donor diet was associated with increased methylation of the Runt-related transcription factor (*Runx3*) gene in the progeny, which resulted in decreased expression of the gene. *Runx3* is known to negatively regulate allergic airway disease, suggesting that the methylation changes induced by a diet high in methyl donors might result in increased atopic diseases.[26] Given the emerging evidence from animal models demonstrating a role for dietary methyl donors in the development of atopic diseases, dietary methyl donors have been investigated in human subjects as a possible cause of the increasing prevalence of atopic disease.

In human subjects dietary methyl groups, such as folate, vitamin B12, and choline, are a source of methyl donors for DNA methylation (Table I). Methyl donors, especially folate, have been extensively studied in the setting of asthma and, to a lesser degree, in the setting of allergy. However, the data for the association of dietary methyl donors with the development of asthma and allergy in human subjects remain unclear. In this review we examine the existing evidence for the role of methyl donors in the development and treatment of asthma and allergy. We have limited this review to articles that have examined specific nutrients rather than foods or diets that contain the nutrient. Food intake and dietary patterns and asthma and allergies have recently been reviewed, and the readers are directed to those reviews.[18,20,27,28]

Folate

Folate is a water-soluble B vitamin that is naturally present in a variety of foods and available in nutritional supplements. It is naturally occurring in the diet as folate, and folic acid is a fully oxidized monoglutamate form that is used as a dietary supplement.[29] Folic acid consists of a p-aminobenzoic molecule linked to a pteridine ring and a single molecule of glutamic acid. Dietary folates are polyglutamates, which include additional glutamate residues.[30] Folate is found naturally in foods, including dark leafy vegetables, fruits, nuts, beans, poultry, meat, eggs, seafood, and dairy products. In addition, it is found (in folic acid form) in fortified food products, including breads, cereals, and grain products. However, dietary supplements, including multivitamins, are the

GLOSSARY

EPIGENETIC: Epigenetic changes are those that are heritable but not encoded by DNA sequence changes. Epigenetic changes include chromatin folding, attachment to the nuclear matrix, and histone modifications, including methylation and acetylation.

IL-4, IL-5, TNF-α: IL-4 has a myriad of allergy-promoting effects, including increasing IgE production. Epigenetic changes, such as hypomethylation of the IL-4 promoter in animal models by using diesel exhaust particles, are associated with increased IgE levels. The inhibition of histone deacetylases upregulates IL-5 production, and asthmatic patients have increased levels of histone acetyltransferase that can be improved after inhaled glucocorticoids. Similarly, TNF-α–induced expression of eotaxin occurs through histone acetylation.

METABOLOMICS: A rapid high-throughput characterization of metabolites found in an organism that might reflect genotype-environment interactions. There are at least 2900 metabolites detectable in the human body, and these can be specific to certain body fluids, such as urine, serum, and cerebrospinal fluid.

METASTABLE EPIALLELE: Metastable epialleles are gene alleles that are variably expressed in genetically identical subjects because of epigenetic changes that occur during development (eg, in the fetus) and that are vulnerable to environmental influences.

METHYLATION: DNA methylation normally occurs at CpG dinucleotides and prevents transcription factors from binding to DNA. Methylation also recruits methyl-CpG binding proteins that repress chromatin remodeling. Therefore hypomethylated DNA is thus more readily transcribed. Methylation can also occur on histones (eg, on lysine residues). Although this modification does not directly affect chromatin folding, it provides a binding surface for a variety of histone-modifying enzymes that can alter chromatin to active and inactive states. These enzymes include histone acetyltransferases, deacetylases, methylases, and ATP-dependent chromatin remodeling enzymes.

MICROBIOME: The human microbiome is the collection of microbes, including bacteria and viruses, that are found in the human body. These bacteria are important in both health and disease. These bacteria are involved in our ability to digest food, produce vitamins, and affect our immune system. The community of microbes present in a subject can increase susceptibility to disease. Therefore there is great interest in studying the effect of the microbiome in terms of its relationship to health and disease.

NORMATIVE AGING STUDY: The Normative Aging Study (NAS) is a longitudinal study that has looked at the effects of aging on a number of variables, including cardiovascular disease, obesity, depression, and pollution. The NAS was instituted by the Veterans Administration in 1963 to follow 2280 male subjects with no known chronic medical issues. Participants are examined every 3 to 5 years.

PLATELET-ACTIVATING FACTOR: Platelet-activating factor is a mediator of anaphylaxis. Blood levels of platelet-activating factor are increased after anaphylaxis, and these levels correlate with the severity of the anaphylactic reaction.

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