Editorial
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Role of Murine Asthma Model in Discovering Asthma Susceptible Genes

Choon-Sik Park*

Division of Allergy & Respiratory Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Korea

Asthma is a genetically complex disease associated with the familiar segregation of atopy and increased levels of total serum IgE.[1] Asthma and atopy are also closely associated with increased bronchial hyperreactivity and elevated blood eosinophil count.[2,3] These intermediate phenotypes are highly inheritable and the subject of asthma genetics research. The occurrence of asthma patients within families indicates the likely presence of a genetic component. Ge-nome-wide linkage studies, biologically plausible candidate gene approaches, and genome-wide association scans (GWAS), have been performed over the past 20 years to search for the genetic background of asthma. Recently, whole genome sequencing is applied to reveal the genes (or SNPs) related with the traits of asthma and subphenotypes. However, SNPs discovered by several GWASs have a limited ability to explain genetic effects for the development of asthma despite the significant number of enrolled subjects (more than 10,000). Imprecise disease phenotypes have been regarded as the factor related to the limitations of GWAS. Asthma should be classified into specific phenotypes with the consideration of environmental factors to overcome missing inheritability.[4,5]

Asthma is subgrouped into IgE-dependent Th2 dominant type, aspirin-exacerbated respiratory disease, occupational asthma, exercise-induced asthma, and menstruation-or obesity-associated asthma; it is further divided based on airway inflammatory patterns and immune responses.[6,7] The mapping of susceptibility genes in asthmatics as a whole has been hampered by variability in sub-phenotypes, genetic heterogeneity across populations and uncontrolled environmental influences.[8] To circumvent the complexity of genetic research in asthmatics, mouse model studies of allergic airway diseases have been applied to search for candidate genes related to the development of asthma.

In the present issue, Gergely Temesi *et al.*[9] presented "Novel genes in Human Asthma Based on a Mouse Model of Allergic Airway Inflammation and Human Investigations". In the ovalbumin (OVA)-induced murine model of asthma, they applied microarray gene expression analysis at different time points after allergen challenges.[10] In the late response of OVA-induced experimental asthma, they found more than thousand transcripts that showed statistical significances compared to the control. A total of 90 SNPs were genotyped, and the genotype distributions of 4 SNPs of 2 genes differed significantly: *SCIN* (rs2240572, rs2240571, rs3735222) and *PPARGC1B* (rs32588). They and *ITLN1* (rs4656958), of which a SNP statistically borderline difference, were validated in induced sputum samples by measuring the protein levels of *SCIN*, *PPARGC1B*, and *ITLN1*. Three potentially novel asthma-associated genes were identified based on mouse experiments and human studies.

A Th2 dominant asthma model has been induced by intraperitoneal injection with OVA and aluminum hydroxide as adjuvant, followed by OVA intranasal challenges.[11] The model shows airway hyperreactivity, goblet cell hyperplasia, pulmonary eosinophilia and increase of antigen-specific IgE. This model helps discover a considerable number of asthma candidate genes that include Th2 cytokines (IL-4, IL-15, IL-13, IL-9 and IL-25) and proinflammatory mediators (complements, arginase I, and arginase II).[12,13] Even in this OVA model, inflammatory responses are very different depending on the time point.[11] Asthma in humans is a chronic airway inflammation and the time point of the chronic asthma model represents a

Correspondence to: Choon-Sik Park, MD, PhD, Division of Allergy & Respiratory Medicine, Soonchunhyang University Bucheon Hospital, 170 Jomaru-ro, Wonmi-gu, Bucheon 420-767, Korea.
Tel: +82 32 621 5105; Fax: +82 32 621 5023; E-mail: mdcspark@hanmail.net
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reflection of human asthma.

The results of Gergely Temesi et al indicated that the minor alleles of *SCIN* SNPs, rs2240572 (H61R) on exon 1 and rs3735222 on promoter region, had protective effects against asthma, and that these associations were more prominent when studying the female cohort separately. Consequently, the expression of certain genes, especially related female hormones, are highly likely dependent on gender difference. Allele carrying a 649G4C transversion in exon 4 of the PPARGC1B gene, resulting in an Ala-to-Pro (A203P) substitution, is significantly associated with familial breast cancer risk.[14] Co-transfection assays demonstrated that nuclear receptors associated with the potent co-activator function of PPARGC1B are estrogen receptor alpha and glucocorticoid.[15] Six week old female mice (used in many murine asthma models) are similar to the reproductive maturity of young human adult females. Thus, age factors should be considered in the data interpretation of this mice model.

Age dependency has been observed in several genetic association studies. When SNPs on ORM1-like 3 was analyzed according to the age of asthma onset, the statistical difference of rs 7216389 on 17q21 became more apparent in the age group <16 years in Caucasians and Koreans, whereas the statistical significance disappeared in the group >16 years.[16] Early-onset asthma and the late-onset asthma may have a different immune-pathogenesis; therefore, mice less than 3 or 4 weeks old would be suitable for mice models to reflect childhood asthma. The protein scinderin encoded by the *SCIN* gene is an actin filament–severing and capping enzyme which rearranges the apical actin cap in airway goblet cells.[17,18] *SCIN* is over-expressed following allergen challenge in mice[19]; however, the exact relationship of SCIN with Th2 immune response is unknown.

The gene discovered from one phenotype of asthma should be extended to the other kinds of asthma phenotypes using different animal models.[20,21] Non-Th2 cytokine pathways (such as Th17 and inflammasome activation) underlie airway inflammation in specific subsets of asthma patients, especially non-eosinophilic inflammation.[22,23] Well-characterized murine model mimics the pathophysiology of human allergic asthma in the interpretation of animal model data; however, it is not exactly the same. The development of murine models that reflect several sub-phenotypes of asthma remains an important goal for future human asthma studies.

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