Symposium 3: Asthma and allergy: From bench to bedside

# Epigenetics in allergy

Soonchunhyang Medical Institute, Soonchunhyang University College of Medicine, Cheonan, Korea

Hun Soo Chang

During the last two decades, great efforts have been focused on understanding genetic susceptibility to allergic diseases and have revealed that the diseases are polygenic and multifactorial. However, the genetic approaches could not fully explain heritability of allergic diseases (missing heritability), and the recent increase in incidence and prevalence of atopic diseases[1,2]. The diseases are now thought to be greatly influenced by interactions between genetic predisposition and environmental factors, such as smoking, ozone, diesel exhaust particles (DEPs), SO2 and NO2[3]. The environmental factors can cause epigenetic changes of individuals (or specific tissues and cell types)[4].

Epigenetics are defined as "stably heritable (and non-heritable) phenotype resulting from changes in a chromosome without alterations in the DNA sequence"[5], which include post-translational modification, DNA methylation, histone modifications and small non-coding RNAs. The epigenetic modifications, especially DNA methylation and histone modifications, plays key roles in T cell development[6-8]. For example, Th1-specific genes such as TBX21 and IFNG are demethylated during the Th1 maturation, whereas those are methylated in Th2 or Th17 cell development. DNA methylation of IFNG is in turn preserved in Th2 and Th17 cells. In contrast, Th2-specific cytokines, IL4 and IL13, loci are hypomethylated in Th2 cells

As advances of microarray and sequencing technology, whole-genome epigenetic profiling (epigenome-wide association study; EWAS) has been widely used in epigenetic research. Microarrays have been the most frequently used methods in epigenomic study, with several platforms and protocols available for detecting DNA methylation[9]. The microarrays have also been used to assess genome-wide histone modifications by using chromatin immunoprecipitation using specific antibodies for modified histone molecules, followed by hybridization on microarrays (ChIP-chip). Recently, next-generation sequencing has been applied to profiling DNA methylation (MBD-seq) and histone modifications (ChIP-seq)[9].

Many EWAS in allergic diseases have been performed, and some of them have reported differential methylation patterns between allergic patients and normal controls[10]. Among allergic diseases, asthma has

been main target of EWAS for the last five years. Stefanowicz et al., tried to characterize differences in methylation within airway epithelial cells (AECs) and peripheral blood mononuclear cells (PBMCs) amongst healthy, atopic and asthmatic subjects using[11]. Although they identified 8 differentially methylated sites in AECs derived from asthmatics compared to atopics, there was no difference in the methylation status of PBMCs between disease phenotypes. Kim et al., in a study using bronchial mucosa tissues of atopic asthmatics, non-atopic asthmatics, and normal controls, reported 6 hypermethylated and 49 hypomethylated loci in the bronchial mucosa of atopic asthmatics compared to those of non-atopic asthmatics. However, the methylation levels in the mucosa of asthmatics and normal controls were similar[12]. Taken together, no DNA methylation changes were yet found to be directly associated with asthma in EWAS. In contrast, several EWAS demonstrated significantly different methylation patterns associated with asthma sub-phenotypes such as serum IgE levels[13,14], prenatal tobacco smoke exposure[15], pollutant exposure including diesel exhausted particles[16-19], obesity[20], and aspirin-hypersensitivity[21]. In fact, in our recent unpulished data, although peripheral CD4+ and CD8+ lymphocytes showed no differences between asthmatics and normal subjects, several loci showed different methylation levels in refractory asthmatics compared to those in controlled asthmatics. These results suggest that well-defined phenotypic characterization is important in epigenomic studies in asthma and in other allergic diseases, as well as improvement in sample size, replication efforts, and type of samples analyzed.

## References


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