EPIGENETIC PROGRAMMING OF ASTHMA BY IN UTERO EXPOSURE TO p,p'-DDE

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Background and Aims: Environmental epigenetic is emerging in asthma. Early-life exposure to dichlorodiphenyldichloroethylene (p,p'-DDE) impacts the immune system development and the risk of asthma by unknown mechanisms. We investigated if prenatal exposure to p,p'-DDE induces epigenetic reprogramming involving aberrant DNA methylation of specific genes mechanistically related to asthma.
Methods: Data came from 404 children of a population-based birth cohort of the INMA Project. p,p'-DDE was measured in cord blood. Wheezing phenotype at age 6 years was defined according to parental report of wheezing episodes on each interviewer-led annual questionnaire. The coding variant Ile105Val from *GSTP1* was genotyped. In a subset (n=128), gene-specific methylation was screened along 1505 genomic CpG loci using Illumina GoldenGate panel in DNA from peripheral blood cells collected at age 4 years. Subsequently, a pyrosequencing assay was used to validate the results from the Illumina screening.
Results: Higher levels of p,p'-DDE were associated with higher risk of persistent wheeze among *GSTP1* Val carriers (OR for an interquantile range increase in p,p'-DDE=1.77; 95% CI 1.17-2.68), but not among the Ile homozygotes (OR=1.05; 95% CI 0.80-1.39; p for interaction=0.069). Higher levels of p,p'-DDE were associated with a decrease in methylation of a CpG site in arachidonate 12-lipoxygenase (*ALOX-12*) (beta(sd) for an interquantile range increase in p,p'-DDE =-1.7(0.6), p=0.060). The decrease in methylation was accounted for *GSTP1* Val carriers compared with the Ile homozygotes (beta(sd)=-4.1(0.8) vs. -0.8(0.8); p for interaction=0.007). Higher levels of methylation in *ALOX-12* at age 4 years were associated with a lower probability of being classified as persistent wheezing at age 6 years (OR=0.94; 95% CI 0.90-0.98).
Conclusions: Epigenetic changes in *ALOX-12*, a gene involved in the immune response of the airway, could mediate the lifelong effect of in utero exposure to p,p'-DDE on the risk of asthma in childhood.