Interferon Gamma Promoter is Hypermethylated in Blood DNA from Workers with Confirmed Diisocyanate Asthma

Ouyang B[1], Bernstein D[2], Lummus ZL[2] ,Ying J[1], Cartier A[3], Gautrin, D[3], Sastre J[4], Boulet LP[5], Quirce S[4],Tarlo, SM[6], Cruz, M[7] , Munoz, X[7], Ho, SM[1]

[1] University of Cincinnati College of Medicine, Department of Environmental Health Sciences, Cincinnati, Ohio; [2] University of Cincinnati College of Medicine, Department of Internal Medicine, Cincinnati, Ohio; [3] Université de Montréal, Hôpital du Sacré-Cœur, Montreal, Québec, Canada;
[4] Universidad Autónoma de Madrid, Allergy Department, Madrid, Spain; [5] Université Laval, Hôpital Laval, Sainte-Foy, Québec, Canada; [6] University of Toronto, Toronto, Ontario, Canada; [7] University at Autonoma of Barcelona, Hospital Vall d'Hebron. Barcelona, Spain.

Corresponding author: David I. Bernstein MD, Department of Medicine and Environmental Health Sciences, 3255 Eden Avenue, Suite 350, ML 563 Cincinnati, Ohio 45267-0563 bernstdd@ucmail.uc.edu

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Objectives: Diisocyanates (DIs) are leading causes of occupational asthma. Investigators are still unable to identify or define risk factors that determine susceptibility for development of DI-induced occupational asthma. Occupational chemical exposures could modify promoter regions regulating transcription of cytokine mediators or protective proteins and thereby influence expression of DA. To test this hypothesis, we performed a case control study of DI exposed workers with and without confirmed DA, investigating DNA methylation status of candidate gene promoter regions.

Methods: 131 subjects were studied including: 40 workers with DA (DA+) confirmed by a positive specific inhalation challenge (SIC); 41 exposed workers with lower respiratory symptoms and negative SICs (DA-); and 50 asymptomatic exposed workers (AWs). 10-11 subjects from each aforementioned group were current smokers and the rest never smokers. DNA was extracted from blood and bisulfite-converted for analysis of methylation status of gene promoters using methylation-specific-quantitative PCR.

Results: Promoter methylation status was measured for GSPM1, DUSP22, IFN- , and IL-4 genes. GSPM1and DUSP22 showed no statistically difference in degree of promoter methylation among the three study groups. Non-smoking subjects in DA+ showed 4-7% less-methylation of IL-4 promoter compared to DA- and AW. Interestingly, smoking subjects showed about 14% increased IL-4 promoter methylation in DA+ compared to DA- and AW. The IFN- promoter, however, was found to be hypermethylated in DA+ (median 68.1% methylation) compared to DA- (median 37% methylation) and AW (median 31.7% methylation). The degree of methylation was statistically different among the subjects (p=0.001 in DA+ vs. DA-, p=0.002 in DA+ vs. AW). There was no difference in the degree of IFN- promoter methylation between DA- and AW (p=0.70). Univariate model had modest accuracy of IFN methylation in identifying DA+ workers at 60% sensitivity and 81.3% specificity. Multivariate models through adjusting covariate predictors (exposure, smoking status, PC20 and gender) exhibited improved sensitivity (77.5%) and specificity (80%).

Conclusion: DA+ was highly associated with IFN- promoter hypermethylation. Methylation status of IFN- promoter, combining with multivariate model can differentiate DA from non-DA workers with relative high sensitivity and specificity.

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