EXPOSURE TO METALS AND GENE-SPECIFIC METHYLATION IN COMMUNITY-DWELLING ELDERLY MEN

Angeliki Lambrou, *Departments of Environmental Health and Epidemiology, Harvard School of Public Health, Boston, MA, USA*
Andrea Baccarelli, *Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA*
Robert O. Wright, *Department of Environmental Health, Harvard School of Public Health and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
Laura Cantone, *Center of Molecular and Genetic Epidemiology, Universitá degli Studi di Milano & IRCCS Ca', Granda Policlinico Maggiore Hospital Foundation, Milan, Italy*
Chitra Amarasiriwardena, *Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
Pantel Vokonas, *VA Normative Aging Study, Veterans Affairs Boston Healthcare System and Department of Medicine, Boston University School of Medicine, Boston, MA, USA*
Joel Schwartz, *Departments of Environmental Health and Epidemiology, Harvard School of Public Health, Boston, MA, USA*

Background and Aims: Methylation changes in promoter regions of genes have been linked to gene expression changes and subsequent human disease. Heavy metals are known to trigger oxidative stress, changes in immune response, and inflammation throughout the body. DNA methylation is a potential pathway through which heavy metals exert their toxicity. We aimed to evaluate the association between exposure to arsenic, cadmium, mercury, manganese and lead and DNA methylation in nine different genes related to inflammation, immune response, and endothelial function in a population of environmentally exposed elderly men.
Methods: Our study population was 773 participants from the Normative Aging Study cohort in Boston, USA, with repeated visits between 1999 and 2009. Our associations of interest were explored in a minimum of 423 and a maximum of 611 participants depending on the availability of the exposure and outcome measurements. We measured the concentration of metals in toenails (in mcg/gr) while DNA methylation (in % of 5methyl cytosine) in promoter regions of the IL6, IFN-gamma, iNOS, ICAM, CRAT, OGG, TLR2, F3 and GCR genes was measured in blood leukocytes. The toenail metal concentrations were natural logarithm-transformed. We used multivariable linear mixed effects models to evaluate the associations of interest.
Results: Toenail arsenic and manganese concentrations were negatively associated with the iNOS gene methylation [b=-0.2, 95%CI: -0.3 to -0.1 for ten percent increase in toenail arsenic; b= -0.1, 95%CI: -0.1 to -0.01 for ten percent increase in toenail manganese). We did not find any statistically significant associations between the other metals and gene-specific methylation.
Conclusions: Both arsenic and manganese concentrations were associated with decreased iNOS methylation which can potentially lead to increased iNOS gene function and subsequent increased nitrogen oxide production, a process involved in inflammation. Our results indicate that heavy metal exposures may exert their effects through epigenetic mechanisms.