GENOMIC DNA METHYLATION ALTERATIONS DUE TO METAL-RICH AIR PARTICLE EXPOSURE: POTENTIAL LINKS WITH INFLAMMATION AND COAGULATION MARKERS

Francesco Nordio, Center of Molecular and Genetic Epidemiology, Department of Environmental and Occupational Health, Università degli Studi di Milano, Milan, and Department of Clinical Medicine, Nephrology and Health Sciences, University of Parma Medical School, Parma, Italy
Laura Angelici, Center of Molecular and Genetic Epidemiology, Department of Environmental and Occupational Health, Università degli Studi di Milano, Milan, Italy
Letizia Tarantini, Center of Molecular and Genetic Epidemiology, Department of Environmental and Occupational Health, Università degli Studi di Milano, Milan, Italy
Matteo Bonzini, Department of Experimental Medicine, University of Insubria, Varese, Italy
Armando Tripodi, Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, Department of Medicine and Medical Specialities, Milan, Italy
Pietro Apostoli, Occupational Medicine and Industrial Hygiene, University of Brescia, Department of Experimental and Applied Medicine, Brescia, Italy
Pier Alberto Bertazzi, Center of Molecular and Genetic Epidemiology, Department of Environmental and Occupational Health, Università degli Studi di Milano, and Fondazione Cà Granda, IRCCS Ospedale Maggiore Policlinico, Milan, Italy
Andrea Baccarelli, Exposure, Epidemiology and Risk Program, Department of Environmental Health, Harvard School of Public Health, Boston, Massachusetts, USA

Background and Aims: DNA methylation alterations have been proposed as a novel molecular mechanisms linking inhalable particulate matter (PM) exposure to cardiovascular effects. However, data showing relations among PM exposure, DNA methylation and cardiovascular-related outcomes, such as inflammation and blood coagulation, are limited. We investigated global DNA methylation, inflammation and coagulation markers in foundry workers with well-characterized exposure to a wide range of metal-rich PM.

Methods: We recruited 63 male workers (mean age 44 years) in an electric-steel plant in Italy. Individual exposure to PM with diameter<10 µm (PM10) and its metal components was estimated using work-area measurements and time spent in each area. DNA methylation analysis of Alu and LINE-1 was performed through bisulfite-pyrosequencing on blood DNA obtained on two different work days. We measured PT, aPTT, t-PA antigen, D-dimer, and CRP. Endogenous thrombin potentials (ETPs) were assessed with (TM+) or without (TM-) soluble thrombomodulin, but without exogenous triggers. Covariate-adjusted linear mixed-effect regression was used to evaluate associations between PM or metal exposure and methylation; and between methylation and coagulation/inflammation markers.

Results: Workers were exposed to a wide range of PM10 (between 73-1220 g/m³) and metal components (PM10 metal content between 2%-94%). PM10 showed a negative association with Alu (r = -0.18, p = 0.05) and LINE-1 (r = -0.37, p = 0.04) methylation. Zinc had a marginal negative association with Alu methylation (r = -0.17, p = 0.06). Aluminum was negatively associated with LINE-1 methylation (r = -0.19, p = 0.04). Lower Alu methylation was associated with activated coagulation and inflammation, as indicated by shorter PT (r = -0.18, p = 0.02), and increased ETP TM+ (r = 87.17, p = 0.03), ETP TM- (r = 144.82, p = 0.02), and CRP (r = 0.58, p = 0.01). No associations were found with other markers.

Conclusions: We found novel associations of coagulation markers with Alu repetitive element methylation. DNA methylation was associated with specific metal components, suggesting a possible common path linking PM exposure, methylation, and blood coagulation.