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### EXTRACELLULAR HISTONES AFFECT BLOOD COAGULATION IN SUBJECTS EXPOSED TO METAL-RICH AIR PARTICLES

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**Objectives** Epidemiological findings suggest an association between particulate matter (PM) exposure and hypercoagulability and thrombosis. The underlying mechanism for PM-related procoagulative effects is still unknown, but recently, elevated levels of extracellular histones have been indicated as possible mediators in inflammatory conditions. In 63 steel workers, we evaluated the effects of exposure to PM and PM metal components on two extracellular histone modifications (histone H3 lysine 4 trimethylation: H3K4me3; histone H3 lysine 9 acetylation: H3K9ac), and the association between both H3K4me3 and H3K9ac and coagulation markers.

**Methods** H3K4me3 and H3K9ac were determined in plasma samples through ELISA. Prothrombin time (PT), activated partial thromboplastin time (APTT), endogenous thrombin potentials (ETPs) with/without exogenous triggers and with/without soluble thrombomodulin, tissue-type plasminogen activator (t-PA) antigen, D-dimer, C-reactive protein (CRP) were measured as coagulation markers. Exposure to inhalable metal components (aluminum, manganese, nickel, zinc, arsenic, lead, iron), and to particle mass (PM with aerodynamic diameters, <1 µm (PM1), <10 µm (PM10) and coarse PM (PM10-PM1)) was estimated for each study subject.

**Results** Both H3K4me3 and H3K9ac were increased in association with PM1 ( $\beta$ [H3K4me3]=0.34,  $P=0.01$ ;  $\beta$ [H3K9ac]=0.27,  $P=0.02$ ). H3K4me3 was increased in association with air levels of zinc ( $\beta=0.25$ ,  $P=0.04$ ) and iron ( $\beta=0.38$ ,  $P=0.01$ ). H3K9ac showed borderline positive association with air level of zinc ( $\beta=0.18$ ,  $P=0.07$ ). Histone modifications also showed significant association with ETP TM+ ( $\beta$ [H3K4me3]=355.27,  $P=0.05$ ;  $\beta$ [H3K9ac]=389.03,  $P=0.05$ ), and borderline association with t-PA antigen ( $\beta$ [H3K4me3]=-3.42,  $P=0.06$ ;  $\beta$ [H3K9ac]=-3.23,  $P=0.06$ ).

**Conclusions** Our results indicate a potential role of extracellular histones in hypercoagulability induced by PM exposure