Histone deacetylase 3 (HDAC3), a member of the class I histone deacetylases, is known to have a crucial role in endothelial cell differentiation \(^1\) and maintenance of endothelial integrity in response to disturbed flow.\(^2\) In this study, we investigated the function of HDAC3 in endothelial protection from inflammation, and the underlying mechanism. The inflammatory mediator lipopolysaccharides (LPS) induced HDAC3 and galectin-9 production in a similar pattern in human umbilical vein endothelial cells. Over-expression of HDAC3 by adenoviral gene transfer increased galectin-9 expression. Pharmacological inhibition of HDAC activity with a pan-HDAC inhibitor (TSA) or HDAC3 specific inhibitor (apicidin) reduced the baseline and LPS-induced galectin-9 expression. In addition, knockdown of HDAC3 through shRNA lentiviral transfection abolished the baseline and LPS-induced galectin-9 expression. Similar results were observed on interferon γ (IFNγ)-induced galectin-9 expression. To explore the underlying mechanism, the interaction of HDAC3 with galectin-9 upstream signal pathway phosphorylating kinase (PI3K)/signal transmission and transducer 3 (Stat3)/interferon response factor (IRF3) was assessed. Co-immunoprecipitation assay showed that HDAC3 formed a complex with PI3K/Stat3/IRF3, which was enhanced by LPS and IFNγ treatment. Using truncated forms of HDAC3, it was shown that the C-terminal of HDAC3 was responsible for the formation of the complex. Furthermore, venous administration of LPS or IFNγ to mice increased HDAC3 expression and binding to the above-mentioned proteins, leading to galectin-9 expression in the aorta. These results suggest that HDAC3 may protect endothelial cell from inflammation through galectin-9 expression, which may have an impact on preventing vascular inflammation related to the development of atherosclerosis.

REFERENCES


Histological sections of the brachiocephalic artery from ApoE knockout mice showed large, foam-cell-filled fibrous plaques. Plaque burden was increased (p=0.025; n=5–6) in DEP-treated mice (69±9%) compared with vehicle-treated controls (42±7%). Furthermore, plaques from DEP-treated mice exhibited a greater number of adjoining (2.3±0.2%) and buried (1.2±0.3%) fibrous caps than control mice (1.7±0.2% and 0.2±0.1%, respectively; p<0.05 n=5). There was no evidence of systemic inflammation, increased circulating blood lipids or endothelial dysfunction in DEP-treated animals.

This is the first study to show that pulmonary exposure to the particulate matter within diesel exhaust enhances atherogenesis. This action may, therefore, contribute to the increased cardiovascular morbidity and mortality associated with air pollution. This model will allow identification of the constituents of DEP that mediate this atherogenic effect and provide an important insight into potential interventions to reduce the impact of vehicular emissions.

REFERENCES


Air pollution has been linked to the development of atherosclerosis and cardiovascular disease. Diesel exhaust particulate (DEP) accounts for a substantial proportion of urban air pollution but its effects on atherogenesis are unknown. We hypothesised that DEP will exacerbate plaque formation in a murine model of atherogenesis.

Apolipoprotein E knockout (ApoE) mice (10–12 weeks; n=16) were fed a ‘Western diet’ (21% cholesterol) for 8 weeks to induce the development of complex atherosclerotic plaques. During the last 4 weeks of feeding, mice underwent twice-weekly intratrabecular instillation of 35 μl DEP (1 mg/ml; National Institute of Standards and Technology) or vehicle (saline).