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Lead induces the up-regulation of the protein arginine methyltransferase 5 possibly by its promoter demethylation

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Abstract

The studies on lead (Pb) exposure linking to epigenetic modulations are caused by its differential actions on global DNA methylation and histone modifications. These epigenetic changes may result in increased accessibility of the transcription factors to promoter DNA-binding elements leading to activation and expression of the gene. The protein arginine methyltransferase 5 (PRMT5) and its partner methylosome protein 50 (MEP50) together catalyze the mono- and symmetric dimethylation of arginine residues in many histone and non-histone protein substrates. Moreover, it is overexpressed in many forms of cancer. In the present study, the effects of Pb on the PRMT5 and MEP50 expression and formation of the symmetrically dimethylated arginine (SDMA), the catalytic product of the PRMT5-MEP50 complex were analyzed *in vitro* after exposing the A549 and MCF-7 cells. The results show that exposure to 0.1 and 1 μM of Pb strongly enhanced the expression of both PRMT5 and MEP50 transcript and protein leading to increased SDMA levels globally with H4R3 being increasingly symmetrically dimethylated in a dose-dependent manner after 48 h of Pb exposure in both cell types. The methylation-specific PCR also revealed that the CpG island present on the PRMT5 promoter proximal region was increasingly demethylated as the dose of Pb increased in a 48-h exposure window in both cells, with MCF-7 being more responsive to Pb-mediated PRMT5 promoter demethylation. The bisulfite sequencing confirmed this effect. The findings therefore indicate that Pb exposure increasing the PRMT5 expression might be one of the contributing epigenetic factors in the lead-mediated disease processes as PRMT5 has a versatile role in cellular functions and oncogenesis.

Keywords: DNMTs; MEP50; PRMT5; PRMT5 promoter; epigenetics; lead.

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