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The persistent organochlorine pesticide endosulfan modulates multiple epigenetic regulators with oncogenic potential in MCF−7 cells

Krishna Ghosh [1], Biji Chatterjee [1], Aparna Geetha Jayaprasad [1], Santosh R Kanade [2]

Affiliations

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Abstract

Environmental cues and chemicals can potentially modulate the phenotypic expression of genome through alterations in the epigenetic mechanisms. Endosulfan is one of the extensively used organochlorine pesticides around the world which is known for its endocrine, neuro- and reproductive toxicity. This study was aimed to investigate the potential of α-endosulfan in modulation of multiple epigenetic enzymes in MCF-7 cells. The cells were treated with DMSO (control) or α-endosulfan (1 and 10μM) and the expression of various epigenetic enzymes was assayed by real-time PCR and immunoblotting, in addition to their activity assays. The results shows α-endosulfan, at 1 and 10μM concentration, significantly promoted viability of MCF-7 cells compared to untreated cells after 24h. The expression of DNA methyltransferases (DNMTs) was upregulated while the global DNA methylation status was initially affected, but later recovered. Total intracellular histone deacetylase (HDAC) activity was found to be significantly increased which was correlated with upregulation of class I HDACs (HDAC 1 and 3) while no significant alteration in the other HDAC classes was observed. The expression and activity of arginine and lysine methylation enzymes, protein arginine methyltransferase 5 (PRMT5) and Enhancer of Zeste homolog 2 (EZH2), respectively, were also found to be modulated by α-endosulfan. We found increased expression of histones H3 and H4, trimethylated H3K27 (product of EZH2), symmetric dimethylation of H4R3 (product of PRMT5) and five different (unidentified) proteins whose arginine residues are symmetrically dimethylated (by increased level of PRMT5) were enhanced in response to 10μM α-endosulfan after 24h exposure window. Moreover, overexpression of basal level of estrogen receptor alpha (ERα), suggests estrogenicity of α-endosulfan. In summary, our results shows modulatory impact of α-endosulfan on multiple cellular epigenetic regulators, known to possess oncogenic potential which might contribute to mechanistic insight of its action in future.

Keywords: DNMT; EZH2; Epigenetics; HDAC; Organochlorine pesticide; PRMT5; α-Endosulfan.

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