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DOWN-REGULATION OF P^{53} BY SET CONTRIBUTES TO TCE-INDUCED DNA DAMAGE THROUGH INHIBITION OF H3K79 DI-METHYLATION

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Trichloroethylene (TCE) is an occupational and environmental chemical that can cause severe hepatotoxicity. Previously we have observed in a model of TCE-induced apoptosis of cultured human hepatocytes (L-02 cell line) that SET (a protein encoded by the SET gene in humans) is abnormally elevated which acts as a key mediator in TCE-induced hepatic cytotoxicity, but the underlying mechanisms still remain elusive. In this study we found that TCE induced DNA damage in liver cells using comet assay. Additionally, SET related histone methylation were analyzed using the combination of triton-acid-urea polyacrylamide gel electrophoresis (TAU-SDS-PAGE) and LC-MS/MS. 22 SET-mediated abnormally altered histone methylation were identified and the H3K79 di-methylation (H3K79me2), which was related with DNA damage and gene transcription, was validated by Western-blot analysis. We revealed that SET inhibited H3K79 di-methylation within the promoter region of p^{53} under the treatment of TCE by using chromatin immunoprecipitation-quantitative PCR (CHIP-qPCR) analysis. Further inhibition of H3K79 specific methyltransferase DOT1L verified that SET-mediated decreasing H3K79 di-methylation caused down-regulation of p^{53} and aggregated DNA damage. These findings indicate that SET aggregates TCE-induced DNA damage through partially blocking the repair process via dysregulation of p^{53}.

BIOGRAPHY

Jianjun Liu has completed her M.D. in 1989 from University of Xiangtan, and now, she is post-doctor supervisor of Southern Medical University. Her major research interests include proteomic analysis and biomarker screening of chemical pollutant-induced damage to human, safety assessment of nano-materials, development of testing techniques for food safety. She has published more than 70 research papers. Additionally, in the past five years, she has received over ten grants, such as National Science Foundation of China, the Guangdong Natural Science Foundation, Sanming Project of Medicine in Shenzhen, and so on.

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