
Gene expression signatures affected by alcohol-induced DNA methylomic deregulation in human embryonic stem cells.

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Public Summary:

Teratogenic effect of alcohol has been documented and maternal alcohol abuse during gestation can result in various fetal injuries. The developmental defects from alcohol abuse during gestation have been described, but it is still unanswered about what are the specific mechanisms by which alcohol mediates these injuries. This is important question to address in order for us to identify affected children at an early age and intervene to prevent or mitigate the damage. Due to the inherent limitations of studies conducted in humans, the use of alternative models is important in addressing these unanswered questions. Embryonic stem cells and adult stem cells have been used as study models to unveil molecular and cellular mechanisms in various signaling pathways. They are especially beneficial to developmental studies where in vivo molecular/cellular study models are not available. This report has demonstrated the adverse effect of EtOH on the gene expression signatures in hESCs that are potentially elicited through epigenetic alterations. We have further profiled genome-wide DNA methylomic marks that are affected by EtOH in hESCs. Our understanding on the effect of alcohol on stem cells will be beneficial to design future clinical application of stem cells to improve human health.

Scientific Abstract:

Stem cells, especially human embryonic stem cells (hESCs), are useful models to study molecular mechanisms of human disorders that originate during gestation. Alcohol (ethanol, EtOH) consumption during pregnancy causes a variety of prenatal and postnatal disorders collectively referred to as fetal alcohol spectrum disorders (FASDs). To better understand the molecular events leading to FASDs, we performed a genome-wide analysis of EtOH's effects on the maintenance and differentiation of hESCs in culture. Gene Co-expression Network Analysis showed significant alterations in gene profiles of EtOH-treated differentiated or undifferentiated hESCs, particularly those associated with molecular pathways for metabolic processes, oxidative stress, and neuronal properties of stem cells. A genome-wide DNA methylome analysis revealed widespread EtOH-induced alterations with significant hypermethylation of many regions of chromosomes. Undifferentiated hESCs were more vulnerable to EtOH's effect than their differentiated counterparts, with methylation on the promoter regions of chromosomes 2, 16 and 18 in undifferentiated hESCs most affected by EtOH exposure. Combined transcriptomic and DNA methylomic analysis produced a list of differentiation-related genes dysregulated by EtOH-induced DNA methylation changes, which likely play a role in EtOH-induced decreases in hESC pluripotency. DNA sequence motif analysis of genes epigenetically altered by EtOH identified major motifs representing potential binding sites for transcription factors. These findings should help in deciphering the precise mechanisms of alcohol-induced teratogenesis.

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