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Investigation of the effects of alcohol exposure on the chromatin binding and localization of cohesin and CTCF

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Alcohol exposure is associated with a wide array of medical problems, including both acquired and congenital phenotypes. Examples of these phenotypes include increased incidence of multiple cancer sub-types and diagnoses under the fetal alcohol spectrum disorders umbrella. While much work has attempted to elucidate the downstream molecular mechanisms induced by ethanol exposure, there are large gaps in our understanding. In addition to the large number of patients worldwide affected by alcohol exposure, due at least in part to epigenetic alteration, there are a number of genetic syndromes in which primary disruption of the genes encoding epigenetic machinery is the disease mechanism. Patients with genetic defects in the architectural proteins CTCF or cohesin present with overlapping syndromes characterized primarily by a neurodevelopmental disorder with growth defects and to a lesser degree multiple congenital anomalies, thus representing another patient population impacted by altered epigenetic architecture and chromatin organization. One promising question is how specifically ethanol exposure affects epigenetics, including the impact of ethanol on DNA methylation, histone modifications, and chromatin organization. In cell culture models of ethanol exposure, we performed ChIP-Seq experiments to assess the localization of both CTCF and the cohesin subunit RAD21 on chromatin. We performed these experiments after 24 hours and after 6 days of ethanol treatment, as well as a group which was treated for 6 days with ethanol and then allowed to recover in the absence of ethanol for 6 additional days. A similar experimental set-up is currently underway to perform HiC on these samples to assess the three-dimensional architecture of chromatin. Finally, we are collaborating with a laboratory to obtain brain samples from mice affected by prenatal alcohol exposure, to perform these same experiments in this tissue type. ChIP-Seq experiments found significant alterations to the localization and binding of CTCF and RAD21 along chromatin. Effects were much more pronounced after a 6 day exposure as compared to a 24 hour exposure, and began to normalize (but did not return to baseline levels) after 6 additional days of recovery. In summary, ethanol treatment alters the localization of the architectural protein cohesin on chromatin. This likely influences nearby chromatin organization and may correspond to the observed downstream transcription changes known to be induced by ethanol treatment. Together, this data reveals a previously unknown mechanistic-functional explanation of ethanol exposure phenotypes, indicating that the phenotypes may be due in part to disrupted chromatin organization.