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Epigenetic Toxicity: Preconception Paternal Exposures and the Programming of Offspring Birth Defects.

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Paternally inherited alterations in epigenetic programming are emerging as a relevant factor in numerous developmental disorders. Despite the exclusive association of fetal alcohol spectrum disorders (FASDs) with maternal drinking, research from our lab indicates that paternal alcohol use is a relevant factor in this debilitating condition. Using an established mouse model, our group has linked preconception paternal alcohol use to sex-specific patterns of both fetal and postnatal growth restriction, as well as long-term metabolic defects in the next generation. These phenotypic changes associate with programmed changes in gene expression that arise during fetal gestation and persist into adulthood.

Despite the identification of multiple preconception stressors that can influence offspring development, the mechanisms by which the memory of these exposures transmit to the next generation and impact offspring health remain poorly defined. We hypothesized that alcohol-induced alterations in sperm-inherited DNA methylation patterns, histone post-translational modifications, and non-coding RNAs would correlate with offspring growth defects. We find that alterations in sperm histone structure and the profile of non-coding RNAs, but not DNA methylation, correlate with placental abnormalities and the appearance of alcohol-related congenital defects in the next generation. Importantly, our studies reveal that changes in histone modifications and non-coding RNAs arise during multiple phases of sperm production, including the period immediately before conception. In this talk, I will describe our ongoing efforts to identify the epigenetic mechanisms by which paternally-inherited phenotypes transmit to the offspring and how these alterations in paternal programming influence fetal development.