Molecular Etiology of FAS-Like Craniofacial and Neurodevelopmental Malformations

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Abstract

Fetal Alcohol Spectrum Disorder (FASD) is the most common cause of neurodevelopmental disorders in the western world, affecting 1-5% of North American children. Individuals with FAS have craniofacial malformations and neurodevelopmental deficits, including cognitive, memory and learning impairments. We hypothesize that acute prenatal alcohol exposure overwhelms alcohol metabolizing enzymes that normally also convert retinol (Vitamin A) to retinoic acid; moreover, this reduction of retinoic acid levels during gastrulation drives the malformations and deficits associated with FAS. To model the alcohol competitive inhibition in vivo we genetically engineered a mouse expressing Cyp26A1-eGFP from the endogenous Goosecoid (Gsc) promoter. Cyp26A1 biochemically mimics the reduced retinoic acid levels induced by acute alcohol exposure and the Gsc promoter dictates a specific spatio-temporal expression of the Cyp26A1-eGFP cassette in Spemann's Organizer (at gastrulation). Analysis of newborn F1 mice shows 88% (n=15/17) of mutant mice assessed had a discernable FAS phenotype, compared with 100% of wild-type mice assessed as normal (n=14/14). Scanning Electron Microscopy analysis allowed quantification of the craniofacial malformations using known landmark assessments. Taken together, our data supports the role of alcohol-induced retinoic acid deficiency as an underlying etiology of FAS.