Arsenic Embryotoxicity: Cellular and Molecular Toxicity

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Arsenic represents a ubiquitous environmental contaminant with adult toxicity in humans and developmental toxicity in laboratory animals. While published reports indicate differential strain sensitivity to induction of NTDs in animal models following prenatal arsenic exposure remain unclear. As such, the need exists to understand the mechanisms underlying interactions between arsenic and maternal/embryonic genotype during development, as well as understand the mechanisms by which suspected human developmental toxicants, such as arsenic, interact with critical aspects of embryonic development. This is particularly true regarding precursor cell populations which populate the early embryo and differentiate during early organogenesis. The proposed research program will investigate the developmental hazards associated with arsenic exposure in a genetically sensitive mouse model in which the folate binding proteins, Folbp1 or Folb2 have been inactivated. Preliminary analysis indicates that animals lacking Flobps demonstrate an increased prenatal risk for arsenic-induced NTDs. The hypothesis to be examined in the present application is that an abnormal folate binding protein genotype increases the risk for arsenic-induced NTDs, the resulting phenotype of which is associated with alterations in cranial neural crest gene expression (i.e. neural crest function). Through breeding of Folbp knockout mice to Wnt1-cre/LoxP mice, a novel "composite" mouse model will be generated which is genetically sensitive to arsenic induction of NTDs and in which the neural crest are indelibly (genetically) marked. Such a mouse model will enable analysis of the effects of arsenic on neural crest formation, migration and proliferation under conditions of differing Folbp genotypes (Specific Aim 1). In addition, the application of laser capture microdissection (of neural crest cells) and DNA microarray technologies to this animal model will facilitate generation of isolated neural crest "gene expression profiles" during neural tube morphogenesis and under conditions of arsenic-induced NTDs among embryos of differing Folbp genotypes (Specific Aim 2).

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