Microarray Analysis of Limb Bud Reaction to Teratogen Exposure

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Eludication of the immediate response of embryos to xenobiotic exposure is an aspect of research that could yield significant benefit to the estimation of teratogenic risk. We contend that some part of this stress/adaptive response which is presumable similar across species can negatively impact developmental signaling mechanisms some of which are known to be the same across species. We were led to this hypothesis by the fact that many chemical and physical agents with diverse pharmacodynamic activities induce the same, very localized limb malformation, absence of posterior digits from the forelimb, predominantly on the right side i.e., postaxial right forelimb ectrodactyly. Moreover, a number of these agents are well documented human teratogens such as valproic acid, retinoic acid, and ethanol. This putative cause/effect relationship between an adaptive response and a localized limb malformation is very attractive for exploration because we know a developmental signaling mechanism that is altered in the limb as it develops without posterior digits. Polarizing activity, the ability of posterior limb bud mesoderm to induce a limb duplication when grafted to the anterior margin of a host chick wing, is widely accepted as the basis of anterior/posterior (A/P) patterning of the limb across many species including humans. We have shown that this activity is lost from acetazolamide exposed muring limbs. In Specific Aim 1, we will test the hypothesis that cadmium exposure similarly reduces polarizing activity of the murine limb bud and will examine the consequences on gene expression patterns in the limb. In Specific Aim 2, we propose to elucidate the adaptive response pathway of limb bud cells after exposure to acetazolamide or cadmium, both of which induce postaxial right forelimb ectrodactyly. We will utilize microarray analysis to examine the stress response to teratogen exposures. We hypothesize that a common adaptive response to acetazolamide and cadmium will be induced. Future studies will examine the capability of such an adaptive response to interfere with polarizing activity, thereby leading to congenital malformation. A very exciting additional benefit will be the discovery and identification of new genes important in limb morphogenesis or xenobiotic response or both.

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