### Title
Developmental defects in multiple organ systems in a mouse model of Cornelia de Lange Syndrome




### Journal
Developmental Biology, 295(1)

### ISSN
0012-1606



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### Publication Date
2006-07-01

### DOI
10.1016/j.ydbio.2006.04.083

reported to participate in both the retinoid signaling pathway and the transforming growth factor-beta (TGF-beta) pathway. Smad2 is a intracellular mediator of the TGF-beta signaling cascade, regulating gene transcription. Depending upon the co-activator, Smad2 can function as either an enhancer or repressor. Research has indicated that mice harboring Tgif mutations are more susceptible to teratogenesis induced by exogenous all−trans retinoic acid (RA), resulting in HPE and exencephaly. Smad2 heterozygous embryos are also susceptible to exogenous RA. In addition, the use of a Smad2 hypomorphic allele reinforces the observation that Smad2 is involved in susceptibility, as hypomorphic heterozygous are less susceptible to the effects of RA than hypomorphic homozygotes. There are many factors involved in retinoid signaling, including both the retinoid cascade and RA synthesis and degradation. Analysis of gene transcription to determine the inherent susceptibility to RA in the Smad2+/− embryos was undertaken. Results indicate that Adh4 and Cyp26A1 are affected in early development. When the promoters of these genes were analyzed, many Smad Binding Elements (SBEs) were observed, indicating potential interaction of TGF-beta signaling in the synthesis and degradation of RA.

doi:10.1016/j.ydbio.2006.04.082

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## Developmental defects in multiple organ systems in a mouse model of Cornelia de Lange Syndrome

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Cornelia de Lange Syndrome (CdLS) is a dominantly- inherited, multi-system birth defects syndrome with highly variable presentation. Individuals with CdLS have characteristic facial features, hirsutism, limb defects, heart defects, gastrointestinal system defects, and growth and cognitive retardation. Recent work has shown that CdLS is caused by heterozygous mutation of a gene, NIPBL (Nipped-B like), whose product is involved in regulation of the cohesin system of chromosomal structural proteins (Krantz et al., 2003, Nat. Genet. 36:631). We have developed a mouse model for CdLS, using mice heterozygous for a gene-trap mutation in Nipbl. Surviving Nipbl+/− mice exhibit a number of organ system defects characteristic of CdLS, including small body and head size, heart defects, hearing abnormalities, and delayed bone maturation. Nipbl+/− mice also show a very high incidence (~75%) of perinatal mortality, indicating that these animals have other, as yet undetected, abnormalities. RNase protection assays demonstrate that the phenotypes of Nipbl+/− mice are associated with a decrease in Nipbl transcript levels to only ~75% of wildtype, implying that these developmental events are extremely sensitive to small changes in Nipbl function. Supported by seed grants from the Cornelia de Lange Syndrome Foundation and the Center for Hearing Research at the University of California, Irvine.

doi:10.1016/j.ydbio.2006.04.083

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## Contribution of aberrant placentation to fetal alcohol syndrome

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The teratogen ethanol causes fetal alcohol syndrome, which is associated with intrauterine growth retardation (IUGR) and neurological birth defects. A contributing factor to IUGR is cytotrophoblast cell (CTC) apoptosis during placentation. Using a human first trimester CTC line (HTR-8/SVneo), we examined the relationship between CTC apoptosis and exposure to ethanol. Exposure for 0–2 h to 0, 25, 50 or 100 mM ethanol demonstrated a significant time-and dose-dependent increase in CTC death measured by TUNEL. Proliferation (expression of nuclear antigen Ki-67) was also inhibited by ethanol. Increased externalization of phosphatidyl serine, the presence of pyknotic, TUNEL-positive nuclei and prevention of cell death by caspase inhibitors suggested that ethanol caused apoptosis, as opposed to necrosis. Moreover, there was no evidence of cell rupture and the release of lactate dehydrogenase. Production of heparin-binding EGF-like growth factor (HBEGF), which prevents CTC apoptosis due to low oxygen in the first trimester, increased with exposure to 25–50 mM ethanol. During treatment with 100 mM ethanol, 1 nM HBEGF eliminated cell death and 5 nM restored CTC proliferation. HBEGF antagonists confirmed its specificity. We conclude that CTC apoptosis due to maternal alcohol abuse could cause IUGR; however, ethanol-induced production of HBEGF could provide an endogenous protective mechanism. Supported by NIH grants AA12057, AA11085 and AA014535 and the intramural research program of NICHHD.

doi:10.1016/j.ydbio.2006.04.084

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## Influence of hormones on growth and differentiation of cells that do not express neurofibromin

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The tumor suppressor gene, Neurofibromatosis Type 1 (NF1) is responsible for one of the most common autosomal