ROLE OF CITED GENES IN PLACENTAL MORPHOGENESIS: STUDIES IN NULL MUTANT MICE

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Cited1 and Cited2 interact with CBP and p300. CBP/p300 bind numerous proteins and evidence exists, for Cited2 at least, that Cited binding prevents the binding of other proteins to CBP/p300. Since CBP/p300 interact with many proteins, can acetylate protein and DNA, and act as a ubiquitin ligase, it is likely that Cited1 and Cited2 function at a number of sites during development. We have generated mice that carry a null mutant allele for each of these genes. Analysis of null mutant embryos demonstrates that both Cited1 and Cited2 are required for normal embryonic development and survival. Although both Cited1 and Cited2 are expressed in the developing embryo and placenta, it appears that abnormal placental development and function is the cause of embryonic death.

The defect that develops in the placentas of Cited1 null mutants is not apparent until late in gestation (16.5dpc). Cited1 null mutants are smaller than controls at birth and die during the early postnatal period. The placentas of these mutants are disorganised, with spongiotrophoblasts projecting in to the labyrinthine layer. In addition, resin casts of the maternal blood spaces within these placentas revealed extremely enlarged blood sinuses. We are searching for factors that could result in the increased size of the maternal blood sinuses.

Cited2 null placentas and embryos are significantly smaller than controls; mutants die 3/4 the way through gestation (15.5dpc). The null mutant placentas have proportionally fewer spongiotrophoblasts, trophoblast giant cells and invasive trophoblasts. In addition, resin casts of fetal vasculature of the placenta reveal that the capillary network is underdeveloped. Through the isolation of trophoblast stem (TS) cells we are exploring the possibility that TS cell proliferation and/or differentiation is impaired due to a lack of Cited2. We suspect that the development of the phenotype may relate to the Hypoxia Inducible Factor-1a (HIF1a) transcription factor as Cited2 expression is induced by HIF1 and it acts to negatively regulate its activity.

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