

Without this protein, embryonic development halts: research sheds light on early embryogenesis, genetic disease

Chromosome 22q11 deletion syndrome (also known as DiGeorge syndrome) is the most common human chromosome deletion syndrome, having an estimated incidence of at least one in 4000 live births. It has a range of severity but a multisystem impact, with symptoms that may include congenital heart defects, immunological and endocrine abnormalities, cleft palate, gastrointestinal problems and neuropsychiatric abnormalities.

Nearly three-quarters of patients identified with this deletion syndrome have cardiac defects, and research into the underlying biology of this disorder has uncovered new knowledge of biological processes in both congenital heart disease and early embryonic development.

On page 569 of this issue of *Experimental Biology and Medicine*, Jason Z Stoller, MD, of The Children's Hospital of Philadelphia, collaborating with Jonathan A Epstein, MD, scientific director of the Penn Cardiovascular Institute of the University of Pennsylvania, report on an important interaction of two proteins, Ash2l and Tbx1, during early mammalian development. 'In humans and other mammals, the heart is among the first organs to develop', said Stoller. 'Greater knowledge of biological events that occur in the earliest stages of development helps us to better understand both normal and abnormal heart development'.

In cell and animal studies, the researchers discovered that Ash2l, a core component of a protein complex responsible for epigenetic modifications, is absolutely essential to early embryogenesis; without this protein, mouse embryos did not survive past the first few days of gestation.

The region of chromosome 22 that is most commonly lost in DiGeorge syndrome contains more than 30 genes, among them the gene for the transcription factor Tbx1. The Tbx family of nuclear transcription factor proteins shares a T-box, a conserved DNA binding domain that mediates regulation of downstream genes. In 2005, Epstein and Stoller identified a domain within the Tbx1 protein that,

when not functioning properly, plays a key role in causing DiGeorge syndrome in a subset of patients.

The current study aimed to identify proteins that interact with Tbx1 in a functionally important way that could shed light on the pathogenesis of DiGeorge syndrome. Using a yeast and cell culture studies, the researchers pinpointed the Ash2l protein as interacting with Tbx1. They then generated *Ash2l* knockout mice to further investigate the role of the Ash2l protein. Mouse embryos that did not express Ash2l died early in gestation – demonstrating that the protein is necessary for early development.

'The crucial requirement of the Ash2l protein', said Stoller, 'suggests that it likely acts to regulate many developmental genes in mammals. As part of a histone methyltransferase complex, it regulates gene transcription by epigenetic mechanisms'.

Future clinical implications for children and adults with DiGeorge syndrome are yet unclear. These patients have a normal *Ash2l* gene, but the loss of Tbx1 may alter the interaction between Ash2l and Tbx1 and play a role in their disease, possibly by regulating downstream genes. Stoller added, 'The fact that patients with this genetic syndrome are missing a copy of the *Tbx1* gene suggests that reduced amounts of the Tbx1 protein may have biological effects that cause different features of the disease. Further research is needed to discover these specific mechanisms'.

Dr Steven R Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said 'Stoller *et al.* have demonstrated that protein Ash2l is essential in early embryogenesis. Ash2l interacts with the transcription factor Tbx1 which resides in a chromosomal region commonly deleted in DiGeorge syndrome. This interesting study suggests possible mechanisms leading to congenital heart disease in DiGeorge syndrome'.

DOI: 10.1258/ebm.2010.010f04