USC Researchers Identify Cause of Life-threatening Birth Defect

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Every year in the United States, 7500 infants are born with a cleft lip or cleft palate, amounting to 20 children every day. These devastating birth defects are caused by several different disorders, some more serious than others. One of the most serious is a genetic disorder called Loeys-Dietz syndrome, previously called Marfan syndrome II. Along with facial and cranial defects, children born with Loeys-Dietz syndrome suffer from vascular problems, including potentially fatal heart defects. An early accurate diagnosis for these children is vital for effective treatment, but separating this disorder from others with similar symptoms can be difficult. Researchers at the USC Center for Craniofacial Molecular Research have identified a single protein that could help.

Transforming Growth Factor Beta (TGF – β) In Mice

The study, which was published on February 13th in *The Journal of Clinical Investigation*, was led by Yang Chai and Junichi Iwata at Ostrow School of Dentistry of USC. By studying the fetal development of mice, the researchers found an abnormally high level of the protein Transforming Growth Factor Beta (TGF-β) outside of the cells of patients with the facial defects that are characteristic indicators of Loeys-Dietz syndrome. TGF-β is responsible for numerous functions within the cell and is especially important for proper formation of the palate in the developing embryo. The data gathered from this study suggested that Loeys-Dietz syndrome may be caused by mutations in the way that TGF-β communicates outside the cell. A receptor called TGFRB2 on the outside membrane of the cell usually interacts with TGF-β. However, in Loeys-Dietz syndrome, this receptor appears to be mutated, causing something like a roadblock on the

communication highway between the TGF-β protein and the interior of the cell. TGF-β is then forced to detour, using slower paths, surface streets if you will, to communicate with the cell. Clinical studies seem to indicate that using these side pathways results in palate and facial defects in developing fetuses. One of the telltale signs that these alternate paths are being used is an elevation of TGF-β levels outside the cell due to slowed flow of TGF-β through the receptors.

Using TGF-β to Diagnose and Treat Loeys-Dietz Syndrome

Further work by the researchers showed that additional defects in the TGF-β's alternate pathways sped up the process and decreased the protein's levels outside the cell. These increases also rescued the facial and palate defects, effectively reversing the clefts without surgical intervention. Chai suggests that the next step in research and treatment would occur if fetuses could be tested in the womb and TGF-β levels could then be manipulated to reverse the development of the cleft lip before the child was even born. He even goes so far as to call such possibilities "promising." TGF-β in the space outside of the cells can be measured with a simple blood or tissue test. Screening for extracellular TGF-β elevation after birth in infants that were born with cleft lip, cleft palate, or other facial defects could allow for an early, quick diagnosis of Loeys-Dietz syndrome, and would then inform clinical treatment of the young patients, especially as relates to their dangerous heart defects. Even if the development of an effective means of manipulating TGF-β levels is many years away, the ability to begin testing for this elevated protein may save hundreds of infants by identifying those whose facial defects signal much more serious and potentially fatal underlying vascular problems well before any problems arise.