

# Researchers identify alternate pathway that leads to palate development

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Researchers at the University Of Southern California School Of Dentistry have uncovered another clue behind the causes of cleft palate and the process that leads to palate formation.

Cleft palate is one of the most common congenital birth defects, occurring in one out of every 700 live births. Clefts are more common in children of American Indian, Hispanic or Asian descent. While males are twice as likely to have a cleft lip, females are twice as likely to have a cleft palate.

But genes are not the only factor influencing the malformation says, Yang Chai, professor and director of the USC School of Dentistry's Center for Craniofacial Molecular Biology.

Researchers around the world believe that most cases of cleft lip and cleft palate are caused by an interaction of genetic and environmental factors; however, a specific cause may not be discovered for every baby.

Growth factors responsible for development, including palate and tooth formation, have more than one way to direct cells to make changes, says Chai.

The Discovery by the USC team is spotlighted in the August 12 issue of *Development Cell*.

Chai's group, which includes fellow CCMB researchers Xun Xu, Jun

Han, Yoshihiro Ito and Pablo Bringas Jr., has been specifically scrutinizing the transforming growth factor beta (TGF- $\beta$ ) family's role in palate formation problems.

The TGF-  $\beta$ s are not only involved in palate formation, they plays an important development role all over the body. They work by binding to cell surface receptors and activating signaling molecules within the cell. These signaling molecules then travel to the nucleus, the cell's control center, and prompt DNA expression in order to spur changes in the cell.

"For instance, we've learned that when someone has a haploid insufficiency and is missing one copy of the TGF- $\beta$  gene, he or she is more vulnerable to environmental insults that can cause cleft palate, such as drugs, smoking and alcohol," Chai says.

Smad4 is one of the main signaling molecules used in the TGF- $\beta$  pathway during palate and tooth development. Chai says his team had initially hypothesized that since irregularities in the TGF- $\beta$  gene or its cell surface receptors sparked palate malformation in experimental mouse models, knocking out the Smad4 genes would do the same.

"We found that if we blocked TGF- $\beta$  or the receptors, a cleft palate develops," he says, "But when Smad4 was blocked, normal palate epithelium still covered the palatal shelf.

The team found that p38 MAPK (mitogen activated protein kinase) can take Smad4's place in the pathway and signal DNA expression to form the palate. Normally serving as a stress-response protein and activated by environmental insults, such as ultraviolet radiation on skin cells, p38 MAPK appears to act as a "spare tire" when Smad4 function is compromised, Chai says. When either one or the other is inactivated, the palate epithelium will still form properly, failing to form only if both signaling molecules are knocked out.

P38 MAPK isn't a perfect replacement for Smad4 during oral development –when Smad4 is nonfunctional, teeth only partially form – but the results are still surprising for a molecule better known for its roles during cancer, Chai says.

Further study could have big implications not only on congenital oral birth defects like cleft palate but also on malformations and diseases in tissues throughout the body, and patients could one day be able to take advantage of new genetic counseling and treatment methods stemming from this information, he hopes.

For new parents this latest development offers hope for the future. Those individuals with a family risk of either cleft lip or cleft palate can seek counseling early on and identify craniofacial teams that will assist them in following the best treatment plans for their child.

In addition, the discovery opens up other opportunities for researchers and clinicians.

"This information is useful not just for palate and teeth but also for cancer and cell biology in general," he says. "Ultimately, we have to be translational in order to make ourselves useful to patients."

Source: University of Southern California

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