Proto-teeth migrate along the developing jaw

December 22 2015, by Nicholas Weiler

Smile! For the first time, researchers have captured on video how teeth find their way to the right spot in the jaw to give you that winning grin. The research, led by scientists at UC San Francisco, showed in mice that molar progenitor cells migrate to their final locations during development, rather than forming the teeth in place, as researchers had previously thought.

The findings—published online Dec. 21 in the journal *Developmental Cell*—should give developmental biologists a lot to chew on. They suggest that the progenitor cells that produce other organs could also exhibit as-yet unrecognized wanderlust, and could help explain how teeth and other organs ended up in such diverse configurations in different species over the course of evolution. The insights may even have implications for understanding how cancerous cells migrate to invade other tissues.

For decades, developmental biologists have puzzled over the question of how the genetic code instructs organs to form in the right places in the bodies of different animals. "It's a crucial part of development," said Ophir Klein, MD, PhD, Larry L. Hillblom Distinguished Professor in Craniofacial Anomalies, chair of the Divisions of Craniofacial Anomalies and Orthodontics at UCSF, and senior author of the new study. "For example, you need to get the eyes in the right part of the face. The limb positioning needs to be perfectly balanced. For each particular species, the teeth need to be at the right place in the jaw for the animal to be able to eat or to defend itself. But we knew little to nothing about how they get there, at least in mammals."

The assumption has generally been that biochemical signals mark the cardinal directions and divisions of the body like latitude and longitude on a map, and that budding organs are genetically programmed to form at the correct GPS coordinate. Teeth, for instance, which are commonly used as simple models for the development of more complex organs, were previously thought to grow in place from clusters of homogenous precursor cells expressing a gene called Fgf8.

Recently, however, results from fish and fruit flies have suggested that organ formation might be a much more dynamic process than was previously thought, with organ precursor cells being born in one location and then migrating together to their final destination.

"This gave us an intuition that tooth formation in mammals might be more complicated than what people had surmised," Klein said.

When Klein and colleagues began exploring the timeline of tooth development in mice, they noticed that the cells destined to become molars appeared to shift positions over two crucial days of embryonic development. When the team tracked these cells using video microscopy, they discovered that the tooth precursors first organized themselves into a "rosette"-like structure in the back of the mouth near the jaw's hinge, then broke up and flowed together on cue toward the correct spot to grow a tooth.

Additional experiments revealed that a distinct group of cells act as a target for the migrating tooth precursors. These target cells lead the traveling progenitor cells to the proper position in the jaw for tooth formation, using a signaling protein called Hedgehog as a molecular trail of breadcrumbs. Genetically blocking either Fgf8 or the Hedgehog-producing gene in mice prevented teeth from forming in the correct place.

Though the present research only demonstrated migration of molar precursor cells in mice, Klein speculated that developmental migration may be common to many organs across mammalian species. If so, it could help explain an evolutionary mystery: How does the positioning of teeth and other organs vary so much between species when the early progenitors of the organs are so similar? The new data suggest that evolution could easily move organs around within the body plan of a given species by shifting the locations of the guide cells that instruct the progenitors where to go.

The migrating proto-molars in the present study also display some similarities to certain invasive cancers, Klein said. Understanding the mechanisms that guide organ migration during development could potentially be used to block related processes in tumors.

Advances in video microscopy will continue to open up new avenues to explore these dynamic developmental processes, Klein said. "It turns out that if you want to understand organ migration and positioning, you need to actually watch things happen. As soon as we made these videos of the process, we suddenly saw something very different than what we had expected. It was one of these cases where you've been staring at something forever but never realized what was right in front of you."

More information: Jan Prochazka et al. Migration of Founder Epithelial Cells Drives Proper Molar Tooth Positioning and Morphogenesis, *Developmental Cell* (2015). DOI: 10.1016/j.devcel.2015.11.025

Provided by University of California, San Francisco