Stem-cell disruption induces skull deformity, study shows

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University of Rochester Medical Center scientists discovered a defect in cellular pathways that provides a new explanation for the earliest stages of abnormal skull development in newborns, known as craniosynostosis.

Mutations of the WNT and FGF signaling pathways set off a cascade of events that regulate bone formation at the stem cell level, according to the article, published May 25, 2010, in the journal *Science Signaling*.

"Our work contributes to the overall knowledge of the complex system that controls the stem cell fate," said lead author Wei Hsu, Ph.D., associate professor of Biomedical Genetics and Oncology, and an investigator in the URMC Center for Oral Biology. "More specifically, we found that when a certain type of stem cell goes awry, it leads to a new mechanism for craniosynostosis."

Abnormal head shape due to craniosynostosis affects about one in 2,500 individuals. It can restrict normal brain growth and result in neurodevelopment delays and elevated intracranial pressure. The chief cause, which is already known, is a defect in osteoblasts, the type of cells most important for the making of bone.

But until now scientists did not know about a second mechanism for craniosynostosis, a result of a disruption among the earliest forms of cells. Hsu's lab made the discovery in a study in mice, which have the same skull structure as humans.

Eight bones make up the cranium. Initially these individual plates of skull bone are separated by gaps called sutures. In humans the bone plates gradually fuse together, starting at birth and ending in people's 30s.

Two key events takes place during the first 18 months of life that are critical to the proper formation of bone. The first, called intramembranous ossification, is responsible for final development of the skull bones, jaw-bones and collarbones. The other process, called endochondral ossification, controls development of the long bones in the body.

During intramembranous ossification a type of stem cell - the mesenchymal cell - must transform into bone-forming osteoblast cells, which deposit the bone matrix. The majority of bone is made after the matrix hardens and entraps the osteoblasts.

Hsu's group discovered that the WNT and FGF signaling pathways determine the fate of the mesenchymal stem cells. And, when these pathways are altered, the mesenchymal cells change to chondrocytes and end up inducing endochondral ossification instead of intramembranous ossification. As a result of this switch, the skull sutures close prematurely.

While endochrondal ossification is essential to the development of cartilage and long bones, it has not been shown to play a role in normal skull development. Hsu's research, therefore, implies that endochondral ossification is a culprit for skull deformities.

"There have been some reports of peculiar chondrocytes present in prematurely closed sutures," Hsu said, "and based on our research it is reasonable to believe they might be there for a reason."

Alterations of the mesenchymal stem cells also have been associated with osteoarthritis, osteoporosis and osteoponia, and mutations in either the WNT or FGF pathways are often detected in skeletal disorders and cancer. Thus, additional research might shed light on the complex properties of stem cells, and how they are transformed during the disease process, Hsu said.

Provided by University of Rochester Medical Center

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