Animal model sheds light on rare genetic disorder, signaling pathway

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A team of researchers from the University of Utah and Brigham Young University has developed a mouse model of focal dermal hypoplasia, a rare human birth defect that causes serious skin abnormalities and other medical problems. This animal model not only provides insight into studying the cause of focal dermal hypoplasia (FDH), but also offers a novel way to study a signaling pathway that is crucial for embryonic development.

The findings were published July 19, 2011, online in the Proceedings of the National Academy of Sciences.

FDH is an uncommon X chromosome-linked genetic disorder characterized by distinctive skin abnormalities and a wide variety of defects affecting the eyes, teeth, fingernails, skeleton, and other body systems. The exact prevalence of FDH is not known, but about 90 percent of cases occur in females. The disorder has been associated with at least 24 different mutations in a gene called PORCN located on the X chromosome. Based on studies in cultured cells and in lower model organisms, PORCN is known to promote secretion of Wnt signaling proteins, key regulators of embryonic development.

"In addition to the integral role it plays in the development of nearly all body tissues, the Wnt signaling pathway has also been implicated in the development of diseases such as cancer and diabetes," says L. Charles Murtaugh, Ph.D., associate professor of human genetics at the University of Utah and lead author on the study. "In our research, we

mutated the mouse version of the PORCN gene to better understand its exact functions in the Wnt signaling pathway."

Murtaugh and his colleagues found evidence that PORCN is required for secretion and activity of Wnt proteins, supporting the widely held hypothesis that FDH is a disease of impaired Wnt signaling. They also found PORCN is essential for formation of the mesoderm, the layer of embryonic cells that gives rise to the connective tissues of the body, as well as the linings of several body cavities and the protective layers of most of the internal organs.

Human geneticists have observed that FDH can be passed from mothers to daughters but not sons.

"Females with FDH have two X-chromosomes, one normal and one mutant. Males only have one X-chromosome, and our work suggests that if they get the mutant chromosome, they would die at very early embryonic stages due to a lack of mesoderm," Murtaugh says. "Females survive to birth, because of their normal copy of the PORCN gene, and present with the disease when born. This is true in our mice as well, as we observed that female mice with mutant PORCN displayed skin and limb abnormalities, which varied widely in severity and closely resembled human FDH."

The hallmark of human FDH is thin or absent patches of the inner layer of the skin, or dermis, which develops from mesodermal cells immediately underneath the embryonic skin, or ectoderm. When Murtaugh and his colleagues selectively deleted PORCN from the ectoderm, they found abnormal development of the underlying dermis, suggesting that ectoderm cells require PORCN to send Wnt signals that promote dermis development.

Along with defects of the dermis, human FDH is commonly associated

with defects in the hair, teeth, and nails. Murtaugh and his colleagues found evidence that these and other defects also reflect the function of PORCN in the ectoderm.

"Our development of a PORCN mutant in the mouse gives us a unique genetic tool for studying the precise roles of PORCN in the Wnt signaling pathway and in specific body tissues," says Murtaugh. "In addition to giving us an animal model to study FDH, this PORCN mutant will also be useful for studying cancer and other aspects of development biology that involve Wnt signaling."

Provided by University of Utah Health Sciences

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