Researchers gain insights into severe form of dwarfism

September 3 2014

A better understanding of the pathology of a severe form of dwarfism as well as a possible window of treatment have been discovered by researchers at The University of Texas Health Science Center at Houston (UTHealth).

The preclinical research was published in a recent issue of the *Journal of Bone and Mineral Research*.

Pseudoachondroplasia (PSACH) is a disorder that affects the cells in the growth plate, resulting in dwarfism, limb deformities, joint pain and early onset osteoarthritis. Children with PSACH show no signs of it at birth. Slowing of the long bone growth begins around age 2 and the cellular damage becomes extensive by age 4. The disorder is caused by mutations in the cartilage oligomeric matrix protein (COMP) that is situated near cells known as chondrocytes, which play a key role in bone formation.

"By the time patients are in their late 20s, many have had both knees and hips replaced. They have severe joint pain and their mobility is very restricted," said first author Karen Posey, Ph.D., assistant professor of pediatrics at the UTHealth Medical School.

Previous studies of PSACH have been limited, relying on cultured PSACH cells or samples taken from human biopsies, and have not led to the development of feasible treatment options. Researchers recognized that they need a better method to study the disorder, which affects

approximately 1 in 30,000 people.

"We generated a mouse with the human COMP gene that contains the most common mutation causing PSACH. Similar to how the disease manifests in humans, these genetically engineered mice appear normal at birth, but later show symptoms of PSACH, giving us a unique opportunity to potentially pinpoint when changes occur and when treatment may be most effective," Posey said.

The research team examined the mice at different stages of development to track the disorder's progression. They found that about two weeks after birth (which equates to about four years in humans), a large number of chondrocyte cells have died and symptoms worsen. They also found inflammation in the growth plate and cartilage of the joints, suggesting the beginning of osteoarthritis.

To determine if there was a way to reduce the effects of the disorder at its earliest stages, the researchers administered three different medications—lithium, phenylbutyric acid and valproate. They found that the drugs successfully lessened the damage to chondrocyte cells in the growth plate, but each drug resulted in significant side effects. Nevertheless, the results were promising.

"Although these drugs in particular are not viable treatment options, our findings do provide a foundation for the development of a therapy that would reduce inflammation in the growth plate chondrocytes," Posey said. "We also identified an optimal treatment window—starting around age 2, when most of the cells in the growth plates are still viable and widespread cell death has not yet occurred. Once growth plate chondrocytes have been depleted, generally around age 4, treatments likely would have little effect." Posey said they are now studying other medications.

This work builds on previous research by the paper's senior author Jacqueline T. Hecht, Ph.D., associate dean of research for the UTHealth School of Dentistry, professor and director of the Pediatric Research Center and vice chair for research in the Department of Pediatrics at the UTHealth Medical School. She also serves on the faculty of The University of Texas Graduate School for Biomedical Sciences at Houston. A team led by Hecht discovered the defective COMP gene in 1995.

Provided by University of Texas Health Science Center at Houston