SOUTHWESTERN NEWS

Media Contact: Amanda Siegfried
214-648-3404
amanda.siegfried@utsouthwestern.edu

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Researchers discover molecular timekeeper in bone development

DALLAS – Nov. 11, 2004 – Researchers at UT Southwestern Medical Center at Dallas have discovered a protein that controls an early and significant step in the exquisitely timed process of bone formation.

Dr. Eric Olson, chairman of molecular biology, and colleagues have shown the protein HDAC4 to be essential for proper bone development, or osteogenesis. Their findings, reported in the November issue of the journal *Cell* and available online, may have widespread implications for understanding and preventing osteoporosis or other bone disorders, said Dr. Olson, senior author of the study.

"This was a very unexpected discovery. We were studying the role of the *HDAC4* gene in the control of heart growth. When we created genetically modified mice lacking the *HDAC4* gene, we found that they had excess bone and died because their cartilage was converted into bone," said Dr. Olson, who directs the Nancy B. and Jake L. Hamon Center for Basic Research in Cancer and the Nearburg Family Center for Basic Research in Pediatric Oncology.

The process of bone formation occurs in three stages, orchestrated by specialized bone cells that secrete and absorb materials as needed. First, a soft cartilage-based foundation is laid, upon which mature bone will solidify. Then, minerals containing calcium and phosphate are deposited throughout the foundation, creating a framework for the bone. Finally, this raw material is sculpted and hardened into bone. Missteps in this process can result in developmental defects and bone diseases.

HDAC4 belongs to a family of enzymes that inactivate genes. Unlike other members of this family which are found in numerous tissues, HDAC4 is expressed in only a few tissues, including bone.

Dr. Olson and colleagues studied mice lacking the *HDAC4* gene. At birth these animals had misshapen skulls and spines, and as they got older, failed to thrive.

Backtracking through the bone-formation process, they discovered that the defect was in the earliest steps, where the cartilage foundation was being laid and filled with minerals. Before the foundation was complete, minerals were being deposited too soon, allowing bone to harden before it was ready.

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Biochemical tests revealed that HDAC4 controls the early timing of osteogenesis by preventing the final step, bone hardening from occurring. By specifically blocking a protein called Runx2, which controls the genes for bone hardening, HDAC4 allows the foundation and minerals to be properly laid before hardening can occur.

Dr. Olson said he believes that calcium, which is required for healthy bones, may signal the release of HDAC4 from Runx2 to initiate the bone-hardening program.

"The discovery that bone formation is controlled by HDAC4, an enzyme, raises possibilities for designing drugs to control this process in the settings of bone diseases, such as osteoporosis," he said. "In fact, HDAC inhibitors are currently being used for the treatment of certain cancers. It will be interesting to investigate whether these inhibitors influence the process of bone formation."

Other UT Southwestern contributors to this study include Dr. Rick Vega, former postdoctoral researcher and lead author; Dr. James Richardson, professor of pathology and molecular biology; Dr. John Shelton, research scientist in internal medicine; Dr. Ana Barbosa, postdoctoral researcher in molecular biology; Dr. Junyoung Oh, former postdoctoral researcher in molecular biology; Eric Meadows and John McAnally, research technicians in molecular biology; Chris Pomajzl, former senior histology technician in pathology; and collaborators at Baylor College of Medicine.

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