Study confirms location of stem cells near cartilage-rich regions in bones

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Working with mice, a team of researchers has pinpointed the location of bone generating stem cells in the spine, at the ends of shins, and in other bones. The team also has identified factors that control the stem cells' growth. The research was conducted at the National Institutes of Health and other institutions.

"Identifying the location of bone stem cells and some of the genetic triggers that control their growth is an important step forward," said Alan E. Guttmacher, M.D., acting director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the NIH institute where much of the research took place. "Now, researchers can explore ways to harness these cells so that ultimately they might be used to repair damaged or malformed bone. Also, studies of this stem cell population could yield insight into the formation of bone tumors."

Researchers have long known that stem cells from bone marrow give rise to bone cells and to red and white blood cells. The current study is the first to identify the location of bone stem cells in the adult mouse skeleton. The researchers refer to the newly identified cells as bone stromal cells. "Stroma" is a term used to describe a supportive or connective structure in biological tissue. The term distinguishes the cells from hematopoietic stem cells, which give rise to blood cells, and which are found in bone marrow.

The findings appear online in the Proceedings of the National Academy

of Sciences. The study's first author was NICHD predoctoral fellow Kit Man Tsang, a graduate student of the Chinese University of Hong Kong, who is completing her doctoral thesis as part of an NICHD graduate partnership program. Tsang's thesis advisor and the senior author of the study was Constantine A. Stratakis, M.D., D.Sc., acting director of the NICHD Division of Intramural Research. Other authors of the study were from the NICHD; the NIH's Division of Veterinary Resources and the National Institute of Dental and Craniofacial Research; as well as the Johns Hopkins University School of Medicine and The Ohio State University.

The researchers undertook the study to learn more about the role of two genes, dubbed Prkar1a and prkaca, in a key chemical sequence that provides energy to cells. Prkar1a has been implicated in a variety of rare human cancers, of the bone, nervous system, and thyroid. When the two genes are working normally, bone cell growth proceeds normally and cancerous overgrowth is kept in check. In previous research, the researchers learned that tumors formed in numerous tissues when they inactivated prkar1a.

In the current study, they inactivated one copy each of the two genes. Like human beings, mice have two copies of most genes. The mice in the study had one functioning copy each of prkar1a and prkaca and one non-functioning copy of each gene.

The researchers predicted that disabling only one copy of each gene would offer protection from bone tumor growth. In fact, the combination had the opposite effect. Tumorous growths were unexpectedly prolific and developed much earlier than expected: Tumors appeared in mice as young as 3 months old, compared with 6 to 9 months old in the previous studies, in which only prkar1a had been inactivated. Moreover, abnormal growths formed near cartilage in the legs, along the tail, and the remaining vertebrae of the mice.

The bone tumors were also more extensive in the mice with the two inactivated genes compared with their counterparts having only a single inactivated gene. All mice with the two mutations had abnormal growths on their tail bones by the time they were 9 months old and showed abnormalities in their vertebrae by 12 months.

Examination of the tumor cells and of cells from the same locations in mice that did not have tumors confirmed that the cells were bone stem (stromal) cells. Specifically, proteins on the surface of the cells were identical to proteins found on other types of stem cells. Moreover, the tumors formed only at locations where bone is actively growing, even in the adult mouse skeleton.

"We didn't notice abnormal growth in the skull, for example," said Dr. Stratakis.

The findings open up two avenues for additional research. Studies to identify the chemical signals that initiate the formation of new bone tissue could lead to new techniques for regenerating damaged or injured bone. Similarly, studies of the chemical events that trigger the initial stages of tumor formation may lead to ways to prevent or treat bone tumors.

More information: General information about stem cells is available on the NIH Web site.

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