Genes behind rapid deer antler growth, hardening identified

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Each spring, male deer sprout a new pair of antlers, which are essentially temporary external bones, at a speed unparalleled by the bone growth of other mammals. Now, research led by scientists at the Stanford University School of Medicine has identified two genes that drive the

animals' abnormally quick bone generation.

Although the research is still in its early stages, the scientists hope the findings could one day inform more efficient and effective therapies for bone diseases and fractures in humans.

"Right now, we have two focuses: To understand the genetic regulation of deer antler growth, and to see if we can use this information to build therapeutic agents to potentially prevent or treat bone diseases such as osteoporosis, or more quickly repair bone fractures," said Peter Yang, Ph.D., associate professor of orthopedic surgery.

Antlers are essentially regenerating bone, which is rare in the animal kingdom. During the spring, antlers begin to sprout; by winter, they start to shed.

"Knowing the genetics behind antler regeneration, fast bone growth and mineralization is fundamental to our ultimate therapeutic goal and is critical to understanding rapid bone regeneration in other species, like humans," Yang said.

The genes Yang and his collaborators identified are uhrf1, which supports rapid bone cell proliferation, and s100a10, which supports rapid mineralization, or the hardening of bone tissue. Together, the genes work in a one-two punch fashion, with uhrf1 spurring bone cell generation and s100a10 working to cement the bone's structural matrix.

What lends even more transformative potential to Yang's research is that both uhrf1 and s100a10 are linked to bone development in humans.

A paper detailing the researchers' findings will be published online Oct. 30 in the *Journal of Stem Cell Research and Therapy*. Yang is the senior author. Postdoctoral scholar Dai Fei Elmer Ker, Ph.D., is the lead

author.

Going stag

As an orthopedic researcher, Yang never planned to pursue deer antler genetics. But while on vacation in Alaska in 2009, Yang's tour guide rattled off some fun facts about wild deer, and it piqued his curiosity.

"Deer antlers can grow a whopping 2 centimeters per day when it's summertime and their antlers are growing at full speed," Yang recalled from the guide's spiel. "It made me wonder: Are there special genes that are behind this unusually fast bone growth?"

To investigate, Yang and his lab traveled to a deer farm in California where they collected samples of early antler tissue, which is primarily made up of skeletal stem cells. Antlers grow from the top down; so as they grow upward, a reservoir of stem cells remains at the top of the antlers, continuing to proliferate. In early development, antler tissue is soft, much like the cartilage of your nose, making cell sampling an easy task for Yang and harmless for the buck. Only in the second stage of development does the antler mineralize and become rigid.

Back in the lab, the scientists used a variety of techniques to decipher the genetics behind antler growth, including analyses of RNA, a molecule that help carry out specific gene instructions, and gene "knock-down" and "over-expression" studies, which hinder gene function or rev it up, respectively. Comparative RNA analyses between stem cells in deer antlers and human stem cells from bone marrow led Yang to a collection of genes that seemed to have a unique expression in antlers. From that pool, he narrowed the search by tampering with gene function, watching to see how different levels of gene expression affected tissue growth in mouse cells.

In mouse cells, Yang saw that when the uhrf1 gene was decommissioned, the bone tissue could still grow, just not as quickly; only when uhrf1 was fully functional did the scientists see the rapid cell proliferation characteristic of antler growth. Likewise, when s100a10 was overexpressed, calcium deposits increased and the engineered cells more rapidly mineralized.

"Antler regeneration is a unique phenomenon that, to me, is worth studying just out of pure curiosity, but lo and behold, it may have some really interesting applications for human health," Yang said.

Applying antler genetics to humans

The researchers hope that their insights into antler genes might inform new approaches for treating diseases like osteoporosis. In healthy bones, two types of cells—osteoblasts and osteoclasts—work as opposing forces. Osteoblasts produce new bone tissue, while osteoclasts break down old bone. The two cell types work in a yin and yang style to continuously form and degrade bone to maintain balanced bone structure. In osteoporosis, osteoclast function overtakes osteoblasts, and the bone starts to break down.

"We're just at the beginning of this research, but our ultimate goal is to figure out how we can apply the same underlying biology that allows for rapid bone regeneration in deer antlers to help treat human bone conditions, such as osteoporosis," Yang said.

Yang plans to continue researching multiple kinds of deer to confirm that uhrf1 and s100a10 back speedy antler growth across species. In addition, he plans to test how the genes function in human cell lines, while continuing to parse how uhrf1 and s100a10 work on a molecular level, looking into possible functional pathways.

"There's a lot of work to be done, but this could be a unique model of bone regeneration, and our initial work here has started to lay a foundation for future studies," Yang said.

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