Researchers uncover a pathway that stimulates bone growth

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(Medical Xpress)—Researchers from the University of Pennsylvania School of Veterinary Medicine have discovered that a protein called Jagged-1 stimulates human stem cells to differentiate into bone-producing cells. This protein could help both human and animal patients heal from bone fractures faster and may form the basis of treatments for a rare metabolic condition called Alagille syndrome.

The study, published in the journal Stem Cells, was authored by three members of Penn Vet's departments of Clinical Studies-New Bolton Center and Animal Biology: postdoctoral researchers Fengchang Zhu and Mariya T. Sweetwyne and associate professor Kurt Hankenson, who also holds the Dean W. Richardson Chair in Equine Disease Research.

Last November, on the promise of these and other findings, Hankenson and his former doctoral student Mike Dishowitz launched a company, Skelegen, through Penn's Center for Technology Transfer UPstart program. Skelegen's focus is to continue to develop and improve a system for delivering Jagged-1 to sites that require new bone growth, in the hope of eventually treating bone fractures and other skeletal problems. Penn, through the CTT, has submitted a provisional patent application to protect the inventions of Hankenson and his colleagues.

Although human bones seem static and permanent, bone tissue actually forms and reforms throughout our lives. Cells called osteoblasts form bone and are derived from precursor cells known as mesenchymal stem cells, which are stored in bone marrow. These stem cells must receive

specific signals from the body in order to become osteoblasts.

Prior research had identified a molecule called bone morphogenic protein, or BMP, as one of these proteins that drives stem cells to become bone-forming cells. As a result, BMP has been used clinically to help patients healing from broken bones or to perform spinal fusions without relying on patients' own bone tissue.

"But it has become clear that BMPs have some issues with safety and efficacy," Hankenson said. "In the field we're always searching for new ways for progenitor cells to become osteoblasts so we became interested in the Notch signaling pathway."

This molecular signaling pathway is found in most animal species and is known to play a role in stem cell differentiation. The researchers chose to investigate one of the proteins that acts in this pathway by binding to the Notch receptor, Jagged-1. The Penn Vet team has previously shown that Jagged-1 is highly expressed in bone-forming cells during fracture healing and that introducing Jagged-1 to mouse stem cells blocked the progression of stem cells to osteoblasts.

"That had been our operating dogma for a year or two," Hankenson said.

Next the researchers decided to see what happened when Jagged-1 was introduced to human stem cells. There they came upon a very different result.

"It was remarkable to find that just putting the cells onto the Jagged-1 ligand seemed sufficient for driving the formation of bone-producing cells," he said.

This finding aligns with other evidence linking Jagged-1 to bone formation. Patients with a rare disease known as Alagille syndrome

frequently have mutations in the gene that codes for Jagged-1. Individuals with this condition have problems with their metabolism that severely affect their livers but also tend to have challenges with their skeletal system and break bones easily.

Furthermore, genome-wide association studies, which search large populations for mutations that may be linked with particular characteristics, have found a connection between mutations near the Jagged-1 gene and low bone mass.

Hankenson has multiple collaborations with other researchers at Penn to further investigate how manipulating the Jagged-1 protein may one day help patients. He is working with Kathleen Loomes of Penn's Perelman School of Medicine and the Children's Hospital of Pennsylvania to study pediatric patients with Alagille syndrome to find out whether their bone abnormalities are indeed connected to Jagged-1 malfunctions.

And in addition to partnering with Dishowitz to develop the technology to deliver Jagged-1 to bone repair sites, Hankenson is also collaborating with Jason Burdick in Penn's School of Engineering and Applied Science and Jaimo Ahn and Samir Mehta of Penn Medicine to improve and implement this system.

Provided by University of Pennsylvania