Hormone promises to keep joint injuries from causing long-term osteoarthritis

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An existing osteoporosis drug is the first ever found to prevent cartilage loss from osteoarthritis following injury to a joint, and may also regenerate some cartilage that has been lost to osteoarthritis, according to an early study presented today at the annual meeting of the American Society for Bone and Mineral Research in Denver. While the study was in mice, the model closely mimics human osteoarthritis that develops following knee injuries, according to the study authors.

Cartilage can become damaged by many kinds of injury and by mechanical stresses that come with age. Over time, damaged cartilage deteriorates to cause osteoarthritis (OA), with its attendant joint inflammation and pain. Currently available drugs like steroids or non-steroidal anti-inflammatory agents (e.g. Advil, Aleve) reduce pain but do not address the loss of cartilage behind the osteoarthritis, which is projected to afflict more than 50 million Americans by 2020.

Cartilage forms the sponge-like, shock-absorbing layers that keep the impact of running and jumping and lifting from grinding bones against each other in joints. The cell type at the heart of osteoarthritis is the chondrocyte, the cartilage-producing cell responsible for maintaining the integrity of joint cartilage.

Outside of joints, chondrocytes undergo a normal maturation process that helps to form bone as part of fracture healing and bone growth in children. Disease processes and injury, however, cause chondrocytes in joint surface cartilage to become like those that help to heal bone

elsewhere, but in a place where bone is not supposed to form. This mistaken maturation contributes to the gradual destruction of the joint seen in osteoarthritis.

Parathyroid hormone (PTH), known as teriparatide in drug form, has emerged as a major player in the maintenance and healing of bone, and the race is on to design new applications for it. Past studies have established that PTH prevents chondrocytes from undergoing maturation, and stimulates their proliferation, preserving larger pools of cartilage cells in the joint. Signaling molecules like PTH have their effect in the body by interacting with specifically shaped proteins on the cell surfaces called receptors. PTH docks into its receptors, like a ship coming into port, which changes the shape of the dock such that biochemical signals are sent.

The authors of the current study observed that chondrocytes within injured and degenerating cartilage have more PTH type 1 receptors on their surfaces. This makes them especially sensitive to the PTH signal that prevents harmful chondrocyte maturation into bone in the joint cartilage. Thus, PTH therapy should increase the cartilage supply exactly where cartilage loss is causing disease.

"Right now physicians have no way to bring back cartilage in patients who have lost it to osteoarthritis," said Randy Rosier, M.D., Ph.D., professor within the Department of Orthopaedics and Rehabilitation at the University of Rochester Medical Center. "Our current results, at least in mice, show that we can inhibit cartilage degeneration and improve the volume of cartilage in diseased joints. It's remarkable enough that this compound delays the loss of cartilage, but these results show it also may be able to restore, at least to some extent, cartilage in already degraded joint surfaces."

Researchers examined the impact of a daily dose of

Forteo®/teriparatide, manufactured by Eli Lilly, and a generic version of teriparatide made by Sigma on the progress of OA following injury in study mice.

Experiments established a five-fold increase in PTH type 1 receptor expression in the articular cartilage of mice with injury-related osteoarthritis when compared to healthy cartilage. Injury triggers genetic mechanisms in an attempt to begin repairs, a repair response that may be responsible for the increase in PTH receptor in the joint. This in turn makes damaged cartilage particularly responsive to PTH.

In the current study, one group of mice with cartilage and ligament injuries was randomized to receive either saline as a control, Forteo® or generic PTH daily for 12 weeks. A second group of mice with joint injuries did not receive treatment until 8 weeks after injury. The delay was an attempt to determine the effect of treatment once the osteoarthritic process was already underway and some cartilage lost, a scenario that more closely mimics clinical reality. Patients do not visit their physician after an injury asking the doctor to prevent the onset of osteoarthritis 10 years in the future, Rosier said. They come in when an old injury and time have combined to degrade cartilage to the point where function is lost and pain felt.

Studies revealed that after 12 weeks of Forteo®- or generic PTH treatment, there was approximately 27 percent more joint cartilage compared to saline-treated mice. Strikingly, delayed teriparatide treatment was even more effective in improving the amount of cartilage, with up to 35 percent more cartilage in Forteo®- and PTH-treated groups than in the saline group, suggesting an ability to regenerate at least some of the lost cartilage.

With a new use patent application in place, the team will next seek to confirm the durability of the effect in further animal studies, and

prepare to seek funding from the National Institutes of Health to begin pilot clinical studies of PTH treatment of osteoarthritis in humans, possibly in the later half of 2010.

Along with Rosier, the study was led by Erik Sampson, Todd O'Brien, Di Chen, Susan Bukata, J. Edward Puzas, Regis O'Keefe and Michael Zuscik within the Department of Orthopaedics and by Hani Awad in the Department of Biomedical Engineering at the University of Rochester Medical Center. The study was funded by the National Institutes of Health.

"These pre-clinical findings provide strong proof-of-concept support for the potential use of teriparatide to slow joint cartilage degeneration in OA patients, and perhaps even reverse it," Rosier said. "In the near future, we hope this serves as the foundation of new treatments that restore function to long injured joints, perhaps staving off joint replacement surgeries for some years."

Source: University of Rochester Medical Center (news : web)

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