Protein may alter inevitability of osteoarthritis

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Few things in life are inevitable – death, taxes, and, if you live long enough, osteoarthritis. No treatment will stop or significantly slow the disease, and joint replacement is the only definitive treatment. That may change, however, as researchers such as Dr. Brendan Lee, professor of molecular and human genetics at Baylor College of Medicine, and his colleagues unravel the effects of a naturally occurring protein called lubricin or Proteoglycans 4 that appears to protect against the age as well as post-injury related changes. A report on their research appears online in the journal *Science Translational Medicine*.

"This protein also affects the metabolism of the cartilage and does it in a way that prevents its breakdown," said Lee, who is also director of the Rolanette and Berdon Lawrence Bone Disease Program of Texas and a Howard Hughes Medical Institute Investigator. "This is not just lubrication of the joints."

Osteoarthritis is common, affects more than 70 percent of the population between the ages of 55 and 77, and its prevalence is increasing worldwide. In most cases, treatment addresses only the symptoms. If the disease gets severe enough, surgeons replace the affected joint.

"In spite of a lot of investment, there is no disease-modifying treatment that affects the course of the disease," said Lee.

Studying osteoarthritis is difficult. Only after graduate student Merry Z.C. Ruan, in Lee's laboratory, developed a special imaging technique

called phase contrast ultra-high resolution micro-computed tomography (micro-CT) that allowed her, Lee and their colleagues to not only "see" the tiny cartilage in the knee joint but to also quantify that amount in the mouse joint, were they able to effectively apply the power of mouse genetics to their research.

To identify new targets for treating osteoarthritis, they focused on a genetic disease in which the disorder starts early in children—camptodactyly-arthropathy-coxa vara. These individuals are deficient in lubricin for, the protein in their joints made by special cells in the joint cartilage as well as by the cells that line part of the joint (synovial lining).

Lee asked, "If a deficiency in lubricin hastens osteoarthritis, can higher levels protect against it?"

When he and his colleagues studied mice that produced higher levels of the protein in cartilage, they found first that the animals acted and grew normally, suggesting that increased amounts of this protein was not harmful. However, mice with an injury to their knees did not develop traumatic or injury-induced osteoarthritis.

Using the specially developed microscopy technique in these mice with high levels of lubricin, Lee and his colleagues determined that the mice did not have cartilage changes usually associated with osteoarthritis.

As the mice that made extra lubricin aged, their cartilage resembled that of young mice, he said. There was no osteoarthritis suggesting that this protein may protect against the two common forms of OA- injury-related and age-related.

Eventually, Lee and Ruan tried a gene therapy on normal mice, using a specially developed virus to inject the gene into the joints of the mice.

The viral vector was an engineered adenovirus that did not cause disease but spread the gene throughout the joint.

"The lubricin protein was expressed for the life of the mouse after a single injection into the joint," said Lee. Moreover, the injection similarly protected the mouse against the development of injury-related OA.

He and his colleagues plan to test the gene therapy in large animals, such as horses, that suffer from osteoarthritis similar to in humans. If it is effective in horses, the next step would be to test it in humans.

The most immediate use would probably be to treat osteoarthritis that occurs after a sports- or work-related injury.

"How can you explain this dramatic effect?" said Lee.

Using a special "chip" or microarray panel, they found that the protein not only lubricated the joint, it also affected metabolism and prevented breakdown of cartilage in the joint.

"What else do we need to do to fix osteoarthritis?" said Lee. Sometimes, stopping the destruction is not enough. Eventually, he would like to find ways to regenerate the joint cartilage.

Lee credited Ruan with much of the work that made the findings possible.

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