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Study proves protein filament's role in cartilage strength

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Research conducted by UC Davis Health System and the Shiley Center for Orthopaedic Research and Education at Scripps Clinic shows how the protein filament vimentin provides healthy cartilage with the mechanical strength and flexibility necessary to resist stress. Published in the January 2011 issue of the *Journal of Orthopaedic Research*, the study is the first detailed look at the role of vimentin in cartilage in both healthy and osteoarthritic joints.

Prior to the current study, vimentin was one of the most poorly understood protein filaments. While it is found throughout the body, it is most abundant in chondrocytes — the cells that make up cartilage.

"We have shown for the first time that vimentin plays a big role in helping cells handle mechanical stress in cartilage," said Dominik Haudenschild, the study's lead author and an assistant professor of orthopaedic surgery at UC Davis. "This has important implications for understanding why cartilage breaks down during osteoarthritis and holds potential for developing treatments that prevent filament damage."

Osteoarthritis is the most common joint disease in the United States and is caused by the degeneration of cartilage, which typically maintains its structure due to protein filaments such as actin, tubulin and vimentin. Without a cartilage "cushion," bones rub together and cause pain, stiffness and loss of movement. Osteoarthritis becomes increasingly common as people age and is more likely to develop in overweight people or in those who have had bone or joint injuries.

In a unique series of experiments, Haudenschild embedded human cartilage cells from healthy and osteoarthritic knee joints into a gel that allowed precise measurement of changes in cellular dimensions while the cells underwent mechanical compression. In some cases, cells were first treated with a chemical that specifically caused the vimentin to breakdown, while leaving other protein filaments unaffected.

The investigations demonstrated that vimentin significantly contributes to the strength or stiffness — a measure of how well a cell keeps its shape under mechanical stress — of healthy chondrocytes. Cartilage cells that are less stiff deform more easily and may cause an entire joint to be susceptible to injury. Chondrocytes from osteoarthritic joints had weaker vimentin structures than chondrocytes from normal joints and were less affected by vimentin disruption, likely because the disease process was already under way. This indicates that potential treatments targeting vimentin disruption need to be delivered early in the course of osteoarthritis before vimentin breakdown has occurred.

Using an innovative combination of fluorescent proteins and live-cell imaging on a confocal microscope, the team also obtained some of the highest-resolution 3-D images ever produced of vimentin in chondrocytes. These images confirmed the lab results by revealing that vimentin filaments form a tight cage within normal cartilage cells, keeping individual cells stiff and stable. In chondrocytes from cartilage of patients with osteoarthritis, the vimentin structure was disrupted and less able to maintain cell structure under mechanical stress.

"Healthy vimentin appears to be critical in maintaining cartilage's vitality," said Haudenschild. "Blocking its breakdown early in the disease process or restoring its structure in osteoarthritic cells to look more like it does in healthy cells could be promising avenues of treatment."

Haudenschild, who joined the UC Davis faculty in 2008, conducted the

research for "Vimentin Contributes to Changes in Chondrocyte Stiffness in Osteoarthritis" at UC Davis and while at the Shiley Center and the Scripps Research Institute. Other authors were Jianfen Chen, Nina Pang, Nikolai Steklov, Shawn P. Grogan, Martin K. Lotz and Darryl D. D'Lima of the Scripps Clinic and the Scripps Research Institute.

Haudenschild's UC Davis laboratory group and the Scripps team are continuing their collaboration on defining the role of vimentin in arthritis and aging. The UC Davis scientists are looking at biochemical aspects, while Scripps researchers are using computer modeling techniques to complement the investigations.

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