innovations report

Novel Approach to Treating Osteoarthritis Uses Engineered Proteins and Molecules to Halt Cartilage Degradation

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Researchers from Florida Atlantic University and the Kennedy Institute for Rheumatology in the UK are developing and evaluating a novel approach for osteoarthritis (OA) treatment by employing engineered proteins and other molecules that specifically block the enzymes responsible for degrading cartilage in OA. They have been able to unveil the mechanism of inhibitory proteins, and their recent studies suggest that highly selective inhibitors are essential for therapeutic development for the treatment of OA.

Anzeige

Florida Atlantic University researcher Dr. Keith Brew, Schmidt Senior Fellow and Distinguished Professor in the Charles E. Schmidt College of Biomedical Science, has received a five-year renewal grant for $2.6 million from the National Institutes of Health for a project aimed at developing and evaluating a novel approach for osteoarthritis (OA) treatment by employing engineered proteins and other molecules that specifically block the enzymes responsible for degrading cartilage in OA.

Brew's collaborators on the project include Dr. Hideaki Nagase, a scientist at the Kennedy Institute for Rheumatology in London in the United Kingdom. Using rodent models of the disease and human tissues derived from joint replacement surgery, the researchers will investigate the mechanisms through which these enzymes act and assess their effectiveness.

OA is the most prevalent form of arthritis and afflicts approximately 21 million people in the United States over the age of 25. OA can affect any joint in the body, though it most commonly affects joints in the hands, hips, knees and spines. The hallmark of the disease is a breakdown and eventual loss of the cartilage in one or more joints. Cartilage is a type of connective tissue formed from proteins and other molecules that serves as a cushion between the bones of the joints.

The key enzymes involved in OA include metalloproteinases, a group of zinc-containing enzymes that can break down proteins, such as collagen, that are structural components of cartilage. Metalloproteinases are normally found in the spaces between cells in tissues and are important in many normal biological processes including embryo implantation and wound healing, as well as pathological processes such as inflammation and cancer. They are also involved in the breakdown and remodeling of tissues and organs, and production of regulatory proteins.

"There are currently no effective treatments for osteoarthritis except for joint replacement surgery," said Brew. "Increasing our knowledge of the structures and molecular mechanisms of these key enzymes and finding ways to specifically inhibit these proteinases may provide new opportunities for the development of therapeutics and treatments to prevent the joint destruction seen in osteoarthritis."

Brew and Nagase initially set out to investigate the structure and function of the tissue inhibitors of metalloproteinases (TIMPs), naturally occurring metalloproteinase inhibitory proteins. They were able to unveil the mechanism of inhibition thereby allowing them to engineer TIMPs to make them selectively inhibit specific metalloproteinases. Their recent studies with TIMPs suggest that highly selective inhibitors are essential for therapeutic development for the treatment of OA.

"The first step in the next phase of our research is to understand the molecular basis for selectivity in our TIMP-3 variants using biochemical, biophysical and structural methods, and to use this

information to further develop highly discriminating inhibitors of metalloproteinases," said Brew. The second part of their research will entail the evaluation of the efficacy of available and newly developed metalloproteinase inhibitors using in vitro and in vivo models of OA. They expect to validate target enzymes in human OA using these inhibitors and to further investigate which metalloproteinases are key targets for blocking the progression of OA in humans.

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Florida Atlantic University opened its doors in 1964 as the fifth public university in Florida. Today, the University serves more than 26,000 undergraduate and graduate students on seven campuses strategically located along 150 miles of Florida's southeastern coastline. Building on its rich tradition as a teaching university, with a world-class faculty, FAU hosts ten colleges: College of Architecture, Urban & Public Affairs, Dorothy F. Schmidt College of Arts & Letters, the Charles E. Schmidt College of Biomedical Science, the Barry Kaye College of Business, the College of Education, the College of Engineering & Computer Science, the Harriet L. Wilkes Honors College, the Graduate College, the Christine E. Lynn College of Nursing and the Charles E. Schmidt College of Science.

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