Enzyme research opens doors to developing new inhibitors for arthritis

September 28 2016

Biologists at The University of Texas at Arlington have demonstrated that removing water molecules can deactivate caspase-3 enzymes, which opens new doors for treatment of autoimmune diseases like arthritis, which have been linked to overactive enzymes.

Caspase enzymes have important functions in cell development and cell death. Imbalances in this enzyme's activity can cause too many cells to be killed and not enough to be made, which is the case for arthritis and diabetes. Currently, the activity level required for cell death is undefined, which means that regulating these enzymes continues to be an issue for health professionals.

To facilitate research on the link between enzyme activity and cell development and cell death, the UTA researchers developed a database of caspase-3 mutations that demonstrate different levels of activity, and focused in on the enzyme's reactions with water molecules within the cell.

"Our analysis of water molecules in the database, combined with structural and dynamic studies, showed that removing water molecules deactivates the enzyme," said Clay Clark, UTA chair of biology and leader of the study.

"Genome-editing tools, combined with the database, should provide tools to fine-tune caspase-3 activity and allow us to develop new types of inhibitors for autoimmune diseases," he added.

The research was published this week in The *Proceedings of the National Academy of Sciences* as "Tunable allosteric library of caspase-3 identifies coupling between conserved water molecules and conformational selection." Clark was joined in this research by UTA's Joseph Maciag and Paul Swartz, Joshua Schipper, Matthew Tucker and Sarah Mackenzie from the Department of Molecular and Structural Biochemistry and the Center for Comparative Medicine and Translational Research at North Carolina State University.

The research provides a database of caspase-3 variants with nearly four different orders of magnitude change in activity, which will be far more effective for examining caspase-3 signaling than the current method known as "knockdown" or "knockout strategies." "Knockdown" involves the complete inhibition of the enzyme and cannot explain different levels of activity.

The study also suggests that inhibitors that remove water molecules from the protein chains could effectively fine-tune caspase-3 activity by shifting the enzyme to an inactive state.

"This method is applicable to all enzymes and could open up new possibilities for the sufferers of other diseases like cancer, through research that establishes the correct levels of enzyme activity to activate signaling processes that provoke the death of cancer cells," Clark said.

Morteza Khaledi, dean of UTA's College of Science, congratulated the researchers on this important advancement, which forms part of the university's increasing focus on health and the human condition within the Strategic Plan 2020: Bold Solutions|Global Impact.

"Dr. Clark is a recognized leader in research on the potential therapeutic role of enzymes," Khaledi said. "This high-level interdisciplinary research, between biophysics and biochemistry, is exactly the type of

work that enables real discoveries and advances in science."

Clay Clark came to UTA in 2015 from North Carolina State University, where he led the biochemistry department. His lab studies protein design as well as cancer, neurodegenerative and auto-immune diseases. He has received continuous funding from sources such as the National Institutes for Health and the American Diabetes Association, among others.

More information: Tunable allosteric library of caspase-3 identifies coupling between conserved water molecules and conformational selection, Joseph J. Maciag, DOI: 10.1073/pnas.1603549113 , www.pnas.org/content/early/201 … /1603549113.abstract

Provided by University of Texas at Arlington