First detailed look at crucial enzyme advances cancer research

29 March 2021, by Richard Harth

Petra Fromme is the director of the Biodesign Center for Applied Structural Discovery. She is also a Regents Professor at ASU's School of Molecular Sciences. Credit: The Biodesign Institute at Arizona State University

In order to develop more effective drugs against a range of cancers, researchers have been investigating the molecular structure of many diseased-linked enzymes in the body. An intriguing case in point is Taspase 1, a type of enzyme known as a protease. The primary duty of proteases is to break down proteins into smaller peptide snippets or single amino acids.

Taspase 1 appears to play a vital role in a range of physiological processes, including cell metabolism, proliferation, migration and termination. The normal functioning of Taspase 1 can go awry however, leading to a range of diseases, including leukemia, colon and breast cancers, as well as glioblastoma, a particularly lethal and incurable malignancy in the brain.

Because Taspase 1 dysregulation is increasingly implicated in the genesis and metastasis of various cancers, it has become an attractive candidate for drug development. But before this can happen, researchers will need a highly detailed blueprint of the structure of this protease.

In a new study appearing in the Cell Press journal *Structure*, researchers from Arizona State University describe their investigations, which reveal the structure of Taspase 1 as never before.

The study unveils, for the first time, the catalytically active 3-D structure of Taspase 1, revealing a previously unexplored region that is essential for the functioning of the molecule. The structure was solved using X-ray crystallography and confirmed with electron microscopy.

Petra Fromme, director of the Biodesign Center for Applied Structural Discovery, highlights the great importance of the work: "I am so excited that we were able to solve the first structure of the functional active enzyme, as it will have huge implications for the structure-based development on novel anti-cancer drugs."

The study results show that reducing this critical helical region of Taspase 1 limits protease activity, while eliminating the helical region deactivates Taspase 1 functioning altogether. Earlier research suggests that disabling Taspase 1 activity to block the progression of cancer could be achieved without harmful side-effects.

"We have reported the importance of a previously unobserved long fragment of the protein in the catalytic activity of Taspase1, which can be used as attractive target to inhibit Taspase1," according Jose Martin-Garcia, lead scientist on the project and co-correponding author with professor Fromme. "The crystal structure of the active Taspase1 reported in our article will be greatly beneficial to advance the design of Taspase1 inhibitors for anti-cancer therapy."

More information: Nirupa Nagaratnam et al.

Structural insights into the function of the catalytically active human Taspase1 *Structure* March 29, 2021DOI:doi.org/10.1016/j.str.2021.03.008

Provided by Arizona State University