First detailed look at crucial enzyme advances cancer research

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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

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