3-D protein structure reveals a new mechanism for future anti-cancer drugs

February 15 2019

Credit: CC0 Public Domain

A research team at the Medical University of South Carolina (MUSC) has discovered a new mechanism for a class of anti-cancer drugs known as E1 inhibitors.

Their findings, published in *Nature Communications* on December 4, 2018, reveal a novel binding site that will promote drug design of more efficient E1 inhibitors.

The team was led by Shaun Olsen, Ph.D., an assistant professor of Biology and Molecular Biology at MUSC and a member of the Developmental Cancer Therapeutics Program at Hollings Cancer Center.

Olsen has dedicated his career to solving 3-D structures of proteins. Olsen and his team use these protein structures to model interactions with other molecules, including potential new drugs.

In the article, Olsen and his team report that they have discovered a new site on a protein, SUMO E1, which is a target for E1 inhibitors. The new binding site is located in the center of the protein and was previously thought to be out of reach. Olsen's team discovered an alternative conformation of the protein that exposes the site and allows a new inhibitor (COH000; City of Hope, Duarte, CA) to bind.

"We identified a druggable site on this enzyme that was previously unknown," says Olsen. "The new inhibitor binding site is completely inaccessible in all previous structures, which is pretty remarkable. E1 structures have been solved before, and this site is hidden in all of them."

E1 inhibitors target the ubiquitin proteasome system (UPS). If you think of a cell as a protein-producing factory, the UPS is the quality control center. The system is responsible for making sure proteins are 'up-to-code' and able to perform their jobs. The UPS helps maintain healthy proteins within the cell; however, when it malfunctions, diseases such as cancer can occur.

There are numerous drugs, both on the market and in clinical trials, that target different parts of the UPS. Proteasome inhibitors, for example, are commonly used to treat multiple myeloma.

Based on preclinical studies, E1 inhibitors show potential as antitumor agents, but there have been obstacles to getting them into the clinic.

"When you develop a drug, you want it to be highly specific for your protein of interest with no cross-reactivity with other targets or proteins, because that can cause negative side effects," Olsen explains.

It has been difficult to develop E1 inhibitors with specificity for the target of interest. COH000 was initially discovered by Olsen's collaborator at City of Hope, who screened over 300,000 compounds for E1 inhibitors. COH000 was chosen for this study because of its specificity for inhibiting SUMO enzymes, but how the inhibitor works and where it binds to the enzyme were completely unknown.

Thanks to their high-resolution 3-D structure and COH000's novel mechanism of action, Olsen and his team may have discovered a new way to overcome this obstacle. Discovery of the new binding site "opens the door" to designing specific inhibitors for other related enzymes as well.

"This inhibitor is different from previous inhibitors," explains Zongyang Lv, Ph.D., a postdoctoral fellow in Olsen's laboratory and co-first author on the study. "The pocket where the inhibitor binds provides useful information for the refinement of this drug, or development of similar inhibitors."

To solve protein structures, Olsen's lab uses a powerful technique called X-ray crystallography. This technique requires a high-energy source that produces intense X-ray beams that hit the crystallized protein and create a distinct diffraction pattern used to determine the 3-D structure of the protein.

The most crucial (and often most difficult) part of the process is obtaining a suitable protein crystal.

"Crystals are unique," explains Lv. "They're an ordered repeat of a single

substance with the ability to generate diffraction patterns that allow us to calculate electron density."

The result is a 3-D model that allows them to visualize the interaction of potential drug compounds with target proteins (see accompanying video).

"We're learning the secrets of nature, how these molecules function, and we're doing it in a way that we can actually see with our eyes," Olsen states. "By understanding things at a molecular level, we can use them for the greater good."

Their next step is to use the information from the 3-D structure to design more specific and efficient inhibitors with strong antitumor properties.

More information: Zongyang Lv et al, Molecular mechanism of a covalent allosteric inhibitor of SUMO E1 activating enzyme, *Nature Communications* (2018). DOI: 10.1038/s41467-018-07015-1

Provided by Medical University of South Carolina