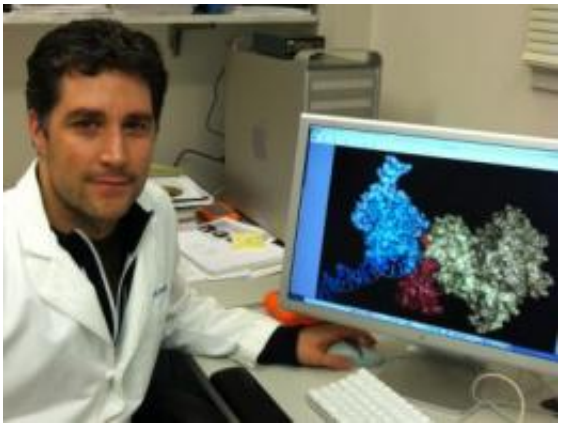
Researchers capture major chemotherapeutic target in complex with DNA damage

May 10 2012



An investigation led by John M. Pascal, Ph.D., an assistant professor in the Department of Biochemistry and Molecular Biology at Thomas Jefferson University and Jefferson's Kimmel Cancer Center, revealed new target sites for drugs aiming to stop PARP-1 activity. Credit: Thomas Jefferson University

A new study published in *Science* May 11 is shedding light on the molecular details of PARP-1, a DNA damage-detecting enzyme that when inhibited has been shown to be effective in fighting cancer and other diseases.

The investigation led by John M. Pascal, Ph.D., an assistant professor in the Department of Biochemistry and Molecular Biology at Thomas Jefferson University and Jefferson's Kimmel Cancer Center, revealed new target sites—including specialized "zinc finger" domains—for drugs

aiming to stop PARP-1 activity.

The idea for this area of research is to identify more specific PARP-1 inhibitors that achieve a targeted inhibition, with less potential for side effects. Drugs inhibiting PARP-1 have also been proven effective in treating inflammation and cardiac disease.

"PARP-1 has been identified as a valuable target, but what's special about it? What really are its weak points in the way it gets activated?" said Dr. Pascal. "We wanted to define a structural and mechanistic framework to better understand how to specifically inhibit PARP-1."

The weak points were found to be multi-domain interfaces that are uniquely found in PARP-1. What researchers now know is that multiple domains of PARP-1 come together and bind to DNA damage, and this "communication" between domains is essential for DNA damage-dependent PARP-1 activity.

PARP-1 is a protein that detects and responds to breaks in the structure of DNA, a potentially lethal form of damage to our genetic information. If PARP-1 activity is impaired, DNA strand breaks are not repaired and instead are converted into more dangerous types of DNA damage. In normal tissue, a repair mechanism called homologous recombination picks up the slack and fixes the damaged DNA. However, in cancers that carry the BRCA mutation, like certain breast and ovarian cancers, homologous recombination is inactivated. Therefore, the cancerous cells have become dependent on the role PARP-1 plays in DNA repair.

In a more general scenario, inhibiting PARP-1 has been successful when combined with DNA-damaging drugs because it enhances the apoptotic activity of these drugs. In other words, it helps halt tumor growth.

Today, many PARP-1 inhibitors being tested in preclinical and clinical

studies target the catalytic active site. But this approach is limiting because the catalytic site is similar to those found in other PARP-like proteins that carry out other essential cellular functions, thus increasing the potential for off target side effects.

"What was exciting in our structure of PARP-1 is that there are specialized sites on the protein that can be inhibited; you can effectively kill catalytic activity without having to touch the catalytic active site," said Dr. Pascal.

Using X-ray crystallography, researchers studied the interaction amongst the component domains of PARP-1 and their combined role in binding to DNA damage. The PARP-1/DNA structure revealed a network of interdomain contacts formed upon DNA binding. These domains have to come together and assemble, the researchers found, to have catalytic activity.

"Our work indicates that we should be looking for inhibitors that prevent these domains from coming together," Dr. Pascal said. "Rather than screen for inhibitors with catalytic activity as a readout, we can screen for inhibitors that disrupt the communication between the PARP-1 domains, which would in turn shut down catalytic activity."

Closer attention to these specialized domains could inspire the design of a new class of PARP inhibitors.

"Dr. Pascal's structural and biochemical characterization reveals how recognition of DNA damage and communication between domains control the activity of PARP-1," said Barbara Gerratana, Ph.D., who oversees enzyme catalysis grants at the National Institutes of Health's National Institute of General Medical Sciences, which partially supported the study. "This work is a major breakthrough in understanding an enzyme essential for regulation of cell proliferation

and a promising target for cancer therapeutics."

Provided by Thomas Jefferson University