Scientists identify structure of crucial enzyme in cell division

March 30 2016

UT Southwestern Medical Center researchers have determined the atomic structure of an enzyme that plays an essential role in cell division, the fundamental process that occurs countless times daily in many life forms on Earth.

Understanding the structure of this enzyme, separase, could lead to better treatments for cancer, which occurs when cells divide out of control, said Dr. Hongtao Yu, Professor of Pharmacology and a Howard Hughes Medical Institute (HHMI) Investigator at UT Southwestern.

"Chromosomes contain the genetic blueprint for life, and must be precisely duplicated and equally partitioned during each cell division. The cohesin complex forms a molecular ring to encircle the duplicated chromosomes and tether them together until the moment of chromosome separation," said Dr. Yu, senior author of the study published online in *Nature*. "In organisms from fungi to humans, separase - an enzyme that breaks down proteins - cleaves and opens the cohesin ring to allow chromosome separation and subsequent partition into the two new daughter cells."

Despite its central role in cell biology, the atomic structure of separase has eluded scientists since its discovery nearly two decades ago. This situation left a void in the understanding of the enzyme's mechanism and regulation, the researchers said.

"We determined the atomic structure of separase from a fungus that can

grow at high temperatures. The structure reveals how separase recognizes and cleaves the cohesin ring, allowing the chromosomes to separate," said Dr. Yu, a Michael L. Rosenberg Scholar in Medical Research and member of the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern. "This particular protein is very unstable in species that grow at normal temperature, such as human body temperature, but was more stable in the high-temperature fungus that we studied."

Because of the enzyme's role in cell division, chemical inhibitors of separase are expected to block cell proliferation and therefore may have therapeutic value in treating cancer.

"The fungal separase that we studied is very similar to human separase. For that reason, we believe our structure will aid in the design of such inhibitors," he said, "because once you have the shape of the structure, you can computationally look for molecules that will bind to it."

Study co-authors included Dr. Zhonghui Lin, a research specialist at the HHMI and in the Department of Pharmacology, and Dr. Xuelian "Sue" Luo, Associate Professor of Pharmacology and Biophysics.

More information: Structural basis of cohesin cleavage by separase, *Nature*, DOI: 10.1038/nature17402

Provided by UT Southwestern Medical Center