Mimicry at the molecular level protects genome integrity

April 13 2009

The new study, which was published on April 12, 2009, in an advanced online edition of the journal *Nature Structural & Molecular Biology,* draws new parallels between the Rad60 DNA repair factor and SUMO, a small ubiquitin-like modifier, which are both essential for maintaining genome stability during replication.

"This collaborative study between our laboratory and the Scripps Research Tainer group shows the very first indication of mimicry in the SUMO pathway," said Scripps Research Assistant Professor Michael "Nick" Boddy, Ph.D., who was senior author of the study. "By mimicking a particular surface feature of SUMO, Rad60 competes for binding to an essential enzyme of the SUMO machinery. Thus, Rad60 is a previously undefined member of the SUMO team."

Maintaining genome stability is critical to an organism's survival because genetic defects can promote tumors, aging, and neurodegenerative disease. The genome is particularly vulnerable to spontaneous and damage induced alterations during the replication or S phase of cell division. To ensure the high-fidelity completion of replication, cells engage critical mechanisms that include cell cycle checkpoints and DNA repair.

The fission yeast (Schizosaccharomyces pombe) DNA repair protein Rad60, part of a unique protein family conserved from yeast to humans, is essential for cell viability; cells with a reduced level of Rad60 activity show sensitivity to a range of genotoxic stresses.

The new study combined structural, biochemical and genetic analyses in the two laboratories. The results showed that the two SUMO-like domains on Rad60 each bind to distinct components of the SUMO pathway.

"Even though the backbones in these two Rad60 domains are similar, their surfaces have been altered during evolution in such a way to maintain interaction with different parts of the SUMO pathway," said Boddy, who just received a prestigious Scholar Award from the Leukemia & Lymphoma Society, and who, with colleagues, first identified the Rad60 family in 2003 and was among the first to characterize SUMO in 1996.

In the study, the team used x-ray crystallography to determine the structure of a Rad60 SUMO-like domain at an ultra high-resolution, which is within the top half a percent of all published structures. "This resolution allowed us to develop and use a novel technique utilizing the Scripps Research supercomputer to solve the structure within a few weeks, which would likely have taken years if attempted on a desktop computer," said Andy Arvai a scientific associate in the Tainer lab.

"The structural data allowed us to clearly understand how mimicry takes place and its importance in the SUMO pathway," said Jeff Perry, Ph.D., a senior research associate at Scripps Research and an adjunct professor at Amrita University in India, one of the lead authors of the study. "In this case, we know that changing a single amino acid can break the binding. When you disrupt this interface, it creates instability and once that happens, the integrity of the genome can't be protected."

John Prudden, Ph.D., a Scripps Research scientist and another lead author of the study, added, "SUMO dysfunction is implicated in cancer and aging. Right now there is more to discover in terms of Rad60 mimicry - it's involved in other interactions within the SUMO pathway,

so we want to know how it might affect those partners. And because these partners are implicated in disease, understanding the roles of these interactions could be important for the clinical side of things."

More information: "Molecular Mimicry of SUMO Promotes DNA Repair," www.nature.com/nsmb/journal/va … t/abs/nsmb.1582.html

Source: The Scripps Research Institute (news : web)