Novel protein critical for cellular proliferation discovered

October 7 2010

Accurate duplication of genetic material and the faithful segregation of chromosomes are critical for cell survival. The initiation of DNA replication is linked both to cell cycle progression and chromatin organization. In plants, animals and other "eukaryotes," the assembly of a multi-protein complex called pre-replicative complex (preRC) is the first step in the initiation of DNA replication. As the name implies, origin recognition complex (ORC) proteins bind to origins of DNA replication. Subsequently, other components of preRC are assembled at these sites. In addition to its role in DNA replication, ORC is also involved in gene silencing and organization of the tightly packed DNA, called heterochromatin. How ORC is brought to the DNA in human cells had previously remained a mystery.

Researchers at the University of Illinois, led by Professor Supriya Prasanth from the school of molecular and cellular biology, have identified a novel protein that is highly conserved in higher eukaryotes. They have shown that in human cells, this protein (once known as LRWD1 but renamed ORCA, for "ORC-associated" protein) associates with ORC and shows similar cell cycle dynamics to ORC. Along with ORC, this protein binds to heterochromatic structures, including centromeres and telomeres, which are important to cell division and chromosome maintenance.

The researchers further demonstrated that ORCA efficiently recruits ORC to chromatin, the DNA and proteins that make up the chromosome. Depletion of ORCA in human primary cells as well as in

embryonic stem cells results in the loss of ORC binding to chromatin and subsequent arrest of cells in a vital phase of the cell cycle. Loss of ORCA results in defects in cellular proliferation, suggesting that a fine-tuned balance in the levels of ORCA is maintained in a normal cell. These results suggest that a novel protein, ORCA, is critical for initiation of DNA replication and heterochromatin organization in mammalian cells.

This work appears in the October 8, 2010 issue of the journal *Molecular Cell*.

"The discovery of this new protein is going to be revolutionary in the field of replication and cell cycle," Prasanth said. "We all know that diseases like cancer are caused by uncontrolled proliferation of cells, and our data demonstrates that ORCA controls proliferation of cells. This work is going to have important implications in cancer biology."

Provided by University of Illinois at Urbana-Champaign