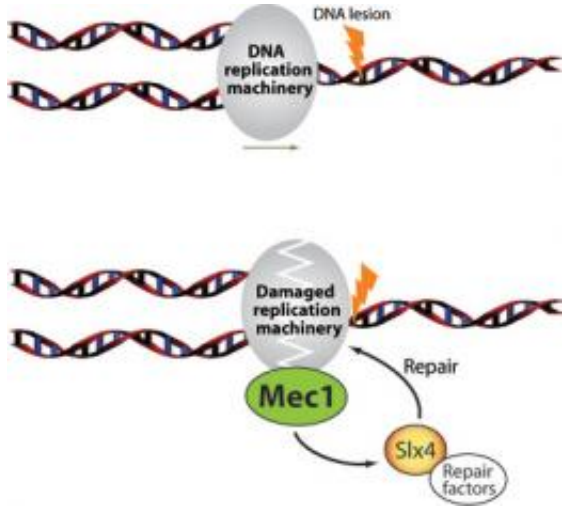
Protein helps fix damaged DNA in yeast

July 30 2010, By Krishna Ramanujan



To replicate the genome, the replication machinery must travel the full extent of the genomic DNA. But the machinery often stalls and is damaged by encountering DNA lesions or replication blocks along the way. Smolka and colleagues discovered how the Mec1 protein mediates the repair and restart of the replication machinery, so cells can complete DNA replication.

(PhysOrg.com) -- Like a scout that runs ahead to spot signs of damage or danger, a protein in yeast safeguards the yeast cells' genome during replication -- a process vulnerable to errors when DNA is copied -- according to new Cornell research.

Researchers from Weill Institute for Cell and Molecular Biology have discovered how a protein called Mec1 plays the role of "guardian of the genome," explained Marcus Smolka, assistant professor of molecular

biology and genetics. The findings are detailed in the July 30 edition of the journal *Molecular Cell*.

Previous studies have shown that cells lacking Mec1 accumulate damaged DNA and become more sensitive to agents that interfere with replication. The researchers report that the Mec1 protein monitors and repairs the machinery responsible for replicating the DNA. At times, when DNA becomes damaged, the replication machinery can actually detach from the DNA -- like a train coming off a track -- but Mec1 coordinates the repair of the machinery and the DNA itself, allowing it to restart and continue replicating.

"Mec1 organizes the cell's response against things that jeopardize the integrity of the genome," Smolka said.

During the replication process, Mec1 accumulates at trouble spots such as lesions in the DNA or other blocks to replication. Mec1 is known as a kinase, a type of enzyme that modifies other proteins by adding a phosphate group to them (a process called phosphorylation), which then leads to a functional change in the protein. The researchers report that Mec1 adds a phosphate group to a protein known as Slx4, which then triggers Slx4 to anchor to the replication machinery. Slx4 then can employ a variety of tools to repair DNA and the replication machinery.

The findings are important because researchers have discovered counterparts (called orthologues) to Mec1, other related proteins with similar biological pathways in humans. Also, mutations to the human genes that produce Mec1 and related proteins can lead to cancer predisposition and neurological disorders. At the same time, cancer cells employ their own similar replication repair system, so understanding the process may help researchers design interventions that interrupt replication of cancer DNA.

Recently, other researchers discovered that the human version of Mec1, called ATR, phosphorylates a protein that is the human counterpart to Slx4. The next step, Smolka said, will be to see if after phosphorylation the human Slx4 also anchors to the replication machinery to repair any damaged machinery or DNA.

Co-authors include Patrice Ohouo, a graduate student in biochemistry, molecular and cell biology; Francisco M. Bastos de Oliveira, a postdoctoral researcher; and Beatriz Almeida, a research support specialist; all members of Smolka's lab.

Provided by Cornell University