SUMO works with replication protein A complex to repair DNA

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A team of investigators led by a physician-scientist at The University of Texas MD Anderson Cancer Center has shown for the first time that the small protein SUMO can team up with the replication protein A (RPA) complex to facilitate DNA repair. The study is published in the Aug. 13 edition of the journal *Molecular Cell*.

RPA 70 is a component of multiprotein machinery called the RPA complex, which plays a crucial role in DNA replication and repair. The researchers discovered that RPA70 is associated with a SUMO-specific protease called SENP6 during a part of the cell cycle in which DNA replication occurs. They also discovered that RPA70 can be modified by SUMO, and this modification is regulated by SENP6.

"In this paper, we show the modification of RPA70 by SUMO is essential to repair DNA double-string breaks by homologous recombination," said corresponding author Edward T.H. Yeh, M.D., professor and chair of MD Anderson's Department of Cardiology. "If a mutant protein that cannot be modified by SUMO is substituted for RPA70, the cells are much more sensitive to chemotherapy and ionized radiation."

The chemotherapy drug camptothecin and ionizing radiation both attack cancer cells by causing double-strand DNA breaks. Cells respond by activating homologous recombination to repair the damage. The newly discovered connection between SUMO and RPA70 offers a potential target for short-circuiting repair, making the cells more vulnerable to

treatment.

Team Has Made Multiple Discoveries

This research is one more piece in a multi-faceted puzzle Yeh and his colleagues have been working on since 1996. Yeh discovered a post-translational protein modification system that rivals ubiquitination in complexity and importance:

- SUMO (small ubiquitin-related modifier) proteins, originally called Sentrin, which attach to other proteins and modify their function or physically move them within the cell (SUMOylation)
- Sentrin/SUMO-specific protease (SENP), which removes SUMO from proteins (de-SUMOylation)

Mammalian cells have six SENPs, and Yeh's group is looking systematically at all of them. Their previous research has shown SENP1 enables cells to survive at low oxygen levels, which is key for development of many kinds of cancer. And, earlier this year, they reported that SENP2 plays an important part in embryonic development.

SENP6 Regulates Several Proteins

To investigate SENP6, the researchers knocked down the messenger RNA that encodes SENP6 in cultured cells. They found that SENP6 plays a key role in progression of the cell cycle, and that it regulates a number of proteins, including RPA70. SENP6 associates with RPA70 in the S-phase of the cell cycle, when DNA is replicated, preventing SUMOylation of RPA70.

"We found that when SENP6 is removed from RPA70, RPA70 has the potential to be modified by a specific type of SUMO called SUMO2/3," Yeh said. "So we asked the question, 'Can we actually cause premature or artificial separation of SENP6 and RPA70?

"This led to the discovery that the chemotherapy drug camptothecin dissociates SENP6 from RPA70, allowing it to be modified by SUMO 2/3. In addition, we found these proteins can be separated by ionized radiation," Yeh said.

SUMO 2/3 Necessary to Repair Cell Damage

RPA70 that has been modified by SUMO 2/3 recruits RAD51, an important protein in the repair of DNA damage through homologous recombination. When a mutant that cannot be SUMOylated is substituted for RPA70, the repair process is defective, giving the cell increased sensitivity to camptothecin and radiation.

"To repair DNA double-string breaks and damages, you need SUMO 2/3 to be there for the repair to occur efficiently," Yeh said. "RPA70 is a crucial protein in both DNA replication and repair, and we've demonstrated its relationship to DNA repair and why SUMOylation is important to this process."

Provided by University of Texas M. D. Anderson Cancer Center

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