MedicalXpress

New insights provide promise for development of tools to protect damaged tissues

September 13 2010

St. Jude Children's Research Hospital investigators have identified a novel structure in cells that serves as a control switch in the body's system for eliminating damaged cells and also offers new therapeutic potential.

The findings provide fresh insight into the machinery at work as cells ramp up production of p53 protein following DNA damage. The p53 protein plays a critical role in how cells respond to the stress that damages DNA. The gene that carries instructions for making p53 protein is the most commonly mutated gene in human cancers.

Investigators also identified molecules that disrupt the system and reduce p53 protein levels in cells damaged by irradiation or chemotherapy. These small molecules helped cells growing in the laboratory survive better after they were damaged. The findings appear in the September 13 online edition of the journal Genes *& Development*.

The work lays the foundation for a new approach to protecting healthy tissue using small molecules to reduce p53 protein levels in cells following damage caused by a wide range of factors, including the radiation and chemotherapy used to treat cancer or accidental exposure to dangerous chemicals or radiation, said Michael Kastan, M.D., Ph.D., director of the St. Jude Comprehensive Cancer Center and the paper's senior author. The same approach might also help ease the tissue damage

that occurs as blood flow and oxygen are restored following a heart attack or stroke.

"We are excited about this because we now theoretically have a way of blunting p53 induction in settings where it is detrimental," he said.

The work builds on previous research from Kastan's laboratory into the mechanics of how p53 protein increases in response to cellular stress and DNA damage. Jing Chen, Ph.D., a postdoctoral fellow in Kastan's laboratory, is first author of the study.

The jump in p53 protein production was widely attributed to a decrease in the breakdown of p53 inside such cells. But in 2005, Kastan and his colleagues showed that affected cells also produce more of the protein. Researchers reported that after DNA damage, a protein called RPL26 binds to a molecule called p53 messenger RNA, leading to a dramatic rise in p53 protein. Messenger RNA (mRNA) is part of the cell's protein production machinery that translates the genetic instructions inside cells into needed proteins.

Efforts to better understand how RPL26 functioned led investigators to this latest discovery. Researchers showed that optimal p53 production required RPL26 to bind to a structure in mRNA not previously seen in mammalian cells.

The structure forms when the ends of the normally single-stranded mRNA molecule come together and make a short region of double-stranded RNA. Those ends must obey the rules of RNA pairing and link only with a complementary molecule, or base pair, on the other strand. "We suspect we will find a whole family of stress-related proteins regulated this way," Kastan said.

Investigators showed that blocking the interaction at either end of the

mRNA was enough to short-circuit RPL26 binding and lead to a dramatic fall in p53 protein levels in stressed or damaged cells.

Researchers used short pieces of DNA, so small they were absorbed by cells after simply being added to cell culture, to target the interactive bases and successfully disrupt formation of the double-stranded structure. Restoring the ability of the bases to bind the two ends of the mRNA restored RPL26 binding and stimulated p53 protein synthesis.

Work is underway to develop a mouse model to speed efforts to find or design small molecules that target this mechanism. "We have a long way to go in terms of drug development, but the better we can define the interaction between RPL26 and the double-stranded RNA structure the more likely we will be able to develop other small molecules to specifically block that interaction," Kastan said.

Provided by St. Jude Children's Research Hospital