Scientists find guardian gene's choices crucial to stopping cancer process

8 January 2007

Scientists at the Kimmel Cancer Center at Thomas Jefferson University in Philadelphia have uncovered a novel pathway by which the anti-cancer gene p53 springs into action, protecting a damaged cell from becoming cancer. The gene can either halt the cell's growth or send it spiraling toward certain death. How this choice is made, the researchers say, could have implications for future strategies in chemotherapy drug development.

According to Steven McMahon, Ph.D., associate professor of cancer biology at Jefferson Medical College, who led the work, the p53 gene's – or rather its protein's – ability to direct a damaged cell to either stop growing or commit suicide depends on turning on separate groups of target genes. He and his co-workers have found that after a cell's DNA is damaged, the p53 protein's ability to bind to the DNA can be affected.

Two enzymes, hMOF and TIP60, can chemically alter an amino acid, lysine 120, at the binding site, in turn influencing p53's decision on which target genes to turn on. The alteration can short-circuit p53's ability to cause the damaged cell to commit suicide, though it can still stop cell growth, suggesting that this change may help explain a mechanism behind p53's choice. They report their findings in the journal *Molecular Cell*.

"It's been known that p53 can induce cell cycle arrest or apoptosis (programmed cell death) as a way of eliminating developing cancer cells in response to cell damage, but no one has known how the choice is made," says Dr. McMahon. "This work narrows how the decision is made."

The findings could have implications for future drug development strategies. "Most chemotherapy strategies are aimed at getting cancer cells to die," Dr. McMahon says. "Figuring out what pathways p53 uses to cause that versus cell cycle arrest is important. It looks like this new modification that we have identified helps p53 make that decision."

"p53 is such an important player in the cancerous process – it's nearly always mutated or inactivated in cancer – that continuing to understand more about how it works will likely have significant implications for cancer research," says Dr. McMahon. "We wouldlike to understand the interplay between this newly identified pathway and others involved in p53 and cancer.

"Since p53 can make this decision, this might give some insight into which function of p53 is more important in which tissues," says co-author Stephen Sykes, a Ph.D. candidate at the University of Pennsylvania. "For example, K120 (lysine 120) mutations cause tumors in the prostate, but are not so much involved in causing immune system cancers such as lymphomas. That could suggest that p53's potential to cause cell death could be more important in certain tissues than in others. In the future, if someone could develop therapies that could specifically activate p53's potential to drive programmed cell death versus the cell cycle arrest potential, it might influence how a doctor might choose to treat a certain type of cancer.

"This may potentially enable the development of a cancer drug that would stimulate the enzymes to promote this modification driving p53 to apoptosis."

Source: Thomas Jefferson University