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Researcher identifies novel pathway that solid tumor cancer cells activate for growth

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A common, yet previously undistinguished protein, which is elevated in many late-stage cancers, may play a strategic role in tumor growth through a non-conventional pathway, researchers at the Indiana University School of Medicine report in the Feb. 10 issue of the *Proceedings of the National Academy of Sciences*.

The protein, Mdm2, an oncogene, has long been thought to play a major role in regulating the effectiveness of the tumor suppressor p53, largely through p53's destruction. New research shows that Mdm2 plays an active role in making p53 ineffective without eradicating it from the cell.

"This work provides new evidence on the mechanism through an unrealized pathway that can spur on cell growth and metastasis," said Lindsey D. Mayo, Ph.D., associate professor of pediatrics, biochemistry and molecular biology, a scientist at the Herman B Wells Center for Pediatric Research at the IU School of Medicine and a researcher at the Indiana University Melvin and Bren Simon Cancer Center.

"The central dogma for almost 20 years has been that the main function of Mdm2 is to bind to a protein and flag it to be destroyed," Dr. Mayo said. "Everyone thought that Mdm2 research had hit a plateau from these findings."

In research published in the *Journal of Clinical Investigation* in 2010, Dr. Mayo and colleagues identified a critical pathway that stimulates the production of Mdm2 causing an increase in the level of protein that

binds to p53, the most common tumor suppressor, as well as other tumor suppressors, and extinguishes tumor suppression activity. Since elevated levels of Mdm2 are found in late-stage cancers, the IU researchers began to test what elevated Mdm2 was doing in the cells.

The tumor uses Mdm2 to either destroy p53, or put p53 in suspended animation. The suspended animation is the revelation that Dr. Mayo's laboratory discovered in the recently published work. In either case this provides a growth advantage, but also requires different therapeutic approaches to turn off Mdm2 for activation of p53 to halt tumor growth.

"What is exciting is finding alternate or novel pathways for Mdm2, changing its perceived manner of blocking p53 as a tumor suppressor," Dr. Mayo said. "This research will provide additional therapeutic options."

Provided by Indiana University