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Scientists uncover process that could drive the majority of cancers

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The gene p53 has been described as the "guardian of the genome" due to its prominent role in preventing genetic mutations. More than half of all cancers are thought to originate from p53 mutations or loss of function, and now a recent study by VCU Massey Cancer Center scientist Richard Moran, Ph.D., explains why.

Published in *Molecular Cancer Therapeutics*, Moran's research results describe how mutations and or loss of function of the p53 gene activate a protein complex known as mammalian target of rapamycin complex 1 (mTORC1), which helps regulate the energy resources needed for cell proliferation. mTORC1 is made up of several dozen proteins, and cells use the intracellular membranes of their lysosome as a scaffold to bring all of these proteins together. In response to the need of a normal cell, the p53 gene helps maintain proper levels of a protein known as tuberous sclerosis complex 2 (TSC2) in the lysosome. When p53 is not functioning properly, Moran's team found that TCS2 levels in the lysosome drop, and a small protein known as RHEB takes its place. It is this accumulation of RHEB that activates mTORC1 and leads to the abnormal control of cell proliferation.

"We have uncovered for the first time the signaling process that leads to excessive growth of cancer when p53 is lost. These protein interactions are like individual links in the chain of events leading to the development of cancer," says Moran, Paul M. Corman, M.D., Chair in Cancer Research, associate director for basic research and co-leader and member of the Developmental Therapeutics research program at VCU

Massey Cancer Center as well as professor of pharmacology and toxicology at the VCU School of Medicine.

In a related study, Moran's team focused on pemetrexed, an existing drug he co-developed that is now used as a first-line treatment for the majority of lung cancers.

In the *Journal of Biological Chemistry*, Moran and his colleagues demonstrate that pemetrexed works by shutting down the mTORC1 protein complex through the inhibition of one of its controlling components, a protein known as raptor. The researchers found that pemetrexed works regardless of whether or not there are p53 mutations or loss of function. Additionally, they found that it works even if the key regulator of mTORC1, TSC2, is no longer functioning.

"Our findings suggest that pemetrexed may have much greater clinical utility than previously imagined," says Moran. "This research lays the foundation for its use against other cancers in which p53 is not functioning properly, as well as tuberous sclerosis complex, a syndrome driven by loss of TSC2 function that causes disastrous growth of benign but progressive tumors in major organs."

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