Researchers identify potential molecular target to prevent growth of cancer cells

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Researchers have shown for the first time that the protein fortilin promotes growth of cancer cells by binding to and rendering inert protein p53, a known tumor suppressor. This finding by researchers at the University of Texas Medical Branch may lead to treatments for a range of cancers and atherosclerosis, which p53 also helps prevent, and appears in the current print issue of the *Journal of Biological Chemistry*.

"The p53 protein is a critical defense against cancer because it activates genes that induce apoptosis, or the death of cells. However, p53 can be made powerless by mutations and inhibitors like fortilin," said Dr. Ken Fujise, lead author of the study and director, Division of Cardiology at UTMB.

Fortilin, an amino acid polypeptide protein, works in direct opposition to p53, protecting cells from apoptosis. Fujise discovered fortilin in 2000 and the protein has become a central focus of his research. This study marks the first time that scientists have been able to show the exact mechanism whereby fortilin exerts its anti-apoptotic activity.

Fujise and his team used cell cultures and animal models to show that fortilin binds to and inhibits p53, preventing it from activating genes, such as BAX and Noxa, that facilitate cell death. Thus, cells that would be killed are allowed to proliferate.

"When normal cells become cancer cells, our bodies' natural biological response is to activate p53, which eliminates the hopelessly damaged

cells," said Fujise. "This process explains why the majority of people are able to stay cancer-free for most of their lives. Conversely, mutated p53 genes are seen in more than half of all human cancers, making them the most frequently observed genetic abnormality in cancer."

According to Fujise, upon further research and validation of the biological mechanism described in this study, scientists can begin exploring compounds that could modulate fortilin's activity on p53.

Such a compound would be a powerful chemotherapy agent and, because p53 inhibition has also been associated with atherosclerosis, could also protect against coronary disease and its many complications, including heart attack and stroke.

"Though we are in the early stages of this research, once screening for compounds is initiated, we could have a potential new drug to investigate in a very short period of time," said Fujise. With the support of National Institutes of Health high-throughput screening programs, which make it possible to screen very large numbers of compounds against a drug target, the process of identifying a new drug could potentially be shortened to months rather than years, he added.

Other authors include scientists at UTMB and other institutions: Yanjie Chen, Takayuki Fujita, Di Zhang, Hung Doan, Decha Pinkaew, Zhihe Liu, Jiaxin Wu, Yuichi Koide, Andrew Chiu, Curtis Chen Jun Lin, Jui-Yoa Chang; and Ke-He Ruan.

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