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Researchers uncover how a potent compound kills prostate cancer cells

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One major hallmark of cancer cells is their ability to survive under stressful conditions. A new study spearheaded by researchers at Sanford-Burnham Medical Research Institute reveals how a promising anticancer compound called SMIP004 specifically kills prostate cancer cells by compromising their ability to withstand environmental stress. The study, recently published in *Oncotarget*, uncovers novel mechanisms of anticancer activity and could lead to the development of more effective therapies for advanced and hard-to-treat forms of prostate cancer, as well as other types of cancer.

Prostate cancer is the second most common cancer and the second leading cause of cancer-related death among men in the United States. One treatment option for these patients is castration—the chemical or surgical removal of the testes—which reduces the production of the male sex hormone testosterone. This strategy works because prostate cancer cells, at least initially, depend on testosterone for their growth and survival. But many patients eventually develop castration-resistant prostate cancer, in which the cancer cells adapt and become insensitive to hormone deprivation therapy.

"For advanced prostate cancer—castration-resistant prostate cancer in particular—when the cancer recurs, the only therapy is Taxol, which will prolong life for only a couple of months," said senior study author Dieter Wolf, M.D., director of the National Cancer Institute-designated Cancer Center proteomics facility at Sanford-Burnham. "There's good potential that our compound could become a novel, much-needed therapy for

castration-resistant prostate cancer."

New compound, new mechanisms

In a previous study, Wolf and his team identified SMIP004 as a promising anticancer agent when they screened for compounds that specifically kill prostate cancer cells while sparing normal cells. But until now, exactly how SMIP004 works was unknown.

In the new study, the researchers found that SMIP004 causes cancer cells to die by interfering with the functioning of mitochondria—structures within cells that are responsible for generating energy and controlling cell growth and death. In a process known as oxidative stress, harmful molecules called reactive oxygen species (ROS) built up within mitochondria, causing the cells to stop replicating and to start dying. Wolf and his team pinpointed the exact molecular signaling pathways underlying SMIP004's effects and identified ROS-mediated activation of the unfolded protein response as the trigger of cancer-cell death. "I'm not aware of any approved drugs with the mechanism of action we identified," Wolf said.

Through one of the newly identified pathways triggered by oxidative stress, SMIP004 caused a decrease in the number of androgen receptors—proteins within prostate cancer cells that are activated by testosterone. In patients with castration-resistant prostate cancer, cancer cells develop the ability to use low levels of testosterone for survival by increasing the production of androgen receptors. In other words, these cancer cells still depend on androgen receptors for their growth and survival, even though they are less reliant on testosterone itself. "Because SMIP004 acts on the androgen receptor, it is particularly promising for castration-resistant prostate cancer," Wolf said.

Targeting cancer cells

Moreover, the researchers found that SMIP004 strongly inhibited the growth of prostate and breast cancer in mice, underscoring the compound's potential value in treating a range of cancers. All types of cancer cells are exposed to stressful conditions, including high levels of oxidative stress resulting from the activation of cancer-causing genes. SMIP004 increased mitochondrial ROS levels by 40 percent, which was enough to tip these cells over the edge and cause them to die.

"The compound increases the stress level beyond what a cancer cell can take, whereas normal cells can cope with it because they have a much lower level of oxidative stress to begin with," Wolf said. "So we think that SMIP004 is likely to be harmless to normal cells, but broadly effective against many types of cancer cells."

Provided by Sanford-Burnham Medical Research Institute

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