Prostate cancer gets around hormone therapy by activating a survival cell signaling pathway

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Cancer is crafty. When one avenue driving its growth is blocked by drugs targeting that path, the malignancy often creates a detour, finding an alternative route to get around the roadblock.

In a study at UCLA's Jonsson Comprehensive Cancer Center, researchers found that when a common type of prostate cancer was treated with conventional hormone ablation therapy blocking androgen production or androgen receptor (AR) function– which drives growth of the tumor – the cancer was able to adapt and compensate by activating a survival cell signaling pathway, effectively circumventing the roadblock put up by this treatment.

The findings could have important clinical implications as this type of prostate cancer, in which the PTEN tumor suppressor gene is inactivated, accounts for about 40 to 50 percent of primary prostate cancers and 70 to 90 percent of cancers that become resistant to hormone therapy, called castration resistant prostate cancers. Based on this study, these prostate cancers could be more effectively treated using a combination of drugs that target the AR cell signaling pathway and the compensating survival pathway, called the PI3K/AKT/mTOR pathway, said study senior author Dr. Hong Wu, a professor of molecular and medical pharmacology and a Jonsson Cancer Center researcher.

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Cancer Cell.

"The most significant take home message from this study is that certain prostate cancers can resist androgen deprivation therapy by activating an alternate pathway to drive its growth," Wu said. "We found that these two pathways are talking to each other, almost like regulatory circuitry, and helping each other get around attempts to kill the cancer. When we suppress one of these pathways, it essentially feeds the other."

Wu characterized the findings as surprising. What they discovered, she said, bucked conventional wisdom about the way PTEN negative or PTEN null prostate cancer operates.

"Most of the hypotheses have suggested that PTEN regulates the function of the androgen receptor pathway, which is opposite of what we show here," said Wu, who also is a researcher with the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA. "We had thought that when PTEN was lost, it activated the androgen receptor pathway, driving cancer growth. What we've found suggests that if PTEN is lost in cancer cells, then the cancer cells become androgen receptor-independent and rely on the PI3K pathway for growth and survival."

Wu's study showed that PTEN loss suppresses AR signaling and that leads cancer cells to become less dependent on the androgen receptor for survival. This is important, Wu said, because it addresses a key mechanism of resistance. Certain prostate cancers may resist hormone therapy and if you withdraw androgen as treatment, it enhances the activity of the PI3K pathway, which then takes over driving cancer growth. Both pathways must be hit to stifle growth of the cancer.

The study has important implications for those prostate patients with late stage disease, who often become resistant to hormone ablation therapy,

said David J. Mulholland, a postdoctoral fellow in Wu's lab and first author of the study. Men who die of prostate cancer are those that become resistant to therapy and, as a consequence, their disease can spread or metastasize to other places, most often the bones.

"What we've shown here is a mechanism that could explain why anti-androgen therapy may fail in some patients," Mulholland said. "Their cancer cells adapted to the low androgen receptor function and compensated by activating a survival pathway. It was a surprising result to show that these cells could continue to live without the androgen receptor signaling. Combining drugs that hit both pathways will be much more effective than using one drug alone."

The study was modeled in a mouse model created by the Wu laboratory in which PTEN and AR are absent in the epithelium. The findings were replicated using samples from cancerous prostates removed from patients, work done in collaboration with researchers at UCLA and the Specialized Program of Research Excellence (SPORE) in prostate cancer.

"We found similar result in both cases," Wu said. "The human cancers may behave the same way as the mouse models."

There are new generations of AR inhibitors that are potentially more effective than their predecessors being tested now in clinical trials. There also are drugs being tested that inhibit the PI3K pathway, which is commonly activated in a variety of cancers. Clinical trials currently are being designed at UCLA that will combine these types of drugs to cut off both the primary path and escape routes that prostate cancers use to survive.

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