Study reveals a reprogrammed role for the androgen receptor

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The androgen receptor - a protein ignition switch for prostate cancer cell growth and division - is a master of adaptability. When drug therapy deprives the receptor of androgen hormones, thereby halting cell proliferation, the receptor manages to find an alternate growth route. A new study by Dana-Farber Cancer Institute and Ohio State University scientists demonstrates how.

The shift from androgen-dependent to androgen-independent cell growth occurs, in part, because the androgen receptor switches on an entirely different set of genes in the latter group than in the former, the researchers report in the July 24 issue of *Cell.* In contrast to androgen-dependent prostate tumors, androgen-independent ones experience an uptick in the activity of genes that control cell division, or mitosis. One such gene, called UBE2C, which causes cells to ignore a natural pause in the division process, becomes especially active, the researchers report. This pause, or "checkpoint," ensures that cell division progresses normally; without it, daughter cells may grow even more aggressively and be harder to stop.

"The evolution of prostate cancer from an androgen-dependent state to an androgen-independent one is a key step in its progression," says study senior author Myles Brown, MD, of Dana-Farber. "The discovery that the androgen receptor directs a distinct gene pathway in androgen-independent prostate cancers may lead to the identification of genes in that pathway that can be targeted by future therapies."

Prostate cancers whose growth is fed by androgen are commonly treated with androgen-blocking drugs. Such medications can hold the disease in check for a period of time that varies from patient to patient, but the tumor almost invariably gains the ability to grow without external androgen.

One of the ways such cells re-start their growth is by producing their own androgen, scientists have discovered. Another way involves the androgen receptor itself - the "keyhole" in the cell nucleus that androgen molecules fit into - but the actual mechanism by which it operates hasn't been known.

To find that mechanism, Brown's team, including co-lead authors Qianben Wang, PhD, now of Ohio State, and Wei Li, PhD, now of Baylor College of Medicine, charted the activity levels, or expression, of genes controlled by the androgen receptor in androgen-dependent and androgen-independent prostate cancer cells. In the androgen-independent cells, they found a group of genes with epigenetic markings - tiny attachments to DNA that switchs genes on and off - that caused them to be especially active. The genes form a completely separate pathway from the one active in androgen-dependent cells.

It's not known what causes those epigenetic changes to occur, but "we are profiling the genome-wide epigenetic landscape of androgen-dependent and -independent cancers, trying both experimental and computational methods to identify additional regulators," says study co-senior author X. Shirley Liu, PhD, of Dana-Farber.

"The androgen receptor clearly works by an entirely different program in androgen-dependent and -independent cancers," says Wang. "Having discovered that program, we'll be in a better position to understand how it operates and how gene-targeted therapies may shut it down."

Source: Dana-Farber Cancer Institute