Researchers find proteins may point way to new prostate cancer drug targets

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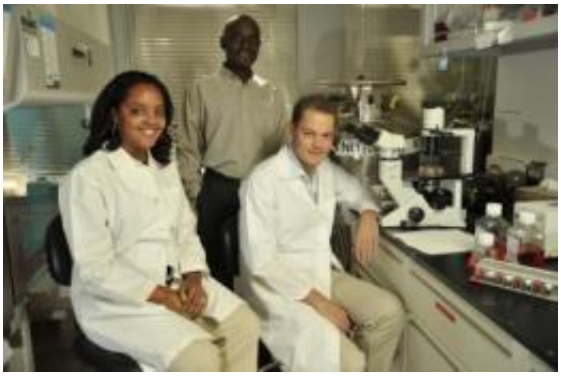

Vanderbilt's Sarki Abdulkadir, M.D., Ph.D., center, Sydika McKissic, Ph.D., left, Philip Anderson, Ph.D., and colleagues are studying the role of two proteins in regulating the same set of genes in prostate cancer. Credit: Photo by John Russell

Two proteins that act in opposing directions – one that promotes cancer and one that suppresses cancer — regulate the same set of genes in prostate cancer, Vanderbilt-Ingram Cancer Center researchers have found.

The findings, reported recently in the *Journal of Clinical Investigation*, point toward potential drug targets and prognostic markers for prostate cancer.

"We are trying to understand the molecular genetics of prostate cancer:

what are the genes that are altered in human prostate cancer, and very importantly, how do they lead to cancer when they are changed?" said Sarki Abdulkadir, M.D., Ph.D., associate professor of Pathology, Microbiology and Immunology and of Cancer Biology.

Abdulkadir's lab uses mouse models to probe the molecular pathways involved in prostate cancer.

Two separate projects in the lab unexpectedly came together for this study — one led by postdoctoral fellow Philip Anderson, Ph.D., and the other spearheaded by (then) graduate student Sydika McKissic, Ph.D.

Anderson was using genomic approaches to understand how loss of a tumor suppressor protein, called NKX3.1, promotes prostate cancer. NKX3.1 is a transcription factor, meaning that it binds to and regulates the expression of other genes, turning them "on" or "off."

"It is one of the genes most commonly deleted in human prostate cancer…and is lost very early," explained Abdulkadir.

Anderson isolated the NKX3.1 protein and identified a set of 9,817 genes that bind to the protein. Of that set, he identified 282 genes that are regulated by the protein – i.e., their expression was altered by loss of NKX3.1.

"So we took those genes...and asked 'what is interesting about these genes?'" said Abdulkadir.

Using bioinformatics tools, the investigators found a quarter of the NKX3.1-regulated genes are also bound by a "famous" oncogene called Myc (which, like NKX3.1, is also a transcription factor).

It was previously known that, as human prostate cancer progresses,

NKX3.1 levels decrease and Myc levels increase. The research team's findings showed that these two proteins with opposing functions regulated a similar set of genes.

"What we showed in this paper is that actually in many instances, NKX binds and represses these genes while Myc binds and activates them," Abdulkadir said. "The way we think about it is this: Myc is the 'accelerator' and NKX3.1 is the 'brake' (on cancer growth)."

Meanwhile, McKissic was working to develop a mouse model of prostate cancer. However, mice lacking NKX3.1 alone developed early stage prostate cancer, but the disease would not progress. Abdulkadir suspected that another genetic "hit" or mutation was necessary to progress fully to prostate cancer and suspected that Myc was a good candidate for that second "hit" based on how commonly the gene is altered in human prostate cancer.

So McKissic developed a mouse model in which NKX3.1 was deleted and Myc was overexpressed in the specific prostate cells where cancer arises.

She showed that mice with this combination of genetic alterations did progress to advanced cancer — and that the same target genes identified in Anderson's project were dysregulated in the mouse model.

To determine clinical relevance, the researchers then analyzed genetic and clinical data from patients with prostate cancer. They found that expression of these target genes was associated with tumor relapse – specifically, that suppression of a subset of the target genes may predict relapse.

In addition to potential prognostic indicators of relapse, these "cross-regulated" genes may present therapeutic targets to halt progression of

prostate cancer.

Future studies on the roles of the individual target genes could help reveal "which of these genes are bigger players than others for things like therapeutics," Abdulkadir said.

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