Targeting MAPK4 emerges as a promising therapy for prostate cancer

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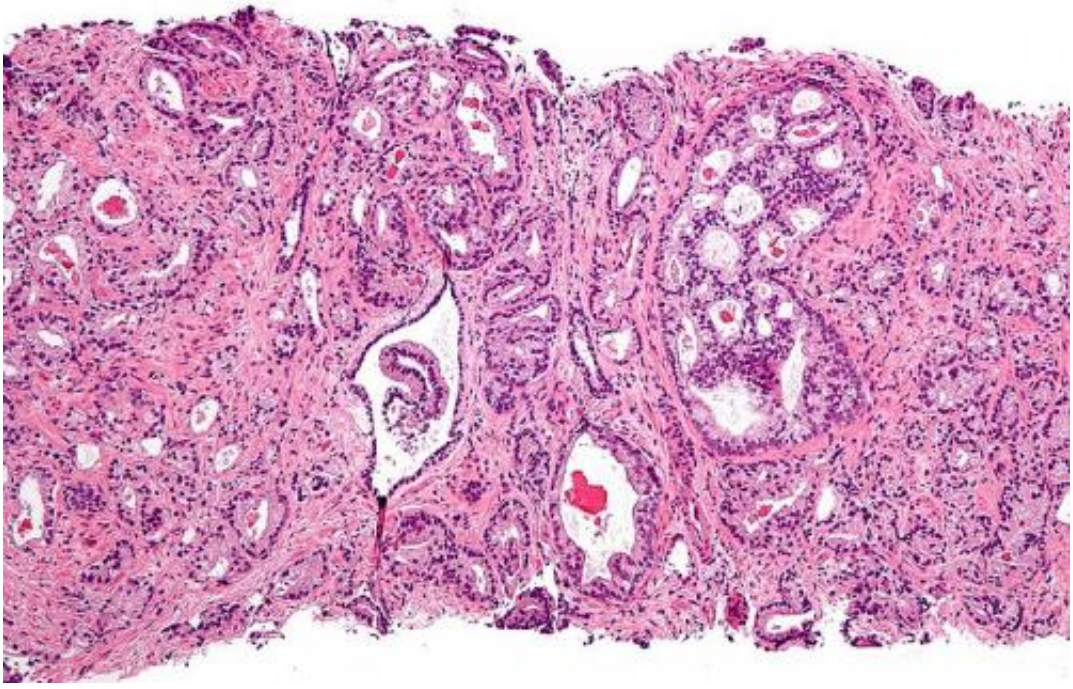

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

The battle against late-stage prostate cancer might have found a potential new strategy to combat this deadly disease. Research led by Baylor College of Medicine reveals in the *Journal of Clinical Investigation* that the enzyme MAPK4 concertedly activates androgen receptor (AR) and AKT, molecules at the core of two cellular signaling pathways known to promote prostate cancer growth and resistance to standard therapy.

Importantly, inhibiting MAPK4 simultaneously inactivated both AR and AKT and stopped cancer growth in animal models. The findings open the possibility that targeting MAPK4 in human prostate cancer might provide a novel therapeutic strategy for this disease that is the second leading cause of cancer death in American men.

"Scientists already knew that both the AR and the AKT pathways can drive prostate cancer," said corresponding author Dr. Feng Yang, assistant professor of molecular and cellular biology and member of the Dan L Duncan Comprehensive Cancer Center at Baylor. "One complication with targeting AR (for instance, with medical castration therapy, including the most advanced agents such as enzalutamide, apalutamide and abiraterone) or AKT is that there is a reciprocal crosstalk between these pathways. When AR is inhibited, AKT gets activated, and vice-versa, therefore tackling these pathways to control cancer growth is complex."

In previous work, the Yang lab studied the little-known enzyme MAPK4.

"One interesting aspect of MAPK4 is that it is rather unique because it does not work as conventional MAPK enzymes do," Yang said. "To our knowledge, we are one of the few groups studying MAPK4 and the first to uncover its critical roles in human cancers."

In their previous study, Yang and his colleagues discovered that MAPK4 can trigger the AKT pathway, not only in prostate cancer but in other cancers as well, such as lung and colon cancers.

In the current study, the researchers found that MAPK4 also activates the AR signaling pathway by enhancing the production and stabilization of GATA2, a factor that is crucial for the synthesis and activation of AR.

Further experiments showed that MAPK4 triggered the concerted activation of both AR and AKT pathways by independent mechanisms, and this promoted prostate cancer growth and resistance to castration therapy, a standard medical treatment for advanced/metastatic prostate cancer. Importantly, genetically knocking down MAPK4 reduced the activation of both AR and AKT pathways and inhibited the growth, including castration-resistant growth, of prostate cancer in animal models. The researchers anticipate that knocking down MAPK4 also could reduce the growth of other cancer types in which MAPK4 is involved.

"Our findings suggest the possibility that regulating MAPK4 activity could result in a novel therapeutic approach for prostate cancer," Yang said. "We are interested in finding an inhibitor of MAPK4 activity that could help better treat prostate cancer and other cancer types in the future."

More information: Tao Shen et al, MAPK4 promotes prostate cancer by concerted activation of androgen receptor and AKT, *Journal of Clinical Investigation* (2021). DOI: 10.1172/JCI135465

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