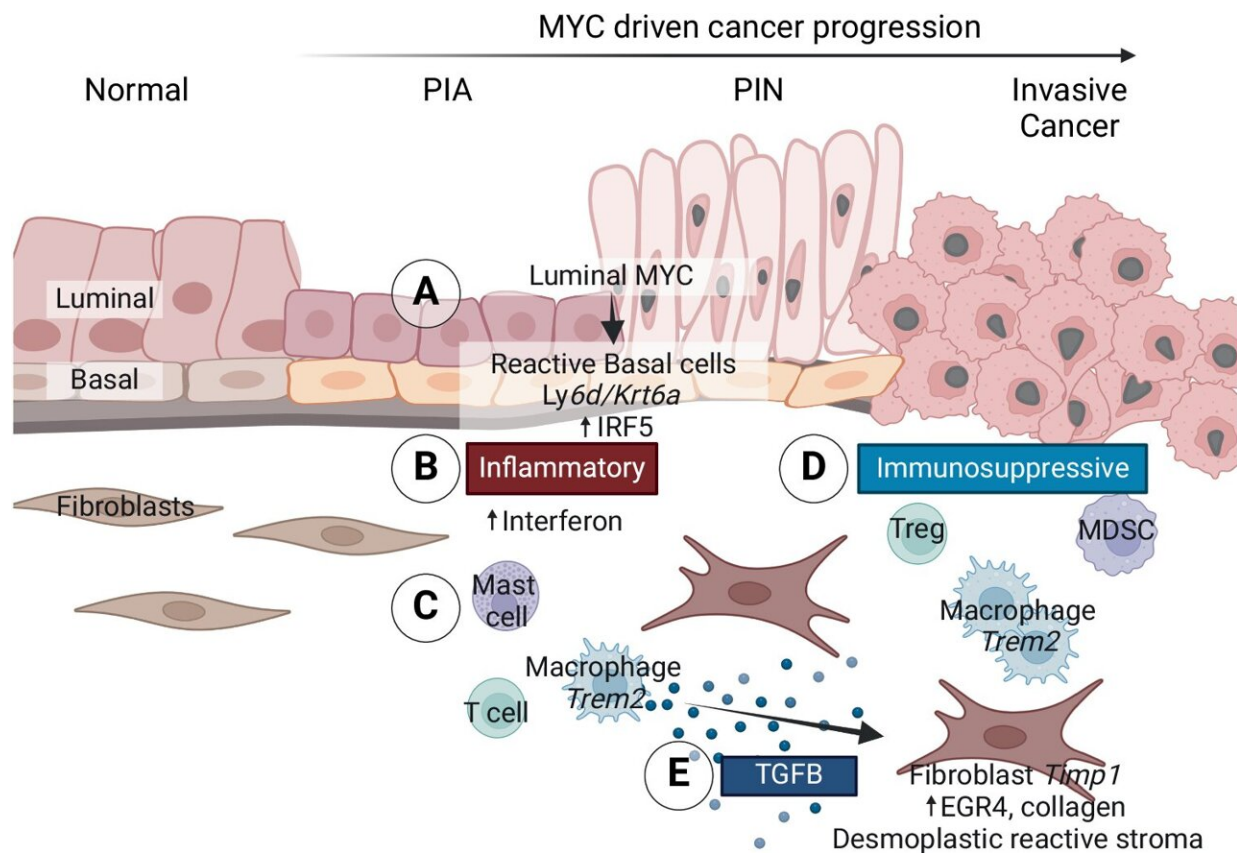


Oncoprotein activity increases prostate cancer progression, finds study

August 29 2024, by Melissa Rohman



MYC activation in neoplastic cells reprograms the prostate TME. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-51450-2

Investigators have discovered that aberrant activation of a specific oncoprotein drives key tumor-promoting changes in the prostate tissue

microenvironment during cancer progression, according to a Northwestern Medicine study [published](#) in *Nature Communications*.

The study, co-led by Mindy Graham, Ph.D., research assistant professor of Urology, could inform new targeted therapeutic strategies for all stages of [prostate cancer](#).

Prostate cancer is the second leading cause of death in men in the U.S., and 1 in 8 men will be diagnosed with prostate cancer during their lifetime, according to the American Cancer Society.

Prostate cancer is a heterogenous disease, with various genomic and [epigenetic alterations](#) driving cancer development. Despite this heterogeneity, prostate cancer tumors share several molecular and cellular characteristics in common, but how [prostate cancer cells](#) mediate these changes over time has remained poorly understood.

In the current study, Graham and colleagues performed single-cell RNA-sequencing analysis and complementary in situ tissue staining, and compared the biology of human prostate cancer tissue samples with mouse models of prostate cancer.

"We were very interested in doing a comparative biology study where we have patient tissues that we could rigorously investigate, but then we could do some informative experimental analysis with an appropriate [mouse model](#)," Graham said.

These analyses revealed every human [tumor](#) that was analyzed had aberrant activation of the MYC oncoprotein, which is well-known to be upregulated in prostate cancer, and is a "common denominator" across the tumor samples, despite their molecular and pathological heterogeneity.

"This observation was supported when performing differential gene expression and pathway analysis of the publicly available TCGA dataset of primary prostate cancer," the authors wrote.

To further confirm their findings, the scientists analyzed mouse models of prostate cancer driven by human MYC and found that the increased MYC activity leads to a cascade of alterations in surrounding healthy cells, causing the tissue to be proinflammatory at the precursor stage and then eventually become immunosuppressive as the cancer progressed.

"What was so fascinating to us is we were seeing convergent changes in the mouse model that we could see in the human data," Graham said.

"People think of prostate cancer as an immunologically cold tumor microenvironment. But at the very beginning, at the earliest stages in the precursor setting, it's actually very inflammatory, but it's only until it becomes invasive carcinoma when you see this switch that happens from inflammatory to something that resembles an immunologically cold environment with immunosuppressive cell types."

According to Graham, the findings may inform the development of new targeted treatment approaches for prostate cancer as well as future research that evaluates these key cell state alterations that occur in prostate cancer and many other invasive cancer types.

"My hypothesis is that the changes that happened in the primary setting with MYC oncogene activation are recapitulated in the metastatic setting," Graham said. "So, the idea is that although you have a different tumor site, the MYC activation in the cancer cells are still there, and so when they're establishing themselves in this new metastatic site, the same cell type changes in the primary setting are occurring in the metastatic setting."

"Those insights then will help us to develop therapies that might not only

target the primary but also the metastatic setting."

More information: Mindy K. Graham et al, Convergent alterations in the tumor microenvironment of MYC-driven human and murine prostate cancer, *Nature Communications* (2024). [DOI: 10.1038/s41467-024-51450-2](https://doi.org/10.1038/s41467-024-51450-2)

Provided by Northwestern University

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