

Y Chromosome Affects Cancer Growth

Study results help explain why some cancers have different prognosis in men and women, and also suggest novel treatment strategies.

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The X and Y chromosomes determine biological sex. Males have one X and one Y chromosome, and females have two X chromosomes. As males age, some cells can lose their Y chromosome due to errors in cell division. This loss of the Y chromosome is associated with health problems. Notably, it occurs in up to 40% of bladder cancers. But it's not known how loss of the Y chromosome affects tumor growth and patient outcomes.

To find out, an NIH-funded research team led by Dr. Dan Theodorescu at Cedars-Sinai Medical Center investigated the relationships between loss of the Y chromosome, patient prognosis, and treatment outcomes in patients with bladder cancer. They began by examining data on gene expression, or whether genes are turned on or off, for 300 male patients with muscle-invasive bladder cancer. They identified loss of the Y chromosome based on lack of expression of certain Y chromosome genes. The study [appeared in Nature](#) on June 21, 2023.

Patients without the Y chromosome, the researchers found, were much less likely to survive than those with one. To understand why loss of the Y chromosome might lead to worse outcomes, the team created two lines of mouse bladder cancer cells, one with and one without the Y chromosome.

Both cell lines grew equally well in culture. But when the cells were injected into mice, cells without Y chromosomes formed tumors that grew about twice as fast as those with Y chromosomes.

This difference in tumor growth was only seen in mice with a working immune system. In mice lacking immune cells called T cells, both cell types grew at the same rate. In both mice and human patients, cancers without the Y chromosome showed signs of T cell exhaustion or dysfunction in the tumor vicinity.

These results suggest that losing the Y chromosome helps tumors to grow by suppressing the local immune response. They also suggest that tumors without a Y chromosome might be particularly vulnerable to a type of therapy called immune checkpoint inhibition. Indeed, tumors lacking a Y chromosome in mice responded better to this therapy than those with a Y chromosome. And in a previous clinical trial of an immune checkpoint inhibitor, patients with loss of the Y chromosome

had better outcomes after treatment than those without.

A related NIH-funded study, led by Ronald DePinho at The University of Texas MD Anderson Cancer Center, was [published in Nature](#) on the same day. This team showed that certain colorectal cancers led to worse outcomes in male mice than female mice. They found a gene on the Y chromosome, KDM5D, that was responsible for this difference. KDM5D turned off several other genes, including those involved in how cells attach to each other and in cell recognition by the immune system. Deleting KDM5D in cancer cells led to stronger cell-cell attachments, making the cancer cells less invasive. It also made it easier for T cells to kill the cancer cells.

“The fundamental new knowledge we provide here may explain why certain cancers are worse in either men or women, and how best to treat them,” Theodorescu says. “It also illustrates that the Y chromosome does more than determine human biologic sex.”

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