Tough-to-Treat Prostate Cancer Metastasizes by Evading Immune System

Building on this discovery, researchers have designed a new treatment that showed promise in a study of mice.

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An aggressive form of prostate cancer known as double-negative prostate cancer (DNPC) metastasizes, or spreads from its original location, by evading the immune system. Building on such research findings, investigators at the University of Texas MD Anderson Cancer Center have developed a new treatment that when combined with a pair of approved immunotherapies, apparently arrested or even reversed the spread of such cancer among mice.

DNPC is difficult to treat and may arise in men previously treated with androgen receptor (AR) inhibitors, such as Erleada (apalutamide) or the recently approved Nubeqa (darolutamide), which prevent androgen hormones from spurring prostate cancer cell growth.

The findings of these investigations were published in Cancer Cell.

The study authors, led by Filippo Giancotti, MD, PhD, a professor of cancer biology at MD Anderson, found that an epigenic regulator called the polycomb repressor complex 1 (PRC1) plays a key role in prostate cancer metastasis. PRC1 promotes the capacity of metastatic cells to regenerate by suppressing the immune system and driving the growth of tumor blood vessels, or angiogenesis.

“The findings open up potential new approaches to treating DNPC, which has been recognized recently as a new subtype that emerges at least in part in response to treatment with next-generation AR inhibitors,” Giancotti said in a press release. “We showed that PRC1 plays a role with immunosuppression at metastatic sites in DNPC, and we developed a novel in-class inhibitor of PRC1. This inhibitor exhibited efficacy as a single treatment and cooperated with double checkpoint immunotherapy to completely suppress metastasis in preclinical DNPC models.”

In laboratory experiments, Giancotti and his team found that PRC1 induced a gene for a cytokine known as CCL2 and that this was the major force promoting metastasis. CCL2 binds to a receptor on the surface of tumor cells called CCR4, which increases the cells’ ability to regenerate. The

cytokine also binds to the CCR2 receptor on immune cells, which inhibits their ability to combat the metastasis.

Additionally, CCL2 attracts immune cells known as tumor-associated macrophages (TAMs) as well as regulatory T cells (Tregs), an effect that suppresses the immune response to metastasis while also stimulating angiogenesis.

The study authors found that inhibiting PRC1 reduced the volume of TAMs and Tregs recruited to the tumors and ultimately suppressed metastasis.

In a mouse study, the investigators combined a PRC1 inhibitor with two types of checkpoint inhibitor immunotherapy. Doing so, they found, attracted CD4 and CD8 immune cells to the tumor sites, ultimately leading to a maximal amount of tumor-cell death.

“This indicates that the inhibiting TAMs and Tregs with PRC1 inhibitors enables double checkpoint therapy to not only recruit but also to activate T cells, thus causing metastasis regression,” said Giancotti.

To read the study abstract, click here.
