

Discovery shows how difficult-to-treat prostate cancer evades immune system

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Researchers at The University of Texas MD Anderson Cancer Center have discovered how an aggressive form of prostate cancer called double-negative prostate cancer (DNPC) metastasizes by evading the immune system. The investigators also reported on the pre-clinical development of a new therapy, which, when given in combination with existing immunotherapies, appears to stop and even reverse metastasis in mouse models.

DNPC is difficult to treat and frequently arises in patients previously treated with therapies that inhibit [androgen receptors](#) (AR), known to spur prostate [cancer](#) cells growth. Study findings were published in the July 18 online issue of *Cancer Cell*.

Filippo Giancotti, M.D., Ph.D., professor of Cancer Biology, reported that an epigenetic regulator known as the polycomb repressor complex 1 (PRC1) coordinates the initiation of metastasis by increasing the regenerative capacity of metastatic cells and by suppressing the [immune system](#) and spurring tumor blood vessel growth 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," said Giancotti, "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 pre-clinical DNPC models."

Through in vivo genetic screening, the team identified a cytokine called CCL2 as the major pro-metastatic gene induced by PRC1. CCL2 binds to a tumor cell receptor called CCR4 to boost regenerative capacity and to CCR2 in immune cells, creating an immunosuppressive microenvironment and boosting tumor blood vessel growth.

"CCL2 also attracts tumor-associated macrophages (TAMS) and regulatory T cells (Tregs), which suppresses the immune system and stimulates angiogenesis," said Giacotti. "Our study showed that targeting PRC1 inhibits recruitment of TAMS and Tregs, suppressing tumor metastasis."

Giacotti's team combined PRC1 with two types of immunotherapy agents, which attracted important immune cells called CD4 and CD8 T cells, resulting in "maximal induction" of tumor cell death in mice.

"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 Giacotti.

Provided by University of Texas M. D. Anderson Cancer Center

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