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PROSTATE CANCER

New model to test immunotherapy combinations

Immunotherapy using antibodies against cytotoxic-T-lymphocyte-associated protein 4 (CTLA4), programmed cell death 1 (PD-1) or its ligand PD-L1 (immune checkpoint blockade (ICB)) has shown efficacy in various cancer types, but activity in prostate cancer is insufficient. Now, a paper published in *Nature* describes a new prostate cancer mouse model that enables testing of therapies that target components of the immune system. Using this model, researchers demonstrated that combination of ICB with agents that target myeloid-derived suppressor cells (MDSCs) is significantly more effective than use of either treatment strategy alone.

Xin Lu and colleagues from the MD Anderson Cancer Center in Houston, Texas, USA, set out to create a mouse model of prostate cancer that overcomes the limitations of current germline-mutation-based systems, such as low numbers of mice with the capacity to develop the disease. In their chimera-based system, which is derived from mouse embryonic stem cells with *PB-Cre⁺ Pten^{L/L} p53^{L/L} Smad4^{L/L} mTmG^{L/+} LSL-LUC^{L/+}* genotype (termed CPPSML), ~50% of high-percentage chimeras had GFP⁺ cancer cells in the prostate, draining lymph nodes

and lungs at 3 months. Areas of the prostate that were GFP⁺ demonstrated adenocarcinoma histology and were positive for cytokeratin 5 and cytokeratin 8. “This approach allowed us to gain fourfold increase of the efficiency of producing the mouse cohorts, thus, dramatically shortening the time required for our preclinical trials,” Y. Alan Wang, one of the corresponding authors of the study, told *Nature Reviews Urology*.

Mice in which castration-resistant prostate cancer (CRPC) was induced by surgical castration followed by an enzalutamide-containing diet were used for testing of therapy regimens. The team used a mix of anti-CTLA4 and anti-PD1 antibodies for ICB and, for suppression of MDSCs, the tyrosine kinase inhibitors dasatinib, cabozantinib or the PI3K–mTOR inhibitor BEZ235. At 4 weeks of treatment, all single-therapy regimens showed limited effects on tumour mass. By contrast, the combination of ICB with cabozantinib or BEZ235, but not dasatinib, had significant effects on both primary tumour growth and metastasis.

The team then analysed the pattern of immune cells present in tumours treated with the varying regimens. They found that dasatinib treatment significantly reduced

the number of tumour-infiltrating T cells. By contrast, cabozantinib and BEZ235 treatment significantly reduced the number of granulocytic MDSCs. In mice who had received ICB, tumours of animals treated with ICB only had a significantly increased ratio of CD8⁺ T cells to regulatory T cells, characteristic for ICB-based therapies. Addition of cabozantinib or BEZ235 to ICB further elevated this T cell subtype ratio.

“We observed striking synergistic efficacy against primary and metastatic CRPC when ICB was combined with MDSC-inactivating therapies that preserve T-cell functions,” summarize Wang and Ronald DePinho, who is also corresponding author. “This finding strengthens the existing idea of enhancing immunotherapy by blocking immunosuppressive myeloid cells, positioning this combination strategy as a viable approach for lethal prostate cancer.”

To explore the molecular effects underlying these findings, the researchers examined tyrosine kinase receptor signalling pathways and found that cabozantinib and BEZ235 reduced MDSC activity through inhibition of PI3K signalling. In addition, investigation of cytokine signalling showed that cabozantinib and BEZ235 treatment impaired cytokine expression from prostate cancer cells that controls MDSC expression of immunosuppression-related genes.

“We continue to investigate more effective and specific approaches to targeting MDSCs in prostate cancer through deeper understanding of the signalling regulation in the tumour microenvironment,” concludes DePinho. “We hope that our findings will promote the establishment of an integrated immunotherapy approach to treating lethal prostate cancer in the clinic in the near future.”

Clemens Thoma

ORIGINAL ARTICLE Lu, X. et al. Effective combinatorial immunotherapy for castration-resistant prostate cancer. *Nature* <http://dx.doi.org/10.1038/nature21676> (2017)

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