CDK inhibitors may improve immune therapy effectiveness for recurrent breast cancer

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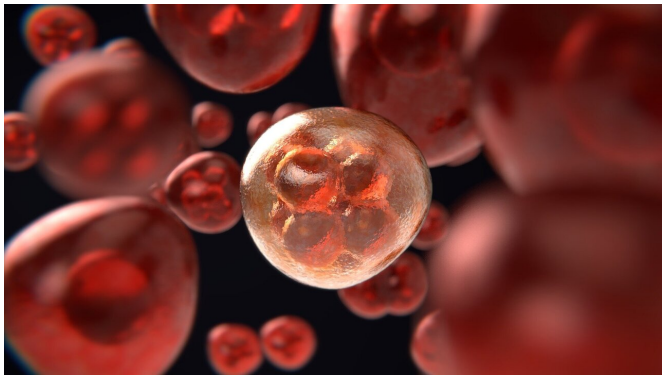

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A class of drugs that inhibits breast cancer progression when used with hormonal therapy might also boost the effectiveness of immune therapy in cases of recurrent, metastatic breast cancer, according to a new study led by researchers at The Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC—James).

Published in the journal *Cell Reports*, the findings of the animal study suggest that drugs called CDK4 and CDK6 (CDK4/6) inhibitors might improve the effectiveness of immune therapies for metastatic, estrogen-receptor-positive (ER+) breast cancer.

"We know that CDK4/6 inhibitors effectively slow the progression of newly diagnosed breast cancer, but they don't kill cancer cells," says principal investigator Anna Vilgelm, MD, a member of the OSUCCC—James Translational Therapeutics Program and assistant professor at the Ohio State College of Medicine. "Consequently, the disease often recurs, and then it is usually fatal because we have no effective therapies for recurrent disease.

"Our findings suggest that combining CDK4/6 inhibitors with immunotherapy might offer an effective treatment for recurrent, metastatic ER+ breast cancer," Vilgelm says.

Specifically, the study shows that CDK4/6 inhibitors can improve the efficacy of T-cell-based therapies such as adoptive T-cell transfer or T-cell-activating antibodies in animal models of breast cancer.

Immune therapies are proving to be effective treatments for a variety of cancers but not for advanced breast cancer. One problem is that breast tumors often have low numbers of cancer-killing T lymphocytes within the tumor. Such tumors tend to respond poorly to immune therapies.

"In addition, breast cancer patients with low numbers of tumor-infiltrating lymphocytes often have worse survival compared to patients with high numbers of infiltrating lymphocytes in their tumors," says Vilgelm.

The new study shows that CDK4/6 inhibitors cause breast tumors to secrete small proteins called chemokines that attract T cells. This can help to improve patients' response to cancer immunotherapies.

For this study, Vilgelm and her colleagues used the oral CDK inhibitor palbociclib, mouse models, breast cancer cell lines and analyses of The Cancer Genome Atlas (TCGA) to study the influence of CDK4/6 inhibitors and chemokine production in the tumor immune microenvironment and on patient outcomes.

Key findings include:

- Pre-treatment with a CDK4/6 inhibitor improves recruitment of T cells into tumors and improved the outcome of adoptive cell therapy in animal models;
- CDK4/6 inhibitor-treated human breast cancer cells produce T-cell-recruiting chemokines;
- TCGA analysis showed that chemokine expression is a favorable prognostic factor in breast cancer patients;
- mTOR-regulated metabolic activity is required for chemokine induction by CDK4/6 inhibition;
- T-cell-recruiting chemokines may be useful prognostic markers for stratifying patients for immunotherapy treatment.

"Overall," Vilgelm says, "our findings suggest that CDK4/6 inhibitors may offer a therapeutic strategy that can attract T cells into breast cancer tumors, which may increase their sensitivity to immune therapies."

More information: Roman V. Uzhachenko et al, Metabolic modulation by CDK4/6 inhibitor promotes chemokine-mediated recruitment of T cells into mammary tumors, *Cell Reports* (2021). DOI: 10.1016/j.celrep.2021.108944

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