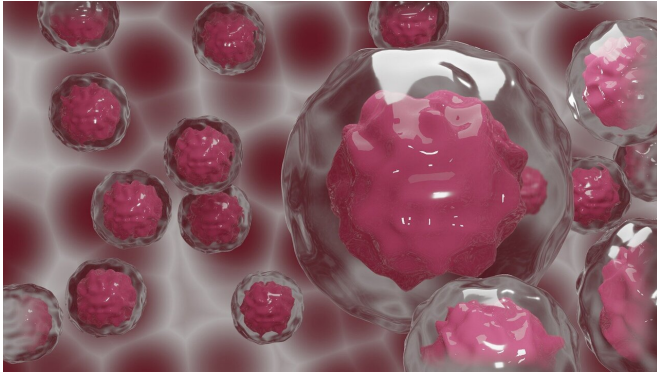


Study reveals new strategy for reducing tumor growth, metastasis

18 December 2020, by Leigh MacMillan



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A team of Vanderbilt investigators has discovered that blocking a certain signaling pathway boosts antitumor immunity and reduces tumor growth and metastasis in models of breast cancer and melanoma.

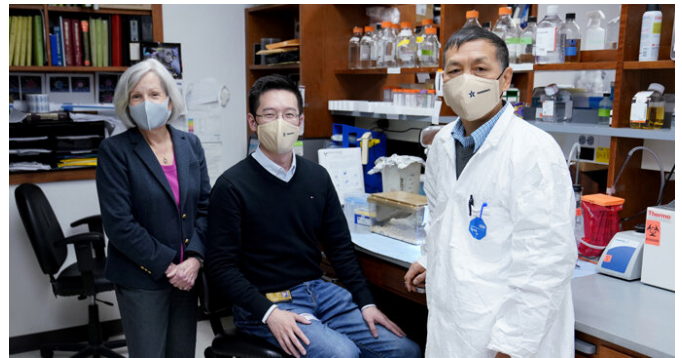
The findings, reported in the journal *Cancer Immunology Research*, add mechanistic insight and support for the therapeutic potential of drugs that are currently being tested in clinical trials for various types of cancer.

The studies focus on the complex interplay of signaling factors and [immune system cells](#) in the tumor microenvironment. To grow and survive, a tumor must evade the body's immune response against it. One way tumors do this is by secreting factors that recruit a set of cells called myeloid-derived [suppressor cells](#) (MDSCs), which originate in the bone marrow and can suppress the T cell-mediated immune response.

Ann Richmond, Ph.D., Ingram Professor of Cancer Research and professor of Pharmacology, and her team have long studied tumor-secreted chemokine factors and their receptors on MDSCs, in particular

the receptor CXCR2. CXCR2 is a key chemokine receptor involved in the movement of MDSCs into developing tumors and the pre-metastatic niche.

"We had the hypothesis that if we could target CXCR2 in [myeloid cells](#), we might ablate the trafficking of MDSCs into the tumor microenvironment and thereby enhance the immune response to a developing tumor," Richmond said.



Ann Richmond, MD, Chi Yan, PhD, Jinming Yang, PhD, and colleagues are studying ways to boost antitumor immunity and reduce tumor growth in breast cancer and melanoma. Credit: Donn Jones

The researchers, led by Jinming Yang, Ph.D., staff scientist, and Chi Yan, Ph.D., research instructor in Pharmacology, did just that.

They developed a [mouse model](#) with a targeted deletion of the CXCR2 gene in myeloid cells and studied the development of tumors from implanted breast cancer or melanoma cells. They found reduced tumor growth and metastasis for both types of tumors in mice missing CXCR2 signaling in myeloid cells.

An in-depth analysis of immune cells and

chemokine factors in the tumors revealed surprises, among breast cancer and melanoma patients.

Richmond said. In addition to a reduction in MDSCs in the tumors, the researchers found increased numbers of B cells (of the B1b type) and CD8+ T cells, which kill tumor cells, along with increased levels of the chemokine CXCL11.

"This is a [paradigm shift](#)—the idea that by simply blocking CXCR2 expression by myeloid cells, there is an influx of B cells making CXCL11, which then recruits T cells into the [tumor microenvironment](#)," Richmond said. "Moreover, since the loss of CXCR2 expression in myeloid cells led to depletion of MDSCs, there is also reduction in MDSC suppression of the CD8+ T cell antitumor activity.

The final result is stronger antitumor immunity that suppresses tumor growth and metastasis."

The researchers demonstrated that the effect was dependent on both the B cells and the CD8+ T cells and that when either of these cell populations were depleted from mice missing CXCR2 expression in myeloid cells, the inhibition of [tumor growth](#) was markedly reduced.

Importantly, Richmond noted, using systemic delivery of a drug that blocks the CXCR2 receptor produced the same effects in tumors implanted in control mice.

"The CXCR2 antagonist we used is currently in clinical trials in combination with immune therapy for patients with melanoma, and our studies have now substantiated the intricate mechanism that's involved," Richmond said. "Patients don't all respond to any one therapy, so being able to see how these various immune cells are being modulated with CXCR2 antagonist provides mechanistic insight into how CXCR2 antagonist combined with immune checkpoint inhibitor therapies might work in patients."

To explore whether the B cell-CXCL11 signaling axis may be important in breast cancer and melanoma prognosis, the researchers queried databases of human molecular cancer data (TCGA and GEO-NCBI). They found positive correlations among B cell markers, CXCL11 and a CD8+ T cell marker in association with increased survival

"These data appear to confirm that B cells and CXCL11 are working together to bring in more T [cells](#) to enhance [tumor](#) killing and survival," Richmond said.

Moving forward, the researchers are testing combinations of CXCR2 inhibitors, immune therapies and other signaling pathway inhibitors in various [cancer](#) models.

More information: Jinming Yang et al. Targeted Deletion of CXCR2 in Myeloid Cells Alters the Tumor Immune Environment to Improve Antitumor Immunity, *Cancer Immunology Research* (2020). [DOI: 10.1158/2326-6066.CIR-20-0312](https://doi.org/10.1158/2326-6066.CIR-20-0312)

Provided by Vanderbilt University

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