Researchers discover how breast cancer cells hide from immune attack

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Researchers at the Indiana University Melvin and Bren Simon Comprehensive Cancer Center have identified how breast cancer cells hide from immune cells to stay alive. The discovery could lead to better immunotherapy treatment for patients.

Xinna Zhang, Ph.D., and colleagues found that when breast cancer cells have an increased level of a protein called MAL2 on the cell surface, the cancer cells can evade immune attacks and continue to grow. The findings are published this month in *The Journal of Clinical Investigation* and featured on the journal's cover.

"Like other cancer cells, breast cancer cells present tumor-specific antigens on the cell membrane, which immune cells recognize so they can kill the tumor cells," Zhang said. "But our study found that MAL2 can reduce the level of these antigens, so these tumor cells are protected and can no longer be recognized as a threat by these immune cells."

The lead author of the study, Zhang is a member of the IU Simon Comprehensive Cancer Center and assistant professor of medical and molecular genetics at IU School of Medicine.

Considered the future of cancer treatment, immunotherapy harnesses the body's immune system to target and destroy cancer cells. Understanding how cancer cells avoid immune attacks could offer new ways to improve immunotherapy for patients, explained Xiongbin Lu, Ph.D., Vera Bradley Foundation Professor of Breast Cancer Innovation and cancer center researcher.

"Current cancer immunotherapy has wonderful results in some patients, but more than 70% of breast cancer patients do not respond to cancer immunotherapy," Lu said. "One of the biggest reasons is that tumors develop a mechanism to evade the immune attacks."

The collaborative research team set out to answer key questions: How do breast cancer cells develop this immune evasion mechanism, and could targeting that action lead to improved immunotherapies?

Zhang and Lu, members of the Vera Bradley Foundation Center for

Breast Cancer Research, turned to biomedical data researcher Chi Zhang, Ph.D., assistant professor of medical and molecular genetics at IU School of Medicine. Chi Zhang developed a computational method to analyze data sets from more than 1,000 breast cancer patients through The Cancer Genome Atlas. That analysis led researchers to MAL2; it showed that higher levels of MAL2 in breast cancer, and especially in triple-negative breast cancer (TNBC), was linked to poorer patient survival.

"Dr. Chi Zhang used his advanced computational tool to build a bridge that connects cancer genetics and cancer genomics with a clinical outcome," Lu said. "We can analyze molecular features from thousands of breast tumor samples to identify potential targets for cancer immunotherapy. From that data, MAL2 was the top-ranked gene that we wanted to study."

Xinna Zhang took that data to her lab to determine MAL2's purpose in the cells, how it affects breast cancer cell growth and how it interacts with immune cells. Using breast cancer tissue samples from IU patients, cell models and animal models, she found that breast cancer cells express more MAL2 than normal cells. She also discovered that high levels of MAL2 significantly enhanced tumor growth, while inhibiting the protein can almost completely stop tumor growth.

In Lu's lab, he used a three-dimensional, patient-derived model called an organoid to better understand how reducing MAL2 could improve patient outcomes.

"Tumor cells can evade immune attacks; with less MAL2, the cancer cells can be recognized and killed by the immune system," Lu said. "MAL2 is a novel target. By identifying its function in cancer cells and cancer immunology, we now know its potential as a cancer immunology target."

Researchers now are exploring ways these findings could be used to develop and improve breast cancer therapies.

More information: Yuanzhang Fang et al, MAL2 drives immune evasion in breast cancer by suppressing tumor antigen presentation, *Journal of Clinical Investigation* (2020). DOI: 10.1172/JCI140837

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