

PUBLIC/LAY ABSTRACT

Breast cancer is the most common cancer in women. An enormous success of immunotherapy has benefited patients with a variety of cancer types including melanoma, lung cancer and bladder cancer. However, immunotherapy has had limited success for breast cancer and breast cancer-caused life loss remains a big threat to women's health worldwide. It is reported that more than 40,000 women die from breast cancer every year in the United States and metastatic breast cancer causes the majority of those deaths.

Chemo-immunotherapy refers to the combination of chemotherapy and immunotherapy. In 2019, the FDA approved the chemo-immunotherapy regimen where nab-paclitaxel plus atezolizumab (anti-PD-L1) is used as first-line treatment for PD-L1⁺ locally advanced or metastatic triple-negative breast cancer. This treatment can slow down the disease progression by an average of 2.6 months. Apparently, it is far from an adequate solution to the cure of metastatic breast cancer. The moderate response rate and the resistance remain major obstacles.

What are the factors that limit the efficacy of chemo-immunotherapy? How can we better the current therapeutics for breast cancer, especially metastatic breast cancer? These questions represent the most pressing unmet needs for the clinical care of breast cancer patients. Recently, myeloid-derived suppressor cells (MDSCs) are identified to inhibit the anti-tumor immunity during cancer progression and metastasis. And mounting studies, including the ones published from our own group, have demonstrated that functional inactivation of MDSCs significantly increased the sensitivity of solid tumors to immunotherapy. This has provided a new rationale for improving breast cancer chemo-immunotherapy by co-targeting these "bad" immune cells. MDSCs exert immunosuppressive effects through multiple mechanisms. Therefore, identifying the precise mechanism underlying the functional activity of MDSCs in metastatic breast cancer is a crucial step prior to applying any MDSC-targeted therapy to enhancing chemo-immunotherapy for breast cancer patients. It is also critical to use nontoxic or lowly toxic agents for MDSC targeting, because the patients treated with the existing chemo-immunotherapy regimen already experience strong and sometimes hard-to-manage side effects.

Recently, my study has shown that tumor-infiltrating granulocytic MDSCs (G-MDSCs), which is the dominating subtype of MDSCs in the tumors, greatly express arginase-1, an enzyme used by G-MDSCs to deplete the critical nutrient arginine in the tumor microenvironment, which results in the suppression of tumor-killing cytotoxic T cells. I used genetically engineered mice with deletion of arginase-1 specifically in G-MDSCs as the host for a lung metastasis model of breast cancer and showed that genetic abolishment of G-MDSC-derived arginase-1 significantly reduced the metastasis burden and increased the survival of mice compared with control mice bearing the same metastasis. Moreover, I discovered that arginase-1 upregulation in G-MDSCs is triggered by certain secreted factors from dying tumor cells. Because tumor cell death can be induced by chemotherapy such as paclitaxel, cisplatin or doxorubicin, this finding provides a clue for how G-MDSCs may activate the expression of arginase-1 as a response to systemic chemotherapy, and more importantly, why it is critical to debilitate G-MDSCs through targeting arginase-1 in order for chemo-immunotherapy to work more effectively to eradicate metastatic breast cancer. The goal of my proposed research is to (1) decipher the cellular crosstalk mechanisms and find the key molecular players for how chemotherapy-induced tumor cell death stimulates arginase-1 in G-MDSCs, and (2) demonstrate the superior efficacy of a triple combination therapy (chemotherapy plus immunotherapy plus arginase-1 inhibitor, or chemotherapy plus immunotherapy plus L-arginine supplementation) in comparison to chemo-immunotherapy or arginase-1 inhibitor or L-arginine supplementation alone in three independent preclinical models of lung metastatic breast cancer.

My project merges basic research with preclinical translational research, and the results will be highly relevant to clinical applications. By unraveling the mechanisms and identifying new combination treatment strategies, this research will help correct a key loophole of current chemo-immunotherapy. The animal model experiments will inform a set of combination therapy strategies that may outperform the recently approved chemo-immunotherapy for stage IV metastatic breast cancer without an increase of toxicity. By disseminating the research results via publication and conference presentations, I hope to instigate the motivation for clinical trials to translate the triple combination therapy strategies to clinical approvals that could benefit patients with metastatic breast cancer in near future. I will remain focused on this overall goal until it is achieved through persistent hardworking and motivated collaborations between basic researchers and clinicians.