Public Abstract

Every hour, ~5 women die from metastatic breast cancer in the U.S. Thus, it is urgent to develop new strategies to improve outcomes for stage IV metastatic breast cancer patients. Apart from malignant cells, breast tumors are composed of many other non-malignant cell types, such as resident tissue cells and recruited immune cells. These cells—especially macrophages and T cells—play a critical role in breast cancer progression, metastasis, and resistance to therapy. Recently, a method called checkpoint blockade succeeded in treating some cancer patients by activating T cells (part of the adaptive immune system) to kill tumors. However, this method is limited by the immune-suppressive microenvironment, which is found in many solid tumors, including in breast cancer. These tumors harbor a great number of tumor-associated macrophages—a type of macrophage (part of the innate immune system) that promotes tumor growth and metastasis and inhibits cytotoxic T cells from killing cancer cells. A high ratio of tumor-associated macrophages to cytotoxic $CD8^+$ T cells predicts shorter patient survival, suggesting that these macrophages play a major role in suppressing T cell activity against tumors. However, some macrophages can kill cancer cells and stimulate the cancer killing ability of T cells. Since both the innate and adaptive immune systems are involved in the immune microenvironment, both must be considered when developing new therapies. Thus, to eradicate metastatic breast cancer, we should not only activate T cells but also reprogram tumor-associated macrophages to alter the immune-suppressive microenvironment in parallel.

Recently, we tested an immunotherapeutic approach that reprograms tumor-associated macrophages to make them tumoricidal. When we administered monophosphoryl lipid A (MPLA) and cytokine interferon gamma (IFNγ) together, the combined treatment **reprogrammed macrophages isolated from pleural effusions of stage IV metastatic breast cancer patients to kill 80–90% of cancer cells isolated from the same pleural effusions.** In mouse models of luminal B and triple negative breast cancers, injection of MPLA+IFNγ reprogrammed the macrophages, leading to reduced primary tumor growth. Most excitingly, the treatment led to the recruitment of $CD8^+$ T cells into the lung, where **metastatic cancer cells were eradicated in ~75% of the mice**. These data suggest that MPLA+IFNγ can reprogram tumor-associated macrophages and activate T cells so they work together in the entire body to attack both primary and metastatic tumor cells.

However, the elimination of metastatic breast cancer cells in some mice was incomplete. To fine-tune the strategy, we will determine mechanistically how the MPLA+IFNγ treatment alters the tumor immune-suppressive microenvironment, especially how it reprograms tumor-associated macrophages (Aim 1). Furthermore, we will determine how MPLA+IFNγ-treated macrophages stimulate T cells (Aim 2). These insights will set the stage for developing a novel therapy for stage IV metastatic breast cancer. This MPLA+IFNγ reprogramming strategy could be applied as a stand-alone treatment, could be modified with identified molecules, or could be used in conjunction with checkpoint blockade to achieve the best therapeutic effects against stage IV metastatic breast cancer. Most importantly, MPLA and IFNγ are already FDA-approved: MPLA is used in a vaccine to prevent cervical cancer, and IFNγ is approved to treat chronic granulomatous disease and osteoporosis. Thus, MPLA+IFNγ could be tested directly in human clinical trials for immediate patient impact.