PUBLIC ABSTRACT

Targeting endosomal trafficking to enhance immune recognition of breast cancer brain metastasis

Significance: The spread of cancer throughout the body, via a process called metastasis, is terrifying for patients. Brain metastasis is particularly devastating because of the obvious importance of the brain, and the lack of effective treatment options. With better treatment of primary breast cancer, patients are living longer, which unfortunately is leading to an increasing incidence of brain metastasis, without a corresponding increase in treatment options. The relatively recent introduction of immunotherapy has shown that the immune system can be harnessed to fight and potentially cure metastatic cancer, but the percentage of patients that respond is low. Only 20% of patients with breast cancer brain metastasis have an objective response to immunotherapy. Fortunately, this is not entirely due to the brain metastatic site, as 60% of patients with melanoma brain metastasis respond to immunotherapy. This suggests that breast cancer cells suppress the immune response in the brain, which further suggests that we can reverse this suppression. To expand the number of breast cancer brain metastasis patients that derive a survival benefit from immunotherapy, we must first understand how cancer cells are hiding from the immune system.

Background and approach: A successful immune response to metastatic cancer cells requires the interaction of three main cell types: cancer cells, antigen presenting cells, and cytotoxic T cells. As with all cell-cell interactions, interactions between these three cell types require the correct localization of specific proteins on the cell surface. Protein localization within all cells is directed by a system known as the endosomal trafficking system, which is controlled by Rab proteins that coordinate and move proteins between intracellular compartments. We recently made the exciting discovery that a component of the endosomal trafficking system, Rab11b, is required for breast cancer cells to successfully interact with the brain microenvironment. Loss of Rab11b dramatically changed the cell surface proteome, preventing cancer cells from interacting with the brain microenvironment, and ultimately suppressing brain metastasis. The localization of proteins, particularly on the cell surface, is critically important for the ability of a cancer cell to interact with the microenvironment and surrounding immune cells. Importantly, immunotherapy relies on the surface expression of specific proteins (CTLA-4, PD-1/PD-L1), further highlighting the importance of trafficking. Here we will extend our study of trafficking to test the **hypothesis that trafficking mediated-control of the cell surface proteome dictates immune recognition and response**. We will test this hypothesis via the following aims:

Aim 1: Identify trafficking genes that modulate T cell activation. Using a CRISPR library containing gRNAs targeting Rab proteins and known effectors we will determine how trafficking controls: dendritic cell-mediated T cell activation, and T cell-mediated killing of breast cancer cells.

Aim 2: Pharmacologically target trafficking for brain metastasis treatment. We will screen a library of 5,000 bioactive compounds for their ability to inhibit geranylgeranylation of Rab proteins, a lipid modification that is required for Rab activation and function.

Impact on patients: The treatment options available for patients with breast cancer brain metastasis are limited, and are often not effective. Immunotherapy has shown strong benefits for melanoma patients with brain metastases, but this efficacy hasn't been replicated in breast cancer patients. We propose that breast cancer metastases are preventing immune recognition by using trafficking to hide proteins required for recognition. This proposal will take the first steps to systematically explore how trafficking controls immune recognition (Aim 1), and screen compounds for their ability to inhibit the Rab proteins that control trafficking (Aim 2). This will lay the foundation for future studies targeting trafficking to improve the efficacy of immunotherapy for patients with breast cancer brain metastasis.