Lay Abstract

Disease metastasis is the main cause of breast cancer mortality. Metastasis results from cancer cells that survive in circulation and seed distant organ sites (circulating tumor cells; CTCs). Enumeration of CTCs demonstrates that the prevalence of individual CTCs and CTC clusters is strongly prognostic of poor outcome in breast cancer patients. But it is also clear that not very CTC is capable of metastatic seeding and growth. Increasing evidence suggests that non-cancer cells in the tumor microenvironment (TME) also play a pivotal role in facilitating breast cancer metastasis. Using a novel microfluidic technique to isolate and enumerate CTCs, we observed non-cancer, non-immune cells in peripheral blood from patients with metastatic (Stage IV) breast cancer, and we identified these cells as circulating Cancer Associated Fibroblasts (cCAFs). CAFs are non-cancer cells resident in the tumor microenvironment that provide critical support to breast cancer cells at primary and metastatic sites.

We found that CAFs circulate both individually and clustered with CTCs in patient blood. These cCAFs were found in the majority of breast cancer patients with metastatic disease and were absent from the circulation of patients with "cured" breast cancer (i.e. no evidence of disease for at least 5 years). cCAFs which cluster with CTCs (cCAF/CTC clusters) are of extreme interest as it was recently shown that clusters of CTCs, rather than individual CTCs, are the likely culprits responsible for establishment of metastatic lesions and re-seeding of breast cancer metastases. We hypothesize that cCAFs are not only biomarkers of breast cancer metastasis, but that they directly facilitate metastasis by protecting CTCs and by setting up the "soil" for metastatic seeding. Thus, elimination of CAFs present in circulation and at metastatic lesions may be a potent therapy for breast cancer metastasis. Preclinical studies have shown that targeting CAFs has a therapeutic benefit in mouse models, and early phase clinical studies demonstrated that treatments which inhibit CAF functions were well tolerated in patients.

One major challenge in metastatic breast cancer is therapy resistance. Breast cancer cells have unstable genomes with high mutation rates that enable the emergence of innate or acquired resistance to drugs and chemotherapy. Unlike cancer cells, CAFs have a normal, stable genome, and are limited in their ability to adapt in response to treatment; this makes CAFs an attractive candidate for targeted therapy.

We hypothesize that delivering toxic chemotherapy specifically to CAFs with a CAF-targeting ADC (antibody-drug conjugate) will eliminate CAFs and cut off their critical support to metastatic breast cancer lesions. Further, it will eliminate CAFs in the circulation, a likely cause of metastatic reseeding. We will evaluate the efficacy of targeting CAFs with ADCs in preclinical mouse models of breast cancer metastasis alone or in combination with other breast cancer therapies. We anticipate that treatment with CAF-targeting ADCs will reduce metastatic burden, reduce or eliminate cCAFs and cCAF/CTC clusters, and improve survival. With the successful completion of the proposed work, we anticipate the rapid translation of this approach to the clinic where we would engage in tolerance and efficacy studies of using CAF-ADCs in patients with Stage IV metastatic breast cancer.