Abstract

Immunotherapy is among the most promising cancer treatments today. However, while treatments targeting immune checkpoints, which place a break on immune reaction, can offer significant benefits to cancer patients, the number of patients that respond to the treatment is disappointingly low. Clinical trials in patients with metastatic breast cancer show that only 5-20% of patients respond to the treatment, indicating that in addition to checkpoint activation, cancer cells may apply other immunosuppressive mechanisms.

We have recently shown that stress-induced signaling that activates the c-Jun N-terminal kinase (JNK) enzyme is crucial for the induction of a pro-metastatic microenvironment in breast cancer. Previous results suggest that specific matrix proteins downstream of JNK can repress aspects of checkpoint-regulated immune responses against cancer. We hypothesize that inhibition of JNK can substantially enhance the therapeutic efficacy of checkpoint inhibitors and potentially expand the patient pool that benefits from immunotherapy. Moreover, considering that immunotherapy is enhanced when combined with chemotherapy and that chemotherapy activates JNK signaling, we hypothesize that JNK inhibition, prior to chemotherapy and checkpoint inhibition, may simultaneously improve sensitivity to these treatments.

Using mouse models for metastatic breast cancer and advanced 3D in vitro platforms, in collaboration with Dr. Duy Nguyen at the Moffitt Bioengineering Department, we aim to define the role of JNK in immune repression and determine the potential of JNK inhibition to improve the efficacy of checkpoint inhibitors against metastatic breast cancer. We will determine the functional role of JNK signaling as a regulator of immune responses to metastasis in mouse models. As a 3D in vitro platform, we have developed a bio-conjugated liquid-like solid (LLS) medium to support long-term immune cells and solid tumor co-cultures. We will utilize this platform to characterize mechanistic tumor-immune interactions and responses to checkpoint inhibitors. The platform provides the flexibility to precisely adjust these properties independently, allowing for faithful recapitulation or modulation of the matrix. Together, these studies will elucidate the role of JNK stress signaling in immune regulation and determine its potential as a target to sensitize metastatic breast cancer to immunotherapy