

MCC-C3 Padres Pedal the Cause Spring 2021

Crosstalk between EMT and immune cells in breast cancer immunotherapy resistance



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Scientific Abstract:

Immune surveillance is hypothesized to be a key mechanism in controlling tumor progression, metastasis, and response to therapy. In particular, our groups have shown that epithelial-mesenchymal transition (EMT) state shifts have huge impact on immune evasion. However, there are no experimental studies on how the mechanisms governing tumor cell states influence B cell recognition during tumor progression and therapy. In creating faithful triple-negative breast cancer mouse models with high and low tumor mutation burdens, the Hollern lab has shown that B cells regulate the response to immunotherapy and more recently has found evidence that tumors with high stemness and EMT-like features are associated with loss of B cell recognition. To test the hypothesis that EMT leads to loss of B cell recognition and immunotherapy responsiveness, the Yanglab has developed a murine breast cancer model enabling synchronized and controlled induction of EMT. Therefore, this proposal will combine two innovative models to create new breast tumor models, in which EMT states can be shifted in high and low tumor mutation burden tumors or be used to control expression of tumor neoantigens and to test temporal crosstalk between EMT and B cell-dependent antitumor immunity during breastcancer development and metastasis.

This proposal takes advantage of the expertise in breast cancer metastasis and mouse modeling (the Yanglab) and in tumor immunology and bioinformatics (the Hollern lab) to uncover new molecular targets to overcome immunotherapy resistance in breast cancer.

Lay Abstract:

Current immune checkpoint inhibitors generally only generate anti-tumor responses in about 15% breast cancer patients already presenting recurrent metastatic lesions. Here we propose to establish new breast tumor models to study whether and how crosstalk between tumor cells and B-cells impact anti-tumor immunity and tumor responses to immune checkpoint inhibitors. Results from the proposed research could lead to publications and extramural funding to further this study in the short term. Our proposed research also has direct therapeutic implication in the long run. Currently, immune checkpoint inhibitors are largely given to breast cancer patients that have failed conventional chemotherapies and present metastatic lesions. Since conventional chemotherapy cannot kill dormant disseminated tumor cells that are not proliferating, many breast cancer patients that are considered "high risk" for metastatic recurrence can only wait and see whether their breast cancer will come back as distant metastases. Yet patient data tells us that B cell recognition of metastasis leads to longer survival. If our proposed research is successful, it would provide much needed new treatment option for high-risk breastcancer patients. This is especially important for triple-negative breast cancer, which no other targeted therapy is currently available to prevent metastasis recurrence. In addition, our research also explores new molecular mechanisms that help dormant tumor cells to evade immune surveillance in distant organs. Uncovering new molecular targets to

boost anti-tumor immunity could significantly improve patient responses to immunecheckpoint inhibitors. Therefore, **our research could also lead to reducing the mortality associated with metastatic breast cancer.**