Jones, Dennis

Public Abstract

Cancer cells can metastasize, or spread, from the initial tumor development site to distant organs. **There are no curative drugs for breast cancer patients with distant metastases**. Because most cancer patients die from the growth of metastatic cells, we seek to identify ways to effectively attack these metastasized cancer cells and improve patient outcomes. To better understand the biology of metastatic growth, my laboratory studies cancer cells in their "new" environment, specifically within lymph nodes.

T lymphocytes constitute a major population of cells in lymph nodes and play a critical role in eliminating cancer cells. Unfortunately, T lymphocytes in most breast cancer patients lack the ability to kill cancer cells. We've shown that cancer cells evade killing in lymph nodes, then exit to distant organs. A potential therapy that inhibits the growth of cancer cells in lymph nodes may reduce further metastasis and death from breast cancer. Therapies that harness the killing potential of T lymphocytes could effectively eradicate metastatic disease.
However, we do not understand how breast cancer cells avoid attack from T lymphocytes in the seemingly hostile environment of the lymph node.

My laboratory has established breast cancer models that metastasize to lymph nodes of animals with intact immune systems to study how cancer cells escape killing. Our preliminary data show that breast cancer cells impair T lymphocyte entry into lymph nodes and directly impair T lymphocyte activation. We hypothesize that tumor growth in lymph nodes results in both local and systemic immune suppression that permits metastatic growth and promotes distant metastasis.

T lymphocytes need access to tumors for effective killing. This crucial process is regulated by blood vessels. In human and mouse breast cancer, our data suggest that tumor growth compresses lymph node blood vessels, impairing the ability of blood vessels to facilitate T lymphocyte entry into lymph nodes. Our multidisciplinary team will use innovative engineering and imaging methods to observe in real time how lymph node tumors and blood vessels respond to decompression strategies.

Once T lymphocytes enter tumors, they face cancer cells that have evolved mechanisms to weaken their killing ability. Our preliminary data implicate a known pathway with an unexpected role in impairing T lymphocyte function. We aim to use in vitro studies to uncover molecular details of how cancer cells inhibit the activation of T lymphocytes. We will perform in vivo studies that tailor chemotherapy to the properties of metastatic tumors. We expect that chemotherapy, combined with immune therapy, will enhance blood vessel function, T lymphocyte infiltration, and T lymphocyte function to eradicate metastatic tumors.

Our work seeks to overcome the limitations of non-responsiveness and temporary response to current therapies for treating metastatic breast cancer. Targeting lymph node metastases may improve the survival of breast cancer patients by preventing the seeding of distant organ metastases from lymph nodes. In addition, reversing immune suppression may unleash an effective immune response against metastatic tumors.