How Primary Tumor Cells are Preset for Dormancy and Evade Chemo Post Metastasis

Julio Aguirre-Ghiso, PhD, Professor, Director of Head and Neck Cancer Research

Mount Sinai researchers have discovered the conditions by which specific signals in primary tumors of the head and neck pre-program cancer cells to become dormant and evade chemotherapy after spreading. Their findings, published in the January 31, 2017 issue of Nature Cell Biology, could lead to new drug development and treatment options for patients with metastatic head and neck squamous cell carcinoma (HNSCC).

Hypoxia is a microenvironmental hallmark of solid tumors that induces stress responses, quiescence programs, and chemo and radio-resistance. Until now it has been unclear how hypoxic HNSCC influences the fate of disseminated tumor cells (DTCs) in target organs and how this is related to patient outcome. This study reveals that primary tumor hypoxic microenvironments give rise to a sub-population of dormant DTCs that evade therapy and may be the source of disease relapse and poor prognosis.

Aguirre-Ghiso and a team of investigators from Albert Einstein College of Medicine, SUNY Polytechnic Institute and University of Wisconsin-Madison developed a device using a nanotechnology tool, biosensors, and advanced imaging technology to manipulate primary tumor microenvironments. They created controlled hypoxic and non-hypoxic niches in tumors by implanting the devices loaded with drugs that induced hypoxia. These ‘fine-tuned’ microenvironments in live tumors allowed the researchers to isolate the cancer cells to determine how they behaved when they moved from the primary tumor to the lungs. The investigators tracked the DTCs with genetically encoded biosensors to see which cells were exposed to low oxygen, which cells were dormant, and how they reacted to therapy.

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A Note from Department Chair Eric Genden, MD, MHA, FACS

The staggering rate at which oropharyngeal cancer and thyroid cancer incidences have increased continues to serve as the impetus for Mount Sinai’s Head and Neck Cancer Research Program to accelerate bench to bedside translational research. Dr. Aguirre-Ghiso’s laboratory focusing on tumor cell dormancy recently published in Nature Cell Biology. This work holds great promise for the development of new drugs targeting patients with metastatic head and neck squamous cell carcinoma. The Advaxis immunotherapy trial for patients with HPV-related oropharyngeal cancers recently advanced to phase II with phase I findings reported in this edition of Research Focus.

Personalized Genomic Vaccines is a novel program that utilizes tumor sequencing technologies to identify tumor-specific neoantigens to produce patient-specific tumor vaccines. The program is progressing with two enrolled subjects.

Our multidisciplinary team of basic and translational scientists and clinicians strive toward cures through groundbreaking research programs. While many programs are funded by the National Institutes of Health (NIH), recent budget cuts mean that novel programs now depend on philanthropy for pilot research. Please refer to page 4 for a list of studies to identify one that resonates with your scientific interests. We greatly appreciate your consideration in funding these critical efforts.
Personalized Genomic Vaccines
Nina Bhardwaj, MD, PhD, Medicine, Hematology and Medical Oncology

When tumor cells appear in the bloodstream of a cancer patient, the immune system is mobilized to attack and kill them through the action of white cells called killer T cells. Despite the initial immune response, tumors become highly adept at escaping the immune system. Fortunately, new immune-based therapeutics, in particular, checkpoint inhibitors, demonstrate clinical efficacy in several solid malignancies, including head and neck cancer by expansion of killer T cells that recognize neoantigens in tumor cells and target these cells. These agents are available as part of the Tisch Cancer Institute’s Solid Tumor Program at the Icahn School of Medicine at Mount Sinai.

Unfortunately, not all patients respond to checkpoint inhibitors, and therefore novel strategies are being explored at Mount Sinai to combat this problem. As part of the Personalized Medicine Program at the Tisch Cancer Institute, we are currently implementing a Phase I proof-of-concept study, which is a fully personalized multi-peptide therapeutic vaccine, which is designed to target tumor-derived neoantigens for individual patients. The investigational vaccine is based on the Personalized Genomic Vaccine (PGV) platform, which utilizes tumor sequencing technologies to identify tumor-specific neoantigens for specific patients. The goal of this therapy is to induce a robust anti-tumor immune response and minimize the risk of non-specific immune activity. If effective, this would represent a significant contribution to the fields of tumor immunology and medical oncology. The first patient enrolled in this trial had head and neck cancer and should this trial prove successful, it will demonstrate the utility of the PGV therapeutic vaccine design platform, and pave the way for further cancer type-specific trials to demonstrate therapeutic efficacy.

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This multipronged approach allowed linking primary tumor microenvironments to fate of DTCs in a way that was never before attempted and at single cell resolution, allowing definitive tests of mechanism. The investigators discovered DTCs from hypoxic regions were still able to metastasize and were more likely to enter dormancy, as opposed to cells from high oxygen levels in primary tumors. The researchers thus found that hypoxic regions of the tumor could not only spread rapidly, but also send a large amount of cells into a dormant mode, hence, creating cells that were more efficient at evading chemotherapy. This discovery of chemotherapy resistant behavior of cancer cells in distant organs suggest that a marker test might be able to predict which patients may be prone to carry more dormant drug resistant cancer cells.
Advaxis Immunotherapy: AXAL Head and Neck Window of Opportunity Trial Update

The Head and Neck Cancer Research Program at the Icahn School of Medicine at Mount Sinai (ISMMS) is conducting a novel phase II trial to investigate the treatment of human papillomavirus (HPV)-related head and neck cancer with AXAL, a Listeria monocytogenes (Lm)-based immunotherapy treatment developed by Advaxis. This clinical-stage biotechnology company is developing multiple cancer immunotherapies based on its proprietary Lm Technology™. Brett Miles, DDS, MD, FACS, a robotic head and neck cancer surgeon, is the Site Principal Investigator of the Advaxis Window of Opportunity Trial for ISMMS, and Andrew Sikora, MD, PhD, is the Study Chairperson and Co-Director of the Head and Neck Cancer Program at the Baylor College of Medicine in Houston, Texas (the coordinating site for the trial). They work closely with Marshall Posner, MD, Medical Director of the Head and Neck Oncology Center and Associate Director of the Center for Personalized Cancer Therapeutics at The Tisch Cancer Institute. Together they collaborate with a team of researchers who are currently investigating the safety and efficacy of the vaccine.

How AXAL Works
Axalimogene filolisbac (AXAL) is a live-attenuated Lm vector system that secretes an antigen-adjuvant protein (Lm-LLO) targeting HPV. It is undergoing clinical trials for three potential indications: phase III for invasive cervical cancer, phase II for head and neck cancer, and phase II for anal cancer.

Advaxis has two additional immunotherapy products in human clinical development: ADXS-PSA for prostate cancer and ADXS-HER2 for HER2-expressing solid tumors. In addition, Advaxis and Amgen are developing ADXS-NEO, a preclinical investigational cancer immunotherapy treatment designed to activate a patient’s immune system to respond against unique mutations, or neoepitopes, identified in his or her tumor.

The Prevalence of Extranodal Extension in Metastatic Lymph Nodes Stratified by Size in Papillary Thyroid Cancer

Mark Urken, MD, Head and Neck Surgical Oncology

A study by Mount Sinai researchers suggests that the traditional way of gauging the danger of thyroid cancer—based on the size of metastatic lymph nodes—may not be correct.

Researchers examined extranodal extension (ENE), an established prognostic indicator of more virulent disease in thyroid cancer patients. A common presumption in thyroid cancer management is that small-lymph-node metastases do not indicate aggressive disease, and that ENE occurs only in metastatic lymph nodes that have reached a critical size. However, The research team found no previous studies that had investigated the relationship between the size of these lymph nodes and the presence of ENE. Our multidisciplinary research group conducted a retrospective study that compared the prevalence of ENE in metastatic nodes with the diameter of the node to clarify the relationship between metastatic lymph node diameter and the risk of ENE.

A thorough pathological review in 1,126 metastatic lymph nodes from 171 thyroid cancer patients who received surgery by a single surgeon at Mount Sinai Beth Israel was conducted from 2004 to 2015. We evaluated histological features that included primary tumor histopathology, number and size of metastatic lymph nodes, and the presence of ENE in each node. One hundred seventy three (15.4%) of the 1,126 lymph nodes demonstrated ENE. Lymph nodes manifesting ENE
The Prevalence of Extranodal Extension in Metastatic Lymph Nodes Stratified by Size in Papillary Thyroid Cancer
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ranged from 1.5 to 44.0 mm in size. Increased lymph node size had a statistically significant association with ENE status.

Results showed that a significant percentage of even small metastatic lymph nodes exhibited ENE. Previously ENE had been established as a negative prognostic factor associated with further lymph node metastases, distant metastases, biochemically incomplete response to therapy, and higher rates of disease-related death. This study has prompted a reevaluation of protocols at the Department, and plans are underway for future studies to further elucidate the prognostic significance of small metastatic lymph nodes which demonstrate ENE relative to patients with larger nodes demonstrating that adverse feature.