Reinvigorating Immune Response to Advanced Melanoma

Melanoma represents a small fraction of skin cancer-related malignancies, yet accounts for the majority of its mortalities—and the incidence of cutaneous melanoma is rising. While treatments using small-targeted inhibitors and immune checkpoint antibodies have increased long-term survival in advanced-stage cutaneous melanoma, many patients still do not realize any benefit from the treatments. Another group of patients initially have beneficial results but ultimately find their disease progressing, in part due to cancer cells' acquired resistance to immune response. And still other patients have difficulty with the treatment's high toxicity.

Emad Alnemri, PhD, Thomas Eakins Professor of Biochemistry and Molecular Biology, and **Andrew Aplin, PhD**, Kalbach-Newton Professor of Cancer Research, have been leading a series of studies of the molecular processes that determine whether or not current inhibitor and immune checkpoint treatments will work well in melanoma patients, and for how long. Now, based on the results of those studies, they are working to develop new, more-effective treatment approaches that address three goals: triggering a robust anti-tumor immune response that has significant clinical effect, preventing onset of acquired resistance and minimizing patient toxicities.

Over the past two years, their research team announced a series of important findings that help to address the question of why initially successful immune system-focused therapies for patients with stage III and stage IV melanoma often fail within 13 months, due primarily to tumor cells acquiring resistance to the drugs. "Previously, the field has lacked detailed knowledge of exactly how targeted inhibitors and immune checkpoint agents work together to fight melanoma tumors—how they prompt both tumor-cell death and alterations in the tumor-immune environment," Dr. Alnemri explains. "However, our studies have described a molecular mechanism of targeted inhibitor regulation of an immune-stimulatory form of cell death. In identifying the mechanism, we have been able to describe a proof-of-principle therapy concept for melanoma tumors that are resistant to inhibitor-based treatments."

A key to the new therapeutic approach is the researchers' discoveries on the molecular mechanisms by which the gasdermin E gene and its expressed protein function. The gasdermin E protein normally participates in the cell-death program—which, among other purposes, is intended to kill malignant cells. And in many cancers, gasdermin E expression is much lower than it is in healthy cells.

The researchers found that gasdermin E participates in the cell-death process by spurring creation of holes in a cell's outer membrane and its mitochondrial membrane. "Next," Dr. Aplin says, "looking at the role that gasdermin E plays in malignancies, we found that cancer-cell lines without gasdermin E multiplied about twice as fast as normal cells. Moreover, in mice models of melanoma, cells lacking gasdermin E grew larger tumors—where, in contrast, cancer cells retaining some gasdermin E expression had slower growth."

Thus, Drs. Alnemri and Aplin concluded, gasdermin E could provide several clinical opportunities. "Not only could it be used as a marker to distinguish aggressive tumors from less-aggressive ones," Dr. Alnemri explains, "it could be employed to help design effective treatment strategies."

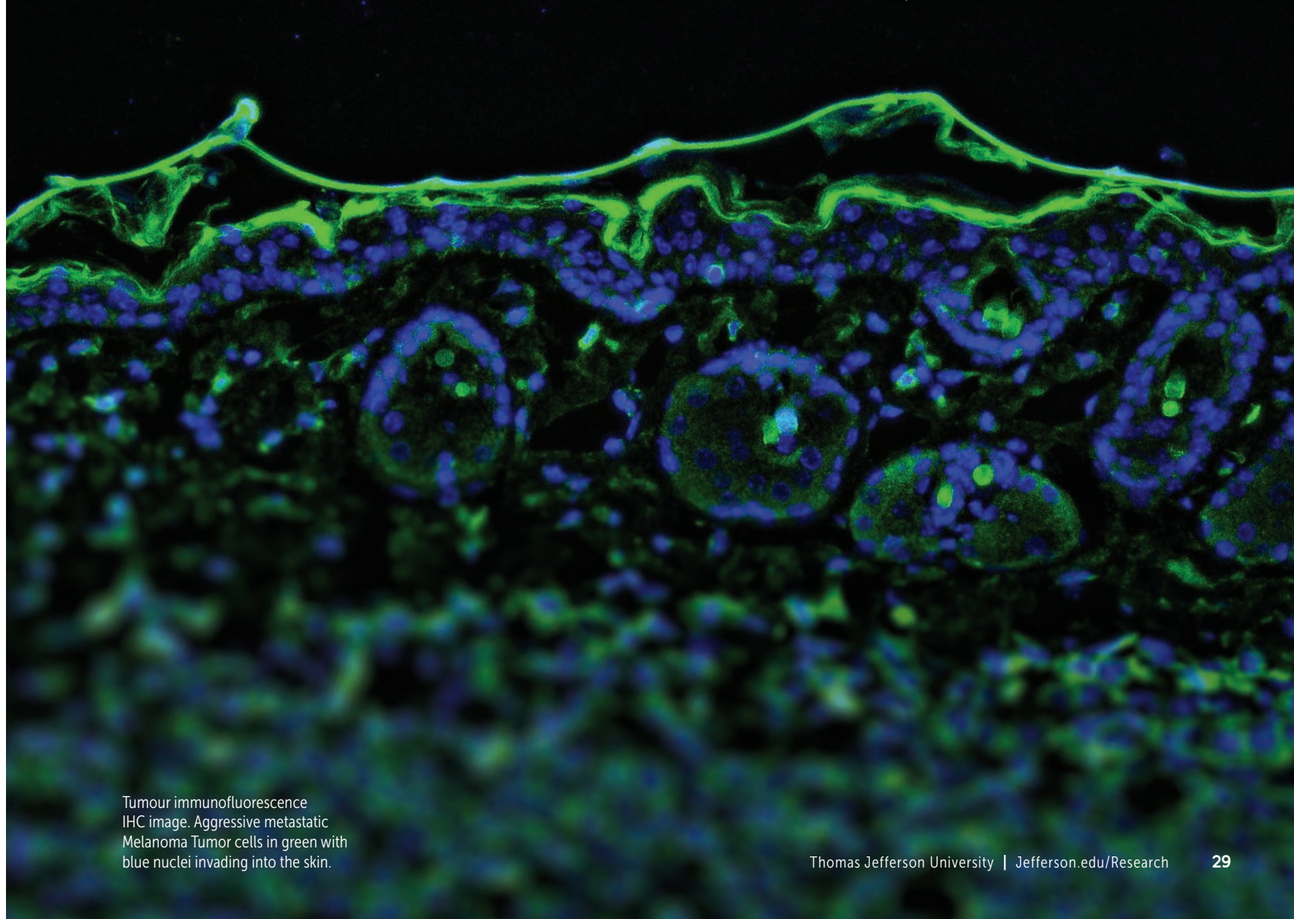
Perhaps more exciting is the potential for using gasdermin E as a new therapeutic target.

To that end, they are now developing approaches for promoting gasdermin E expression as a method for reinvigorating the immune system in melanoma tumors that have proven resistant to current treatments. "In simplified terms, we are working to boost and restore the immune system's natural ability to kill melanoma cells," says Dr. Aplin. "And we hope that it may also prove effective in other cancers where gasdermin E expression is suppressed." ■

New Target for Treating Triple-Negative Breast Cancer

Triple-negative breast cancer is an aggressive and difficult to cure form of the disease—and is prevalent in Black and Latinx women. With his research colleagues, **Adam Bailis, PhD**, associate dean for research in the Jefferson College of Health Professions, has been exploring the potential of a protein named RAD52 to be an effective target for drugs that fight the condition. RAD52 is a factor in the tumor suppression network that, when mutated, can reduce the risk of breast cancer in carriers of the BRCA2 gene mutations that are associated with many breast cancers. In the first report of the protective effect of RAD52, the researchers identified two potential mechanisms for suppressing tumorigenesis in BRCA2-deficient cells. And their continuing work provides further evidence that the RAD52 gene may be a promising target for drugs that kill BRCA2-related cancers.

This body of work complements major efforts by Sidney Kimmel Cancer Center at Jefferson investigators to understand DNA repair regulation in cancer, and to tailor cancer therapies for DNA repair-defective tumors.



Tumour immunofluorescence IHC image. Aggressive metastatic Melanoma Tumor cells in green with blue nuclei invading into the skin.