CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP180778

Project Title:
Metabolic Enablers of Melanoma Progression

Award Mechanism:
Multi-Investigator Research Awards (Version 2)

Principal Investigator:
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Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

Melanoma is responsible for over 80% of deaths from skin cancer and the incidence of melanoma is increasing over time. A number of effective new therapies for melanoma have been introduced into common use in recent years but most people diagnosed with stage IV disease still die of their disease. New therapies are required.

Stage IV melanoma arises when melanoma cells metastasize (move around the body) to distant sites. After “distant metastasis”, disease is systemic: it can no longer be cured by surgery and it is much more likely to be resistant to other therapies. If we could prevent distant metastasis we could reduce the fraction of patients that progress to stage IV disease and cure rates would go up dramatically. But despite the fact that most cancer deaths are a consequence of distant metastasis (not just in melanoma), the mechanisms that allow cancer cells to move from a primary tumor in one part of the body to grow in other parts of the body are unknown.

What is known is that distant metastasis is a very inefficient process in which most cancer cells that try to migrate from a primary tumor to another part of the body die before they are able to form a metastatic tumor. That is why early detection is critical in melanoma and in other cancers: if the primary tumor can be found before it acquires the ability to metastasize, it can usually be surgically removed. Unfortunately, many tumors are not discovered in time, raising the question of whether we can figure out how melanoma cells metastasize and inhibit those processes to prevent disease progression.

To study this question, the Morrison laboratory developed a system to transplant melanoma cells from patients into specialized mice that allow human melanoma cells to form tumors and to metastasize in the mice in a way that mirrors their behavior in patients. This is commonly described as a patient-derived xenograft (PDX) model (published in Nature 456:593). The Morrison lab has studied melanomas from more than 100 patients in this model, and discovered that there are intrinsic differences among melanomas from different patients in their metastatic potential: some melanomas are better at metastasizing than others, and these are the melanomas that tend to kill patients (Science Translational Medicine 4: 159ra149).

The Morrison lab used the PDX model to study the molecular mechanisms that regulate metastasis and discovered that the metastasis of human melanoma cells is limited by oxidative stress (Nature 527:186). Oxidative stress is caused by the generation of highly

reactive molecules, called reactive oxygen species (ROS), inside cancer cells. All cells generate ROS at some level, mainly as a consequence of the chemical reactions that generate energy inside of the cell. Cancer cells can generate unusually high levels of ROS because they are highly metabolically active and rapidly growing. We discovered that melanoma cells experience a dramatic increase in ROS levels during metastasis and that most metastasizing cells die of oxidative stress. The rare melanoma cells that survive during metastasis undergo metabolic changes that allow them to withstand the oxidative stress. Treatment of mice with anti-oxidants promoted metastasis and increased metastatic disease burden. This raises the possibility that patients with serious melanomas who take dietary supplements that contain large doses of anti-oxidants (such as vitamins A, C, and E) might inadvertently increase their risk of disease progression as a result of the ability of anti-oxidants to promote melanoma cell survival.

In fact, our discovery that oxidative stress limits distant metastasis is consistent with the results from large clinical trials that found that dietary supplementation with anti-oxidants promotes the initiation and/or progression of multiple cancers (e.g. JAMA 306:1549; J. Natl. Cancer Inst. 96:1743; JAMA 302:2119). Our results suggest that instead of treating cancer patients with anti-oxidants, we should treat with pro-oxidants that either exacerbate the oxidative stress cancer cells experience or that inhibit the metabolic changes that cancer cells undergo to survive during metastasis. This would represent a fundamental shift in strategy away from treating cancer with anti-oxidants. However, to enable this strategy it is necessary to better understand how metastatic cells change their metabolism to survive oxidative stress. The Morrison, DeBerardinis, and Mishra laboratories in Children's Research Institute at UT Southwestern Medical Center propose to apply their complementary expertise in the areas of melanoma biology, cancer metabolism, and mitochondrial function (the part of the cell that generates energy) to unravel these mechanisms and to identify new strategies to prevent cancer progression.

The DeBerardinis laboratory made two significant advances that are instrumental to the proposed studies. First, they discovered that cancer cells consume lactate as an energy source (Cell 171:358). This was surprising and important because lactate has been considered a waste product that cancer cells must eliminate. This discovery raises the question of whether lactate consumption regulates melanoma metastasis or oxidative stress. Second, the DeBerardinis laboratory has pioneered methods to study cancer cell metabolism in living humans by performing infusions of nutrients (such as glucose, lactate, or glutamine) that are labeled with a distinct, but non-toxic form, of carbon that makes it possible to trace how tumors metabolize the labeled nutrients (Cell 171:358). These labeled nutrients are infused into patients soon before their tumors are surgically removed, and then the DeBerardinis lab analyzes samples of the removed tumors to trace the fates of the labeled nutrients, and to compare these fates between normal cells and cancer cells, between primary and metastatic tumors, and between tumors from different patients. This will allow us to test whether the metabolic mechanisms that we are discovering in PDXs are also active in melanomas growing in real patients.

The Morrison, DeBerardinis, and Mishra laboratories are taking a variety of approaches to unravel the mechanisms that regulate distant metastasis by human melanoma cells. In Project 1, the Morrison laboratory will use the PDX model they developed to test whether melanomas from different patients have intrinsic metabolic differences that cause differences in oxidative stress resistance and metastatic potential. They will explore the function of multiple metabolic pathways that have the potential to regulate oxidative stress including pathways that metabolize folate, lactate, and glucose. In each case, they will compare melanomas that are highly metastatic in patients and in mice to melanomas that metastasize more slowly in patients and in mice.

In Project 2, the Mishra laboratory will test whether there are intrinsic differences among mitochondria from melanomas in different patients that confer differences in oxidative stress and metastatic potential. Mitochondria are specialized structures within cells that generate energy. They have their own DNA, called mitochondrial DNA (mtDNA), that encodes some of the proteins that mitochondria use to generate energy. Defects in mtDNA and mitochondrial proteins can affect energy metabolism and increase the generation of ROS, causing oxidative stress. Cancer cells often have mutations in mtDNA that can influence oxidative stress and tumor growth but no one has studied if these mutations can influence metastatic potential. The Mishra lab will test if differences in

mitochondrial function or mtDNA among melanomas from different patients cause differences in metastatic potential.

In Project 3, the DeBerardinis laboratory will test whether melanomas in humans have distinct metabolic features at primary and metastatic sites and whether the metabolic features of these tumors influence immune cell function in the tumor environment. They will test this by infusing labeled nutrients into patients prior to surgery and then tracing the fates of the labeled nutrients in melanoma cells and in immune system cells from the tumor samples that are removed. They will also transplant melanomas removed from patients into mice to created PDXs that will be used to test the effects of changes in the tumor environment on melanoma cell metabolism.

The overall objective of the proposed research is to integrate studies of melanoma metabolism from several systems (including tissue culture, PDXs, immunocompetent mouse models, and humans) to identify mechanisms that regulate intrinsic differences in metastatic potential and immune responsiveness among melanomas from different patients. By discovering such mechanisms, we hope to identify new therapeutic strategies that inhibit melanoma progression by exacerbating oxidative stress or by increasing the effectiveness of immunotherapy by modulating immune cell metabolism within tumors.