MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

Section Editor: John M. Kirkwood, MD

Tumor and T-Cell Metabolism: New Insights Into Melanoma Therapy

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H&O What is the definition of tumor and T-cell metabolism as it applies to cancer?

GD The term *metabolism* is defined as the set of pathways that keep cells alive and functioning. This includes everything that cells do—from taking in nutrients to generating energy and producing new cells.

We have understood for more than a century that tumors possess an altered metabolism. Otto Heinrich Warburg (1883-1970), an Austrian biochemist, hypothesized that cancer is a metabolically distinct disease, and that cancer cells have a deregulated metabolism. Tumor cells are high-level metabolizers that use every means available to continue to proliferate rather than follow tightly regulated pathways. The result is that any noncancerous cell entering the tumor microenvironment must compete for nutrients with cells that have no form of metabolic pathway regulation. In other words, T cells are at a disadvantage from the time they enter the tumor microenvironment.

What the researchers in our laboratory are working to learn is how the tumor microenvironment acts as a metabolic barrier to antitumor immunity, and how we can level the playing field so that T cells are able to compete for nutrients in the microenvironment. I feel that we will never be able to cure cancer without being able to employ T cells.

H&O In what ways do tumor cells evade attack by T cells?

GD Tumor cells are evolution machines; their job is to keep going. They can and do develop mutations in order to evade the immune response in a number of ways. First, they alter the proteins that T cells recognize. Second, they turn on the ligands for inhibitory receptors on T cells, such as by producing programmed death ligand 1 (PD-L1) to inhibit programmed death 1 (PD-1). Third, they learn over time how to secrete molecules that turn off T cells directly, such as transforming growth factor beta (TGF-β), interleukin 10 (IL-10), and adenosine.

What is becoming very clear from work being done in our laboratory and others is that tumor cells deplete the local environment of nutrients, which allows them to evade attack. They effectively starve the T cells that have entered the tumor microenvironment.

H&O Are tumor cells able to affect regulatory T (Treg) cells?

GD Yes, they are. In most patients, tumor cells evade the immune response, in part, by recruiting Treg cells and other populations of suppressive immune cells, including myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs). Our laboratory is looking into whether Treg cells might be metabolically supported by a tumor-derived metabolite.

H&O How do specific metabolites in the mitochondrial mass affect the function of effector cytotoxic T cells and Treg cells?

GD Our laboratory has shown that effector T cells, which are tasked with finding the tumor and eliminating it, can be affected by the toxic by-products of

tumor metabolism, such as lactic acid and hypoxia. One of the key deficiencies seen in cytotoxic T cells that infiltrate tumors is loss of mitochondrial mass, which occurs because the tumor microenvironment inhibits the ability of the T cells to make new mitochondria. T cells can lose functional mitochondria over time if the mitochondria do not actively replicate while the T cell is dividing. The loss of mitochondrial mass in tumor-infiltrating cytotoxic T cells has a profound effect on their ability to function.

Treg cells are able to thrive in a nutrient-poor environment, which gives them a proliferative advantage compared with their effector T-cell counterparts. As a result, the tumor microenvironment becomes enriched in Treg cells.

H&O How can this knowledge be used to target melanoma cells?

GD Melanoma is a type of cancer that tends to promote T-cell infiltration. Having T cells in the microenvironment before we begin is a good thing. After the T cells have found the tumor, our job is to help them do theirs. In our laboratory, we are studying how we can alter the metabolism of the tumor microenvironment so that it becomes hospitable to T-cell function, and how to re-program T cells genetically to express genes that promote mitochondrial replication. We are using novel pharmacologic strategies in order to target tumor cell metabolism and create an environment that is less harsh for T cells.

H&O What studies have looked at the role of metabolism in targeting melanoma?

GD A number of studies have been conducted that examine whether tumor cells can be killed by inhibiting their metabolism. It also has become popular to investigate whether T cells can be stimulated to target melanoma cells via specific metabolic pathways. These types of studies are inherently flawed, however, if the tumor cells are using the same metabolic pathways that the T cells are using. Inhibiting glucose metabolism, for example, might slow the growth of tumor cells, but it will also slow the growth of T cells, which explains why this approach has not yet borne fruit.

More recently, studies have examined in greater detail how T cells and tumor cells compete for nutrients. The laboratory of Dr Erika Pearce at the Max Planck Institute and that of Dr Susan Kaech at Yale have explored what the competition for nutrients looks like in the tumor microenvironment, and studies from our laboratory that have not yet been published suggest that this equation can be changed.

H&O How may the interventions that are currently available improve the activity of other immune checkpoint interventions?

GD We are working on what we can do to inhibit metabolic pathways with drugs that already are available. For example, we have good data—including a 2005 study by Evans and colleagues and a 2010 study by Bodmer and colleagues—to suggest that people who take metformin to treat type 2 diabetes are at a decreased risk for cancer. This is an exciting finding, and a logical one because metformin changes the way that cells metabolize their nutrients. Metformin alone has had little effect on cancer in animal studies, but we hypothesized that it might be used to improve the response to immunotherapy. Remember that a variety of T-cell inhibitory strategies are still at play, so filling up the tank with gas is not enough—we also need to release the brakes or press the accelerator. That is why we are studying combination therapies: metformin to fill up the gas tank and a PD-1 inhibitor such as pembrolizumab (Keytruda, Merck) or nivolumab (Opdivo, Bristol-Myers Squibb) to release the brakes. We find in our mouse models than either of these treatments on its own does not work very well, but the combination has produced outstanding results. The vast majority of mice are able to clear their tumors completely, whereas the untreated mice or those treated with a single agent progress to terminal disease.

We are very excited that we have been able tip the balance in favor of the T cells in mice by using a very safe and inexpensive drug. We are also interested in other types of approved drugs that can modulate metabolism.

H&O What other work has your laboratory done related to T-cell metabolism?

GD So far, the work I have discussed here is related to enhancing effector T-cell function. However, we have a new set of experiments focused on inhibiting Treg cell function. Because Treg cells have their own metabolism, we can target specific pathways in the tumor microenvironment to prevent them from inhibiting antitumor immunity. These studies are ongoing, and we are very excited about this line of work.

H&O Do you have any caveats?

GD As we learn more about tumor microenvironments, we have to bear in mind that the relationship goes beyond tumor vs T cell. Most immunotherapy research has focused on looking on specific immune parameters, along with biomarkers to predict response. However, a number of different factors affect the microenvironment. There is a whole other side of regulation that occurs when the T cells are unable to get enough fuel to do their job. We may be able to restore the efficacy of immunotherapies—whether currently approved

treatments or experimental ones—simply by normalizing and changing the metabolic balance in the tumor microenvironment so that T cells are able to function. That is a key component that we need to explore going forward.

Disclosures

Dr Delgoffe has no relevant disclosures to report.

Suggested Readings

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HCC IN FOCUS

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this time, we expect that approximately 150 to 200 of these individuals may develop HCC. We will then be able to test the blood samples of these patients using the new biomarkers not only to determine how often the test is positive when a patient has the disease (ie, sensitivity), but also to determine how often the test is negative when a patient does not have the disease (ie, specificity). We will also be able to see how far in advance of the clinical diagnosis the biomarker was elevated and, thus, how far in advance the biomarker could tell us which people will develop HCC.

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Suggested Reading

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