Metabolic Checkpoint of Immune Cells in Melanoma Brain Metastases

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Summary: Metabolic features of both cancer cells and immune cells shift with nutrient availability in the tumor microenvironment, resulting in differential effects on antitumor immune function. The work of Fischer and colleagues demonstrates that increased oxidative phosphorylation in brain metastases in patients with melanoma is a key regulator of intracranial immune surveillance and that inhibition of oxidative phosphorylation could reduce the incidence of intracranial brain metastases in a murine model of melanoma.

See related article by Fischer et al., p. 628 (2).

Differential energy metabolism by cancer cells was famously first described as a shift from oxidative phosphorylation (OXPHOS) to glycolysis. This well-known “Warburg effect” has recently resurfaced in light of understanding a complex and competitive interplay between immune cells and cancer cells in the tumor microenvironment. Cancer cells, in a heavily proliferative and increased glycolytic state, have been demonstrated to outcompete immune effector cells for available glucose. It is now becoming clear that, in addition to increased glycolysis, increased OXPHOS by cancer cells and the resulting oxygen deprivation (hypoxia) in the tumor microenvironment has a significant detrimental impact on immune cell function. Thus, immune cells such as effector T cells have reduced functional capacity in the tumor microenvironment directly as a result of depleted nutrient ability and a resulting environmental metabolic checkpoint. Ramifications of such metabolic competition in the tumor microenvironment have attracted attention for potential therapeutic intervention in combination with immunotherapies, such as checkpoint blockade.

In this issue, Fischer and colleagues demonstrate that melanoma brain metastases could be segregated by gene-expression analysis into two distinct types: immune enriched and immune deficient. As expected, patient survival was greater in patients with immune-enriched brain metastases. Of interest, however, was that immune enrichment did not correlate with current “likely suspects” for driving immune activity, such as increased mutational load, increased PTEN alterations, or decreased B-catenin levels. Surprisingly, then, the major correlate with upregulated immune-deficient brain metastases was found to be an increase in OXPHOS pathways. Impressively, the inhibition of OXPHOS activity demonstrated increased survival in both murine tumor implantation models and spontaneous models of brain metastases. Intriguingly, OXPHOS inhibition specifically resulted in reduced brain metastasis incidence, as primary tumor growth and lung metastasis incidence were not changed.

Melanoma brain metastases have recently been demonstrated to be responsive to checkpoint blockade with a similar response rate to extracranial metastases. However, Fischer and colleagues demonstrate that in matched intracranial and extracranial metastatic samples, intracranial metastases have fewer CD3+ T cells, CD8+ cells, dendritic cells, and monocytes. Similarities in their incidences of PTEN alterations, β-catenin levels, and mutation loads between intracranial and extracranial samples suggest that the intrinsic molecular characteristics of melanoma cells responsible for brain metastasis do not in themselves confer reduced immunogenicity. This observation was elegantly supported by the authors’ demonstration that cell lines injected intracranially and subcutaneously had a divergent metabolic profile with increased levels of OXPHOS metabolites in the intracranial implants. Together, these data clearly identify increased oxidative activity in melanoma brain metastases as an important process that interferes with potential brain-localized antitumor immune responses.

Further studies to explore mechanisms for the association between increased tumor OXPHOS and increased immune suppression are warranted. Certainly, T cells have been shown to exhibit a dysfunctional metabolic profile, such as decreased mitochondrial biogenesis, in the tumor microenvironment. Thus, cancer cell depletion of available oxygen coupled with T-cell inherent metabolic dysfunction may have significant effects on T-cell antitumor potential. Although oxygen metabolism in T-cell effector function is less critical, memory formation and perhaps proliferation do require oxygen metabolism. Fischer and colleagues’ observation that brain metastases had decreased numbers of T cells may therefore reflect a hindrance of local expansion due to metabolic dysregulation. However, reduced levels of dendritic cells and monocytic cells suggest tumor trafficking may also play a role. Certainly, effects of hypoxia-related irregular vasculature formation and integrity may play a key role in immune trafficking to...
metastatic sites. How hypoxic conditions interplay with TGFβ signaling, now well accepted to promote T-cell exclusion from tumor beds, merits exploration in future studies of brain metastases (5). Finally, effects of hypoxic conditions on regulatory immune cell composition, either function or frequency, in the tumor microenvironment of brain metastases would be of interest in future studies.

Previous preclinical studies demonstrated the efficacy of OXPHOS modulation in MAPK inhibitor–resistant cell lines using mTORC1/2 inhibitors (6). Additionally, other preclinical studies observed increased intratumoral T-cell numbers and tumor clearance with a combination of anti–PD-1 antibodies and metformin, a mitochondrial OXPHOS inhibitor (7). Concurrent studies by Najjar and colleagues revealed that anti–PD-1 resistance both in preclinical melanoma models and from melanoma patient samples is tightly linked to oxygen metabolism in tumor tissues (8). Intriguingly, Fischer and colleagues also identified increased levels of intratumoral immune cells in brain metastases with prior radiotherapy. Evidence for targeting unique properties of intracranial melanoma metastases, such as AKT hyperactivation and activated STAT3, is increasingly apparent (9, 10). Together, these studies suggest an opportunity for creative treatments of melanoma brain metastases using combinations of targeted therapies, radiation, checkpoint blockade, and OXPHOS inhibitors (metformin, mTORC1/2 inhibitors, etc.; Fig. 1).

Key questions that remain are: (i) How do unique metabolic features of brain metastases coupled with unique immune trafficking patterns to brain metastases affect immune cell function and composition? (ii) How do unique metabolic features of melanoma brain metastases mechanistically alter responses to checkpoint blockade? (iii) What is the role of increased hypoxia and decreased oxygen availability on antigen-presenting cell availability and function? (iv) What is the correct sequencing for complex therapeutic combinations including OXPHOS inhibitors and checkpoint blockade? (v) How do immune responses to intracranial and extracranial metastases concert together for an effective relapse-free outcome of patients with melanoma?

Three major implications of the work of Fischer and colleagues are that (i) OXPHOS dependency of brain metastases is druggable, and future clinical trials should address combinatorial OXPHOS inhibition with various immunotherapy targets, keeping in mind the importance of studying the impact of these interventions on immune-mediated and molecularly targeted mechanisms of melanoma eradication, which may also be adversely affected by the same therapeutic approach; (ii) brain metastases are metabolically unique and need further research to interrogate mechanisms of intrinsic and acquired immunotherapeutic resistance; and (iii) treatment of patients with melanoma with multiple organ metastases may require a multipronged approach in which different organ metastases require different intervention strategies to ensure complete responses required for long-term control and potential curative outcomes for patients with advanced melanoma.

Disclosure of Potential Conflicts of Interest

K. Margolin is a consultant/advisory board member for Iovance, ImaginAb, Guidepoint, and Nektar. No potential conflicts of interest were disclosed by the other author.

Published online May 1, 2019.

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