JEM Journal of Experimental Medicine

INSIGHTS

Breathing down resistance: Tackling hypoxia to overcome immunotherapy barriers in lung cancer

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In this issue of *JEM*, Robles-Oteiza et al. (https://doi.org/10.1084/jem.20231106) present compelling evidence linking tumor hypoxia to acquired resistance mechanisms in non-small cell lung cancer (NSCLC) treatments involving immune checkpoint inhibitors (ICIs). Their research advocates targeting these hypoxic tumor regions with hypoxia-activated pro-drugs like TH-302, which may substantially delay the onset of resistance and herald a significant advancement in cancer therapy.

Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy by unleashing the body's immune system to attack tumor cells. These therapies typically target molecules like PD-1/PD-L1 or CTLA-4, which cancer cells exploit to evade immune detection (Pardoll, 2012). By blocking these pathways, ICIs reactivate T cells, leading to the regression of tumors. In diseases like non-small cell lung cancer (NSCLC), which often present a high tumor mutational burden (TMB), ICIs have shown substantial promise due to the increased neoantigen load that enhances T cell recognition of cancer cells. Despite their initial effectiveness, the long-term utility of ICIs in NSCLC is hampered by the development of resistance. The resistance emerges characterized by diminished T-cell infiltration within the tumor, or decreased expression of major histocompatibility complex (MHC) molecules, MHC-I and MHC-II, on tumor cells, which are crucial for antigen presentation and subsequent T-cell recognition (Garrido et al., 2016; Ferris et al., 2014).

Tumor hypoxia has been evident to be particularly detrimental to ICI resistance because it creates a hostile environment for immune cells. Hypoxic conditions can lead to several resistance mechanisms: (1) cancer cells in hypoxic areas adapt their metabolism to survive in low-oxygen conditions, making them fundamentally different and potentially more resistant to therapies designed for their oxygen-rich counterparts. (2) Hypoxia induces the expression of factors like VEGF, TGF-β, and PD-L1 in tumor cells, which contribute to an immunosuppressive microenvironment that stifles T-cell activity and survival (Noman et al., 2014). (3) The stress of hypoxia can also lead to genetic and epigenetic changes that further enhance tumor survival and resistance (Watson et al., 2010).

In this background, this study (Robles-Oteiza et al., 2024) first investigates the role of the DNA mismatch repair enzyme Msh2 in lung adenocarcinoma models and how its knockout (KO) affects tumor growth, immune response, and resistance to ICIs. Using CRISPR/Cas9, Msh2 was knocked out in Kras-driven lung cancer mouse models, leading to an increased TMB. Although Msh2 KO cells did not show impaired growth in immunodeficient mice, they demonstrated significant tumor regression upon treatment with anti-PD-1 and anti-CTLA-4 antibodies, in a T-cell-dependent manner, specifically in the LKR13 model but not in 368T1 tumors. This suggests that TMB alone does not dictate immune responsiveness; the tumor's microenvironment plays a crucial role. Further analysis revealed that T-cell infiltration and IFNγ production increased in LKR13 KO tumors, whereas 368T1 tumors did not respond similarly despite similar TMB levels. Notably, LKR13 tumors developed acquired resistance to ICIs, characterized by reduced T-cell abundance and increased expression of T-cell exhaustion markers. Single-cell RNA sequencing and flow cytometry analyses confirmed that resistant tumors harbored fewer tumor-infiltrating lymphocytes and exhibited impaired effector functions. The research also emphasizes that while ICIs can effectively reduce tumor mass initially by activating T-cell responses, they fail to target hypoxic segments of the tumor, which continue to evolve and escape immune surveillance.

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Hypoxia, a condition of low oxygen availability, is commonly encountered within the microenvironment of solid tumors. It plays a pivotal role in tumor progression and therapy resistance, primarily through the stabilization of hypoxia-inducible factors (HIFs), such as HIF-1α. Under normal oxygen levels, HIF-1α is rapidly degraded; however, hypoxia stabilizes HIF-1α, allowing it to activate a variety of genes involved in angiogenesis, metabolism, and cell survival (Semenza, 2012). Additionally, metabolic reprogramming in hypoxic tumor regions appears to cultivate an immunosuppressive milieu conducive to regulatory T-cell stability and myeloid-derived suppressor cell activity. The paper also explores the intricate dynamics within the tumor microenvironment (TME), such as cytokine signaling, cellular metabolism, and the role of the extracellular matrix in fostering resistance. It further discusses how Msh2 deficiency not only elevates mutation burden but also compromises genomic stability, impacting tumor immunogenicity and ICI responsiveness.

Since hypoxia was identified as a key feature in resistant tumors, associated with decreased MHC-II expression and reduced T-cell infiltration, the finding advocates for combining ICIs with therapies that target metabolic pathways influenced by hypoxia or directly manipulate HIFs through advanced gene-editing technologies. Given the role of hypoxia in fostering an environment conducive to resistance, targeting hypoxic tumor segments appears to be a promising strategy (Wilson and Hay, 2011; Melillo, 2007). By alleviating hypoxia, these therapies could improve T-cell penetration and functionality within tumors, thus boosting the effectiveness of ICIs. Additionally, therapies targeting the unique metabolic adaptations of hypoxic tumor cells could inhibit their ability to thrive in low-oxygen conditions. Reducing hypoxia may also diminish the production of immunosuppressive factors, promoting a more robust and sustained immune response. Consequently, integrating hypoxia-targeted strategies, such as the use of hypoxia-activated prodrugs, could maintain ICI effectiveness and prevent the decline in patient response commonly observed, potentially transforming cancer treatment paradigms (Li et al., 2021).

Moreover, the paper emphasizes the importance of advanced genomic and transcriptomic profiling techniques. These methods allow for the dynamic monitoring of how tumors adapt to therapies and evolve resistance mechanisms. By understanding these patterns, clinicians can tailor treatments to the individual genetic and molecular makeup of each patient's tumor, potentially leading to more personalized and effective cancer therapy. Additionally, the article encourages the exploration of next-generation ICIs designed to more effectively infiltrate and modulate the hypoxic zones of tumors or tailored to function optimally within various TME contexts. It speculates on the future role of artificial intelligence and machine learning in oncology (Gao et al., 2021), envisioning these technologies as tools for predicting resistance pathways and dynamically optimizing combination therapy schedules for enhanced precision and effectiveness in treatments.

Collectively, these findings reveal the transformative potential of targeting hypoxia in revolutionizing the treatment landscape for NSCLC and potentially other cancers with similar resistance mechanisms. This strategy promises not only to extend the efficacy of current treatments but also to open new avenues for sustained responses and improved outcomes in advanced cancer therapies.

Acknowledgments

We extend our gratitude to the members of Joyce Chen's lab at the University of Chicago, and Dr. Fuyu Duan and Shuang Wu for their invaluable advice and discussion.

This work was supported by grants from the U.S. Department of Defense (HT9425-23-1-0636) and a Lung Cancer Research Foundation Pilot Project Award.

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