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EDITORIAL VIEW **CANCER CARE INSIGHTS**

Cancer care insights: hypoxia in the tumor microenvironment, a biomarker, barrier, or breakthrough?

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ABSTRACT

A characteristic of the tumor microenvironment (TME), hypoxia has two functions in the biology of cancer. From one perspective, oxygen deprivation causes metabolic reprogramming, interferes with normal immune surveillance, and increases resistance to treatment. Conversely, hypoxia-inducible pathways have changed the way precision oncology is approached by showing promise as biomarkers and therapeutic targets. Novel approaches for taking advantage of this hostile niche are being revealed by developments in imaging technologies, nanomedicine, and hypoxia-activated prodrugs (HAP). Nevertheless, dynamic oxygen fluctuations and tumor heterogeneity continue to pose a challenge to clinical translation. This editorial discusses whether hypoxia serves primarily as a treatment barrier, a prognostic biomarker, or an intriguing novel therapeutic approach for cancer.

Abbreviations: HAP: Hypoxia-Activated Prodrugs; PKR: Protein Kinase R; TME: Tumor Microenvironment

Keywords: Hypoxia; Tumor; Microenvironment; Prognostic Biomarkers; Immunotherapy; Hypoxia-Inducible Factor 1; alpha (HIF-1α)

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The use of hypoxia in the tumor microenvironment (TME) as a biomarker in cancer research is gaining momentum. Hypoxic/TME-high tumors have distinct genomic patterns and poorer prognosis, which can help guide customized immunotherapy strategies, according to a recent pan-cancer study that divided tumors into subtypes based on hypoxia levels and TME immunologic context. Likewise, molecular subtypes linked to hypoxia and lactate metabolism were strongly associated with immune infiltration and prognosis in colorectal cancer. Long non-coding ribonucleic acids (lncRNAs) linked to hypoxia served as risk markers and predicted immunologic characteristics in uveal melanoma. When taken as a whole, these studies demonstrate that hypoxia is measurable, clinically significant, and capable of providing stratification tools for therapies that are customized for each patient.[1]

Hypoxia, however, continues to be a significant obstacle to effective cancer treatment, particularly immunotherapy. Hypoxia inhibits CD8+ T cell recognition of tumor cells by downregulating major histocompatibility complex (MHC) class I expression and reducing antigen presentation through the protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) arm of the unfolded protein response and autophagy, according to mechanistic research.[2] In addition, hypoxic areas also attract immunosuppressive populations including myeloid-derived suppressor cells (MDSCs), regulatory T cells, and tumor-associated macrophages (TAMs), which results in the formation of

an immune-cold microenvironment. Hypoxia also disrupts the efficacy of traditional chemotherapy and targeted agents, and enhances genomic instability and adaptive survival pathways, which further limits the efficacy of immunotherapy. This multifaceted resistance mechanism underscores the need to pay attention to hypoxia consideration when making routine clinical decisions, as well as in experimental studies.[3]

If this hypoxia can be targeted carefully, however, recent research suggests it may be a breakthrough. With immune checkpoint blockade, hypoxia-activated prodrugs such as evofosfamide (TH-302) improved T cell infiltration and the composition of suppressive immune cells in preclinical models of prostate cancer. The hemoglobin nanoclusters carrying oxygen when applied in combination with photodynamic therapy decreased hypoxia, downregulated karyopherin subunit alpha 4 (KPNA4), and eradicated sorafenib resistance in hepatocellular carcinoma cells. Another novel therapeutic approach is modification of the extracellular matrix (ECM) stiffness and the tumor vasculature to restore the normal blood flow and oxygenation.[4] Hypoxia's function in immune regulation and metabolic reprogramming is an additional dimension. Under hypoxic conditions, increased glycolysis and lactate accumulation facilitates tumor growth and immune exhaustion. In protein kinase R, glycolysis-enriched clusters of B cells and TAMs were associated with poor prognosis, as well as T cell exhaustion. Likewise, the immune evasion and lactate metabolism axis is being investigated as a potential targetable axis.[3]

Blocking them may lead to new treatment possibilities, particularly for immune cold tumors that are resistant to conventional treatments. Therapies that target just the hypoxia-sensing system are progressing rapidly. Hypoxia-inducible factors (HIFs) and downstream signaling pathways such as PERK-autophagy or metabolic checkpoints can be targeted to restore antigen presentation and improve immune visibility of tumors, and to make tumors more susceptible to checkpoint inhibitors.[5] Researchers are exploring ways to supplement oxygen, including using vascular perfusion modulators and engineered oxygen carriers, as a complement to immunotherapy and radiation therapy. However, challenges for clinical translation remain, including monitoring oxygenation in tumors precisely, patient selection and avoiding off-target effects.

Hypoxia is a dynamic aspect of cancer biology rather than just a passive state in the TME. It can be a breakthrough, a drug resistance mechanism, or a prognosis/drug resistance marker when it is used judiciously with the right strategies. They encompass the development of reliable hypoxia markers to identify those patients who will benefit most from hypoxia modifying therapy and the enhancement of non-invasive imaging techniques that would allow monitoring of the oxygenation of tumors in real-time.[4] Modulating well-designed clinical trials that use hypoxia-targeted drugs with proven therapies such as immunotherapy, radiation, and chemotherapy is also a critical step.

REFERENCES

1. Chen Z, Han F, Du Y, Shi H, Zhou W. Hypoxic microenvironment in cancer: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther. 2023;8(1):70. PMCID: PMC9935926 DOI: 10.1038/s41392-023-01332-8
2. Fan P, Zhang N, Candi E, Agostini M, Piacentini M, Shi Y, et al. Alleviating hypoxia to improve cancer immunotherapy. Oncogene. 2023;42(49):3591–604. PMID: 37884747 DOI: 10.1038/s41388-023-02869-2
3. Bhuniya S, Vrettos EI. Hypoxia-activated theragnostic prodrugs (HATPs): current state and future perspectives. Pharmaceutics. 2024;16(4):557. PMCID: PMC11054426 DOI:10.3390/pharmaceutics16040557
4. Wu C, Xu T, Zhang H, Hu Y, Jiao J, Qiu K, et al. Hypoxia and immunometabolism in the tumor microenvironment: insights into mechanisms and therapeutic potential. Cancer Lett. 2025;631:217913. PMID: 40653189 DOI: 10.1016/j.canlet.2025.217913
5. Kao TW, Bai GH, Wang TL, Shih IM, Chuang CM, Lo CL, et al. Novel cancer treatment paradigm targeting hypoxia-induced factor in conjunction with current therapies to overcome resistance. J Exp Clin Cancer Res. 2023;42(1):171. PMCID: PMC10353250 DOI: 10.1186/s13046-023-02724-y

