

## The Impact of Hypoxia on Tumor-Associated Immune Cells

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### DESCRIPTION

Tumor microenvironments are complex ecosystems where the cancer cells interact with various stromal and immune cells, creating conditions that significantly influence disease progression and treatment response. One of the most critical features of the tumor microenvironment is hypoxia, a state of low oxygen tension. Hypoxia arises due to the rapid proliferation of tumor cells outpacing the development of adequate vasculature. Beyond being a mere byproduct of tumor growth, hypoxia actively shapes the immune landscape of tumors, modulating the function, recruitment, and survival of tumor-associated immune cells. Understanding the impact of hypoxia on immune cells within tumors is crucial for developing effective cancer therapies, particularly those targeting immune pathways.

### Hypoxia and immune cell function in tumors

Hypoxia exerts profound effects on the behavior of tumor-associated immune cells, often creating an immunosuppressive environment that facilitates tumor progression. Among immune cells, macrophages are particularly sensitive to low oxygen conditions. Tumor-Associated Macrophages (TAMs) can polarize into either pro-inflammatory (M1-like) or anti-inflammatory (M2-like) phenotypes. Hypoxia promotes the polarization of TAMs toward the M2-like phenotype, which supports tissue remodeling, angiogenesis, and suppression of cytotoxic T-cell activity. This shift is largely mediated by Hypoxia-Inducible Factors (HIFs), transcription factors that regulate the expression of genes involved in metabolism, angiogenesis, and immune modulation. For instance, HIF-1  $\alpha$  stabilization in hypoxic regions of tumors increases the expression of Vascular Endothelial Growth Factor (VEGF) and arginase-1, fostering an environment conducive to tumor growth while impairing antitumor immune responses.

Beyond macrophages, hypoxia significantly impacts T lymphocytes, which are central to the antitumor immune response. Cytotoxic CD8<sup>+</sup> T cells rely on high-energy metabolism to perform their effector functions, including the secretion of perforin and granzyme to kill tumor cells. Hypoxia disrupts cellular metabolism and reduces the proliferative and

cytotoxic capacities of these T cells, rendering them less effective against tumor cells. Regulatory T cells (Tregs), on the other hand, thrive under hypoxic conditions. HIF-1  $\alpha$  promotes the recruitment and survival of Tregs, further reinforcing an immunosuppressive microenvironment. Similarly, Natural Killer (NK) cells exhibit impaired cytotoxicity and cytokine production under hypoxia, limiting their ability to detect and destroy malignant cells. Collectively, these alterations illustrate hypoxia can subvert the immune system's natural antitumor activities.

### Mechanisms linking hypoxia to immune modulation

The immunomodulatory effects of hypoxia are mediated through multiple interconnected molecular and cellular mechanisms. One major pathway involves the stabilization of hypoxia-inducible factors (HIF-1  $\alpha$  and HIF-2  $\alpha$ ), which act as master regulators of gene expression under low oxygen conditions. HIFs induce the expression of immunosuppressive molecules such as Programmed Death-Ligand 1 (PD-L1), which binds to PD-1 on T cells to inhibit their activity. This mechanism is a key contributor to immune evasion in tumors, reducing the efficacy of antitumor immunity and limiting responses to immunotherapy.

Metabolic reprogramming under hypoxia also plays a pivotal role. Tumor cells shift toward glycolysis in the absence of sufficient oxygen, producing lactate as a byproduct. Accumulation of lactate in the tumor microenvironment creates an acidic milieu that impairs T cell and NK cell function, while promoting M2-like TAM polarization. Moreover, hypoxia induces the secretion of chemokines such as CCL28, which attracts Tregs to the tumor site, reinforcing immune suppression. Myeloid-Derived Suppressor Cells (MDSCs), another immunosuppressive population, are also recruited and activated under hypoxic conditions, further dampening antitumor immunity.

Interestingly, hypoxia not only suppresses effector immune cells but also alters antigen presentation. Dendritic cells in hypoxic regions of tumors exhibit impaired maturation and reduced ability to present tumor antigens, limiting T cell priming and reducing the likelihood of effective immune surveillance. The

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combined effect of these mechanisms is a tumor microenvironment that is both hostile to antitumor immune cells and supportive of tumor growth, angiogenesis, and metastasis.

## CONCLUSION

Hypoxia is a defining feature of solid tumors that profoundly shapes the immune microenvironment, often tipping the balance toward immunosuppression and tumor progression. By modulating the phenotype and function of tumor-associated immune cells, hypoxia creates conditions that limit the effectiveness of cytotoxic T cells, NK cells, and dendritic cells,

while promoting the survival and recruitment of immunosuppressive populations such as Tregs, M2-like TAMs, and MDSCs. These effects are mediated through HIF-dependent gene regulation, metabolic reprogramming, and altered chemokine signaling. Understanding the complex interplay between hypoxia and immune cells is essential for the design of new therapeutic strategies, including hypoxia-targeted therapies, metabolic interventions, and immune checkpoint inhibitors. Ultimately, targeting hypoxia-driven immunosuppression holds the potential to enhance antitumor immunity and improve clinical outcomes for patients with solid tumors.