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Hypoxic niches attract and sequester tumor-associated macrophages and cytotoxic T cells and reprogram them for immunosuppression

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Abstract

Glioblastoma (GBM), a highly lethal brain cancer, is notorious for immunosuppression, but the mechanisms remain unclear. Here, we documented a temporospatial patterning of tumor-associated myeloid cells (TAMs) corresponding to vascular changes during GBM progression. As tumor vessels transitioned from the initial dense regular network to later scant and engorged vasculature, TAMs shifted away from perivascular regions and trafficked to vascular-poor areas. This process was heavily influenced by the immunocompetence state of the host. Utilizing a sensitive fluorescent UnaG reporter to track tumor hypoxia, coupled with single-cell transcriptomics, we revealed that hypoxic niches attracted and sequestered TAMs and cytotoxic T lymphocytes (CTLs), where they were reprogrammed toward an immunosuppressive state. Mechanistically, we identified chemokine CCL8 and cytokine IL-1β as two hypoxic-niche factors critical for TAM trafficking and co-evolution of hypoxic zones into pseudopalisading patterns. Therefore, perturbation of TAM patterning in hypoxic zones may improve tumor control.

Keywords: CCL8; CTLs; GBM; IL-1β; TAM; cytotoxic T lymphocytes; immune landscape; immunosuppression; tumor hypoxia; tumor vasculature; tumor-associated microglia/macrophages.