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Astrocytes in glioblastoma tumor microenvironment

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Abstract

Glioblastoma (GBM) remains one of the most aggressive and lethal brain tumors in adults, characterized by extensive heterogeneity, robust therapeutic resistance, and a dismal prognosis despite maximal surgical resection, radiotherapy, and chemotherapy. A defining hallmark of GBM is its complex tumor microenvironment (TME), a dynamic ecosystem comprising immune cells, vascular networks, extracellular matrix, and various stromal components that collectively drive tumor progression and therapeutic evasion. Within this intricate niche, astrocytes, traditionally regarded as passive support cells in the central nervous system (CNS), have emerged as pivotal orchestrators of GBM pathogenesis. These cells undergo profound phenotypic reprogramming upon interaction with GBM cells, adopting diverse roles that encompass metabolic support, immune suppression, promotion of invasive growth, and induction of therapy resistance. Regulated by key signaling pathways and influenced by GBM-derived exosomes, blood-brain barrier disruption, and tumor-associated hypoxia, astrocytes exhibit remarkable plasticity and heterogeneity, including putative subtypes such as metabolic homeostasis, immune-inflammatory reactive, gliomagenic, and senescence-associated subtypes. Their ability to shape the TME through immunosuppressive axis activation, energy support, metabolic crosstalk, and intercellular communication via tunneling nanotubes (TNTs) and extracellular vesicles (EVs) underscores their critical role in GBM biology. This review focuses on the multifaceted contributions of astrocytes within the GBM microenvironment, exploring their phenotypic diversity, regulatory mechanisms, therapeutic potential as emerging targets to dismantle the pro-tumor niche as well as to improve patient outcomes and advances in technologies for investigating astrocytes in GBM.

Keywords: Glioblastoma; Immune modulation; Tumor associated astrocytes; Tumor microenvironment.