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Systemic and local dysregulation of the complement system in glioma: a comprehensive systematic review

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Background: Gliomas, particularly glioblastoma (GBM), are characterized by aggressive progression and profound immune evasion. The complement system which is a fundamental component of innate immunity comprising classical, alternative, and lectin activation pathways converging on target cell lysis, is frequently dysregulated within the tumor microenvironment, where it plays a pivotal role in promoting tumor survival and immune shielding. The complement system, often dysregulated in the tumor microenvironment, plays a pivotal role in these processes via regulators like Factor H (CFH), Factor I (CFI), and Clusterin (CLU). This systematic review analyzes their expression, regulation, and dual roles in immune shielding and oncogenic signaling.

Methods: A systematic review was conducted following PRISMA 2020 guidelines. Major databases (PubMed, Scopus, Embase, Web of Science) were searched up to November 2025. Eligible studies included in vitro, in vivo, and clinical investigations of complement regulators in glioma.

Results: Twenty-one experimental studies met inclusion criteria, demonstrating that glioma cells actively synthesize, secrete, and epigenetically regulate complement inhibitors to subvert immune surveillance. Soluble regulators such as CFH, FHL-1, and FHR5 bind to tumor cell surfaces, accelerate convertase decay, and protect cells from complement-mediated cytolysis. Mechanistically, the review identified critical "non-canonical" oncogenic functions beyond immune shielding. CFH acts as a novel ligand for the ICOS receptor on regulatory T cells, activating the PI3K/Akt pathway to enhance immunosuppression, while circ-CFH sponges miR-149 to drive AKT1-mediated proliferation. Factor I is similarly upregulated in high-grade gliomas, promoting tumor invasion via VEGF-FAK signaling. Clusterin plays a pivotal role in therapeutic resistance; glioblastoma stem-cell-derived extracellular vesicles transfer Clusterin to macrophages, inducing M2 polarization and conferring resistance to temozolomide. Furthermore, Clusterin silencing sensitizes glioma cells to senolytic therapy by triggering oxidative stress and apoptosis. Among membrane-bound regulators, CD59 was identified as the dominant inhibitor of the terminal lytic complex, surpassing CD46 in functional importance.

Conclusion: Complement regulators in glioma extend beyond passive immune evasion to actively drive tumorigenesis and therapeutic resistance. The identification of non-canonical mechanisms, such as the CFH-ICOS axis and Clusterin-mediated drug resistance, highlights these proteins as critical prognostic biomarkers and promising therapeutic targets to sensitize tumors for efficient immune and chemotherapy.

Keywords: Clusterin; Complement system; Factor H; Glioma; Immune evasion.