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Unfolded Protein Response and ER Stress in Microglia/TAMs in Glioblastoma: A Systematic Review

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Abstract

Background: Glioblastoma (GBM) is the most aggressive primary malignant brain tumor in adults, characterized by a profoundly immunosuppressive tumor microenvironment (TME) dominated by tumor-associated microglia and macrophages (TAMs). Severe metabolic bottlenecks within the hypoxic GBM core impose chronic proteostatic stress, engaging the Unfolded Protein Response (UPR). While traditionally viewed as cell-autonomous survival circuits, emerging evidence indicates that UPR sensors actively drive myeloid cell infiltration, metabolic rewiring, and immune evasion. This systematic review evaluates how ER stress and UPR networks operate within microglia, TAMs, and myeloid-derived suppressor cells (MDSCs) to shape GBM progression.

Methods: Following PRISMA guidelines, a comprehensive search of PubMed and Scopus was conducted. Studies investigating ER stress or UPR pathways specifically within microglial, TAM, or myeloid populations in the context of glioblastoma were included. Methodological quality and risk of bias were assessed using a customized *robvis*-compatible evaluation framework across four core domains.

Results: A total of 34 publications met the predefined eligibility criteria, comprising primary research studies and secondary review articles. The included literature was synthesized qualitatively, with primary research findings distinguished from evidence and interpretations reported in secondary reviews. The synthesis indicates that UPR signaling may contribute to glioblastoma microenvironmental remodeling and immunosuppressive myeloid-cell functions, although its effects appear to depend on the specific signaling branch, cellular context, and experimental model.

The PERK-eIF2α-ATF4 axis promotes myeloid chemotaxis via CSF-1 and CCL2 while driving GLUT1-mediated glycolysis and histone lactylation (K_{la}) at the IL-10 promoter to suppress $CD8^+$ T-cell function. Concurrently, the IRE1α-XBP1s axis functions as an immunometabolic switch that regulates UBE2D3/NF-kB signaling, lipid droplet accumulation, and immunosuppressive cytokine production. Furthermore, cell-surface GRP78 (csGRP78) and Transmissible ER Stress (TERS) via extracellular vesicles horizontally propagate pro-tumoral M2-like polarization. Preclinical interventions targeting UPR sensors (e.g., iPERK, DDRGK1/UFMylation inhibition) combined with immunotherapies (such as CD47-SIRPα

blockade or sonodynamic immunogenic cell death) successfully reverse immunosuppressive phenotypes and inhibit tumor recurrence.

Conclusion: Endoplasmic reticulum stress and UPR signaling within the GBM myeloid compartment critically drive tumor progression and immune escape. Targeting selected UPR pathways in combination with macrophage-directed immunotherapeutic approaches represents a potential therapeutic strategy that warrants further preclinical validation and clinical investigation.

Keywords: Glioblastoma; Unfolded Protein Response (UPR); Endoplasmic Reticulum (ER) Stress; Tumor-Associated Macrophages (TAMs); Microglia; Immunosuppression; Immunotherapy.

1. Introduction

1.1. Glioblastoma and Tumor Microenvironment

Glioblastoma (GBM), is the most frequent, aggressive, and universally fatal primary malignant central nervous system (CNS) tumor in adults, representing roughly 45% to 50% of all malignant gliomas (Price et al., 2024). Epidemiologically, GBM displays an annual incidence of approximately 3.2 per 100,000 individuals, a modest male predominance, and a median age of diagnosis of approximately 64 years (Thakkar et al., 2014). Originating primarily from glial progenitors or astrocytic lineage cells, GBM is clinically characterized by aggressive, diffuse infiltration into adjacent normal brain parenchyma, making complete surgical eradication anatomically difficult (Seker-Polat et al., 2022). Despite current multimodal standard-of-care protocols, consisting of maximal safe surgical resection followed by the Stupp protocol, which combines fractionated radiotherapy with concurrent and adjuvant alkylating chemotherapy using temozolomide (TMZ), the prognosis remains exceedingly poor (Adegboyega et al., 2021). The median overall survival is approximately 15 months, with a 5-year survival rate below 10% (Sipos et al., 2025). This dismal clinical outcome is driven by rapid local recurrence, profound cellular plasticity, and robust intrinsic mechanisms of therapeutic resistance.

GBM exhibits profound inter- and intra-tumoral heterogeneity at both histological and genetic tiers (Adegboyega et al., 2021). Under the 2021 World Health Organization (WHO) classification of Central Nervous System Tumors, IDH-wild-type glioblastoma is defined by specific diagnostic hallmarks such as microvascular proliferation (MVP), necrosis, pTERT promoter mutations, EGFR amplification, or whole-chromosome 7 gain coupled with chromosome 10 loss (Louis et al., 2021). Crucially, the 2021 guidelines formalize a major taxonomic shift by restricting the term "Glioblastoma" exclusively to IDH-wildtype tumors, whereas former IDH-mutant glioblastomas have been reclassified as Astrocytoma, IDH-mutant, Grade 4, thereby underscoring the distinct clinical and biological entity of true GBM (Louis et al., 2021). Transcriptomically, GBM tumors segregate into distinct molecular subtypes, proneural, classical, and mesenchymal, governed by signature alterations including PDGFRA amplifications, high-level EGFR modifications, and NF1 mutations or loss, fueling therapeutic evasion and cellular adaptability. (Verhaak et al., 2010). Crucially, this dynamic intra-tumoral heterogeneity actively orchestrates the profound remodeling of the surrounding tumor microenvironment (TME), driving a systematic reprogramming of infiltrating immune cells from an anti-tumor phenotype to

a tumor-tolerant state (Bayona et al., 2026). Through the continuous secretion of immunosuppressive cytokines, chemokines, and metabolic subproducts, glioblastoma cells successfully subvert host surveillance (Granda-Díaz et al., 2026). This creates an immunological "cold" tumor niche characterized by T-cell exhaustion, impaired antigen presentation, and the recruitment of regulatory populations (Nikitina et al., 2026). Within this reprogrammed landscape, resident microglia and bone marrow-derived macrophages are heavily hijacked, shifting toward a protumorigenic and tolerant state that actively shields the tumor from immune destruction and promotes tissue remodeling, angiogenesis, and invasion (Z. Amiri et al., 2026).

In stark contrast to immunogenic tumors, the GBM tumor microenvironment (TME) functions as a profoundly immunosuppressive immunological sanctuary (J. Yang et al., 2026). The TME is severely deficient in functional, tumor-infiltrating cytotoxic CD8+ T cells and is instead dominated by an overwhelming accumulation of myeloid lineage cells (Kumar et al., 2021). Malignant glioblastoma cells actively blunt anti-tumor immunity by secreting potent immunosuppressive cytokines such as transforming growth factor-beta (TGF-β) and interleukin-10 (IL-10), alongside expressing surface immune checkpoints including PD-L1 (Nduom et al., 2015). Furthermore, uncontrolled tumor expansion outstrips the aberrant vascular supply, generating a harsh biochemical milieu characterized by severe hypoxia, localized necrosis, nutrient deprivation, and extracellular acidosis (Domènech et al., 2021). Hypoxia stabilizes hypoxia-inducible factor 1-alpha (HIF-1α), which redirects cellular metabolism toward aerobic glycolysis via the upregulation of GLUT1 and hexokinase II (HK2) while driving VEGF-independent vascular mimicry (Basheeruddin & Qausain, 2024).

Within this metabolically starved and immunosuppressive TME, Tumor-Associated Microglia and Macrophages (TAMs) constitute an expansive cellular compartment, accounting for up to 30% of the total tumor mass (Andersen et al., 2021). TAMs represent a dual-origin population composed of long-lived, brain-resident microglia derived from embryonic yolk-sac progenitors and bone-marrow-derived monocytes recruited from the systemic circulation through a compromised blood-brain barrier (BBB) (Ma et al., 2026). While resident microglia initially attempt to mount a protective, pro-inflammatory surveillance response, persistent tumor-derived cues such as colony-stimulating factor 1 (CSF-1) and TGF-β aggressively reprogram TAMs toward an anti-inflammatory, pro-tumoral M2-like polarization state (S. Huang et al., 2026). These reprogrammed TAMs lose their phagocytic capacity and instead secrete pro-angiogenic factors

like VEGF, extracellular matrix-remodeling enzymes including matrix metalloproteinases (MMPs), and immunosuppressive mediators that actively foster tumor growth, local infiltration, and resistance to radio-chemotherapy (Xu, Ding, et al., 2025). Because targeting malignant tumor cells in isolation has consistently proven insufficient, decoding the molecular and metabolic programs governing the TAM compartment represents a core prerequisite for modern neuro-oncology (Kzhyshkowska et al., 2024).

Crucially, the severe metabolic bottlenecks of the GBM TME, specifically severe hypoxia, glucose deprivation, lactic acidosis, and high secretory demand, place an immense pathological burden on the protein-folding machinery within the endoplasmic reticulum (ER) of both malignant glioblastoma cells and infiltrating TAMs and microglia (Omene, 2026). The resulting intracellular accumulation of unfolded or misfolded proteins induces chronic endoplasmic reticulum (ER) stress (Haeri & Knox, 2012). To survive these proteostatic insults, cells engage the Unfolded Protein Response (UPR) through three principal ER transmembrane sensors: IRE1α (inositol-requiring enzyme 1 alpha), PERK (protein kinase RNA-like ER kinase), and ATF6 (activating transcription factor 6) (Chalmers et al., 2019). Recent literature highlights that UPR signaling branches, particularly the PERK–eIF2α-ATF4 and IRE1α-XBP1 axes, are not merely passive survival mechanisms, but active metabolic and immunomodulatory drivers within the glioblastoma ecosystem (Mai et al., 2025). Specifically, tumor-intrinsic and microenvironmental UPR activation actively promotes myeloid cell infiltration, shapes macrophage polarization dynamics by supporting metabolic rewiring and immunosuppressive phenotypes, and assists survival under severe proteostatic constraint (Mahadevan & Zanetti, 2011). Consequently, investigating how ER stress and UPR networks operate within microglia and TAMs provides a critical mechanistic bridge for understanding glioblastoma progression, immune evasion, and novel therapeutic vulnerabilities (Petrosyan et al., 2023).

1.2. Molecular Characterization and Ontogeny of TAMs in GBM: Ontogeny, Spatial Heterogeneity, and Transcriptional Plasticity

While the distinct developmental ontogenies of CNS-resident microglia and bone marrow-derived macrophages (BMDMs) are now well-established, precisely dissecting their individual

contributions within the heavily infiltrated GBM microenvironment remains a significant technical and biological challenge (Mahadevan & Zanetti, 2011; Petrosyan et al., 2023). Historically, flow cytometry strategies relied heavily on differential CD45 expression levels to separate these populations, characterizing resident microglia as $CD11b^{+}/CD45^{low}$ and infiltrating peripheral macrophages as $CD11b^{+}/CD45^{high}$ (Petrosyan et al., 2023).

However, this binary classification often fails in the context of GBM, as chronic exposure to tumor-derived inflammatory cues, such as TGF-β, GM-CSF, and IFN-γ, dynamically upregulates CD45 expression on resident microglia, confounding accurate quantification (Brandenburg et al., 2021; Buonfiglioli & Hambardzumyan, 2021). This loss of resolution at the CD45 locus reflects a broader phenotypic convergence, where activated microglia and BMDMs not only exhibit overlapping marker intensities but also adopt an identical amoeboid morphology and co-express pan-macrophage markers like Iba1 and CD11b (Brandenburg et al., 2021; Buonfiglioli & Hambardzumyan, 2021) .

Consequently, this technical artifact has historically led to a significant overestimation of peripheral macrophage infiltration in flow cytometry datasets, masking the true proliferative and spatial dynamics of the local, tissue-resident microglial population during tumor progression (Friebel et al., 2020). To overcome these limitations, recent high-resolution transcriptomic and proteomic analyses have identified lineage-specific homeostatic markers (Gautiar et al., 2012; Haage et al., 2019) . Under physiological conditions, resident microglia uniquely express markers such as TMEM119, P2RY12, SALL1, and CX3CR1 (Bowman et al., 2016; Gautiar et al., 2012; Haage et al., 2019) . Conversely, peripheral BMDMs are characterized by the expression of CCR2 and CD49d (ITGA4) (Bowman et al., 2016).

Beyond markers, the formation and spatial organization of Tumor-Associated Microglia and Macrophages (TAMs) are deeply rooted in their unique cellular origins and distinct life cycles (Sevenich, 2018) . CNS-resident microglia originate exclusively from embryonic yolk-sac erythromyeloid progenitors during early embryogenesis (around embryonic days E8.5 to E9.5 in mice) and populate the developing neural tube long before the formation of the blood-brain barrier (BBB) (Sevenich, 2018; Tay et al., 2016). Throughout adulthood, these resident microglia maintain themselves via localized, self-renewing proliferation independent of circulating blood monocytes, possessing a remarkably slow turnover rate (Sevenich, 2018) . In stark contrast, BMDMs originate from hematopoietic stem cells in the bone marrow, circulate as mature

monocytes, and are recruited into the brain parenchyma only when pathological insults, such as the formation of a glioblastoma, compromise the blood-brain barrier and establish an intense chemotactic gradient (Hambardzumyan et al., 2015).

The recruitment and accumulation of both populations into the GBM mass are orchestrated by a complex network of tumor-derived chemoattractants (Chen et al., 2017; Pyonteck et al., 2013). Malignant glioma cells and reactive stromal elements constitutively secrete high levels of chemokines and growth factors, including Colony-Stimulating Factor 1 (CSF-1), Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), CCL2 (MCP-1), CCL5, and Stromal Cell-Derived Factor 1 (SDF-1/CXCL12) (Coniglio et al., 2012). These soluble factors bind to corresponding receptors on myeloid cells (such as CSF1R, CCR2, and CXCR4), driving rapid migration, accumulation, and morphological transformation from ramified surveillance states into enlarged, amoeboid phagocytes, hence why they ultimately constitute up to 30% of the total tumor volume (Brandenburg et al., 2021) . In tandem with resident microglia and BMDMs, the GBM myeloid landscape is further compounded by the massive recruitment of Myeloid-Derived Suppressor Cells (MDSCs), subdivided into polymorphonuclear (PMN-MDSCs) and monocytic (M-MDSCs) subpopulations (De Leo et al., 2021). These immature myeloid cells act synergistically with TAMs, forming a redundant and highly potent cellular shield that orchestrates T-cell apoptosis and antigen-presentation arrest (Nikitina et al., 2026).

Crucially, the spatial architecture of TAMs within the GBM ecosystem is not uniformly distributed, rather, microglial and macrophage subsets exhibit distinct spatial segregation and niche-dependent adaptations (Lu et al., 2026) . Single-cell spatial transcriptomics reveal that resident microglia are predominantly enriched within the infiltrative peripheral margins of the tumor, where they maintain partial homeostatic signatures and interact closely with healthy neural circuits and invading tumor edges (Friebel et al., 2020). Conversely, infiltrating BMDMs are preferentially drawn deep into the hypoxic core, perivascular niches, and necrotic zones of the tumor mass, where they are exposed to severe microenvironmental stress, hypoxia, and necrotic debris (Yin et al., 2022) .

These microenvironmental conditioning forces a profound functional and metabolic reprogramming of both resident microglia and BMDMs(Fan et al., 2026; J. Wang et al., 2024). Under the influence of glioma-derived immunosuppressive cytokines, such as TGF-β, IL-10, and prostaglandin E_2, TAMs undergo a phenotypic shift away from anti-tumoral effector states

toward an immunosuppressive, M2-like polarization program (J. Chen et al., 2025; Wei et al., 2025). While this M1/M2 dichotomy provides a valuable framework for operationalizing macrophage activation, state-of-the-art single-cell RNA sequencing (scRNA-seq) profiles reveal that TAMs in GBM do not conform to discrete binary states; rather, they exist across a continuous, highly dynamic spectrum of activation, frequently co-expressing both pro-inflammatory and immunosuppressive markers simultaneously (Müller et al., 2017; Serangeli et al., 2026). Reprogrammed TAMs lose their intrinsic phagocytic capacity and instead upregulate molecules like Arginase-1 (Arg1), CD163, and Mannose Receptor (CD206), while actively secreting vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs such as MMP2 and MMP9), and epidermal growth factor. Through these mechanisms, TAMs remodel the extracellular matrix, drive aberrant neo-angiogenesis, suppress local cytotoxic T-cell immunity, and directly stimulate glioma stem cell (GSC) self-renewal and therapeutic resistance, making the TAM compartment a critical focal point for understanding brain tumor pathophysiology (J. Chen et al., 2025; Wei et al., 2025) .

Importantly, the sustained operational plasticity and secretory demands of these heavily reprogrammed myeloid populations are deeply dependent on cell-intrinsic coping mechanisms (Caglar, 2026). In the harsh, metabolically starved GBM niche, this adaptive capacity is heavily regulated by the activation of specific proteostatic stress networks, a phenomenon governed by the Unfolded Protein Response (UPR), as detailed in the following section (Caglar, 2026).

1.3. ER Stress and the Unfolded Protein Response

Endoplasmic reticulum (ER) stress arises as a fundamental physiological bottleneck within the glioblastoma microenvironment, occurring when cellular protein-folding demand systematically exceeds the organelle's chaperone capacity (Chalmers et al., 2026). To counteract this proteostatic insult and ensure survival, cells activate an evolutionarily conserved intracellular signaling cascade known as the Unfolded Protein Response (UPR), which is orchestrated via three primary ER transmembrane sensors: protein kinase RNA-like ER kinase (PERK), inositol-requiring enzyme 1 alpha (IRE1α), and activating transcription factor 6 (ATF6) (Kim, 2024). Under physiological homeostasis, these three sensors are maintained in an inactive, monomeric state through direct binding of the luminal ER chaperone Binding Immunoglobulin Protein (BiP/GRP78) to their stress-sensing domains (Chalmers et al., 2026; Kim, 2024). However, upon

the severe accumulation of misfolded or unfolded protein aggregates, driven by the harsh intratumoral conditions of hypoxia, localized nutrient deprivation, and lactic acidosis, BiP preferentially dissociates from the sensors to bind these aberrant proteins (M. Wang et al., 2009). This competitive sequestration of BiP relieves the inhibitory constraints on PERK, IRE1α, and ATF6, triggering their immediate activation and initiating distinct yet highly cross-regulated downstream signaling networks that transcend canonical cell survival to drive tumor progression, metabolic adaptation, and immune subversion (Anspach et al., 2020).

The PERK arm represents an immediate adaptive response designed to enforce global translational control (M. Wang et al., 2009). BiP dissociation, PERK undergoes homodimerization and trans-autophosphorylation, activating its cytosolic kinase domain to phosphorylate eukaryotic initiation factor 2 alpha (eIF2α) at Serine 51 (Malhi & Kaufman, 2011). This phosphorylation event globally attenuates cap-dependent translation initiation, effectively reducing the influx of nascent polypeptide chains into the overburdened ER lumen (Baird & Wek, 2012). Despite this widespread translational arrest, eIF2α phosphorylation paradoxically facilitates the selective, alternative translation of mRNAs containing inhibitory upstream open reading frames (uORFs), most notably the transcription factor activating transcription factor 4 (ATF4) (M. Amiri et al., 2024). Under acute stress conditions, ATF4 transactivates genes involved in amino acid metabolism, glutathione synthesis, and antioxidant defenses to restore proteostasis, however, if the stress remains chronic and unresolved, ATF4 upregulates C/EBP homologous protein (CHOP) (Peng et al., 2026). CHOP functions as a pro-apoptotic transcription factor that commits the cell to death by directly downregulating anti-apoptotic Bcl-2 families, upregulating pro-apoptotic BH3-only proteins, and triggering downstream caspase cascades (Peng et al., 2026). Crucially, while this PERK–eIF2α–ATF4–CHOP pathway is classically defined by its commit-to-death endpoint, malignant glioblastoma cells successfully hijack this cascade to execute non-apoptotic, protumorigenic programs (Peng et al., 2026; Rozpedek et al., 2016). Under sub-lethal, chronic ER stress, tumor-intrinsic ATF4 upregulates the transcription of myeloid-recruiting chemokines, specifically Colony-Stimulating Factor 1 (CSF-1) and CCL2 (MCP-1), thereby acting as a primary driver of Tumor-Associated Macrophage (TAM) and Myeloid-Derived Suppressor Cell (MDSC) infiltration into the tumor parenchyma (Liu et al., 2017). Simultaneously, within the infiltrated TAM compartment itself, persistent PERK signaling facilitates metabolic adaptation by upregulating specialized amino acid transporters and sustaining the expression of vascular

endothelial growth factor A (VEGF-A), ensuring macrophage survival and structural angiogenesis within the severely nutrient-deprived niches of the GBM core (Ran et al., 2026) .

In parallel, the IRE1α pathway functions as a primary immunomodulatory and metabolic rheostat within the GBM microenvironment (Lhomond et al., 2018). As an ER-bound bifunctional kinase and endoribonuclease (RNase), IRE1α oligomerizes and undergoes autophosphorylation upon stress, inducing a conformational change that aligns and activates its cytosolic endonuclease domain and while active, IRE1α mediates the unconventional cytoplasmic splicing of a 26-nucleotide intron from the mRNA encoding X-box binding protein 1 (XBP1) (S. Huang et al., 2019). This frame-shift splicing event generates a highly stable, potent transcription factor designated as spliced XBP1 (XBP1s), which coordinates the upregulation of ER chaperones, protein folding catalysts, and components of the ER-associated degradation (ERAD) machinery to enhance clearance of misfolded proteins (S. Huang et al., 2019; Lhomond et al., 2018). Concurrently, hyper-activated IRE1α can engage in Regulated IRE1-Dependent Decay (RIDD), a process wherein the RNase domain selectively degrades specific localized mRNAs and microRNAs to further alleviate the ER folding burden (S. Huang et al., 2019). Furthermore, through physical scaffold interactions, active IRE1α recruits the adapter protein tumor necrosis factor receptor-associated factor 2 (TRAF2), assembling a signaling platform that activates c-Jun N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB) pathways, thus directly interfacing proteostatic stress with pro-inflammatory and cell death cascades (Shen et al., 2015; Siegmund et al., 2022). Within the immunosuppressive glioblastoma landscape, the IRE1α–XBP1s axis operates as a master regulator of myeloid cell subversion (Obacz et al., 2024). Microenvironmental cues, particularly severe hypoxia and tumor-derived factors, induce p300-mediated acetylation of XBP1s in infiltrating TAMs and MDSCs, vastly extending its transcriptional half-life, as this hyper-stable XBP1s directly transactivates the promoters of potent immunosuppressive cytokines, including transforming growth factor-beta (TGF-β), interleukin-6 (IL-6), and interleukin-10 (IL-10), while simultaneously inducing lipid biosynthetic enzymes (Z. Chen et al., 2026; W. Wang et al., 2022). The resulting intracellular accumulation of lipid droplets rewires TAM metabolism, causing severe antigen-presentation dysfunction and transforming these cells into potent suppressors of $CD8^+$ cytotoxic T-cell immunity and active promoters of glioma stem cell (GSC) self-renewal (Z. Chen et al., 2026; Wu et al., 2019).

The third sensor, ATF6, contributes an additional layer of structural and metabolic adaptation (Lei et al., 2024). ATF6 is an ER membrane-bound transcription factor that, upon experiencing proteostatic stress, is packaged into COPII vesicles and translocated to the Golgi apparatus (Schindler & Schekman, 2009). Within the Golgi, ATF6 is sequentially cleaved by site-1 and site-2 proteases (S1P/S2P), releasing its active, cytosolic N-terminal basic leucine zipper fragment (ATF6f) (Schindler & Schekman, 2009). ATF6f rapidly translocates into the nucleus, where it binds to ER stress response elements (ERSE) to upregulate major structural ER chaperones, including BiP/GRP78, GRP94, and protein disulfide isomerases, while working synergistically with IRE1α to amplify basal *XBP1* expression (Karin & Kim, 2025). Possessing structural homology to sterol regulatory element-binding proteins (SREBPs), ATF6 activation uniquely modulates lipid homeostasis, fatty acid oxidation, and cytoprotective macroautophagy (Karin & Kim, 2025). In glioblastoma, the massive transcriptional upregulation of BiP/GRP78 driven by ATF6 causes a critical fraction of these chaperones to escape the KDEL-mediated ER retention machinery and translocate directly to the plasma membrane (Lee, 2025). This cell-surface GRP78 (csGRP78) acts as a non-canonical signaling receptor that binds extracellular ligands to activate downstream PI3K/Akt and MAPK pro-survival cascades, directly conferring resistance against standard-of-care alkylating chemotherapy with temozolomide (TMZ) in both malignant glioma cells and neighboring TAM populations (Y. Yang et al., 2025).

Crucially, the interaction between tumor-intrinsic and microenvironmental UPR signaling is not merely parallel but deeply interconnected through a highly coordinated intercellular phenomenon known as Transmissible ER Stress (TERS) (Jiang et al., 2020). Glioblastoma cells undergoing chronic proteostatic stress actively package UPR-associated transcripts, microRNAs, and damaged proteins into extracellular vesicles (EVs) or release specialized chaperones into the extracellular fluid (Jiang et al., 2020). When naive infiltrating monocytes, resident microglia, or MDSCs internalize these tumor-derived secretory vectors, they experience an unprovoked, secondary ER stress response (Jiang et al., 2020). This horizontally transmitted UPR activation selectively engages the recipient cells' IRE1α and PERK branches, forcing a rapid phenotypic and metabolic transition toward the pro-tumoral, immunosuppressive M2-like state without requiring direct cell-to-cell contact, thereby expanding the immunosuppressive sanctuary of the GBM far beyond the immediate tumor core (Jiang et al., 2020).

Collectively, the UPR operates as a dual-faceted survival and immunomodulatory mechanism in glioblastoma, systematically reducing new protein entry (via eIF2α), expanding folding capacity (via chaperones), enhancing intracellular degradation (via ERAD and autophagy), and shifting lipid metabolism to match microenvironmental constraints (Mai et al., 2025).

2. Methods

2.1 Databases and article acquisition

The systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, searching PubMed and Scopus databases. A combination of keyword searches was performed to generate a search strategy. The search keywords, including “glioblastoma”, “glioma”, “GBM”, “unfolded protein response”, “UPR”, “endoplasmic reticulum stress”, “ER stress”, “IRE1”, “PERK1”, “ATF6”, “GRP78”, “BiP”, “XBP1”, “microglia”, “macrophage”, “macrophages”, “TAM”, “TAMs”, “tumor-associated macrophage” and “myeloid” were used in both AND and OR combinations. Studies were retrieved using the following for Scopus: (("glioblastoma" OR "glioma" OR "GBM") AND ("unfolded protein response" OR "UPR" OR "endoplasmic reticulum stress" OR "ER stress" OR "IRE1" OR "PERK" OR "ATF6" OR "GRP78" OR "BiP" OR "XBP1") AND ("microglia" OR "macrophage" OR "macrophages" OR "TAM" OR "TAMs" OR "myeloid" OR "tumor-associated macrophage")) and the following for PubMed: ("Unfolded Protein Response" OR "UPR" OR "Endoplasmic Reticulum Stress" OR "ER stress") AND ("Microglia" OR "Tumor-Associated Macrophages" OR "TAMs" OR "Tumor microenvironment") AND ("Glioblastoma" OR "GBM" OR "Glioma"). No search filter was set, as all shown publications were initially added to the roster due to specificity of the topic.

All studies were selected based on the following inclusion criteria: (1) Pathology: Context of Glioblastoma (GBM) or high-grade gliomas; (2) Molecular Pathway: Direct investigation of Endoplasmic Reticulum (ER) Stress or Unfolded Protein Response (UPR) pathways.; (3) Cellular Focus: Explicit evaluation of Microglia, Tumor-Associated Macrophages (TAMs), or infiltrating myeloid cells.; and (4) Study Type: Original empirical research (in vitro, in vivo, or clinical/single-cell bioinformatic studies) and focused systematic reviews with accessible abstracts. The following exclusion criteria were employed: (1) No Microglia/TAMs (Wrong Cellular Focus): Studies

focusing solely on glioblastoma tumor cells, astrocytes, or non-myeloid populations without evaluating microglia or macrophages; (2) No UPR/ER Stress (Wrong Mechanism): Studies investigating microglia/macrophages in glioblastoma but without analyzing ER stress or UPR mechanisms; and (3) Wrong Disease/Model: Studies on ER stress/microglia in non-glioma CNS pathologies (e.g., Alzheimer's, stroke, Parkinson's) or systemic cancers outside the CNS; and (4) Publication Format: Editorials, conference abstracts, letters, commentaries, or non-English articles without full text.

The list of identified studies was imported into Rayyan.ai, and duplicates were removed. The researcher checked the results according to the inclusion and exclusion criteria with the blind mode active. Then, the eligible articles were subject to full-text screening. Title and abstract screening and subsequent full-text eligibility assessment were conducted by one reviewer. Rayyan's blind mode was used to support independent decision-making during the screening process. As a single reviewer performed the selection, the possibility of selection-related error cannot be excluded and is acknowledged as a methodological limitation.

The included publications comprised both primary research studies and secondary review articles. Primary research publications included *in vitro* and *in vivo* experimental studies, as well as clinical, transcriptomic, single-cell, spatial, and other bioinformatic investigations. Secondary publications included focused systematic reviews addressing ER stress, UPR signaling, and myeloid-cell biology in glioblastoma or closely related glioma contexts. Secondary reviews were retained because they provide relevant synthesis of the biological mechanisms and therapeutic context addressed in this review.

The literature search was conducted on 05/10/2026. All records available in PubMed and Scopus up to this date were considered. No publication-date restriction was applied. The search was limited to publications available in English, in accordance with the eligibility criteria.

2.2. Data Extraction

Data from the included studies were extracted and standardized using a predefined data extraction form. The extracted information was organized into a master database to facilitate comparison across studies. For each study, it was extracted the following core information: (1) study identifiers (author and year), (2) study design and experimental models (in vitro cell lines, in vivo mouse/rat orthotopic models, human clinical single-cell/spatial datasets, and bioinformatic

cohorts), (3) key ER stress and Unfolded Protein Response (UPR) molecular targets, (4) tumor microenvironment (TME) cellular focus (tumor-associated macrophages, microglia, myeloid-derived suppressor cells, and T cells), and (5) primary mechanistic findings regarding immune modulation, metabolic crosstalk, and therapeutic synergy.

In addition to these variables, each publication was classified according to its publication type (primary research or secondary review). For primary research studies, the experimental or analytical model, the cellular population investigated, the UPR/ER stress pathway examined, and the principal findings were recorded. For secondary review articles, the scope of the review, the mechanisms discussed, and their relevance to the present research question were documented. Where a review discussed findings from primary studies also included in this review, these findings were not counted as additional independent experimental observations. This distinction was maintained throughout the synthesis to reduce the risk of double-counting evidence.

2.3 Outcomes

The primary outcomes of interest were mechanistic, and microenvironmental alterations associated with ER stress and UPR pathway activation in glioblastoma. Specifically, these included:

- Myeloid and Immune Cell Repolarization: Shifts in macrophage/microglial phenotypes (such as M1 vs. M2 polarization ratio).
- Molecular and Metabolic Crosstalk: Downstream pathway interactions, including glycolysis, ferroptosis, histone lactylation, and antigen presentation defects.
- Tumor Progression and Therapeutic Synergy: Effects on glioma stemness, angiogenesis, immune evasion, and synergistic responses to immunotherapies or targeted therapies.

3. Results and Discussion

3.1 Literature Review Results

A total of 269 records were initially identified through database searching across PubMed and Scopus. Following the removal of 15 duplicate records, 254 unique articles underwent primary

title and abstract screening. During this initial stage, 207 records were excluded based on predefined criteria (E3: $n = 153$; E1: $n = 49$; E4: $n = 4$; E2: $n = 1$).

A total of 47 articles were retrieved for full-text eligibility assessment. Following full-text evaluation, 13 articles were excluded for the predefined criteria (E2: $n = 5$; E1: $n = 4$; and E3: $n = 4$). Ultimately, 34 studies met all inclusion criteria and were incorporated into the qualitative synthesis. The complete screening and selection workflow is summarized in accordance with the PRISMA guidelines in Figure 1.

The 34 included publications were considered as a combined evidence base comprising primary research and secondary review literature. These publication types were distinguished during data extraction and interpretation. Primary studies were used to identify experimental and bioinformatic evidence concerning UPR activation, ER stress, and myeloid-cell behavior in glioblastoma. Secondary reviews were used to contextualize these findings, summarize previously established mechanisms, and identify broader therapeutic implications. This approach allowed relevant literature to be retained while maintaining a distinction between original findings and previously published interpretations.

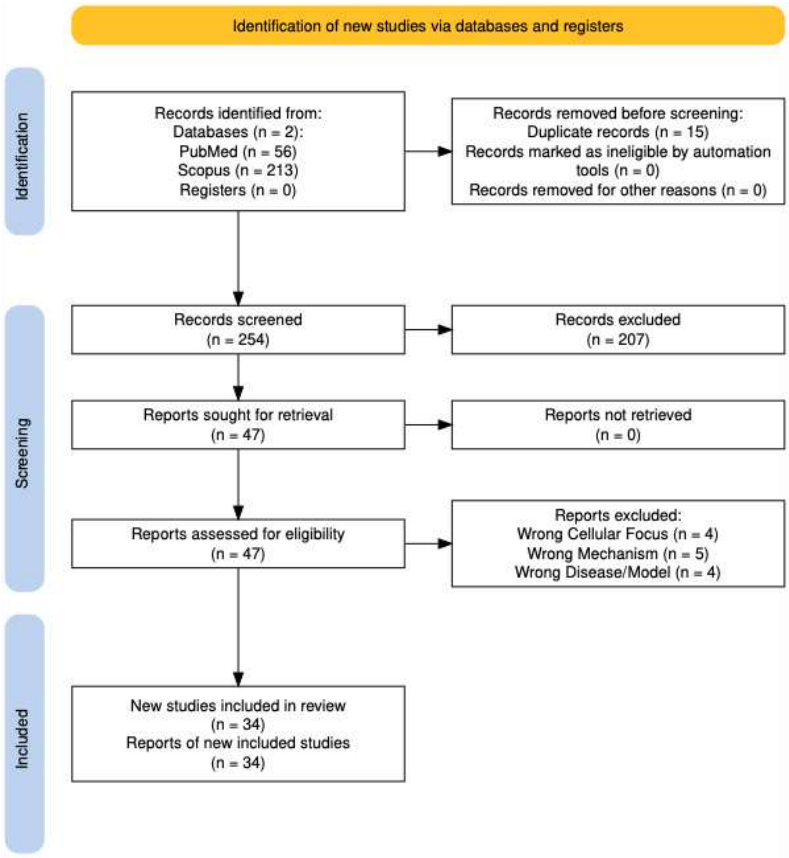


Figure 1. PRISMA 2020 flow diagram detailing the literature search, screening, and selection process for the systematic review investigating endoplasmic reticulum stress and unfolded protein response pathways in microglia and tumor-associated macrophages within glioblastoma. A total of 269 records were identified across PubMed and Scopus databases. Following the removal of 15 duplicates, 254 unique records underwent title and abstract screening, resulting in the exclusion of 207 articles. Forty-seven full-text reports were assessed for eligibility, of which 13 were excluded based on predefined criteria (wrong mechanism, wrong cellular focus, or wrong disease/model). Ultimately, 34 studies met all inclusion criteria and were incorporated into the qualitative synthesis (Haddaway et al., 2022).

3.2 Risk of Bias Assessment

Given the methodological heterogeneity of the included literature, methodological quality and risk of bias were considered in relation to publication type and study design. For primary experimental and bioinformatic studies, a customized domain-based framework was used to assess four areas: (D1) Selection/Allocation Bias, concerning the description and selection of experimental models and allocation to study groups where applicable; (D2) Performance Bias, concerning the control of experimental conditions, blinding, and potential deviations from the intended procedures; (D3) Detection Bias, concerning the reliability, objectivity, and validation of outcome measurements; and (D4) Reporting Bias, concerning the completeness of outcome reporting and the possibility of selective reporting.

Because the included literature also contained secondary review articles, these publications were considered separately from primary studies. The four-domain framework was not interpreted as a direct measure of the methodological quality of a systematic review, nor were review articles treated as independent experimental datasets. The risk-of-bias assessment was therefore interpreted in the context of the methodological design and applicability of each publication. Where a domain could not be meaningfully assessed for a particular study design, this was considered unclear or not applicable rather than automatically classified as low risk.

Risk-of-bias judgements were based on the methodological information reported in each publication. A low-risk judgement indicated that the available information provided sufficient evidence that the relevant source of bias was adequately addressed. An unclear-risk judgement was assigned when reporting was insufficient to permit a reliable judgement. The absence of a reported methodological procedure was not interpreted as evidence that the procedure had been adequately performed. These assessments were used to qualify the interpretation of the findings rather than to exclude otherwise eligible publications.



Figure 2. Risk of bias assessment traffic-light plot evaluating the 34 included studies across four core methodological domains using a standardized, *robvis*-compatible evaluation framework. Domains assessed include: D1, Selection / Allocation Bias; D2, Performance Bias; D3, Detection Bias; and D4, Reporting Bias. Symbols represent individual domain judgments: plus signs (+ in yellow circles) denote a low risk of bias, while minus signs (− in orange circles) denote an unclear risk of bias.

3.2 Data analysis

The primary characteristics, experimental models, key molecular targets, cellular foci, and primary mechanistic findings of all 34 included studies are systematically summarized in Table 1.

Table 1. Data Extraction and Synthetic Summary of Included Studies Investigating Endoplasmic Reticulum (ER) Stress and Unfolded Protein Response (UPR) Pathways in Myeloid Cells within the Glioblastoma Microenvironment.

Study ID / Author & Year	Study Design & Experimental Model	Key UPR / ER Stress Target	TME & Cellular Focus	Primary Mechanism / Key Findings
(Beltran-Huarac et al., 2023)	In vitro (stem cells, RAW264.7, U87 glioblastoma cells)	ER stress / UPR (PERK, ATF6, XBP1, GRP78, PDI)	Macrophages (RAW264.7) and stem cell cellular vehicles	Magneto-mechanical actuation of magnetic nanoparticles induces ER stress/UPR, remotely regulating TRAIL protein secretion to kill GBM cells.
(Booth et al., 2014)	In vitro (primary GBM cells & activated microglia); In vivo orthotopic GBM6 mouse model	ATF6, IRE1/XBP1, PERK/eIF2α/ATF4, CHOP	Primary human GBM cells and freshly isolated activated microglia	DMF/MMF + FTY720/proteasome inhibitors induces ER stress (IRE1/XBP1 and PERK arms), ROS generation, and autophagic cell death.
(D. Zhao et al., 2026)	In vitro cell lines + in vivo murine prophylactic/intracranial GBM models	PERK-CHOP pathway triggered by ferroptosis (GMX1778 NAMPT inhibition)	Macrophages / Myeloid cells	NAMPT inhibition depletes mitochondrial NAD+, suppressing SIRT3 and inducing ferroptosis/ROS to activate PERK-CHOP, driving M2-to-M1 polarization.
(De Leo et al., 2024)	In vivo mouse GBM models (GL261, CT-2A); Human glioma scRNA-seq	PERK (Eif2ak3) and GLUT1 (Slc2a1)	Monocyte-derived macrophages (MDMs) vs. Microglia; T cells	PERK-ATF4 axis upregulates GLUT1 on MDMs, driving high glycolysis/lactate production; lactate induces histone lactylation (K_{la}) at IL10 promoter to suppress T cells.
(Dent et al., 2020)	In vitro (human GBM PDX & patient active microglia); In vivo NRG mice	PERK, eIF2α, ATF6, XBP1, ATF4, CHOP	Primary human GBM cells and freshly isolated activated microglia	MMF + fingolimod activates protective ER stress (PERK/eIF2α) and toxic autophagy, targeting GBM cells and activated microglia via ROS and ATM-AMPK pathways.
(Dong et al., 2026)	Multi-omics (scRNA-seq, scATAC-seq, spatial transcriptomics) + in vitro assays	NUPR1, GPX4, ER stress response suppression	BMDMs / NUPR1$^+$ MDSCs, Mesenchymal-like (MES) GBM cells	NUPR1$^+$ MDSCs form a spatially restricted, ferroptosis-resistant hypoxic niche driving mesenchymal transition and tumor evolution via CEBPA.
(Guan et al., 2026)	Preclinical In vitro & In vivo mouse GBM models	ER stress mediated by HAX1 knockdown (si-HAX1)	Tumor-Associated Macrophages (TAMs) / Myeloid cells	Localized ER stress triggers immunogenic cell death (CRT translocation), synergizing with CD47-SIRPα blockade to increase M1/M2 ratio and recruit CD8$^+$ T cells.
(Guo et al., 2025)	In vitro & In vivo GBM mouse models	PERK pathway (Targeted PERK inhibitor: iPERK)	Microglia and Glioblastoma-Associated Macrophages (GAMs)	Biomimetic membrane vesicles deliver iPERK to M2 microglia, inhibiting M2 polarization and reprogramming them to M1 via PERK/HIF-1\alpha/glycolysis pathway.
(H. Yang et al., 2025)	In vitro NHA/glioma cell lines, hypoxia models; In vivo orthotopic mouse model	HSPA5 (GRP78) / ER stress-associated hypoxia tolerance	Glioblastoma; Tumor-Associated Macrophages (TAMs)	Hypoxia upregulates HIF-1α/HSPA5 axis to drive M2 polarization; HSPA5 silencing mitigates hypoxia tolerance and reprograms TAMs to M1.
(J. L. Zhao et al., 2026)	Multi-omics pan-cancer bioinformatic analysis + in vitro co-culture models	RCN1 (calcium signaling agent) & IRE1α -XBP1s-CHOP pathway	Macrophages (THP-1 derived, M2 polarization markers)	RCN1 links ER stress/calcium homeostasis to tumor progression, PD-L1 expression, and M2 macrophage polarization in co-culture models.
(Javid et al., 2025)	Systematic Review (Cannabinoids in gliomas)	Endocannabinoid signaling, ER stress, ISR (eIF2α), ferroptosis	Glioblastoma cells, T cells, Tumor-Associated Macrophages (TAMs)	Cannabinoids (CBD, THC) induce glioma cytotoxicity via ER stress, autophagy, ferroptosis, and immunomodulation of the microenvironment.
(K. Chen et al., 2021)	In vitro cell lines, U87MG subcutaneous GBM model, osteosarcoma model	Basal ER Stress / UPR (eIF2α phosphorylation, BiP, CLIMP63)	U87MG Glioblastoma; Macrophages (TAM polarization)	Fullerenol nanoparticles induce basal ER stress and calreticulin (CRT) exposure, enhancing macrophage-mediated phagocytosis and M1 polarization.
(L. Yang et al., 2025)	Narrative Literature Review (Oncology)	PERK-eIF2α-ATF4 pathway and IRE1α -UBE2D3-NF-kB axis	GBM tumor cells, immunosuppressive myeloid cells, MDSCs	Details tumor stressors triggering UPR; PERK regulates glycolysis (via HK2), while IRE1α drives pro-recruitment chemokine secretion to recruit myeloid cells.
(Lhomond et al., 2018)	In vitro (cell lines/primary cultures), orthotopic mouse models, TCGA/GBMmark cohorts	IRE1α (XBP1s vs. RIDD / miR-17)	GBM cells, stroma, macrophages/microglia, endothelial cells	IRE1 outputs show opposing roles: XBP1s drives pro-tumorigenic immune infiltration and angiogenesis, whereas RIDD acts protectively.
(Li et al., 2022)	Bioinformatic analysis (TCGA, CGGA, GEO)	7-ER-stress gene signature (PDIA5,	Bulk glioma microenvironment,	High-risk scores correlate with advanced WHO grade, hypoxia, apoptosis, and UPR

Study ID / Author & Year	Study Design & Experimental Model	Key UPR / ER Stress Target	TME & Cellular Focus	Primary Mechanism / Key Findings
		CASP8, HMOX1, CYBB, CCL2, ERN1, TP53)	infiltrating immune cells, immune checkpoints	activation, with elevated checkpoint expression (PD-1, CTLA-4).
(Lin et al., 2025)	Pan-cancer & GBM bioinformatic analysis + functional assays	Ribophorin 1 (RPN1; OST complex component)	GBM tumor cells, M2 tumor-associated macrophages (TAMs)	RPN1 is overexpressed in GBM, correlating with advanced stage, HRD, increased M2 macrophage infiltration, and reduced T-cell presence.
(Liwei et al., 2025)	In silico (CGGA transcriptomic datasets, ferroptosis/hypoxia markers)	HIF-1α / XBP1 axis (ER UPR / Hypoxia-induced ferroptosis)	Tumor microenvironment; Infiltrating immune cells (M0 macrophages)	Hypoxia-induced ferroptosis model identifies co-expression of VEGF-α and UPR sensor XBP1 as a prognostic factor linked to M0 macrophage infiltration.
(M. F. Wang et al., 2025)	In Vitro & In Vivo (Platelet-mediated sonodynamic therapy in GL261)	Ferroptosis pathways and macrophage autophagy	Glioblastoma cells (GBCs) and Glioblastoma-Associated Macrophages (GAMs)	Targeted sonodynamic therapy induces quasi-immunogenic ferroptosis in GBCs and immunostimulatory autophagy in macrophages to inhibit GBM.
(Obacz et al., 2024)	In vitro human/mouse cells, in vivo syngeneic GB mouse models, TCGA datasets	IRE1α, XBP1s, RIDD	Microglia, Monocyte-derived macrophages (MDMs), PMNs	IRE1 signaling controls UBE2D3 expression via XBP1s/RIDD to activate NF-kB and promote proinflammatory chemokine production and myeloid infiltration.
(R. Huang et al., 2021)	Bioinformatics & In Vitro validation (TCGA, CGGA, glioma cell lines)	ER stress response pathways (P4HB, PDIA4 markers)	Diffuse gliomas and Tumor-Associated Macrophages (M2 phenotype)	ER stress activation correlates with malignant grade, predicts poor prognosis, and promotes M2 macrophage infiltration and tumor progression.
(Ren et al., 2021)	Bioinformatic multi-omics profiling (TCGA, CGGA, GSE16011 LGG cohorts)	Integrated Stress Response (ISR) / ER Stress (ERS)	Lower-Grade Gliomas (LGG); Macrophages (M0/M2) & neutrophils	Stratified LGG into stress-response clusters; high-stress risk scores correlated strongly with an enriched immunosuppressive macrophage microenvironment.
(Roberts et al., 2018)	In Vitro & Ex Vivo (Murine KR158/GL261 glioma models & BMDMs)	ER stress response (eIF2α phosphorylation) and STAT3 activity	Glioma cells and Bone Marrow-Derived Macrophages (BMDMs)	Sub-cytotoxic oxaliplatin treatment induces ER stress, reduces STAT3 activity, downregulates MGMT, and reverses pro-tumor macrophage phenotypes.
(Shao et al., 2026)	Single-cell multi-omics, hydrogel engineering, in vivo rat GBM models	Sphingolipid-metabolism-associated ER stress	Glioblastoma cells, Antigen-Presenting Cells (APCs), Myeloid networks	Tumor-treating fields (TTF) trigger immunogenic cell death (ICD) via ER stress, synergistically enhanced by an ATP-responsive hydrogel adjuvant.
(Simbilyabo et al., 2024)	Narrative Literature Review (Glioma UPR)	UPR sensors (IRE1, PERK, ATF6) and chaperone GRP78/BiP	Glioblastoma Stem Cells (GSCs), tumor vasculature, ECM	Outlines dual role of UPR (survival vs. CHOP apoptosis); UPR machinery drives GBM stemness (via SOX2 regulation), angiogenesis, and ECM remodeling.
(T. Wang et al., 2023)	In silico (scRNA-seq/TCGA), In vitro, In vivo (GL261 & transgenic mice), Clinical specimens	PERK / ATF4 arm of UPR & ER stress pathways	Glioma-associated microglia/macrophages (GAMs), dendritic cells	IDH mutation-induced PERK activation enhances cholesterol export from glioma cells via miR-19a/LDLR/ABCA1, driving anti-tumoral M1 polarization.
(Tan et al., 2026)	In vitro assays, bulk RNA-seq, orthotopic mouse models	Core E3 UFMylation protein DDRGK1 (ER-phagy & ER stress)	GBM cells, infiltrating immune cells, M1 macrophages, T cells	UFMylation inhibition disrupts DDRGK1-UFL1 interaction, suppresses ER-phagy, induces severe ER stress, and reprograms TAMs toward M1 phenotype.
(Tsai et al., 2023)	In vitro (GBM cell lines, HUVECs, THP-1); In vivo orthotopic human GBM xenograft mice	PERK, ATF6, ATF4, p-eIF2α, CHOP, BIP, EDEM1	Glioblastoma cells, HUVECs, and TAMs (THP-1 macrophages)	KDELC2 promotes angiogenesis via ROS activation, ER stress (PERK/ATF6/ATF4/CHOP), NLRP3 inflammasome, autophagy, and M2 TAM polarization.
(Vats et al., 2026)	In vitro (NRK, RG2 cell lines); In vivo syngeneic orthotopic RG2 rat model	UPR pathway, GRP78/BiP, p-eIF2α, ATF4/ATF6	RG2 glioblastoma cells, TME, infiltrating macrophages/microglia ($Iba1^+$)	VAMP7-dependent endosomal secretion mediates ER/mitochondrial protein release; VAMP7 KO induces severe ER stress, necrosis, and altered macrophage infiltration.
(Wulandari et al., 2025)	Bioinformatic multi-omics (TCGA, CGGA, GDSC) + in vitro validation (U87, A172)	ORMDL2 (sphingolipid biosynthesis & ER stress regulation)	TME, tumor-associated macrophages (TAMs), GSCs	Promoter hypomethylation upregulates ORMDL2, linking ER stress, mitochondrial dysfunction, and defective antigen presentation (MHC-I) to immune evasion.
(Xu, Guo, et al., 2025)	Bioinformatics (TCGA/CPTAC/CGGA) + clinical human tissue validation	Heat Shock Proteins / ER chaperones (HSP90B1, HSPA5)	Glioma-associated myeloid cells / M2 Macrophages	HSP90B1 and HSPA5 are overexpressed in HGG, correlate with Wnt/PI3K-AKT, enhance LDHA-mediated glycolysis, and drive M2 macrophage infiltration.
(Ye et al., 2023)	In vitro GL261/U87MG cells; In vivo post-resection GL261-Luc murine model	Temozolomide (TMZ)-induced ER stress & CRT translocation	Post-resection cavity macrophages, Microglia, NK cells, T cells	TMZ induces ER stress and CRT surface exposure, synergizing with CD47-SIRPα blockade hydrogels to enhance phagocytosis and immune recruitment. (Note: Missing mechanism populated)
(Yuxiao et al., 2024)	Systematic Review (Arginine Deprivation Therapy)	ER stress (IRE1α, ATF6, PERK/eIF2α), UPR pathways	Glioblastoma cells, microglial cells (M2 to M1 repolarization), T cells	Arginine deprivation therapy (ADT via ADI-PEG20) induces ER stress/autophagy in GBM while reprogramming

Study ID / Author & Year	Study Design & Experimental Model	Key UPR / ER Stress Target	TME & Cellular Focus	Primary Mechanism / Key Findings
				immunosuppressive microglia into anti-tumor M1.
(Z. Xu et al., 2026)	In silico (TCGA/CGGA), In vitro (U87/U251), In vivo (Nude mouse xenografts)	ER stress / Unfolded Protein Response (UPR) programs	TME; Infiltrating immune cells (Th2 cells, macrophages, cytotoxic T cells)	ZCCHC4 regulates DNA replication and activates ER stress/UPR signatures, correlating with immunosuppressive macrophage and Th2 cell infiltration.
(Zhong et al., 2026)	Bioinformatic, scRNA-seq & spatial transcriptomics (TCGA, CGGA, spatial human datasets)	ER stress signaling pathways (G1 malignant GBM subpopulation)	Malignant GBM tumor cells, cDCs, TAMs, microglia	TNF-α secreted by macrophages/microglia/cDCs drives a malignant state (G1) with enhanced ER stress via the TNF-CP-KLF10 axis.

The synthesis of the included studies reveals that endoplasmic reticulum (ER) stress and the Unfolded Protein Response (UPR) operate not merely as cell-autonomous survival circuits, but as master drivers of microenvironmental remodeling, metabolic adaptation, and immune subversion in glioblastoma (GBM). This multi-faceted role manifests across distinct yet deeply interconnected dimensions: clinical transcriptomic stratification, cell-intrinsic UPR branch regulation of tumor-associated microglial and macrophage (TAM) activation, and non-cell-autonomous intercellular crosstalk via Transmissible ER Stress (TERS) and immunogenic cell death (ICD).

Accumulating multi-omics evidence across large patient cohorts firmly links UPR pathobiology to advanced glioma grade, immunosuppressive cellular infiltration, and poor clinical survival. Li et al. established a 7-gene ER stress signature (PDIA5, CASP8, HMOX1, CYBB, CCL2, ERN1, and TP53) using datasets from TCGA, CGGA, and GEO, demonstrating that high UPR risk scores strongly correlate with WHO grade IV classification, localized tissue hypoxia, elevated apoptotic indices, and prominent upregulation of immune checkpoints such as PD-1 and CTLA-4. In parallel, R. Huang et al. interrogated diffuse glioma transcriptomic profiles to show that core UPR mediators, specifically protein disulfide isomerase family members P4HB and PDIA4, directly predict malignant transformation, overall survival deficits, and massive accumulation of M2-polarized TAMs within the tumor stroma. Extending these multi-omics insights to lower-grade gliomas (LGG), Ren et al. categorized patient cohorts into integrated stress response (ISR) clusters and established that elevated stress risk scores correspond to an enriched immunosuppressive compartment dominated by non-polarized M0 and protumorigenic M2 macrophages.

Further high-throughput bioinformatic and transcriptomic analyses have isolated specific UPR-associated genes that drive microenvironmental subversion. Lin et al. identified Ribophorin

1 (RPN1), an essential component of the oligosaccharyltransferase (OST) complex involved in N-linked protein glycosylation and ER quality control, as an independent prognostic factor in diffuse gliomas. Lin et al. demonstrated that RPN1 overexpression significantly correlates with homologous recombination deficiency (HRD), accelerated tumor cell proliferation, marked M2 macrophage enrichment, and a reciprocal exclusion of functional $CD8^+$ cytotoxic T cells. Bioinformatic work by Liwei et al. integrated hypoxia-induced ferroptosis programs with UPR sensors, establishing that co-expression of vascular endothelial growth factor A (VEGFA) and spliced X-box binding protein 1 (XBP1) serves as a robust prognostic marker linked to unpolarized macrophage infiltration and salvage therapy resistance. Similarly, Wulandari et al. identified promoter hypomethylation of ORMDL2, a key transmembrane regulator of sphingolipid biosynthesis and ER calcium homeostasis, as a primary driver of ER stress amplification and mitochondrial dysfunction, which directly impairs major histocompatibility complex class I (MHC-I) antigen presentation machinery.

Heat shock proteins and structural ER chaperones also feature prominently in these clinical prognostic networks. Xu, Guo, et al. profiled high-grade gliomas to show that HSP90B1 and HSPA5 (GRP78/BiP) are markedly overexpressed, driving lactate dehydrogenase A (LDHA), mediated aerobic glycolysis via canonical Wnt and PI3K-Akt signaling axes while simultaneously promoting M2 macrophage infiltration. Beyond classical chaperones, Z. Xu et al. revealed that the zinc finger protein ZCCHC4 accelerates glioma cell cycle progression and DNA replication by activating downstream ER stress networks, an effect that strongly correlates with infiltration by both immunosuppressive M2 macrophages and Th2 helper T cells. Utilizing single-cell and spatial transcriptomics, Zhong et al. mapped a distinct malignant GBM cell subpopulation (G1) characterized by severe ER stress signaling. Zhong et al. demonstrated that microenvironmental tumor necrosis factor-alpha (TNF-α), continuously secreted by infiltrating macrophages, microglia, and conventional dendritic cells (cDCs), actively enforces this G1 state through a TNF-CP-KLF10 signaling loop. Finally, pan-cancer transcriptomic analyses by J. L. Zhao et al. identified Reticulocalbin-1 (RCN1), an ER luminal calcium-binding protein, as a central node linking ER stress, disruption of cellular calcium homeostasis, elevated PD-L1 expression, and M2 TAM polarization across co-culture models.

The PERK branch of the UPR acts as an immediate translational checkpoint under proteostatic stress. Upon activation, PERK autophosphorylates and phosphorylates eukaryotic

initiation factor 2 alpha (eIF2α) at Serine 51, causing widespread suppression of cap-dependent translation while selectively permitting the translation of activating transcription factor 4 (ATF4). Work by De Leo et al. uncovered a fundamental epigenetic mechanism regulated by this axis, demonstrating that PERK (Eif2ak3) upregulates glucose transporter 1 (GLUT1, encoded by Slc2a1) on monocyte-derived macrophages (MDMs). De Leo et al. showed that the resulting increase in glycolytic flux generates elevated intracellular levels of lactate, which serves as a substrate for glucose-driven histone lactylation at lysine residues (K_{la}) within the IL-10 promoter, directly driving IL-10 transcription and locking MDMs into a functional immunosuppressive state that suppresses $CD8^+$ T-cell proliferation and effector function.

Recognizing the central role of PERK in TAM polarization, several novel therapeutic interventions have targeted this pathway. Guo et al. engineered biomimetic membrane vesicles to selectively deliver a targeted PERK inhibitor (iPERK) to M2-polarized microglia. Guo et al. demonstrated that pharmacological blockade of PERK abolished M2 polarization and successfully reprogrammed cells toward an anti-tumoral M1 phenotype by modulating the PERK/HIF-1α /glycolysis axis. Interestingly, the functional output of PERK signaling can be context-dependent. T. Wang et al. demonstrated that in IDH-mutant gliomas, IDH mutation-induced PERK activation drives microRNA-19a (miR-19a)-mediated repression of LDLR and upregulation of ABCA1. T. Wang et al. showed that this alteration promotes cholesterol efflux from glioma cells, paradoxically inducing anti-tumoral M1 polarization in neighboring microglia.

Other strategies aimed at inducing metabolic and proteostatic stress have confirmed the link between UPR disruption and TAM repolarization. D. Zhao et al. showed that inhibiting nicotinamide phosphoribosyltransferase (NAMPT) depletes mitochondrial NAD^+ pools and downregulates SIRT3, inducing reactive oxygen species (ROS)-mediated ferroptosis and activating the downstream PERK-CHOP arm to force an M2-to-M1 phenotypic shift in TAMs. Similarly, Tan et al. targeted the core E3 UFMylation protein DDRGK1, demonstrating that pharmacological disruption of the DDRGK1-UFL1 complex inhibited endoplasmic reticulum phagy (ER-phagy), provoking unresolved ER stress that reprogrammed TAMs toward an anti-tumorigenic M1 state and achieved durable GBM regression in vivo. Tsai et al. demonstrated that KDELC2 promotes tumor angiogenesis and M2 TAM polarization via ROS generation and activation of the PERK/ATF6/ATF4/CHOP signaling cascade, NLRP3 inflammasome assembly, and macroautophagy.

Reviewing the dual roles of UPR activation, Simbilyabo et al. contrasted survival signaling mediated by PERK and IRE1α against terminal CHOP-dependent apoptosis, emphasizing how tumor cells hijack sub-lethal PERK activity to maintain glioma stem cell (GSC) stemness through SOX2 regulation, promote microvascular proliferation, and orchestrate extracellular matrix (ECM) remodeling. Narrative synthesis by L. Yang et al. further detailed how PERK signaling directly regulates glycolytic enzymes such as hexokinase 2 (HK2) in tumor cells, while simultaneously upregulating the production of Colony-Stimulating Factor 1 (CSF-1) and chemokine CCL2 (MCP-1) to drive the chemotactic recruitment of circulating monocytes and MDSCs into the tumor parenchyma.

The IRE1α pathway functions as a bifunctional transmembrane kinase and endoribonuclease (RNase) that serves as a core immunometabolic rheostat within the GBM microenvironment. Upon autophosphorylation, the cytosolic RNase domain of IRE1α catalyzes the unconventional cytoplasmic splicing of a 26-nucleotide intron from XBP1 mRNA, generating the active transcription factor spliced XBP1 (XBP1s). Concurrently, IRE1α can engage in Regulated IRE1-Dependent Decay (RIDD) to selectively degrade localized mRNAs and microRNAs, or scaffold with adapter proteins such as TRAF2 to activate downstream NF-kB and JNK signaling.

Obacz et al. established that IRE1α endoribonuclease signaling regulates myeloid cell dynamics within glioblastoma. Obacz et al. proved that the IRE1-XBP1s/RIDD axis controls the expression of ubiquitin-conjugating enzyme E2 D3 (UBE2D3), which in turn triggers NF-kB activation and the subsequent secretion of pro-inflammatory chemokines that drive monocyte-derived macrophage and neutrophil infiltration. Earlier work by Lhomond et al. highlighted the opposing outputs of IRE1α signaling in GBM biology, as it showed that while the XBP1s arm promotes pro-tumorigenic myeloid cell recruitment, immunosuppression, and microvascular sprouting, the RIDD pathway, partially through the cleavage of miR-17 exerts protective, tumor-suppressive effects.

H. Yang et al. systematically evaluated the role of HSPA5 (GRP78) under microenvironmental hypoxia, demonstrating that hypoxia-stabilized HIF-1α directly upregulates the HSPA5 axis to promote M2 macrophage polarization. H. Yang et al. showed that silencing HSPA5 abrogates hypoxia tolerance and reprograms TAMs toward an anti-tumoral M1 phenotype. At the organelle level, Vats et al. demonstrated that vesicle-associated membrane

protein 7 (VAMP7)-dependent late endosomal secretion mediates the unconventional release of ER and mitochondrial chaperones into the extracellular matrix. Vats et al. showed that genetic knockout of VAMP7 induces severe unresolved ER stress, localized tissue necrosis, and marked alterations in microglial and macrophage infiltration patterns.

A central theme across recent literature is that ER stress is communicated non-cell-autonomously across the glioblastoma microenvironment via Transmissible ER Stress (TERS), extracellular vesicles (EVs), and secretory chaperones. Stress-conditioned tumor cells package UPR transcripts, microRNAs, and damaged proteostatic products into EVs, transferring them to naive infiltrating monocytes and resident microglia. Recipient myeloid cells internalize these vectors and undergo an unprovoked secondary UPR, driving their functional transformation into immunosuppressive M2-like phenotypes even in the absence of direct cell-to-cell contact.

To turn this survival mechanism into a therapeutic vulnerability, recent studies have aimed to convert sub-lethal UPR activation into lethal Immunogenic Cell Death (ICD). ICD is characterized by the translocation of the luminal ER chaperone calreticulin (CRT) to the outer cell membrane, serving as an "eat-me" signal for phagocytes. Guan et al. developed an in situ hydrogel system that triggers localized ER stress via HAX1 knockdown, inducing surface CRT exposure. Guan et al. showed that when combined with CD47-SIRPα antiphagocytic checkpoint blockade, this system elevated the M1/M2 TAM ratio, recruited functional $CD8^+$ cytotoxic T cells, and effectively prevented post-resection GBM recurrence. Similarly, Ye et al. proved that standard-of-care temozolomide (TMZ) induces ER stress and CRT surface exposure in glioma cells. Ye et al. demonstrated that co-delivering TMZ and anti-CD47 antibodies within an in-situ hydrogel enhanced macrophage phagocytosis, stimulated anti-tumor immunity, and suppressed local tumor recurrence in post-resection mouse models.

Advanced biomaterial and physical delivery systems further amplify these responses. Shao et al. demonstrated that Tumor-Treating Fields (TTF) induce ICD via sphingolipid-associated ER stress pathways, an effect synergistically enhanced by an ATP-responsive hydrogel adjuvant that promotes antigen presentation and myeloid activation. K. Chen et al. showed that fullerenol nanoparticles induce basal ER stress upregulating phosphorylated eIF2α, BiP, and CLIMP63 and trigger robust CRT exposure, boosting anti-CD47 antibody efficacy to elicit macrophage-mediated tumor clearance. M. F. Wang et al. utilized platelet-mediated sonodynamic therapy to

induce quasi-immunogenic ferroptosis in glioblastoma cells alongside immunostimulatory autophagy in surrounding macrophages.

Conversely, Dong et al. identified a spatially restricted, ferroptosis-resistant myeloid niche defined by $NUPR1^{+}$ MDSCs. Dong et al. demonstrated that, driven by ER stress suppression and the transcription factor CEBPA, these MDSCs protect against lipid peroxidation and foster a hypoxic environment that drives the mesenchymal transition of neighboring glioma stem cells. From a metabolic standpoint, Yuxiao et al. systematically reviewed arginine deprivation therapy (ADT using ADI-PEG20), demonstrating that depleting exogenous arginine provokes severe ER stress and autophagy in GBM cells while repolarizing M2 microglia back into anti-tumoral M1 effectors.

Pharmacological combinations targeting stress and survival pathways have also shown promise. Booth et al. and Dent et al. demonstrated that combining dimethyl fumarate (DMF/MMF) with proteasome inhibitors or fingolimod (FTY720) activates protective ER stress (PERK/eIF2α and IRE1/XBP1) and induces ROS generation. Booth et al. and Dent et al. showed that this activation engages ATM-AMPK pathways to induce autophagic cell death in both malignant glioma cells and activated microglia. Beltran-Huarac et al. used magneto-mechanical actuation of iron oxide nanocubes to induce ER stress/UPR (PERK, ATF6, XBP1, GRP78), enabling remote control over TRAIL protein secretion from stem cell carriers to induce GBM cell apoptosis. Roberts et al. showed that sub-cytotoxic oxaliplatin treatment induces eIF2α phosphorylation, reduces STAT3 activity, downregulates MGMT, and reverses pro-tumoral macrophage phenotypes independent of apoptosis. Finally, Javid et al. systematically reviewed the therapeutic potential of cannabinoids (CBD and THC) in gliomas, concluding that cannabinoid receptor engagement activates the eIF2α arm of the Integrated Stress Response, inducing autophagy, ferroptosis, and favorable microenvironmental remodeling.

4. Strengths and Limitations

The major study-level limitations are the evidence base is predominantly composed of preclinical experiments, spanning *in vitro* cell lines, orthotopic mouse/rat models, and multi-omics bioinformatic cohorts (TCGA, CGGA, GEO). Sample sizes were diverse, and only a minority of studies explicitly reported methods to reduce bias, such as investigator blinding or animal randomization. Outcomes were frequently biomarker-driven (e.g., gene/protein expression of UPR

sensors or M2 polarization markers) rather than direct patient-centered clinical endpoints. Furthermore, reporting was subject to potential selective outcome publication favoring significant UPR alterations. As summarized in the risk-of-bias traffic-light plot (Figure 2), a notable proportion of studies demonstrated unclear risks in selection bias (D1) and performance bias (D2) due to omitted procedural descriptions, whereas detection (D3) and reporting (D4) biases were uniformly low due to robust multi-omics and molecular assay validation.

Additionally, the review-level limitations were constrained by the available data. The synthesis was restricted by the heterogeneous nature of the available literature. While PubMed and Scopus search strategy was comprehensive, limiting reports to English-language publications may introduce language bias. The vast methodological diversity, ranging from bioinformatic transcriptomics to single-cell spatial profiling and pharmacological screening, precluded any formal statistical meta-analysis. Consequently, we relied on a qualitative synthesis, which limits direct cross-study quanlitative comparability. Finally, while IRE1α and PERK mechanisms are well-characterized, individual contributions of ATF6 remain comparatively underexplored. A key strength of this review, however, is its breadth: by thematic grouping of 34 recent studies, we captured an overarching matrix of ER stress-mediated immune subversion that is not apparent from isolated investigations.

An additional limitation concerns the inclusion of both primary research studies and secondary review articles. Although this approach allowed a broader overview of the available literature, secondary reviews may summarize primary studies that are also included independently in the present review. To minimize potential double-counting, publication type was distinguished during data extraction and interpretation, and review articles were used primarily for contextual and comparative purposes rather than as independent sources of experimental observations. Nevertheless, the inclusion of different publication types increases the methodological heterogeneity of the evidence base and should be considered when interpreting the overall conclusions.

Furthermore, the customized risk-of-bias framework may not capture all methodological limitations associated with the different study designs represented in the literature. Detection and reporting bias were considered in relation to the methods and validation procedures reported in each study. Although several studies used multi-omics approaches and molecular assays to support their findings, these methodological features do not necessarily eliminate the risk of bias.

Therefore, the assessment considered the strengths and limitations of each study individually. These limitations reinforce the need for cautious interpretation and further validation in standardized experimental and clinical settings.

5. Interpretation and Implications

The unfolded protein response (UPR) and endoplasmic reticulum (ER) stress are important regulators of cellular adaptation in the glioblastoma microenvironment. Their effects on tumor-associated microglia and macrophages (TAMs) appear to depend on the intensity and duration of ER stress, as well as the cellular and molecular context.

Specifically, tumor-intrinsic and microenvironmental stresses hijack UPR branches, such as the PERK-eIF2α-ATF4 pathway driving GLUT1-mediated glycolysis and IL-10 promoter lactylation, the IRE1α-XBP1s axis driving immunosuppressive cytokine production, and the ATF6/csGRP78 axis promoting therapy resistance to lock tumor-associated microglia and macrophages (TAMs) into protumorigenic, M2-like states.

An important distinction in interpreting the available evidence is the difference between experimentally demonstrated mechanisms and associations identified through transcriptomic, single-cell, spatial, or other bioinformatic analyses. Experimental studies involving pathway modulation, genetic manipulation, or functional assays can provide evidence supporting a mechanistic relationship between UPR signaling and myeloid-cell behavior. In contrast, the identification of UPR-associated gene-expression signatures alongside immunosuppressive myeloid-cell populations demonstrates an association but does not, by itself, establish a causal relationship. Accordingly, bioinformatic findings are interpreted as supportive evidence of biological relationships and potential mechanisms, rather than definitive proof of causation. The strength of each mechanistic conclusion should therefore be considered in relation to the experimental design and the level of functional validation available.

Although several included publications associate UPR activation with immunosuppressive myeloid-cell functions and glioblastoma progression, UPR signaling should not be considered a uniformly pro-tumoral process. Its biological consequences may vary according to the specific UPR branch activated, the cell population in which activation occurs, the intensity and duration of ER stress, and the metabolic and genetic context of the tumor. Individual UPR pathways may contribute to cellular adaptation and survival under stress, but their activation may also promote

inflammatory, cytotoxic, or cell-death-related responses under conditions. Furthermore, effects observed in tumor cells should not automatically be attributed to microglia or TAMs, and vice versa. These distinctions are particularly relevant when interpreting studies using different glioma models or examining distinct cellular compartments. Thus, the relationship between UPR signaling and immunosuppression in glioblastoma is best understood as context-dependent rather than as a single, uniform pathway response.

In practical terms, high ER stress signaling in the myeloid compartment correlates with aggressive disease and poor clinical survival in GBM patients. Our findings imply that disrupting UPR pathways in TAMs could safely reprogram the immune milieu. For example, combining selective UPR modulators (such as PERK or IRE1α inhibitors) or anti-ER-phagy/UFMylation targets (e.g., DDRGK1 disruption) with immunotherapy (such as CD47-SIRPα checkpoint blockade or sonodynamic ICD induction) represents a powerful strategy to overcome T-cell exclusion and convert "cold" GBM tumors "hot".

However, caution is mandatory. UPR pathways are vital for maintaining homeostasis in normal, non-malignant tissues, meaning systemic inhibition carries potential off-target toxicities. Because none of the 34 reviewed studies evaluated direct clinical trial outcomes, translational benefits remain speculative. Future clinical guidelines do not yet target UPR or TAM phenotype directly, but our findings suggest that tracking ER stress signatures (e.g., GRP78, CHOP, or UPR risk scores) in tumor biopsies could evolve into a powerful prognostic tool.

6. Sources of Heterogeneity and Sensitivity Analyses

Heterogeneity across the 34 included studies stems from diverse experimental models and modulation techniques. Studies utilized varying systems, including standard *in vitro* co-cultures, patient-derived xenografts (PDXs), orthotopic murine/rat intracranial models, and bioinformatic tumor cohorts. Furthermore, UPR was manipulated through distinct methodologies, ranging from pharmacological stress agents and nanotherapy (e.g., fullerenols, magnetic actuation) to genetic knockdowns and specialized hydrogel delivery systems.

Mechanistic endpoints also varied, with some studies focusing on metabolic shifts (glycolysis, ferroptosis, histone lactylation) and others examining cytokine secretion, phagocytic arrest, or tumor burden. Notably, microenvironmental context significantly shaped outcomes; for instance, studies incorporating strict physiological hypoxia or orthotopic architecture reported

more pronounced UPR-driven immunosuppression than standard normoxic mono-cultures. Across differing biological subsets (*in vivo* vs. *in vitro*, human vs. mouse), the directional impact of UPR activation on driving pro-tumoral TAM phenotypes remained consistent, indicating biological robustness rather than random error.

7. Recommendations for Research and Practice

- **Standardize experimental models.** Future investigations must establish consensus definitions for myeloid subsets (clearly distinguishing tissue-resident TMEM119+/P2RY12+ microglia from recruited CCR2+ peripheral macrophages) and utilize standardized UPR activation assays.
- **Increase *in vivo* and clinical research.** Given the heavy reliance on *in vitro* platforms, upcoming work must validate UPR modulation in orthotopic intracranial animal models, incorporating longitudinal survival tracking and human tissue sample correlations.
- **Dissect individual UPR branches:** Researchers should isolate the distinct, occasionally opposing roles of PERK, IRE1α (and its RNase/RIDD outputs), and ATF6 within myeloid populations utilizing cell-specific knockout models.
- **Explore combined therapies:** Preclinical evaluations should prioritize testing whether selective UPR inhibitors (such as iPERK or IRE1α RNase blockers) synergize with existing immunotherapies, CSF1R inhibitors, or anti-CD47/SIRPα hydrogel systems.
- **Advance translational diagnostics:** While direct pharmacological UPR targeting remains premature for human trials, translational researchers should incorporate ER stress markers (e.g., GRP78, CHOP, XBP1s) into clinical tissue registries to evaluate their true prognostic predictive value.

8. Conclusion

This systematic review demonstrates that endoplasmic reticulum (ER) stress and the Unfolded Protein Response (UPR) act as key regulators of tumor progression, metabolic adaptation, and immune subversion within the glioblastoma microenvironment.

This occurs primarily through Microenvironmental Reprogramming**,** as proteostatic stress within the hypoxic glioblastoma niche reprograms resident microglia and infiltrating monocyte-

derived macrophages into protumorigenic, immunosuppressive M2-like states. This is done by core Pathway Mechanistic Outputs, such as the PERK-eIF2α-ATF4 axis, as it drives myeloid chemotaxis via CSF-1 and CCL2, while altering macrophage metabolism through GLUT1-dependent glycolysis and histone lactylation (K_{la}) at the IL-10 promoter. The IRE1α-XBP1s axis functions as an immunometabolic switch, where IRE1α endoribonuclease activity regulates UBE2D3/NF-kB signaling and chemokine secretion to control myeloid cell infiltration. Finally, the ATF6/GRP78 axis mediates hypoxia tolerance and cell-surface chaperone translocation, promoting pro-survival signaling and therapeutic resistance.

Disruption of UPR stress sensors (via PERK, IRE1α, or UFMylation inhibitors) combined with macrophage-directed therapies (such as CD47-SIRPα checkpoint blockades, biomimetic hydrogels, or sonodynamic ICD induction) represents a promising therapeutic approach to dismantle the glioblastoma immunosuppressive niche and improve clinical outcomes.

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10. Ethics and Consent Declaration

Not applicable.

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