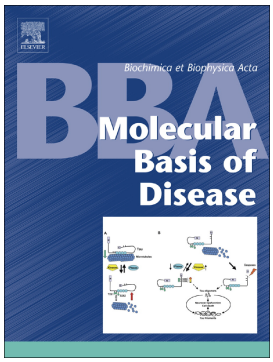

From protection to progression: How CCT/TRiC shapes therapy-induced senescence in Glioblastoma multiforme

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From protection to progression: How CCT/TRiC shapes therapy-induced senescence in Glioblastoma multiforme

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Abstract

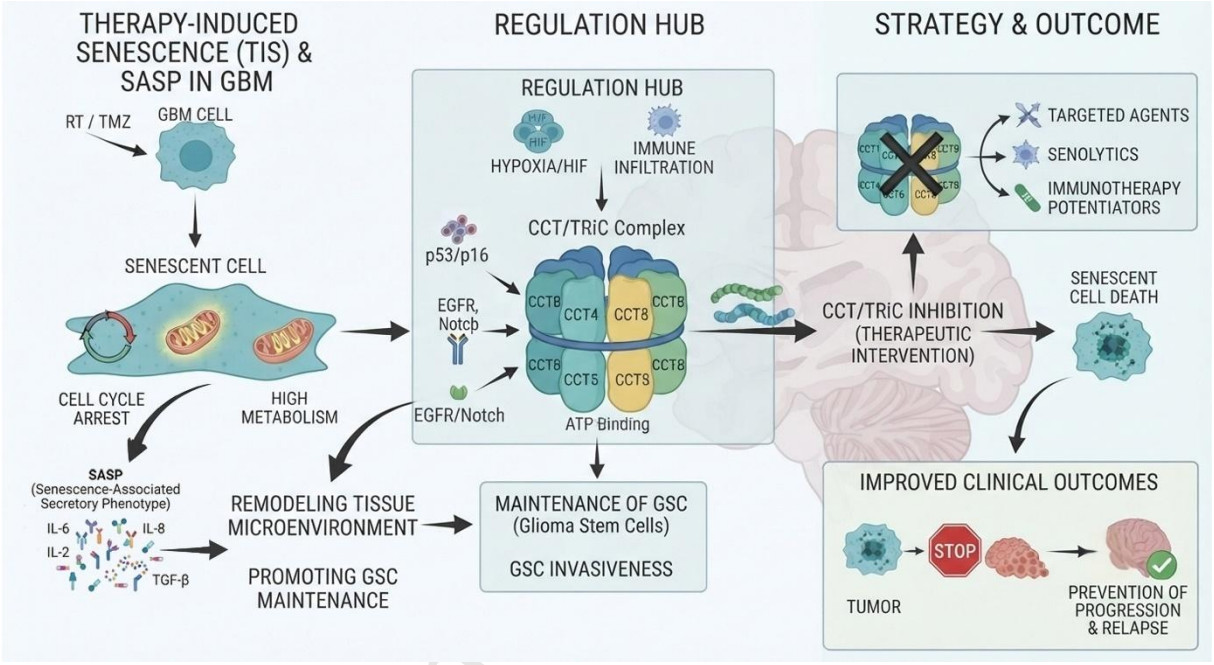
Glioblastoma multiforme (GBM) is the most lethal primary brain tumor despite maximal resection, radiotherapy, and temozolomide. Growing evidence indicates that standard therapies drive many GBM cells into therapy-induced senescence (TIS), marked by permanent proliferation arrest, high metabolic activity, and secretion of the senescence-associated secretory phenotype (SASP). Although senescent cells may initially limit growth, their persistence can fuel recurrence by altering the microenvironment while driving immunosuppression and stem-like traits. GBM is also "chaperone dependent," relying on proteostasis networks for rapid growth, invasion, and treatment resistance. The eukaryotic chaperonin CCT/TRiC, an ATP-dependent complex of eight subunits (CCT1–CCT8), is essential for folding actin and tubulin and for the maturation of multiple oncogenic clients. We review recent findings on CCT/TRiC subunit dysregulation in GBM and propose a mechanistic link between chaperonin activity and senescence, integrating p53/p21 and p16INK4a/Rb signaling, EGFR-driven survival, hypoxia/HIF-mediated metabolic reprogramming, and immune infiltration in high-SASP tumors. We discuss how CCT/TRiC is probably involved in maintaining glioma stem cell (GSC) proteostasis by modulating EGFR, TGF-β, mTOR, Wnt/β-catenin, and Notch pathways, thereby supporting GSC survival, self-renewal, and invasiveness. We also propose how CCT/TRiC inhibition can lead to impaired macroautophagy by disrupting mTOR signaling—both crucial for sustaining senescence and SASP—thereby compromising proteostasis and autophagic flux. Finally, we outline possible therapeutic strategies based on this axis, including novel combinations of senolytics,

immunotherapy potentiators, and CCT/TRiC-targeted agents to prevent SASP-driven progression and relapse.

Keywords

glioblastoma; cellular senescence; therapy-induced senescence; SASP; CCT/TRiC; proteostasis; senolytics; EGFR; hypoxia

Graphical abstract



1. Introduction

Cellular senescence has emerged as a cornerstone of modern oncology, representing a complex physiological state where cells exit the proliferative cycle while remaining metabolically [1]. Traditionally viewed as a critical fail-safe mechanism, senescence imposes a permanent growth arrest in response to oncogenic stress or DNA damage, functioning as a potent tumor suppressor that thwarts malignant expansion [2, 3]. In healthy tissues, this system serves as a sophisticated quality-control mechanism, fundamental to homeostasis and embryonic tissue remodeling [1, 4].

While therapy-induced senescence (TIS) initially restrains tumor growth, the survival of these non-proliferative cells depends on a highly specialized protein-folding machinery that prevents proteotoxic collapse [5]. Central to this "survival shield" is the chaperonin-containing TCP-1 complex (CCT, also known as TRiC), a hetero-oligomeric chaperonin that ensures the structural integrity and functional maturation of key oncoproteins [6].

A unique and clinically challenging feature of the senescent state is its high metabolic signaling. Unlike apoptotic cells, senescent glioblastoma multiforme (GBM) cells remain alive and secrete a potent cocktail of inflammatory cytokines and growth factors, known as the senescence-associated secretory phenotype (SASP) [7–9].

In the aggressive environment of GBM, the CCT/TRiC complex acts as a metabolic and structural hub, supporting the SASP and protecting the "resistant reservoir" of senescent cells from being cleared [10]. By stabilizing the proteome under the extreme stress of chemo- and radiotherapy, the CCT/TRiC complex can effectively transform senescence from a tumor-suppressive dead-end into a strategic frontier for therapeutic resistance and eventual recurrence [11]. In GBM, the most aggressive diffuse glioma, senescence is increasingly recognized as a frequent outcome of genotoxic therapy and a potential reservoir for relapse [12].

Crucially, the multifaceted role of the CCT/TRiC complex in glioblastoma can be conceptualized through two distinct temporal phases. Phase I (Pre-treatment and during therapy): In actively proliferating tumor cells, high expression levels of CCT/TRiC act as a protective shield, helping cancer cells avoid premature senescence by properly folding key cell-cycle regulators and oncogenic clients. Phase II (Post-TIS induction): Following genotoxic therapies such as temozolomide and radiation, a subset of GBM cells enters therapy-induced senescence (TIS). These arrested cells become uniquely "addicted" to chaperonin activity (chaperone addiction) to sustain the high metabolic demands of the senescence-associated secretory phenotype (SASP) and preserve essential cytoskeletal structures. This metabolic and structural dependency creates a critical therapeutic window, transforming CCT/TRiC into a prime target for novel senolytic strategies aimed at eliminating treatment-resistant reservoirs.

Concurrently, GBM cells experience profound proteotoxic stress due to genomic instability, hypoxia, and high biosynthetic flux, while the complex—in particular the CCT5 subunit—appears to play a key role in this process. To survive, they amplify proteostasis programs, including molecular chaperones [13]. CCT/TRiC is a central ATP-driven folding machine that assists the folding of a subset of cytosolic proteins, notably actin and tubulin, thereby enabling cytoskeletal dynamics and cell migration. Since GBM is characterized by its high motility and "tentacle-like" infiltration into healthy brain tissue, the constant supply of functional cytoskeletal proteins provided by CCT/TRiC is what enables this lethal invasiveness. In the aggressive landscape of GBM, the CCT/TRiC complex functions as a master regulator of proteostasis, acting as a "folding factory" that sustains the tumor's rapid

growth and structural integrity. GBM cells hijack this machinery to manage the high volume of misfolded proteins generated by their rapid mutation rates and metabolic stress [14].

Beyond structural support, the complex also folds critical oncoproteins such as STAT3, cyclin D1, and von Hippel-Lindau (VHL), effectively shielding the tumor from the proteotoxic stress that would otherwise trigger cell death [15].

The CCT/TRiC complex represents a bridge between basic protein folding and advanced clinical oncology, and increasing evidence indicates that CCT/TRiC subunits are overexpressed in GBM, detectable in extracellular vesicles, and linked to malignant phenotypes and patient outcome [16–18]

As we move toward personalized medicine, analyzing the specific subunit signatures within a patient's tumor could allow for more precise prognostic modeling and the development of inhibitors that strike at the very heart of the GBM's survival mechanism [19].

This Perspective integrates current evidence on: senescence and SASP biology in GBM,; CCT/TRiC subunit functions relevant to tumor progression, and plausible mechanistic links connecting CCT/TRiC activity to therapy-induced senescence and resistance. We highlight translational implications and outline testable hypotheses for targeting the chaperonin–senescence axis.

2 Senescence in glioblastoma multiforme: from cancer inhibition to recurrence mechanisms

Recent investigations highlight cellular senescence as a critical biological state that constitutes a major cellular response to standard-of-care interventions, including temozolomide (TMZ) chemotherapy and ionizing radiation in GBM [8]. Although the induction of senescence effectively constrains further proliferation of the primary tumor cell population, the long-term persistence of these metabolically active, non-proliferative cells within the brain parenchyma may be detrimental. Sustained secretion of the SASP within the GBM microenvironment can paradoxically enhance the stem-like properties (“stemness”) of adjacent tumor cells and promote an immunosuppressive milieu, thereby fostering tumor recurrence and/or increased invasiveness [20] [Table 1]. Consequently, in GBM, senescence functions as a double-edged sword: it initially contributes to disease stabilization via durable growth arrest, yet over time it may facilitate the establishment of a pro-tumorigenic niche [9, 21–23].

Although senescence is classically characterized as an irreversible cell-cycle arrest, in GBM it frequently manifests as a “senescence-associated reprogramming,” enabling tumor cells to evade cytotoxic therapies and adopt more aggressive, mesenchymal-like states [24].

The mechanistic link between therapy resistance and the mesenchymal phenotype is therefore of central biological and clinical relevance [24].

Clinically and experimentally, biomarkers such as p21 overexpression, reduced lamin B1 levels, and increased cell size are increasingly employed to identify these senescent-like tumor cell subpopulations [25]. For example, induction of p21-dependent senescence—despite its apparent role in enforcing growth arrest—can sensitize cells to specific senolytic agents, thereby revealing a metabolic vulnerability ("soft spot") within otherwise treatment-refractory tumors [25] [Table 1].

Table 1. *Representative biomarkers and functional consequences of senescence-like states in GBM.*

Marker	**Biological effect**	**Clinical implication**	**Reference(s)**
p21↑, lamin B1↓, increased cell size	Nuclear instability and senescent cell population induced	Vulnerability to senolytics	[25]
p21/p53 axis	CDK inhibition/cell cycle arrest	Potential markers of post-therapy recurrence	[25]
High SASP score	Inflammation	Worse prognosis	[26]
EGFR/Netrin-4 (NTN4) axis	Protection from DNA damage/induced senescence and ECM remodeling	Associated with poor overall survival	[27]
Hypoxia (HIF-1α / HIF-2α)	Metabolic reprogramming	Promotion of resistance and recurrence	[22]

The SASP further adds complexity to this framework. Recent SASP-based transcriptional scoring systems demonstrate that IDH–wild-type gliomas (which are associated with significantly poorer prognosis than their IDH-mutant counterparts) exhibit higher levels of SASP activation [26]. These high-SASP tumor microenvironments are enriched in MES-like tumor cells and tumor-associated macrophages (TAMs), supporting the concept that the inflammatory secretome of senescent cells actively reshapes the microenvironment to promote therapeutic resistance, immune evasion, and malignant progression [26] [Table 1].

At the molecular level, regulation of senescence in GBM is controlled by a finely balanced interplay between pro-survival signaling pathways and the machinery enforcing programmed proliferative arrest. As a canonical downstream effector of p53, p21 (CDKN1A) mediates its function predominantly through inhibition of cyclin-dependent kinases (CDKs), thereby imposing a quiescent G0/G1 state [25]. In GBM, although acute overexpression of p21 can trigger cell death in a fraction of tumor cells, a distinct subset persists and acquires a stable senescent phenotype. This senescent reservoir may serve as a source for tumor regrowth and recurrence following apparently successful initial therapy [25] [Table 1].

Pro-survival signaling mediated by epidermal growth factor receptor (EGFR) cooperates with Netrin-4 (NTN4), a laminin-like axon guidance molecule, to protect GBM cells from DNA damage–induced senescence [27]. This cooperative interaction not only mitigates premature cell cycle arrest but also modulates extracellular matrix (ECM) organization and caspase activity, both of which have been associated with unfavorable clinical outcomes and reduced overall survival in patients [27] [Table 1].

The tumor microenvironment, particularly hypoxic conditions, plays a pivotal role in shaping these responses [28]. Hypoxia-inducible factors HIF-1α and HIF-2α are key regulators of senescence-associated cellular reprogramming [22]. Exposure to standard-of-care therapies such as temozolomide and ionizing radiation can activate these hypoxia-inducible factors, resulting in: hypermetabolic reprogramming, which supports the elevated energetic demands of therapy-resistant cells; activation of the DNA damage response (DDR), which attenuates apoptosis while maintaining cells in a viable senescent state; and acquisition of stemness characteristics, enabling senescent cells to re-enter the cell cycle with enhanced stem-like properties. Collectively, these processes foster the emergence of more therapy-resistant and recurrent GBM cell populations [22] [Table 1].

3 The CCT/TRiC chaperonin in GBM: subunit-specific roles and vulnerabilities

The CCT/TRiC complex is composed of two identical rings containing eight subunits (CCT1–CCT8) organized around a central cavity where protein folding occurs [29] [**Figure 1**]. It must be emphasized that CCT/TRiC functions as an obligatory hetero-oligomer. Although individual subunits (e.g., CCT4, CCT6A) exhibit unique patterns of overexpression with oncogenes in GBM, the inhibition of single elements often results in the destabilization of the entire chaperonin ring, representing a universal critical point for tumor cell survival.

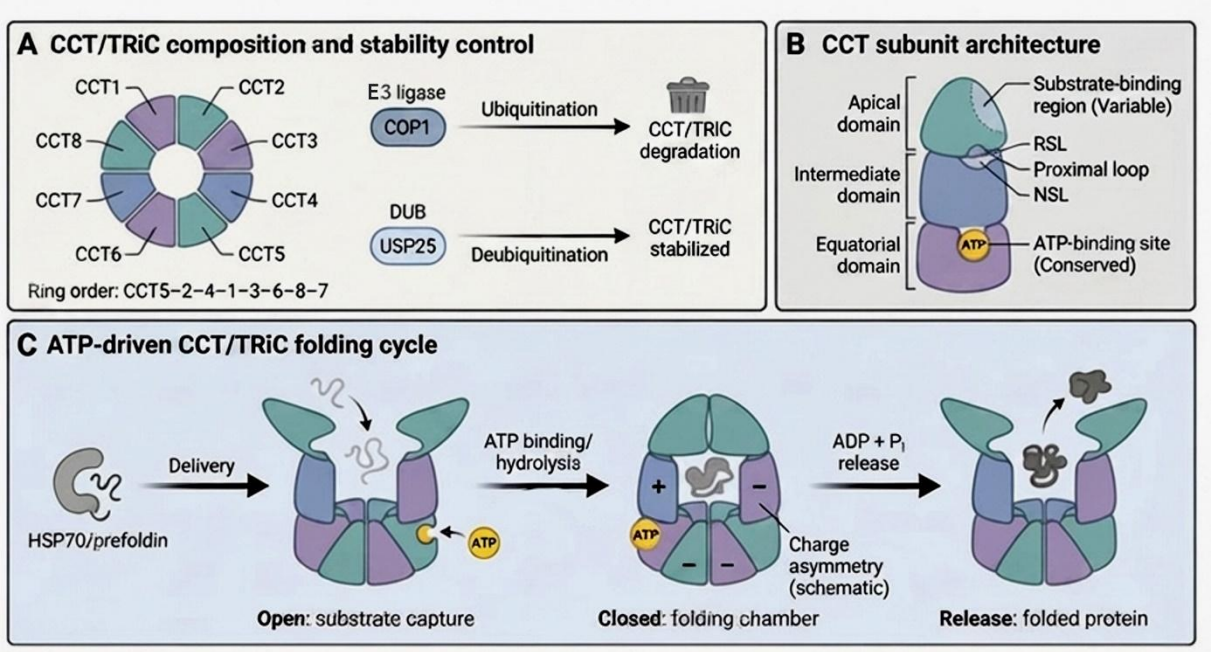


Figure 1: *Structural organization, regulation, and catalytic cycle of the CCT/ TRiC chaperonin.*

The CCT/TRiC complex is a sophisticated hetero-oligomeric molecular machine essential for cellular proteostasis. (A) CCT/TRiC composition and stability control: The complex consists of two back-to-back stacked rings, each composed of eight distinct subunits (CCT1–CCT8) arranged in a specific stoichiometric order (CCT5–2–4–1–3–6–8–7) [29]. *The cellular abundance of the complex is post-translationally regulated via the ubiquitin-proteasome system; the E3 ligase COP1 mediates ubiquitination to trigger degradation, while the deubiquitinase USP25 stabilizes the complex by preventing its proteasomal targeting* [30, 31]. *(B) CCT/TRiC subunit architecture: Each monomeric subunit comprises three functional domains: a conserved equatorial domain containing the ATP-binding site, a flexible intermediate domain acting as a hinge, and a variable apical domain featuring a substrate-binding region and loops (RSL, NSL) that facilitate chamber closure* [32]. *(C) ATP-driven CCT/TRiC folding cycle: The functional process begins with the delivery of unfolded polypeptides by co-chaperones (HSP70/prefoldin). In the Open state, the chaperonin captures the substrate within its central cavity. Upon ATP binding and hydrolysis, the complex undergoes a massive conformational rearrangement into a Closed state, creating a sequestered "folding chamber" where charge asymmetry facilitates protein maturation. The cycle concludes with the release of ADP+P_i, triggering the reopening of the apical domains and the discharge of the correctly folded protein into the cytosol* [33].

It is responsible for the folding of approximately 10% of newly synthesized proteins and plays a role in preventing protein aggregation associated with neurodegenerative diseases [**Figure 2**].

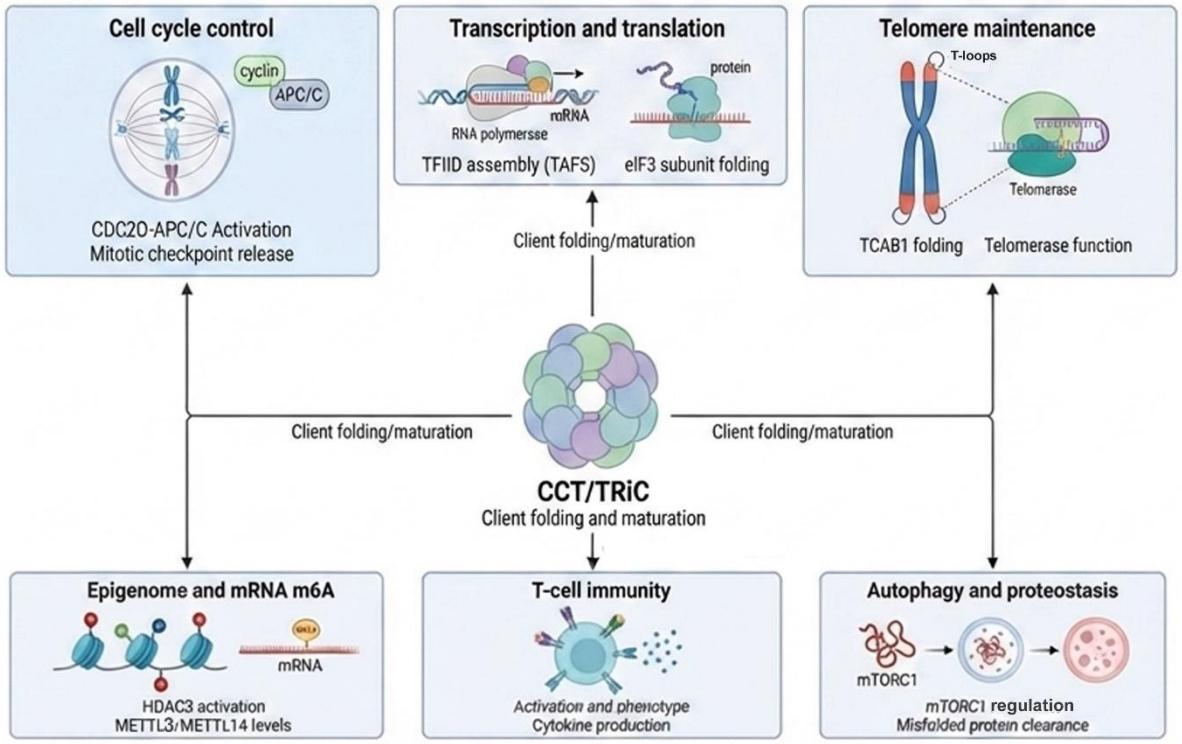


Figure 2. *The protein interactome and pleiotropic biological functions of CCT/TRiC. The CCT/TRiC chaperonin complex serves as a central hub for cellular proteostasis, governing a wide array of physiological processes through the folding and maturation of specific client proteins. Cell cycle control: CCT/TRiC facilitates the activation of the CDC20–APC/C complex, ensuring proper mitotic checkpoint release and chromosomal segregation* [34]. *Transcription and translation: The complex is essential for the assembly of the TFIID basal transcription factor (via TAF5 maturation) and the folding of eIF3 subunits, thereby regulating protein synthesis* [35]. *Telomere maintenance: TRiC promotes telomerase function by folding TCAB1, a key factor in the trafficking and stabilization of telomerase within T-loops* [36]. *Epigenome and mRNA m6A: The chaperonin modulates gene expression by supporting HDAC3 activation and maintaining steady-state levels of the METTL3/METTL14 methyltransferase complex, which is responsible for m6A RNA modification* [37, 38]. *T-cell immunity: CCT/TRiC is critical for T-cell activation, phenotype determination, and the regulated production of cytokines* [39]. *Autophagy and proteostasis: the complex interacts with the mTORC1 signaling pathway to regulate misfolded protein clearance and balance anabolic versus catabolic cellular states. Collectively, these interactions highlight the*

indispensable role of the CCT/TRiC-chaperonin axis in maintaining homeostatic control across diverse biological systems [38, 40].

Each subunit has an ATP-binding domain, a substrate-binding domain, and a domain involved in conformational changes [**Figure 1]** [41–43]. The heterogeneity of the subunits gives CCT/TRiC a high recognition specificity and a specialized allosteric mechanism, thus allowing it to guide the correct folding of proteins [44].

Recent research highlights that the individual subunits—CCT1 through CCT8—are not merely passive components but active drivers of malignancy. Studies in the literature report the presence of CCT/TRiC subunits in extracellular vesicles (EVs) obtained from neurosurgical aspirates of patients with GBM, with increased expression in higher-grade GBM [16, 45]. Specifically, the subunits CCT1, CCT2, CCT5, CCT6A, and CCT7 show statistically significant differences in expression [16] [Table 2].

Table 2. *Selected CCT/TRiC subunits implicated in GBM biology.*

CCT/TRiC subunit	**Role in GBM**	**Pathway involved**	**Clinical implications**	**Reference (s)**
CCT1	Increased expression in neurosurgical aspirates	Present in extracellular vesicles	Association with high-grade GBM	[16]
CCT2	Increased expression in neurosurgical aspirates; Potential "bottleneck" subunit	Present in extracellular vesicles; Influences KRAS stability	Association with high-grade GBM; Depletion inhibits GBM progression	[16]
CCT4	Overexpressed in GBM patients	Activation via mTOR (YB-1/CCT4/mLST8/mTOR axis)	Promotes cell growth, survival, motility and metabolism	[11]
CCT5	Increased expression in	Present in extracellular	Association with high-grade GBM;	[16, 46]

	neurosurgical aspirates; Involved in ciliogenesis	vesicles; Signaling associated with Aurora A and AKT	Key role in GBM cells division process	
CCT6A	Increased expression in neurosurgical aspirates; Linked to stemness; Involved in EMT	Present in extracellular vesicles; TGF-β signaling pathway	Association with high-grade GBM; Resistance to standard radiation and chemotherapy; knockdown reduces migration and invasion	[16, 47, 48]
CCT7	Increased expression in neurosurgical aspirates	Present in extracellular vesicles	Association with high-grade GBM	[16]
CCT8	Associated with tumor grade	Cell cycle regulation	Knockdown reduces migration and invasion	[49]

CCT6A has also been linked to the TGF-β signaling pathway, which promotes the "stem-like" properties of GBM cells, contributing to their notorious resistance to standard radiation and chemotherapy [47] [Table 2].

Collectively, available evidence suggests that CCT/TRiC subunits contribute to GBM through partially distinct mechanisms: CCT2 may act as a structural bottleneck, CCT4 links the complex to mTOR signaling, whereas CCT6A and CCT8 are associated with migration, invasion, and stress adaptation[11, 47–50] [Table 2].

One important thing to highlight is that the CCT4 subunit in GBM patients was found to play a critical role in the activation of the mTOR signaling pathway, and consequently in cell growth, survival, motility and metabolism [11][Table 2]. This aberrant activation of the mTORC1/2 signaling pathways is sustained by a specialized feed-forward regulatory loop involving the YB-1–CCT4–mLST8 axis [11] [Figure 3].

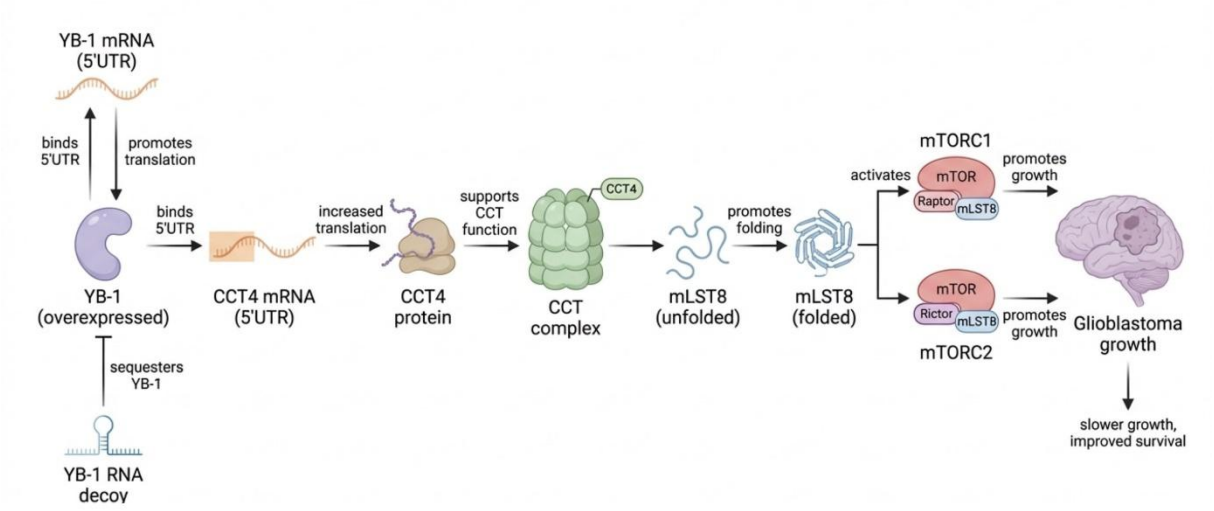


Figure 3: *The YB-1–CCT4–mLST8 signaling axis drives mTORC1/2 activation and glioblastoma progression. This schematic illustrates a feed-forward regulatory mechanism where the chaperonin complex facilitates oncogenic signaling in GBM. Translational Regulation by YB-1: Overexpressed YB-1 (Y-box binding protein 1) binds to the 5'UTR of its own mRNA and the CCT4 mRNA, promoting their translation. This positive feedback loop ensures a high abundance of the CCT4 subunit, which is integrated into the functional CCT/TRiC complex* [11]. *Chaperone-mediated maturation of mLST8: The CCT/TRiC complex provides essential proteostatic support for mLST8, a core component of both mTOR complexes. CCT/TRiC facilitates the transition of mLST8 from an unfolded polypeptide to its native, folded conformation. mTORC1/2 Activation and Tumor Growth: Folded mLST8 associates with mTOR and specialized adaptor proteins—Raptor (for mTORC1) and Rictor (for mTORC2). The activation of these complexes promotes robust glioblastoma growth and metabolic activity. Therapeutic Intervention: The use of a YB-1 RNA decoy effectively sequesters YB-1 protein, disrupting the translational upregulation of the CCT4-mLST8 axis. This inhibition leads to decreased mTORC1/2 activity, resulting in slower tumor growth and improved survival outcomes in preclinical models* [11].

At the translational level, overexpressed YB-1 (Y-box binding protein 1) binds to the 5'UTR of both its own mRNA and that of CCT4, driving their coupled translation and ensuring a robust supply of the CCT/TRiC chaperonin subunits [11]. This elevated chaperonin capacity provides critical proteostatic support for mLST8, a requisite component for the assembly of both mTOR complexes [6]. By facilitating the transition of mLST8 from an unfolded polypeptide to its functional, native conformation, the CCT/TRiC complex effectively licenses the formation of the mTOR-Raptor (mTORC1) and mTOR-Rictor

(mTORC2) signaling hubs [6, 51]. Crucially, the hyperactivation of these mTOR complexes serves as a molecular switch that regulates TIS following chemo- or radiotherapy [52, 53]. Rather than allowing for terminal growth arrest, CCT/TRiC-driven mTOR signaling enables senescent GBM cells to maintain high metabolic activity and a robust SASP, which collectively promote aggressive tumor proliferation and metabolic reprogramming [53, 54]. Conversely, the deployment of a YB-1 RNA decoy—which sequesters YB-1 and disrupts the translational upregulation of the CCT4-mLST8 axis—results in a significant reduction of mTORC1/2 activity [11]. This targeted intervention not only slows tumor growth but also impairs the survival of the senescent cell reservoir, identifying the CCT/TRiC-chaperonin-mTOR axis as a high-value therapeutic target for overcoming treatment resistance in GBM [11].

Furthermore, the CCT/TRiC complex, and in particular the CCT5 subunit, appear to have a key role in the ciliation process of GBM [46] [Table 2].

Therefore, individual subunits appear linked to distinct pathways (e.g., mTOR signaling, EMT programs, ciliogenesis, KRAS stability) and may represent “bottlenecks” for complex integrity [55]. These observations motivate systematic efforts to map subunit-specific dependencies and identify druggable nodes. Importantly, although several CCT/TRiC-dependent mechanisms have been directly demonstrated in GBM, including the YB-1/CCT4/mLST8/mTOR axis, EGFR-CCT6A co-amplification, and EV-associated CCT subunit expression, other proposed functions derive from studies performed in different cancer types. Therefore, caution is warranted when extrapolating these findings to GBM and dedicated functional studies will be required to validate their relevance in glioblastoma biology (TABLE 3).

Table 3. *Evidence demonstrated in GBM or other models.*

Mechanism	**Experimental model**	**Disease**	**Major limitations**	**References**
YB-1/CCT4/mLST8/ mTOR axis	Patients’ tissues and cell lines	GBM	Possible compensation for the many mTOR-activating pathways	[11]

CCT6A overexpression in GBM EVs and co-amplification with EGFR	Cavitron ultrasonic surgical aspirator (CUSA) fluid	GBM	Some evidence regarding the role of CCT/TRiC still requires mechanistic validation	[16]
CCT2 as a bottleneck subunit regulating GBM progression through KRAS stability	Patients' tissues and cell lines	GBM	The CCT2–KRAS axis still requires mechanistic validation	[50]
CCT6A involvement in EMT and invasion	Patients' tissues and cell lines	GBM	Partial mechanistic support	[47, 48]
CCT8 promotes glioma proliferation, migration and invasion	Patients' tissues and cell lines	GBM	Partial mechanistic evidence	[49]
CCT/TRiC regulation of p53 folding and activity	Cell lines	Various tumors	Confirmed interaction	[56]
CCT8-mediated inhibition of p53 activity	Patients' tissues, murine model and cell lines	Colorectal cancer	Confirmed interaction	[57]
CCT3-mediated YAP stabilization	Cell lines	Colorectal cancer	Limited study model	[58]
CCT/TRiC involvement in autophagy regulation through mTOR signaling	*Drosophila melanogaster*		Possible compensatory mechanisms involving other mTOR pathways	[6, 38]

CCT5 association with immune infiltration and inflammatory phenotype	In silico study	Pan-cancer analysis (including GBM)	Current lack of experimental data	[59]

4. Mechanistic links between CCT/TRiC activity and senescence programs in GBM

CCT/TRiC complex emerges as a pivotal regulator of cellular senescence, a state of permanent cell-cycle arrest that tumors often seek to bypass [60]. In healthy tissue, senescence acts as a natural barrier against malignancy; however, in GBM, the CCT/TRiC complex may contribute an anti-senescence engine that allows cancer cells to maintain an "immortal" proliferative capacity.

The relationship between CCT/TRiC and senescence is primarily driven by the complex's role in folding proteins essential for cell-cycle progression and DNA repair [11, 44, 57, 58, 61–63][Figure 4].

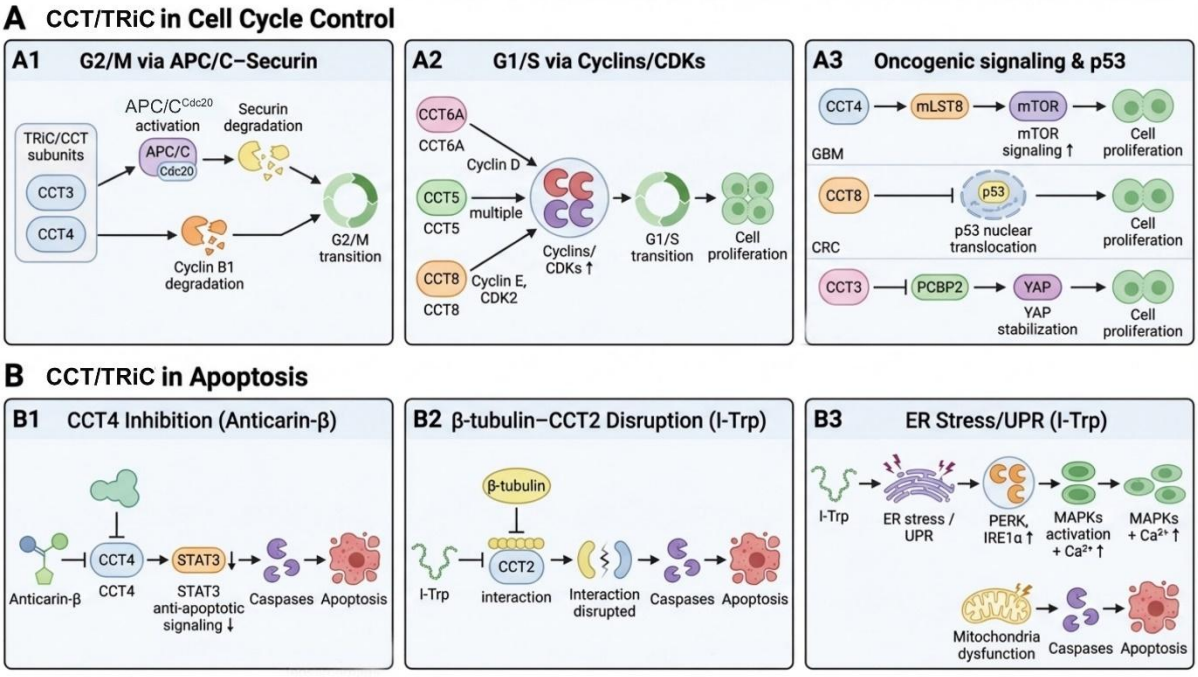


Figure 4: *Regulatory roles of CCT/TRiC in cell cycle progression and apoptosis. (A) CCT/TRiC in Cell Cycle Control: The complex regulates multiple transition points within the cell cycle* [44]. *(A1) During the G2/M transition, CCT3 and CCT4 subunits are required for the activation of the APC/C–Cdc20 complex, leading to the degradation of Securin and Cyclin B1* [61, 62]. *(A2) At the G1/S transition, various subunits (CCT6A, CCT5, CCT8) facilitate the maturation of Cyclins (D, E) and CDKs, driving cell proliferation* [63] *(A3) In*

oncogenic signaling, CCT/TRIC subunits support aberrant growth: CCT4 enhances mTOR signaling via mLST8 in GBM [11]*; CCT8 inhibits p53 nuclear translocation in colorectal cancer (CRC)* [57]*; and CCT3 promotes YAP stabilization, collectively driving uncontrolled proliferation.* [58] *(B) CCT/TRiC in Apoptosis: Targeted disruption of the chaperonin complex triggers programmed cell death through multiple mechanisms.* [64] *(B1) Inhibition of CCT4 (e.g., by Anticarin-β) suppresses STAT3 anti-apoptotic signaling, activating the caspase cascade.* [65] *(B2) Small molecules like I-Trp disrupt the β-tubulin–CCT2 interaction, leading to proteotoxic stress and apoptosis.* [66] *(B3) Pharmacological interference with CCT/TRiC induces severe ER Stress and the Unfolded Protein Response (UPR), characterized by PERK/IRE1\alpha activation and MAPK signaling* [67]*. This pathway results in mitochondrial dysfunction, Ca2+ release, and caspase-mediated cell death, highlighting the CCT/TRiC complex as a high-value therapeutic vulnerability in cancer* [68, 69]

When CCT/TRiC subunits, particularly CCT2 or CCT6A, are highly expressed, they ensure the correct folding of proteins like Cdc20 and cyclin B, which are necessary to push the cell through mitosis. By maintaining these levels, the CCT/TRiC complex effectively suppresses the activation of the p53/p21 and p16INK4a/Rb pathways, the two primary signaling axes that trigger senescence [60, 69]. In GBM cells where CCT/TRiC is inhibited, these pathways are rapidly reactivated, leading to characteristic phenotypic changes including enlarged cell morphology, increased β-galactosidase activity, and the secretion of proinflammatory factors known as the Senescence-Associated Secretory Phenotype (SASP). Notably, CCT/TRiC plays a central and nuanced role in these processes; while p53 is a well-documented folding substrate of the complex [56, 69, 70], the functional outcome of this interaction is context-dependent. It is important to note that the role of the CCT/TRiC complex in regulating p53 activity is highly context-dependent. While CCT/TRiC is required for the stabilization and proper folding of wild-type p53 under physiological or early oncogenic stress conditions, its pharmacological inhibition in established GBM cells appears to trigger a stress-dependent reactivation of the p53/p21 pathway. This functional duality is likely governed by the cellular mutational status of TP53 and the magnitude of proteotoxic stress; therefore, the therapeutic impact of CCT inhibition on p53-dependent senescence requires further validation across various GBM genetic backgrounds. Although this has been demonstrated directly in gastrointestinal cancers [57], we hypothesize that an analogous mechanism occurs in GBM; CCT/TRiC supports the correct folding of wild-type p53, yet the ultimate suppression of senescence likely depends on the TP53 mutational status, levels of cellular stress, and the

activity of parallel oncogenic networks [Table 3] [Figure 5]. Several mechanisms identified in other cancer models, such as the CCT3-YAP signaling axis or specific chaperonin-autophagy interplay, provide a strong theoretical framework for our understanding of GBM [Table 3]. Beyond p53 regulation, the CCT/TRiC complex also plays a pivotal role in modulating the Hippo signaling pathway by stabilizing the YAP oncoprotein[58] [Table 3]. However, it must be emphasized that while this interaction has been explicitly established in gastrointestinal malignancies, these pathways are currently extrapolated from non-GBM cellular environments. We propose that a comparable mechanism functions in glioblastoma, where CCT3-mediated folding and stabilization of YAP promotes transcriptional activity, cell proliferation, and resistance to senescence. While these data suggest potential targets, their specific operational role and clinical relevance in glioblastoma require dedicated, model-specific experimental confirmation.

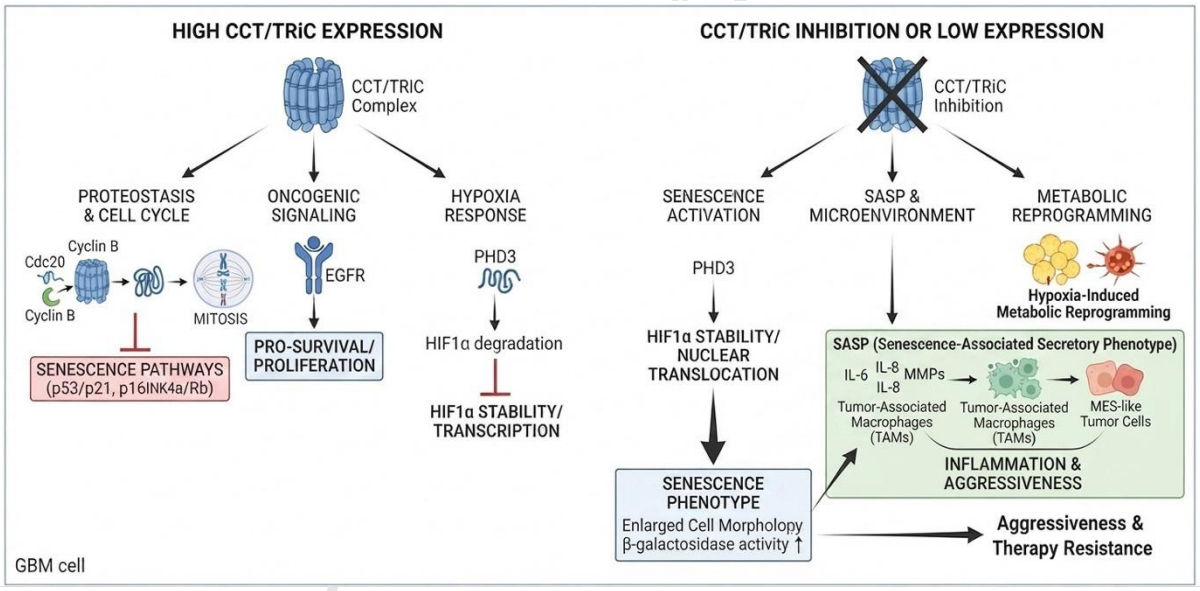


Figure 5: *The figure illustrates the central role of the CCT/TRiC complex in regulating senescence in GBM. CCT/TRiC acts as a facilitator of this process. This is possible thanks to the complex's ability to correctly fold key proteins in the cell cycle and DNA repair* [56, 70, 71], *as well as cellular factors, including EGFR* [16, 72] *and hypoxia-associated pathways* [14, 22], *promoting key pro-senescence pathways. CCT/TRiC contribution to the senescence-associated secretory phenotype (SASP) and to the modulation of the tumor microenvironment is also depicted* [59]. *Overall, CCT/TRiC appears as an integrating node linking cell cycle control, proteostasis, hypoxia response, and interactions with the microenvironment, supporting the survival and aggressiveness of GBM.*

As mentioned, EGFR plays a key role in senescence and it has been shown that the CCT6A subunit of the CCT/TRiC complex colocalizes with EGFR at the 7p11.2 locus, showing also a strong tendency for coamplification. This was also confirmed by immunohistochemical analyses, showing a potential link between tissue expression of EGFR and CCT6A [16, 72].This link between EGFR and the CCT/TRiC complex could therefore represent a possible cooperation of the two proteins, together with NTN4, in the reorganization of the cellular matrix typical of senescent cells [Figure 5].

A bioinformatics analysis of CCT5 shows its overexpression in several tumor types, including GBM, and is significantly correlated with clinical outcome [59]. Furthermore, in addition to being a potential biomarker and possible oncogene, CCT5 expression has been shown to be linked to tumor infiltration by immune cells, particularly those that predispose to an inflammatory phenotype [59]. In senescent cells, the high SASP score, discussed above, is associated with an increase in MES-like tumor cells and tumor-associated macrophages (TAMs), which lead to inflammation. In this context, it could be hypothesized that the CCT/TRiC complex, and in particular subunit 5, contributes to this characteristic of the senescent phenotype [Figure 5].

Finally, the roles of HIF1α and HIF2α in the induction of senescence were discussed earlier [22]. In a recent work, it was hypothesized that in hypoxic cells, HIF-1α can translocate to the nucleus, where it regulates the transcription of key factors for the pathogenesis of GBM and that the CCT/TRiC complex may influence indirectly by modulating the folding of PHD3 [14]. In IDH-wild-type GBM, in fact, hypoxia alters cellular metabolism, reducing available α-KG and leading to the formation of aggresomes (TRiC-PHD3), impaired pVHL folding and the failure of HIF degradation and its nuclear translocation, with consequent increase in lipid biosynthesis, oxidative stress and finally to a major tumor aggressiveness [14]. Considering this, it is possible that CCT/TRiC also plays a key role in hypoxia-induced metabolic reprogramming of senescent cells [Figure 5].

Overall, we propose that CCT/TRiC influences senescence in GBM through three interconnected layers: direct folding of senescence gatekeepers and DNA repair proteins; maintenance of oncogenic signaling that antagonizes senescence, and support of microenvironment-shaping outputs that reinforce SASP-driven resistance. The CCT/TRiC complex emerges as a central molecular hub in cell cycle control, proteostasis, hypoxic response, metabolism, and interactions with the immune microenvironment. Notably, we do not propose that CCT/TRiC acts as a direct inducer of senescence. Rather, current evidence supports a model in which CCT/TRiC contributes to the maintenance, survival, and metabolic

adaptation of therapy-induced senescent cells, thereby sustaining SASP production and recurrence-promoting activities. Its function in GBM is highly strategic and could represent a promising target in the context of senescence processes and strategies.

5. *The senescence-stemness axis: SASP-mediated TME remodeling and CCT/TRiC-dependent proteostasis in GSC maintenance*

Beyond its direct role in senescence, the CCT/TRiC complex appears to contribute to the emergence of a therapy-induced microenvironment that promotes glioblastoma recurrence. Indeed, the clinical recurrence of glioblastoma is increasingly attributed to a resilient subpopulation of glioma stem-like cells (GSCs) that survive standard-of-care radiotherapy and temozolomide[8, 73] [Figure 6]. Emerging evidence suggests that this survival is not solely an intrinsic property of GSCs but is actively fostered by the therapy-induced senescent microenvironment and the specialized proteostasis provided by the CCT/TRiC complex [8, 14]. Following therapeutic insult, both GBM cells and surrounding astrocytes enter a state of senescence characterized by the development of a SASP [73, 74] [Figure 6]. This secretome, rich in IL-6, IL-8, CCL2, and TGF-β, fundamentally remodels the tumor microenvironment and is proposed to support the paracrine reprogramming of differentiated GBM cells toward a progenitor-like state, effectively expanding the GSC pool [8, 73] [Figure 6]. In particular, SASP-derived IL-6 has been implicated in activating the STAT3 signaling pathway in neighboring cells, a key pathway associated with the regulation of stemness markers such as SOX2, Nestin, and CD133 [75, 76] [Figure 6]. Furthermore, the chronic inflammatory environment generated by SASP is suggested to facilitate immune evasion and protects GSCs from the pro-apoptotic effects of chemotherapy, allowing them to persist in a slow-cycling state naturally resistant to TMZ [73, 77] [Figure 6].

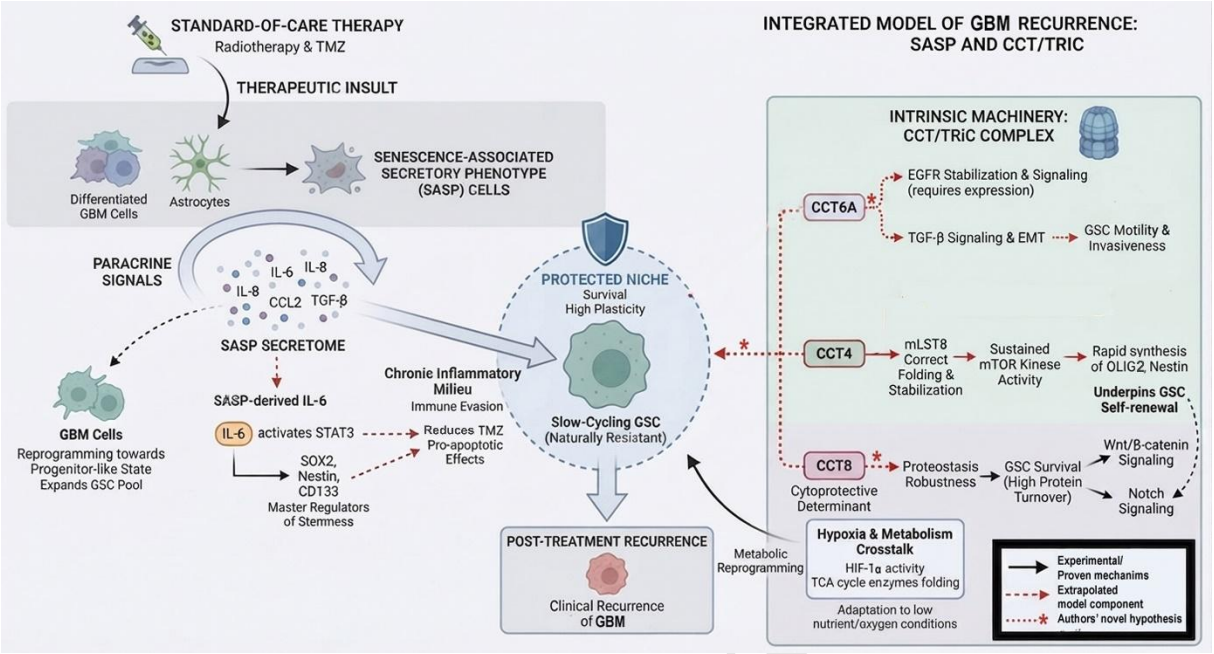


Figure 6: Proposed interaction between the senescence-associated secretory phenotype (SASP) and the chaperonin CCT/TRiC leading to glioma stem cell support and promotion of GBM recurrence. CCT6A, coexpressed with EGFR, is suggested to promote TGF-β-dependent epithelial-mesenchymal transition (EMT); CCT4 is proposed to support, via mTOR, protein synthesis and self-renewal programs of GSCs; CCT8 may maintain proteostasis under cellular stress conditions, potentially supporting Wnt/β-catenin and Notch signaling and HIF-1α-dependent metabolic adaptation in hypoxic and nutrient-starved niches. The convergence of these mechanisms may generate a resistant niche that preserves the survival, plasticity, and stemness of GSCs, ultimately contributing to post-treatment GBM recurrence.

The chaperonin CCT/TRiC complex is reported to be responsible for the maturation of numerous principal regulators of GBM stemness [78, 79]. Within this complex, CCT4, CCT6A, and CCT8 emerge as functionally critical subunits. As noted in the context of senescence (Section 2), CCT6A co-amplifies with EGFR at the 7p11.2 locus to sustain receptor signaling [16]. Furthermore, CCT6A directly interfaces with the TGF-β cascade to facilitate a mesenchymal-like state transition [16, 80–82] [Figure 6]. CCT4, which has a pivotal element of the YB-1/CCT4/mLST8/mTOR axis [11], sustains elevated mTOR kinase activity, which indirectly supports the maintenance and self-renewal programs of GSCs [11, 83] via rapid synthesis Oligodendrocyte transcription factor 2 (OLIG2) [84] and Nestin [85] [Figure 6]. CCT8 functions as a key cytoprotective determinant under conditions of cellular stress, preserving proteostatic capacity [78] [Figure 6]. This resultant proteostasis robustness

is proposed to support GSC survival in the context of high protein turnover driven by Wnt/β-catenin and Notch signaling, rather than representing established direct CCT-client interactions [76, 78].

5. From mTOR inhibition to lysosomal collapse: The role of CCT/TRiC in Autophagy

The primary negative regulator of ULK1-dependent autophagy initiation is the mTORC1 complex [11, 86]. CCT/TRiC influences this process indirectly by supporting the correct folding of mLST8, which is essential for mTOR complex activity [11, 87]. Simultaneously, CCT integrity supports actin-dependent lysosomal function and autophagosome degradation. This creates a fascinating dual relationship: CCT/TRiC may support mTOR-dependent restriction of autophagy initiation while also maintaining late-stage autophagic clearance [15, 88, 89]. Under basal conditions, CCT-mediated support of mTOR activity inhibits the ULK1 complex, thereby suppressing the initiation of macroautophagy and maintaining the high rates of protein synthesis and cell growth that characterize GBM cells. At the same time, CCT/TRiC is required for the maturation of the actin cytoskeleton, which is essential for efficient autophagosome-lysosome fusion and lysosomal clearance. Thus, CCT activity is proposed to support autophagic flux by preserving the structural integrity of the degradative machinery, even while mTOR signaling restricts autophagy initiation [88].

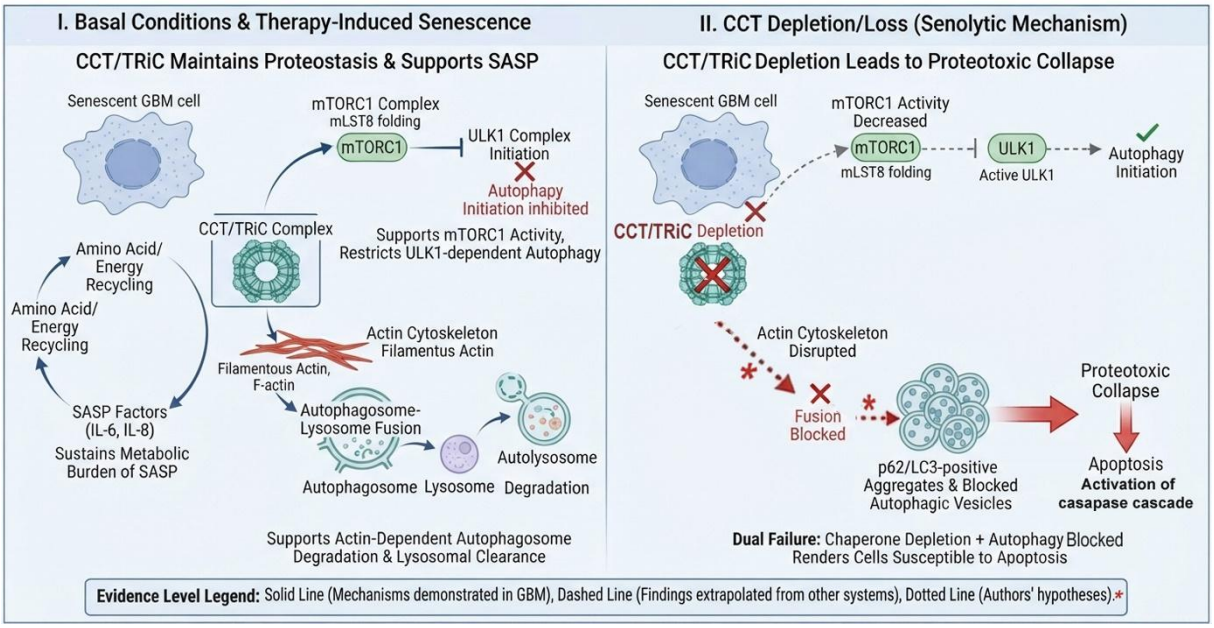


Figure 7: Role of the CCT/TRiC complex in regulating the mTOR axis and autophagy in senescent GBM cells. The CCT/TRiC complex indirectly influences mTORC1/2 activity (via mLST8 folding), thereby contributing to the restriction of ULK1-dependent autophagy

initiation, while simultaneously supporting actin-dependent autophagosome degradation and lysosomal clearance. In senescent cells, mTOR and macroautophagy may cooperate to produce the SASP and support the survival of GSCs under hypoxic and nutrient-starved conditions [84, 85]. Thus, CCT/TRiC inhibition is hypothesized to simultaneously impair mTOR-dependent signaling and lysosomal clearance, potentially leading to proteotoxic collapse and apoptosis of therapy-resistant senescent cells [15, 83].

In therapy-induced senescent GBM cells, both macroautophagy and mTOR signaling may be co-opted to sustain the substantial metabolic burden associated with SASP production, a phenomenon referred to as TOR–autophagy spatial coupling [90]. Through the recycling of intracellular substrates, autophagy supplies the amino acids and energy required for the continuous secretion of SASP factors such as IL-6 and IL-8 [90, 91]. While autophagy inhibition can enhance the induction of senescence, it may also qualitatively reshape the SASP repertoire, potentially shifting it from a pro-tumorigenic phenotype toward a more anti-tumorigenic and inflammatory "M1-like" secretome [91]. Moreover, within hypoxic niches, CCT/TRiC may cooperate with macroautophagy and metabolic adaptation programs to maintain cellular energy homeostasis, allowing senescent GSCs to survive in nutrient-poor environments [14, 92].

Evidence demonstrating that CCT depletion impairs autophagic flux has been generated primarily in HeLa cells, neurons, and *Drosophila*, rather than directly in GBM or therapy-induced senescent GBM cells. Although an analogous mechanism can be proposed for GBM, it has not yet been directly demonstrated. Furthermore, it must be emphasized that the accumulation of LC3-II or p62 proteins alone cannot define autophagic flux impairment without dedicated lysosomal-inhibitor experiments (e.g., using bafilomycin A1) or an appropriate tandem fluorescent reporter analysis [15, 88].

Although CCT/TRiC inhibition might theoretically promote the early initiation of autophagy by relieving mTOR-dependent suppression, the resulting proteotoxic collapse observed in our model is not a product of inhibited initiation, but rather a catastrophic failure of autophagic completion. This is likely due to the structural requirement of the CCT complex for proper actin cytoskeleton dynamics and lysosomal organization. Consequently, the depletion of CCT leads to an abortive autophagic response, characterized by failed autophagosome-lysosome fusion and the subsequent accumulation of toxic protein aggregates, rather than a productive autophagic clearance.

Rather than inducing a functional protective autophagy, available evidence suggests that CCT depletion leads to the accumulation of p62/LC3-positive aggregates and autophagic vesicles that cannot be efficiently cleared [88, 93]. A plausible mechanism is that the simultaneous disruption of mTOR-dependent survival signaling and autophagic clearance of misfolded proteins drives senescent GBM cells toward proteotoxic collapse [11, 93]. This dual failure of the proteostasis network, characterized by both chaperone depletion and autophagy blockade, could be a possibility to render senescent cells highly susceptible to apoptosis and may therefore act as a senolytic mechanism capable of eliminating therapy-resistant populations [90, 93].

6 Targeting CCT/TRiC as a pro-senescence or senolytic lever

Targeting CCT/TRiC to induce pro-senescence therapy represents a burgeoning strategy in neuro-oncology [Figure 8].

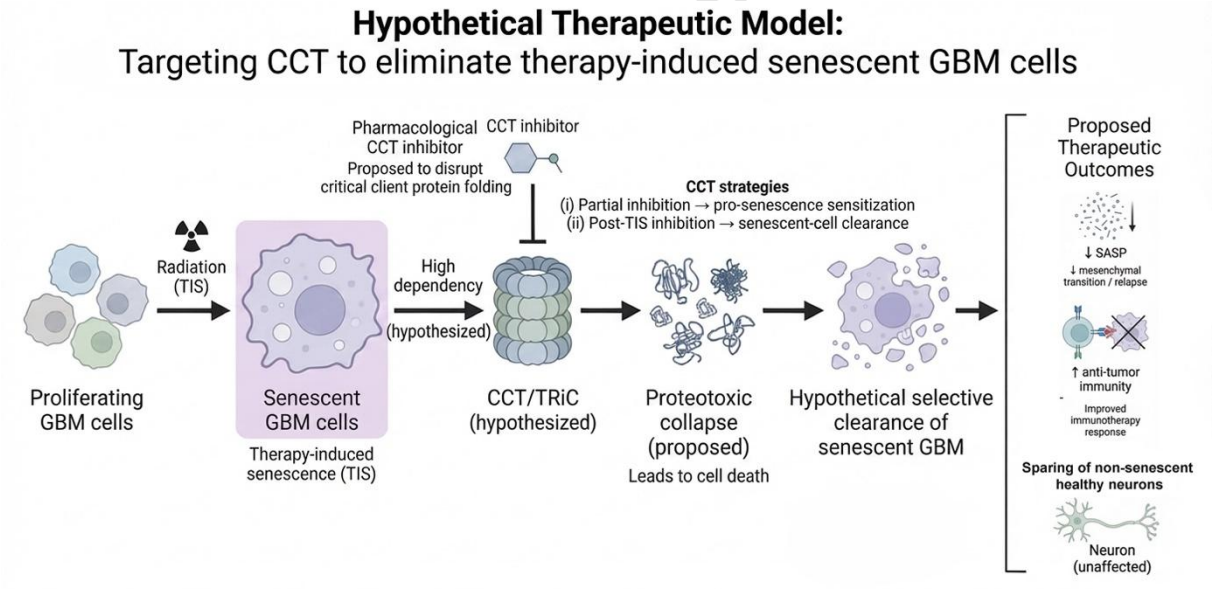


Figure 8: Hypothetical therapeutic model for targeting the CCT/TRiC complex in therapy-induced senescent glioblastoma cells. This diagram illustrates a conceptual framework for targeting the CCT/TRiC complex in GBM. Induction of Senescence: Proliferating GBM cells subjected to genotoxic stress, such as radiation, enter a state of therapy-induced senescence (TIS). These cells are hypothesized to develop a high dependency on the CCT/TRiC chaperonin complex to maintain proteostasis and survive. Hypothetical Mechanism of CCT/TRiC Inhibition: Pharmacological or genetic CCT/TRiC interference is proposed to disrupt critical client protein folding, potentially leading to proteotoxic collapse and the selective clearance of senescent GBM cells while theoretically sparing non-senescent, healthy

cells such as neurons. Proposed Therapeutic Outcomes: If validated, this strategy could result in downstream clinical benefits, including: Reduction of the SASP: Decreasing the senescence-associated secretory phenotype to limit the pro-tumorigenic inflammatory environment. Inhibition of relapse: Suppressing mesenchymal transition and tumor recurrence. Enhanced immunity: Potentially activating anti-tumor immunity and improving responses to immunotherapy.

Unlike traditional chemotherapy, which often induces a complex resistance phenomenon (determined by multiple molecular alterations, such as variations in cellular signaling pathways and in DNA alkylation and repair processes)[94] or could cause necrosis with concomitant radiation [95], it could be induced the senescence via CCT/TRiC inhibition, that could theoretically "freeze" tumor growth and make the cells more susceptible to senolytic drugs that specifically clear these arrested cells. This two-step approach, as discussed previously, consists in using CCT/TRiC depletion to force senescence and then clearing the senescent cells and offers a promising avenue for overcoming the high recurrence rates typical of GBM [96] [**Table 4**].

Also, senescent GBM cells are uniquely reliant on the CCT/TRiC complex, as discussed; inhibiting this chaperonin system triggers a "proteotoxic collapse" that specifically eliminates senescent cells while sparing healthy, non-senescent neurons [**Figure 5**]. So another “one-two punch” strategy could be applied, for example in an experimental *in vitro* model, which would be the first step in testing this hypothesis, first we can induce senescence with standard-of-care radiation, temozolomide or etoposide (whose use is well established in the literature e.g., [97, 98]), then clearing the senescent population with CCT/TRiC-targeted inhibitors, such as HSF1A or CT20p [99, 100], aimed to prevent the SASP-driven mesenchymal transition that typically leads to lethal GBM relapse. Furthermore, disrupting this axis may sensitize tumors to immunotherapy by halting the secretion of factors like IL-6 and CSF1, which normally recruit M2-like macrophages to shield the tumor from T-cell attack [96, 101] [Table 4].

As researchers move toward clinical validation, the chaperonin-senescence axis could represent a critical vulnerability in the otherwise resilient GBM landscape [8]. Overall, we suggest that CCT/TRiC-directed strategies could be deployed in at least two non-mutually exclusive ways. (i) Pro-senescence sensitization: partial CCT/TRiC inhibition may raise proteotoxic stress and promote senescence, enhancing the efficacy of radio and chemotherapy. (ii) Senescent-cell clearance: senescent GBM cells may exhibit heightened dependency on

chaperonin-mediated proteostasis; thus, CCT/TRiC inhibition after TIS induction could trigger selective proteotoxic collapse of senescent reservoirs. Either approach should be evaluated with careful neurotoxicity profiling and pharmacokinetic optimization for CNS delivery [102]. Immediate priorities focus on four complementary lines of work. First, it is crucial to clarify how different CCT/TRiC subunits specifically contribute to the biological dependencies of the various molecular subtypes of GBM [19]. In parallel, a systematic mapping of the CCT/TRiC client proteins most relevant to senescence processes, SASP modulation, and immune evasion mechanisms is needed. A third objective is to link CCT/TRIC subunit expression to key clinical biomarkers (such as IDH status and mesenchymal signatures) to make prognostic models more accurate and clinically useful [14].

The proposed proteotoxic-collapse model is compelling and represents a novel framework; nevertheless, it is essential to acknowledge that there is currently no direct evidence that CCT/TRiC inhibition selectively eliminates senescent GBM cells, functions as a validated GBM senolytic, prevents recurrence through senescent-cell clearance, or spares healthy neurons. These concepts must be strictly presented as testable hypotheses. To validate this model, future investigations should outline key experiments, including: CCT-subunit depletion in proliferating versus senescent GBM cells, evaluation of LC3 turnover with and without bafilomycin A1, tandem mCherry-GFP-LC3 analysis, lysosomal-function assays and genetic rescue experiments, utilization of patient-derived GSC models, and comparative toxicity evaluations with normal astrocytes and neurons.

Table 4. *Established and proposed therapeutic strategies targeting senescence and CCT/TRiC in GBM.*

Strategy	**Mechanism**	**Expected effect**	**References**
TMZ + senolytic	Elimination of therapy-induced senescent (TIS) cells generated after standard treatment	Reduction of recurrence-driving senescent cell populations and improved therapeutic response	[73, 96]
Senolytic targeting of p21-dependent senescent GBM cells	Selective elimination of senescent cells induced by BMP4 or therapy-induced	Increased susceptibility of GBM cells to senolytic	[24, 70]

	senescence programs	treatment	
CCT/TRiC-targeting approaches	Disruption of proteostasis and inhibition of oncogenic pathways dependent on CCT/TRiC activity	Reduced GBM growth, proliferation, migration, and survival	[11, 50]
SASP-directed immunomodulation	Targeting senescence-associated inflammatory signaling and immunosuppressive microenvironment	Enhanced anti-tumor immune response and sensitization to immune-based therapies	[12, 101]

7 *Conclusions*

This study highlights how the CCT/TRiC complex is poised to become a critical future modulator of cellular senescence in GBM. [Figure 9]

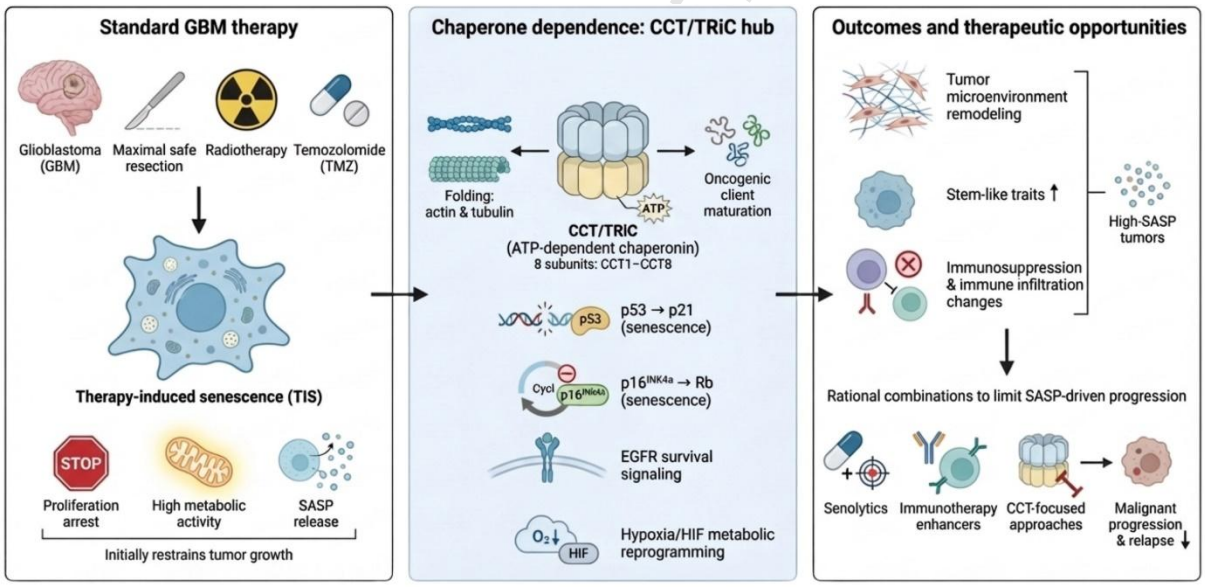


Figure 9: *The CCT/TRiC chaperonin hub as a master regulator of the senescence-to-progression transition in GBM. This schema outlines the multi-stage cascade from standard therapy to malignant relapse in GBM. Standard GBM therapy and TIS: Treatment consisting of maximal safe surgical resection, radiotherapy, and TMZ initially induces TIS. TIS is a phenotype characterized by stable proliferation arrest, high metabolic activity, and the release of the senescence-associated secretory phenotype (SASP). While this initially restrains tumor growth, it also establishes a resistant cell reservoir. Chaperone dependence on the CCT/TRiC Hub: Continued survival and metabolic reprogramming in TIS are heavily dependent on the*

CCT/TRiC chaperonin complex. This ATP-dependent hub folds essential structural components (actin and tubulin), facilitates the maturation of multiple oncoproteins, maintains signaling hubs such as EGFR, and supports HIF-mediated metabolic reprogramming under hypoxic conditions. It also regulates the entry into senescence itself via the p53→p21 and p16INK4a→Rb pathways. Outcomes and therapeutic opportunities: The persistent CCT/TRiC-dependent SASP drives remodeling of the tumor microenvironment, promotes stem-like traits, and modifies immune infiltration, leading to immunosuppression. These high-SASP tumors inevitably progress towards relapse. Targeted therapeutic opportunities (CCT/TRiC-focused approaches) are visualized, including senolytics, immunotherapy enhancers, and specific CCT/TRiC inhibitors, which aim to disrupt SASP-driven progression and prevent malignant relapse.

Within the unique landscape of the brain tumor microenvironment, the CCT/TRiC complex acts as a central hub for protein homeostasis, interacting directly with essential regulatory proteins such as p53, EGFR, and HIF1α [14, 16, 56]. By ensuring the structural integrity and folding of these clients, CCT/TRiC effectively regulates high-stakes signaling pathways, most notably the PI3K/AKT/mTOR (PAM) axis, which is frequently dysregulated in high-grade gliomas [11, 103, 104].

TIS in GBM, primarily triggered by the standard-of-care regimen of TMZ and ionizing radiation, represents a significant clinical hurdle. Although these treatments initially suppress tumor volume, they paradoxically drive a subset of cells into a senescent state [70]. These cells do not die; instead, they undergo a phenotypic shift toward a more aggressive, mesenchymal-like profile, fostering a resistant tumor reservoir that may contribute to relapse and poor prognosis of GBM.

Consequently, there is an imperative need for novel molecular markers and innovative therapeutic interventions to break this cycle of recurrence. At this juncture, CCT/TRiC subunits appear to be excellent candidates for targeted "*negative chaperonotherapy*." By disrupting the chaperonin-senescence axis, it may be possible to selectively eliminate senescent GBM cells or dampen their pro-tumorigenic secretome, offering a promising pathway to enhance the efficacy of current treatments and improve patient outcomes [10].

Further evidence suggests that the CCT/TRiC complex plays a central role not only in maintaining therapy-induced senescence but also in creating a favorable microenvironment for stemness, survival, and therapeutic resistance [8, 14, 73, 75, 77]. Therefore, the

CCT/TRiC complex can be considered a potential therapeutic target to limit disease relapse and improve the efficacy of conventional treatments.

Furthermore, as discussed, through its role in macroautophagy, the complex is a possible positioned as a key regulator of cellular proteostasis, balancing anabolic growth with catabolic adaptation, which is crucial in senescent cells because autophagy supports SASP production and long-term cell survival, even under hypoxic conditions. Consequently, CCT/TRiC inhibition may disrupt both mTOR-dependent survival pathways and autophagy mechanisms, likely leading to proteotoxic collapse [15, 83–87].

The concept of "chaperone addiction" suggests that GBM cells are probably more dependent on the CCT/TRiC complex than healthy brain cells. This presents a therapeutic opportunity. By inhibiting the CCT/TRiC complex, we can theoretically: i) induce proteotoxic crisis, forcing the accumulation of misfolded oncoproteins and impairing autophagic clearance, leading to selective apoptosis in cancer cells; ii) inhibit invasion, disrupting the folding of actin and tubulin to "paralyze" the tumor's ability to migrate; iii) interfere with mTOR-dependent adaptive signaling and SASP maintenance; and iv) reverse therapeutic resistance by removing a central proteostatic hub that sustains stemness and senescent cells survival.

Overall, we propose that the CCT/TRiC complex influences cellular senescence in GBM through three interconnected layers: (i) the direct folding of senescence gatekeepers and DNA repair proteins, (ii) the maintenance of oncogenic signaling pathways, and (iii) the support of microenvironment-shaping outputs that reinforce SASP-driven resistance. Rather than acting as a direct inducer of senescence, CCT/TRiC functions as a critical proteostatic support system. In proliferating tumor cells, the complex prevents premature senescence, whereas in cells undergoing therapy-induced senescence (TIS), it promotes survival, metabolic adaptation, and the intensification of the senescence-associated secretory phenotype (SASP). Consequently, CCT/TRiC should be viewed as a strategic factor facilitating the survival, plasticity, and recurrence-promoting activities of senescent GBM cells, rather than as an element initiating the senescence process itself.

The senescence in GBM, leading to the formation of more aggressive and resistant tumor cells, results in a poor prognosis. For this reason, given the critical role of CCT/TRiC in GBM proteostasis, the chaperonin-senescence axis represents a promising, albeit highly experimental, therapeutic target that warrants rigorous validation in future preclinical studies. This study highlights how the CCT/TRiC complex is poised to become a critical future modulator of cellular senescence in GBM [Figure 9].

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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References

1. Lee S, Lee J-S (2019) Cellular senescence: a promising strategy for cancer therapy. BMB Rep 52:35–41. https://doi.org/10.5483/BMBRep.2019.52.1.294

2. Ewald JA, Desotelle JA, Wilding G, Jarrard DF (2010) Therapy-Induced Senescence in Cancer. JNCI: Journal of the National Cancer Institute 102:1536–1546. https://doi.org/10.1093/jnci/djq364

3. Rodier F, Campisi J (2011) Four faces of cellular senescence. Journal of Cell Biology 192:547–556. https://doi.org/10.1083/jcb.201009094

4. Wilkinson HN, Hardman MJ (2020) Senescence in Wound Repair: Emerging Strategies to Target Chronic Healing Wounds. Front Cell Dev Biol 8:773. https://doi.org/10.3389/fcell.2020.00773

5. Yalamarty SSK, Filipczak N, Li X, et al (2023) Mechanisms of Resistance and Current Treatment Options for Glioblastoma Multiforme (GBM). Cancers 15:2116. https://doi.org/10.3390/cancers15072116

6. Cuéllar J, Ludlam WG, Tensmeyer NC, et al (2019) Structural and functional analysis of the role of the chaperonin CCT in mTOR complex assembly. Nat Commun 10:2865. https://doi.org/10.1038/s41467-019-10781-1

7. Colucci M, Sarill M, Maddalena M, et al (2025) Senescence in cancer. Cancer Cell 43:1204–1226. https://doi.org/10.1016/j.ccell.2025.05.015

8. Tarumi W, Murai K, Nakahata Y, Masui K (2026) The Paradox of Senescence in Glioblastoma: SASP as an Emerging Cancer Hallmark. Cancers 18:550. https://doi.org/10.3390/cancers18040550

9. Bloniarz D, Adamczyk-Grochala J, Lewinska A, Wnuk M (2021) The lack of functional DNMT2/TRDMT1 gene modulates cancer cell responses during drug-induced senescence. Aging 13:15833–15874. https://doi.org/10.18632/aging.203203

10. Alessio N, Aprile D, Squillaro T, et al (2019) The senescence-associated secretory phenotype (SASP) from mesenchymal stromal cells impairs growth of immortalized prostate cells but has no effect on metastatic prostatic cancer cells. Aging 11:5817–5828. https://doi.org/10.18632/aging.102172

11. Wang J-Z, Zhu H, You P, et al (2022) Upregulated YB-1 protein promotes glioblastoma growth through a YB-1/CCT4/mLST8/mTOR pathway. Journal of Clinical Investigation 132:e146536. https://doi.org/10.1172/JCI146536

12. Wang Z, Zhang Y, Wu F, et al (2025) Therapy-induced senescent glioblastoma cells sustain a procancer immune microenvironment by activating DDX58-mediated STAT1 signaling. Neuro-Oncology 27:2265–2280. https://doi.org/10.1093/neuonc/noaf107

13. Auzmendi-Iriarte J, Otaegi-Ugartemendia M, Carrasco-Garcia E, et al (2022) Chaperone-Mediated Autophagy Controls Proteomic and Transcriptomic Pathways to Maintain Glioma Stem Cell Activity. Cancer Research 82:1283–1297. https://doi.org/10.1158/0008-5472.CAN-21-2161

14. Alberti G, D'Amico G, Augello MA, et al (2025) The TRiC/CCT Complex at the Crossroads of Metabolism and Hypoxia in GBM: Implications for IDH-Dependent Therapeutic Targeting. IJMS 27:373. https://doi.org/10.3390/ijms27010373

15. Vallin J, Grantham J (2019) The role of the molecular chaperone CCT in protein folding and mediation of cytoskeleton-associated processes: implications for cancer cell biology. Cell Stress and Chaperones 24:17–27. https://doi.org/10.1007/s12192-018-0949-3

16. Hallal S, Russell BP, Wei H, et al (2019) Extracellular Vesicles from Neurosurgical Aspirates Identifies Chaperonin Containing TCP1 Subunit 6A as a Potential Glioblastoma Biomarker with Prognostic Significance. Proteomics 19:1800157. https://doi.org/10.1002/pmic.201800157

17. Liu H, Chen L, Chen Y, et al (2025) TCP1 promotes the progression of malignant tumours by stabilizing c-Myc through the AKT/GSK-3β and ERK signalling pathways. Commun Biol 8:563. https://doi.org/10.1038/s42003-025-07867-6

18. Noori L, Filip K, Nazmara Z, et al (2023) Contribution of Extracellular Vesicles and Molecular Chaperones in Age-Related Neurodegenerative Disorders of the CNS. IJMS 24:927. https://doi.org/10.3390/ijms24020927

19. Augello MA, Shadan N, D'Amico G, et al (2025) Beneficial Handling of Molecular Chaperones (Chaperonotherapy) in Glioblastoma and Neuroblastoma: Novel Therapeutic Targets or Potential Agents? Cells 14:1447. https://doi.org/10.3390/cells14181447

20. Zhang F, Guo J, Yu S, et al (2024) Cellular senescence and metabolic reprogramming: Unraveling the intricate crosstalk in the immunosuppressive tumor microenvironment. Cancer Commun 44:929–966. https://doi.org/10.1002/cac2.12591

21. Kaina B, Christmann M (2025) Senotherapeutics in Malignant Brain Cancer Therapy. Curr Oncol Rep 27:1524–1536. https://doi.org/10.1007/s11912-025-01733-8

22. Wang P, Liao B, Gong S, et al (2025) Temozolomide promotes glioblastoma stemness expression through senescence-associated reprogramming via HIF1α/HIF2α regulation. Cell Death Dis 16:317. https://doi.org/10.1038/s41419-025-07617-w

23. Adamczyk-Grochala J, Bloniarz D, Zielinska K, et al (2023) DNMT2/TRDMT1 gene knockout compromises doxorubicin-induced unfolded protein response and sensitizes cancer cells to ER stress-induced apoptosis. Apoptosis 28:166–185. https://doi.org/10.1007/s10495-022-01779-0

24. Niklasson M, Dalmo E, Segerman A, et al (2025) p21-Dependent Senescence Induction by BMP4 Renders Glioblastoma Cells Vulnerable to Senolytics. IJMS 26:3974. https://doi.org/10.3390/ijms26093974

25. Mansour MA, Rahman M, Ayad AA, et al (2023) P21 Overexpression Promotes Cell Death and Induces Senescence in Human Glioblastoma. Cancers 15:1279. https://doi.org/10.3390/cancers15041279

26. Liu Y, Feng Y, Cheng L, et al (2025) Profiling with senescence-associated secretory phenotype score identifies GDC-0879 as a small molecule sensitizing glioblastoma to anti-PD1. Cell Death Dis 16:602. https://doi.org/10.1038/s41419-025-07915-3

27. Li L, Huang Y, Gao Y, et al (2018) EGF/EGFR upregulates and cooperates with Netrin-4 to protect glioblastoma cells from DNA damage-induced senescence. BMC Cancer 18:1215. https://doi.org/10.1186/s12885-018-5056-4

28. Yu A, Wang Y, Qin J, et al (2024) Hypoxia-responsive gene *F3* Promotes GBM Cell Proliferation and Migration through Activating NF-κB/p65 Signaling Pathway. J Cancer 15:4477–4489. https://doi.org/10.7150/jca.97357

29. Joachimiak LA, Walzthoeni T, Liu CW, et al (2014) The Structural Basis of Substrate Recognition by the Eukaryotic Chaperonin TRiC/CCT. Cell 159:1042–1055. https://doi.org/10.1016/j.cell.2014.10.042

30. Kim S, Lee D, Lee J, et al (2015) Vaccinia-Related Kinase 2 Controls the Stability of the Eukaryotic Chaperonin TRiC/CCT by Inhibiting the Deubiquitinating Enzyme USP25. Molecular and Cellular Biology 35:1754–1762. https://doi.org/10.1128/MCB.01325-14

31. Yokota S, Kayano T, Ohta T, et al (2000) Proteasome-Dependent Degradation of Cytosolic Chaperonin CCT. Biochemical and Biophysical Research Communications 279:712–717. https://doi.org/10.1006/bbrc.2000.4011

32. Ditzel L, Löwe J, Stock D, et al (1998) Crystal Structure of the Thermosome, the Archaeal Chaperonin and Homolog of CCT. Cell 93:125–138. https://doi.org/10.1016/S0092-8674(00)81152-6

33. Dekker C, Stirling PC, McCormack EA, et al (2008) The interaction network of the chaperonin CCT. EMBO J 27:1827–1839. https://doi.org/10.1038/emboj.2008.108

34. Piano V, Alex A, Stege P, et al (2021) CDC20 assists its catalytic incorporation in the mitotic checkpoint complex. Science 371:67–71. https://doi.org/10.1126/science.abc1152

35. Roobol A, Roobol J, Carden MJ, et al (2014) The chaperonin CCT interacts with and mediates the correct folding and activity of three subunits of translation initiation factor eIF3: b, i and h. Biochemical Journal 458:213–224. https://doi.org/10.1042/BJ20130979

36. Freund A, Zhong FL, Venteicher AS, et al (2014) Proteostatic Control of Telomerase Function through TRiC-Mediated Folding of TCAB1. Cell 159:1389–1403. https://doi.org/10.1016/j.cell.2014.10.059

37. Guenther MG, Yu J, Kao GD, et al (2002) Assembly of the SMRT–histone deacetylase 3 repression complex requires the TCP-1 ring complex. Genes Dev 16:3130–3135. https://doi.org/10.1101/gad.1037502

38. Tang H-W, Weng J-H, Lee WX, et al (2021) mTORC1-chaperonin CCT signaling regulates m^6 A RNA methylation to suppress autophagy. Proc Natl Acad Sci USA 118:e2021945118. https://doi.org/10.1073/pnas.2021945118

39. Hodeify R, Nandakumar M, Own M, et al (2018) The CCT chaperonin is a novel regulator of Ca^{2+} signaling through modulation of Orai1 trafficking. Sci Adv 4:eaau1935. https://doi.org/10.1126/sciadv.aau1935

40. Kim A-R, Choi K-W (2019) TRiC/CCT chaperonins are essential for organ growth by interacting with insulin/TOR signaling in Drosophila. Oncogene 38:4739–4754. https://doi.org/10.1038/s41388-019-0754-1

41. Antona V, Scalia F, Giorgio E, et al (2020) A Novel CCT5 Missense Variant Associated with Early Onset Motor Neuropathy. IJMS 21:7631. https://doi.org/10.3390/ijms21207631

42. Scalia F, Vitale AM, Santonocito R, et al (2021) The Neurochaperonopathies: Anomalies of the Chaperone System with Pathogenic Effects in Neurodegenerative and Neuromuscular Disorders. Applied Sciences 11:898. https://doi.org/10.3390/app11030898

43. Scalia F, Marino Gammazza A, Conway De Macario E, et al (2019) Myelin Pathology: Involvement of Molecular Chaperones and the Promise of Chaperonotherapy. Brain Sciences 9:297. https://doi.org/10.3390/brainsci9110297

44. Gestaut D, Roh SH, Ma B, et al (2019) The Chaperonin TRiC/CCT Associates with Prefoldin through a Conserved Electrostatic Interface Essential for Cellular Proteostasis. Cell 177:751-765.e15. https://doi.org/10.1016/j.cell.2019.03.012

45. Vitale AM, Santonocito R, Vergilio G, et al (2020) Brain Tumor-Derived Extracellular Vesicles as Carriers of Disease Markers: Molecular Chaperones and MicroRNAs. Applied Sciences 10:6961. https://doi.org/10.3390/app10196961

46. Nishimura Y, Yamakawa D, Shiromizu T, Inagaki M (2021) Aurora A and AKT Kinase Signaling Associated with Primary Cilia. Cells 10:3602. https://doi.org/10.3390/cells10123602

47. Liao J, Chen R, Lin B, et al (2024) Cross-Talk between the TGF-β and Cell Adhesion Signaling Pathways in Cancer. Int J Med Sci 21:1307–1320. https://doi.org/10.7150/ijms.96274

48. Yun Liu, Lianrong Yu, Xiaoyan Wu, et al (2017) Silencing CCT6A suppresses cell migration and invasion in glioblastoma in vitro

49. Qiu X, He X, Huang Q, et al (2015) Overexpression of CCT8 and its significance for tumor cell proliferation, migration and invasion in glioma. Pathology - Research and Practice 211:717–725. https://doi.org/10.1016/j.prp.2015.04.012

50. Zhao F, Yao Z, Li Y, et al (2024) Targeting the molecular chaperone CCT2 inhibits GBM progression by influencing KRAS stability. Cancer Letters 590:216844. https://doi.org/10.1016/j.canlet.2024.216844

51. Ghozlan H, Cox A, Nierenberg D, et al (2022) The TRiCky Business of Protein Folding in Health and Disease. Front Cell Dev Biol 10:906530. https://doi.org/10.3389/fcell.2022.906530

52. Leontieva OV, Blagosklonny MV (2016) Gerosuppression by pan-mTOR inhibitors. Aging 8:3535–3551. https://doi.org/10.18632/aging.101155

53. Laberge R-M, Sun Y, Orjalo AV, et al (2015) MTOR regulates the pro-tumorigenic senescence-associated secretory phenotype by promoting IL1A translation. Nat Cell Biol 17:1049–1061. https://doi.org/10.1038/ncb3195

54. Herranz N, Gallage S, Mellone M, et al (2015) mTOR regulates MAPKAPK2 translation to control the senescence-associated secretory phenotype. Nat Cell Biol 17:1205–1217. https://doi.org/10.1038/ncb3225

55. Zeng C, Han S, Pan Y, et al (2024) Revisiting the chaperonin T-complex protein-1 ring complex in human health and disease: A proteostasis modulator and beyond. Clinical & Translational Med 14:e1592. https://doi.org/10.1002/ctm2.1592

56. Trinidad AG, Muller PAJ, Cuellar J, et al (2013) Interaction of p53 with the CCT Complex Promotes Protein Folding and Wild-Type p53 Activity. Molecular Cell 50:805–817. https://doi.org/10.1016/j.molcel.2013.05.002

57. Liao Q, Ren Y, Yang Y, et al (2021) CCT8 recovers WTp53-suppressed cell cycle evolution and EMT to promote colorectal cancer progression. Oncogenesis 10:84. https://doi.org/10.1038/s41389-021-00374-3

58. Liu Y, Chen L, Wang J, et al (2024) Repurposing cyclovirobuxine D as a novel inhibitor of colorectal cancer progression via modulating the CCT3/YAP axis. British J Pharmacology 181:4348–4368. https://doi.org/10.1111/bph.16494

59. Ahmed MdZ, Billah MM, Ferdous J, et al (2025) Pan-cancer analysis reveals immunological and prognostic significance of CCT5 in human tumors. Sci Rep 15:14405. https://doi.org/10.1038/s41598-025-88339-z

60. Cao Y, Xu C, Liu Y, et al (2026) CCT3-mediated regulation of XPO1/RB1 axis stability promotes cellular senescence and tumor progression in clear cell renal carcinoma. iScience 29:114840. https://doi.org/10.1016/j.isci.2026.114840

61. Camasses A, Bogdanova A, Shevchenko A, Zachariae W (2003) The CCT Chaperonin Promotes Activation of the Anaphase-Promoting Complex through the Generation of Functional Cdc20. Molecular Cell 12:87–100. https://doi.org/10.1016/S1097-2765(03)00244-2

62. Kaisari S, Sitry-Shevah D, Miniowitz-Shemtov S, et al (2017) Role of CCT chaperonin in the disassembly of mitotic checkpoint complexes. Proc Natl Acad Sci USA 114:956–961. https://doi.org/10.1073/pnas.1620451114

63. Yokota S, Yanagi H, Yura T, Kubota H (2001) Cytosolic chaperonin-containing t-complex polypeptide 1 changes the content of a particular subunit species concomitant with substrate binding and folding activities during the cell cycle. European Journal of Biochemistry 268:4664–4673. https://doi.org/10.1046/j.1432-1327.2001.02393.x

64. Tracy CM, Gray AJ, Cuéllar J, et al (2014) Programmed Cell Death Protein 5 Interacts with the Cytosolic Chaperonin Containing Tailless Complex Polypeptide 1 (CCT) to Regulate β-Tubulin Folding. Journal of Biological Chemistry 289:4490–4502. https://doi.org/10.1074/jbc.M113.542159

65. Wang G, Zhang M, Meng P, et al (2022) Anticarin-β shows a promising anti-osteosarcoma effect by specifically inhibiting CCT4 to impair proteostasis. Acta Pharmaceutica Sinica B 12:2268–2279. https://doi.org/10.1016/j.apsb.2021.12.024

66. Liu Y-J, Kumar V, Lin Y-F, Liang P-H (2017) Disrupting CCT-β : β-tubulin selectively kills CCT-β overexpressed cancer cells through MAPKs activation. Cell Death Dis 8:e3052–e3052. https://doi.org/10.1038/cddis.2017.425

67. Lin Y-F, Lee Y-F, Liang P-H (2012) Targeting β-tubulin:CCT-β complexes incurs Hsp90- and VCP-related protein degradation and induces ER stress-associated apoptosis by triggering capacitative Ca2+ entry, mitochondrial perturbation and caspase overactivation. Cell Death Dis 3:e434–e434. https://doi.org/10.1038/cddis.2012.173

68. Boudiaf-Benmammar C, Cresteil T, Melki R (2013) The Cytosolic Chaperonin CCT/TRiC and Cancer Cell Proliferation. PLoS ONE 8:e60895. https://doi.org/10.1371/journal.pone.0060895

69. Ghozlan H, Showalter A, Lee E, et al (2021) Chaperonin-Containing TCP1 Complex (CCT) Promotes Breast Cancer Growth Through Correlations With Key Cell Cycle Regulators. Front Oncol 11:663877. https://doi.org/10.3389/fonc.2021.663877

70. Schwarzenbach C, Rinke J, Vilar JB, et al (2025) Therapy-induced senescence of glioblastoma cells is determined by the p21CIP1-CDK1/2 axis and does not require activation of DREAM. Cell Death Dis 16:357. https://doi.org/10.1038/s41419-025-07651-8

71. Vilar JB, Christmann M, Tomicic MT (2022) Alterations in Molecular Profiles Affecting Glioblastoma Resistance to Radiochemotherapy: Where Does the Good Go? Cancers 14:2416. https://doi.org/10.3390/cancers14102416

72. Li L, Huang Y, Gao Y, et al (2018) EGF/EGFR upregulates and cooperates with Netrin-4 to protect glioblastoma cells from DNA damage-induced senescence. BMC Cancer 18:1215. https://doi.org/10.1186/s12885-018-5056-4

73. Riviere-Cazaux C, Carlstrom LP, Neth BJ, et al (2023) An untapped window of opportunity for glioma: targeting therapy-induced senescence prior to recurrence. npj Precis Onc 7:126. https://doi.org/10.1038/s41698-023-00476-8

74. Fletcher-Sananikone E, Kanji S, Tomimatsu N, et al (2021) Elimination of Radiation-Induced Senescence in the Brain Tumor Microenvironment Attenuates Glioblastoma Recurrence. Cancer Research 81:5935–5947. https://doi.org/10.1158/0008-5472.CAN-21-0752

75. Bradshaw A, Wickremsekera A, Tan ST, et al (2016) Cancer Stem Cell Hierarchy in Glioblastoma Multiforme. Front Surg 3:. https://doi.org/10.3389/fsurg.2016.00021

76. Liu W, Lu Y, Yan X, et al (2022) Current understanding on the role of CCT3 in cancer research. Front Oncol 12:961733. https://doi.org/10.3389/fonc.2022.961733

77. Gupta K, Burns TC (2018) Radiation-Induced Alterations in the Recurrent Glioblastoma Microenvironment: Therapeutic Implications. Front Oncol 8:503. https://doi.org/10.3389/fonc.2018.00503

78. Hadizadeh Esfahani A, Sverchkova A, Saez-Rodriguez J, et al (2018) A systematic atlas of chaperome deregulation topologies across the human cancer landscape. PLoS Comput Biol 14:e1005890. https://doi.org/10.1371/journal.pcbi.1005890

79. Babi A, Menlibayeva K, Bex T, et al (2022) Targeting Heat Shock Proteins in Malignant Brain Tumors: From Basic Research to Clinical Trials. Cancers 14:5435. https://doi.org/10.3390/cancers14215435

80. Chen F, Liu C, Jiang R, Wang H (2026) CCT6A Promotes Colon Cancer Cell Proliferation, Migration, and Invasion by Modulating Fatty Acid Metabolism and Activating the TGF-β1/Smad Signaling Pathway. Molecular Carcinogenesis 65:269–282. https://doi.org/10.1002/mc.70070

81. Liao J, Chen R, Lin B, et al (2024) Cross-Talk between the TGF-β and Cell Adhesion Signaling Pathways in Cancer. Int J Med Sci 21:1307–1320. https://doi.org/10.7150/ijms.96274

82. Wang H, Wang X, Xu L, et al (2022) CCT6A and CHCHD2 Are Coamplified with EGFR and Associated with the Unfavorable Clinical Outcomes of Lung Adenocarcinoma. Disease Markers 2022:1–16. https://doi.org/10.1155/2022/1560199

83. Ka M, Condorelli G, Woodgett JR, Kim W-Y (2014) mTOR regulates brain morphogenesis by mediating GSK3 signaling. Development 141:4076–4086. https://doi.org/10.1242/dev.108282

84. Tyler WA, Gangoli N, Gokina P, et al (2009) Activation of the Mammalian Target of Rapamycin (mTOR) Is Essential for Oligodendrocyte Differentiation. J Neurosci 29:6367–6378. https://doi.org/10.1523/JNEUROSCI.0234-09.2009

85. Magri L, Cambiaghi M, Cominelli M, et al (2011) Sustained Activation of mTOR Pathway in Embryonic Neural Stem Cells Leads to Development of Tuberous Sclerosis Complex-Associated Lesions. Cell Stem Cell 9:447–462. https://doi.org/10.1016/j.stem.2011.09.008

86. Wei B, Wang L, Zhao J (2021) Identification of an autophagy-related 10-lncRNA-mRNA signature for distinguishing glioblastoma multiforme from lower-grade glioma and prognosis prediction. gpb 40:257–274. https://doi.org/10.4149/gpb_2021008

87. Wan S, Zhang G, Liu R, et al (2023) Pyroptosis, ferroptosis, and autophagy cross-talk in glioblastoma opens up new avenues for glioblastoma treatment. Cell Commun Signal 21:115. https://doi.org/10.1186/s12964-023-01108-1

88. Pavel M, Imarisio S, Menzies FM, et al (2016) CCT complex restricts neuropathogenic protein aggregation via autophagy. Nat Commun 7:13821. https://doi.org/10.1038/ncomms13821

89. Wang L, Wang L, Li M, et al (2025) Clinical characterization of CCT2 and its role in autophagy regulation during age-related macular degeneration. Sci Rep 15:16849. https://doi.org/10.1038/s41598-025-01907-1

90. Masliah E (2025) Role of the Interplay Between Autophagy and Cell Senescence in the Pathogenesis and Therapeutics of Glioblastoma in the Aging Population. Cells 14:1764. https://doi.org/10.3390/cells14221764

91. Peng N, Kang HH, Feng Y, et al (2023) Autophagy inhibition signals through senescence to promote tumor suppression. Autophagy 19:1764–1780. https://doi.org/10.1080/15548627.2022.2155794

92. Jawhari S, Ratinaud M-H, Verdier M (2016) Glioblastoma, hypoxia and autophagy: a survival-prone ‘ménage-à-trois.’ Cell Death Dis 7:e2434–e2434. https://doi.org/10.1038/cddis.2016.318

93. Boridy S, Le PU, Petrecca K, Maysinger D (2014) Celastrol targets proteostasis and acts synergistically with a heat-shock protein 90 inhibitor to kill human glioblastoma cells. Cell Death Dis 5:e1216–e1216. https://doi.org/10.1038/cddis.2014.182

94. Lee SY (2016) Temozolomide resistance in glioblastoma multiforme. Genes & Diseases 3:198–210. https://doi.org/10.1016/j.gendis.2016.04.007

95. Yaman E, Buyukberber S, Benekli M, et al (2010) Radiation induced early necrosis in patients with malignant gliomas receiving temozolomide. Clinical Neurology and Neurosurgery 112:662–667. https://doi.org/10.1016/j.clineuro.2010.05.003

96. Tomimatsu N, Di Cristofaro LFM, Kanji S, et al (2025) Targeting cIAP2 in a novel senolytic strategy prevents glioblastoma recurrence after radiotherapy. EMBO Mol Med 17:645–678. https://doi.org/10.1038/s44321-025-00201-x

97. Isakova AA, Mazur DV, Antipova NV, et al (2025) Temozolomide-induced senescent glioblastoma cells acquire sensitivity to TRAIL death receptor 5-mediated apoptosis. Med Oncol 43:4. https://doi.org/10.1007/s12032-025-03130-4

98. Sato Y, Kurose A, Ogawa A, et al (2009) Diversity of DNA damage response of astrocytes and glioblastoma cell lines with various p53 status to treatment with etoposide and temozolomide. Cancer Biology & Therapy 8:452–457. https://doi.org/10.4161/cbt.8.5.7740

99. Jia J, Zoeschg M, Barth H, et al (2024) The Chaperonin TRiC/CCT Inhibitor HSF1A Protects Cells from Intoxication with Pertussis Toxin. Toxins 16:36. https://doi.org/10.3390/toxins16010036

100. Carr AC, Khaled AS, Bassiouni R, et al (2017) Targeting chaperonin containing TCP1 (CCT) as a molecular therapeutic for small cell lung cancer. Oncotarget 8:110273–110288. https://doi.org/10.18632/oncotarget.22681

101. Liu B, Peng Z, Zhang H, et al (2025) Regulation of cellular senescence in tumor progression and therapeutic targeting: mechanisms and pathways. Mol Cancer 24:106. https://doi.org/10.1186/s12943-025-02284-z

102. Bartusik-Aebisher D, Tylutki J, Tylutki M, et al (2025) Navigating the Central Nervous System (CNS): A Pharmacokinetic Approach to the Treatment of CNS Tumors, Glioblastoma Multiforme (GBM), in Particular. IJMS 26:9418. https://doi.org/10.3390/ijms26199418

103. Hashemi M, Etemad S, Rezaei S, et al (2023) Progress in targeting PTEN/PI3K/Akt axis in glioblastoma therapy: Revisiting molecular interactions. Biomedicine & Pharmacotherapy 158:114204. https://doi.org/10.1016/j.biopha.2022.114204

104. Weng H, Feng X, Lan Y, Zheng Z (2021) TCP1 regulates PI3K/AKT/mTOR signaling pathway to promote proliferation of ovarian cancer cells. J Ovarian Res 14:82. https://doi.org/10.1186/s13048-021-00832-x

Highlights

- CCT/TRiC is proposed to maintain proteostasis in senescent glioblastoma cells.
- The chaperonin is hypothesized to support glioma stem cell survival and self-renewal.
- CCT/TRiC inhibition is suggested to disrupt mTOR signaling and macroautophagy flux.
- Targeting this axis represents a novel, testable strategy to help prevent relapse.