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Review Article

Rethinking glioma-associated senescence: Drivers of heterogeneity and therapeutic resistance

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Abstract

Cellular senescence, traditionally defined as a stress-induced irreversible cell-cycle arrest program with tumor-suppressive functions in normal somatic cells, exhibits remarkable heterogeneity in malignant gliomas, particularly in glioblastoma (GBM, WHO grade IV). Glioma-associated senescence represents a dynamic and context-dependent cellular state rather than a uniform endpoint and can be broadly categorized into therapy-induced senescence (TIS) and spontaneous senescence (SS) based on induction mechanisms. The phenotypic and functional heterogeneity of glioma-associated senescence is a key driver of intratumoral complexity, adaptive tumor survival, and resistance to conventional glioma therapies, and engages in bidirectional crosstalk with the brain tumor microenvironment to modulate disease progression. In this review, we rethink the current understanding of the core characteristics and multi-dimensional heterogeneity of glioma-associated senescence, including phenotypic, functional, spatial and temporal heterogeneity. We further elaborate on the critical molecular drivers underlying glioma-associated senescence heterogeneity, encompassing alterations in core cell-cycle regulatory pathways, dysregulation of oncogenic signaling including epidermal growth factor receptor (EGFR), phosphoinositide 3-kinase/protein kinase B (PI3K-AKT), and mitogen-activated protein kinase (MAPK) pathways, epigenetic modifications, metabolic reprogramming, and the regulatory role of the tumor microenvironment. We also discuss the senescence-associated secretory phenotype (SASP) as a core functional feature of senescent or senescence-like glioma cells, its composition and functional heterogeneity, and its pivotal role in remodeling the glioma microenvironment and mediating non-cell-autonomous effects in therapy resistance. Additionally, we analyze the dual role of TIS in glioma treatment and the mechanisms by which TIS-associated senescence-like states may contribute to tumor recurrence. Finally, we outline emerging senescence-targeted therapeutic strategies, including senolytics and senomorphics, as well as optimized combination regimens with conventional therapies, and highlight the challenges and future perspectives in translating these strategies into clinical practice. This review aims to provide a comprehensive framework for understanding the biological significance of glioma-associated senescence heterogeneity and to guide the development of innovative precision interventions to overcome therapy resistance and improve clinical outcomes for glioma patients.

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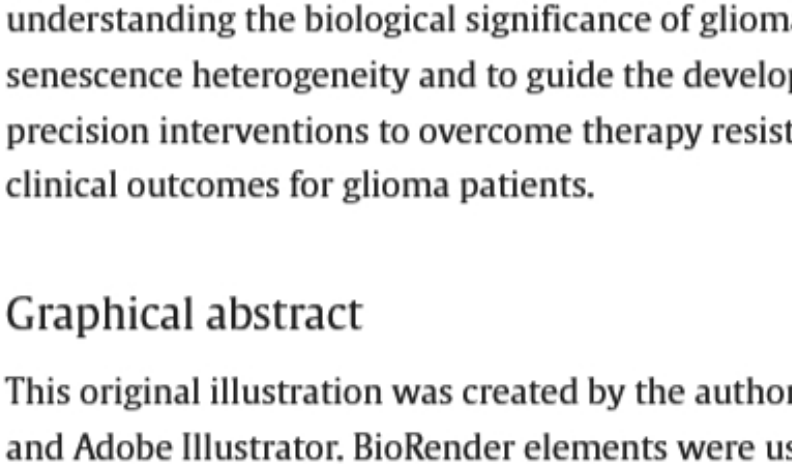

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Introduction

Cellular senescence has traditionally been defined as a stress-induced cellular program characterized by irreversible cell-cycle arrest [[1], [2], [3]], which is typically triggered by telomere attrition [[4], [5], [6], [7], [8], [9]], DNA double-strand breaks, oncogene activation, or oxidative stress. In normal somatic cells, this process serves as a potent tumor-suppressive mechanism by halting the proliferation of damaged or pre-malignant cells [[10], [11]]. However, recent evidence, particularly from single-cell transcriptomic studies in malignant tumors, has challenged this traditional view, demonstrating that senescence in cancer cells—especially in glioma cells—is a highly heterogeneous, dynamic, and context-dependent cellular state, rather than a uniform, static endpoint of irreversible cell-cycle arrest [[12], [13], [14], [15], [16], [17]]. In this review, we use the term "senescent glioma cells" in a broad and context-dependent manner to describe glioma cells displaying senescence-associated features, including cell-cycle arrest programs, DNA damage responses, metabolic remodeling, and SASP activation. However, we acknowledge that cancer cells, including glioma cells, may not always fulfill the strict classical definition of irreversible senescence. Therefore, tumor cells with incomplete, reversible, therapy-induced, or plastic senescence programs are referred to as "senescence-like glioma cells," "senescence-like states," or "senescence-associated phenotypes," depending on the specific context. This distinction is intended to avoid conflating bona fide senescence with quiescence, stem-like states, or transient therapy-induced arrest, and to emphasize that glioma-associated senescence exists along a continuum of arrest depth, plasticity, stemness, and reversibility. The concept of "depth of cell-cycle arrest" refers to the extent to which proliferative inhibition is stably maintained during senescence, ranging from transient p21-dependent arrest to more stable p16/RB-associated senescence states, reflecting a continuum of proliferative restraint rather than a binary condition. This spectrum is associated with variability in metabolic activity, secretory profiles, and potential reversibility, and is influenced by genetic background and tumor microenvironmental context [[18], [19], [20], [21], [22]].

In gliomas, particularly in glioblastoma (GBM, WHO grade IV), glioma-associated senescence displays remarkable diversity and engages in bidirectional crosstalk with the unique brain tumor microenvironment, including hypoxia, gliosis, tumor-associated macrophages, and neural stromal cells, to either suppress or promote disease progression [[23], [24], [25], [26], [27]]. For organizational purposes, this review discusses glioma-associated senescence under two major induction contexts: therapy-induced senescence (TIS) and spontaneous senescence (SS) [[28], [29]]. These terms describe how senescence-associated or senescence-like states arise, rather than defining cellular hallmarks or fixed biological subtypes [[30], [31], [32]]. TIS is primarily induced by anticancer therapies such as radiotherapy and temozolomide (TMZ), the standard-of-care for GBM [[33], [34], [35], [36]], while SS arises from intrinsic stresses including telomere attrition, oncogene activation, and metabolic perturbations [[37], [38], [39], [40]]. These two induction contexts are associated with distinct senescent or senescence-like glioma cell populations, each displaying unique senescence-associated secretory phenotype (SASP) profiles, stress response profiles, and abilities to modulate neighboring tumor cells, stromal cells, and immune cells—with TIS typically exhibiting more robust secretory activity and SS characterized by relatively stable growth arrest [[41], [42], [43], [44]].

This phenotypic heterogeneity of glioma-associated senescence directly contributes to intratumoral complexity by generating diverse tumor cell subpopulations with distinct functional properties [[45], [46], [47], [48], [49]], enables adaptive tumor cell survival under therapeutic stress through phenotypic plasticity and senescence-like states, and drives resistance to conventional glioma therapies—including surgical resection, radiotherapy, and TMZ-based chemotherapy [50], [51], [52]. Clinically, high heterogeneity of glioma-associated senescence in GBM tissues is closely associated with higher recurrence rates and shorter overall survival in patients, highlighting its clinical significance [53], [54]. Additionally, this heterogeneity modulates immune surveillance in the glioma microenvironment, with some senescence phenotypes promoting immune activation and others inducing immunosuppression, further complicating tumor progression and therapeutic responses [55], [56], [57].

In this review, we summarize current knowledge on the phenotypic heterogeneity of glioma-associated senescence, with a particular focus on the molecular, epigenetic, metabolic, and microenvironmental drivers that underlie this heterogeneity. Specifically, we discuss how core cell-cycle regulators, oncogenic signaling, chromatin remodeling, metabolic reprogramming, and brain microenvironmental cues collectively shape diverse senescence phenotypes. We also integrate insights from single-cell transcriptomics and spatial profiling, which have improved our understanding of glioma-associated senescence heterogeneity. We further examine how SASP, as a core senescence-associated feature, remodels the glioma microenvironment and modulates immune surveillance, thereby contributing to therapy resistance. Finally, we discuss emerging senescence-targeted therapeutic strategies and their clinical translation potential, aiming to provide a comprehensive framework for understanding the role of glioma-associated senescence in glioma biology and guiding the development of innovative interventions to overcome therapy resistance and improve patient outcomes. Importantly, given that direct in vivo evidence for bona fide senescent glioblastoma cells after radiotherapy or temozolomide treatment remains limited, we first summarize representative experimental studies that detected therapy-induced senescence or senescence-like features in glioma models, together with the methods used for detection (Table 1).

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Limitations of classic senescence markers in gliomas

Classic senescence markers identified in normal somatic cells, such as p16INK4a, p21, and senescence-associated β-galactosidase (SA-β-gal), are widely used to identify senescent cells [63], [64], [65]. Unlike normal somatic cells, glioma cells often harbor alterations in core senescence pathways, leading to dysregulated expression of these classic markers [66], [67]. For example, p16INK4a is frequently silenced by promoter methylation in GBM, resulting in its low or absent expression in a …

Alterations in core cell-cycle regulatory pathways

The p53-p21 and p16INK4a-RB pathways are the two core cell-cycle regulatory pathways that drive the induction and maintenance of cellular senescence, and their genetic and epigenetic alterations are key molecular drivers of glioma-associated senescence heterogeneity [76]. The p53-p21 pathway is activated in response to DNA damage or oxidative stress, leading to the transcription of p21 and subsequent inhibition of CDKs, thereby inducing cell-cycle arrest. In gliomas, p53 is frequently mutated …

Composition and functional heterogeneity of SASP

SASP is a core functional senescence-associated feature, and its composition and functional heterogeneity are key factors mediating the role of senescent or senescence-like glioma cells in tumor progression and microenvironment remodeling [140], [141]. SASP factors secreted by senescent or senescence-like glioma cells comprise a complex mixture of soluble factors and extracellular vesicles, including cytokines, chemokines, growth factors, MMPs, and proteases, whose composition varies …

Dual roles of TIS in glioma therapy resistance

TIS is a common response of glioma cells to conventional therapies (radiotherapy, TMZ chemotherapy) and targeted therapies, and it plays dual roles in glioma treatment: while TIS initially inhibits tumor growth by inducing cell-cycle arrest, it also contributes to long-term therapy resistance and tumor recurrence, making it a key driver of treatment failure in gliomas [96], [156]. The tumor-suppressive effect of TIS is primarily mediated by the stable or partially stable cell-cycle arrest of …

Core senescence-targeting strategies: senolytics and senomorphics

Targeting senescent or senescence-like glioma cells and their senescence-associated vulnerabilities has emerged as a promising therapeutic strategy to overcome therapy resistance and improve patient outcomes, with two core approaches: senolytics and senomorphics. Senolytics are agents that selectively eliminate senescent cells by targeting their unique vulnerabilities, such as anti-apoptotic dependencies, while sparing non-senescent cells [179]. In gliomas, BCL-2 family anti-apoptotic proteins, …

Discussion and conclusion

Glioma-associated senescence comprises highly heterogeneous, dynamic, and context-dependent cellular states that may range from relatively stable senescent phenotypes to senescence-like or post-treatment plastic states, and these states may contribute to glioma progression, therapy resistance, and tumor recurrence [96], [104]. This review summarizes the current knowledge on glioma-associated senescence, covering their phenotypic characteristics, molecular drivers, interactions with the tumor …

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Ethics approval and consent

This is a review article without involving original experiments, human participants, or animals. Therefore, ethical approval and consent are not applicable. …

Declaration of generative AI use

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Declaration of competing interest

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References (200)

L. Spray *et al.*
Cardiovascular inflammaging: mechanisms, consequences, and therapeutic perspectives
Cell Rep. Med. (2025)

S. Cui *et al.*
Astrocytes in glioblastoma tumor microenvironment
Biochim. Biophys. Acta Rev. Cancer (2026)

G. Torres *et al.*
Genetic origins, regulators, and biomarkers of cellular senescence
Trends Genet. (2024)

M. Hassan *et al.*
Non-genetic heterogeneity and immune subtyping in breast cancer: implications for immunotherapy and targeted therapeutics
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L. Zeng *et al.*
Risk model based on minichromosome maintenance 2 using objective assessment for predicting survival of neuroblastoma
iScience (2023)

J. Yao *et al.*
Human tau promotes Warburg effect-like glycolytic metabolism under acute hyperglycemia conditions
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L. Chibaya *et al.*
Senescence and the tumor-immune landscape: implications for cancer immunotherapy
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M. D'Ambrosio *et al.*
Reshaping of the tumor microenvironment by cellular senescence: an opportunity for senotherapies
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W. Li *et al.*
Cellular senescence triggers intracellular acidification and lysosomal pH alkalinized via ATP6AP2 attenuation in breast cancer cells
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G. Tarantino *et al.*
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S. Yamauchi *et al.*
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A. G *et al.*
Patient-derived organoids and orthotopic xenografts of primary and recurrent gliomas represent relevant patient avatars for precision oncology
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Senescence-associated secretory phenotypes in mesenchymal cells contribute to cytotoxic immune response in oral lichen planus
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Y. Peng *et al.*
Unveiling oncogene-induced senescence: a new frontier in prostate cancer prognosis and therapy
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S. Seo *et al.*
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RAB32 promotes glioma cell progression by activating the JAK/STAT3 signaling pathway
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T. Suter *et al.*
Ligand-specific regulation of a binary enhancer code dictating cellular senescence
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X. Fei *et al.*
Glioma stem cells remodel immunotolerant microenvironment in GBM and are associated with therapeutic advancements
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S. Sun *et al.*
Molecular and clinical characterization of PTRF in glioma via 1,022 samples
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W. Shen *et al.*
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Emerging advancements in metabolic properties of macrophages within disease microenvironment for immune therapy
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A. Domen *et al.*
Prognostic implications of cellular senescence in resected non-small cell lung cancer
Transl. Lung Cancer Res. (2022)

A. Chakrabarty *et al.*
Senescence-induced chemoresistance in triple negative breast cancer and evolution-based treatment strategies
Front. Oncol. (2021)

J.H. Kim *et al.*
Raman spectroscopy in cellular and tissue aging research
Aging Cell (2025)

J. Tkemaladze
Editorial: molecular mechanism of ageing and therapeutic advances through targeting glycative and oxidative stress
Front. Pharmacol. (2023)

K. Ostrowska *et al.*
Senescence in head and neck squamous cell carcinoma: relationship between senescence-associated secretory phenotype (SASP) mRNA expression level and clinicopathological features
Clin. Transl. Oncol. (2024)

Y. Zou *et al.*
Cancer cell-mitochondria hybrid membrane coated Gboxin loaded nanomedicines for glioblastoma treatment
Nat. Commun. (2023)

S.B. Artzi *et al.*
Spatial transcriptomic analysis reveals lack of response to PD-1 blockade in recurrent glioblastoma
Acta Neuropathol. (2025)

X. Chen *et al.*
Dual-targeted delivery of temozolomide by multi-responsive nanoplatform via tumor microenvironment modulation for overcoming drug resistance to treat glioblastoma
J. Nanobiotechnol. (2024)

J.P. Truusalu *et al.*
LSTA1-GBM-2A: study protocol for an exploratory phase 2a randomised controlled trial evaluating tumour-homing peptide certepetide with temozolomide in glioblastoma multiforme
BMJ Open (2025)

R. Xiao *et al.*
Revolutionizing senescence detection: advancements from traditional methods to cutting-edge techniques
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T. Chin *et al.*
The role of cellular senescence in skin aging and age-related skin pathologies
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S. Alqahtani *et al.*
SASP modulation for cellular rejuvenation and tissue homeostasis: therapeutic strategies and molecular insights
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M. Akhtari *et al.*
Autophagy in the cellular consequences of tobacco smoking: insights into senescence
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C. Ravensbergen *et al.*
Association of biological age with tumor microenvironment in patients with esophageal adenocarcinoma
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Senescent skeletal muscle fibroadipogenic progenitors recruit and promote M2 polarization of macrophages
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V. Ramponi *et al.*
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