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Review Article

Cellular Senescence-injury Axis in Traumatic Brain Injury, Spinal Cord Injury, and Ischemic Stroke

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Abstract

Traumatic brain injury, spinal cord injury, and ischemic stroke share secondary pathological processes that may persist beyond the acute insult. Cellular senescence and senescence-like states may contribute to this persistence, but it remains unclear when injury-associated changes represent stable, harmful cell states rather than transient stress responses, and whether their causal relevance is comparable across diseases and cell types. This review compares evidence across cell types and disease stages to address these gaps and examine implications for biomarkers, patient selection, and treatment timing. Evidence strength is disease- and cell-type specific: traumatic brain injury is most consistently associated with chronic glial abnormalities; spinal cord injury provides the clearest mechanistic links among infiltrating macrophages, neurons, and the microvasculature; and ischemic stroke has stronger support in myeloid and neurovascular compartments than in neurons or astrocytes. We use the term senescence-injury axis as a comparative framework for the possibility that persistent injury-induced senescence-related states contribute to secondary tissue dysfunction. However, reliance on single markers, tissue-level associations, and non-cell-specific interventions limits causal inference. Establishing causality requires longitudinal, cell-resolved studies with temporally controlled, cell-specific manipulation, while translation requires biomarkers that identify a persistent, potentially modifiable target state. Overall, the senescence-injury axis is a disease- and cell-type-specific framework for testing mechanisms and guiding therapeutic development, rather than an established universal causal pathway.

Introduction

Traumatic brain injury (TBI), spinal cord injury (SCI), and ischemic stroke are major causes of death and long-term neurological disability. Global Burden of Disease 2021 estimates indicate that TBI accounted for about 20.84 million new cases worldwide, with 37.93 million people living with TBI and approximately 5.48 million years lived with disability. SCI is less common but often leaves persistent motor, sensory, and autonomic deficits; an estimated 15.4 million people were living with SCI in 2021, accounting for more than 4.5 million years lived with disability. Ischemic stroke remains a major source of mortality and disability, with approximately 69.9 million prevalent cases, 7.8 million incident cases, 3.59 million deaths, and 70.4 million disability-adjusted life years in 2021. Despite their different causes, anatomical sites, and clinical manifestations, all three disorders can leave substantial long-term functional impairment. A central unresolved issue is how an acute insult gives rise to pathological changes that persist after the initial injury has passed.[1-3]

Although the primary injury mechanisms of TBI, SCI, and ischemic stroke differ, each initiates an evolving secondary-injury cascade that extends damage beyond the initial insult. Mechanical trauma in TBI and SCI directly disrupts neurons, glia, axons, and vascular structures, whereas ischemic stroke begins with loss of blood flow and bioenergetic failure and may be further complicated by reperfusion injury. These insults converge on ionic imbalance, excitotoxicity, oxidative and mitochondrial stress, sterile inflammation, and disruption of the blood–brain or blood–spinal cord barrier. Cellular debris and damage-associated molecular patterns further activate resident glia and recruit peripheral immune

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cells, reshaping the local inflammatory and reparative environment. Unlike the primary insult, which occurs at or near the time of injury, secondary injury evolves over hours, days, and sometimes months and is potentially modifiable. Yet cell death, oxidative stress, and inflammation alone do not fully explain why viable cells can remain dysfunctional after the initiating insult has subsided. Persistent maladaptive cell states may help account for this gap.[4-9]

One possible explanation for this persistent dysfunction is cellular senescence. In its classical form, senescence is a relatively stable remodeling state induced by sustained or irreparable stress. Proliferative cells show durable cell-cycle arrest together with changes in metabolism, chromatin organization, organelle function, and secretory activity. The injured brain and spinal cord are exposed to several senescence-promoting stresses at the same time, including DNA damage, oxidative and mitochondrial stress, metabolic disturbance, and inflammatory signaling. A subset of surviving cells may retain these features after the acute response has subsided. In glial, immune, and vascular-associated cells with proliferative capacity, the resulting phenotype may resemble classical senescence. Mature neurons require a different interpretation because they are already post-mitotic; persistent DNA damage, metabolic dysfunction, and altered secretory behavior are more appropriately described as a senescence-like state. If such states persist, they could influence immune signaling, tissue repair, and the function of neighboring cells rather than simply marking prior injury. How often this occurs, in which cell types, and at what stage after injury remain open questions.[10-14]

Senescence-related biology has been reported in TBI, SCI, and ischemic stroke, although the strength and cellular localization of the evidence vary across conditions.[4,9,15-20] We compare the evidence across cell types and disease stages, with particular attention to the distinction between association and causation and to the modifying effects of lesion location, age, and biological sex. We also refine the senescence-injury axis into a framework that can be tested experimentally. The aim of this review is to identify when senescence-related states are most likely to become persistent and harmful, what evidence is required to demonstrate a causal role, and how this knowledge could inform biomarkers, patient selection, and treatment timing.

Biological basis of cellular senescence

Figure 1 integrates the multidimensional criteria used to identify senescence-related states with the mechanisms that may maintain them and the cell-type context needed for interpretation.[11,12,21-31]

Induction and core biological features of senescence

Cellular senescence usually develops under sustained or poorly repaired stress. DNA damage, oxidative stress, mitochondrial dysfunction, metabolic disturbance, and inflammatory signaling can all contribute. Acute neurological injury produces several of these insults at once through DNA breaks, ischemia or hypoxia, reactive oxygen species, calcium dysregulation, and sterile inflammation. In proliferative cells, persistent p53-p21 or p16INK4a-RB signaling can maintain cell-cycle arrest and help stabilize a senescent phenotype. These pathways are not specific to senescence, however. Both p16 and p21 also participate in development, tissue homeostasis, repair, and immune regulation, so increased expression must be interpreted in relation to cell identity and the injury context.[5,6,11,13,32,33]

For this reason, senescence should be assessed using several complementary features rather than a single marker or time point. In proliferating cells, persistent resistance to cell-cycle re-entry is a central feature of classical senescence. Additional evidence may include increased senescence-associated β-galactosidase (SA-β-gal) activity, lipofuscin accumulation, loss of Lamin B1, altered mitochondrial or lysosomal function, persistent γH2AX-53BP1 DNA-damage foci, and a senescence-associated secretory phenotype (SASP). Combining proliferative status with structural, metabolic, DNA-damage, and functional readouts improves confidence that the observed state is senescence rather than a transient response to injury.[11,21,22]

None of the commonly used senescence markers is fully specific. SA-β-gal activity can increase in non-senescent cells with high lysosomal activity, and lipofuscin can accumulate simply with age or increased phagocytic load. Their interpretation is stronger when paired with persistent DNA damage, Lamin B1 loss, proliferative status, and a clearly defined cell identity. The same caution applies when distinguishing senescence from quiescence, terminal differentiation, or transient cell-cycle arrest. After acute injury, surviving cells can recover, die, pause temporarily, or remain in a more stable dysfunctional state when stress persists or repair is incomplete. In this context, senescence is better treated as a persistent cell state that emerges in some survivors rather than as another name for the acute stress response.[11,21,22,32,33]

SASP, DNA damage, and propagation of the senescent phenotype

The SASP is particularly relevant to neurological injury because it allows senescent cells to alter their local environment. Its composition depends on cell type, initiating stress, and disease stage and may include IL-1α/β, IL-6, TNF-α, chemokines, matrix metalloproteinases, and vascular regulators. These mediators can recruit immune cells, change glial responses, remodel extracellular matrix, alter vascular function, and, in some settings, induce senescence-related changes in neighboring cells. This provides a mechanism by which a relatively small senescent population could have effects beyond its own abundance. The limitation is specificity: an increase in inflammatory mediators, by itself, does not demonstrate stable senescence.[11,13,14]

Persistent DNA damage is one mechanism that can connect injury-related stress to SASP production. DNA damage can generate micronuclei and cytoplasmic chromatin fragments, activating cyclic GMP-AMP synthase (cGAS)-STING and downstream TBK1, type I interferon, and NF-κB signaling. This pathway links unresolved genomic damage with inflammatory secretion. Because cGAS–STING is also activated during acute tissue injury and sterile inflammation, its activation should be interpreted as part of a broader senescence phenotype rather than as a standalone marker.[23-25]

Mitochondrial dysfunction can reinforce this response. Loss of membrane potential, accumulation of reactive oxygen species, and release of mitochondrial DNA can increase DNA damage and innate immune signaling; persistent inflammation, in turn, adds further mitochondrial and metabolic stress. Such feedback may help maintain a senescent phenotype and its secretory program.

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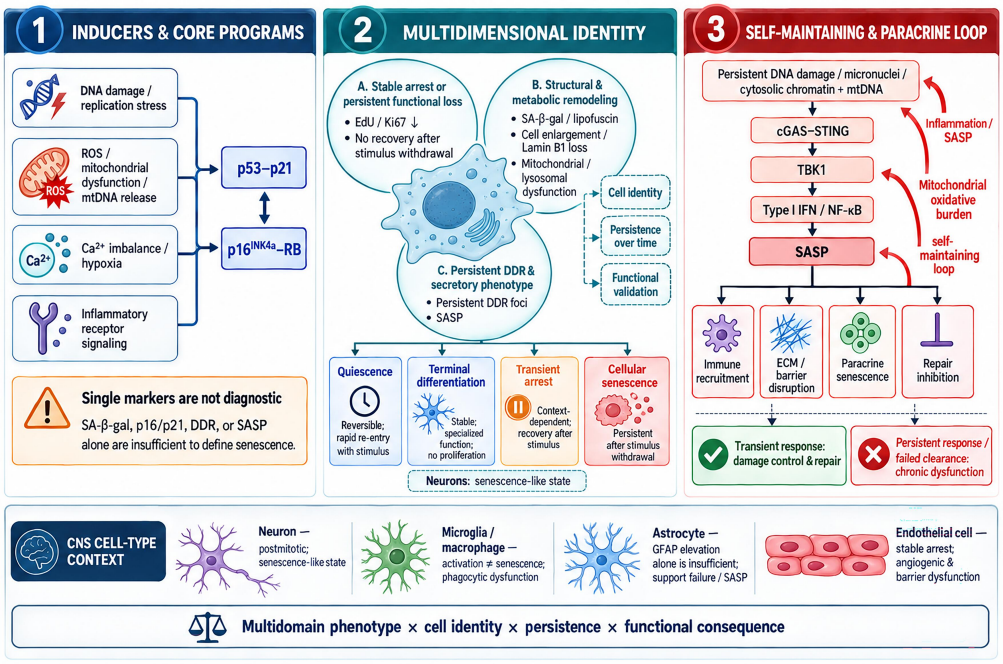


Fig. 1. Multidimensional identification and maintenance of senescence-related states after acute central nervous system injury. Module 1 summarizes injury-related stressors and core senescence pathways. Module 2 shows that a senescence-related state should be inferred from cell identity, persistence beyond the acute stress response, a multidomain phenotype, and a functional consequence; no single marker is diagnostic. Module 3 shows how unresolved injury stress may sustain DNA-damage responses, mitochondrial dysfunction, cGAS-STING/NF-κB signaling, SASP, failed clearance, barrier dysfunction, and impaired repair, forming a potential feedback loop. The separate CNS cell-type context emphasizes that interpretation is cell-type dependent: persistent abnormalities in mature neurons are described as a senescence-like state, whereas activation or reactive states must be distinguished from senescence in glial populations.[11,12,21-31] cGAS, cyclic GMP–AMP synthase; CNS, central nervous system; DDR, DNA-damage response; ECM, extracellular matrix; EdU, 5-ethynyl-2′-deoxyuridine; GFAP, glial fibrillary acidic protein; IFN, interferon; mtDNA, mitochondrial DNA; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; SA-β-gal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1.

Mitochondrial abnormalities and oxidative stress are common to many injury responses, however, and remain nonspecific without cell-state information. The effects of SASP are also spatially constrained: their influence on immune recruitment, extracellular matrix, and barrier function depends on which cells are secreting the factors, when they do so, and where they are located within the lesion.[23-26] In SCI, persistent myelin and lipid debris can impose substantial phagolysosomal and metabolic stress on macrophages, providing an injury-specific example of how the local tissue environment may favor a persistent dysfunctional state.[34,35]

Senescence-related features across central nervous system cell types

Senescence-related phenotypes must be interpreted in the context of cell identity because central nervous system (CNS) cell types differ markedly in proliferative capacity and physiological function. In glial, immune, and vascular-associated cells with proliferative potential, persistent growth arrest can be combined with molecular and functional readouts to support a diagnosis of classical senescence. Mature neurons are terminally differentiated and post-mitotic, so cell-cycle arrest is not a useful defining feature. In this review, persistent neuronal DNA damage, metabolic or lysosomal remodeling, altered secretory signaling, and loss of function are described as a senescence-like state.[11,12,21,22,27-31]

Microglia illustrate the difficulty of distinguishing senescence from a prolonged injury response. They normally survey tissue, clear debris, regulate inflammation, and support synaptic homeostasis, but after injury they also increase Iba1 expression, become hypertrophic, and produce cytokines. None of these changes is specific for senescence. A stronger assignment requires confirmed microglial identity together with persistent senescence-associated features and demonstrable impairment of phagocytic, lysosomal, metabolic, or homeostatic function. Aging and demyelination studies show that lipofuscin accumulation, lysosomal loading, and altered secretory profiles can impair microglial clearance and repair.[27-30] TBI studies have also identified age-like or interferon-enriched microglial states, although it remains uncertain whether these or comparable states after acute neurological injury meet criteria for stable senescence.[36,37]

Astrocytes pose a similar interpretive problem. Their normal functions include ion and neurotransmitter homeostasis, metabolic support, and regulation of the blood-brain barrier (BBB) interface, whereas increased GFAP after injury primarily reflects reactive astrogliosis. An astrocytic senescence phenotype is more convincing when several features occur in the same defined population—

for example, altered proliferative capacity, SA-β-gal activity, p16/p21 expression, Lamin B1 loss, mitochondrial dysfunction, or SASP—together with loss of neuronal or vascular support. Reported phenotypes vary substantially across studies and appear to depend on age, injury model, and the surrounding inflammatory environment.[31,38-42]

Endothelial cells and pericytes offer somewhat clearer functional readouts because persistent dysfunction can be linked directly to barrier integrity and vascular repair. Senescent endothelial cells may show reduced nitric oxide production, impaired migration and angiogenesis, increased adhesion-molecule expression, and greater permeability, all of which can favor leukocyte entry and further tissue injury. In endothelial cells, growth arrest can also be assessed alongside these vascular functions. Even so, co-localization of an endothelial marker with a DNA-damage marker is not enough to define senescence.[43-49]

From acute injury to secondary damage: Formation and amplification of the senescence-injury axis

Figure 2 places the proposed senescence-injury axis within a causal framework and shows the types of evidence needed to distinguish association from a disease-driving cell state.[15,18-22,38,41,42,44,50-54]

Stress responses and cell-fate divergence after acute injury

Mechanical stretching, shearing, and compression in TBI and SCI, and interruption and restoration of blood flow in ischemic stroke, rapidly disturb membranes and cytoskeletal structures and trigger ionic imbalance, calcium overload, excitotoxicity, adenosine triphosphate depletion, and DNA damage. Mechanical forces can also affect the nuclear envelope and chromatin, while reactive oxygen species generated during ischemia-reperfusion add further cellular damage. These events create an upstream environment in which senescence-associated programs can be initiated. Acute energy failure, oxidative stress, or DNA damage by themselves, however, should not be equated with stable senescence.[5-7,9,17]

The initial stress does not lead to a single cell fate. Mildly injured cells may repair and return to homeostasis, severely damaged cells may die, and some survivors may remain transiently arrested or move into a more stable senescent state when damage is not resolved. The defining feature here is persistence: the cell remains alive but its metabolism and function do not return to baseline. For mature neurons, which are already post-mitotic, persistent DNA damage, metabolic abnormalities, and altered secretory activity are better described as a senescence-like state. The relevant transition is thus from a reversible injury response to a durable abnormal state, not simply the persistence of an early injury marker.[10-12,20-22,50]

Mechanisms by which acute injury induces senescence

Several injury-induced stresses can converge on senescence-related programs. Persistent DNA-damage response (DDR) is one important hub. When damage caused by mechanical or ischemic stress is not effectively repaired, ATM/ATR-p53-p21 and p16INK4a-RB signaling can maintain cell-cycle suppression, while Lamin B1 loss and chromatin remodeling further stabilize the phenotype.[11,22-25,32]

Mitochondrial dysfunction can amplify these signals. Calcium overload, impaired electron transport, and reduced antioxidant capacity increase reactive oxygen species and damage DNA, proteins, and lipids. Defective mitochondrial clearance and release of mitochondrial DNA can also activate innate immune pathways. Cytosolic nuclear or mitochondrial DNA can engage cGAS-STING and downstream inflammatory signaling.[23-26] In SCI, mitochondrial DNA escape has specifically been linked to microglial cGAS-STING activation.[55] Barrier breakdown and the accumulation of necrotic cells and myelin debris further increase local immune and phagocytic load. In SCI, macrophages that ingest large amounts of lipid and myelin can develop lipid accumulation, lysosomal dysfunction, impaired clearance, and abnormal inflammatory secretion, creating a local environment that may favor persistence of senescence-related states.[34,35]

These pathways are tightly coupled rather than independent. DDR can feed mitochondrial stress and cytosolic DNA sensing, while changes in the local tissue environment can reinforce each of them. What matters for senescence is not their transient activation during the acute phase, but whether they remain unresolved long enough to stabilize an abnormal state in surviving cells.[23-26,55]

From transient stress to stable senescence: Thresholds, time windows, and susceptibility

For practical purposes, the ‘senescence threshold’ can be defined as the point at which a reversible stress response becomes persistent. In proliferative CNS-associated cells, evidence that this threshold has been crossed would include failure to re-enter the cell cycle after the initiating stress has been removed, together with sustained signs of damage or remodeling such as γH2AX/53BP1 foci, Lamin B1 loss, chromatin changes, SA-β-gal activity, or lipofuscin accumulation. Molecular evidence should be accompanied by a lasting functional abnormality, such as abnormal SASP production, impaired phagocytosis or efferocytosis, barrier dysfunction, or loss of trophic support, and the phenotype should remain detectable in the same defined cell population over time. No individual marker can establish this transition. In post-mitotic neurons, the cell-cycle criterion is not applicable; persistent DDR, metabolic or lysosomal remodeling, altered secretory signaling, and measurable functional impairment provide a more appropriate basis for defining a senescence-like state.[11,12,21,22]

Current data are too sparse to define a universal timetable for this transition. After TBI, DDR and related stress responses can be detected within hours to days, whereas the better-supported glial senescence-related phenotypes generally emerge weeks later, often between about 5 weeks and 4 months. Repeated mild TBI can produce neuronal senescence-like transcriptional features by approximately 7 days. In SCI, neuronal and endothelial abnormalities have been reported from roughly 3 to 14 days and can persist for weeks, while astrocytic remodeling appears more prominent later. After ischemic stroke, senescence-associated signals may be detectable within 24 hours and continue to evolve through the first 1–2 weeks, particularly in myeloid and vascular compartments. These intervals are best used to guide serial sampling rather than as diagnostic cutoffs.[18,19,36,38-40,45-47,54-58]

When persistence develops may also depend on injury severity and repetition, debris clearance, and lesion context.[56,59] Age and biological sex may further modify this transition.[48,49,57,60-62]

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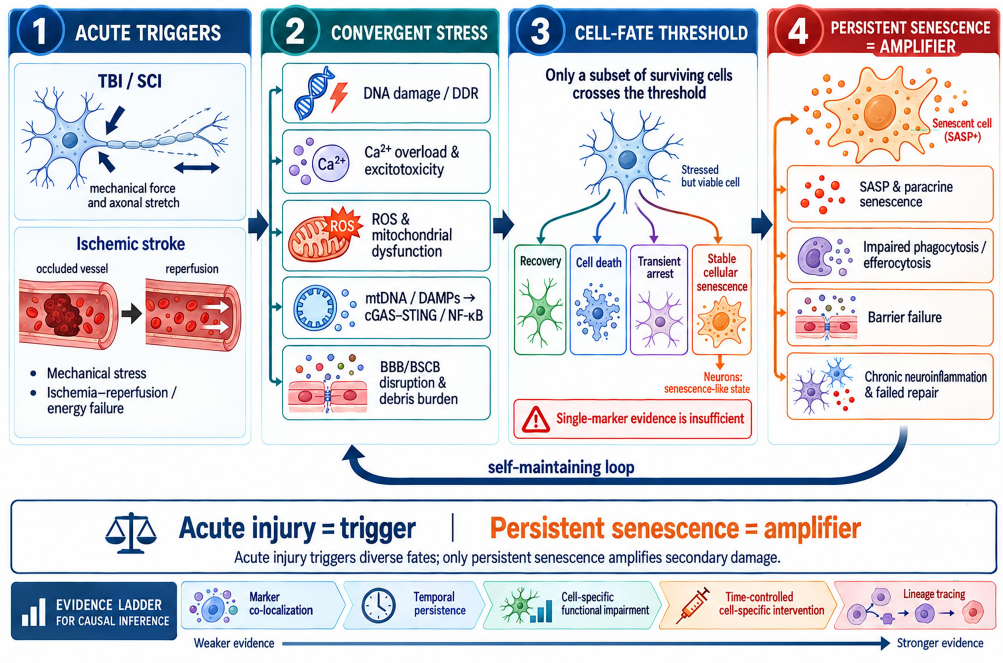


Fig. 2. Mechanistic model and causal evidence for the senescence-injury axis. Steps 1–4 illustrate how acute injury generates convergent cellular stress and divergent cell fates. A subset of surviving cells may enter a persistent senescent or senescence-like state whose secretory and functional outputs amplify secondary tissue dysfunction; the feedback arrow denotes a proposed, context-dependent relationship that requires stronger causal validation. The framework predicts that suppressing upstream stress should reduce later formation of persistent states, whereas delayed, cell-specific clearance or reprogramming should improve chronic tissue function if those cells are active drivers. The evidence ladder shows that causal inference becomes stronger as marker co-localization is complemented by temporal persistence, cell-specific functional impairment, temporally controlled cell-specific intervention, and lineage or fate tracing. Disease-specific tests include distinguishing persistent glial activation from stable senescence in TBI, resolving lesion-core, perilesional, and remote spatial dynamics in SCI, and separating pre-existing vascular aging from injury-induced senescence after ischemic stroke.[11,12,15,18-22,38,41,42,44,50-54] BBB, blood–brain barrier; BSCB, blood–spinal cord barrier; cGAS, cyclic GMP–AMP synthase; DAMPs, damage-associated molecular patterns; DDR, DNA-damage response; mtDNA, mitochondrial DNA; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; SCI, spinal cord injury; STING, stimulator of interferon genes; TBI, traumatic brain injury.

Distinguishing transient stress from senescence requires more than a single late time point. Serial measurements should cover the early response, the suspected transition period, and a later persistence phase. Recovery or washout experiments are especially informative when they are feasible: a phenotype that disappears after the initiating stress is removed is more consistent with reversible activation, whereas continued dysfunction in the same cell population argues more strongly for senescence or a senescence-like state.[19,21,22]

Senescence is also heterogeneous in origin and duration. In the setting of acute neurological injury, stress-induced premature senescence is the most relevant framework because the initiating event is an acquired mechanical or ischemic insult rather than progressive telomere-driven replicative exhaustion. Developmental senescence is mechanistically distinct and is not the focus of this review. Even within injury-induced states, transient senescence-associated programs may contribute to wound containment or repair, whereas persistent states that remain after the acute response has resolved are more likely to be maladaptive. Current evidence does not yet support a stable molecular taxonomy of senescence subtypes across TBI, SCI, and ischemic stroke; therefore, duration, cell identity, initiating stress, and functional consequence should be reported explicitly rather than assuming that all senescence-associated cells are biologically equivalent.[10,11,13,15]

From injury consequence to secondary driver: Maintenance and amplification of senescent states

Once such a state persists, senescence may become part of the machinery that maintains secondary injury rather than simply a consequence of the original insult. SASP mediators such as IL-1, IL-6, TGF-β, and matrix metalloproteinases can alter immune-cell recruitment, extracellular matrix, vascular function, and neighboring cell states.[13,14] Endothelial dysfunction can increase barrier permeability and leukocyte infiltration,[43,44,46,47] while dysfunctional glia can impair neural repair and remyelination.[30] Even a relatively small number of persistently abnormal cells could influence a much larger tissue compartment.

Failure to clear damaged material may further reinforce this loop. Myeloid cells normally remove dying cells and tissue debris, but a sustained burden of myelin, lipid, and cellular remnants can produce phagolysosomal and metabolic dysfunction and perpetuate inflammation and impaired repair.[34,35] In SCI, macrophage-derived TGF-β1-SMAD2 signaling can promote neuronal senescence-like changes.[63] KDM6A/MMP-3-related

macrophage senescence has also been linked to impaired regenerative signaling.[64] Endothelial senescence is regulated in part by KDM6A/UTX-related mechanisms.[46,47] In parallel, UTX-dependent immune–vascular crosstalk can alter blood–spinal cord barrier permeability and macrophage polarization.[65,66] Together, these findings support a broader intercellular network in which senescence-related changes may interact with non-senescence-specific immune–vascular signaling.

The dominant feedback mechanisms differ among the three diseases. Chronic glial abnormalities are prominent in TBI.[36,38] SCI is characterized by a heavy myelin-debris burden and relatively well-defined macrophage-neuron-endothelial crosstalk.[35,46,47,59,63,64] Ischemic stroke combines energy failure and reperfusion-associated oxidative stress with substantial myeloid involvement and age-related neurovascular dysfunction.[18,19,43,44,48,49,52,53] For this reason, the senescence-injury axis is better viewed as a disease-modified network than as a single pathway. Importantly, co-localization of a senescence marker with a cell-type marker does not establish that the cell is senescent, nor does it show that the state drives tissue injury. A causal link requires evidence that the phenotype persists in a defined cell population and that temporally controlled, cell-specific manipulation of that population or one of its effector pathways changes downstream pathology.[21,22] Lineage tracing can further test whether chronic senescence-related populations arise from cells exposed to the original injury.

Relationship to conventional secondary-injury pathways

Much of the senescence-injury axis overlaps with established secondary-injury biology. The distinction lies less in the upstream pathways than in what happens to the cells that survive them. Oxidative stress, mitochondrial dysfunction, excitotoxicity, sterile inflammation, and barrier disruption can be transient and can occur in cells that ultimately recover or die.[5-7] The senescence-injury axis focuses instead on cells that remain viable but are durably remodeled after the acute trigger has waned. In this model, conventional secondary-injury pathways can drive the formation of senescent cells, whereas established senescent cells can subsequently sustain inflammation, defective clearance, metabolic stress, and vascular dysfunction.[10,11,13-15] This difference can be tested experimentally: an intervention directed at an acute upstream pathway should mainly reduce the later emergence of senescent cells, whereas delayed clearance or reprogramming of those cells should still improve chronic tissue function if they are active drivers rather than residual markers of injury.[67-70]

Aging and biological sex as modulators of the senescence threshold

Age changes the biological starting point at which an acute injury occurs. Before injury, the aging central nervous system already shows greater DNA damage, mitochondrial dysfunction, vascular fragility, impaired proteostasis, and a higher burden of senescent cells. The same insult may therefore have very different consequences in a young and an older brain or spinal cord. This is particularly relevant to ischemic stroke, because endothelial senescence and other features of neurovascular aging may predate the vascular event, increase susceptibility to ischemia, and limit subsequent repair. Age-matched sham controls are needed to separate this background burden from newly induced changes; pre-injury measurements or contralateral tissue can provide additional context when biologically appropriate.[10,13,48,49]

Biological sex may also shift the response, although the direction and magnitude are likely to vary by cell type and injury model. Sex chromosomes, gonadal hormones, immune responses, vascular biology, and DNA-damage handling all offer plausible mechanisms.[60] Sex-dependent senescence signatures have been reported after repeated mild TBI.[57] Sexual dimorphism has also been described after SCI and ischemic stroke.[61,62] Progesterone has been extensively investigated in acute TBI, but clinical evidence has not established a treatment benefit.[71] Studies designed around both sexes, with hormonal status considered where relevant, are needed to determine whether sex changes the timing, cellular distribution, or molecular profile of senescence-related states.

Senescence-related changes after acute neurological injury: Disease-specific evidence

Traumatic brain injury

Early TBI studies relied mainly on tissue-level measurements of SA-β-gal, p16/p21, DDR markers, and SASP. Repeated mild TBI can increase p21, p53, and 53BP1 at early time points, often alongside cognitive deficits, but both the magnitude and timing vary with age and injury paradigm. These observations establish a senescence-related molecular response to TBI, not the identity of the cells carrying it or a causal role for senescence in the neurological phenotype.[17,56,58]

In neurons, repeated mild TBI has been associated with DNA double-strand breaks, oxidative damage, R-loop accumulation, and p16/p21- and cGAS–STING-related transcriptional changes. ABT263 reduced several of these markers and improved cognitive performance in male mice. Because cell localization remains incomplete and the intervention was not neuron specific, these findings support a neuronal senescence-like state rather than classical neuronal senescence, and they do not yet show that this state directly causes long-term cognitive impairment.[57,58]

The chronic glial evidence is more substantial. Weeks to months after TBI, Iba1- or GFAP-positive cells can co-express p16/p21, alongside persistent inflammation and increased tissue SASP. Delayed dasatinib plus quercetin (D+Q) treatment reduces neurodegeneration and improves long-term behavioral outcomes.[38] Long-term models also show lipofuscin accumulation, altered iron handling, and increased lysosomal burden, some of which can be partially reversed after microglial depletion and repopulation.[36] Altered microglial lipid-droplet metabolism has also been reported after TBI.[72] These observations are compatible with persistent senescence-related dysfunction, but an age-like, exhausted, or otherwise reversible glial state remains a plausible alternative explanation. Many studies also fail to distinguish resident microglia clearly from infiltrating macrophages. Evidence for endothelial senescence after TBI is much weaker and rests largely on vascular co-localization with DNA-damage markers rather than multidimensional phenotyping or cell-specific intervention.[45]

The main interpretive difficulty in TBI is the overlap between chronic glial activation and senescence. Increased Iba1 or GFAP, cellular hypertrophy, inflammatory cytokines, and even p16/p21 expression can all occur in reactive cells and therefore cannot,

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alone or in simple co-localization, distinguish activation from senescence. A stronger assignment would require several senescence-associated features to persist within a defined glial population after the acute inflammatory response has begun to resolve, together with loss of normal microglial or astrocytic function and evidence that the phenotype is not readily reversible. Delayed D+Q treatment and microglial depletion show that chronic glial abnormalities are functionally relevant, but neither approach identifies a senescent glial population as the causal target. More decisive experiments would combine longitudinal phenotyping with resident-microglia-specific or astrocyte-specific inducible genetic manipulation, while separately tracking infiltrating macrophages. Lineage or fate-mapping approaches could then determine whether cells that acquire the chronic phenotype derive from populations exposed to the original injury. Such studies are needed before chronic glial reactivity after TBI can be interpreted as causal cellular senescence rather than persistent activation or functional exhaustion. This distinction is particularly important because STING/type I interferon signaling can be activated in microglia and peripheral immune cells after TBI, including in aged animals, without by itself demonstrating a stable senescent state.[21,22,37,73-75]

The TBI literature supports a temporal distinction between early injury responses and later glial abnormalities, but the strength of evidence varies by cell type. Neuronal findings are consistent with a senescence-like state, chronic changes in microglia/macrophages and astrocytes are better supported, and endothelial evidence remains limited.[36,38,45,56-58]

Spinal cord injury

SCI provides some of the strongest mechanistic evidence among the three disorders reviewed here. Cell-localized senescence-related phenotypes have been linked to functional deficits and, in several studies, to pathway-specific interventions. This fits the biology of SCI, where recovery depends on debris removal, control of inflammatory-cell infiltration, preservation of neuronal function, and restoration of the blood-spinal cord barrier. Failure in one compartment can influence several others, creating conditions in which persistent abnormal states may be maintained across cell types.[9,34,35,39,40,46,47,50,59,63-66]

Neuronal senescence-like changes after SCI are supported by relatively detailed temporal and localization data. SA-β-gal, p16, and γH2AX have been detected from several days to weeks after injury, with a subset of positive cells co-localizing with NeuN. ABT263 or D+Q treatment improved white-matter preservation and sensorimotor recovery. More direct mechanistic evidence comes from macrophage-derived TGF-β1-SMAD2 signaling: macrophage depletion or SMAD2 inhibition reduced the neuronal senescence-like phenotype and improved outcome, supporting a functional link between myeloid cells and injured neurons.[50,63]

Within the myeloid compartment, the strongest evidence concerns infiltrating or bone-marrow-derived macrophages. Uptake of large amounts of lipid and myelin debris produces foamy macrophages with lipid-droplet accumulation, DNA damage, increased SA-β-gal activity and SASP, and impaired efferocytosis. Exendin-4 improves efferocytosis.[34,35] KDM6A/UTX-MMP-3 signaling contributes to macrophage senescence and influences neighboring endothelial cells; macrophage-specific UTX deletion reduces macrophage senescence and promotes vascular and neurological repair.[64] These experiments place infiltrating macrophages at an important point in the propagation of senescence-associated signals after SCI. The same conclusion cannot yet be extended to the entire myeloid compartment because resident microglia and infiltrating macrophages share many markers and transcriptional features.[59]

Astrocytes may also undergo persistent senescence-related remodeling after SCI. Age/TNF-YAP signaling and the more recently described Ski-KLF4-JAK2/STAT3 pathway provide mechanistic support for this possibility, particularly in the chronic phase. The evidence, however, comes from a limited number of studies and has not yet been independently replicated across models.[39,40]

Evidence for microvascular endothelial senescence after SCI is also relatively strong. Increased endothelial KDM6A/UTX has been associated with higher SA-β-gal activity and p16/p21 expression, reduced Lamin B1, and impaired migration and tube formation. Endothelium-specific UTX deletion, restoration of CNN1, and local D+Q delivery can partially restore vascular function.[46,47] Work implicating UTX-Top2β points to an endothelial-intrinsic epigenetic mechanism.[47] By contrast, macrophage-associated KDM6A/UTX signaling and endothelial–macrophage crosstalk may provide extrinsic influences on the vascular environment.[64-66] The endothelial phenotype may therefore reflect both cell-intrinsic regulation and the surrounding immune environment.

Spatial context in SCI remains poorly resolved and is likely to determine where the proposed senescence-injury axis is most relevant. The lesion core contains extensive tissue destruction, hemorrhage, debris, and cell death, so senescence markers measured there may largely reflect severe acute damage or infiltrating cells rather than a stable state in viable resident cells. By contrast, the peri-lesional rim retains neurons, glia, vascular cells, and infiltrating myeloid cells and is therefore a more plausible site for persistent macrophage-neuron-endothelial interactions. Remote segments can develop later inflammatory and metabolic abnormalities despite limited exposure to the initial mechanical insult, raising the possibility that they reflect propagation of secondary signals rather than local induction alone. Whole-cord measurements can obscure these differences and may generate an averaged time course that does not represent any single compartment. Spatially resolved profiling of the core, lesion border, and remote tissue, combined with cell-specific perturbation and lineage analysis, will be needed to determine whether senescence-related states arise independently in each region or spread through intercellular signaling, and whether disrupting a defined compartment alters pathology in adjacent or remote tissue.[9,40,46,47,50,59]

SCI provides the clearest current example of senescence-related pathology spanning several cell types, particularly the link between infiltrating macrophage dysfunction, neuronal senescence-like changes, and microvascular injury. Astrocytes may also contribute, but the evidence is less mature. The strong spatial heterogeneity of the injured cord remains an important limitation when interpreting these interactions.[39,40,46,47,50,59,63,64]

Ischemic stroke

After ischemic stroke, an important question is why some viable cells remain dysfunctional even after blood flow is restored.

Energy failure, excitotoxicity, and oxidative stress rapidly provoke neuroinflammation, neurovascular-unit injury, and impaired repair, while reperfusion status and age modify these responses. Senescence-related signals can emerge early, but their distribution and persistence differ across lesion regions and age groups.[5-7,18-20]

Histological and time-course studies have reported changes in SA-β-gal, p16/p21, Chk1/Chk2, Lamin B1, and SASP from approximately 24 hours to 14 days after stroke, with different markers peaking at different times. Similar signals have been observed in human brain tissue, but cell of origin, premorbid disease, and postmortem interval complicate interpretation. These studies support the presence of a sustained senescence-related environment after stroke; they do not, by themselves, demonstrate that a particular cell population has entered stable senescence.[18-20]

Several studies have reported neuronal co-localization of NeuN with p16 or p21-related signals, although subcellular localization and baseline expression have not been fully consistent. Given the post-mitotic nature of mature neurons, these findings are best described as a neuronal senescence-like state. Persistent DNA damage and defective repair may contribute, but a direct role in post-stroke pathology remains uncertain because neuron-specific causal interventions are lacking.[12,18-20]

Among post-stroke cell populations, myeloid cells have received the most attention. In aged mice, small extracellular vesicles derived from induced pluripotent stem cells reduce senescence-associated markers and alter myeloid inflammatory responses through TGF-β1-Rictor/pAKT signaling, with accompanying neurological improvement. Targeted exosome delivery to CD86-positive myeloid cells likewise reduces p21-positive cells, barrier leakage, and neutrophil infiltration. Because p21 and CD86 are also expressed by activated cells, these findings fit a senescence-related myeloid state more securely than classical senescence. Single-cell and bulk transcriptomic studies have also identified myeloid subpopulations with high senescence-gene-set scores, but these scores are best treated as a way to nominate candidate states. Histological and intervention data together support substantial senescence-related myeloid changes, particularly in aged models, while the relative contributions of resident microglia and infiltrating macrophages remain unresolved.[19,52,53,76]

Evidence in astrocytes is less consistent and differs between *in vitro* and *in vivo* systems. Oxygen-glucose deprivation/reoxygenation can induce SA-β-gal, p16, and SASP changes in primary astrocytes, whereas *in vivo* co-localization of GFAP with p16 or p21 has varied across studies. Astrocytes may acquire senescence-related features after stroke, but current *in vivo* data do not yet define a stable, cell-specific senescent population.[18,19,41,42]

Brain endothelial cells have comparatively stronger support. Photothrombotic stroke models show vascular SA-β-gal activity, CD31-p21 co-localization, and reduced eNOS function, while interventions that improve endothelial function can also improve senescence-related vascular phenotypes and barrier permeability. Other studies indicate that restoring BBB function in aged animals or locally eliminating senescence-associated cells can reduce vascular and neural injury. Because several of these interventions are not endothelial specific, it remains uncertain how much of the benefit is mediated directly through senescent endothelial cells.[42-44,48,49]

Interpretation after stroke is further complicated by the condition of the neurovascular unit before ischemia occurs. Older animals and patients may already have endothelial senescence, impaired BBB transport, reduced vascular repair, and age-related changes in pericytes and other vascular cells. These pre-existing abnormalities can increase susceptibility to ischemia and can also make post-stroke senescence appear greater than the injury-induced component actually is. Neurovascular aging therefore needs to be treated as part of the baseline rather than inferred from post-stroke marker levels alone. Age-matched sham groups are essential, and studies in aged models should compare pre-existing or contralateral vascular states with the evolving ipsilateral lesion across multiple time points. Where feasible, inducible senescence reporters or lineage-labeling strategies initiated before injury could help distinguish cells that were already senescence-associated from those that acquire a persistent phenotype after ischemia-reperfusion. Cell-specific endothelial perturbation would then be required to determine whether the newly induced component, the pre-existing component, or both contribute causally to BBB failure and neurological outcome.[43,48,49]

On balance, the strongest stroke evidence lies in myeloid cells and brain endothelium, with less cell-specific support for neurons and astrocytes. Both lesion location and the pre-injury aging state affect how these findings should be interpreted. The infarct core is dominated by irreversible cell death and intense inflammation, whereas the penumbra contains more viable cells capable of entering a persistent abnormal state. A convincing injury-induced senescence phenotype should therefore show a change beyond the age-matched baseline, persist within a defined viable cell population, and ideally respond to a temporally and cell-specific intervention. Without those elements, post-stroke increases in p16/p21, DDR, SASP, or vascular dysfunction remain compatible with pre-existing vascular aging or prolonged injury responses rather than newly established causal senescence.[18-20,41-44,48,49,52,53,76]

Figure 3 summarizes the relative strength of cell-specific evidence across the three disorders, while Table 1 provides the corresponding study-level details and limitations.[18,19,35,36,38-47,50,52,53,56-59,63,64,76]

From mechanisms to therapy: Strategies, timing, and translational barriers

Figure 4 integrates therapeutic strategy, biological timing, biomarker-guided patient enrichment, and proof-of-mechanism considerations for clinical translation.[38,44,46,50,52,54,67-70,77,78]

Therapeutic strategies: From cell clearance to functional reprogramming

Senolytics have attracted the greatest attention because they offer a direct way to reduce the burden of senescence-associated cells. Navitoclax and D+Q, for example, improve several histological and functional outcomes in experimental neurological injury. Their interpretation is less straightforward than the term ‘senolytic’ implies. These compounds are not restricted to a single senescent population and can also affect inflammatory, vascular, or survival pathways. A reduction in p16/p21 or SASP accompanied by behavioral improvement therefore does not, by itself, show that selective elimination of senescent cells produced the benefit. Studies intended to support senolysis as a mechanism should identify which cell

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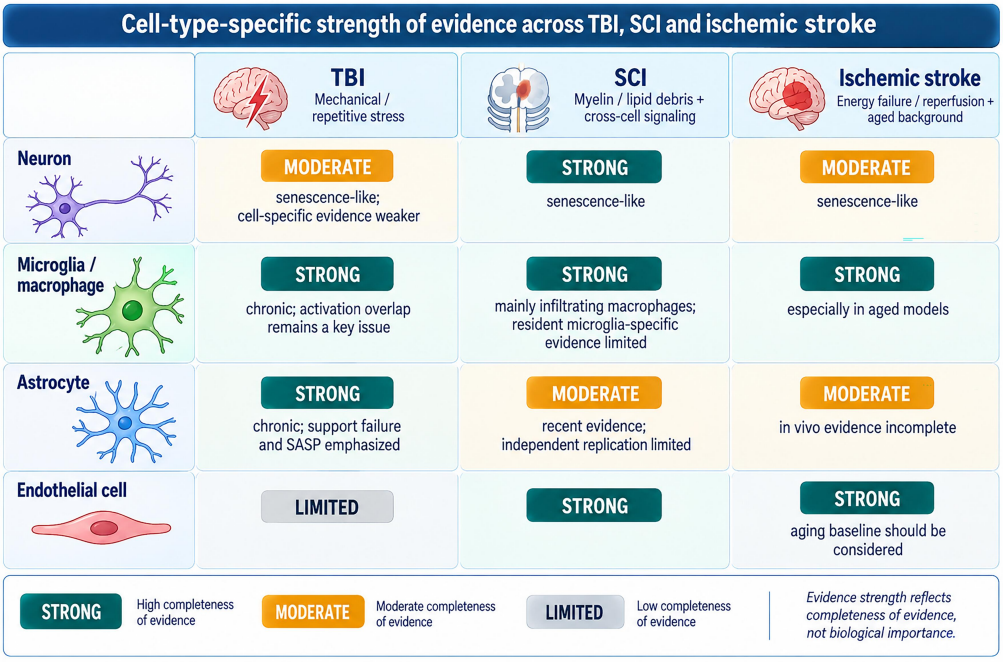


Fig. 3. Relative strength of cell-type-specific evidence for senescence-related states in TBI, SCI, and ischemic stroke. Evidence categories reflect the completeness of the evidence chain rather than the presumed biological importance of a cell type. Strong evidence combines cell-resolved, multidomain phenotyping with temporal persistence and functional or causal support. Moderate evidence is reproducible or mechanistically informative but lacks complete cell-specific causality or independent replication. Limited evidence is based mainly on tissue-level associations, marker co-localization, or small datasets. Neuronal findings are described as senescence-like rather than classical senescence. In SCI, the strongest myeloid evidence derives mainly from infiltrating macrophages; SCI astrocytes and ischemic-stroke astrocytes are graded as Moderate, consistent with Table 1.[18,19,35,36,38-47,50,52,53,56-59,63,64,76] SASP, senescence-associated secretory phenotype; SCI, spinal cord injury; TBI, traumatic brain injury.

population is lost, demonstrate that the relevant senescence phenotype is reduced in that population, and relate this change to the downstream tissue response.[38,41,42,50,54,67-69]

For some CNS cell types, altering the dysfunctional state may be preferable to eliminating the cell. Senomorphics suppress harmful outputs of senescence-associated cells without necessarily inducing cell death, with NF-κB, JAK/STAT, mTOR, and cGAS-STING among the pathways of interest. This distinction is particularly relevant to neurons and endothelial cells, where broad depletion could carry an obvious functional cost. Experimental work that restores efferocytosis in foamy macrophages after SCI, or improves myeloid and blood-brain barrier function after stroke, supports the broader principle that recovery of cell function can be therapeutically meaningful even when the abnormal population is not removed.[35,43,68-70,76]

A clinically realistic strategy may ultimately combine these approaches rather than rely on one class of senotherapeutic. Early neuroprotective or anti-inflammatory treatment could reduce the number of cells that enter a persistent abnormal state, whereas a later senolytic or senomorphic intervention could be reserved for cells that fail to recover. The sequence matters because inflammatory and secretory responses that are harmful when prolonged can still contribute to debris clearance and repair early after injury. Cellular and regional targeting may help separate these phases. Targeted extracellular vesicles, local hydrogel delivery, and photobiomodulation have already been used experimentally to restrict where an intervention acts, although none currently provides true senescent-cell specificity. The more plausible translational goal is therefore not broad senolysis throughout the nervous system, but selective modification of a defined dysfunctional cell population at a stage when its persistence has become maladaptive.[10,44,46,50,52,67-70]

Therapeutic timing: From early stress to persistent pathology

Timing is another unresolved variable. Early after injury, cell death, inflammation, debris clearance, and tissue repair occur simultaneously, and transient cell-cycle arrest or secretory responses may be adaptive. Indiscriminate removal of senescence-associated cells, or broad suppression of SASP, could interfere with these early repair processes. Senescence-directed treatment therefore cannot simply follow a 'the earlier, the better' rule.[10,13,50,67-70]

A different rationale may apply once a persistent abnormal population has formed. Senolytics could be most useful after pathological senescence is established but before secondary damage becomes irreversible. Senomorphics and functional reprogramming may permit a broader window because they do not necessarily eliminate the target cell. In practice, the relevant treatment window is likely to depend more on the biological state of the target population than on a fixed number of hours or days after injury.[10,13,38,50,54,67-70]

Delayed treatment already has some preclinical support. D+Q

Table 1. Cell-type-specific evidence of senescence-related states in TBI, SCI, and ischemic stroke

Disease	Cell type	Direct evidence/level	Main temporal dynamics	Core markers	Functional consequences/interventions	Key limitations and references
TBI	Neuron	Moderate; senescence-like	~7 d after rmTBI; some signals persist to 35 d	DDR, R-loop, p16/p21, cGAS–STING; transcriptional changes	ABT263 improved cognition in male mice; intervention was not neuron specific	Limited cell localization; tissue-level markers cannot be assigned to neurons[56-58]
TBI	Microglia/Macrophages	Strong in chronic phase; limited in acute phase	5 weeks to 4 months; age-like profile reported up to 1 year	Iba1 + p16/p21, lipofuscin, lipid/iron accumulation, lysosomal burden	D+Q and microglial depletion/repopulation reduced chronic neurodegeneration and improved long-term outcomes	D+Q is not cell specific; age-like or exhausted states may be reversible and are not synonymous with senescence[36,38]
TBI	Astrocytes	Strong in chronic phase; limited in acute phase	Increases reported from 5 weeks to 4 months; acute 24-h data mainly reflect DDR	GFAP + p16/p21; acute GFAP + γH2AX	D+Q reduced tissue SASP and improved long-term outcomes	No astrocyte-specific clearance; acute γH2AX alone is insufficient[38]
TBI	Endothelium	Limited	~4 weeks after severe TBI	CD31/PECAM-1 + γH2AX	No endothelial-specific intervention	Small datasets and mainly DNA-damage co-localization[45]
SCI	Neuron	Strong; senescence-like	3–60 d	NeuN + SA-β-gal/p16/γH2AX; TGF-β1-SMAD2	ABT263/D+Q and SMAD2 blockade improved recovery	Post-mitotic neurons are classified as senescence-like rather than classically senescent[50,63]
SCI	Microglia/Macrophages	Strong, mainly infiltrating macrophages	Foamy macrophage state develops after lipid/myelin uptake, with impaired efferocytosis	SA-β-gal, DDR, lipid accumulation, SASP, reduced Gas6/Axl	Exendin-4 or myeloid UTX deletion improved clearance and repair	Evidence is strongest for infiltrating macrophages; resident-microglial specificity remains limited[35,59,64]
SCI	Astrocytes	Moderate	Predominantly chronic; some studies report a peak around 4 weeks	SA-β-gal, p16/p21, SASP, ROS; YAP or Ski-KLF4-JAK2/STAT3 signaling	Pathway inhibition reduced astrocyte dysfunction and improved repair-related outcomes	Mechanistic evidence is recent and requires independent replication across models[39,40]
SCI	Endothelium	Strong	3–14 d; UTX peaks at ~7 d in reported models	CD31 + p21/p53, SA-β-gal, reduced Lamin B1; impaired migration/tube formation	Endothelial UTX deletion, CNN1 restoration, and local D+Q improved vascular function	Evidence is mainly from rodents; some studies rely heavily on p16-related readouts[46,47]
Ischemic	Neuron	Moderate;	30 min to 14 d; signals	NeuN + p16/p21; partial	No neuron-specific causal intervention	Subcellular localization and

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Table 1. Cell-type-specific evidence of senescence-related states in TBI, SCI, and ischemic stroke (*continued*)

Disease	Cell type	Direct evidence/level	Main temporal dynamics	Core markers	Functional consequences/interventions	Key limitations and references
stroke		senescence-like	also reported in later human tissue	Lamin B1 abnormalities		baseline/contralateral expression remain difficult to interpret[18,19]
Ischemic stroke	Microglia/Macrophages	Strong, particularly in aged models	1–14 d; SASP changes are prominent early	p16/p21/p53, γH2AX, SA-β-gal, Iba1; myeloid senescence gene-set scores	iPSC-sEVs and targeted exosomes improved barrier and neurological outcomes	p21 and CD86 overlap with activation; transcriptomic scores alone are not direct evidence[19,52,53,76]
Ischemic stroke	Astrocytes	Moderate	Clear OGD/R phenotype *in vitro*; *in vivo* findings are acute and inconsistent	SA-β-gal, p16, SASP; limited *in vivo* GFAP co-localization	ABT263 clears senescence-like astrocytes *in vitro*; non-specific treatment improved animal outcomes	*In vivo* multidomain phenotyping and astrocyte-specific causal intervention are limited[18,19,41,42]
Ischemic stroke	Endothelium	Strong	Acute to ~7 d; aged BBB may contain pre-existing senescence	CD31 + p21, vascular SA-β-gal, γH2AX, reduced eNOS	Photobiomodulation and iPSC-sEVs improved barrier-related outcomes	Some studies use pretreatment or non-cell-specific clearance[42-44]

Evidence grading: Strong, cell-resolved and multidimensional evidence with temporal persistence plus functional or causal support; Moderate, reproducible or mechanistically informative evidence with incomplete cell-specific causality or limited independent replication; Limited, evidence based mainly on tissue-level associations, marker co-localization, or small datasets.[21,22] BBB, blood-brain barrier; D+Q, dasatinib plus quercetin; DDR, DNA-damage response; eNOS, endothelial nitric oxide synthase; GFAP, glial fibrillary acidic protein; iPSC-sEVs, induced pluripotent stem cell-derived small extracellular vesicles; OGD/R, oxygen-glucose deprivation/reoxygenation; rmTBI, repeated mild traumatic brain injury; ROS, reactive oxygen species; SA-β-gal, senescence-associated β-galactosidase; SASP, senescence-associated secretory phenotype; SCI, spinal cord injury; TBI, traumatic brain injury.

administered after the acute phase of TBI can improve long-term neurobehavioral outcomes, and navitoclax given several days after experimental stroke reduces senescence-related markers and improves function. The navitoclax studies also expose a practical concern: thrombocytopenia may be unacceptable in patients who are already at risk of bleeding. Preclinical work should therefore compare treatment start times and durations and should include follow-up after drug withdrawal rather than assuming that a single schedule will translate across diseases or cell types.[38,54,67-69]

Translational barriers: From experimental mechanisms to actionable targets

The first translational problem is identifying a persistent senescence-related state in patients without access to brain or spinal cord tissue. A single circulating SASP factor is unlikely to solve this problem. IL-6, TNF-α, and related mediators vary with infection, systemic inflammation, age, injury severity, and treatment, and an acute increase may simply reflect the expected injury response. A more informative approach would combine serial measurements rather than rely on one marker at one time point. Cerebrospinal fluid (CSF) or plasma profiles of SASP-related proteins could be considered alongside cell-type-enriched extracellular-vesicle cargo, markers of neuroaxonal injury, and indices of vascular or barrier dysfunction. Their value would lie less in 'diagnosing senescence' than in identifying a persistent biological pattern that tracks with the cell states defined in experimental studies. Imaging may add regional information on prolonged BBB leakage, neuroinflammation, vascular dysfunction, or tissue atrophy, but no imaging method currently provides a validated, senescence-specific readout in the injured human CNS.[21,22,69]

Such biomarkers would also affect how patients are selected for treatment. Age alone is unlikely to be sufficient because an older patient may have a high pre-existing senescence burden without showing substantial injury-induced persistence.[48,49] Conversely, repeated mild TBI can induce marked senescence-related responses in experimental models.[57] A more useful

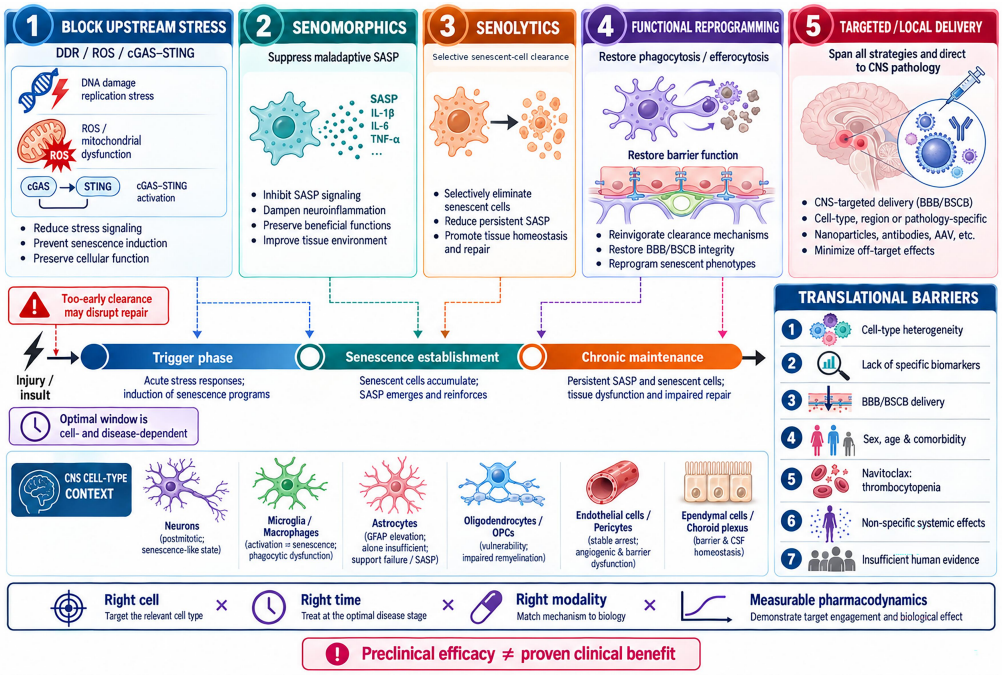


Fig. 4. Translational framework for senescence-targeted intervention after acute neurological injury. The upper sequence links definition of a persistent senescence-related target state with patient selection, biological timing, and proof-of-mechanism testing. The middle sections summarize therapeutic strategies and cellular or regional approaches discussed in the text, including targeted extracellular vesicles, local hydrogel delivery, and photobiomodulation; these approaches do not establish senescent-cell specificity. The lower sections emphasize interpretation in neurons, microglia/macrophages, astrocytes, and endothelial cells, together with timing and translational limitations. Early clearance may disrupt repair, and navitoclax-associated thrombocytopenia is a particular concern. Preclinical efficacy does not establish clinical benefit without evidence of target engagement and acceptable safety.[38,44,46,50,52,54,67-70,77,78] AAV, adeno-associated virus; BBB, blood–brain barrier; BSCB, blood–spinal cord barrier; cGAS, cyclic GMP–AMP synthase; CNS, central nervous system; CSF, cerebrospinal fluid; DDR, DNA-damage response; GFAP, glial fibrillary acidic protein; IL-1β, interleukin-1 beta; IL-6, interleukin-6; OPCs, oligodendrocyte precursor cells; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype; STING, stimulator of interferon genes; TNF-α, tumor necrosis factor alpha.

enrichment strategy would combine clinical context with evidence that the abnormal state persists: age and comorbidity, injury severity or repetition, prolonged BBB dysfunction, and a longitudinal biomarker pattern could all contribute. The same reasoning argues against treating patients whose deficits are dominated by irreversible tissue loss, because there may be too little viable but dysfunctional tissue left to rescue. These variables should be regarded as candidate stratification factors rather than validated criteria; prospective studies will be needed to determine which combination actually identifies a senescence-enriched subgroup.[69]

This uncertainty has implications for clinical study design. The earliest trials in acute neurological injury should probably be designed as proof-of-mechanism studies rather than conventional efficacy trials. In addition to standard neurological outcomes, they would need to show that the intervention reaches the intended biological state. Serial blood or CSF sampling, together with imaging or physiological measures relevant to the target compartment, could provide pharmacodynamic evidence of target engagement. Treatment timing should be explored rather than fixed arbitrarily: enrollment by hours or days after injury is clinically convenient, but the relevant biology may depend on whether a persistent senescence-related population has actually emerged. This is particularly important when comparing senolytics with approaches that modulate cell function without eliminating the target population.[67-70,77,78]

Safety will be a major determinant of whether this strategy can move beyond proof of concept. Navitoclax-associated thrombocytopenia is especially problematic after TBI or hemorrhage-prone stroke, where even a modest increase in bleeding risk may be unacceptable. More broadly, eliminating cells during a period of active tissue repair could worsen barrier integrity, immune defense, or regeneration, and these effects may not be captured by short-term neurological scores. Early studies should therefore include predefined hematologic, infectious, hepatic, and vascular monitoring and follow patients long enough to detect delayed effects on recovery. Experience with senolytic trials outside acute neurological injury shows that target engagement and tolerability can be assessed in humans, but it does not establish efficacy or an appropriate therapeutic window for TBI, SCI, or stroke. The translational question is therefore not simply whether a senotherapeutic can be administered, but whether a biologically defined, still-modifiable cell state can be identified in the right patient at the right time.[54,67-70,77,78]

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Future perspectives

Future studies should move beyond demonstrating the presence of senescence-associated markers toward defining when, where, and in which cell populations a persistent senescence-related state becomes functionally important.[21,22] Longitudinal and spatially resolved studies across disease stages, age groups, and both sexes will be needed to distinguish transient injury responses from persistent cell states. This distinction is particularly important in TBI, where an age-like microglial phenotype after injury may remain reversible.[36] Single-cell and spatial multi-omics may help identify candidate populations, but stronger causal inference will require lineage tracing and temporally controlled, cell-specific perturbation. Resident microglia should also be distinguished from infiltrating macrophages, particularly after SCI.[59] Likewise, pre-existing vascular senescence should be separated from changes induced by acute injury.[48,49]

Translation will require equally careful definition of the target state in patients. Rather than relying on a single circulating SASP factor or isolated imaging abnormality, future studies should evaluate longitudinal combinations of blood or CSF biomarkers, extracellular-vesicle cargo, imaging, and measures of vascular or barrier dysfunction. These approaches may help identify patients with persistent and potentially modifiable biology and determine when a senescence-directed intervention is biologically appropriate. Early clinical studies should prioritize proof of mechanism, target engagement, treatment timing, and safety before efficacy is inferred, particularly because interventions that are beneficial after a persistent maladaptive state has formed may be inappropriate during early tissue repair.[67-70,77,78]

More broadly, the future value of the senescence-injury axis will depend on whether it generates testable, disease-specific predictions rather than simply relabeling persistent secondary injury. The framework should therefore be challenged as well as supported: studies should define where it applies, where it fails, and whether it improves mechanistic stratification or therapeutic decision-making beyond existing models of secondary injury. A useful framework should ultimately narrow the range of plausible mechanisms, identify the patients and disease stages in which senescence-related biology is most relevant, and equally clarify when senescence-directed intervention is unlikely to be beneficial.

Limitations of the review and current evidence

This review has several limitations. First, it is a narrative review without a predefined systematic search strategy, formal risk-of-bias assessment, or quantitative synthesis; selection and interpretation bias therefore cannot be excluded. The included studies vary in injury models, cell types, senescence markers, sampling times, and interventions, limiting direct comparisons across diseases. The evidence grades are interpretive rather than a validated scoring system. Accordingly, the proposed senescence-injury axis should be regarded as a hypothesis-generating framework, not as evidence of a universal causal pathway.

Second, the underlying evidence is constrained by the limited specificity of senescence markers and heterogeneous sampling methods. Senescent cells may be rare and spatially clustered, making bulk-tissue assays difficult to interpret. Tissue dissociation, processing delays, fixation, and lysosomal stress may also alter measured signals. Injury-associated activation can reproduce parts of the p16/p21, DDR, SASP, Iba1, or GFAP profile, complicating the distinction between stable senescence and prolonged or transient injury responses.[11,21,22]

Finally, most *in vivo* studies use young, otherwise healthy rodents, limiting generalizability to older patients with vascular and metabolic comorbidities. Many senolytic and senomorphic interventions also have senescence-independent anti-inflammatory or vascular effects; improved behavioral or tissue outcomes alone therefore do not establish a senescence-specific mechanism.[67-70]

Conclusions

Across TBI, SCI, and ischemic stroke, senescence-related states may become maladaptive when they persist beyond the acute phase in viable cells and are accompanied by sustained functional impairment. Their distribution and strength of evidence differ by disease and cell type, with chronic glial abnormalities most consistently supported in TBI, macrophage-neuron-microvascular interactions best defined in SCI, and myeloid and neurovascular changes better supported in ischemic stroke. Establishing a causal role requires evidence of temporal persistence, multidimensional phenotyping, and functional improvement after temporally controlled, cell-specific manipulation. Clinical translation will further require biomarkers that identify a persistent and potentially modifiable state, appropriate patient selection, and treatment timing matched to that biological state. Overall, the senescence-injury axis should be regarded as a disease- and cell-type-specific comparative framework rather than an established universal causal pathway.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Review conception and design (JL, ZC), literature search and collection (ZC, YA, TC, YJ, YW, ZD), evidence synthesis and appraisal (ZC, YA, TC, YJ, YW, ZD), figure preparation (ZC), manuscript drafting (ZC), critical revision of the manuscript (YA, TC, YJ, YW, ZD, JL), supervision (JL). All authors read and approved the final manuscript.

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