



Review article

Cellular senescence in brain aging and neurodegeneration

LS Melo dos Santos^{a,d}, M. Trombetta-Lima^{b,c}, BJL Eggen^b, M. Demaria^{a,*}^a European Research Institute for the Biology of Ageing (ERIBA), University Medical Center Groningen (UMCG), University of Groningen, Antonius Deusinglaan 1, 9715RA, Groningen, the Netherlands^b Department of Biomedical Sciences of Cells and Systems, section Molecular Neurobiology, University Medical Center Groningen (UMCG), University of Groningen, Antonius Deusinglaan 1, 9715RA Groningen, the Netherlands^c Department of Pharmaceutical Technology and Biopharmacy, Groningen Research Institute of Pharmacy, University of Groningen, Antonius Deusinglaan 1, 9713AV Groningen, the Netherlands^d School of Sciences, Health and Life, Pontifical Catholic University of Rio Grande do Sul, Ipiranga Avenue, 6681, 90619-900 Porto Alegre, Brazil

ARTICLE INFO

Keywords:

Aging
Cellular senescence
Neurodegeneration
Senolytics

ABSTRACT

Cellular senescence is a state of terminal cell cycle arrest associated with various macromolecular changes and a hypersecretory phenotype. In the brain, senescent cells naturally accumulate during aging and at sites of age-related pathologies. Here, we discuss the recent advances in understanding the accumulation of senescent cells in brain aging and disorders. Here we highlight the phenotypical heterogeneity of different senescent brain cell types, highlighting the potential importance of subtype-specific features for physiology and pathology. We provide a comprehensive overview of various senescent cell types in naturally occurring aging and the most common neurodegenerative disorders. Finally, we critically discuss the potential of adapting senotherapeutics to improve brain health and reduce pathological progression, addressing limitations and future directions for application and development.

1. Cellular senescence in the central nervous system (CNS)

Aging, an intricate and universal process, orchestrates a gradual decline in both cellular and tissue functions. This phenomenon significantly elevates the susceptibility to a spectrum of non-communicable diseases, rendering advancing age a primary risk factor (López-Otín et al., 2023). Within the context of CNS health, the aging trajectory of the brain is intimately linked with the accumulation of cellular damage and the development of neurodegenerative processes. An emerging pivotal factor for the deterioration of brain structure and function is cellular senescence, a state of stable growth arrest accompanied by a hypersecretory and proinflammatory phenotype, recognized as the senescence-associated secretory phenotype (SASP) (Gorgoulis et al., 2019). Senescence, a pivotal biological phenomenon, entails a cell cycle arrest state that is intricately linked to the elevated expression of cyclin-dependent kinase (CDK) inhibitors, notably *CDKN2A/p16^{Ink4a}*, and *CDKN1A/p21^{CIP1/WAF1}* (Idda et al., 2020). This stasis in cell cycle progression is accompanied by discernible shifts in cellular morphology and architecture. Senescent cells manifest an augmented cellular volume, accompanied by heightened activity within the lysosomal compartment, evident through the prominent manifestation of

senescence-associated β -galactosidase activity (SA- β -gal).

Furthermore, nuclear transformations come to the fore, evidenced by the sustained nuclear localization of DNA damage response proteins such as γ -H2AX, and the concurrent attenuation of the nuclear lamina protein Lamin B1 (LMNB1) (Lee et al., 2006; Rodier et al., 2011). Amidst these intricate changes, the SASP emerges as a salient player. This intricate milieu boasts an enrichment of proinflammatory cytokines, chemokines, extracellular matrix proteases, microRNAs, bioactive lipids, and extracellular vesicles. Employing a dual modus operandi involving both paracrine and autocrine signaling, these bioactive agents orchestrate a diverse array of biological functions (Basisty et al., 2020).

Senescent cells accumulate with age in diverse tissues leading to the sustained release of SASP factors that contribute to inflammaging, the chronic inflammatory milieu of aging, and an environment favorable to disease and dysfunction (Franceschi et al., 2018). Strikingly, interventions targeting senescent cells have demonstrated significant promise in delaying dysfunction and extending health span (Chaib et al., 2022). Different cell types are shown to accumulate in the aging brain, each with unique characteristics and functions.

Among the intricate senescence-related dynamics within the brain and their implications for neurodegeneration, an urgent need emerges to

* Corresponding author.

E-mail address: m.demaria@umcg.nl (M. Demaria).<https://doi.org/10.1016/j.arr.2023.102141>

Received 28 September 2023; Received in revised form 10 November 2023; Accepted 21 November 2023

Available online 27 November 2023

1568-1637/© 2023 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

comprehensively discern the attributes of senescent cells, elucidate their pathological roles, and unravel the underlying mechanisms. In this review article, we focus on the recent advances in understanding the accumulation of senescent cells in brain aging. We discuss senescence-associated features expressed by different brain cell types in aging and in neurodegenerative disorders, highlighting the need to consider senescence heterogeneity as an important component for physiology and pathology. Finally, we try to focus on how senotherapeutics can be adapted for improving brain health and reducing pathological progression, while also addressing limitations and future directions for their application and development.

2. Accumulation of senescent cells during brain aging

In line with observations in other tissues, a notable rise in the expression of cells positive for classical senescence-associated markers (Fig. 1) has been found in the brain of aging organisms.

Using an approach for wide screening of senescent cells in human brain tissues, researchers have found a population of excitatory neurons expressing cyclin-dependent kinase inhibitor 2D (*CDKN2D*/p19) (Dehkordi et al., 2021). Moreover, a human brain survey showed p16^{Ink4a} in glial cells as the senescent marker elevated in elderly individuals (Idda et al., 2020). Furthermore, in naturally aging mice brains, a closer examination using Digital Spatial Profiling revealed senescent features within both myeloid and non-myeloid populations in the cortex and

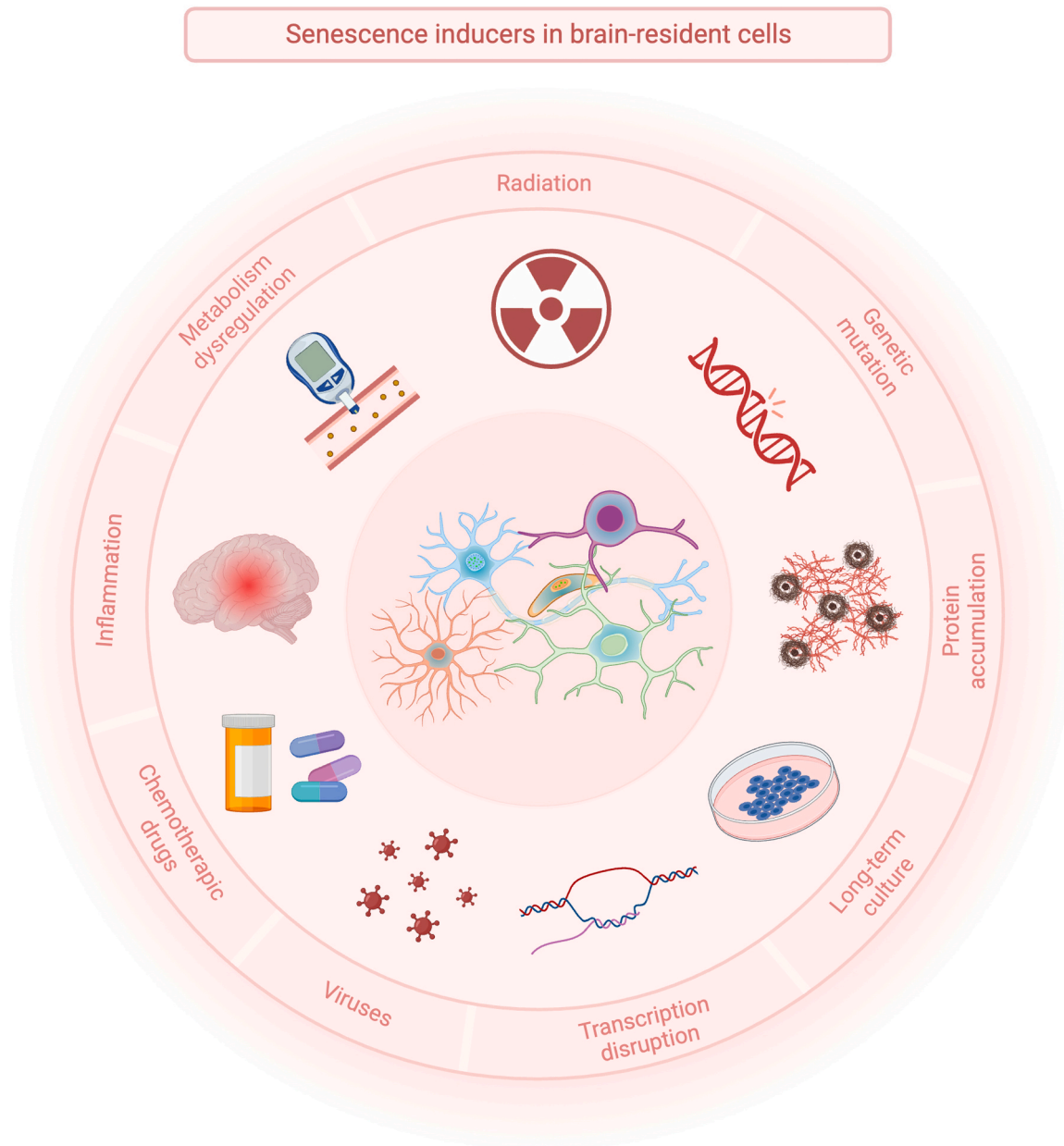


Fig. 1. Shared features of brain-resident senescent cells. Understanding the senescent markers expressed in different brain cell types is of utmost importance. Here we exemplified some of the shared markers found in the literature covering brain aging. Neurons (Blue): Represents the neuronal population in the brain and their susceptibility to senescence. Microglia (Green): Represents the microglial cells involved in neuroinflammation and their potential senescent state. Astrocytes (Red): Represents the astrocytic population and their role in maintaining CNS homeostasis, including their senescence characteristics. Oligodendrocytes (Purple): Represents the oligodendrocyte population and their involvement in demyelinating disorders and senescence-related changes. Endothelial Cells (Yellow): Represents the vascular cells and their contribution to vasculature dysfunctions. The SASP is represented by the red spheres, and the protein aggregation is represented by the neurofibrillary tangles. Created with BioRender.com.

hippocampus (Carver and Schafer, 2022). Notably, employing a senescence-reporter transgenic mouse model (p16-3MR) that allows the isolation of p16^{Ink4a}-positive cells through cell sorting, researchers identified distinct, age-dependent p16^{Ink4a}-positive microglia populations (Talma et al., 2021). Additionally, in a mouse model of tau-dependent neurodegenerative disease, astrocytes, and microglia express p16^{Ink4a}. Elimination of senescent cells in the transgenic mouse model INK-ATTAC prevented both soluble and insoluble tau deposition and preserved cognitive function (Bussian et al., 2018).

As the aging process unfolds in mice, microglia cells increase in number, and display altered phenotypes, including reduced prolongations, increased soma size, and heightened interactions with dopaminergic neurons in areas such as the substantia nigra pars compacta and the ventral tegmental area (Shaerzadeh et al., 2020). Further insight from another senescence-reporter transgenic mouse model (INK-ATTAC) revealed age-dependent increases in p16^{Ink4a}-expressing cells within microglia and oligodendrocyte progenitor cells (OPCs), accompanied by the expression of SASP factors. Remarkably, genetically eliminating these *CDKN2A*-expressing cells resulted in a reduction in proinflammatory factors and microglial activation (Ogrodnik et al., 2021).

Intriguingly, senescent astrocytes have also been observed in the post-mortem brain tissues of elderly individuals and in the brains of aged mice. These senescent astrocytes tend to cluster in specific regions, such as the hippocampal and granular cell layer in humans, and the dentate gyrus in mice. A key marker of senescent astrocytes is the loss of LMNB1,

shedding light on the potential role of LMNB1 dysfunction in astrocytes during the aging process (Matias et al., 2022).

Collectively, these studies underscore the diverse and multifaceted nature of senescence within the aging brain, manifesting in distinct cell types and playing varying roles in specific brain regions.

3. Induction and development of senescence in different types of brain cells

With a diverse array of senescent cell types that accumulate in the aging brain, and a variety of stresses potentially promoting senescence (Fig. 2. 3), the characterization of the senescence-associated phenotypes and pathological functions of the different cellular subtypes is key to understanding the interplay between cellular aging and brain health.

3.1. Neural precursor cells

In the intricate milieu of the adult mammalian brain, Neural Precursor Cells (NPCs) emerge as critical players in the ongoing saga of neurogenesis, pivotal for cognitive function and brain adaptability. These versatile cells primarily inhabit two distinct niches: the subgranular zone (SGZ) within the hippocampal dentate gyrus (DG) and the ventricular-subventricular zone (V-SVZ) encircling the lateral ventricles. A growing body of evidence has shown that senescence also plays a role in the NPCs' functions (Brunet et al., 2023).

For example, senescent NPCs were identified in the SGZ of the

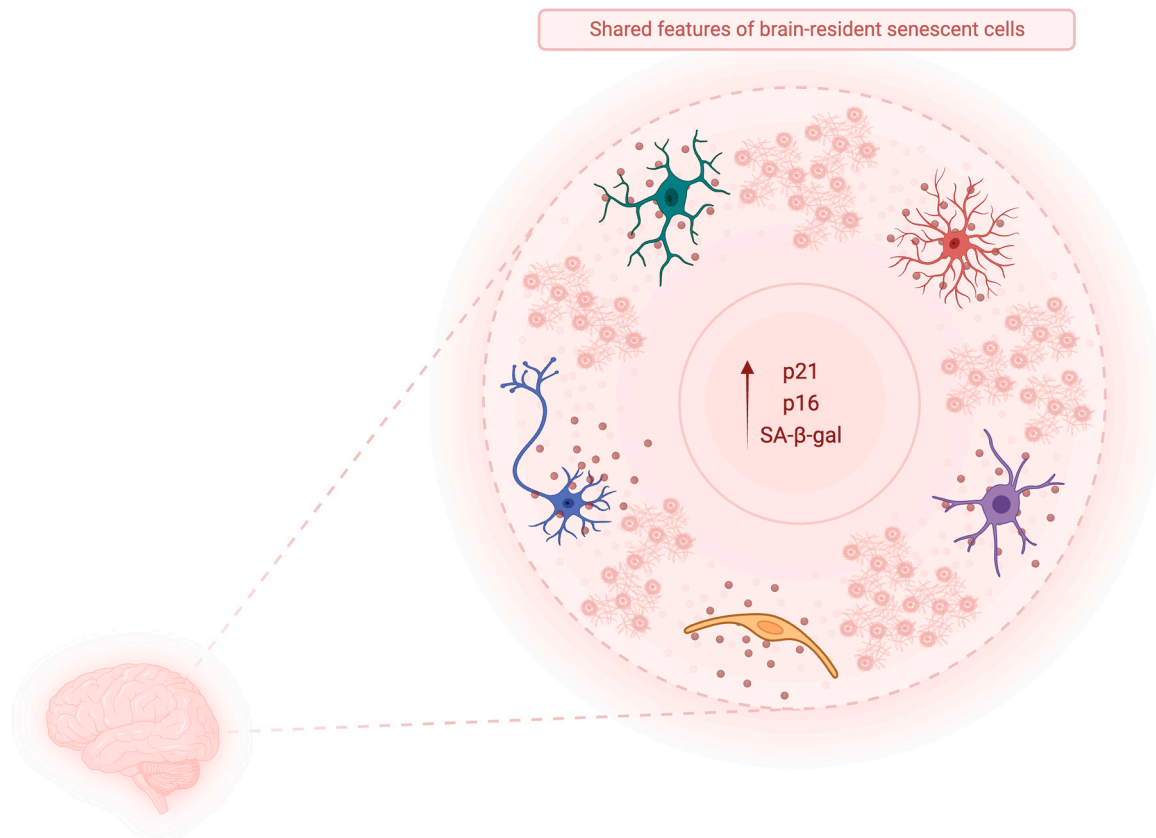


Fig. 2. Distinct types of senescence induction in brain-resident cells. As a universal phenomenon in distinct organisms, it is important to understand how senescent cells can be induced in the aging brain and neurodegenerative diseases. Here we illustrate some of the distinct types of cellular senescence in the brain. Central panel: Brain-senescent cells. Depicts brain-resident cells that have entered a senescent state. Represents the cellular phenotype associated with senescence in the brain. Surrounding factors: Extrinsic factors. Radiation, Viruses, Chemotherapeutic Drugs: Represents external factors that can induce senescence in brain cells. Illustrates the influence of radiation exposure, viral infections, and chemotherapeutic drugs on the senescence induction process. Intrinsic Factors: Genetic Mutation, Protein Accumulation, Long-Term Culture, Transcription Disruption, Inflammation, and Metabolism Dysregulation. Represents intrinsic factors within brain cells that can lead to senescence. Highlights the impact of genetic mutations, protein accumulation, long-term cell culture, transcriptional disturbances, inflammation, and metabolic dysregulation on the induction of senescence in brain-resident cells. Created with BioRender.com.

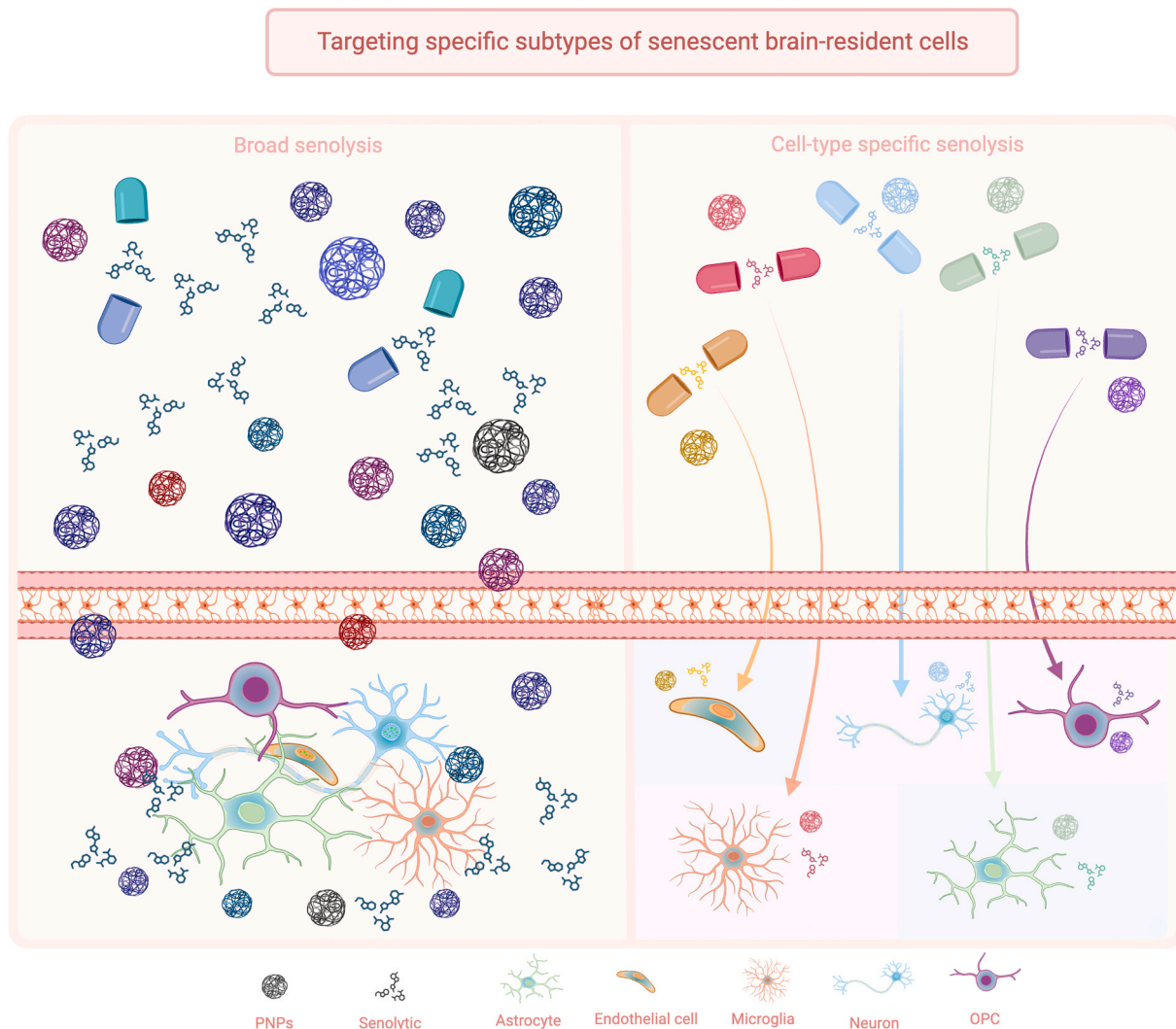


Fig. 3. PNPs and Senolytics Crossing the BBB. Senolytics have been considered an efficient way to eliminate senescent cells in the brain. However, we should keep in mind their broad target spectrum. In an urge to overcome this problem, different approaches such as PNPs came to light. Here we show the differences between a broad intervention and the ideal scenario where heterogeneous senescent cells can be targeted individually without interfering with different subpopulations. Left Side: Broad and Non-specific Senolytic Therapy. Represents a therapeutic strategy that targets senescent cells in a general manner. Depicts the administration of senolytics that aim to eliminate senescent cells in the brain. The approach does not differentiate between different cell types or specific senescence markers expressed by the cells. Right Side: Cell-Type Specific Therapy. Represents a targeted approach for senescent cell elimination. Illustrates the delivery of senolytics specifically tailored to different cell types in the brain. Highlights the specificity of the therapy toward the type of senescence markers expressed by the cells. This approach considers the heterogeneity of senescent cells and aims to selectively eliminate them based on their cell type and associated markers. Created with BioRender.com.

hippocampus, evident through heightened SA- β -gal activity, reduced EdU incorporation, and elevated p16^{INK4a} expression in aged mice. These senescent NPCs showed impairment in neurogenesis and cognitive performance (Michael P. Fatt et al., 2022). Furthermore, a groundbreaking study, employing chronic in vivo imaging of labeled NPCs in middle-aged mice, unveiled a compromised cell cycle entry of quiescent NPCs and diminished clonal output within the dendritic gyrus (Wu et al., 2023).

As a proof of concept, external behavioral factors were shown to exert a significant impact on aging NPCs and cellular senescence. NPCs expressing p16^{INK4a} exhibit reduced proliferative potential. Intriguingly, a p16^{INK4a} mouse model demonstrates that stimulating neurogenesis through physical activity enhances NPC proliferation in the dentate gyrus (von Bohlen et al., 2019). Moreover, a notable experiment employing 12-month-old p16-3MR mice unveiled a significant outcome. In this study, researchers observed a remarkable decrease of approximately 33% in SA- β -gal positive cells within the SGZ when genetically eliminating the p16^{INK4a} cells (Michael P Fatt et al., 2022).

Radiation emerges as an inducer factor in the realm of NPC senescence. Gamma radiation, often used in brain cancer treatments, exerts a profound influence by stalling NPC cell cycles and impeding neuron production, as shown by a decrease in the EdU+ cells in the adult hippocampus (Shetty et al., 2019).

Delving into potential interventions, researchers uncover promising avenues. Introducing glial progenitor cells (GPCs) into the aging mouse brain triggers their differentiation into astrocytes, resulting in improved behavioral outcomes, notably reducing escape response latency (Yang et al., 2021). Notably, the ER272 drug, known for its capacity to enhance neurogenesis in the adult hippocampus, presents an intriguing avenue. Administration of this drug to SAMP8 mice hints at its mechanism, involving the release of TGF α through PKC α activation, potentially facilitating NPC niche restoration (Gómez-Oliva et al., 2023).

3.2. Neurons

The assessment of neuronal senescence poses significant challenges,

particularly when relying on classical markers (Fig. 1). These conventional indicators harbor context disparities that mask their accurate interpretation. Neurons are post-mitotic cells constituting approximately half of the brain cells and play a crucial role in cognitive and motor functions. Considering the different context outcomes, as neurons are already in a state of terminal growth arrest, loss of proliferation cannot be used as a senescence-associated feature.

Deciphering the intricate implications of senescence-like attributes within neuronal populations is of notable complexity. Yet, an enlightening perspective emerges from the long-term culture of rodent primary neurons. Notably, markers including SA- β -gal, SASP components, *Cdkn1a*, and γ -H2AX, alongside compromised autophagic flux and proteostasis, demonstrated alignment with anticipated manifestations of cellular senescence (Moreno-Blas et al., 2019). However, it is essential to acknowledge the potential influence of the environment, particularly the stressors inherent to the cell culturing process, which can potentially impact the observed outcomes (Fig. 2) (Hernandez-Segura et al., 2018).

This intricate landscape becomes more comprehensible when observing certain markers associated with neuronal senescence in the presence of stressors or altered environmental conditions. High glucose levels or a high-fat diet showed to be a phenomenon that contributes to the appearance of classical senescence markers such as SA- β -gal and *Cdkn2a/p16^{Ink4a}* mRNA and protein in neurons (Ogrodnik et al., 2019; Xue et al., 2022). Moreover, the two-bottle choice (2BC)-Drinking in the Dark (DID), a model of binge-like drinking, revealed a disruption in the neuronal folate mechanism, inducing the upregulation of *Cdkn1a* through disturbance in the DNA repair machinery (Sun et al., 2023). These neuronal sensing of the systemic metabolic dysregulation suggest a different dimension to senescence induction, highlighting its role as a stress response mechanism. Senescence seems to extend beyond an age-associated phenomenon.

Senescence seems also to be activated in instances where neurons face challenges or altered surroundings, as shown in models of transcriptional shifts and brain injury such as the inhibition of the REST/NRSF transcriptional repressor complex, and the transient middle cerebral artery occlusion (tMCAO). In both cases, a SASP signature and p21^{CIP1/WAF1} were identified (Rocchi et al., 2021; Torres-Querol et al., 2021). Adding to the realm of injuries, elevated intraocular pressure (IOP) at the retina, an important risk factor for Glaucoma, holds a population of senescent cells characterized by the expression of p16^{Ink4a}. Its genetic elimination proved to be beneficial to protecting non-senescent retinal ganglion cells (RGC), a type of neuron located near the inner surface of the retina of the eye (Rocha et al., 2020). As shown above, the manifestation of distinct senescence markers is not confined to natural aging processes alone. Instead, it unveils itself in conditions characterized by environmental shifts and stressors, as exemplified by the influence of a proinflammatory milieu. In this case, exposure to the cytokine tumor necrosis factor (TNF- α) can trigger a cascade of senescence-associated factors such as TP53, p21^{CIP1/WAF1}, C12FDG, interleukins 6 and 1 α (IL-6, and IL-1 α) (Bae et al., 2022). Variations in the types of SASP factors expressed and their downstream effects, including α -synuclein secretion, emphasize the multifaceted nature of senescence-associated responses. Furthermore, the induction of senescence-like features in models of chemotherapy-induced peripheral neuropathy (CIPN) and viral infections, stress risk factors, underscores the heterogeneity of cellular responses. While cisplatin induces characteristic senescence markers, including SA- β -gal activity and p21^{CIP1/WAF1} accumulation, the intricate crosstalk between these markers and specific stressors remains unknown (Calls et al., 2021). Similarly, investigations into the impact of viral infections on neuronal senescence demonstrate the complexity of cellular responses, influenced by factors such as DNA-repair mechanisms and gene expression changes (Valeri et al., 2021; H. H. Zhang et al., 2023; L. Zhang et al., 2023). These studies highlight important insights into neurons' remarkable adaptability to external pressures.

As researchers dive into this intricate matter, disparities in

senescence markers and outcomes across various studies become increasingly notable (Herdy et al., 2022). Recent investigations have challenged the validity of SA- β -gal as a marker for senescent neurons. Interestingly, SA- β -gal activity has demonstrated a propensity to naturally increase over time in the murine postnatal olfactory epithelium, suggesting a dual association with both neuronal differentiation and classical senescence (de de Mera-Rodríguez et al., 2022). This revelation underscores the complexity of interpreting SA- β -gal as a sole marker for senescence, at least in the neuronal context. It serves as a reminder that, while certain markers may hold canonical significance, their interpretation must consider a broader context. The cell type, the specific context in which the marker was studied, and the potential dual roles it might play should be weighed carefully. These nuances emphasize the need for a comprehensive understanding of makers' multifaceted roles within the intricate neurobiological milieu.

When considering neuronal senescence, classic markers evolve, mixing with complex neuron responses under different conditions. Moreover, the development of an adaptive senescence as a stress response is intricate. Neuronal senescence is a delicate balance of markers, context, and changing neural dynamics which require further exploration.

3.3. Microglia

Like in neurons, identifying definitive and unequivocal markers of microglial senescence remains a challenge. Microglia orchestrate a symphony of functions pivotal to CNS homeostasis, including microenvironmental vigilance, phagocytic clearance, immune modulation, and synaptic sculpting, and are involved in neuroinflammatory cascades and the pathogenesis of different neurological disorders (Yin et al., 2017).

Primary murine microglia in culture develop telomere attrition and increased expression of *Cdkn2a/p16^{Ink4a}*, *Cdkn1a/p21^{CIP1/WAF1}*, and *Tp53/p53* mRNA and protein expression, and SA- β -gal activity over time. However, microglia isolated from aged murine brains exhibit only marginal telomere attrition and modest elevation in p16^{Ink4a} expression, suggesting profound differences between the ex vivo and in vivo milieu (Stojiljkovic et al., 2019). Furthermore, an evident morphological variation characterized by cytoplasmic fragmentation and swelling is observed in the aging microglia but fails to consistently correlate with other canonical senescence markers (Neumann et al., 2023; Shahidehpour et al., 2021). Because various microglia subtypes co-exist in the brain, it is possible that senescence needs to be measured within the same subset. Disease-associated microglia (DAM) manifest a senescence-like signature intertwined with the expression of triggering receptors expressed on myeloid cell 2 (TREM2) and perturbations in autophagy, which in turn promotes the expression of senescence markers such as *Cdkn1a/p21^{CIP1/WAF1}* (Choi et al., 2023). Similarly, Ng et al., 2023 showed that, in a pathogenic tau mouse model, a subset of p16^{Ink4a} positive microglia expressed features of DAM (Ng et al., 2023). The nexus between pro-inflammatory microglia and senescence markers introduces yet another layer of complexity. Treating microglia with the pro-inflammatory agent phorbol-12-myristate-13-acetate (PMA) results in augmented expression of *Tp53/p53*, *Cdkn1a/p21^{CIP1/WAF1}*, and SA- β -gal. This suggests that senescent microglia might interplay with cerebral tumorigenesis, underscoring the multifaceted roles microglia can assume beyond conventional immune responses (Cao et al., 2020).

Genotoxic insults, particularly from ionizing radiation, serve as potent triggers of premature microglial senescence. Instances wherein microglia, both in vivo and in vitro, are exposed to ionizing radiation depict heightened tissue inflammation through some of the SASP components. These manifestations hint at the dynamics governing immune reconstitution and microglial responses (Osman et al., 2020).

As therapeutic avenues potentially evolve based on the modulation of senescent microglia, a promising strategy emerges in the form of the Colony-Stimulating Factor 1 Receptor (CSF1R) antagonist, PLX5622, which leads to microglia depletion. PLX5622 promotes a decline in p16

expression within the aging brain milieu and attenuation in the expression of pro-inflammatory markers such as TNF- α , IL-1 β , IL-6, and IL-10, leading to improved astrocyte activation (Stojiljkovic et al., 2022).

In navigating the intricate landscape of senescent microglia, a critical and well-rounded perspective is shown to be of utmost importance. The quest for therapeutic interventions, though promising, necessitates meticulous evaluation considering the intricate and multifaceted nature of microglial senescence and its ramifications in CNS pathophysiology.

3.4. Astrocytes

Astrocytes, prominent glial cells in the central nervous system (CNS), play a pivotal role in supporting neurons and maintaining ion and neurotransmitter concentrations. Their intricate interactions with endothelial cells are vital for upholding the integrity of the blood-brain barrier (Sidoruk-Wegrzynowicz et al., 2011). Under overextended culture periods, astrocytes exhibit a senescence-associated profile characterized by elevated expression of several markers, including *Cdkn2a*, *Cdkn1a*, *Tp53*, IL-6, TIMP-1, Matrix Metalloproteinase 3 (MMP-3), transforming growth factor (TGF- β 1), High-Mobility Group Box 1 (HMGB1), and SA- β -gal (Willis et al., 2020).

The onset of premature senescence in astrocytes can be prompted by various external stressors. In vivo models simulating blood-brain barrier dysfunction (BBBD) illustrate how astrocytes respond by elevating *Cdkn2a* expression, SASP, SA- β -gal activity, and antiapoptotic markers when exposed to albumin, a prevalent plasma protein. This response is likely mediated by TGF- β signaling (Preininger et al., 2023). Oxidative stress and inflammatory cues also drive astrocyte senescence. Rat astrocytes subjected to IL-1 β or H₂O₂ demonstrate heightened senescence marker expression (Shang et al., 2020). Furthermore, human astrocytes respond to ionizing radiation by increasing p16^{Ink4a}, p21^{CIP1/WAF1}, SA- β -gal, and SASP levels. This insight clarifies the increased prevalence of senescent astrocytes in human brains exposed to radiotherapy (Turnquist et al., 2019).

Chronic infections exert an influential role in promoting astrocyte senescence. Exposure of primary human astrocytes to human immunodeficiency virus (HIV-1) leads to the expression of senescence markers, including SA- β -gal, reactive oxygen species, inflammatory cytokines, p16^{Ink4a}, and p21^{CIP1/WAF1}. Similar outcomes emerge in transgenic rats, confirming the clinical relevance of these observations. A distinctive player in driving HIV-1-induced astrocyte senescence is the long non-coding RNA TUG1. Its suppression effectively diminishes the expression of senescence-associated features (Pillai et al., 2023). Notably, the mammalian target of rapamycin (mTOR) and the DNA damage response are recognized as key drivers of astrocyte senescence induction (Simmnacher et al., 2020). Moreover, modulation of yes-associated protein (YAP) levels has shown an impact on astrocytic senescence, involving alterations in p53 expression. Interestingly, overexpression of cyclin-dependent kinase 6 (*Cdk6*) partially counteracts YAP-related effects, offering insights into potential interventions for mitigating astrocytic senescence (Xu et al., 2021).

In summary, the intricate interplay between astrocytes and various stressors underscores the heterogeneous nature of astrocytic senescence. These observations illuminate potential avenues for targeted interventions that could alleviate senescence-related complications in the CNS. Further exploration into the underlying molecular mechanisms holds promise for advancing our understanding of astrocyte senescence and its implications for brain health.

3.5. Oligodendrocytes

Oligodendrocytes play a crucial role in the formation and maintenance of myelin and provide additional structural and metabolic support to neurons (Kipp, 2020). Oligodendrocyte progenitor cells (OPCs) are precursor cells for oligodendrocytes. OPCs derived from naturally aged

mice showed an increased percentage of cells expressing *Cdkn2a*, suggesting the accumulation of senescent OPCs with age (Neumann et al., 2019; Ogrodnik et al., 2021).

Remarkably, mice harboring a cell-autonomous deletion of the nuclear COP9 signalosome component CSN5 (JAB1) in oligodendrocytes manifested DNA damage and defective DNA repair in myelinating cells. Interestingly, JAB1-deficient oligodendrocytes presented a senescence-like phenotype, leading to chronic inflammation and oxidative stress, and the mutant mice experienced progressive demyelination in the CNS, accompanied by microglia inflammation, neurodegeneration, severe motor deficits, and premature death. Notably, blocking microglia inflammation through PLX3397, another antagonist of the CSF1R, did not prevent neurodegeneration, but the deletion of the p21 pathway, but not p16, ameliorated the disease. This suggests that senescence-related factors might have a different role during neurodegeneration or that *Cdkn2a* and *Cdkn1a* positive subpopulations might have a different pathological role (Rivellini et al., 2022). Further exploration involving RNAseq of primary oligodendrocytes and microglia cells uncovered gene expression patterns associated with activated stress responses and increased post-mitotic cellular senescence (Schlett et al., 2023). This finding was confirmed by elevated levels of SA- β -gal activity and expression of SASP genes.

In conclusion, the connection between oligodendrocytes, senescence, and its implications for CNS health is underscored by these findings. Senescent OPCs and JAB1-mediated senescence in oligodendrocytes illuminate potential avenues for therapeutic interventions aimed at mitigating neurodegenerative processes. An enhanced understanding of the underlying molecular mechanisms offers a promising trajectory for unraveling the complex interplay between cellular senescence and CNS dysfunction.

3.6. Endothelial cells

The potential therapeutic implications of targeting vascular dysfunction in age-related diseases have raised investigations into senescent endothelial cells within the realm of neurodegeneration (Sweeney et al., 2018).

Upon incubation with soluble tau aggregates, primary human brain microvascular endothelial cells (HBEC) displayed induction of key senescent markers, including *CDKN2A*, *CDKN1A*, and *TP53*, accompanied by the upregulation of inflammatory mediators such as IL-6, TNF, and plasminogen activator inhibitor (PAI-1). The intriguing mechanistic link to endothelial microtubule destabilization tantalizes the potential interplay between this phenomenon and a senescence-like state (Husong et al., 2023). Similarly, A β 1–42 oligomer treatment invoked a senescence profile in HBEC, with heightened *CDKN1A*/p21^{CIP1/WAF1} levels. Notably, though cytokines associated with the SASP remained unchanged, an elevation in proangiogenic vascular endothelial growth factor receptor (VEGFR-1) emerged, juxtaposing the complexity of senescence-associated angiogenic responses (Angom et al., 2019).

The peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1 α), known for its role in mitochondrial function and lipid metabolism, took center stage in γ -ray-ionized HBEC cells. Correlation between PGC1 α acetylation pattern, SA- β -gal increase, and γ -H2AX elevation suggested a link between PGC1 α and irradiation-induced senescence. Overexpression of PGC1 α emerged as a promising strategy for mitigating senescent markers, hinting at potential avenues for targeted interventions in irradiation-induced senescence (S. Bin S. Bin, Heo S. Bin, Heo S. Bin, Heo Kim et al., 2019; K.H. Kim et al., 2019). Furthermore, human samples from AD patients have shown specific genes associated with endothelial cell functions and leukocyte adhesion, such as PAI-1, IL-8, chemokine ligand 1 (CXCL1), intercellular adhesion molecule 2 (ICAM-2), and TIE1. Interestingly, PAI-1 and CXCL8 can also be identified as being part of the SASP (Bryant et al., 2020).

The exploration of senescent endothelial cells within the neurodegenerative landscape underscores the intricate web of mechanistic

connections and divergent signatures. As we navigate the complexities of endothelial senescence in neurodegeneration, further investigations are warranted to unravel the intricate mechanisms underpinning these observations, bridging the gap between cellular senescence and neurodegenerative pathophysiology.

4. Accumulation and function of cellular senescence during neurodegeneration

While studies on naturally occurring age-associated senescent cells remain limited, recent years have seen significant advancement in our understanding of the accumulation and pathophysiological mechanism of senescent cells in various neurodegenerative diseases. Varying experimental approaches employed in studying the role of senescent cells in neurodegeneration yield disparate results, while reconciling the divergent outcomes and establishing a cohesive framework for understanding senescence in neurodegenerative diseases remains a challenge.

4.1. Alzheimer's disease

Postmortem brains of patients with Alzheimer's Disease (AD), a predominant neurodegenerative disorder, showed a subset of excitatory neurons expressing senescence-associated features, particularly *CDKN2D/p19* (Dehkordi et al., 2021). These senescent neurons share attributes with neurons harboring neurofibrillary tangle (NFT) tau pathology, suggesting an intertwined relationship between AD mechanisms and senescence. Furthermore, NFT-containing neurons from postmortem AD patients share a heightened expression of pro-inflammatory factors including interferon-gamma (IFN- γ) (Musi et al., 2018). Such observations, however, raise questions about whether these senescent characteristics directly contribute to AD pathology or emerge as a pathological sequela.

Moving from humans to mice, the APP/PS1 mouse model, which expresses amyloid precursor and mutant presenilin 1 protein, accumulates senescent neural progenitor cells in the ventricular-subventricular zone (V-SVZ) (Hu et al., 2022). P301S mice, a model for tauopathy, accumulate microglia with increased SA- β -gal and SASP components associated with an initial enhanced phagocytosis of neurons expressing tau aggregates and a later overall reduction in total phagocytic activity (Brelstaff et al., 2021). This paradoxical effect underscores the multifaceted nature of cellular responses in neurodegenerative contexts, where protein accumulation might simultaneously contribute to cellular clearance and dysfunction (Ungerleider et al., 2022). However, the applicability of such interventions in complex neurodegenerative environments remains uncertain. A similar senescence induction by A β peptides emerges from studies involving OPCs. Senescence biomarkers including *CDKN2A/p16^{Ink4a}* are upregulated by direct exposure to A β peptides inducing cellular senescence (Zhang et al., 2019a). These observations add to the mosaic of senescence accumulation across different neural cell types.

4.2. Parkinson's Disease

Parkinson's Disease (PD), a progressive neurodegenerative disorder primarily affecting the dopaminergic system, introduces a dynamic interplay between cellular aging markers and disease progression. However, the interpretation of senescent markers in PD remains a nuanced challenge, given the intricate diversities across various studies.

In the quest to identify senescent markers in PD, post-mortem analyses unveiled a population of astrocytes expressing heightened *CDKN2A*, IL-8, and IL-6. However, the implications of these specific markers in the context of PD pathogenesis and their role in cellular dysfunction remain open questions (Chinta et al., 2018). The link between astrocytic senescence and pro-inflammatory factors further underscores the intricate interplay between senescence and neuroinflammation in PD.

Transcriptional disturbances, such as in REST, as described in the Neurons section, may offer an important risk factor for the development of neurodegenerative diseases such as PD, as demonstrated by tissue analysis of human old PD brain sections. Indeed, REST was found to increase its expression in dopaminergic neurons and accumulate in the nucleus, and Lewy bodies, attenuating its transcriptional availability (Kawamura et al., 2019). It is becoming clear that loss or disturbances in REST signaling may lead to neurodegeneration. However, the specific trigger of REST expression, specifically during aging and senescence onset needs to be further investigated.

Special AT-rich sequence binding protein 1 (SATB1) is a DNA binding protein associated with PD, and a study showed that its knockout causes activation of cellular senescence state in dopaminergic neurons. SATB1 is capable of directly inhibiting *CDKN1A*, a canonical marker of senescence, and its loss in neurons was also identified in human PD samples (Riessland et al., 2019).

Environmental factors also contribute to the PD-related senescence landscape. Paraquat injections, a potentially contributing factor to idiopathic PD, induced senescence and SASP in astrocytes, and paraquat-induced senescent astrocytes altered the function and survival of neighboring dopaminergic neurons in the p16-3MR mice model, suggesting a potential senescence-driven cascade in neurodegenerative processes. Elimination of the senescent cells using ganciclovir proved to be beneficial for neurogenesis preservation and reduction of PD symptoms progression (Chinta et al., 2018). Further nuances in how senescence might be involved in PD emerge from the investigation of α -synuclein, a protein genetically linked to PD pathogenesis. α -synuclein preformed fibrils (α -syn PFF) administration in mice led to reductions in LMNB1 and HMGB1, combined with increased *Cdkn1a* expression in reactive astrocytes and microglia, and high levels of the pro-inflammatory cytokine TNF- α (Bae et al., 2022). In contrast, the role of senolytics in PD remains an evolving narrative. The p21^{CIP1/WAF1} inhibitor UC228 exhibited the potential to reduce senescent cell numbers and inflammation in a PD mouse model, highlighting the importance of exploring diverse pathways for targeted interventions (Chinta et al., 2018; Riessland et al., 2019).

Further studies are needed to dissect the causal relationships between senescent cells and PD pathological progression, particularly considering testing and developing anti-senescence therapeutics.

4.3. Other neurodegenerative diseases

By evaluating the characteristics of cellular senescence in PD and AD, it is becoming clear that patterns of senescence-associated phenotypes, including the senescent cell types involved, are appealingly pathology-specific.

Among other important and common neurodegenerative disorders is Amyotrophic Lateral Sclerosis (ALS), a progressive motor neuron disorder. ALS-derived astrocytes exhibit elevated levels of p21 and p16, and brain samples from ALS patients show increased p16^{Ink4a} and p21^{CIP1/WAF1} expression in glial cells and astrocytes (Vazquez-Villaseñor et al., 2020).

Examining induced pluripotent stem cells (iPSCs) derived from ALS patients carrying the C9orf72 mutation, neuronal progenitor cells show enhanced CXCL8 expression, linking ALS to the SASP (Porterfield et al., 2020). Similarly, a rat model carrying ALS-linked SOD1G93A mutations revealed microglia with a senescent and SASP signature, characterized by SA- β -Gal activity, p16^{Ink4a}, p53, matrix metalloproteinase-1 (MMP-1), and nitrotyrosine expression (Trias et al., 2019). Interestingly, transgenic hSOD1-G93A mice exhibit high *Cdkn2a/p16^{Ink4a}* and *Cdkn1a/p21^{Cip1}* levels in spinal cord microglia and astrocytes, yet lack SA- β -gal activity, once more highlighting the necessity to combine the measurement of various markers to validate the presence of senescence-associated patterns in vivo (Torres et al., 2022). iPSC patient-derived progenitor stem cells from Huntington's disease (HD), another progressive neurodegenerative disorder, exhibit signs of

premature senescence, driven by the FOXO3-ETS2-p16 axis (Voisin et al., 2020). Here, the interplay between genetic factors and cellular senescence raises questions about causality and potential therapeutic interventions.

4.4. Brain injuries

Brain injuries, often isolated from neurological deficits, exhibit a complex landscape of cellular senescence responses. In acute traumatic brain injury in old mice, microglia exhibit heightened proliferation 72 h post-injury, accompanied by impaired phagocytosis and elevated IL-1 β production. Furthermore, *Cdkn2a/p16^{Ink4a}* and *Cdkn1a/p21^{Cip1}*, lipofuscin, and γ -H2AX appear, revealing a complex senescent profile. Similar observations were made in a mouse model of spared nerve injury, where microglia showed increased SA- β -gal activity and SASP marker expression (Ritzel et al., 2019). These studies prompt questions about the interplay between trauma-induced responses and intrinsic aging processes and suggest that the natural onset of senescence in the brain might be, at least partially, due to responses to acute or chronic injuries and not only the consequence of chronological age (Borgonetti and Galeotti, 2023).

5. Targeting cellular senescence to improve brain health and cognitive functions

The intricate connection between cellular senescence and neurodegenerative diseases is yielding divergent outcomes that underscore the multifaceted nature of this relationship. Many potential approaches against senescent cells have been proposed, some leading to the selective death of senescent cells and some inhibiting the SASP. Among these approaches, the combination of Dasatinib, Quercetin, and ABT263 has been shown to hold promise in eliminating senescent cells within the brain.

5.1. Current approaches to target cellular senescence

An innovative study in aged rats introduced an 8-week combination treatment with Dasatinib (D), a Src/tyrosine kinase inhibitor, and Quercetin (Q), a natural flavonoid with multi-faceted effects on cellular processes. D + Q treatment yielded remarkable enhancements in memory and cognitive abilities that endured for at least 5 weeks post-treatment. Notably, these cognitive improvements were concomitant with a reduction in peripheral markers of the SASP (Krzystyniak et al., 2022). Of particular significance, whole-body elimination of senescent cells via D+Q treatment demonstrated specific ablation of p16^{Ink4a}-positive microglial cells within the brain (Ogrodnik et al., 2021). Advancing these insights, the study delved into the depletion of p16-positive cells in a p16^{Ink4a}^{-/-} mouse model. Strikingly, the elimination of these cells unleashed augmented neuronal proliferation, presenting intriguing prospects for ameliorating age-associated neuronal loss. The most pronounced effects were observed within the cerebellum, with the added dimension of sex-specific responses and involvement of the estrogen receptor β (ER β) expression (K. H. S. Bin, Heo S. Bin, Heo S. Bin, Heo Kim et al., 2019; K.H. Kim et al., 2019). In a mouse model of cisplatin-induced peripheral neuropathy, treatment with the BCL2 inhibitor ABT263 eliminated senescent cells at the dorsal root ganglia (Acklin et al., 2020). Strikingly, the potency of this approach extended beyond the peripheral nervous system. ABT263 intervention also contributed to the improvement of neurovascular coupling (NVC) responses in naturally aged mice, offering a new dimension of combating age-related cognitive decline. This improvement in NVC response coincided with significant enhancements in neurocognitive functions, most notably memory, within the hippocampus (Tarantini et al., 2021).

Using a combination of dasatinib D+Q as senolytics, along with ABT-263, comes with several potential downsides and considerations. D and Q have been chosen for their safety profiles and Food and Drug

Administration (FDA) approval for other indications, making them attractive candidates for repurposing as senolytics. However, this combination may not be universally effective against all senescent cells. Some respond to D but not Q or Fisetin (F), while others react to Q or F but not D, highlighting the heterogeneity of senescent cell populations. This suggests that a single combination therapy may not eliminate all senescent cells, limiting its overall efficacy (Chaib et al., 2022).

ABT-263 targets the BCL-2 pathway and effectively induces apoptosis in specific senescent cell types. However, its use is associated with potential toxicity concerns, such as thrombocytopenia and neutropenia, even with brief exposures. This raises concerns about its safety as a senolytic, especially if high doses are needed to suppress the BCL-2 pathway. Careful consideration of the risk-benefit profile of ABT-263 and close monitoring of potential side effects is essential.

5.2. Next generation of senotherapeutics

The field of senotherapeutics is evolving, with first-generation and second-generation senotherapeutics under investigation. First-generation senolytics target various signaling pathways, including tyrosine kinase receptors, growth factor receptors, kinases, and molecules like BCL-2, p53 modulation, and caspase inhibition. While these compounds show promise in eliminating senescent cells, questions linger about their specificity and potential off-target effects. Refining these first-generation senolytics is crucial to improving selectivity and reducing side effects (L. H. Zhang et al., 2023; L. Zhang et al., 2023).

Second-generation senotherapeutics are emerging, and include lysosomal activators, SA- β -gal-activated prodrugs, nanoparticles, immune-mediated clearance by CAR T cells, antibody-drug conjugates, or vaccines, and SASP inhibitors (senomorphics). These approaches offer alternative strategies for eliminating senescent cells, potentially with improved specificity and safety profiles. Nevertheless, their effectiveness and safety require thorough evaluation in pre-clinical models and clinical trials (Gasek et al., 2021) (Table 1).

The permeability of senolytic compounds through the BBB is critical for potential treatments of age-related neurodegenerative diseases. In vitro studies and pre-clinical models must assess whether senolytics can penetrate the BBB effectively and reach target cells in the brain. Ensuring their ability to access senescent cells in the central nervous system is essential for successful senolytic development for neurological conditions associated with aging.

5.3. Senolytics and neurodegenerative diseases

Studies using transgenic animals have highlighted the causative role of senescent p16^{Ink4a}⁺ in the progression of various neurodegenerative disorders, including AD and PD, prompting the exploration of senotherapeutics as a novel strategy to mitigate neurodegenerative disease progression and enhance brain health.

The application of senolytics in different mouse models of AD offers compelling insights into their potential impact. Clearing senescent cells using ABT263 led to reductions in critical AD features such as tau hyperphosphorylation, neuronal degeneration, and insoluble tau aggregates. Additionally, the elimination of senescent cells in a tau-dependent mouse model led to a decrease in senescence markers such as *Cdkn1a* (Bussian et al., 2018). Similarly, short-term D+Q administration in an AD mouse model revealed the elimination of p16-expressing OPCs linked to A β plaque accumulation, along with reductions in microglia activation and proinflammatory cytokine levels. These observations underscore the potential utility of senolytics in modulating neurodegenerative disease pathways (Zhang et al., 2019b). Moreover, administration of D+Q in aged mice was shown to have benefits for cognitive function (Ogrodnik et al., 2021). A similar effect was observed in aged rats, where D+Q administration improved cognitive abilities such as memory and learning, and these improvements were shown to last for at least 5 weeks post-treatment

Table 1

Senotherapeutic compounds and mechanisms of action. Here we present a comprehensive overview of senotherapeutic compounds, categorizing them into two generations, and outlining their respective mechanisms of action. Senotherapeutics are substances or drugs with the potential to selectively target and eliminate senescent cells or their consequences such as the SASP, which are associated with aging and age-related diseases. In the first generation, various compounds such as D, Q, and ABT-263 are listed, along with their specific mechanisms of action. The second generation encompasses newer approaches, including senomorphics.

Generation	Class	Compound	Mechanism of action
First generation	BCL-2 family inhibitors	Dasatinib (D)	Inhibits tyrosine kinase receptors (TKRs)
		Navitoclax (ABT-263)	Inhibit BCL-2, BCL-XL, and BCL-W
		ABT-737	Inhibit BCL-2, BCL-XL, and BCL-W
	HSP90 inhibitors	A1331852	Inhibits BCL-XL
		A1155463	Inhibits BCL-XL
		Alvespimycin (17-DMAG)	Disrupt HSP90-AKT interaction
		17-AAG (tanespimycin)	HSP90 inhibitor
	Targeting p53	Geldanamycin	Disrupt FOXO4-p53 interaction
		FOXO4-DRI	Inhibits BCL-2, BCL-XL, and BCL-W
	Natural products	Quercetin (Q)	BCL-2, PI3K/AKT, p53, and NF-κB
Fisetin (F)		Inhibitor of JAK 1/2 family	
Second Generation	Senomorphics	Ruxolitinib	NF-κB inhibitor
		8 K-NBD peptide	ATM kinase inhibitor
		KU-60019	NF-κB inhibitor and AMPK enhancer
		Metformin	Protein-target antibody: IL-1α blocker
		MABp1 Ab	Protein-target antibody: IL-8 blocker
		ABX-IL-8 Ab	Protein-target antibody: IL-6 blocker
	Mab-IL-6,8 Ab (Olokizumab)		

(Krzystyniak et al., 2022).

Heading into traumatic brain injuries and the elimination of senescent cells in damaged areas, intermittent administration of D+Q significantly reduced the levels of p16^{Ink4a} and p21^{CIP1/WAF1}, and the SASP, showing as a consequence an attenuation of defects in spatial reference memory, recognition memory, and depression-like behavior in mice (Wang et al., 2023). As a similar readout, the administration of ABT263 in a rat model of brain ischemia was shown to improve neurological function in behavioral tests (Lim et al., 2021). Furthermore, ABT263 treatment in a middle cerebral artery occlusion (MCAO) mouse model seemed to reduce the number of senescent astrocytes, reduced SASP factors, and p16, and its localized administration into the mouse brain showed to have a protective effect towards acute ischemic brain injury (Lu et al., 2023). Moreover, ABT263 has also been shown to eliminate senescent endothelial cells, rescuing the BBB integrity, and improving the cognitive performance in a mouse model of chemotherapy-induced cognitive impairment (Ahire et al., 2023).

Even though D+Q and ABT263 treatments exert positive effects on the brain and behavior, a remaining question is about their pathogenomic effects. A study compared both treatments in aged rats, showing that, indeed, both drugs exert different effects. As an example, TNF-α showed to be more responsive to D+Q, contrasting with IFN-γ, whose response was attenuated mostly by ABT263. Moreover, D+Q was shown to have higher efficacy in modulating the microglia morphology, which can probably result in different outcomes (Torres et al., 2022; Voisin et al., 2020).

5.4. Challenges and considerations for senolytic therapies

Despite their potential to eliminate senescent cells within the brain (Raffaele and Vinciguerra, 2022), both D+Q and ABT263 exhibit a crucial limitation—a lack of specificity. While they demonstrate efficacy in eliminating senescent cells, the inability to precisely discriminate specific subtypes of senescent cells raises concerns. It is possible that elimination of certain subtypes in certain contexts (i.e., neurons in normal brain aging) might actually be detrimental. Thus, more selective and targeted approaches might achieve better outcomes. Moreover, the shared molecular targets of these compounds with other cell states or their poorly understood mechanisms add another layer of complexity, potentially sparing pathological senescent subtypes and yielding unintended side effects (Zhu et al., 2016).

Of paramount importance is the issue of brain accessibility—a pivotal factor for effective neurodegenerative disease interventions. Data on the bio-distribution of D+Q and ABT263 within the brain remain limited, hampering the comprehensive evaluation of their efficacy. As the blood-brain barrier poses a formidable obstacle, innovative strategies like polymeric nanoparticles (PNPs) hold the potential to enhance drug delivery. These particles, through their unique properties, could aid in traversing the blood-brain barrier and optimizing drug distribution within the brain, potentially improving therapeutic outcomes (Mitchell et al., 2021).

5.5. Clinical trials and future directions

Efforts to translate these discoveries into practical applications for humans appear to be on a lengthy trajectory. Presently, three clinical trials focusing on mild cognitive impairment (MCI) and AD are taking strides in exploring the potential of senolytic interventions (Phase I/II NCT04785300^I, Phase I/II NCT04063124^{II}, and Phase II randomized NCT04685590^{III}). While this represents notable progress, the studies exhibit a lack of diversity in evaluating various senolytic types, primarily concentrating on the D+Q combination (Table 2). Looking ahead, there is a compelling need to delve into clinical inquiries concerning diverse senolytic variants across a spectrum of neurodegenerative diseases. For instance, the effects of distinct classes of senolytics such as Digoxin, 17-DMAG, and BET protein degrader (ARV825) on brain health remain ambiguous, underscoring the importance of further investigation.

Yet, the senolytics also prompt a critical appraisal of the challenges—specificity, brain accessibility, patient stratification, and the intricate interplay of senescent subtypes—involved in translating these strategies from preclinical models to human trials.

6. Concluding remarks

Recent findings have provided valuable insights into the role of cellular senescence in the pathogenesis of neurodegenerative diseases and brain injuries. However, several important aspects still require further investigation.

First, a precise mapping of what cell types, in which context, and under which conditions they enter senescence during brain aging or neuropathology is needed. Considering the potential beneficial functions of certain subtypes of senescent cells for tissue repair and regeneration, it is crucial to characterize the various senescent cellular subpopulations and their involvement in brain physiology and pathology. Second, we need deep phenotyping of the senescent state and senescence-associated features of the different brain cell types. Considering that brain cells have different functions and properties at steady state and upon activation, their entrance into a senescent state needs to be determined by using type-specific markers. For instance, loss of proliferation is inappropriate as a senescence-associated marker for neurons, while the SASP might be difficult to use for determining a senescent state of already chemokine and cytokine-secreting cells such as

Table 2

Senolytics applied in pre-clinical and clinical studies. Here we show a compiled overview of senolytics compounds that have been applied in both pre-clinical and clinical studies, together with their compounds of choice and main readouts within a 5-year range.

Type of study	Condition	Specie	Compound	Main readout	Reference
Pre-clinical	Alzheimer's Disease	Mouse	ABT263	Reduction of senescent markers	Bussian et al. (2018)
	Alzheimer's Disease	Mouse	D+Q	Reduction of proinflammatory cytokines and p16-expressing OPCs	Zhang et al., 2019b
	Aging	Rat	D+Q and ABT263	Pathognomonic effects of the drugs	Torres et al. (2022);Voisin et al. (2020)
	Aging	<i>INK-ATTAC</i> ^{+/-} mouse	D+Q	Elimination of p16 ^{Ink4a} -positive microglial cells	Ogrodnik et al. (2021)
	Cisplatin-induced peripheral neuropathy	Wild-type mouse	ABT263	Memory improvement	Tarantini et al. (2021)
	Brain ischemia	Mouse	ABT263	Improvement of neurological functions	(Lim et al. (2021)
	Aging	Wild-type rat	D+Q	Memory improvement and reduction of SASP	Krzystyniak et al. (2022)
	Traumatic brain injury	Mouse	D+Q	Improvement of memory and depression-like behavior	(Wang et al. (2023)
	Middle cerebral artery occlusion	Mouse	ABT263	Protective effect towards acute ischemic brain injury	(Lu et al. (2023)
Clinical	Chemotherapy-induced cognitive impairment	Mouse	ABT263	Rescue of BBB integrity	Ahire et al. (2023)
	Early Alzheimer's Disease	Human	D+Q	Ongoing	NCT 04785300
	Early Alzheimer's Disease	Human	D+Q	Ongoing	NCT 04063124
	Amnesic mild cognitive impairment or Early-stage Alzheimer's Disease	Human	D+Q	Ongoing	NCT 04685590

Abbreviation: C12FDG, 5-Dodecanoylaminofluorescein Di-β-D-Galactopyranoside; CIPN, Chemotherapy-induced peripheral neuropathy; CXCL, Chemokine ligand; CSF1R, Colony-stimulating factor 1 receptor; DAM, Disease associated microglia; HMGB1, High-mobility group box 1; HBEC, Human bronchial epithelial cells; iPSCs, Induced pluripotent stem cells; IOP, Intraocular pressure; JAB1, Jun activating binding protein 1; LMNB1, Lamin B1; MMP, Matrix metalloproteinase; mTOR, Mechanistic target of rapamycin; MCI, Mild cognitive impairment; NFT, Neurofibrillary tangles; NVC, Neurovascular coupling; OPCs, Oligodendrocytes progenitor cells; PGC1α, Peroxisome proliferator-activated receptor gamma coactivator 1-α; PAI-1, Plasminogen activator inhibitor 1; REST/NRSF, RE1-silencing transcription factor/neuron-restrictive silencer factor; RGC, Retinal Ganglion Cells; SATB1, Special AT-rich sequence-binding protein 1; TIE1, Tyrosine Kinase With Immunoglobulin Like And EGF Like Domains 1; tMCAO, Transient middle cerebral artery occlusion; VEGFR-1, Vascular endothelial growth factor receptor 1; V-SVZ, Ventricular-subventricular zone; YAP, Yes-associated protein; α-syn PFF, Alpha-synuclein preformed fibrils; γ-H2AX, gamma-H2AX.

microglia. Third, the safety and efficacy of senotherapeutic approaches in pre-clinical models and clinical studies need to be further validated. While important studies are undergoing to evaluate the first generation of senolytics in clinical trials (Chaib et al., 2022), more studies are needed to define whether broad-spectrum or subtype-specific senotherapeutics are more efficient.

Overall, the studies reviewed highlight the heterogeneous nature of senescence, with different cell types expressing senescence markers in distinct ways and playing diverse roles in brain regions. Cellular senescence emerges as a common feature in neurodegenerative diseases, and targeting senescent cells holds promise for therapeutic interventions. Continued research efforts are necessary to advance our understanding of cellular senescence in these conditions and translate these findings into effective treatments for human patients.

Resources

- I <https://classic.clinicaltrials.gov/ct2/show/study/NCT04785300>.
- II <https://classic.clinicaltrials.gov/ct2/show/NCT04063124>.
- III <https://classic.clinicaltrials.gov/ct2/show/NCT04685590>.

Funding

This work was supported by the Dutch Research Council (NWO) scheme VIDI to M.D [09150172010029].

Declaration of Competing Interest

Authors declare no conflicts of interest regarding the work covered in the manuscript.

Data Availability

No data was used for the research described in the article.

Acknowledgments

We thank all the Demaria laboratory for fruitful discussions.

References

- Acklin, S., Zhang, M., Du, W., Zhao, X., Plotkin, M., Chang, J., Campisi, J., Zhou, D., Xia, F., 2020. Depletion of senescent-like neuronal cells alleviates cisplatin-induced peripheral neuropathy in mice. *Sci. Rep.* 10 <https://doi.org/10.1038/S41598-020-71042-6>.
- Ahire, C., Nyul-Toth, A., Delfavero, J., Gulej, R., Faakey, J.A., Tarantini, S., Kiss, T., Kuan-Celariar, A., Balasubramanian, P., Ungvari, A., Tarantini, A., Nagaraja, R., Yan, F., Tang, Q., Mukli, P., Csipo, T., Yabluchanskiy, A., Campisi, J., Ungvari, Z., Csiszar, A., 2023. Accelerated cerebrovascular senescence contributes to cognitive decline in a mouse model of paclitaxel (Taxol)-induced chemobrain. *Aging Cell.* <https://doi.org/10.1111/acer.13832>.
- Angom, R.S., Wang, Y., Wang, E., Pal, K., Bhattacharya, S., Watzlawik, J.O., Rosenberry, T.L., Das, P., Mukhopadhyay, D., 2019. VEGF receptor-1 modulates amyloid β 1–42 oligomer-induced senescence in brain endothelial cells. *FASEB J.* 33, 4626–4637. <https://doi.org/10.1096/fj.201802003R>.
- Bae, E.J., Choi, M., Kim, J.T., Kim, D.K., Jung, M.K., Kim, C., Kim, T.K., Lee, J.S., Jung, B. C., Shin, S.J., Rhee, K.H., Lee, S.J., 2022. TNF-α promotes α-synuclein propagation through stimulation of senescence-associated lysosomal exocytosis. *Exp. Mol. Med.* 54, 788–800. <https://doi.org/10.1038/S12276-022-00789-X>.
- Basisty, N., Kale, A., Jeon, O.H., Kuehnemann, C., Payne, T., Rao, C., Holtz, A., Shah, S., Sharma, V., Ferrucci, L., Campisi, J., Schilling, B., 2020. A proteomic atlas of senescence-associated secretomes for aging biomarker development. *PLoS Biol.* 18, e3000599 <https://doi.org/10.1371/journal.pbio.3000599>.
- von Bohlen, O., Alvarez-Bolado, G., Thomas Schafer, S., Micheli, L., Ceccarelli, M., Ferri, A., Scardigli, R., Tirone, F., 2019. p16Ink4a Prevents the Activation of Aged Quiescent Dentate Gyrus Stem Cells by Physical Exercise. <https://doi.org/10.3389/fncel.2019.00010>.
- Borgonetti, V., Galeotti, N., 2023. Microglia senescence is related to neuropathic pain-associated comorbidities in the spared nerve injury model. *Pain.* <https://doi.org/10.1097/j.pain.0000000000002807>.
- Brelstaff, J.H., Mason, M., Katsinelos, T., Mcewan, W.A., Ghetti, B., Tolkovsky, A.M., Spillantini, M.G., 2021. Microglia become hypofunctional and release

- metalloproteases and tau seeds when phagocytosing live neurons with P301S tau aggregates. *Sci. Adv.* 7.
- Brunet, A., Goodell, M.A., Rando, T.A., 2023. Ageing and rejuvenation of tissue stem cells and their niches HHS Public Access. *Nat. Rev. Mol. Cell Biol.* 24, 45–62. <https://doi.org/10.1038/s41580-022-00510-w>.
- Bryant, A.G., Hu, M., Carlyle, B.C., Arnold, S.E., Frosch, M.P., Das, S., Hyman, B.T., Bennett, R.E., 2020. Cerebrovascular senescence is associated with tau pathology in Alzheimer's disease. *Front Neurol.* 11 <https://doi.org/10.3389/fneur.2020.575953>.
- Bussian, T.J., Aziz, A., Meyer, C.F., Swenson, B.L., van Deursen, J.M., Baker, D.J., 2018. Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline (Oct). *Nature* 562 (7728), 578–582. <https://doi.org/10.1038/s41586-018-0543-y>. Epub 2018.
- Calls, A., Torres-Espin, A., Navarro, X., Yuste, V.J., Udina, E., Bruna, J., 2021. Cisplatin-induced peripheral neuropathy is associated with neuronal senescence-like response. *Neuro Oncol.* 23, 88–99. <https://doi.org/10.1093/NEUONC/NOAA151>.
- Cao, D., Li, X.H., Luo, X.G., Yu, H.M., Wan, L.S., Wei, L., Ren, Y., 2020. Phorbol myristate acetate induces cellular senescence in rat microglia in vitro. *Int J. Mol. Med.* 46, 415–426. <https://doi.org/10.3892/ijmm.2020.4587>.
- Carver, C., Schafer, M., 2022. Spatially resolved mapping of cell-specific senescence profiled in aging mouse brain. *Innov. Aging* 6, 590–591.
- Chaib, S., Tchkonja, T., Kirkland, J.L., 2022. Cellular senescence and senolytics: the path to the clinic. *Nat. Med.* <https://doi.org/10.1038/s41591-022-01923-y>.
- Chinta, S.J., Woods, G., Demaria, M., Rane, A., Zou, Y., McQuade, A., Rajagopalan, S., Limbad, C., Madden, D.T., Campisi, J., Andersen, J.K., 2018. Cellular senescence is induced by the environmental neurotoxin paraquat and contributes to neuropathology linked to Parkinson's disease. *Cell Rep.* 22, 930–940. <https://doi.org/10.1016/j.celrep.2017.12.092>.
- Choi, I., Wang, M., Yoo, S., Xu, P., Seegobin, S.P., Li, X., Han, X., Wang, Q., Peng, J., Zhang, B., Yue, Z., 2023. Autophagy enables microglia to engage amyloid plaques and prevents microglial senescence. *Nat. Cell Biol.* <https://doi.org/10.1038/s41556-023-01158-0>.
- Dehkordi, S.K., Walker, J., Sah, E., Bennett, E., Atrian, F., Frost, B., Woost, B., Bennett, R. E., Orr, T.C., Zhou, Y., Andhey, P.S., Colonna, M., Sudmant, P.H., Xu, P., Wang, M., Zhang, B., Zare, H., Orr, M.E., 2021. Profiling senescent cells in human brains reveals neurons with CDKN2D/p19 and tau neuropathology. *Nat. Aging* 1, 1107–1116. <https://doi.org/10.1038/s43587-021-00142-3>.
- Fatt, Michael P., Tran, L.M., Vetere, G., Storer, M.A., Simonetta, J.V., Miller, F.D., Frankland, P.W., Kaplan, D.R., 2022. Restoration of hippocampal neural precursor function by ablation of senescent cells in the aging stem cell niche. *Stem Cell Rep.* 17, 259–275. <https://doi.org/10.1016/j.stemcr.2021.12.010>.
- Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., Santoro, A., 2018. Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nat. Rev. Endocrinol.* <https://doi.org/10.1038/s41574-018-0059-4>.
- Gasek, N.S., Kuchel, G.A., Kirkland, J.L., Xu, M., 2021. Strategies for targeting senescent cells in human disease. *Nat. Aging*. <https://doi.org/10.1038/s43587-021-00121-8>.
- Gómez-Oliva, R., Martínez-Ortega, S., Atienza-Navarro, I., Domínguez-García, S., Bernal-Utrera, C., Geribaldi-Doldán, N., Verástegui, C., Ezzanad, A., Hernández-Galán, R., Nunez-Abades, P., Garcia-Alloza, M., Castro, C., 2023. Rescue of neurogenesis and age-associated cognitive decline in SAMP8 mouse: Role of transforming growth factor- α . *Aging Cell* 22. <https://doi.org/10.1111/ACEL.13829>.
- Gorgoulis, V., Adams, P.D., Alimonti, A., Bennett, D.C., Bischof, O., Bishop, C., Campisi, J., Collado, M., Evangelou, K., Ferbeyre, G., Gil, J., Hara, E., Krizhanovsky, V., Jurk, D., Maier, A.B., Narita, M., Niedernhofer, L., Passos, J.F., 2019. Cellular Senescence: Defining a Path Forward. *Cell* 813–827. <https://doi.org/10.1016/j.cell.2019.10.005>.
- Herdy, J.R., Traxler, L., Agarwal, R.K., Karbacher, L., Schlachetzki, J.C.M., Boehnke, L., Zangwill, D., Galasko, D., Glass, C.K., Mertens, J., Gage, F.H., 2022. Increased post-mitotic senescence in aged human neurons is a pathological feature of Alzheimer's disease. *Cell Stem Cell* 29, 1637–1652.e6. <https://doi.org/10.1016/j.stem.2022.11.010>.
- Hernandez-Segura, A., Brandenburg, S., Demaria, M., 2018. Induction and validation of cellular senescence in primary human cells. *J. Vis. Exp.* 2018. <https://doi.org/10.3791/57782>.
- Hu, Y., Huang, Y., Xing, S., Chen, C., Shen, D., Chen, J., 2022. A β promotes CD38 expression in senescent microglia in Alzheimer's disease. *Biol. Res.* 55. <https://doi.org/10.1186/S40659-022-00379-1>.
- Hussong, S.A., Banh, A.Q., Van Skike, C.E., Dorigatti, A.O., Hernandez, S.F., Hart, M.J., Ferran, B., Makhlof, H., Gaczynska, M., Osmulski, P.A., McAllen, S.A., Dineley, K. T., Ungvari, Z., Perez, V.I., Kaye, R., Galvan, V., 2023. Soluble pathogenic tau enters brain vascular endothelial cells and drives cellular senescence and brain microvascular dysfunction in a mouse model of tauopathy. *Nat. Commun.* 14 <https://doi.org/10.1038/s41467-023-37840-y>.
- Idda, M.L., McClusky, W.G., Lodde, Valeria, Munk, R., Abdelmohsen, K., Rossi, M., Gorošpe, M., 2020. Survey of senescent cell markers with age in human tissues. *Aging* 12, 4052–4066.
- Kawamura, M., Sato, S., Matsumoto, G., Fukuda, T., Shiba-Fukushima, K., Noda, S., Takashi, M., Mori, N., Hattori, N., 2019. Loss of nuclear REST/NRSF in aged-dopaminergic neurons in Parkinson's disease patients. *Neurosci. Lett.* 699, 59–63. <https://doi.org/10.1016/j.neulet.2019.01.042>.
- Kim, K.H., Cho, Y., Lee, J., Jeong, H., Lee, Y., Kim, S.I., Kim, C.H., Lee, H.W., Nam, K.T., 2019. Sexually dimorphic leanness and hypermobility in p16Ink4a/CDKN2A-deficient mice coincides with phenotypic changes in the cerebellum. *Sci. Rep.* 9, 11167 <https://doi.org/10.1038/s41598-019-47676-6>.
- Kim, S.Bin, Heo, Kim, J.I., Kim, K.S.H., 2019. Acetylation of PGC1 α by histone deacetylase 1 downregulation is implicated in radiation-induced senescence of brain endothelial cells. *J. Gerontol. - Ser. A Biol. Sci. Med. Sci.* 74, 787–793. <https://doi.org/10.1093/gerona/gly167>.
- Kipp, M., 2020. Oligodendrocyte Physiology and Pathology Function. *Cells*. <https://doi.org/10.3390/cells9092078>.
- Krzystyniak, A., Wesierska, M., Petrazzo, G., Gadecka, A., Dudkowska, M., Bielak-Zmijewska, A., Mosienia, G., Figiel, I., Włodarczyk, J., Sikora, E., 2022. Combination of dasatinib and quercetin improves cognitive abilities in aged male Wistar rats, alleviates inflammation and changes hippocampal synaptic plasticity and histone H3 methylation profile. *Aging* 14.
- Lee, B.Y., Han, J.A., Im, J.S., Morrone, A., Johung, K., Goodwin, E.C., Kleijer, W.J., DiMaio, D., Hwang, E.S., 2006. Senescence-associated β -galactosidase is lysosomal β -galactosidase. *Aging Cell* 5, 187–195. <https://doi.org/10.1111/j.1474-9726.2006.00199.x>.
- Lim, S., Kim, T.J., Kim, Y.J., Kim, C., Ko, S.B., Kim, B.S., 2021. Senolytic therapy for cerebral ischemia-reperfusion injury. *Int J. Mol. Sci.* 22 <https://doi.org/10.3390/ijms222111967>.
- López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2023. Hallmarks of aging: An expanding universe. *Cell*. <https://doi.org/10.1016/j.cell.2022.11.001>.
- Lu, K.J., Sheu, J.R., Teng, R.D., Jayakumar, T., Chung, C.L., Hsieh, C.Y., 2023. Ability of brain injury of senescent cells in ipsilateral hemisphere to mitigate acute ischemic brain injury in mice. *Int J. Biol. Sci.* 19, 2835–2847. <https://doi.org/10.7150/ijbs.84060>.
- Matias, I., Diniz, L.P., Damico, I.V., Araujo, A.P.B., Neves, L. da S., Vargas, G., Leite, R.E. P., Suemoto, C.K., Nitri, R., Jacob-Filho, W., Grinberg, L.T., Hol, E.M., Middeldorp, J., Gomes, F.C.A., 2022. Loss of lamin-B1 and defective nuclear morphology are hallmarks of astrocyte senescence in vitro and in the aging human hippocampus. *Aging Cell* 21. <https://doi.org/10.1111/acel.13521>.
- de Mera-Rodríguez, J.A., Álvarez-Hernán, G., Gañán, Y., Santos-Almeida, A., Martín-Partido, G., Rodríguez-León, J., Francisco-Morcillo, J., 2022. Endogenous pH 6.0 β -galactosidase activity is linked to neuronal differentiation in the olfactory epithelium. *Cells* 11. <https://doi.org/10.3390/CELLS11020298>.
- Mitchell, M.J., Billingsley, M.M., Haley, R.M., Wechsler, M.E., Peppas, N.A., Langer, R., 2021. Engineering precision nanoparticles for drug delivery. *Nat. Rev. Drug Discov.* <https://doi.org/10.1038/s41573-020-0090-8>.
- Moreno-Blas, D., Gorostieta-Salas, E., Pommer-Alba, A., Muciño-Hernández, G., Gerónimo-Olvera, C., Maciel-Barón, L.A., Konigsberg, M., Massieu, L., Castro-Obrigón, S., 2019. Cortical neurons develop a senescence-like phenotype promoted by dysfunctional autophagy. *Aging* 11, 6175–6198. <https://doi.org/10.18632/AGING.102181>.
- Musi, N., Valentine, J.M., Sickora, K.R., Baeuerle, E., Thompson, C.S., Shen, Q., Orr, M. E., 2018. Tau protein aggregation is associated with cellular senescence in the brain. *Aging Cell* 17. <https://doi.org/10.1111/acel.12840>.
- Neumann, B., Baror, R., Zhao, C., Segel, M., Dietmann, S., Rawji, K.S., Foerster, S., McClain, C.R., Chalut, K., van Wijngaarden, P., Franklin, R.J.M., 2019. Metformin restores CNS remyelination capacity by rejuvenating aged stem cells. *Cell Stem Cell* 25, 473–485.e8. <https://doi.org/10.1016/j.stem.2019.08.015>.
- Neumann, P., Lenz, D.E., Streit, W.J., Bechmann, I., 2023. Is microglial dystrophy a form of cellular senescence? An analysis of senescence markers in the aged human brain. *Glia* 71, 377–390. <https://doi.org/10.1002/glia.24282>.
- Ng, P.Y., Zhang, C., Li, H., Baker, D.J., 2023. Senescent microglia represent a subset of disease-associated microglia in P301S mice. *J. Alzheimers Dis.* 95 (2), 493–507. <https://doi.org/10.3233/JAD-230109>. PMID: 37545233.
- Ogrodnik, M., Zhu, Y., Langhi, L.G.P., Tchkonja, T., Krüger, P., Fielder, E., Victorelli, S., Ruswhandi, R.A., Giorgadze, N., Pirtskhalava, T., Podgorni, O., Enikolopov, G., Johnson, K.O., Xu, M., Inman, C., Palmer, A.K., Schafer, M., Weigl, M., Ikeno, Y., Burns, T.C., Passos, J.F., von Zglinicki, T., Kirkland, J.L., Jurk, D., 2019. Obesity-induced cellular senescence drives anxiety and impairs neurogenesis. *Cell Metab.* 29, 1061–1077.e8. <https://doi.org/10.1016/j.cmet.2018.12.008>.
- Ogrodnik, M., Evans, S.A., Fielder, E., Victorelli, S., Kruger, P., Salmonowicz, H., Weigand, B.M., Patel, A.D., Pirtskhalava, T., Inman, C.L., Johnson, K.O., Dickinson, S.L., Rocha, A., Schafer, M.J., Zhu, Y., Allison, D.B., von Zglinicki, T., LeBrasseur, N.K., Tchkonja, T., Neretti, N., Passos, J.F., Kirkland, J.L., Jurk, D., 2021. Whole-body senescent cell clearance alleviates age-related brain inflammation and cognitive impairment in mice. *Aging Cell* 20. <https://doi.org/10.1111/acel.13296>.
- Osman, A.M., Sun, Y., Burns, T.C., He, L., Kee, N., Oliva-Vilarnau, N., Alevyzaki, A., Zhou, K., Lohivouri, L., Uhlén, P., Hedlund, E., Betscholtz, C., Lauschke, V.M., Kele, J., Blomgren, K., 2020. Radiation triggers a dynamic sequence of transient microglial alterations in juvenile brain. *Cell Rep.* 31 <https://doi.org/10.1016/j.celrep.2020.107699>.
- Pillai, P.P., Kannan, M., Sil, S., Singh, S., Thangaraj, A., Chivero, E.T., Dagur, R.S., Tripathi, A., Hu, G., Periyasamy, P., Buch, S., 2023. Involvement of lncRNA TUG1 in HIV-1 tat-induced astrocyte senescence. *Int J. Mol. Sci.* 24 <https://doi.org/10.3390/IJMS24054330>.
- Porterfield, V., Khan, S.S., Foff, E.P., Koseoglu, M.M., Blanco, I.K., Jayaraman, S., Lien, E., McConnell, M.J., Bloom, G.S., Lazo, J.S., Sharlow, E.R., 2020. A three-dimensional dementia model reveals spontaneous cell cycle re-entry and a senescence-associated secretory phenotype. *Neurobiol. Aging* 90, 125–134. <https://doi.org/10.1016/j.neurobiolaging.2020.02.011>.
- Preininger, M.K., Zaytseva, D., Lin, J.M., Kaufner, D., 2023. Blood-brain barrier dysfunction promotes astrocyte senescence through albumin-induced TGF β signaling activation. *Aging Cell* 22. <https://doi.org/10.1111/ACEL.13747>.
- Raffaele, M., Vinciguerra, M., 2022. The costs and benefits of senotherapeutics for human health. *Lancet Healthy Longev.* [https://doi.org/10.1016/S2666-7568\(21\)00300-7](https://doi.org/10.1016/S2666-7568(21)00300-7).
- Riessland, M., Kolisnyk, B., Kim, T.W., Cheng, J., Ni, J., Pearson, J.A., Park, E.J., Dam, K., Acehan, D., Ramos-Espiritu, L.S., Wang, W., Zhang, J., Shim, J. won, Cicceri, G.,

- Brichta, L., Studer, L., Greengard, P., 2019. Loss of SATB1 induces p21-dependent cellular senescence in post-mitotic dopaminergic neurons. *Cell Stem Cell* 25, 514–530.e8. <https://doi.org/10.1016/j.stem.2019.08.013>.
- Ritzel, R.M., Doran, S.J., Glaser, E.P., Meadows, V.E., Faden, A.I., Stoica, B.A., Loane, D. J., 2019. Old age increases microglial senescence, exacerbates secondary neuroinflammation, and worsens neurological outcomes following acute traumatic brain injury in mice. *Neurobiol. Aging* 77, 194. <https://doi.org/10.1016/j.neurobiolaging.2019.02.010>.
- Rivellini, C., Porrello, E., Dina, G., Mrakic-Spota, S., Vezzoli, A., Bacigaluppi, M., Gullotta, G.S., Chaabane, L., Leocani, L., Marenga, S., Colombo, E., Farina, C., Newcombe, J., Nave, K.A., Pardi, R., Quattrini, A., Previtali, S.C., 2022. JAB1 deletion in oligodendrocytes causes senescence-induced inflammation and neurodegeneration in mice. *J. Clin. Invest* 132. <https://doi.org/10.1172/JCI145071>.
- Rocchi, A., Carminati, E., De Fusco, A., Kowalska, J.A., Floss, T., Benfenati, F., 2021. REST/NRSF deficiency impairs autophagy and leads to cellular senescence in neurons. *Aging Cell* 20. <https://doi.org/10.1111/ACEL.13471>.
- Rocha, L.R., Nguyen Huu, V.A., Palomino La Torre, C., Xu, Q., Jabari, M., Krawczyk, M., Weinreb, R.N., Skowronska-Krawczyk, D., 2020. Early removal of senescent cells protects retinal ganglion cells loss in experimental ocular hypertension. *Aging Cell* 19. <https://doi.org/10.1111/acel.13089>.
- Rodier, F., Muñoz, D.P., Teachenor, R., Chu, V., Le, O., Bhaumik, D., Coppé, J.P., Campeau, E., Beauséjour, C.M., Kim, S.H., Davalos, A.R., Campisi, J., 2011. DNASCARS: Distinct nuclear structures that sustain damage-induced senescence growth arrest and inflammatory cytokine secretion. *J. Cell Sci.* 124, 68–81. <https://doi.org/10.1242/jcs.071340>.
- Schlett, J.S., Mettang, M., Skaf, A., Schweizer, P., Errerd, A., Mulugeta, E.A., Hein, T.M., Tsemlis, K., Tsemlis, M., Büttner, U.F.G., Wendt, H., Abaei, A., Rasche, V., Prex, V., Nespoli, E., Alami, N.O., Tew, D., Walthert, P., Yilmazer-Hanke, D., Oswald, F., Dimou, L., Wirth, T., Baumann, B., 2023. NF- κ B is a critical mediator of post-mitotic senescence in oligodendrocytes and subsequent white matter loss. *Mol. Neurodegener.* 18, 24. <https://doi.org/10.1186/s13024-023-00616-5>.
- Shaerzadeh, F., Phan, L., Miller, D., Daquell, M., Hachmeister, W., Hansen, C., Bechtle, A., Tu, D., Martcheva, M., Foster, T.C., Kumar, A., Streit, W.J., Khoshbouei, H., 2020. Microglia senescence occurs in both substantia nigra and ventral tegmental area. *Glia* 68, 2228–2245. <https://doi.org/10.1002/glia.23834>.
- Shahidehpour, R.K., Higdon, R.E., Crawford, N.G., Neltner, J.H., Ighodaro, E.T., Patel, E., Price, D., Nelson, P.T., Bachstetter, A.D., 2021. Dystrophic microglia are associated with neurodegenerative disease and not healthy aging in the human brain. *Neurobiol. Aging* 99, 19–27. <https://doi.org/10.1016/j.neurobiolaging.2020.12.003>.
- Shang, D., Hong, Y., Xie, W., Tu, Z., Xu, J., 2020. Interleukin-1 β drives cellular senescence of rat astrocytes induced by oligomerized amyloid β peptide and oxidative stress. *Front Neurol.* 11. <https://doi.org/10.3389/FNEUR.2020.00929>.
- Shetty, A.K., Peruzzi, F., Pacary, E., Zanirati, G., Shen, Q., Enikolopov, G.N., Mineyeva, O.A., Bezriadnov, D.V., Kedrov, A.V., Lazutkin, A.A., Anokhin, K.V., Anokhin, P.K., 2019. Radiation Induces Distinct Changes in Defined Subpopulations of Neural Stem and Progenitor Cells in the Adult Hippocampus. <https://doi.org/10.3389/fnins.2018.01013>.
- Sidoryk-Wegrzynowicz, M., Wegrzynowicz, M., Lee, E., Bowman, A.B., Aschner, M., 2011. Role of astrocytes in brain function and disease. *Toxicol. Pathol.* 39, 115–123. <https://doi.org/10.1177/0192623310385254>.
- Simmaacher, K., Krach, F., Schneider, Y., Alecu, J.E., Mautner, L., Klein, P., Roybon, L., Prots, I., Xiang, W., Winner, B., 2020. Unique signatures of stress-induced senescent human astrocytes. *Exp. Neurol.* 334. <https://doi.org/10.1016/j.expneurol.2020.113466>.
- Stojilkovic, M.R., Ain, Q., Bondeva, T., Heller, R., Schmeer, C., Witte, O.W., 2019. Phenotypic and functional differences between senescent and aged murine microglia. *Neurobiol. Ageing*. <https://doi.org/10.1016/j.neurobiolaging.2018.10.007>.
- Stojilkovic, M.R., Schmeer, C., Witte, O.W., 2022. Pharmacological depletion of microglia leads to a dose-dependent reduction in inflammation and senescence in the aged murine brain. *Neuroscience* 488, 1–9. <https://doi.org/10.1016/j.neuroscience.2022.02.018>.
- Sun, J.K.L., Wu, D., Wong, G.C.N., Lau, T.M., Yang, M., Hart, R.P., Kwan, K.M., Chan, H. Y.E., Chow, H.M., 2023. Chronic alcohol metabolism results in DNA repair infidelity and cell cycle-induced senescence in neurons. *Aging Cell* 22. <https://doi.org/10.1111/acel.13772>.
- Sweeney, M.D., Kisler, K., Montagne, A., Toga, A.W., Zlokovic, B.V., 2018. The role of brain vasculature in neurodegenerative disorders. *Nat. Neurosci.* <https://doi.org/10.1038/s41593-018-0234-x>.
- Talma, N., Gerrits, E., Wang, B., Eggen, B.J.L., Demaria, M., 2021. Identification of distinct and age-dependent p16High microglia subtypes. *Aging Cell* 20. <https://doi.org/10.1111/acel.13450>.
- Tarantini, S., Balasubramanian, P., Delfavero, J., Csipo, T., Yabluchanskiy, A., Kiss, T., Nyúl-Tóth, Á., Mukli, P., Toth, P., Ahire, C., Ungvari, A., Benyo, Z., Csizsar, A., Ungvari, Z., 2021. Treatment with the BCL-2/BCL-xL inhibitor senolytic drug ABT263/Navitoclax improves functional hyperemia in aged mice. *Geroscience* 43, 2427–2440. <https://doi.org/10.1007/s11357-021-00440-z>.
- Torres, P., Aneurillas, C., Rami, O., Ferna, A., Encinas, M., Povedano, nica, Andre, Ferrer, P., Ayala, ria, I., Pamplona, R., Portero-Oti, M., 2022. A motor neuron disease mouse model reveals a non-canonical profile of senescence biomarkers. *Dis. Model Mech.* <https://doi.org/10.1242/dmm.049059>.
- Torres-Querol, C., Torres, P., Vidal, N., Portero-Otín, M., Arque, G., Purroy, F., 2021. Acute ischemic stroke triggers a cellular senescence-associated secretory phenotype. *Sci. Rep.* 11. <https://doi.org/10.1038/S41598-021-95344-5>.
- Trias, E., Beilby, P.R., Kovacs, M., Ibarburu, S., Varela, V., Barreto-Núñez, R., Bradford, S. C., Beckman, J.S., Barbeito, L., 2019. Emergence of microglia bearing senescence markers during paralysis progression in a rat model of inherited ALS. *Front Aging Neurosci.* 10. <https://doi.org/10.3389/fnagi.2019.00042>.
- Turnquist, C., Beck, J.A., Horikawa, I., Obiorah, I.E., Von Muhlinen, N., Vojtesek, B., Lane, D.P., Grunseich, C., Chahine, J.J., Ames, H.M., Smart, D., Harris, B.T., Harris, C.C., 2019. Radiation-induced astrocyte senescence is rescued by Δ 133p53. *Neuro Oncol.* 21, 474–485. <https://doi.org/10.1093/neuonc/noz001>.
- Ungerleider, K., Beck, J.A., Lissa, D., Jorui, S., Horikawa, I., Harris, C.C., 2022. Δ 133p53 α protects human astrocytes from amyloid-beta induced senescence and neurotoxicity. *Neuroscience* 498, 190–202. <https://doi.org/10.1016/j.neuroscience.2022.06.004>.
- Valeri, A., Chiricosta, L., Calcaterra, V., Biasin, M., Cappelletti, G., Carelli, S., Zuccotti, G. V., Bramanti, P., Pelizzo, G., Mazzon, E., Gugliandolo, A., 2021. Transcriptomic analysis of HCN-2 cells suggests connection among oxidative stress, senescence, and neuron death after SARS-CoV-2 infection. *Cells* 10. <https://doi.org/10.3390/CELLS10092189>.
- Vazquez-Villaseñor, I., Garwood, C.J., Heath, P.R., Simpson, J.E., Ince, P.G., Wharton, S. B., 2020. Expression of p16 and p21 in the frontal association cortex of ALS/MND brains suggests neuronal cell cycle dysregulation and astrocyte senescence in early stages of the disease. *Neuropathol. Appl. Neurobiol.* 46, 171–185. <https://doi.org/10.1111/nan.12559>.
- Voisin, J., Farina, F., Naphade, S., Fontaine, M., Tshilenge, K.T., Galicia Aguirre, C., Lopez-Ramirez, A., Dancourt, J., Ginisty, A., Sasidharan Nair, S., Lakshika Madushani, K., Zhang, N., Lejeune, F.X., Verny, M., Campisi, J., Ellerby, L.M., Neri, C., 2020. FOXO3 targets are reprogrammed as Huntington's disease neural cells and striatal neurons face senescence with p16INK4a increase. *Aging Cell* 19. <https://doi.org/10.1111/acel.13226>.
- Wang, J., Lu, Y., Carr, C., Dhandapani, K.M., Brann, D.W., 2023. Senolytic therapy is neuroprotective and improves functional outcome long-term after traumatic brain injury in mice. *Front Neurosci.* 17. <https://doi.org/10.3389/fnins.2023.1227705>.
- Willis, C.M., Nicaise, A.M., Bongarzono, E.R., Givogri, M., Reiter, C.R., Heintz, O., Jellison, E.R., Sutter, P.A., TeHennepe, G., Ananda, G., Vella, A.T., Crocker, S.J., 2020. Astrocyte support for oligodendrocyte differentiation can be conveyed via extracellular vesicles but diminishes with age. *Sci. Rep.* 10. <https://doi.org/10.1038/S41598-020-57663-X>.
- Wu, Y., Bottes, S., Fisch, R., Zehnder, C., Darby Cole, J., Pilz, G.-A., Helmchen, F., Simons, B.D., Jessberger, S., 2023. Chronic in vivo imaging defines age-dependent alterations of neurogenesis in the mouse hippocampus. *Nat. Aging* 3, 380–390. <https://doi.org/10.1038/s43587-023-00370-9>.
- Xu, X., Shen, X., Wang, J., Feng, W., Wang, M., Miao, X., Wu, Q., Wu, L., Wang, X., Ma, Y., Wu, S., Bao, X., Wang, W., Wang, Y., Huang, Z., 2021. YAP prevents premature senescence of astrocytes and cognitive decline of Alzheimer's disease through regulating CDK6 signaling. *Aging Cell* 20. <https://doi.org/10.1111/ace.13465>.
- Xue, W.J., He, C.F., Zhou, R.Y., Xu, X.D., Xiang, L.X., Wang, J.T., Wang, X.R., Zhou, H.G., Guo, J.C., 2022. High glucose and palmitic acid induces neuronal senescence by NRSF/REST elevation and the subsequent mTOR-related autophagy suppression. *Mol. Brain* 15. <https://doi.org/10.1186/s13041-022-00947-2>.
- Yang, Z., Gong, M., Jian, T., Li, J., Yang, C., Ma, Q., Deng, P., Wang, Y., Huang, M., Wang, H., Yang, S., Chen, X., Yu, Z., Wang, M., Chen, C., Zhang, K., 2021. Mesenchymal stem cells ameliorate renal fibrosis by galectin-3/Akt/GSK3 β /Snail signaling pathway in adenine-induced nephropathy rat. <https://doi.org/10.1186/s13287-022-02959-0>.
- Yin, J., Valin, K.L., Dixon, M.L., Leavenworth, J.W., 2017. The role of microglia and macrophages in CNS homeostasis, autoimmunity, and cancer. *J. Immunol. Res.* <https://doi.org/10.1155/2017/5150678>.
- Zhang, H., Li, J., Yu, Y., Ren, J., Liu, Q., Bao, Z., Sun, S., Liu, X., Ma, S., Liu, Z., Yan, K., Wu, Z., Fan, Y., Sun, X., Zhang, Y., Ji, Q., Cheng, F., Wei, P.H., Ma, X., Zhang, S., Xie, Z., Niu, Y., Wang, Y.J., Han, J.D.J., Jiang, T., Zhao, G., Ji, W., Izpisua Belmonte, J.C., Wang, S., Qu, J., Zhang, W., Liu, G.H., 2023. Nuclear lamina erosion-induced resurrection of endogenous retroviruses underlies neuronal aging. *Cell Rep.* 42. <https://doi.org/10.1016/j.celrep.2023.112593>.
- Zhang, L., Pitcher, L.E., Prahalad, V., Niedernhofer, L.J., Robbins, P.D., 2023. Targeting cellular senescence with senotherapeutics: senolytics and senomorphics. *FEBS J.* <https://doi.org/10.1111/febs.16350>.
- Zhang, P., Kishimoto, Y., Grammatikakis, Ioannis, Gottimukkala, Cutler, K., Zhang, R.G., Abdelmohsen, S., Bohr, K., Misra Sen, V.A., Gorospe, J., Mattson, M., Neurosci Author manuscript, N. M.P., 2019a. Senolytic therapy alleviates A β -associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. *Nat. Neurosci.* <https://doi.org/10.1038/s41593-019-0372-9>.
- Zhu, Y., Tchkonja, T., Fuhrmann-Stroissnig, H., Dai, H.M., Ling, Y.Y., Stout, M.B., Pirtskhalava, T., Giorgadze, N., Johnson, K.O., Giles, C.B., Wren, J.D., Niedernhofer, L.J., Robbins, P.D., Kirkland, J.L., 2016. Identification of a novel senolytic agent, navitoclax, targeting the Bcl-2 family of anti-apoptotic factors. *Aging Cell* 15, 428–435. <https://doi.org/10.1111/ace.12445>.