PNAS NEXUS

PNAS Nexus, 2025, 4, pgaf103
https://doi.org/10.1093/pnasnexus/pgaf103
Advance access publication 22 April 2025
Research Report

Depletion of senescent cells improves surgery-induced neuroinflammation in aged mice

Sajeeshkumar Madhurakkat Perikamana[a], Hunter Newman[a,b], Yuru Vernon Shih[a], Lavonia Duncan[b], Hilal Ahmad Rather[a], Jiaoni Li[b], Ravikanth Velagapudi[c], Niccolò Terrando[c,d,e] and Shyni Varghese[a,b,f,*]

[a]Department of Orthopaedic Surgery, Duke University School of Medicine, Durham, NC 27710, USA
[b]Department of Biomedical Engineering, Duke University, Durham, NC 27710, USA
[c]Department of Anesthesiology, Duke University Medical Center, Durham, NC 27710, USA
[d]Department of Integrative Immunobiology, Duke University Medical Center, Durham, NC 27710, USA
[e]Department of Cell Biology, Duke University Medical Center, Durham, NC 27710, USA
[f]Department of Mechanical Engineering and Materials Science, Duke University, Durham, NC 27710, USA
*To whom correspondence should be addressed: Email: shyni.varghese@duke.edu
Edited By Hülya Bayir

Abstract

Aging has been identified as a leading risk factor for many diseases, including neurodegenerative disorders. While cellular senescence has been linked to age-related neurodegenerative conditions, its involvement in peripheral stress-associated brain disorders is just beginning to be explored. In this study, we investigated the impact of senescent cells on peripheral stress-induced neuroinflammation using orthopedic surgery as a model. Our results demonstrate an increased accumulation of senescent cells and neuroinflammation in the aged mouse hippocampus following surgery. Intermittent treatment of the mice with the senolytic drugs dasatinib and quercetin (D/Q) showed a significant reduction in surgery-induced senescent cell burden. This reduction in senescent cell accumulation was correlated with reduced surgery-induced neuroinflammation, as evidenced by decreased glial cell activity. Consistent with these observations, we also observed reduced levels of proinflammatory senescence-associated secretory phenotype factors in circulation, following fracture surgery, in mice treated with D/Q. Overall, our findings underscore the pivotal role of cellular senescence in surgery-induced neuroinflammation and highlight the therapeutic potential of eliminating senescent cells as a potential strategy to manage peripheral stress-induced neuroinflammatory conditions.

Keywords: cellular senescence, orthopedic trauma, neuroinflammation, senolytics, inflammaging

Significance Statement

Our study highlights the critical role of cellular senescence in peripheral stress-induced neuroinflammation in geriatric populations. The results demonstrate an increase in orthopedic trauma-associated senescent cell burden within the hippocampus of aged mice. Depletion of senescent cells using senolytics significantly reduced orthopedic trauma-induced neuroinflammation. These findings provide valuable insights into the mechanisms underlying postoperative neurocognitive complications and suggest senescent cell targeting as a therapeutic intervention to mitigate neuroinflammation.

Introduction

Abnormal neurological manifestations, including perioperative neurocognitive disorders such as delirium, are reported in aged populations following various peripheral insults including infections and surgeries such as orthopedic and cardiac surgeries (1–3). Neuroinflammation is central to all these pathologies and, in fact, is a key pathological hallmark of most neurological dysfunctions (4). The mechanisms driving increased vulnerability to neuroinflammation with age are less understood but are essential to reduce the clinical and socioeconomic burdens. Hallmarks of aging that drive susceptibility to acute and chronic diseases include genomic instability, telomere shortening, epigenetic changes, mitochondrial dysfunction, altered microenvironment and cellular compartments including stem/progenitor cell exhaustion, and cellular senescence (5). Cellular senescence is a key biological process that prevents abnormal cell proliferation; however, senescent cells can accumulate excessively in organs as a response to stress. In addition to cell cycle arrest, accumulation of senescent cells is characterized by the production of senescence-associated secretory phenotypes (SASPs) (6). Senescent cells exhibit up-regulation of cyclin-dependent kinase inhibitors—Cdkn2a (p16-Ink4a) and Cdkn1a (p21-Cip1)—and

Competing Interest: The authors declare no competing interests.
Received: June 19, 2024. **Accepted:** March 17, 2025

demonstrate resistance to apoptosis via up-regulation of senescent cell antiapoptotic pathways (7).

The secretome associated with the SASPs is enriched with proinflammatory cytokines, chemokines, extracellular matrix fragments, and degrading enzymes that can drive tissue dysfunction when accumulated excessively (8, 9). In addition to the autocrine effect, the senescent cells also induce senescence of the surrounding cells and spread the effect via paracrine signaling (10). Senescent cells resist apoptosis by up-regulating the senescent cell antiapoptotic pathway (SCAP), enhancing their survival and antiapoptotic capabilities (11). Different types of senescent cells employ various SCAPs to resist apoptosis (11). To date, several senolytics have been studied and found effective in eliminating senescent cells (12). Drugs targeting multiple SCAP network nodes are more effective at eliminating senescent cells and reducing off-target effects on nonsenescent cells compared with those targeting a single node (11). Among these, the combination of dasatinib and quercetin (D/Q) has shown promise by targeting multiple prosurvival pathways (13, 14). Dasatinib (D), an FDA-approved drug, promotes apoptosis by inhibiting Src kinase (15). Quercetin (Q), a naturally occurring flavonoid, inhibits BCL-2 family members such as BCL-xL, as well as HIF-1α, PI3-kinase pathways, and other SCAP components (11). This combination demonstrates a synergistic effect, clearing a broader range of senescent cells than either agent alone (11). The D/Q combination has been shown to clear senescent cells in cell culture experiments, in peripheral organs, and in the brain in animal studies (16–18). The results from the human clinical trial of D/Q are starting to emerge, and the initial studies showed that patients with idiopathic pulmonary fibrosis significantly improved gait functions with D/Q treatment (19).

Cellular senescence is associated with many neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis (20–23). Senescent cell markers have been identified in various brain cell populations under multiple pathological conditions (21, 24, 25). Senescent cell clearance from the brain using senolytics has been shown to alter disease pathologies in mouse models of Parkinson's disease and tau-dependent neurodegenerative diseases including Alzheimer's disease (20, 25, 26). In this study, we employed an orthopedic surgery model to study perioperative neuroinflammation to investigate the potential of cellular senescence on peripheral insult-induced neuroinflammation in aged mice (27). Previous studies have shown that surgery elevates the systemic inflammatory factors, blood–brain barrier (BBB) breaching, and neuroinflammation, and this phenomenon was particularly exacerbated in aged animals (28, 29). Leveraging these observations, we examined the role of cellular senescence in perioperative neuroinflammation where senescence was modulated using a clinically relevant senolytic drug, D/Q. Our studies found that fracture surgery resulted in significant accumulation of senescence cells in the hippocampal region of aged mice and depletion of senescent cells alleviated surgery-induced neuroinflammation. These findings were correlated with elevation of SASP secretory factors in circulation. Using in vitro cell culture, we showed that the SASP secretory factors from the peripheral immune cells can induce senescence of the brain cells.

Results

Aged mice exhibit enhanced senescence in the hippocampus following orthopedic surgery

Hippocampal tissues of 22-month-old C57BL/6 mice that underwent tibial fracture surgery were analyzed for senescence accumulation at 24 h following surgery and compared against a control group without surgery (Fig. 1A). RT^2 Profiler PCR analysis of hippocampal tissue showed an elevation of various gene markers associated with cellular senescence (Fig. 1B). The cellular senescence following fracture surgery was further assessed by gene expression analyses of hippocampal cells, which showed a significant increase in p21 expression for the surgery group compared with the control group (Fig. S2B). Concomitant with these findings, histochemical analyses for senescent markers, p2, p16, and senescence-associated β-gal (SA-β-gal) showed a significant increase in hippocampi of aged mice that underwent surgery (Figs. IC–F and S1A). No such increase in senescent cell accumulation following tibial fracture surgery was observed in 3-month-old animals (Fig. S2A–C). To assess whether pretreating the animals with senolytic drugs could prevent surgery-induced hippocampal senescence, the mice were treated with a cocktail of D/Q for four intermittent cycles (termed as D/Q-4) as described in the Supplementary Methods. Animals treated with D/Q showed a significant reduction in surgery-induced senescent cell accumulation as evident by the gene expression, SA-β-gal staining, and immunofluorescent staining for p21 and p16 (Figs. 1B–F and S1A and B).

Next, we examined the cell populations that exhibit senescence. To this end, we costained the major hippocampal cells—neurons, microglia, and astrocytes—with the senescent marker p21 (Fig. 2A–C). We observed a significant increase in ionized calcium-binding adaptor molecule 1 (IBA1)-positive microglial cells expressing p21 following surgery in the vehicle-treated group compared with the D/Q-treated group and no-surgery control group (i.e. no surgery, no treatment) (Fig. 2A). Similarly, the percentage of NeuN-positive neurons that express p21 was also found to be significantly increased following surgery in the vehicle-treated group compared with the D/Q-treated group and no-surgery control group (Fig. 2B). Costaining of glial fibrillary acidic protein (GFAP) with p21 showed no significant change in astrocyte population in the vehicle-treated group (Fig. 2C). The senescence of the brain cells and the effect of D/Q treatment postsurgery were further confirmed by flow cytometry. Analysis of the whole brain revealed the presence of senescent microglia ($IBA1^+/p21^+$), neurons ($NeuN^+/p21^+$), and astrocytes ($GFAP^+/p21^+$) following surgery, which were significantly reduced with the D/Q treatment (Fig. 2D–F).

Given the effect of D/Q treatment on surgery-induced hippocampal cell senescence, we next examined whether a short duration of D/Q treatment would yield the same outcome. Towards this, we subjected the animals to two intermittent cycles of 5 days of treatment followed by 4 days of rest (D/Q-2) or one cycle of 5 consecutive days of treatment (D/Q-1) prior to surgery. The surgery-induced changes in senescent cell accumulation in the hippocampus were assessed and compared against the D/Q-4 group. Analyses of the p21-positive cells in the hippocampus showed that the cohorts subjected to D/Q-2 exhibited a significant reduction in surgery-induced senescence, similar to D/Q-4, while D/Q-1 had minimal to no effect (Fig. 3A). A similar trend was also observed with the senescent marker p16 and SA-β-gal (Figs. 3B and S3).

D/Q treatment reduced systemic SASPs following orthopedic surgery

To determine surgery-induced changes in SASPs in the circulation, we performed multiplex analysis of the peripheral blood using a customized cytokine array at 6 and 24 h following surgery. The cytokine values were normalized to the corresponding baseline value for each animal (i.e. cytokines levels prior to surgery) and expressed as fold change. To determine the effect of age on surgery-induced SASP factors, the cytokine levels of aged animals

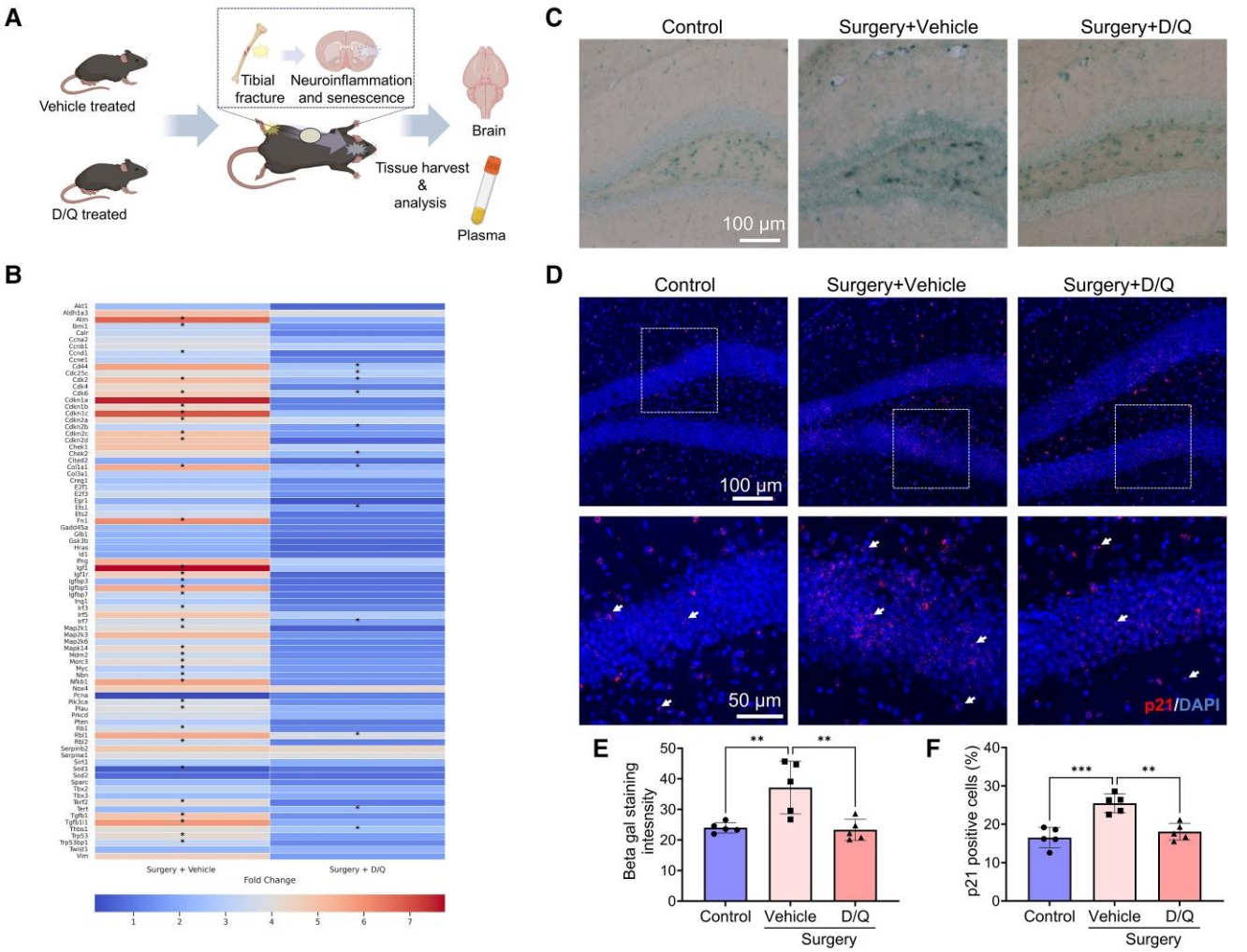

Fig. 1. D/Q treatment-attenuated surgery-induced hippocampal senescence. A) Twenty-two-month-old mice were divided into control (i.e. no surgery, no treatment), vehicle, or D/Q treatment groups. After the drug administration, mice were subjected to tibial fracture. Mice were sacrificed 24 h after fracture surgery, the brain was harvested, and the hippocampus was used for various analyses. B) Experimental condition-dependent gene expression analysis of core senescence and SASP transcripts in the hippocampus ($n = 3$) analyzed using RT² Profiler PCR Array. C) and E) Histochemical analysis of SA-β-gal in the hippocampus ($n = 5$). D) and F) Immunohistochemical analysis of senescence marker p21 showed an elevation in senescence accumulation following surgery in the hippocampal tissue, which was attenuated with D/Q treatment ($n = 5$). Statistical significances were determined using one-way ANOVA with post hoc Tukey's test in GraphPad Prism 10.2.1. *$P < 0.05$; **$P < 0.01$. Sub-figure (A) was created using Biorender.com.

were compared to the young animals. This analysis showed that many of the key SASP factors were significantly increased in the plasma of aged animals compared with the young animals at 6 h posttibial fracture surgery (Fig. 4A). Specifically, we found that SASP factors IL-17a, IL-1β, IL-6, TNF-alpha, MCP-1, IP-10, and MIP-1α were significantly elevated in the plasma of aged animals at 6 h postsurgery. Many of these SASP factors were returned to the baseline by 24 h postsurgery. To determine the effect of D/Q treatment on surgery-induced changes in SASP factors, we compared the aged animals with (i.e. D/Q treatment) and without (i.e. vehicle treatment) the drug treatment. The D/Q-treated aged animals showed an attenuation of the SASP factors IL-27, IL-33, IL-1β, IL-6, SDF-1, MCP-1, IP-10, and MIP-1α in the peripheral blood following surgery (Fig. 4B). In agreement with the SASP levels in the peripheral blood, flow cytometry analyses of peripheral blood cells showed a significant decrease in p21-positive senescent cells with D/Q treatment compared with vehicle-treated group (Fig. S4A). Additionally, SA-β-gal staining revealed an accumulation of senescent cells at the fracture site, which was reduced by D/Q treatment (Fig. S4B).

SASP factors induce brain cell senescence in an in vitro cell culture model

Using an in vitro cell culture model, we next examined whether SASP factors from the peripheral cells can induce senescence of brain cells. To this end, we used human iPSC-derived neurons and astrocytes, human microglia cells HMC3, and human monocytic cells THP-1. To induce senescence of THP-1 cells and promote secretion of SASP factors, the cells were cultured for 2 consecutive days in the presence of bleomycin, a senescence-inducing drug (30). The cells were then cultured in medium with and without D/Q drugs for 12 days, and the conditioned medium was collected as detailed in the Supplementary Methods. Gene expression analysis showed an increase in p21 expression following bleomycin treatment, while the cells cultured with D/Q exhibited significantly reduced p21 levels (Fig. S5A). The in vitro cell cultures of neurons, astrocytes, and microglial cells were exposed to the conditioned medium generated from the THP-1 cell cultures with or without D/Q, or those without any exposure to bleomycin. The brain cells exposed to the conditioned medium showed culture condition-dependent changes in senescence induction (Fig. S4B–G).

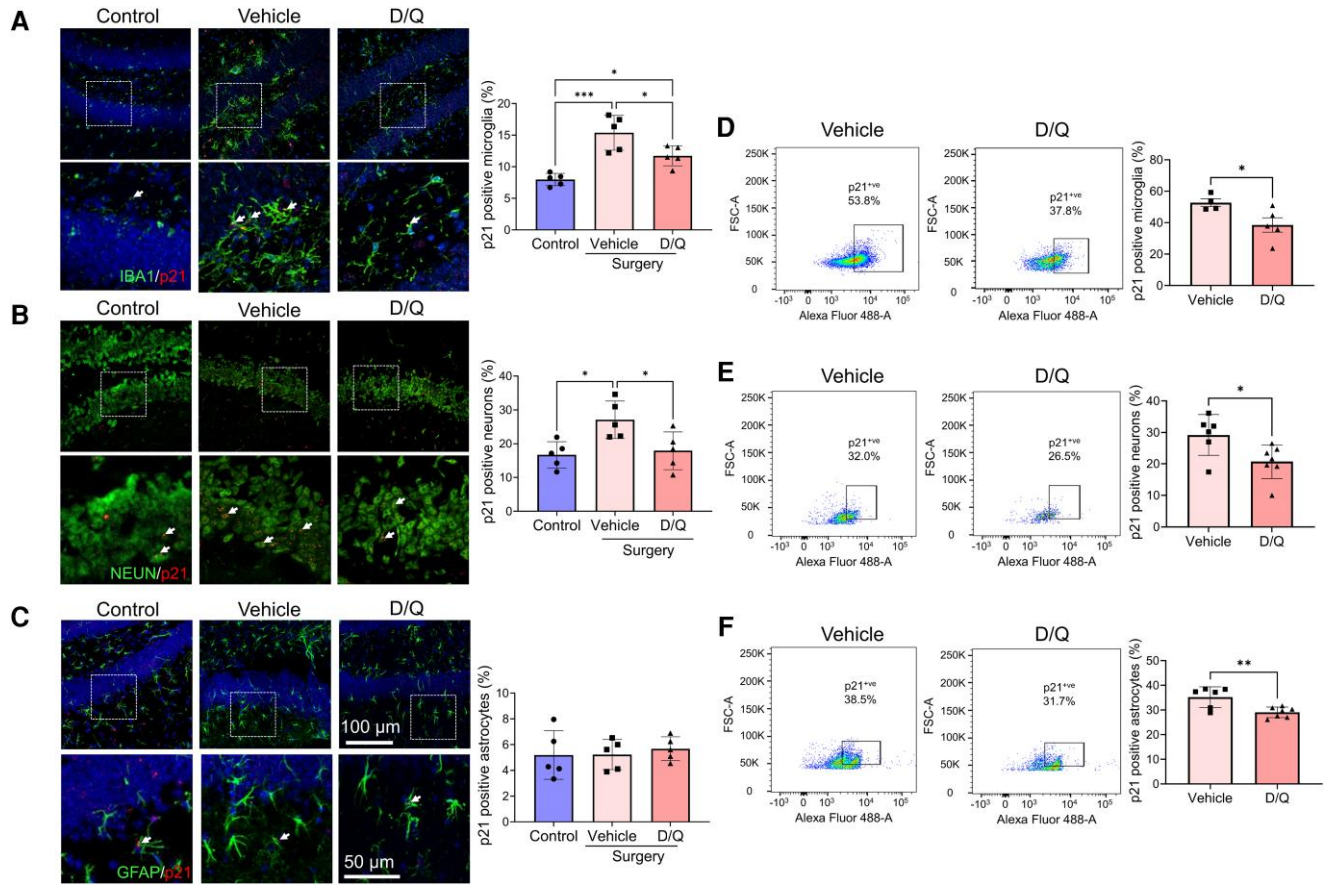

Fig. 2. D/Q treatment-mediated changes in surgery-induced senescent cell burden in hippocampal cell population. Analyses of p21-positive: A) microglia, stained using antibody against IBA1; B) neurons, stained using antibody against NeuN; and C) astrocytes, stained using antibody against GFAP. $n = 5$. Statistical significances were determined using one-way ANOVA with post hoc Tukey's test in GraphPad Prism 10.2.1. *$P < 0.05$; **$P < 0.01$; ****$P < 0.0001$. Flow cytometry analysis of p21-positive D) microglia, E) neurons, and F) astrocytes ($n = 4$–7). Statistical significances were determined using Student's t test in GraphPad Prism 10.2.1.

Specifically, the brain cells cultured in THP-1-conditioned medium exposed to bleomycin exhibited significantly higher levels of SA-β-gal-positive staining compared with THP-1 cultures treated with D/Q or the control cultures (i.e. THP-1 without bleomycin exposure) (Fig. S5B, D, and F). Gene expression analysis of p21 further corroborated these findings (Fig. S5C, E, and G).

Depletion of senescent cells mitigated the orthopedic surgery-induced neuroinflammation in male and female mice

Previous studies have shown significant neuroinflammation following fracture surgery in aged animals (29). Consistent with the prior studies, aged mice that underwent tibial fracture surgery exhibited postsurgical neuroinflammation compared with the control (i.e. without surgery) as indicated by the changes to the glial cells—microglia and astrocytes—in the hippocampus of the brain (Fig. 5A and B). Fluorescence intensity analyses for IBA1 and GFAP showed higher levels in vehicle-treated surgery group compared with the control (i.e. no treatment, no surgery). Immunostaining of IBA1 (a microglial marker) with CD68, a marker for reactive microglia, revealed a significant increase in activated microglia in the vehicle-treated surgery group compared with the control groups (Fig. 5C). The surgery-induced activation of glial cells was alleviated in animals subjected to D/Q-4 or D/Q-2 treatment regime (Figs. 5A–C and S5A–C). No such change in glial cell activation was observed with the D/Q-1 treatment (Figs. 5A–C and S6A–C).

We also performed gene expression analysis of key proinflammatory molecules—IL-1β, IL-6, and TNF-α—in the hippocampus, which revealed a significant down-regulation of these markers in the hippocampus with the D/Q treatment (Fig. 5D).

Finally, the effect of sex on D/Q treatment was examined by using C57BL6 female mice of the same age. Akin to the male cohorts, the female mice that were subjected to tibial fracture surgery showed a significant increase in senescent cell accumulation compared with the no-surgery group. This increase in senescent cell accumulation was attenuated with D/Q treatment (Figs. 6A and S7A and B). The D/Q treatment-mediated decrease in senescent cell accumulation also resulted in reduced neuroinflammation following surgery, as evident by the immunohistochemical analysis of astrocyte marker GFAP and microglial marker IBA1 (Fig. 6B and C).

Discussion

In this study, we investigated the role of senescent cells in peripheral stress-induced neuroinflammation using orthopedic surgery as a model system. We found that the surgery resulted in a dynamic shift in the age-dependent senescent cell landscape in the mouse hippocampus. Although previous studies have shown that direct trauma can promote cellular senescence in the brain cell population, our results demonstrate accumulation of senescent cell populations in the hippocampus of aged mice following

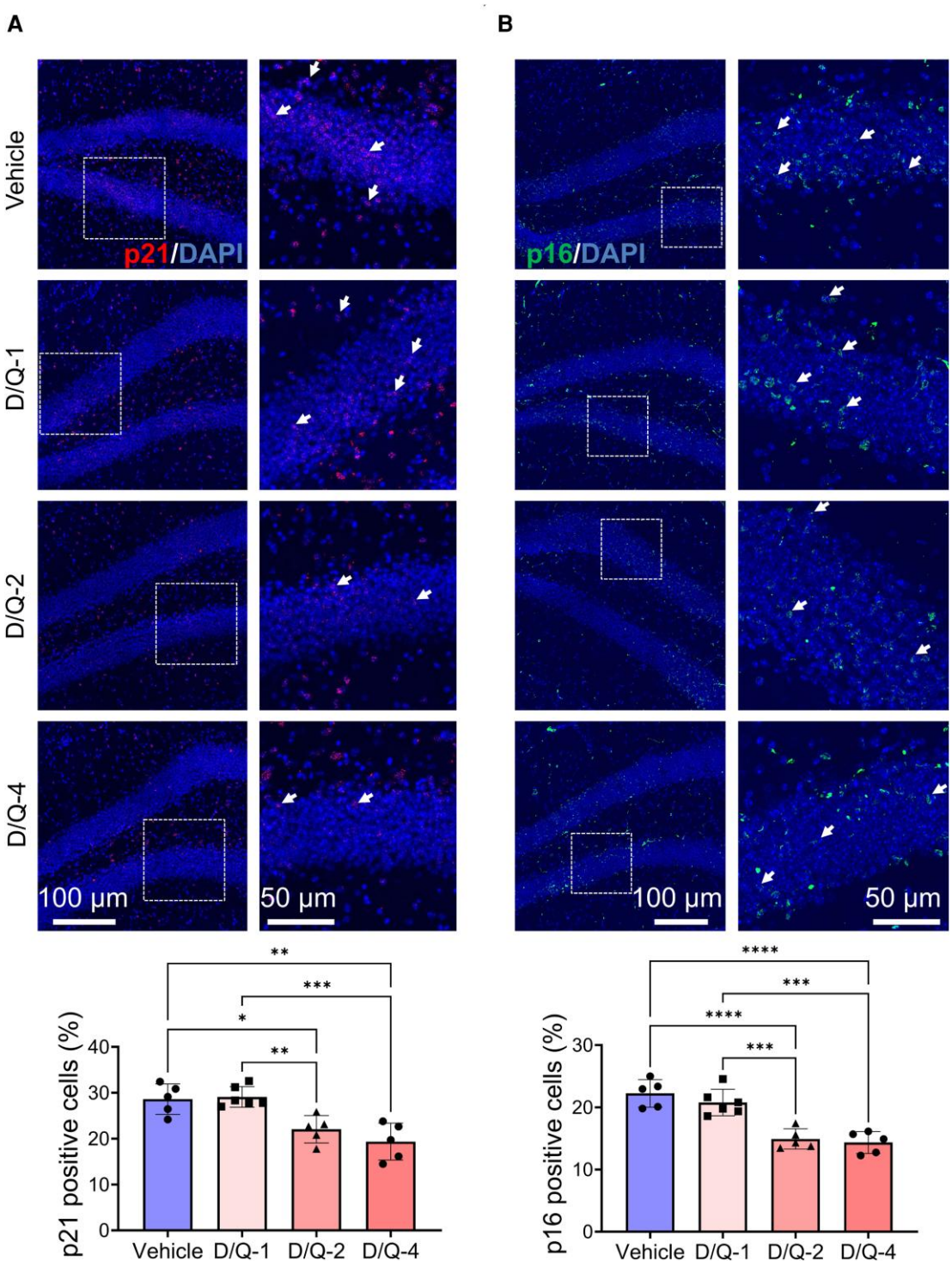

Fig. 3. D/Q treatment regimen-mediated changes in surgery-induced senescence accumulation in the hippocampus. Immunohistochemical analysis for senescence markers A) p21 and B) p16 showing treatment duration-dependent changes in senescent cell accumulation in the hippocampus ($n = 5$–6). Statistical significances were determined using one-way ANOVA with post hoc Tukey's test in GraphPad Prism 10.2.1. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

an orthopedic surgery (20, 31–33). In an effort to modulate the senescent cell accumulation, we used the widely studied senolytic drug D/Q (13, 14).

Our results showed that the aged mice intermittently administered with D/Q, long and short duration, prior to surgery showed decreased senescent cell accumulation in the hippocampus. Previous work has shown neuroinflammation of aged mice that underwent tibial fracture surgery (29). Increased senescent cell burden in the brain has also been shown to contribute to neuroinflammation (34, 35). Consistent with these findings, aged animals that underwent tibial fracture surgery showed higher glial cell activity, which was attenuated with the D/Q treatment regimen that was effective in reducing senescent cell burden. Together, the results show a strong association between cellular senescence and neuroinflammation. Several studies have shown that the combination of D and Q can target senescent cells by interfering with

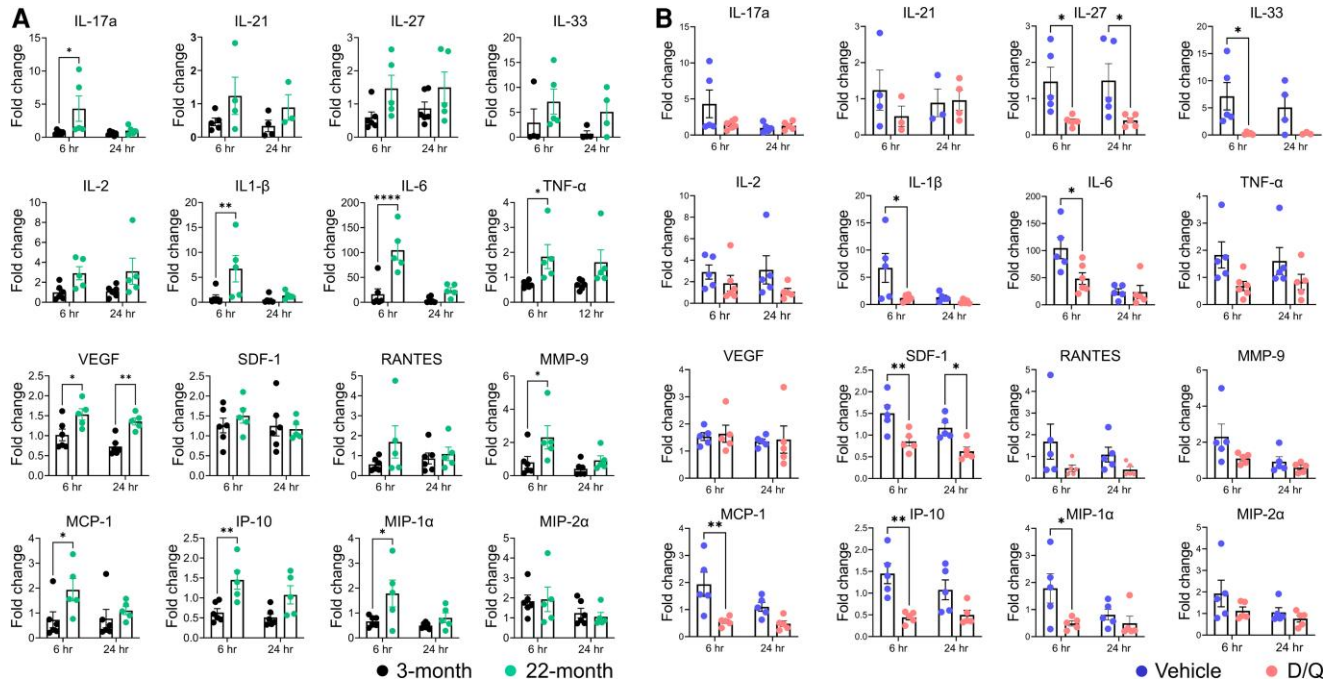

Fig. 4. Systemic SASP factors were elevated in the aged animals following surgery, and D/Q treatment attenuated the elevation of systemic SASP factors. A) Multiplex analysis of the major SASP factors in the plasma of young and aged animals at 6 and 24 h posttibial fracture surgery. B) Multiplex analysis of the major SASP factors in the plasma of vehicle- and D/Q-treated aged animals posttibial fracture surgery at 6 and 24 h. Statistical significances were determined using two-way ANOVA in GraphPad Prism 10.2.1. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$; ****$P < 0.0001$.

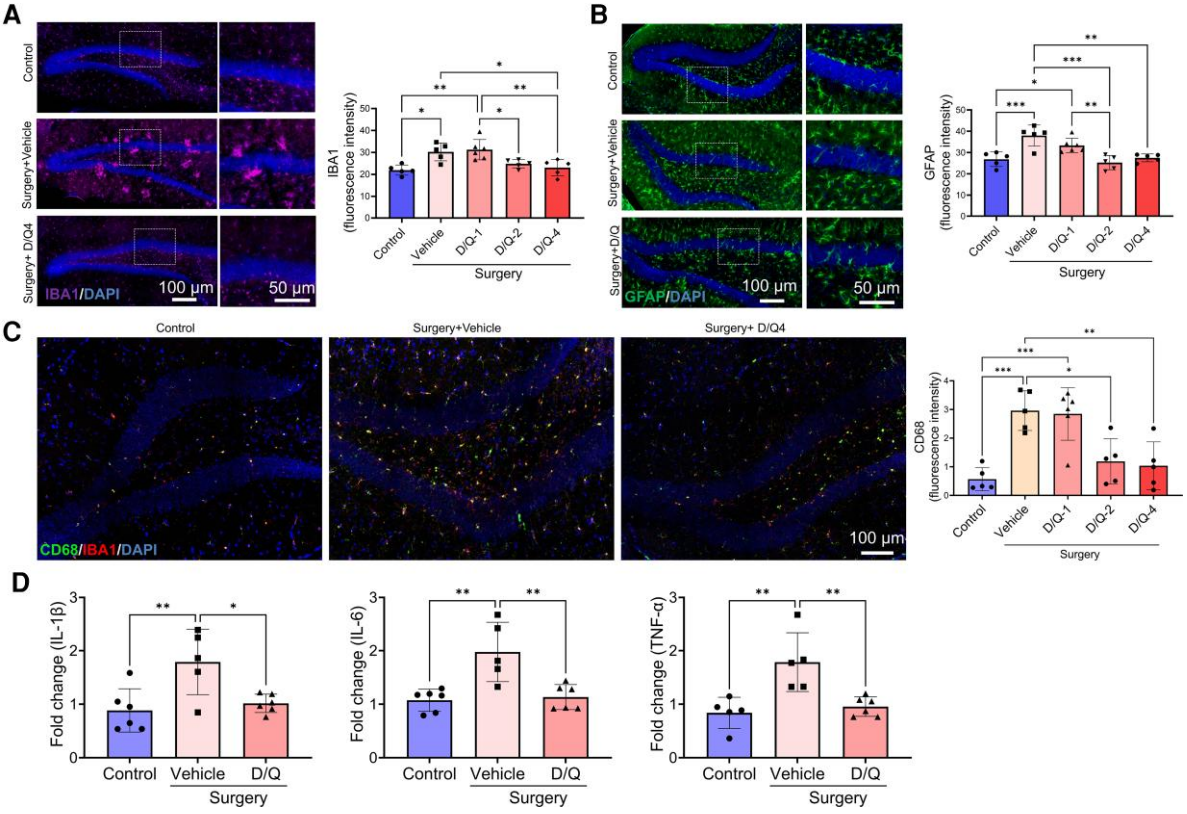

Fig. 5. D/Q treatment-induced changes in senescent cell accumulation in the hippocampus correlate with the surgery-induced neuroinflammation. Immunohistochemical analysis of A) microglia, stained using antibody against IBA1, and B) astrocytes, stained using antibody against GFAP. C) Representative images of immunofluorescence staining of IBA1 and reactive microglial marker, CD68, in the hippocampus. D) Relative gene expression of various inflammatory markers in the mouse hippocampus ($n = 5$–6). Statistical significances were determined using one-way ANOVA with post hoc Tukey's test in GraphPad Prism 10.2.1. *$P < 0.05$; **$P < 0.01$.

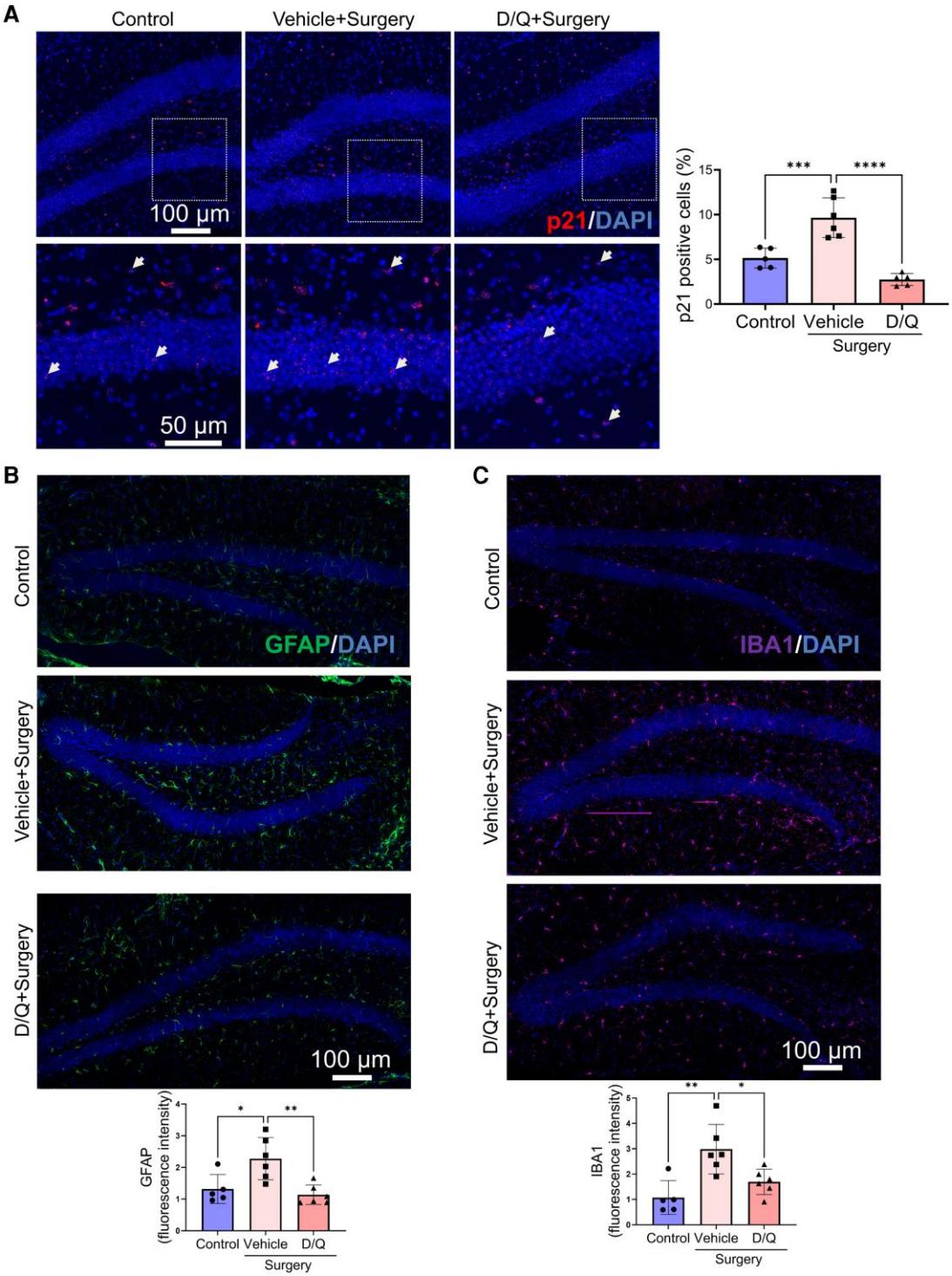

Fig. 6. D/Q treatment-attenuated surgery-induced hippocampal senescence and neuroinflammation in female mice. Immunohistochemical staining of the hippocampus tissue for A) senescence marker p21, B) astrocyte maker GFAP, and C) microglial marker IBA1 ($n = 5$–6). Statistical significances were determined using one-way ANOVA with post hoc Tukey's test in GraphPad Prism 10.2.1. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

their prosurvival network of tyrosine kinases, BCL-2, p53, p21, serpine, PI3K/AKT, and others (36, 37). Preclinical animal studies and clinical trials have demonstrated that D/Q treatment reduces the number of senescent cells (13, 14, 19). In line with these findings, our results show reduced senescence following D/Q treatment, though our study does not specifically demonstrate selective targeting of senescent cells. Study by Ogrodnik et al. (18) has shown that the elimination of senescent cells throughout the body alleviated brain inflammation and cognitive impairment. Another study by Ryu et al. (38) has shown that dasatinib alleviates lipopolysaccharide-induced neuroinflammation by acting through inhibiting TLR4/AKT and/or TLR4/ERK signaling, suggesting additional organ- and/or disease-specific mechanisms. Nonetheless, irrespective of the specific molecular mechanism, D/Q treatment individually or in combination results in a significant reduction in proinflammatory cytokine levels.

A key characteristic of senescent cells is the proinflammatory SASP, which can influence the surrounding and distant environment through autocrine, juxtacrine, and paracrine effects (10, 39). Besides the conventional cellular senescence resulting from telomere shortening after repeated cell division, accumulation of cellular senescence can also be accelerated by stressful stimuli and injuries (40, 41). It is increasingly evident that senescent cell burden can result in pathologies that can transform acute organ injuries into a chronic state (42, 43). In our study, multiplex cytokine assay from the peripheral blood plasma showed increased levels of SASP factors in the circulation of the aged animals following surgery. The proinflammatory SASP factors were transiently increased following surgery, akin to prior studies that assessed surgery-induced proinflammatory molecules in circulation (44, 45). As anticipated, the D/Q treatment mitigated the elevated SASPs level in the circulation following surgery. Further, the flow cytometric analyses of p21-positive senescent cells in the peripheral blood plasma showed a similar trend, with a significantly reduced percentage of p21-positive cells in the D/Q-treated animals compared with the vehicle-treated group. We also observed significantly reduced senescent cell accumulation at the fracture site in D/Q-treated animals. Together, these results suggest that D/Q treatment reduced the senescent cell burden both locally and systemically, leading to reduced systemic inflammation. Many emerging preclinical and clinical studies have shown that the elevated proinflammatory factors in the systemic circulation can potentially breach the BBB and thereby make the brain tissue accessible to different blood-borne factors (46, 47). Our in vitro cell culture studies suggest that SASP factors from peripheral monocytes can induce senescence of the brain cells, which we posit is the possible mechanism we observe in vivo. Noteworthy, studies have suggested that SASP is one of the principal mechanisms promoting tissue degeneration and inflammation.

In summary, our findings collectively show a strong correlation between cellular senescence and surgery-induced neuroinflammation. The highly inflammatory state following fracture, as suggested by the SASP measurements, in circulation, may contribute to the senescent cell accumulation in the hippocampus. Further studies are needed to test this hypothesis and identify the key contributions made by the SASP factors in crossing the BBB and contributing to the senescent cell burden in the hippocampus. Similarly, additional studies are needed to determine the specific molecular mechanisms underlying senolytic treatment in cells and its effects on alleviating neuroinflammation. Nevertheless, our findings show the key role played by senescence in surgery-induced neuroinflammation. There are also clear implications for common postoperative neurological complications, such as delirium where this model has been previously applied, to evaluate SASP factors from clinical samples in correlation with cognitive testing. In conclusion, these findings have further clinical implications for the development of therapeutic interventions to address neuroinflammation and ultimately improve patient outcomes.

Methods

Animal care

Animal experiments were performed under protocol (A116-23-05) approved by the Institutional Animal Care and Use Committee of the Duke University and performed in accordance with the NIH and national and international guidelines for laboratory animal care.

Acknowledgments

The authors thank Raina Kikani, Giwon Cho, and Minhaj Bhuiyan for their help in preparing the manuscript. The authors would also like to thank the Duke Biomarker Core Facility for their assistance in conducting the multiplex cytokine analysis.

Supplementary Material

Supplementary material is available at *PNAS Nexus* online.

Funding

This work was funded by the National Institutes of Health (RF1AG076203 and R01AG074491).

Data Availability

All data generated or analyzed during this study are included in the manuscript or the supplementary materials.

References

1 Chae JHJ, Miller BJ. 2015. Beyond urinary tract infections (UTIs) and delirium: a systematic review of UTIs and neuropsychiatric disorders. *J Psychiatr Pract.* 21(6):402–411.
2 Lascola CD, *et al.* 2023. Blood-brain barrier permeability and cognitive dysfunction after surgery–A pilot study. *J Clin Anesth.* 86: 111059.
3 Garcez FB, *et al.* 2020. Delirium and adverse outcomes in hospitalized patients with COVID-19. *J Am Geriatr Soc.* 68(11):2440–2446.
4 Khodkam M. 2022. Neuroinflammation and neurodegenerative disease. *Neurol Lett.* 1(1):19–20.
5 Melzer D, Pilling LC, Ferrucci L. 2020. The genetics of human ageing. *Nat Rev Genet.* 21(2):88–101.
6 Di Micco R, Krizhanovsky V, Baker D, di Fagagna F. 2021. Cellular senescence in ageing: from mechanisms to therapeutic opportunities. *Nat Rev Mol Cell Biol.* 22(2):75–95.
7 Soto-Gamez A, Quax WJ, Demaria M. 2019. Regulation of survival networks in senescent cells: from mechanisms to interventions. *J Mol Biol.* 431(15):2629–2643.
8 Byun H-O, Lee Y-K, Kim J-M, Yoon G. 2015. From cell senescence to age-related diseases: differential mechanisms of action of senescence-associated secretory phenotypes. *BMB Rep.* 48(10):549.
9 Özcan S, *et al.* 2016. Unbiased analysis of senescence associated secretory phenotype (SASP) to identify common components following different genotoxic stresses. *Aging.* 8(7):1316–1329.
10 Hoare M, Narita M. 2013. Transmitting senescence to the cell neighbourhood. *Nat Cell Biol.* 15(8):887–889.
11 Zhu Y, *et al.* 2015. The Achilles' heel of senescent cells: from transcriptome to senolytic drugs. *Aging Cell.* 14(4):644–658.
12 Kirkland J, Tchkonia T. 2020. Senolytic drugs: from discovery to translation. *J Intern Med.* 288(5):518–536.
13 Novais EJ, *et al.* 2021. Long-term treatment with senolytic drugs dasatinib and quercetin ameliorates age-dependent intervertebral disc degeneration in mice. *Nat Commun.* 12(1):5213.
14 Xu M, *et al.* 2018. Senolytics improve physical function and increase lifespan in old age. *Nat Med.* 24(8):1246–1256.
15 Chan CM, *et al.* 2012. Targeted inhibition of Src kinase with dasatinib blocks thyroid cancer growth and metastasis. *Clin Cancer Res.* 18(13):3580–3591.
16 Aguayo-Mazzucato C, *et al.* 2019. Acceleration of β cell aging determines diabetes and senolysis improves disease outcomes. *Cell Metab.* 30(1):129–142.e4.
17 Wang H, *et al.* 2020. Senolytics (DQ) mitigates radiation ulcers by removing senescent cells. *Front Oncol.* 9:1576.

18 Ogrodnik M, *et al.* 2021. Whole-body senescent cell clearance alleviates age-related brain inflammation and cognitive impairment in mice. *Aging Cell*. 20(2):e13296.
19 Petr M, *et al.* 2024. Pharmacological interventions in human aging. *Ageing Res Rev*. 95:102213.
20 Baker DJ, Petersen RC. 2018. Cellular senescence in brain aging and neurodegenerative diseases: evidence and perspectives. *J Clin Invest*. 128(4):1208–1216.
21 Guerrero A, De Strooper B, Arancibia-Cárcamo IL. 2021. Cellular senescence at the crossroads of inflammation and Alzheimer's disease. *Trends Neurosci*. 44(9):714–727.
22 Chinta SJ, *et al.* 2013. Environmental stress, ageing and glial cell senescence: a novel mechanistic link to Parkinson's disease? *J Intern Med*. 273(5):429–436.
23 Gaikwad S, *et al.* 2021. Tau oligomer induced HMGB1 release contributes to cellular senescence and neuropathology linked to Alzheimer's disease and frontotemporal dementia. *Cell Rep*. 36(3):109419.
24 Jurk D, *et al.* 2012. Postmitotic neurons develop a p21-dependent senescence-like phenotype driven by a DNA damage. *Aging Cell*. 11(6):996–1004.
25 Bussian TJ, *et al.* 2018. Clearance of senescent glial cells prevents tau-dependent pathology and cognitive decline. *Nature* 562(7728): 578–582.
26 Martínez-Cué C, Rueda N. 2020. Cellular senescence in neurodegenerative diseases. *Front Cell Neurosci*. 14:16.
27 Xiong C, Zhang Z, Baht GS, Terrando N. 2018. A mouse model of orthopedic surgery to study postoperative cognitive dysfunction and tissue regeneration. *J Vis Exp*. 132:e56701.
28 Wang P, *et al.* 2020. Neurovascular and immune mechanisms that regulate postoperative delirium superimposed on dementia. *Alzheimers Dement*. 16(5):734–749.
29 David-Bercholz J, *et al.* 2022. Conserved YKL-40 changes in mice and humans after postoperative delirium. *Brain Behav Immun Health*. 26:100555.
30 Lozano-Torres B, *et al.* 2019. The chemistry of senescence. *Nat Rev Chem*. 3(7):426–441.
31 Fletcher-Sananikone E, *et al.* 2021. Elimination of radiation-induced senescence in the brain tumor microenvironment attenuates glioblastoma recurrence. *Cancer Res*. 81(23):5935–5947.
32 Ritzel RM, *et al.* 2019. Old age increases microglial senescence, exacerbates secondary neuroinflammation, and worsens neurological outcomes after acute traumatic brain injury in mice. *Neurobiol Aging*. 77:194–206.
33 Hussong SA, *et al.* 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(1):2367.
34 Nelke C, Schroeter CB, Pawlitzki M, Meuth SG, Ruck T. 2022. Cellular senescence in neuroinflammatory disease: new therapies for old cells? *Trends Mol Med*. 28(10):850–863.
35 Zhang P, *et al.* 2019. Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. *Nat Neurosci*. 22(5):719–728.
36 Kirkland JL, Tchkonia T. 2017. Cellular senescence: a translational perspective. *EBioMedicine*. 21:21–28.
37 Prašnikar E, Borišek J, Perdih A. 2021. Senescent cells as promising targets to tackle age-related diseases. *Ageing Res Rev*. 66: 101251.
38 Ryu K-Y, *et al.* 2019. Dasatinib regulates LPS-induced microglial and astrocytic neuroinflammatory responses by inhibiting AKT/STAT3 signaling. *J Neuroinflammation*. 16:190.
39 Narita M. 2019. Juxtacrine regulation of cellular senescence. *BMB Rep*. 52(1):3.
40 de Magalhães JP, JF P. 2018. Stress, cell senescence and organismal ageing. *Mech Ageing Dev*. 170:2–9.
41 Khan SJ, *et al.* 2010. Stress-induced senescence exaggerates post-injury neointimal formation in the old vasculature. *Am J Physiol Heart Circ Physiol*. 298(1):H66–H74.
42 Kelly J, Khan AA, Yin J, Ferguson TA, Apte RS. 2007. Senescence regulates macrophage activation and angiogenic fate at sites of tissue injury in mice. *J Clin Invest*. 117(11):3421–3426.
43 Aravinthan AD, Alexander GJ. 2016. Senescence in chronic liver disease: is the future in aging? *J Hepatol*. 65(4):825–834.
44 Cibelli M, *et al.* 2010. Role of interleukin-1β in postoperative cognitive dysfunction. *Ann Neurol*. 68(3):360–368.
45 Terrando N, *et al.* 2010. Tumor necrosis factor-α triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci U S A*. 107(47):20518–20522.
46 Varatharaj A, Galea I. 2017. The blood-brain barrier in systemic inflammation. *Brain Behav Immun*. 60:1–12.
47 Jeon M-T, *et al.* 2021. Emerging pathogenic role of peripheral blood factors following BBB disruption in neurodegenerative disease. *Ageing Res Rev*. 68:101333.