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Systematic Review

Evidence for a Conserved Metabolic Architecture of Cellular Senescence Across Neurodegenerative Diseases: A Systematic Review

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Abstract

Background: Cellular senescence contributes to neurodegenerative disease through chronic inflammatory signaling, mitochondrial dysfunction, and metabolic remodeling. Although metabolomic studies have identified numerous metabolic abnormalities in neurodegeneration, their relationship with cellular senescence has not been systematically evaluated. **Methods**: This systematic review followed PRISMA 2020 guidelines. An artificial intelligence-assisted semantic search using Elicit was supplemented by investigator-led screening and additional PubMed and Embase searches. Twenty-three peer-reviewed studies met predefined eligibility criteria. Data were verified against the original publications and synthesized qualitatively according to recurring metabolic pathways and senescence-associated mechanisms. **Results**: Four recurrent metabolic themes emerged: (1) disruption of NAD^+ homeostasis, purine/nucleotide, and redox metabolism; (2) mitochondrial dysfunction and glycolytic reprogramming; (3) lipid remodeling, including cholesterol, oxysterol, sphingolipid, and lipid-droplet dysregulation; and (4) circulating metabolic signatures with potential translational relevance. These alterations repeatedly converged on senescence-associated features including oxidative stress, mitochondrial dysfunction, chronic inflammatory signaling, and activation of $p16^{INK4a}$-, $p21^{Cip1}$-, and SASP-related pathways. In preclinical models, interventions targeting NAD^+ metabolism, mitochondrial function, lipid homeostasis, autophagy, or senescent cells attenuated senescence-associated phenotypes and improved metabolic homeostasis. **Conclusions**: Current evidence supports a close association between metabolic remodeling and cellular senescence in neurodegenerative disease. Rather than a single senescence-specific metabolite, coordinated alterations across interconnected metabolic networks appear to provide more informative indicators of the senescent phenotype. Integrated multi-omic approaches may therefore improve biomarker development and identify metabolism-based therapeutic strategies, although methodological heterogeneity and limited longitudinal human data remain important barriers to clinical translation.

Keywords: cellular senescence; metabolomics; neurodegenerative disease; Alzheimer's disease; Parkinson's disease; biomarkers; NAD^+ metabolism; lipid metabolism; mitochondrial dysfunction; systematic review

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Academic Editor: Stewart Graham

Received: 21 September 2026
Revised: 21 October 2026
Accepted: 27 October 2026
Published: 16 November 2026

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1. Introduction

Cellular senescence is a stress-induced cellular state characterized by stable cell-cycle arrest accompanied by extensive phenotypic, molecular, and metabolic remodeling. Senescence can be triggered by persistent DNA damage, telomere attrition, oxidative stress, mitochondrial dysfunction, proteotoxic stress, and oncogenic signaling. Senescent cells commonly exhibit increased senescence-associated β-galactosidase (SA-β-gal) activity, chromatin remodeling, altered metabolism, and expression of cell-cycle inhibitors such as $p16^{INK4a}$ and $p21^{CIP1}$ [1,2]. Many also develop a senescence-associated secretory phenotype (SASP), characterized by secretion of pro-inflammatory cytokines, chemokines, growth factors, proteases, extracellular matrix-modifying enzymes, and bioactive lipids [3]. Although transient senescence contributes to processes such as tissue repair and tumor suppression, the long-term persistence of senescent cells disrupts tissue homeostasis through chronic inflammation, altered intercellular communication, and metabolic dysfunction [2,4].

Increasing evidence implicates cellular senescence in both normal brain aging and the pathogenesis of neurodegenerative disease. Senescence-associated phenotypes have been identified in astrocytes, microglia, endothelial cells, neural progenitor cells, and, under certain conditions, post-mitotic neurons, although the molecular features of senescence differ among these cell populations [5–7]. Through SASP signaling and other paracrine mechanisms, senescent neural and vascular cells promote chronic neuroinflammation, impair neuronal metabolic support, alter extracellular matrix composition, and increase the vulnerability of neighboring cells. Consistent with a functional contribution, experimental clearance of senescent cells reduces neuroinflammation and improves cognitive function in several models of aging and neurodegeneration [8].

Neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS), are clinically distinct but share numerous pathogenic mechanisms, including mitochondrial dysfunction, oxidative stress, impaired proteostasis, chronic neuroinflammation, lipid dysregulation, and altered cellular energy metabolism [9,10]. Because aging is the greatest risk factor for many of these disorders, cellular senescence has emerged as a potential mechanistic bridge linking age-associated cellular stress with progressive neurodegeneration. However, no single molecular marker reliably defines senescence across tissues or cell types. Instead, senescence is increasingly recognized as a multidimensional cellular state best characterized by integrating phenotypic, molecular, functional, and metabolic features.

Metabolomics and lipidomics provide powerful approaches for capturing these features because they measure the downstream products of cellular physiology. Unlike genomic information, metabolite concentrations dynamically reflect mitochondrial activity, substrate utilization, redox balance, inflammatory signaling, and interactions among neurons, glia, vascular cells, and peripheral tissues [11]. Senescent cells undergo profound metabolic reprogramming to sustain survival and continued SASP production despite irreversible cell-cycle arrest. Reported alterations include dysregulated glycolysis, impaired oxidative phosphorylation, disrupted NAD^+ metabolism, amino acid remodeling, altered lipid storage, and changes in sphingolipids, ceramides, cholesterol, and oxysterols [12]. Many of these metabolic changes are detectable in tissues and biofluids, raising the possibility that metabolomic signatures could serve as biomarkers of senescent-cell burden or activity. However, these signatures frequently overlap with metabolic changes associated with aging, inflammation, and neurodegeneration, making their specificity and translational value uncertain.

Although previous reviews have examined metabolomic alterations in aging or neurodegenerative disease and others have summarized the role of cellular senescence in

neurodegeneration, the literature directly linking metabolomic remodeling to experimentally defined cellular senescence has not been systematically synthesized. Consequently, it remains unclear whether the metabolic changes reported across neurodegenerative diseases represent disease-specific abnormalities or reflect a conserved metabolic architecture associated with cellular senescence.

The present systematic review addresses this gap by synthesizing evidence linking metabolomic alterations with cellular senescence across neurodegenerative diseases and related experimental models. Specifically, we sought to identify recurrent metabolic pathways associated with senescence, compare findings across diseases, biological models, cell types, and biospecimens, distinguish direct evidence of senescence from broader age-associated metabolic remodeling, and evaluate the potential of these metabolic signatures as mechanistic biomarkers and therapeutic targets in neurodegenerative disease.

2. Methods

2.1. Review Design

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement (PRISMA 2020) [13]. The review question was: "What metabolomic biomarkers have been associated with cellular senescence in human or animal models of neurodegenerative disease?" A review protocol was not prospectively registered. The research question and eligibility criteria were defined before investigator-led screening of the records included in the Elicit report. The PRISMA checklist is included as Table S3.

2.2. Information Source and Search Strategy

Literature identification was conducted using Elicit, an artificial intelligence-assisted literature discovery platform that performs semantic searches across records indexed in Semantic Scholar and OpenAlex, in addition to other scholarly sources incorporated by Elicit as Elicit's indexing evolves [14]. At the time of the search, Elicit reported searching a corpus of more than 138 million academic publications.

The Elicit search was conducted and accessed on 11 June 2026, using the following natural-language research question: "What metabolomic biomarkers have been associated with cellular senescence in human or animal models of neurodegenerative disease?" Results were limited to English-language publications according to Elicit's native parameters. No restrictions were applied by publication year, disease type, study design, or publication status at the initial search stage. All default Elicit search, screening, extraction, and ranking settings were retained.

2.3. AI-Assisted Screening, Ranking, and Report Generation

The semantic search returned 4975 records that Elicit identified as relevant to the research question. Elicit subsequently applied automated abstract-level and full-text screening criteria to assess relevance.

At the abstract level, Elicit assessed whether records addressed:

1. A chronic neurodegenerative disease, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple sclerosis, or another progressive neurodegenerative condition;
2. Cellular senescence as a biological process, mechanism, pathway, phenotype, or marker;
3. Metabolomics, lipidomics, metabolite profiling, or another form of metabolic analysis;
4. A relationship between one or more metabolites or metabolic pathways and cellular senescence;

5. Human participants or mammalian experimental models; and
6. A metabolomic component rather than an exclusively genomic, transcriptomic, or proteomic investigation.

During its reported full-text screening stage, Elicit further assessed whether studies:

1. Examined an established chronic or progressive neurodegenerative disease;
2. Explicitly investigated cellular senescence using recognized senescence markers, phenotypes, or mechanisms;
3. Used targeted or untargeted metabolomics, lipidomics, metabolite profiling, or related metabolic methods;
4. Reported a qualitative or quantitative relationship between metabolites and cellular senescence;
5. Used human participants, human tissues, mammalian animal models, or mammalian cell-based systems;
6. Represented original research or another study type allowed under the Elicit screening configuration; and
7. Focused on chronic neurodegenerative processes rather than exclusively acute neurological conditions.

Elicit considered the screening criteria collectively and applied a holistic relevance assessment rather than treating each criterion as an independent binary exclusion rule. According to the Elicit report, 546 records met the automated full-text screening threshold and proceeded to AI-assisted data extraction.

The 546 records were subsequently ranked according to their screening scores. Because Elicit's report-generation model could process a maximum of 80 sources, the 80 highest-ranked records were incorporated into the generated report and made available for investigator-led review. Studies ranked below the top 80 were therefore not manually evaluated by the investigators. This approach reflects the maximum number of sources supported by Elicit's report-generation function and may have excluded additional relevant lower-ranked studies. To mitigate this limitation, supplementary PubMed and Embase searches were performed.

2.4. Investigator-Led Study Selection and Eligibility Criteria

The 80 records included in the Elicit-generated report were exported for investigator-led review. Two investigators independently examined the titles, abstracts, publication types, and available full texts and applied predefined inclusion and exclusion criteria. Final eligibility decisions were based on investigator review of the original publications rather than Elicit's screening scores or AI-generated summaries. Any disagreements were resolved through discussion and consensus.

Studies were eligible if they investigated an established chronic or progressive neurodegenerative disease, including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia, multiple sclerosis, or another clearly defined neurodegenerative condition. Stress-induced premature cellular senescence models were eligible when explicitly used to model an established neurodegenerative disease or when they:

1. Examined cellular senescence as a biological mechanism, process, phenotype, pathway, or experimentally measured cellular state;
2. Used metabolomics, lipidomics, targeted metabolite analysis, untargeted metabolic profiling, or another clearly defined metabolic-analysis method;
3. Reported a relationship between metabolites or metabolic pathways and cellular senescence, senescence-associated markers, or senescence-related mechanisms;

4. Used human participants, human tissues, mammalian animal models, or mammalian cell-based systems; and
5. Were original, peer-reviewed research articles.

Studies were excluded if they:

1. Focused on generic accelerated-aging models without a defined neurodegenerative disease context, acute neurological injury, acute infection, or another nonprogressive neurological condition;
2. Did not examine cellular senescence;
3. Did not include a metabolomic, lipidomic, or metabolic-analysis component;
4. Did not evaluate a relationship between metabolism and senescence;
5. Used only plant, invertebrate, or other nonmammalian models;
6. Were review articles, systematic reviews, meta-analyses, conference abstracts, editorials, commentaries, opinion articles, case reports, or preprints; or
7. Reported findings from a participant cohort or experimental dataset that duplicated another included publication without contributing distinct metabolomic or senescence-related analyses.

For full-text eligibility assessment, evidence of cellular senescence included established markers or phenotypes such as senescence-associated β-galactosidase activity, $p16^{INK4a}$, $p21^{CIP1}$, p53 pathway activation, persistent DNA-damage signaling, telomere dysfunction, senescence-associated heterochromatin changes, senescence-associated secretory phenotype factors, stable cell-cycle withdrawal, or a validated composite senescence signature. For interpretation of the evidence, studies demonstrating stable cell-cycle arrest together with multiple canonical senescence features were treated as providing more direct evidence of cellular senescence, whereas studies relying primarily on individual molecular markers, inflammatory signatures, or transcriptional associations were described as demonstrating senescence-associated or senescence-like phenotypes. Studies based solely on chronological aging without direct evidence connecting the reported metabolic findings to cellular senescence were not considered sufficient unless the experimental model was explicitly designed and validated as a senescence model.

Duplicate publications were assessed by comparing article title, authors, publication year, and digital object identifier. Potential overlap in human cohorts, animal cohorts, datasets, or experimental samples was evaluated separately from bibliographic duplication. Disagreements regarding eligibility were resolved through discussion and consensus among the investigators. Following eligibility assessment by the first and senior authors, 16 studies identified through Elicit met all inclusion criteria and proceeded to the qualitative synthesis. The excluded articles are listed in the Supplemental Table S1 [15–77].

2.5. Data Extraction

Data were organized using a standardized evidence table. Elicit's large language model-assisted extraction functions were used to generate preliminary summaries of study characteristics and findings. The investigators compared the AI-generated summaries with the original publications and corrected incomplete, unclear, or inaccurate information before inclusion in the final evidence table.

The evidence table included the following fields:

- **Study:** citation information identifying each publication.
- **Disease context:** the neurodegenerative disease or disease model investigated.
- **Model and sample:** the biological model, species, cell type, tissue, cohort, or experimental system used in the study.

- **Primary metabolic theme:** the principal metabolic pathway, metabolite class, or biological process investigated.
- **Major metabolic findings:** the principal metabolomic or lipidomic findings reported by the study.
- **Senescence evidence:** the cellular senescence markers, mechanisms, phenotypes, or experimental evidence linking senescence to the reported metabolic alterations.

The principal metabolic theme examined in each study was recorded together with the major metabolomic findings and the evidence supporting cellular senescence. When studies included multiple experimental models or sample types, these were documented within the evidence table as appropriate. Human, animal, and in vitro findings were distinguished to facilitate comparison across biological systems.

Terminology was harmonized where appropriate to improve consistency in disease names, model systems, metabolic pathways, and senescence-related terminology. Scientific interpretation, final classification of metabolic themes, and assessment of relevance to the review question were performed by the investigators rather than by the AI-assisted extraction system. Disagreements regarding extracted information were resolved through discussion and consensus.

2.6. Secondary Search

To assess the comprehensiveness of the Elicit-based literature search, a secondary search was conducted using PubMed on 30 June 2026. The supplementary PubMed search was also performed to mitigate any ranking bias introduced by Elicit. The PubMed search strategy was designed to identify studies related to cellular senescence, metabolism/metabolomics, and neurodegenerative diseases. The following search string was used:

((“Neurodegenerative Diseases” [Mesh] OR neurodegenerative disease* OR Alzheimer* OR Parkinson* OR Huntington* OR dementia) AND (“Cellular Senescence” [Mesh] OR senescence*) AND (“Metabolomics” [Mesh] OR metabolom* OR metabolomic* OR metabolite* OR “metabolic profiling” OR “metabolic signature”)).

The search returned 141 records [18,25,27,29,31,37,55,64,67,71–73,77–206]. The retrieved studies were then screened using the same inclusion and exclusion eligibility criteria applied during the Elicit search. To compare the performance of the two search strategies, the studies identified through PubMed were evaluated against those included from the Elicit search. Of the 16 peer-reviewed studies included through Elicit, 15 were identified by the PubMed search. The PubMed search also identified two additional relevant studies that were not retrieved through Elicit but met the inclusion criteria and were added to the final qualitative synthesis. The cumulative evidence set comprised 18 studies after the PubMed search, before the additional Embase search. The full-text articles from the PubMed search are listed in Supplemental Table S2.

2.7. Additional Embase Search

To further reduce potential selection bias associated with Elicit’s relevance-ranking procedure and improve the comprehensiveness of the literature search, an additional Embase search was conducted on 10 October 2026. The following search strategy was used: “(‘neurodegenerative disease’/exp OR ‘alzheimer disease’/exp OR alzheimer*:ti,ab,kw OR ‘parkinson disease’/exp OR parkinson*:ti,ab,kw OR ‘huntington disease’/exp OR huntington*:ti,ab,kw OR ‘amyotrophic lateral sclerosis’/exp OR ‘amyotrophic lateral sclerosis’:ti,ab,kw OR ‘frontotemporal dementia’/exp OR ‘frontotemporal dementia’:ti,ab,kw OR ‘multiple sclerosis’/exp OR ‘multiple sclerosis’:ti,ab,kw OR ‘age related macular degeneration’/exp OR ‘age-related macular degeneration’:ti,ab,kw OR ‘neurodegenerative disease*’:ti,ab,kw) AND (‘cell aging’/exp OR senescen*:ti,ab,kw OR ‘cellular senes-

cence':ti,ab,kw OR 'senescence-associated secretory phenotype':ti,ab,kw OR sasp:ti,ab,kw) AND ('metabolomics'/exp OR 'lipidomics'/exp OR metabolom*:ti,ab,kw OR lipidom*:ti,ab,kw OR metabolite*:ti,ab,kw OR 'metabolic profiling':ti,ab,kw OR 'metabolic phenotype':ti,ab,kw OR 'metabolic pathway*':ti,ab,kw)."

The Embase search identified 307 records. To facilitate screening, a Python 3.15 title-and-abstract screening script was used to flag records containing predefined terms corresponding to the neurodegenerative diseases specified in the eligibility criteria. The procedure identified 195 records as potentially relevant to the predefined disease scope and 112 records without a matching disease term. Records were not automatically excluded by the computational procedure; all 307 records remained subject to investigator review using the same predefined inclusion and exclusion criteria applied to the Elicit and PubMed searches. Manual review confirmed that none of the 112 records without a matching disease term met the eligibility criteria. Among the 195 records flagged as potentially relevant, 182 were excluded because they did not meet the predefined eligibility criteria, eight corresponded to studies already included through the Elicit and/or PubMed searches, and five additional studies met all eligibility criteria and were added to the qualitative synthesis. This resulted in a total of 23 studies being included in this review.

2.8. Assessment of Study Quality and Risk of Bias

Risk of bias assessment was not performed because the objective of the review was mechanistic synthesis rather than estimation of intervention effects, and the included studies consisted of heterogeneous preclinical, translational, and clinical investigations for which no single validated risk-of-bias assessment tool was appropriate.

2.9. Data Synthesis

Owing to anticipated heterogeneity in disease context, biological model, sample type, metabolomic platform, senescence definition, and reported outcome measures, a quantitative meta-analysis was not performed. Because the objective of the review was to synthesize mechanistic evidence rather than estimate treatment effects, findings were organized according to recurring metabolic pathways instead of intervention type or disease. Accordingly, findings were synthesized qualitatively.

Metabolites and metabolic pathways were grouped according to recurring biological domains identified across the included studies. These domains included lipid remodeling, cholesterol and oxysterol metabolism, glycolysis and lactate metabolism, mitochondrial and tricarboxylic acid cycle dysfunction, NAD^+/redox metabolism, amino acid and neurotransmitter pathways, and cell-type-specific metabolic changes. Findings from human, animal, and in vitro studies were compared to identify areas of convergence, divergence, and model-specific effects. The domains emerged inductively after reviewing the evidence table.

A metabolic alteration was treated as more strongly supported when it was reported across multiple independent studies, disease contexts, model systems, or analytical platforms. Findings reported in only one study or one experimental system were interpreted as preliminary. Because the included studies differed substantially in methodology and outcome reporting, no pooled effect estimates were calculated.

2.10. Use of Artificial Intelligence

Elicit was used for semantic literature retrieval, automated relevance screening and ranking, report generation, and preliminary extraction and organization of study information. The investigators were responsible for final eligibility decisions, verification of extracted data against the original publications, classification of findings, and development of the scientific interpretation and narrative synthesis. The literature identification, AI-

assisted screening, ranking, and investigator-led study selection process is summarized in Figure 1. Table 1 presents a summary of the studies included in this systematic review.

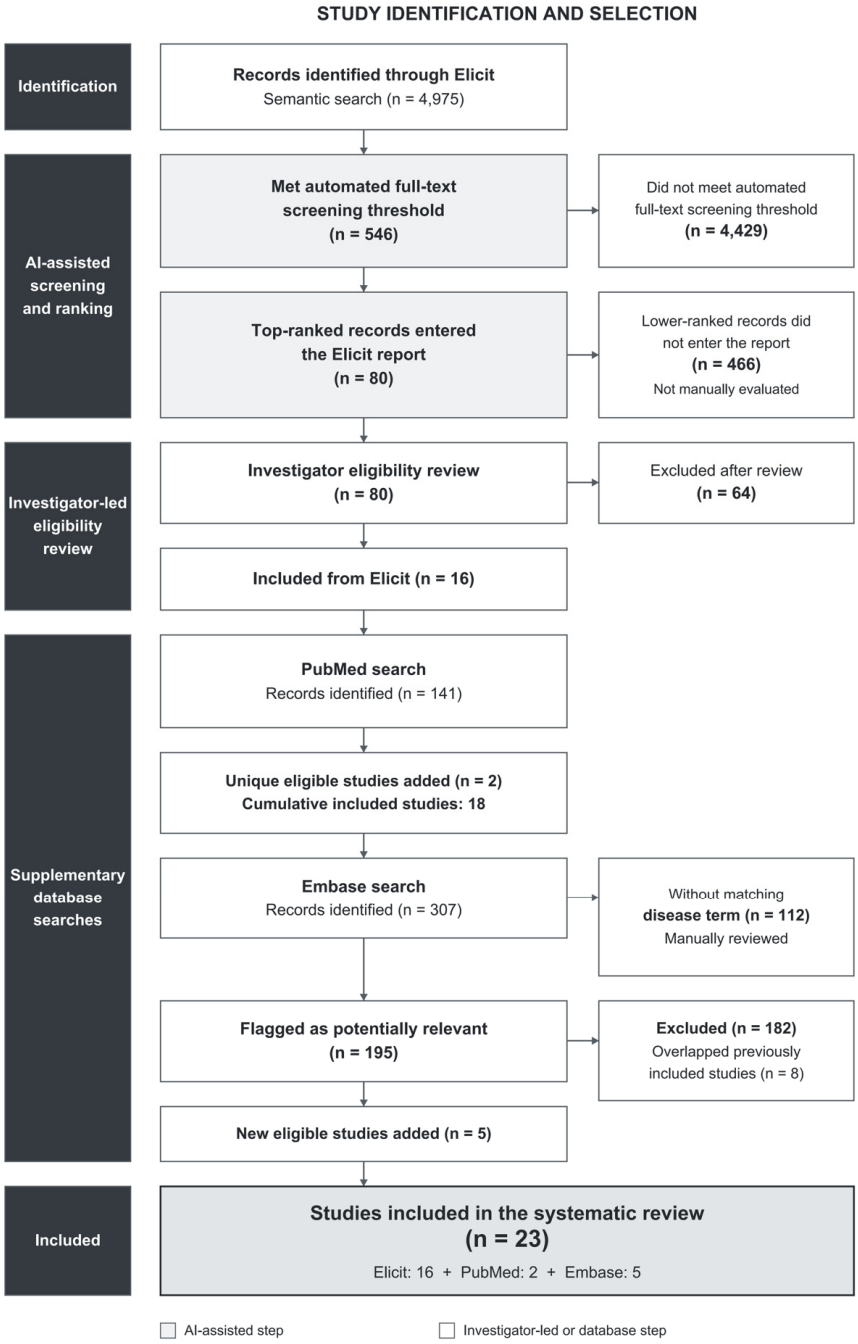


Figure 1. Flow diagram of literature identification and study selection. The Elicit semantic search conducted on 11 June 2026, identified 4975 records, of which 546 met the automated full-text screening threshold and 4429 did not. The 80 highest-ranked records entered the Elicit-generated report and underwent investigator-led eligibility assessment; the remaining 466 lower-ranked records did not enter the report and were not manually evaluated. Investigator review excluded 64 records and retained 16 studies. Supplementary PubMed searching identified 141 records and contributed two unique eligible studies, increasing the cumulative total to 18. Embase searching identified 307 records, including 195 flagged as potentially relevant and 112 without a matching disease term that were also manually reviewed. Among the 195 flagged records, 182 were excluded, eight overlapped previously included studies, and five additional unique eligible studies were included. The final qualitative synthesis comprised 23 studies.

Table 1. Summary of studies included in this systematic review.

Study	Disease/Model	Experimental System	Metabolic Pathway	Senescence Evidence	Major Finding
Hou et al., 2021 [112]	Alzheimer's disease (AD) mouse model	Brain tissue and isolated neural cells	NAD^+ homeostasis and mitochondrial metabolism	$p16^{INK4a}$, $p21^{CIP1}$, SA-beta-gal and SASP-related changes	NAD+ depletion and CD38-associated dysfunction linked senescence to impaired mitochondrial function; NAD+ precursor treatment improved metabolic and senescence phenotypes.
Lee et al., 2022 [131]	Parkinson's disease (PD)-related model	Human iPSC-derived midbrain organoids exposed to TMAO	Gut-derived metabolite signaling, mitochondrial and endoplasmic-reticulum stress	p53, $p21^{CIP1}$, $p16^{INK4a}$, lamin A/C loss and reduced H3K9 trimethylation	Chronic TMAO exposure induced senescence-associated and neurodegenerative changes before widespread neuronal loss, linking a circulating microbial metabolite to early brain aging phenotypes.
Hu et al., 2022 [207]	AD	Amyloid-beta-treated BV2 microglia and APP/PS1 mice	CD38-dependent NAD+ metabolism and mitochondrial bioenergetics	SA-beta-gal, $p16^{INK4a}$, $p21^{CIP1}$ and inflammatory cytokines	Amyloid-beta increased CD38, depleted NAD+ and impaired mitochondria; genetic or pharmacologic CD38 inhibition attenuated senescence, inflammation and cognitive impairment.
Groveman et al., 2023 [108]	Prion protein-deficient neurodegeneration-related model	Adult neural stem cells isolated from PrP-deficient mice	Mitochondrial respiration and bioenergetics	$p21^{CIP1}$ and senescence-like cell-cycle/stress responses	Impaired respiration and bioenergetic failure accompanied a senescence-associated phenotype in neural stem cells.
Wei et al., 2023 [208]	Aging and AD (5xFAD; APP/PS1)	Doxorubicin-induced senescent microglia and mouse hippocampus	Glycolysis, lactate and protein lactylation	IL-6, IL-8 and SASP; elevated histone H3K18 lactylation	Increased lactate promoted H3K18 lactylation at *Rela* and *NFkB1* promoters and activated NF-kB-dependent inflammatory transcription; LDH inhibition reduced lactate.
Russo et al., 2024 [209]	PD	SATB1-deficient dopaminergic neurons	Sphingolipid and lysosomal metabolism	SA-beta-gal, $p16^{INK4a}$ and senescence-associated gene expression	GBA loss and glucosylceramide accumulation disrupted lysosomal and mitochondrial function; GCase restoration or synthesis inhibition improved the phenotype.

Table 1. *Cont.*

Study	Disease/Model	Experimental System	Metabolic Pathway	Senescence Evidence	Major Finding
Terao et al., 2024 [210]	Cholesterol-overload model relevant to neurodegeneration	Cholesterol-loaded macrophages	Cholesterol-LXRalpha-CD38-NAD+ axis	$p16^{INK4a}$, $p21^{CIP1}$ and SASP factors	Cholesterol overload activated LXRalpha-CD38, depleted NAD+ and impaired respiration; NMN or CD38 inhibition attenuated senescence-associated changes.
Yang et al., 2024 [182]	Human AD	Plasma proteomics and serum metabolomics	Gut-host co-metabolite and integrated circulating signatures	Senescence relevance inferred from inflammatory, stress and secretory profiles	PAGln and a combined protein classifier distinguished AD from cognitively normal controls, supporting multimarker detection strategies.
Riccardi et al., 2025 [157]	VPS13A disease (chorea-acanthocytosis)	Patient-relevant skeletal-muscle and cellular models	Autophagy, NAD+ homeostasis and mitochondrial energy metabolism	Premature aging/senescence-associated phenotype; canonical senescence evidence was limited	VPS13A loss impaired autophagy, depleted NAD+ and increased oxidative and inflammatory stress; rapamycin improved metabolic and aging-associated abnormalities.
Zhang et al., 2026 [211]	Preclinical AD-associated skeletal dysfunction	Type H bone vascular endothelial cells and AD mouse model	PKM2-mediated glycolysis and mitochondrial function	Endothelial-cell senescence and mitochondrial dysfunction-associated senescence	Sympathetic norepinephrine signaling suppressed c-Maf/PKM2 and disrupted glycolytic flux; beta-adrenergic inhibition or PKM2 activation rescued endothelial senescence and bone loss.
Zhao et al., 2026 [212]	Age-related macular degeneration-related retinal degeneration	Human iPSC-derived RPE cells, induced RPE cells and mouse iron-overload models	Iron-induced glucose metabolic reprogramming	SA-beta-gal and molecular senescence markers with ROS and mitochondrial dysfunction	A transient increase in glucose flux promoted mitochondrial ROS and RPE senescence; early inhibition with 2-DG or PKM2 inhibition preserved mitochondrial and visual function.
Wang et al., 2025 [177]	APOE4-associated AD model	APOE4 transgenic mice and cellular trafficking assays	Cholesterol trafficking and oxysterol metabolism	$p16^{INK4a}$, $p21^{CIP1}$, SA-beta-gal and neuroinflammatory markers	Lysosomal ABCA1 sequestration and mTOR activation linked cholesterol dysregulation to senescence; HPCD restored trafficking and improved cognition.

Table 1. *Cont.*

Study	Disease/Model	Experimental System	Metabolic Pathway	Senescence Evidence	Major Finding
Li et al., 2025 [213]	Human AD	Human molecular datasets and pathway analyses	Cholesterol and lipid pathways	Senescence-associated molecular signatures	Coordinated cholesterol-pathway and microglial senescence signatures suggested biomarker and mechanistic relevance.
Fang et al., 2025 [214]	APPNL-F/NL-F AD mice	Brain and peripheral tissues; systemic metabolomic phenotyping	Whole-body glucose, lipid and energy metabolism	Hippocampal $p16^{INK4a}$, $p21^{CIP1}$, SA-beta-gal, TNF-alpha and circulating cytokines	Dasatinib plus quercetin improved systemic metabolism, neuropathology and cognition, predominantly in females, linking senescent-cell clearance to metabolic remodeling.
Garbarino et al., 2025 [104]	Mild human AD; phase 1 SToMP-AD study	Paired plasma, CSF, urine and PBMC profiling before and after D + Q	Circulating lipid remodeling	Inflammatory and stress-response transcripts; treatment-response context	Plasma phospholipid and acylcarnitine profiles changed after senolytic treatment; results were exploratory and sensitive to normalization in a five-person cohort.
Yu et al., 2026 [70]	27-hydroxycholesterol-induced neurodegeneration	Microglial, neuronal and mouse experimental models	Oxysterols, iron homeostasis and ferroptosis-related pathways	Microglial senescence and inflammatory polarization	Deferoxamine reduced iron accumulation, restored mitochondrial potential and improved neuronal survival and cognition.
Basak et al., 2026 [215]	AD- and PD-relevant aging brain biology	Midbrain astrocytes from CD38-deficient mice	CD38-regulated NAD+/nicotinamide homeostasis and mitochondrial bioenergetics	Overlap with astrocyte senescence transcriptional signatures; $p16^{INK4a}$, $p21^{CIP1}$ and SA-beta-gal were not measured	CD38 loss altered NAD+ levels, mitochondrial function and disease-associated astrocyte programs, providing indirect evidence of a senescence-associated metabolic state.
Tian et al., 2026 [170]	Human AD	Brain proteomics/transcriptomics and brain/serum metabolomics	Amino acid, glycerophospholipid and related lipid metabolism	Senescence-associated proteins and risk scores	Cross-tissue multi-omic signatures tracked disease severity and identified serum metabolites correlated with brain senescence programs.
Rosety et al., 2023 [216]	GBA-associated PD	Patient-derived *GBA*-N370s iPSC midbrain organoids	Lipid metabolism, sphingolipid/glycerophospholipid metabolism, and mitochondrial bioenergetics	S-phase cell-cycle arrest; increased SA-β-gal; reduced LAMINB1 and HP1γ; oxidative DNA damage	*GBA*-PD organoids showed mitochondrial and autophagic dysfunction together with lipidomic remodeling; altered lipid metabolism accompanied premature senescence and impaired dopaminergic-neuron differentiation.

Table 1. *Cont.*

Study	Disease/Model	Experimental System	Metabolic Pathway	Senescence Evidence	Major Finding
Song et al., 2024 [217]	Premature AMD/ stress-induced senescence-associated AMD model	Stress-induced premature senescence-associated AMD mouse model; human dry-AMD transcriptomic comparison	Glycerophospho-lipid, glycerolipid, amino-acid-related and systemic metabolic pathways	SASP factors and activation of the p53- $p21^{CIP1}$ -Rb1 senescence axis	Luteoloside corrected abnormal circulating metabolites, including LysoPC and 4-guanidinobutanoic acid, altered gut microbiota and reduced retinal SASP through suppression of the p53-$p21^{CIP1}$ -Rb1 pathways
Kadir et al., 2026 [218]	APOE-associated AD	Humanized APOE2/3/4 knock-in mice, isogenic human iPSC-derived pericytes and in vitro BBB model	Lipid metabolism, β-oxidation, lipid transport and lipid-droplet homeostasis	SA-β-gal, $p16^{INK4a}$, $p21^{CIP1}$, γH2AX, lamin B1 after senescence induction	APOE2 enhanced pericyte and BBB function and produced a distinct lipidomic profile; increased lipid processing was associated with reduced senescence and lipid-droplet accumulation, and recombinant APOE2 rescued APOE3/4 pericyte phenotypes.
Hall et al., 2026 [219]	Sporadic ALS	SALS patient-derived iAstrocytes, CSF and postmortem motor-cortex tissue	ADA-dependent purine metabolism and nucleotide homeostasis	Increased $p16^{INK4a}$ and senescence-associated p53 isoform with impaired 53BP1-mediated DNA repair	ADA loss disrupted purine metabolism in SALS astrocytes and human biofluids/tissue; experimental ADA inhibition increased senescence and DNA damage, directly linking purine dysfunction to impaired DNA repair and cellular senescence.
Rachmian-Cooper et al., 2026 [153]	AD-associated senescent brain cells	Primary human fibroblasts, senescent microglia in an AD mouse model and human AD single-nucleus datasets	Glycolysis, triacylglycerol metabolism and lipid-droplet accumulation	Experimentally induced cellular senescence and senescent microglial/cellular signatures	Metabolic profiling showed increased glycolytic and triacylglycerol-related metabolites in senescent cells; lipid droplets accumulated in senescent cells and were associated with senescent microglia in mouse and human AD brain.

The table summarizes the disease contexts, experimental systems, metabolic pathways, senescence measures, and principal findings reported across the 23 studies included in the qualitative synthesis. Abbreviations: AD, Alzheimer's disease; BBB, blood–brain barrier; CSF, cerebrospinal fluid; D + Q, dasatinib plus quercetin; GBA, glucocerebrosidase gene; GCase, glucocerebrosidase; HPCD, hydroxypropyl-beta-cyclodextrin; LDH, lactate dehydrogenase; NAD+, nicotinamide adenine dinucleotide; PBMC, peripheral blood mononuclear cell; PD, Parkinson's disease; SA-beta-gal, senescence-associated beta-galactosidase; SASP, senescence-associated secretory phenotype; AMD, age-related macular degeneration; ALS,

amyotrophic lateral sclerosis; ADA, adenosine deaminase; SALS, sporadic amyotrophic lateral sclerosis.

3. Results

Twenty-three studies met the eligibility criteria and were included in the qualitative synthesis. The studies encompassed AD, PD, VPS13A disease, ALS, AMD, and related neurodegenerative models and included human cohorts, postmortem tissues, induced pluripotent stem cell-derived cultures, organoids, mammalian animal models, and cultured mammalian cells. Targeted and untargeted metabolomics, lipidomics, and integrated multi-omic approaches were represented. Despite considerable heterogeneity in experimental systems and analytical methodologies, recurring metabolic themes involved NAD^+ metabolism and redox regulation, mitochondrial bioenergetics and glycolysis, lipid and cholesterol homeostasis, amino acid metabolism, and circulating metabolic signatures associated with cellular senescence.

3.1. NAD^+ Redox Dysregulation and Cellular Senescence in Neurodegenerative Disease

Nicotinamide adenine dinucleotide (NAD^+) is a central regulator of cellular metabolism, mitochondrial function, DNA repair, and stress responses [220]. Age-related declines in NAD^+ have emerged as a conserved feature of aging tissues and are increasingly recognized as an important contributor to neurodegenerative disease. Recent evidence suggests that disruption of NAD^+ homeostasis not only impairs cellular bioenergetics but may also contribute to cellular senescence through mechanisms involving mitochondrial dysfunction, persistent DNA damage, inflammatory signaling, and activation of the SASP [221].

One of the primary regulators of NAD^+ metabolism in the aging brain is the NADase CD38 [222]. CD38 hydrolyzes NAD^+ to nicotinamide (NAM), and its expression increases with aging and in several neurodegenerative diseases. Basak and colleagues demonstrated that CD38 is highly enriched in midbrain astrocytes and plays a critical role in maintaining NAD^+/NAM homeostasis [215]. Using CD38-deficient mice, they showed that loss of CD38 significantly altered astrocytic metabolism, increased tissue NAD^+ levels, disrupted mitochondrial bioenergetics, and produced widespread transcriptional changes involving metabolic pathways, oxidative stress responses, astrocyte reactivity, mitochondrial function, and numerous genes previously associated with both PD and AD. Importantly, transcriptomic analysis revealed substantial overlap with previously described astrocyte senescence signatures, although direct senescence markers such as $p16^{INK4a}$, $p21^{CIP1}$, or senescence-associated β-galactosidase were not measured [215].

More direct evidence linking NAD^+ depletion to cellular senescence comes from studies of AD mouse models. Hou and colleagues demonstrated that APP/PS1 mice exhibit age-dependent reductions in brain NAD^+ accompanied by increased neuroinflammation, DNA damage, activation of the cGAS–STING innate immune pathway, and widespread expression of senescence markers [112]. Chronic supplementation with the NAD^+ precursor nicotinamide riboside (NR) restored brain NAD^+ levels, reduced activation of microglia and astrocytes, suppressed NLRP3 inflammasome signaling, decreased DNA damage, lowered expression of $p16^{INK4a}$, $p21^{CIP1}$, and SA-β-gal, and improved cognitive performance. Mechanistically, the authors showed that NAD^+ restoration reduced cytoplasmic mitochondrial DNA release through enhanced mitophagy, thereby preventing activation of the cGAS–STING pathway [223]. Knockdown or pharmacologic inhibition of cGAS or STING abolished many of the anti-inflammatory effects of NR [112].

Complementary work has identified CD38 itself as an important mechanistic link between amyloid pathology, NAD^+ depletion, and microglial senescence. Hu and colleagues demonstrated that exposure of BV2 microglia to $A\beta_{1-40}$ induced classical senescence mark-

ers, including increased SA-β-gal staining and elevated $p16^{INK4a}$ and $p21^{CIP1}$ expression, while simultaneously reducing intracellular NAD^+, ATP production, mitochondrial membrane potential, and mitochondrial function [207]. These metabolic changes were accompanied by increased CD38 expression and elevated production of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. Genetic knockdown of CD38 restored NAD^+ levels, improved mitochondrial function, reduced inflammatory cytokine production, and attenuated cellular senescence. Likewise, pharmacologic inhibition of CD38 in APP/PS1 mice improved cerebral NAD^+ metabolism, reduced amyloid pathology and neuroinflammation, and significantly improved cognitive performance. CD38 inhibition therefore reduced NAD^+ depletion, mitochondrial dysfunction, inflammatory signaling, and senescence-associated phenotypes in these experimental models [207].

Although most studies have focused on AD, similar metabolic mechanisms appear to operate across other neurodegenerative disorders. Riccardi and colleagues investigated VPS13A disease (chorea-acanthocytosis), a rare hereditary neurodegenerative disorder, and demonstrated that loss of VPS13A disrupted autophagy, depleted intracellular NAD^+, impaired mitochondrial energy metabolism, increased oxidative damage, and promoted premature aging and cellular senescence in skeletal muscle [157]. The resulting phenotype included activation of unfolded protein response pathways, NF-κB-mediated inflammaging, and accumulation of aging and senescence markers, all of which were substantially improved following rapamycin-mediated restoration of autophagy [157].

Across these studies, reduced NAD^+ availability was repeatedly associated with mitochondrial dysfunction, impaired DNA-damage responses, inflammatory signaling, and senescence-associated phenotypes. Interventions that restored NAD^+ availability or inhibited NAD^+-consuming pathways reduced several of these abnormalities in experimental models. NAD^+ dysregulation was therefore a recurrent finding across several included neurodegenerative disease models.

Hall et al. (2026) [219] extended senescence-associated metabolic dysfunction in neurodegenerative disease to purine metabolism in sporadic amyotrophic lateral sclerosis (SALS). Using patient-derived induced astrocytes, LC-MS-based metabolomics demonstrated altered ADA-dependent purine metabolism together with reduced levels of purine-metabolism enzymes including adenosine deaminase (ADA), CD73, and HGPRT. Reduced ADA activity was associated with altered purine and dNTP profiles, including changes in deoxyinosine, dATP, and total purine nucleotide pools. SALS astrocytes also exhibited increased $p16^{INK4a}$ and reduced 53BP1-mediated DNA-repair activity. Experimental inhibition of ADA with pentostatin in control astrocytes reproduced increased $p16^{INK4a}$ expression and impaired 53BP1 responses, while further ADA inhibition in SALS astrocytes increased DNA-damage-associated γH2AX. Purine-metabolism abnormalities were also detected in CSF and postmortem tissue from individuals with SALS, with several CSF purine metabolites showing age-, sex-, and disease-progression-associated relationships [219].

3.2. Energy Metabolism, Glycolytic Reprogramming, and Mitochondrial Dysfunction

Alterations in cellular bioenergetics were among the most recurrent findings across the included studies. Reported changes included impaired mitochondrial respiration, altered glycolytic flux, disrupted pyruvate utilization, ATP depletion, changes in NAD^+/NADH balance, lactate accumulation, and increased oxidative stress. These metabolic abnormalities frequently occurred together with $p16^{INK4a}$-, $p21^{CIP1}$-, p53-, SA-β-gal-, or SASP-associated changes, suggesting close coupling between energy metabolism and senescence across diverse experimental systems [108,208,214].

3.3. Early Metabolic Dysfunction Precedes Overt Neurodegeneration

Several included studies reported metabolic and senescence-associated abnormalities before overt neurodegenerative pathology or widespread neuronal loss [131,214]. Fang et al. (2025) examined these relationships using the $APP^{NL-F/NL-F}$ knock-in mouse model of AD [214]. At only four months of age, prior to significant amyloid plaque deposition or measurable cognitive decline, these mice exhibited widespread metabolic abnormalities accompanied by increased senescence markers in both peripheral tissues and the hippocampus. Visceral white adipose tissue demonstrated increased expression of *Cdkn2a*, *Cdkn1a*, and multiple SASP mediators, including IL-6, TNF-α, MCP-1, IL-10, MIP-1α, and CXCL16, while hippocampal tissue simultaneously displayed elevated $p21^{CIP1}$, MCP-1, and MIP-1α expression [214].

These early abnormalities were subsequently modified by D + Q treatment in female mice, whereas male mice showed comparatively limited metabolic responses; the intervention findings are described in greater detail below [214]. Lee et al. (2022) examined the effects of trimethylamine N-oxide (TMAO), a gut microbiota-derived metabolite that accumulates during aging and PD, in induced pluripotent stem cell-derived midbrain organoids [131]. Chronic TMAO exposure induced multiple hallmarks of cellular senescence, including increased expression of p53, $p21^{CIP1}$, and $p16^{INK4a}$, impaired endoplasmic reticulum homeostasis, reduced lamin A/C expression, decreased H3K9 trimethylation, and suppression of CREB signaling before widespread neuronal loss was observed [131]. These molecular changes were accompanied by impaired BDNF signaling, reduced ERK1/2 and CaMKII activation, decreased dopaminergic neuron survival, diminished dopamine secretion, astrocyte activation, increased inflammatory cytokine production, and pathological phosphorylation of both α-synuclein and tau proteins. These molecular changes occurred before substantial apoptosis or widespread neuronal loss [131].

3.4. Glycolysis–Mitochondrial Coupling and Cellular Senescence

Several included studies identified concurrent alterations in glycolytic flux, pyruvate utilization, mitochondrial respiration, ATP production, and senescence-associated markers [108,211,212]. One mechanism linking impaired bioenergetics to senescence involves disruption of epidermal growth factor receptor (EGFR) signaling. Using adult neural stem cells (NSCs) isolated from prion protein (PrP)-deficient mice, Groveman et al. (2023) demonstrated that loss of PrP resulted in reduced cellular proliferation accompanied by a marked increase in senescence-associated β-galactosidase activity and elevated $p21^{CIP1}$ expression [108]. These changes were associated with significantly reduced EGFR expression, and pharmacological inhibition of EGFR signaling in wild-type NSCs recapitulated the senescent phenotype. Conversely, supplementation with epidermal growth factor partially reduced the senescent phenotype in PrP-deficient cells [108].

Transcriptomic and metabolomic analyses further revealed that PrP deficiency profoundly altered central carbon metabolism. Genes encoding multiple components of the mitochondrial electron transport chain, particularly Complex I, were broadly downregulated, resulting in impaired oxidative phosphorylation and diminished mitochondrial ATP production. Metabolomic profiling demonstrated accumulation of pyruvate together with depletion of acetyl-CoA and multiple TCA cycle intermediates, indicating failure to efficiently channel glycolytic carbon into mitochondrial oxidative metabolism. This metabolic pattern was accompanied by reduced NAD+, NADH, ATP, and purine nucleotide pools. Functional studies confirmed these molecular findings, demonstrating reduced oxygen consumption, diminished maximal respiratory capacity, and impaired mitochondrial ATP generation in PrP-deficient NSCs [108].

A similar metabolic mechanism has recently been identified in vascular endothelial cells during the preclinical stages of AD. Zhang et al. (2026) demonstrated that sympathetic nervous system hyperactivity increases norepinephrine release within bone tissue, suppressing expression of pyruvate kinase M2 (PKM2), the glycolytic enzyme responsible for catalyzing the conversion of phosphoenolpyruvate to pyruvate [211]. Because endothelial cells rely heavily on glycolysis to satisfy their energetic demands, suppression of PKM2 markedly impaired glycolytic flux, reducing intracellular pyruvate, lactate production, ATP synthesis, and the NAD^+/NADH ratio while simultaneously promoting mitochondrial dysfunction-induced senescence (MiDAS). Endothelial cells exposed to norepinephrine exhibited increased expression of p53, $p21^{CIP1}$, and $p16^{INK4a}$ together with enhanced senescence-associated β-galactosidase activity and nuclear loss of HMGB1, confirming activation of a classical senescence program [211].

Importantly, restoration of glycolytic metabolism reversed these changes. Pharmacological activation of PKM2 using TEPP-46 or supplementation with pyruvate restored glycolytic activity, improved ATP production, normalized metabolic homeostasis, reduced endothelial senescence, and rescued secretion of osteogenic factors required for vascularized bone formation. Likewise, supplementation with nicotinamide mononucleotide (NMN), a precursor of NAD^+, restored intracellular NAD^+ availability, attenuated MiDAS, reduced senescence-associated β-galactosidase activity, and improved endothelial function [211].

Whereas Groveman et al. (2023) and Zhang et al. (2026) identified impaired glycolysis as the initiating metabolic defect, Zhao et al. (2026) demonstrated that excessive glycolytic activation can likewise promote senescence when mitochondrial metabolism becomes overwhelmed [108,211,212]. Using human induced pluripotent stem cell-derived retinal pigment epithelial (RPE) cells exposed to ferric ammonium citrate, the authors observed a transient surge in glycolytic activity immediately following iron overload. Early increases in pyruvate production, pyruvate dehydrogenase activity, and ATP synthesis were followed by progressive mitochondrial dysfunction characterized by declining ATP levels, reduced NAD^+/NADH ratios, mitochondrial membrane depolarization, increased mitochondrial iron accumulation, and excessive reactive oxygen species production. Ultimately, this metabolic transition culminated in robust activation of senescence, including increased expression of *Cdkn2a* and *Cdkn1a*, senescence-associated β-galactosidase activity, and multiple SASP components [212].

Pharmacological inhibition of glycolysis with either 2-deoxy-D-glucose or the PKM2 inhibitor PKM2-IN-1 prevented the initial glycolytic surge, reduced mitochondrial ROS production, preserved mitochondrial membrane potential, and substantially attenuated iron-induced senescence. Conversely, inhibition of lactate dehydrogenase using sodium oxamate, which promotes intracellular pyruvate accumulation by blocking pyruvate-to-lactate conversion, exacerbated oxidative stress and accelerated senescence [212].

Across these studies, impaired or dysregulated glycolytic flux was consistently accompanied by mitochondrial dysfunction, reduced ATP production, altered NAD+/NADH balance, oxidative stress, and increased senescence-associated markers. Experimental restoration or modulation of glycolytic and mitochondrial metabolism attenuated several of these abnormalities.

3.5. Lactate-Mediated Epigenetic Remodeling and the Senescent Phenotype

Wei et al. (2023) investigated lactate metabolism and protein lactylation using senescent microglia together with multiple mouse models of aging and AD [208]. Prematurely senescent microglia generated by doxorubicin treatment, as well as hippocampal tissue from naturally aged mice and two AD models (5 × FAD and APP/PS1), exhibited significantly elevated intracellular lactate concentrations compared with controls. Pharmacological

inhibition of lactate dehydrogenase reduced intracellular lactate levels, indicating that lactate accumulation was primarily attributable to increased glycolytic metabolism rather than impaired clearance.

Lactylomic analysis demonstrated widespread increases in protein lysine lactylation in senescent microglia, including increased histone H3K18 lactylation. Differentially lactylated proteins were enriched in pathways related to oxidative phosphorylation, lysosomal function, phagocytosis, cell-cycle regulation, and AD [208]. Mechanistic analyses further identified histone H3K18 lactylation as a prominent feature associated with inflammatory signaling.

Chromatin immunoprecipitation sequencing demonstrated increased H3K18 lactylation at the promoters of *Rela* and *NFκB1*, accompanied by activation of the canonical NF-κB pathway. RNA sequencing identified increased expression of downstream inflammatory genes, including the SASP-associated cytokines IL-6 and IL-8 [208]. Pharmacologic inhibition of NF-κB signaling reduced lactate-induced IL-6 and IL-8 expression despite continued lactate exposure, supporting a role for H3K18 lactylation upstream of NF-κB activation in this experimental model. Together, these findings showed that increased lactate and H3K18 lactylation accompanied NF-κB activation and increased SASP-associated IL-6 and IL-8 expression in senescent microglia [208].

3.6. Lipid Remodeling and Cholesterol Homeostasis

Cholesterol Homeostasis and Cellular Senescence

Included studies reported associations between disrupted cholesterol trafficking, cholesterol accumulation, oxysterol metabolism, and cellular senescence in AD and related experimental models [177,210]. Single-nucleus transcriptomic analyses of more than 980,000 human brain nuclei demonstrated that AD is characterized by marked activation of cellular senescence pathways within microglia and oligodendrocytes, accompanied by widespread alterations in transcriptomic pathways related to cholesterol transport, biosynthesis, efflux, esterification, and storage [213]. Cholesterol pathway activity strongly correlated with cellular senescence scores at the single-cell level. Similar relationships have been observed across multiple brain cell populations, where expression of cholesterol transport genes, including *ABCA1*, *ABCG1*, *APOE*, and *NR1H3* (LXRα), closely tracks with senescence-associated transcriptional signatures in postmortem human AD tissue [177].

In AD, particularly in APOE4-associated models, cholesterol accumulation was associated with lysosomal sequestration of ABCA1, reduced cholesterol efflux, mTORC1 activation, increased $p16^{INK4a}$ and $p21^{CIP1}$ expression, DNA-damage signaling, and SASP-associated inflammatory changes [177]. Postmortem AD brain tissue similarly showed increased lysosomal ABCA1 localization and senescence-associated markers. In APOE4 transgenic mice, hydroxypropyl-β-cyclodextrin restored ABCA1 trafficking, reduced lysosomal cholesterol accumulation and mTOR activation, decreased neuroinflammation, and improved cognitive performance [177].

In cholesterol-loaded macrophages, intracellular cholesterol accumulation increased LXRα-dependent CD38 expression, accelerated NAD^+ degradation, impaired mitochondrial respiration, and increased $p16^{INK4a}$, $p21^{CIP1}$, SA-β-gal activity, and SASP factors [210]. NMN supplementation or pharmacologic CD38 inhibition restored NAD^+ availability, improved mitochondrial respiration, and reduced several senescence-associated phenotypes [210].

3.7. Microglial Cholesterol Dysregulation During Neurodegeneration

Single-nucleus RNA sequencing demonstrates that senescence is not uniformly distributed across the microglial population but instead preferentially affects distinct functional states. Analysis of more than 160,000 human microglial nuclei revealed that inflammatory,

lipid-processing, phagocytic, and homeostatic microglial states progressively acquired senescence-associated transcriptional signatures during AD progression [213]. Notably, these same populations demonstrated coordinated dysregulation of cholesterol transport, efflux, metabolism, and storage pathways, with cholesterol pathway activity exhibiting a strong positive correlation with cellular senescence scores.

Inflammatory microglia showed particularly strong co-activation of cholesterol-associated and senescence-associated pathways. Integration of independent single-cell datasets from the Religious Orders Study and Memory and Aging Project (ROSMAP) and the Seattle Alzheimer's Disease Brain Cell Atlas (SEA-AD) demonstrated that inflammatory microglia consistently exhibited simultaneous activation of cholesterol-associated pathways and senescence programs in individuals with dementia [213,224,225]. Weighted gene co-expression network analysis identified conserved modules linking cholesterol metabolism, lysosomal trafficking, DNA-damage responses, and senescence [213].

Emerging evidence also implicates cholesterol-rich myelin debris as an important upstream trigger of cholesterol-associated microglial senescence [226]. Myelin debris is exceptionally rich in cholesterol and must be continuously cleared by microglia throughout life [227]. Reanalysis of induced pluripotent stem cell-derived microglia exposed to multiple pathological substrates, including amyloid-β fibrils, apoptotic neurons, synaptosomes, and myelin debris, demonstrated that myelin produced the strongest induction of disease-associated microglia (DAM) while simultaneously activating cellular senescence pathways and cholesterol-associated transcriptional programs [213]. Following myelin exposure, the proportion of senescent microglia nearly doubled, accompanied by increased expression of canonical DAM markers including *ABCA1*, *APOE*, *GPNMB*, and *TREM2*, as well as increased nuclear *CDKN2A* expression and characteristic alterations in nuclear morphology associated with cellular senescence [213].

3.8. Lipid-Droplet Remodeling and Cellular Senescence

Rachmian-Cooper et al. (2026) [153] investigated lipid-droplet accumulation as a metabolic feature of cellular senescence using complementary in vitro, mouse, and human datasets. Metabolic and lipidomic profiling of etoposide-induced senescent primary human fibroblasts identified increased glycolysis-related metabolites together with broad lipid remodeling, including marked enrichment of triacylglycerol species, which serve as major precursors of lipid droplets. Senescent fibroblasts also exhibited significantly increased lipid-droplet abundance and elevated expression of the lipid-droplet-associated genes *PLIN2* and *APOE*. Treatment with several AMPK activators reduced lipid-droplet accumulation and was accompanied by decreased IL-8 expression and inflammatory signaling. In 5 × FAD mice, senescent microglia co-expressed canonical senescence markers with increased lipid-droplet markers, including *Plin2* and *Apoe*. Reanalysis of human AD single-nucleus RNA-sequencing data similarly showed increased PLIN2 expression in microglia with high senescence scores [153].

Kadir et al. (2026) further linked lipid-droplet homeostasis with cellular senescence in the neurovascular compartment [218]. Using humanized APOE2, APOE3, and APOE4 knock-in mice together with isogenic human iPSC-derived pericytes, the investigators found that APOE2 was associated with greater pericyte abundance and blood–brain barrier integrity and increased resistance to experimentally induced senescence. Following ionizing-radiation-induced senescence, APOE2 pericytes exhibited reduced SA-β-gal activity, lower $p16^{INK4a}$ and $p21^{CIP1}$ expression, fewer γH2AX foci, and greater lamin B1 abundance than APOE3 or APOE4 pericytes. Untargeted lipidomics demonstrated APOE-genotype-specific lipid profiles, with APOE2 pericytes showing reduced levels of several phospholipid classes, increased diacylglycerol and triacylglycerol abundance, but fewer intracellular lipid droplets.

APOE2 pericytes also exhibited increased lysosomal activity, expression of proteins involved in lipid transport and β-oxidation, greater mitochondrial abundance and oxidative capacity, and higher ATP production. Treatment of APOE3 and APOE4 pericytes with recombinant APOE2 reduced lipid-droplet accumulation, including senescence-associated lipid-droplet accumulation, and improved several measures of pericyte function [218].

3.9. Oxysterols as Senescence-Inducing Lipid Mediators

Oxysterol dysregulation was supported by both included studies and contextual clinical literature. Included studies linked altered oxysterol metabolism with senescence-associated phenotypes in AD-related experimental systems [177,228]. Complementary clinical literature has reported altered circulating oxysterol profiles in AD and MCI, including changes in 27-hydroxycholesterol (27-OHC) and 24S-hydroxycholesterol (24S-OHC), with several measures associated with cognitive status [229,230]. Complementing these findings, postmortem ROSMAP brain tissue showed elevated 7-hydroxycholesterol, particularly in APOE4 carriers, where oxysterol abundance correlated with transcriptomic senescence signatures [177].

Experimental studies further demonstrate that 27-OHC directly induces multiple hallmarks of brain aging. Systemic administration of 27-OHC to mice produces impairments in spatial learning, object recognition memory, and social cognition, accompanied by increased anxiety-like behaviors that resemble early neuropsychiatric manifestations of neurodegenerative disease [228]. Histologically, these behavioral deficits coincide with increased senescence-associated β-galactosidase activity and elevated expression of the cyclin-dependent kinase inhibitors $p16^{INK4a}$ and $p21^{CIP1}$ within both the hippocampus and prefrontal cortex. Neuronal degeneration is further evidenced by reductions in Nissl bodies and widespread structural abnormalities, indicating that chronic exposure to elevated oxysterol levels accelerates molecular and cellular features of brain aging [228]. Thus, systemic 27-OHC administration was accompanied by behavioral abnormalities, neuronal injury, and increased senescence-associated markers in vivo [228].

Microglia appear particularly susceptible to oxysterol-induced dysfunction. Exposure to 27-OHC produces characteristic dystrophic microglial morphology, including fragmentation and process retraction, while simultaneously increasing expression of $p16^{INK4a}$ and $p21^{CIP1}$ within IBA1-positive microglia [228]. These senescent microglia exhibit a pronounced shift toward a pro-inflammatory phenotype characterized by increased inducible nitric oxide synthase (iNOS) expression and reduced arginase-1 (Arg1), consistent with polarization toward an M1-like inflammatory state. Similar findings have been reproduced in cultured BV2 microglial cells, where clinically relevant concentrations of 27-OHC induce time-dependent increases in reactive oxygen species, senescence-associated β-galactosidase activity, and inflammatory polarization.

27-OHC exposure was also associated with altered iron homeostasis in microglia. Microglia exposed to 27-OHC accumulate ferritin while exhibiting reduced ferritin light chain expression, indicating pathological intracellular iron overload [228]. Iron accumulation is accompanied by mitochondrial depolarization, reduced glutathione peroxidase-4 (GPX4) expression, increased divalent metal transporter-1 (DMT1), and enhanced oxidative stress, collectively consistent with activation of ferroptosis-associated pathways. Importantly, treatment with the iron chelator deferoxamine restores mitochondrial membrane potential, normalizes iron metabolism, suppresses inflammatory M1 polarization, reduces microglial senescence markers, improves neuronal survival, and rescues cognitive performance in 27-OHC-treated mice [228].

3.10. Sphingolipid Remodeling and Glucocerebrosidase Dysfunction in Parkinson's Disease

Included PD studies linked *GBA*/glucocerebrosidase dysfunction and broader lipid remodeling with lysosomal dysfunction, mitochondrial impairment, and senescence-like phenotypes [209,216]. Russo et al. (2024) identified a regulatory pathway connecting the chromatin organizer SATB1, microRNA-22-3p (miR-22-3p), and *GBA* expression in dopaminergic neurons [209]. Loss of SATB1 increased expression of miR-22-3p, which suppressed translation of *GBA* mRNA despite relatively preserved transcript abundance, resulting in markedly reduced GCase protein levels and enzymatic activity. Inhibition of miR-22-3p increased GCase in SATB1-deficient cells, whereas a miR-22-3p mimic reduced GCase in wild-type cells, providing functional support for this regulatory relationship [209]. *GBA* overexpression also reduced SA-β-gal activity in SATB1-deficient neuronal cells and rescued their heightened vulnerability to hydrogen peroxide and 6-hydroxydopamine. In vivo, *GBA* overexpression mitigated SATB1-knockdown-induced loss of dopaminergic neurons in the substantia nigra [209].

Reduced GCase activity also caused pronounced lysosomal dysfunction. SATB1-deficient neuronal models exhibited accumulation of dysfunctional lysosomes, abnormal membranous structures, and increased intracellular lipid vesicles, while restoration of SATB1 or *GBA* improved lysosomal abnormalities [209]. SATB1-deficient neurons also accumulated both soluble and insoluble α-synuclein. Overexpression of *GBA* reduced α-synuclein aggregation, and treatment of human stem cell-derived dopaminergic neurons with recombinant human GCase reduced both LAMP1 and α-synuclein accumulation [209].

Mitochondrial dysfunction represents another major downstream consequence of disruption of the SATB1-*GBA* pathway. SATB1-deficient neuronal cells demonstrated abnormal mitochondrial ultrastructure, reduced oxygen consumption, diminished ATP production, loss of mitochondrial membrane potential, and impaired oxidative phosphorylation complex integrity [209]. They also exhibited increased parkin-positive mitochondria, persistently elevated PINK1 signaling, and impaired mitochondrial turnover, consistent with accumulation of dysfunctional mitochondria. Importantly, restoration of *GBA* expression improved oxygen consumption and ATP production, whereas suppression of α-synuclein did not restore these bioenergetic defects [209].

Accumulation of GluCer emerged as the central metabolic consequence of impaired GCase activity. Human stem cell-derived dopaminergic neurons and murine neuronal cells lacking SATB1 exhibited increased intracellular GluCer, whereas recombinant GCase treatment reduced GluCer accumulation [209]. Importantly, direct exposure of otherwise normal neuronal cells to GluCer reproduced several abnormalities observed following SATB1 loss. GluCer treatment increased lysosomal accumulation, disrupted lysosomal gene expression, and produced dose-dependent impairment of mitochondrial oxidative phosphorylation; inhibition of GluCer synthesis partially alleviated the mitochondrial phenotype [209].

GluCer exposure also directly induced a senescence-like state. Increasing concentrations of GluCer increased SA-β-gal-positive cells in human dopaminergic neurons and N2A cells and increased expression of *Cdkn2a* ($p16^{INK4a}$), *Cdkn1a* ($p21^{CIP1}$), *S100A9*, and multiple SenMayo SASP-associated genes [209]. *GBA* overexpression also reduced GluCer-induced SA-β-gal activity.

Complementary evidence from patient-derived *GBA*-associated PD organoids further linked lipid remodeling with premature cellular senescence. Rosety et al. (2023) [216] generated midbrain organoids from induced pluripotent stem cells carrying the heterozygous *GBA*-N370S mutation and identified reduced GCase activity, impaired autophagic flux, and mitochondrial dysfunction. Genome-scale metabolic modeling predicted substantial alterations in lipid metabolism, which were supported by lipidomic analysis showing dif-

ferences in phosphatidylethanolamine, phosphatidylcholine, phosphatidylinositol species, triglycerides, and other lipid classes. *GBA*-PD organoids also exhibited impaired dopaminergic and general neuronal differentiation together with an expanded population of neural progenitors showing reduced proliferative capacity and S-phase cell-cycle arrest. These progenitors exhibited increased oxidative DNA damage and multiple senescence-associated features, including reduced nuclear LAMINB1 and HP1γ, increased β-galactosidase activity, and accumulation of SA-β-gal-positive cells [216].

3.11. Interventional Studies Targeting Lipid Remodeling and Cholesterol Homeostasis

In APOE4 transgenic mice, hydroxypropyl-β-cyclodextrin (HPCD) reduced brain oxysterol concentrations, restored membrane localization of ABCA1, decreased lysosomal ABCA1 and mTOR activation, reduced markers of cellular senescence and neuroinflammation [177]. These molecular improvements were accompanied by enhanced expression of synaptic proteins and improved cognitive performance without substantially altering total brain cholesterol levels [177]. In cholesterol-overload models, NMN supplementation reduced $p16^{INK4a}$, $p21^{CIP1}$, and SASP factors and restored mitochondrial respiration, while pharmacologic CD38 inhibition preserved intracellular NAD^+ and attenuated several senescence-associated phenotypes [210]. In 27-hydroxycholesterol-induced neurodegeneration models, deferoxamine reduced intracellular iron accumulation, restored mitochondrial membrane potential, attenuated microglial senescence, normalized inflammatory polarization, improved neuronal survival, and significantly rescued learning and memory deficits [228]. Genetic *GBA* overexpression or recombinant GCase treatment reduced GluCer accumulation, improved lysosomal function and mitochondrial respiration, and reduced α-synuclein accumulation and senescence-associated phenotypes. Pharmacologic inhibition of GluCer synthesis also attenuated mitochondrial dysfunction and senescence-associated gene expression [209].

3.12. Circulating and Translational Metabolic Signatures

Fluid-Based Metabolic Signatures of Senescence and Senolytic Response

Several included studies evaluated plasma, serum, cerebrospinal fluid, or urine metabolites and lipids as potential markers of senescence-associated disease states or treatment response [104,170,182,214,217,219]. Garbarino et al. (2025) evaluated exploratory fluid biomarkers in five older adults with mild AD enrolled in the SToMP-AD phase 1 trial of D + Q [104]. Although the small open-label study was not designed to establish efficacy, paired plasma and CSF lipidomic analyses identified treatment-associated changes in circulating lipids. Among 194 plasma lipid species, global lipidomic profiles showed separation between baseline and post-treatment samples when normalized to total protein. At the lipid-class level, phosphatidylcholine (PC), lysophosphatidylethanolamine (LPE), and acylcarnitines decreased by approximately 17%, 22%, and 16%, respectively, while lysophosphatidylcholine (LPC) showed a similar downward trend. Nine individual plasma lipid species also differed at an unadjusted $p < 0.05$, including several PC species, LPC 18:2, and acylcarnitine 14:2, all of which decreased after treatment [104].

The apparent metabolic response depended substantially on normalization strategy. When plasma lipids were expressed per unit volume rather than relative to total protein, the multivariate separation disappeared and triacylglycerides (TAGs) instead emerged as the principal altered lipid class, increasing by 23% after treatment [104]. Long-chain TAG species accounted for much of this response, whereas LPCs continued to show a tendency toward reduction.

Changes within the CSF lipidome were more modest. Global CSF lipid profiles did not separate clearly between baseline and post-treatment samples, and no lipid class changed

significantly [104]. At the individual-species level, however, LPC 16:1 decreased by 43% following treatment when normalized to protein, representing the largest treatment-associated effect in CSF. Two PC species increased modestly, while volume normalization largely eliminated significant differences [104].

Other biomarkers provided important context for these lipidomic findings. Urinary metabolites and classical CSF biomarkers, including amyloid-β and tau, remained largely unchanged during the treatment period, whereas peripheral blood mononuclear cells demonstrated reduced expression of multiple inflammatory and stress-responsive genes, including *FOS*, *FOSB*, *IL1B*, *IL8*, *JUN*, *JUNB*, and *PTGS2* [104].

3.13. Serum Metabolic Remodeling in Experimental Age-Related Macular Degeneration

Song et al. (2024) [217] examined serum metabolic remodeling in a stress-induced premature senescence-associated model of age-related macular degeneration (AMD). Transcriptomic analysis of retinal tissues from younger individuals with dry AMD identified enrichment of several metabolic pathways, including glycerolipid metabolism, tyrosine metabolism, and pentose and glucuronate interconversions. In sodium iodate-treated middle-aged mice, untargeted serum metabolomics identified 19 metabolites that differed from controls, including increased lysophosphatidylcholine species and reduced 4-guanidinobutanoic acid. Luteoloside treatment partially normalized these metabolic abnormalities, including reductions in several LysoPC species and increases in 4-guanidinobutanoic acid. These metabolic changes occurred alongside reduced serum IL-1β, increased superoxide dismutase activity, preservation of retinal structure, and reduced ocular expression of p53, $p21^{CIP1}$, Rb1, IL-1β, IL-6, TNF-α, and VEGF [217].

3.14. Multi-Omic Circulating Signatures for Alzheimer's Disease Detection

Several studies combined circulating proteomic, metabolomic, and transcriptomic measurements to evaluate potential AD-associated signatures [170,182]. Plasma proteomic profiling identified 516 proteins, of which 334 were sufficiently quantified for differential analysis. Twenty-eight candidate proteins differed significantly between AD and cognitively normal participants, including 21 that were increased and seven that were decreased. Five proteins, including ZNF587B, AQR, C-reactive protein (CRP), fibronectin (FN1), and serum amyloid A1 (SAA1), were subsequently evaluated for diagnostic performance. Individually, FN1 and SAA1 demonstrated particularly strong discrimination, with receiver operating characteristic area-under-the-curve (AUC) values of 0.933 and 0.918, respectively, while ZNF587B and AQR produced AUC values of 0.846 and 0.810. CRP showed weaker individual discrimination, with an AUC of 0.692 [182].

The diagnostic signal improved when circulating proteins were considered jointly. A three-dimensional k-nearest neighbors model incorporating ZNF587B, AQR, and CRP yielded an AUC of 0.941 in the training dataset and 1.000 in both the testing and validation datasets [182]. These performance estimates should be interpreted cautiously because they were derived from small internally partitioned datasets, including only nine participants in the testing set and 17 in the validation set. Perfect discrimination in cohorts of this size is particularly vulnerable to model overfitting and sampling variability, and independent external validation in substantially larger cohorts will be required before clinical utility can be inferred. Metabolomic profiling identified phenylacetylglutamine (PAGln) as an additional circulating signature of AD. Serum PAGln was significantly elevated in individuals with AD and distinguished AD from cognitively normal participants with an AUC of 0.900, closely replicating an earlier plasma finding from the same investigators in which PAGln achieved an AUC of 0.914 [182].

Recent work by Tian et al. (2026) further extends this concept by integrating human brain proteomics with transcriptomic, brain metabolomic, and serum metabolomic datasets to examine how senescence-associated molecular programs relate to metabolic remodeling during AD progression [170]. Rather than focusing on individual biomarkers, the investigators identified patient subgroups defined by coordinated expression of cellular senescence proteins and RNA modification regulators. Individuals with the highest senescence-associated risk scores exhibited greater Braak stage, amyloid plaque burden, and cognitive impairment [170]. Importantly, enrichment analyses consistently identified abnormalities in amino acid metabolism, glycerophospholipid metabolism, and other lipid metabolic pathways across both proteomic and metabolomic datasets. Differential metabolite analyses further demonstrated overlapping alterations in brain tissue and serum, including shared changes in phosphatidylcholine metabolites, histidine-related metabolites, and D-amino acid metabolism. Several of these metabolites, including phosphatidylcholine species, lysophosphatidylcholines, kynurenine, and threonine, correlated strongly with senescence-associated hub proteins [170].

3.15. Systemic Metabolic Remodeling Following Senolytic Intervention

In the APPNL-F/NL-F mouse model of AD, Fang et al. (2025) showed that long-term treatment with dasatinib plus quercetin (D + Q) produced widespread metabolic improvements that paralleled reductions in both peripheral and central senescence markers [214]. These effects were largely restricted to female mice.

Female $APP^{NL\text{-}F/NL\text{-}F}$ mice exhibited evidence of systemic senescence before overt cognitive decline, including increased expression of *Cdkn2a* and *Cdkn1a*, and multiple SASP cytokines within visceral white adipose tissue, together with elevated senescence markers in the hippocampus [214]. Monthly administration of D + Q significantly reduced expression of senescence-associated genes and inflammatory cytokines in both tissues, whereas fisetin produced comparatively modest effects.

Metabolic improvements extended well beyond reductions in senescence markers. D + Q-treated female mice displayed significantly lower body weight and adiposity despite unchanged food intake [214]. Visceral, subcutaneous, and retroperitoneal white adipose depots were reduced, accompanied by lower circulating triglycerides, fasting glucose, fed glucose, plasma insulin concentrations, and increased oxygen consumption and energy expenditure. In contrast, glucose tolerance and insulin sensitivity remained largely unchanged [214].

Peripheral metabolic remodeling was accompanied by substantial improvements in neuropathology. D + Q reduced hippocampal expression of $p16^{INK4a}$, $p21^{CIP1}$, and TNF-α, decreased senescence-associated β-galactosidase activity, lowered soluble Aβ42 levels and amyloid plaque burden, and improved spatial learning and memory in the Morris water maze [214]. Plasma IL-6, TNF-α, and IL-1β concentrations also declined. These effects were largely absent in male mice and were not reproduced by fisetin.

3.16. Peripheral Tissue Metabolic Alterations in VPS13A Disease

Riccardi et al. (2025) used metabolomic and proteomic profiling of skeletal muscle from patients with VPS13A disease and *Vps13a*$^{-/-}$ mice to identify a premature muscle-aging phenotype characterized by impaired autophagy, mitochondrial dysfunction, oxidative stress, and extensive metabolic remodeling [157]. Mass spectrometry-based metabolomics of *Vps13a*$^{-/-}$ skeletal muscle revealed marked depletion of high-energy phosphate metabolites, including ATP, ADP, GTP, GDP, UTP, and phosphocreatine, indicating severe energetic stress [157]. NAD^+ and its nicotinate ribonucleotide precursor were also reduced, while the NAD^+ breakdown products ADP-ribose and nicotinamide accumulated, consistent

with enhanced NAD^+ catabolism. Purine breakdown and salvage metabolites were increased, and several free amino acids accumulated, suggesting altered nucleotide and amino acid metabolism in the setting of impaired cellular energetics [157]. Glycolytic intermediates, including bisphosphoglycerate, phosphoglycerate, and phosphoenolpyruvate, were likewise depleted.

Lipid metabolism was also substantially altered. Multiple acylcarnitine species accumulated in *Vps13a*$^{-/-}$ muscle, which the authors interpreted as evidence of impaired or incomplete fatty acid oxidation [157]. These metabolic abnormalities occurred alongside depletion of the antioxidant metabolites ascorbate and taurine and increased protein oxidation and lipid peroxidation, indicating pronounced redox stress. Proteomic analyses further demonstrated reduced abundance of metabolic enzymes, including PFKP, together with accumulation of ubiquitinated and oxidatively modified proteins, impaired autophagic pathways, and increased pro-apoptotic signaling [157].

Importantly, these metabolic abnormalities occurred in parallel with features of premature skeletal muscle aging. *Vps13a*$^{-/-}$ muscle exhibited accumulation of NCAM1, impaired autophagic flux, activation of NF-κB and Nrf2 signaling, and increased expression of the pro-inflammatory cytokines IL-6, TNF-α, and IL-1β [157]. Muscle from patients with VPS13A disease similarly demonstrated impaired autophagy, increased protein oxidation, NCAM1 accumulation, and NF-κB activation. Pharmacological activation of autophagy with rapamycin reduced NCAM1, LAMP1, and p62 accumulation in *Vps13a*$^{-/-}$ mice, supporting a functional relationship between defective autophagy and the premature muscle-aging phenotype [157]. The major metabolic pathways and candidate biomarkers identified across the included studies are summarized in Tables 2 and 3.

Table 2. Major metabolic pathways linking metabolic remodeling to cellular senescence.

Metabolic Pathway	Representative Metabolites	Principal Mechanism	Major Cell Types	Diseases	Therapeutic Targets
NAD+ metabolism	NAD+, NMN, NR	Reduced sirtuin/DNA-repair capacity and CD38-dependent NAD+ consumption promote mitochondrial dysfunction and senescence signaling.	Neurons, astrocytes, macrophages and microglia	AD and PD-related models	NMN or NR supplementation; CD38 inhibition
Mitochondrial bioenergetics	ATP, NADH and respiratory-chain intermediates	Impaired oxidative phosphorylation increases ROS and activates stress-responsive p53/ $p21^{CIP1}$ and inflammatory programs.	Neurons and glia	AD and PD	Restoration of electron transport, redox balance and mitochondrial quality control
Glycolysis and lactate signaling	Glucose, pyruvate and lactate	Elevated lactate drives histone H3K18 lactylation and NF-kB-dependent SASP expression.	Microglia	Aging and AD	LDH inhibition; modulation of lactylation or NF-kB signaling

Table 2. *Cont.*

Metabolic Pathway	Representative Metabolites	Principal Mechanism	Major Cell Types	Diseases	Therapeutic Targets
Cholesterol trafficking	Cholesterol and oxysterols	ABCA1 sequestration, lysosomal dysfunction and mTOR activation reinforce senescence and neuroinflammation.	Microglia, macrophages and neural cells	AD	HPCD; ABCA1 recycling; mTOR modulation
Oxysterol and iron metabolism	27-hydroxycholesterol, ferritin-related iron pools and lipid peroxides	Oxidative stress, iron dyshomeostasis and ferroptosis-related injury promote microglial senescence and neuronal damage.	Microglia and neurons	AD-related neurodegeneration	Deferoxamine; antioxidant and ferroptosis-directed approaches
Sphingolipid metabolism	Glucosylceramide, phosphatidylethanolamine, phosphatidylcholine, phosphatidylinositol species, and related lipids	Reduced GCase activity is associated with broad lipid remodeling, impaired autophagy and mitochondrial function, oxidative stress, and senescence-associated cell-cycle arrest in neural progenitors	Dopaminergic neurons and neural progenitor cells	PD	GCase restoration; inhibition of glucosylceramide synthesis
Systemic lipid and energy remodeling	Phosphatidylcholines, lysophospholipids, acylcarnitines and triacylglycerides	Senescent-cell burden and inflammatory cross-tissue signaling alter circulating and peripheral metabolic homeostasis.	Adipose tissue, immune cells and brain	AD	Senolytics including D + Q; multimodal metabolic monitoring
Amino acid and glycerophospholipid networks	Histidine-related metabolites, kynurenine, threonine, phosphatidylcholines and lysophosphatidylcholines	Coordinated brain-serum metabolic changes correlate with senescence-associated protein programs and disease progression.	Mixed brain cell populations and peripheral tissues	AD	Patient stratification; pathway-guided interventions
Purine and nucleotide metabolism	Adenosine, inosine, hypoxanthine, xanthine, dATP and purine dNTPs	Reduced ADA activity alters purine and nucleotide homeostasis and is associated with impaired 53BP1-mediated DNA repair and senescence-associated $p16^{INK4a}$ expression	Astrocytes	ALS	ADA/purine-salvage pathway modulation

Table 2. *Cont.*

Metabolic Pathway	Representative Metabolites	Principal Mechanism	Major Cell Types	Diseases	Therapeutic Targets
Lipid-droplet and triacylglycerol metabolism	Triacylglycerols, diacylglycerols, phosphatidylcholine, phosphatidylethanolamine, sphingomyelin, cardiolipin, and lipid droplets	Senescence is associated with altered lipid storage and lipid-droplet accumulation, whereas enhanced lysosomal lipid processing, β-oxidation, mitochondrial function, and lipid transport are associated with greater resistance to senescence.	Microglia, pericytes, and fibroblasts	AD-related models	AMPK activation, APOE2-associated lipid processing, β-oxidation, lysosomal lipid turnover, and lipid-droplet homeostasis
Circulating glycerophospholipid and systemic metabolic remodeling	LysoPC species, phosphatidylcholines, 4-guanidinobutanoic acid, 3-phosphoglyceric acid	Systemic metabolic remodeling occurs alongside oxidative stress, inflammatory signaling, and p53–$p21^{CIP1}$–Rb1-associated retinal senescence	Retinal cells and peripheral metabolic compartments	AMD	Luteoloside; modulation of systemic lipid metabolism and inflammatory signaling

Table 3. Circulating metabolic biomarkers and therapeutic implications.

Biomarker/Signature	Sample	Disease	Clinical Application	Supporting Study
Phenylacetylglutamine (PAGln)	Serum and plasma	AD	Candidate disease-detection marker; replicated across two circulating matrices in the same research program.	Yang et al., 2024 [182]
ZNF587B, AQR and CRP panel	Plasma	AD	Composite diagnostic classification; illustrates the potential advantage of multimarker panels over single analytes.	Yang et al., 2024 [182]
Fibronectin (FN1) and serum amyloid A1 (SAA1)	Plasma	AD	Candidate individual protein classifiers for disease detection.	Yang et al., 2024 [182]
Phosphatidylcholines and lysophosphatidylcholines	Plasma; selected species in CSF	Mild AD treated with D + Q	Exploratory pharmacodynamic monitoring of senolytic-associated lipid remodeling.	Garbarino et al., 2025 [104]
Lysophosphatidylethanolamines and acylcarnitines	Plasma	Mild AD treated with D + Q	Candidate treatment-response signature; interpretation depends on normalization strategy.	Garbarino et al., 2025 [104]
Triacylglyceride profile	Plasma	Mild AD treated with D + Q	Exploratory treatment-response marker under volume-based normalization.	Garbarino et al., 2025 [104]

Table 3. *Cont.*

Biomarker/Signature	Sample	Disease	Clinical Application	Supporting Study
Senescence-linked phosphatidylcholine and lysophosphatidyl-choline species	Serum with matched brain datasets	AD	Accessible surrogate signature of brain metabolic and senescence-associated programs; potential patient stratification.	Tian et al., 2026 [170]
Kynurenine, threonine and histidine-related metabolites	Serum with matched brain datasets	AD	Multi-omic patient stratification and assessment of senescence-associated disease progression.	Tian et al., 2026 [170]
Integrated proteomic-metabolomic senescence signature	Plasma and serum	AD	Disease classification, molecular subgrouping and longitudinal monitoring; preferable to interpretation of a single analyte.	Yang et al., 2024; Tian et al., 2026 [170,182]
ADA-related purine metabolites, including inosine, hypoxanthine, and xanthine	CSF	Sporadic ALS	Exploratory metabolic signature associated with age, sex, and disease-progression measures; requires independent validation	Hall et al., 2026 [219]
LysoPC species and 4-guanidinobutanoic acid	Serum	Experimental AMD	Exploratory treatment-response signature associated with metabolic and senescence-related changes; requires validation in human AMD cohorts	Song et al., 2024 [217]

Multiple metabolic pathways converge on mitochondrial dysfunction, oxidative stress, inflammatory signaling, epigenetic remodeling, and activation of canonical senescence programs. Abbreviations: AD, Alzheimer's disease; ADA, adenosine deaminase; ALS, Amyotrophic lateral sclerosis; D + Q, dasatinib plus quercetin; GBA, glucocerebrosidase gene; GCase, glucocerebrosidase; HPCD, hydroxypropyl-beta-cyclodextrin; LDH, lactate dehydrogenase; NAD+, nicotinamide adenine dinucleotide; NF-kB, nuclear factor kappa B; NMN, nicotinamide mononucleotide; NR, nicotinamide riboside; PD, Parkinson's disease; ROS, reactive oxygen species; SASP, senescence-associated secretory phenotype.

Candidate circulating biomarkers identified in human and experimental studies are summarized with their proposed diagnostic, stratification, or treatment-monitoring applications. All candidates require validation in larger independent cohorts. Abbreviations: AD, Alzheimer's disease; ALS, Amyotrophic lateral sclerosis; AQR, Aquarius intron-binding spliceosomal factor; CRP, C-reactive protein; CSF, cerebrospinal fluid; D + Q, dasatinib plus quercetin; FN1, fibronectin 1; PAGln, phenylacetylglutamine; SAA1, serum amyloid A1; ZNF587B, zinc finger protein 587B.

4. Discussion

This systematic review synthesized evidence from 23 studies examining the relationship between metabolomic alterations and cellular senescence in neurodegenerative disease. Despite substantial heterogeneity in disease models, biological systems, metabolomic platforms, and experimental methodologies, four recurring metabolic themes consistently emerged across the literature: (1) disruption of NAD^+ homeostasis and redox metabolism, (2) impaired mitochondrial bioenergetics and glycolytic reprogramming, (3) lipid remodeling and cholesterol dyshomeostasis, and (4) circulating metabolic signatures with potential

diagnostic and translational relevance [108,112,177,207–210,213,214,216]. Collectively, these findings support a close and recurrent association between metabolic remodeling and cellular senescence across multiple neurodegenerative disorders, while experimental studies suggest that metabolic dysfunction may contribute to the establishment or maintenance of senescence in specific model systems. Rather than identifying a single metabolite specific to senescence, the available evidence supports a model in which coordinated alterations across interconnected metabolic networks, including NAD^+ metabolism, mitochondrial bioenergetics, lipid homeostasis, and inflammatory signaling, more accurately define the senescent phenotype than any individual metabolite alone.

An important concept emerging from this synthesis is that senescence-associated metabolic remodeling is best understood as a coordinated network phenomenon rather than a collection of isolated pathway abnormalities. Across the studies reviewed, disturbances in NAD^+ metabolism, mitochondrial bioenergetics, glycolysis, lipid homeostasis, oxidative stress, inflammatory signaling, and proteostasis rarely occurred independently. Instead, these pathways repeatedly interacted through reciprocal feedback loops in which dysfunction in one metabolic system amplified abnormalities in others, progressively stabilizing the senescent phenotype. This systems-level organization may help explain why diverse neurodegenerative diseases converge on remarkably similar senescence-associated metabolic signatures despite differing initiating pathologies.

One of the most striking observations emerging from this review is the remarkable convergence of metabolic mechanisms across otherwise distinct neurodegenerative diseases. Although AD, PD, ALS, AMD, VPS13A disease, and related experimental models arise from different initiating pathological processes, they repeatedly exhibited similar disturbances involving mitochondrial dysfunction, oxidative stress, impaired cellular bioenergetics, NAD^+ depletion, lipid remodeling, and chronic inflammatory signaling [108,112,131,157,177,207,209]. These metabolic abnormalities frequently occurred in parallel with activation of canonical senescence-associated features, including increased expression of $p16^{INK4a}$ and $p21^{CIP1}$, senescence-associated β-galactosidase activity, DNA-damage signaling, and production of SASP-associated inflammatory mediators [112,207,208,222,228]. Although the specific metabolites and pathways varied among experimental systems, the consistency with which these diverse metabolic disturbances converged on a common senescence phenotype suggests that cellular senescence represents a conserved biological response to persistent metabolic stress rather than a disease-specific phenomenon. These observations further support the concept that senescence functions as an integrative stress program activated by multiple forms of metabolic, oxidative, and proteostatic injury, thereby providing a mechanistic framework that may explain common features of neurodegeneration despite substantial differences in disease etiology [1,2].

The findings synthesized in this review further suggest that metabolic dysfunction is not simply a consequence of cellular senescence but may actively participate in its initiation and maintenance. Across multiple experimental systems, disturbances in NAD^+ metabolism, mitochondrial respiration, glycolytic regulation, autophagy, and cholesterol homeostasis either preceded or accompanied the development of senescence-associated phenotypes, while restoration of metabolic homeostasis consistently attenuated senescence markers, inflammatory signaling, and mitochondrial dysfunction [108,112,177,187,207,210,222]. Likewise, interventions targeting CD38 activity, NAD^+ depletion, glycolytic metabolism, autophagic flux, cholesterol trafficking, glucocerebrosidase activity, or senescent-cell burden improved cellular bioenergetics, reduced oxidative stress, suppressed SASP-associated inflammation, and mitigated senescence-associated phenotypes across diverse preclinical models [112,157,177,207,209–212,214]. Although direct causal evidence in humans remains limited, the remarkable consistency of these findings supports a model in

which metabolic remodeling and cellular senescence participate in a reciprocal feed-forward cycle. Importantly, this feed-forward relationship appears to operate across multiple interconnected metabolic systems rather than within individual pathways, allowing disturbances in mitochondrial function, lipid metabolism, NAD^+ homeostasis, glycolysis, autophagy, and inflammatory signaling to reinforce one another over time. The available evidence is consistent with a reciprocal relationship in which metabolic dysfunction may facilitate the establishment or maintenance of senescence, while senescent cells may further amplify metabolic disruption through mitochondrial dysfunction, chronic inflammatory signaling, persistent SASP production, and altered nutrient-sensing pathways [2,12].

mTOR signaling provides an additional framework for integrating many of these apparently distinct metabolic abnormalities. mTORC1 functions as a nutrient-sensing hub that responds to amino-acid and growth-factor availability and coordinates anabolic metabolism, lipid synthesis, mitochondrial activity, and autophagic flux. Recent studies further illustrate how nutrient-responsive mTORC1 signaling couples extracellular metabolic availability to cellular growth and metabolic programs, while broader work on dietary restriction places mTOR together with AMPK and NAD^+-dependent sirtuins within a conserved nutrient-sensing network regulating autophagy, proteostasis, mitochondrial function, and stress resistance [231–233]. Within the studies included in this review, cholesterol accumulation and lysosomal dysfunction were associated with mTOR activation, whereas rapamycin-mediated enhancement of autophagy improved metabolic and aging-associated abnormalities. These observations support viewing mTOR not as an isolated pathway but as a metabolic hub connecting lipid availability, nutrient sensing, autophagic flux, mitochondrial quality control, and senescence-associated signaling [157,177]. Within this network, AMPK activation during energetic stress favors catabolic and autophagic responses while opposing mTORC1-driven anabolic signaling, whereas NAD^+-dependent pathways contribute to mitochondrial maintenance and cellular stress adaptation; disruption of these interconnected responses may therefore amplify mitochondrial dysfunction, impaired proteostasis, and senescence-associated signaling.

Among the metabolic pathways identified, disruption of NAD^+ homeostasis emerged as one of the most consistently supported mechanisms linking metabolic dysfunction to cellular senescence across diverse neurodegenerative models. NAD^+ depletion was repeatedly associated with impaired mitochondrial respiration, defective DNA repair, oxidative stress, activation of inflammatory signaling pathways, and increased expression of canonical senescence markers, including $p16^{INK4a}$, $p21^{CIP1}$, and senescence-associated β-galactosidase activity [112,157,207,210,215]. Mechanistic studies further identified CD38-mediated NAD^+ degradation as a key upstream event linking age-associated metabolic stress to chronic inflammation and senescence, while cholesterol-induced activation of the LXRα-CD38 pathway provided an additional connection between lipid dysregulation and NAD^+ loss [207,210]. Importantly, restoration of intracellular NAD^+ through supplementation with nicotinamide riboside or nicotinamide mononucleotide, as well as pharmacologic inhibition of CD38, consistently improved mitochondrial function, reduced inflammatory signaling, attenuated senescence-associated phenotypes, and, in several models, improved cognitive or cellular function [112,207,210]. Although these interventions remain largely preclinical, the reproducibility of these findings across independent disease models and experimental systems suggests that preservation of NAD^+ homeostasis may represent a potential therapeutic strategy for modifying senescence-associated neurodegeneration rather than simply treating its downstream consequences.

Recent findings in sporadic ALS extend this nucleotide-centered metabolic framework beyond NAD^+ homeostasis to purine metabolism. Hall et al. identified ADA-dependent purine abnormalities in patient-derived astrocytes together with increased $p16^{INK4a}$ and

impaired 53BP1-mediated DNA-repair responses, while pharmacological ADA inhibition reproduced several of these abnormalities in control cells. Importantly, related purine-metabolism alterations were detected in CSF and postmortem tissue from individuals with sporadic ALS, providing translational support for the cellular findings. These observations suggest that disruption of nucleotide availability and purine salvage may represent an additional metabolic route through which impaired DNA repair becomes linked to senescence-associated phenotypes. However, the direct mechanistic evidence derives primarily from patient-derived cellular models, whereas the human biofluid and tissue findings remain associative [219].

A second major finding was the central role of mitochondrial dysfunction and loss of bioenergetic homeostasis in the establishment of cellular senescence. Rather than reflecting isolated defects in ATP production, mitochondrial dysfunction consistently occurred alongside glycolytic remodeling, oxidative stress, altered redox balance, impaired pyruvate utilization, and chronic inflammatory signaling, suggesting disruption of an integrated metabolic network rather than failure of a single pathway [108,157,211,212]. Across multiple experimental systems, impaired coupling between glycolysis and oxidative phosphorylation reduced ATP production, disrupted NAD^+/NADH homeostasis, increased mitochondrial reactive oxygen species generation, and promoted activation of canonical senescence pathways involving p53, $p21^{CIP1}$, and $p16^{INK4a}$ [108,211,212]. Conversely, excessive glycolytic activation under conditions of impaired mitochondrial oxidative capacity likewise culminated in oxidative stress and stable senescence, indicating that both insufficient and dysregulated glycolytic flux can drive cellular aging when metabolic coordination is lost [212]. Collectively, these findings suggest that preservation of metabolic flexibility and efficient coordination between glycolysis and mitochondrial respiration, rather than simple enhancement or suppression of individual metabolic pathways, may be essential for preventing senescence-associated cellular dysfunction. This relationship is also supported by experimental evidence outside the included neurodegenerative disease studies; for example, Özsan et al. showed that streptozotocin-induced metabolic stress in rats increased hippocampal malondialdehyde and the pro-inflammatory cytokines TNF-α, IL-6, and IL-1 while reducing antioxidant defenses including superoxide dismutase, catalase, and glutathione, further illustrating the close coupling between metabolic stress, oxidative imbalance, and inflammatory signaling [234]. Similarly, in an experimental AMD model, treatment-associated normalization of circulating metabolites occurred in parallel with increased antioxidant activity, reduced inflammatory cytokines, and suppression of retinal p53– $p21^{CIP1}$–Rb1-associated senescence signaling, further supporting the close relationship among systemic metabolism, oxidative stress, inflammation, and cellular senescence [217].

Lipid remodeling likewise emerged as a prominent metabolic feature associated with cellular senescence rather than merely a secondary consequence of neurodegeneration. Across multiple studies, altered cholesterol trafficking, oxysterol accumulation, sphingolipid dysregulation, and phospholipid remodeling were consistently associated with activation of senescence-associated transcriptional programs, particularly within microglia and other glial populations [177,209,213,216,228]. These findings reinforce the growing recognition that lipid metabolism extends well beyond structural membrane maintenance and instead functions as an active regulator of inflammatory signaling, lysosomal integrity, mitochondrial homeostasis, and nutrient-sensing pathways such as mTOR [177,210]. Particularly compelling was the convergence of multiple lipid classes on common downstream mechanisms. Cholesterol accumulation promoted ABCA1 dysfunction, mTOR activation, and CD38-mediated NAD^+ depletion, oxysterols induced oxidative stress, iron dyshomeostasis, and microglial senescence, while glucosylceramide accumulation impaired lysosomal function, mitochondrial respiration, and α-synuclein homeostasis [177,209,210,228].

Rather than representing independent metabolic abnormalities, these observations suggest that diverse lipid species converge upon shared pathways involving mitochondrial dysfunction, chronic inflammation, impaired proteostasis, and persistent cellular senescence, thereby providing a mechanistic link between age-associated lipid dysregulation and progressive neurodegeneration.

The findings of Rosety et al. extend this relationship to an earlier developmental stage in *GBA*-associated PD. Patient-derived midbrain organoids exhibited broad lipidomic alterations together with mitochondrial and autophagic dysfunction, oxidative DNA damage, cell-cycle arrest, and premature senescence of neural progenitors. The accompanying impairment of dopaminergic differentiation suggests that *GBA*-associated metabolic dysfunction may influence not only the survival of mature neurons but also the developmental state and stress resistance of their precursors [216]. Viewed together with the findings on NAD^+ metabolism and mitochondrial dysfunction, these observations further suggest that lipid remodeling functions as one component of a broader metabolic network rather than an isolated pathogenic pathway. Lipid-mediated disturbances in lysosomal function, mitochondrial bioenergetics, nutrient sensing, and inflammatory signaling appear to propagate metabolic dysfunction throughout the cell, reinforcing the establishment and persistence of the senescent phenotype. The findings of Rachmian-Cooper et al. extend this lipid-remodeling framework to lipid-droplet homeostasis. Senescent cells exhibited increased triacylglycerol-associated lipid metabolism and lipid-droplet accumulation, while senescent microglia in both 5 × FAD mice and human AD datasets showed enrichment of lipid-droplet-associated markers. These observations suggest that lipid-droplet accumulation may represent a recurring metabolic feature of the senescent state rather than an isolated consequence of a particular neurodegenerative pathway. The reduction in lipid-droplet abundance and IL-8 following AMPK activation further raises the possibility that altered lipid storage and inflammatory signaling are functionally interconnected. However, because direct metabolomic profiling was performed in experimentally senescent fibroblasts rather than AD brain tissue, the extent to which the same metabolic changes occur directly in human AD microglia remains to be established [153].

Complementary findings from Kadir et al. suggest that efficient lipid processing may be associated with resistance to cellular senescence [218]. APOE2 pericytes accumulated fewer lipid droplets despite increased intracellular triacylglycerol abundance and exhibited enhanced lysosomal activity, lipid transport, fatty-acid β-oxidation, mitochondrial function, and ATP production. These metabolic features were accompanied by reduced susceptibility to senescence and improved blood–brain barrier function compared with APOE3 and APOE4 pericytes. Moreover, recombinant APOE2 reduced lipid-droplet accumulation in APOE3 and APOE4 pericytes, including under senescence-inducing conditions. Considered together with the findings of Rachmian-Cooper et al., these observations suggest that lipid-droplet abundance alone may be less important than the balance among lipid storage, turnover, trafficking, and mitochondrial utilization in determining senescence-associated cellular dysfunction [218].

The translational implications of these findings are substantial but remain at an early stage of development. Because metabolites represent dynamic readouts of cellular physiology, metabolomic and lipidomic profiling offer attractive approaches for monitoring senescence-associated biological activity, disease progression, and therapeutic response rather than simply providing static measures of pathology [104,170,182]. However, the studies included in this review also underscore important barriers to clinical implementation. Few individual metabolites demonstrated sufficient specificity to distinguish cellular senescence from normal aging, systemic inflammation, mitochondrial dysfunction, or neurodegeneration more broadly, and substantial heterogeneity existed across studies with

respect to disease populations, biological specimens, metabolomic platforms, analytical methodologies, and definitions of cellular senescence [104,170,182]. This methodological variability complicates direct comparison among studies and currently precludes identification of a universally applicable metabolomic signature of cellular senescence. Instead, the evidence synthesized here suggests that the greatest clinical utility will likely come from integrated multi-omic approaches that combine metabolomic signatures with transcriptomic, proteomic, imaging, and established senescence biomarkers to improve disease classification, patient stratification, and longitudinal monitoring of therapeutic response [104,170,182].

Preclinical findings in AMD provide additional support for the potential value of circulating metabolic profiles as readouts of senescence-associated biology. Song et al. (2024) [217] identified treatment-responsive changes in serum glycerophospholipid and related metabolites in a stress-induced AMD model, including altered lysophosphatidylcholine species and 4-guanidinobutanoic acid, that occurred alongside changes in oxidative stress, inflammatory signaling, and the retinal p53– $p21^{CIP1}$–Rb1 senescence pathway. These findings suggest that circulating metabolic profiles may reflect intervention-associated changes in tissue senescence, although validation in human AMD cohorts will be necessary before such metabolites can be considered clinically useful biomarkers [217].

Taken together, the evidence synthesized in this review supports a shift in perspective regarding the metabolic basis of cellular senescence. Rather than viewing senescence as the consequence of isolated defects in NAD^+ metabolism, mitochondrial function, glycolysis, or lipid homeostasis, the available evidence supports an integrated model in which these pathways form a highly interconnected metabolic network. In this framework, disturbances in one metabolic process propagate throughout the network, creating self-reinforcing cycles of energetic failure, oxidative stress, impaired proteostasis, inflammatory activation, and persistent senescence. This systems-level perspective may help explain both the remarkable consistency of senescence-associated metabolic remodeling across neurodegenerative diseases and the limited success of therapeutic strategies directed at individual downstream abnormalities in isolation.

The strength of evidence supporting these mechanisms differs substantially across experimental systems. Human studies primarily provide associative and translational evidence. For example, circulating and tissue-based multi-omic studies in AD have identified metabolic signatures that correlate with senescence-associated molecular programs, disease severity, or treatment response, but these observations do not establish that the metabolic abnormalities cause cellular senescence in patients [104,170,182]. The SToMP-AD study similarly demonstrated treatment-associated changes in circulating lipid profiles after senolytic therapy, although the small exploratory cohort limits mechanistic inference [104]. Hall et al. extended the human evidence base in sporadic ALS by identifying purine-metabolism abnormalities in cerebrospinal fluid and postmortem tissue; however, the mechanistic link between adenosine deaminase dysfunction, impaired DNA repair, and senescence was established primarily in patient-derived astrocytes rather than directly in vivo [219]. Song et al. (2024) similarly combined human transcriptomic observations with direct metabolomic and senescence measurements in a mouse AMD model; therefore, the human data support the relevance of the identified metabolic pathways, whereas the intervention-associated metabolic and senescence effects remain preclinical [217]. By contrast, the strongest evidence for mechanistic relationships between metabolic remodeling and senescence comes from preclinical animal and cell-based studies in which specific pathways were experimentally manipulated. Studies targeting NAD+ metabolism, CD38 activity, glycolytic flux, cholesterol trafficking, oxysterol exposure, glucocerebrosidase activity, or senescent-cell burden demonstrated that altering these pathways could modify senescence-associated phenotypes, mitochondrial function, inflammatory signaling, or neurodegenerative out-

comes [112,177,207,209–212,214,228]. These findings support potential causal relationships within the experimental systems studied, but their applicability to human disease remains to be established.

In vitro and molecular models provide additional mechanistic resolution but require similar caution in interpretation. Patient-derived iPSC models, organoids, primary cells, and engineered cellular systems have demonstrated associations among *GBA* dysfunction, lipid remodeling, mitochondrial impairment, lipid-droplet accumulation, and premature senescence [153,209,216,218]. Rosety et al., for example, directly demonstrated lipidomic abnormalities, mitochondrial dysfunction, cell-cycle arrest, and senescence-associated changes in patient-derived *GBA*-PD midbrain organoids, providing mechanistic evidence in a human cellular model but not direct evidence of these processes in patients in vivo [216]. Rachmian-Cooper et al. likewise demonstrated metabolic and lipid-droplet remodeling in experimentally senescent human fibroblasts and identified corresponding lipid-droplet-associated signatures in senescent microglia from an AD mouse model and human post-mortem datasets, although the latter observations remain primarily associative [153]. Kadir et al. similarly used isogenic human iPSC-derived pericytes to demonstrate APOE-genotype-dependent differences in lipid metabolism, lipid-droplet accumulation, and resistance to experimentally induced senescence [218]. Although complementary findings in humanized APOE knock-in mice support an in vivo relationship between APOE genotype, pericyte integrity, and blood–brain barrier function, the direct relationship between lipid metabolism and senescence was established primarily in the cellular model [218]. Such models are particularly useful for testing cell-autonomous mechanisms and rescue strategies, but they do not fully reproduce the multicellular, systemic, and longitudinal features of human neurodegenerative disease. Accordingly, mechanisms demonstrated in these systems should be regarded as biologically plausible and experimentally supported rather than definitively established in patients.

Several limitations of the current evidence base should be considered when interpreting these findings. First, most included studies relied on animal models or in vitro systems, with relatively few investigations conducted in human participants and only a small number incorporating longitudinal clinical data. Consequently, the generalizability of many mechanistic observations to human neurodegenerative disease remains uncertain. Second, substantial heterogeneity existed in disease models, biological specimens, metabolomic platforms, analytical methodologies, and, importantly, the criteria used to define cellular senescence. Because no single biomarker reliably identifies senescent cells across tissues or disease contexts, differences in the use of $p16^{INK4a}$, $p21^{CIP1}$, senescence-associated β-galactosidase activity, SASP components, transcriptomic signatures, or composite phenotypes complicate direct comparison among studies [1,2]. Third, many investigations focused on targeted metabolic pathways rather than comprehensive untargeted metabolomic analyses, raising the possibility that additional senescence-associated metabolic networks remain unidentified. Fourth, because most available studies were cross-sectional or mechanistic, the temporal relationship between metabolic remodeling and cellular senescence cannot yet be established with confidence. Well-designed longitudinal human studies integrating metabolomics with complementary molecular measures of senescence will be essential to determine whether specific metabolic alterations precede senescence, arise because of senescence, or participate in reciprocal feed-forward interactions during disease progression. A major limitation of this review is that only the 80 highest-ranked records among the 546 records meeting the Elicit automated full-text screening threshold were manually assessed during the initial Elicit screening stage. Consequently, 466 lower-ranked records were not directly evaluated for eligibility, and potentially eligible studies may therefore have been missed. Because study selection at this stage depended on Elicit's ranking algorithm, this

procedure also introduces a potential ranking or selection bias that could have influenced the composition of the evidence base and the conclusions drawn from it. The subsequent PubMed and Embase searches broadened database coverage but cannot establish that all potentially eligible studies omitted during the initial Elicit stage were recovered.

Despite these limitations, this review has several notable strengths. To our knowledge, it is the first systematic review to specifically synthesize evidence linking metabolomic alterations with cellular senescence across neurodegenerative diseases. By integrating findings from AD, PD, ALS, AMD, VPS13A disease, and related experimental models, this review identifies recurring metabolic mechanisms that may not be readily apparent when individual diseases are considered in isolation. The systematic search strategy, conducted in accordance with PRISMA guidelines and supplemented by investigator verification of study selection, data extraction, and scientific interpretation, enabled a structured synthesis of a rapidly expanding and methodologically diverse literature [13]. Although the heterogeneity of the included studies precluded quantitative meta-analysis, narrative synthesis was well suited to identifying recurring mechanistic themes and highlighting points of convergence across diverse biological systems, experimental models, and metabolomic platforms. These observations provide an integrated framework for understanding how metabolic remodeling contributes to cellular senescence and suggest common biological pathways that may inform future biomarker development and therapeutic investigation.

The findings of this review also highlight several priorities for future investigation. First, longitudinal human studies integrating metabolomics with complementary transcriptomic, proteomic, epigenomic, and imaging approaches will be essential for defining the temporal relationships between metabolic remodeling, cellular senescence, and neurodegenerative disease progression [170,182]. Such studies should incorporate validated molecular and functional measures of senescence to distinguish metabolic changes that initiate senescence from those that arise as secondary consequences of established cellular dysfunction. Second, greater standardization of metabolomic methodologies, including biospecimen collection, analytical platforms, data-processing pipelines, and operational definitions of cellular senescence, will improve reproducibility and facilitate meaningful comparisons across studies [13]. Finally, mechanistic and interventional studies targeting metabolic pathways, including NAD^+ metabolism, mitochondrial bioenergetics, lipid homeostasis, autophagy, and senescent-cell burden, will be critical for determining whether metabolic remodeling represents a modifiable contributor to neurodegeneration or primarily reflects downstream consequences of disease progression [112,177,207,209,210,214].

In conclusion, the evidence synthesized in this review supports a close and recurrent association between metabolic remodeling and cellular senescence across neurodegenerative diseases and related experimental models. Rather than reflecting isolated abnormalities in individual metabolic pathways, senescence-associated phenotypes frequently occur alongside coordinated alterations in NAD+ homeostasis, mitochondrial bioenergetics, glycolytic regulation, lipid metabolism, inflammatory signaling, and proteostasis. Across diverse neurodegenerative diseases and experimental systems, these pathways repeatedly converged on shared senescence-associated phenotypes, suggesting that metabolic network dysfunction represents a recurring feature associated with cellular senescence across diverse experimental systems [108,112,177,207,210].

Together, these observations suggest that metabolomic alterations are valuable not only as biomarkers of cellular senescence but also as mechanistic readouts of the biological processes that sustain senescent-cell persistence, providing a framework for future precision medicine approaches targeting metabolic vulnerability in neurodegenerative disease. Although no single metabolite emerged as a universal biomarker of cellular senescence, the collective evidence indicates that coordinated metabolic signatures offer greater mechanistic

insight and clinical potential than individual metabolites alone, supporting their use for biomarker development, patient stratification, therapeutic monitoring, and the identification of novel metabolic targets. These findings further suggest that effective interventions may ultimately require restoration of network-wide metabolic homeostasis rather than correction of isolated metabolic abnormalities. Continued integration of metabolomics with complementary multi-omic technologies, standardized measures of cellular senescence, functional validation, and longitudinal clinical investigations will be essential for translating these mechanistic insights into clinically useful strategies for the diagnosis, monitoring, and treatment of neurodegenerative disease. Ultimately, the collective evidence indicates that cellular senescence is defined less by any single metabolic alteration than by a conserved metabolic architecture. Defining this metabolic architecture may provide a useful framework for future biomarker development and therapeutic investigation in neurodegenerative disease.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/metabo16110896/s1: Table S1: Articles excluded from the Elicit search results; Table S2: Full-text PubMed search results; Table S3: PRISMA Checklist.

Author Contributions: Conceptualization, R.L.; Methodology, R.L. and D.D.; Validation, R.L., D.D., L.A. and D.L.S.; Formal Analysis, R.L., D.D. and D.L.S.; Investigation, R.L., D.D., D.L.S. and L.A.; Data Curation, R.L., D.D., D.L.S. and L.A.; Writing—Original Draft Preparation, R.L.; Writing—Review & Editing, R.L., D.D., D.L.S. and L.A.; Visualization, R.L. and D.L.S.; Supervision, R.L.; Project Administration, R.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The original contributions presented in this study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Acknowledgments: During the preparation of this manuscript/study, the authors used Elicit for the purposes of research article harvesting. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

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