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Review

# Mitochondrial Imbalance in Down Syndrome: A Driver of Accelerated Brain Aging?

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**ABSTRACT: Down syndrome (DS), caused by trisomy of chromosome 21 (HSA21), is a complex condition associated with neurodevelopmental impairments and accelerated brain aging, often culminating in early-onset Alzheimer's disease (AD). Central to this accelerated aging is mitochondrial imbalance, characterized by disrupted energy metabolism, increased oxidative stress, impaired dynamics, and defective quality control mechanisms like mitophagy. These abnormalities exacerbate neuronal vulnerability, driving cognitive decline and neurodegeneration. This review examines the genetic and biochemical underpinnings of mitochondrial dysfunction in DS, with a focus on the role of HSA21-encoded genes. We also highlight how mitochondrial dysfunction, amplified by oxidative stress and HSA21 gene dosage effects, converges with cellular senescence and neuroinflammation to accelerate Alzheimer-like pathology and brain aging in DS. Finally, we discuss emerging therapeutic strategies targeting mitochondrial pathways, which hold promise for mitigating neurodegenerative phenotypes and improving outcomes in DS.**

***Key words:*** aging, Down syndrome, oxidative stress, cell senescence, mitochondrial-targeted therapies

## 1. Introduction

Mitochondria, the powerhouses of the cell, produce adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS) and are central to energy metabolism [1]. They also regulate calcium homeostasis, oxidative stress, and programmed cell death, making them indispensable for cellular function and survival. Mitochondrial homeostasis is crucial for cellular integrity but deteriorates with age, contributing to cellular senescence and age-related disease onset. Evidence implicates mitochondrial dysfunction as a fundamental driver of neurodegeneration in Alzheimer's disease (AD), Parkinson's disease, and Huntington's disease [2]. These conditions share a common pathophysiology characterized by impaired ATP production, dysregulated mitochondrial dynamics, and excessive oxidative stress, leading to neuronal degeneration and cognitive decline. Mitochondrial dysfunction is a primary driver of neurodegenerative processes rather than a consequence of aging [3]. Within the brain, which has exceptionally high energy demands, mitochondrial deficits create a vicious cycle of metabolic insufficiency, reactive oxygen species (ROS) accumulation, and neuronal damage, accelerating neurodegeneration and cognitive impairment. Growing recognition of mitochondrial dysfunction as a key contributor to brain aging has spurred interest in targeted therapies to restore mitochondrial function and slow disease progression.

Down syndrome (DS), the most common genetic cause of intellectual disability, arises from complete or partial trisomy of chromosome 21 (HSA21; T21), affecting approximately 1 in 700 live births [4]. While DS is primarily classified as a neurodevelopmental disorder, it has a distinct neurodegenerative component. Individuals with DS have smaller total brain volumes, reduced cortical surface area, impaired neurogenesis, and neural progenitor cell (NPC) proliferation and differentiation deficits detectable in the fetal stage [5, 6], which contribute to characteristic widespread brain hypotrophy and cognitive impairments. Individuals with DS also display accelerated brain aging, with hallmark

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AD-like neuropathology (e.g., amyloid plaques, neurofibrillary tangles [NFTs]) emerging by the fourth decade of life. Dementia symptoms typically manifest in the fifth decade, underscoring the early and aggressive nature of neurodegeneration [7]. Given these pronounced structural and molecular changes, DS is a valuable model for studying interactions between neurodevelopmental and neurodegenerative processes [7, 8].

Studies have identified mitochondrial dysfunction as a central mechanism linking DS with premature brain aging and neurodegeneration [9]. In DS, mitochondria exhibit profound abnormalities as early as the fetal stage, including altered bioenergetics, disrupted dynamics, and excessive ROS production, leading to OXPHOS deficits, reduced ATP synthesis, and mitochondrial membrane potential (MMP) collapse across multiple tissues, including the brain, fibroblasts and erythrocytes. Overexpression of HSA21 genes disrupts gene regulation, leading to both upregulation and downregulation of targets and the shaping of DS phenotypic traits [10]. Overexpression of superoxide dismutase 1 (*SOD1*), amyloid precursor protein (*APP*), dual specificity tyrosine-phosphorylation regulated kinase 1A (*DYRK1A*), and regulator of calcineurin 1 (*RCAN1*) contributes to oxidative stress and mitochondrial dysregulation. Global transcriptional dysregulation of nuclear-encoded mitochondrial genes (NEMGs) further compromises mitochondrial biogenesis and OXPHOS, amplifying energy deficits and ROS accumulation [11]. DS neurons exhibit fragmented mitochondrial networks and reduced connectivity, mirroring mitochondrial defects in other neurodegenerative and progeroid syndromes [12]. Impaired mitophagy exacerbates the accumulation of dysfunctional mitochondria, fueling oxidative stress and neuronal damage. Collectively, these mitochondrial disturbances contribute to early-onset AD-like pathology and systemic cellular dysfunction in DS, establishing a mechanistic link between genetic alterations and accelerated neurodegeneration.

In this review, we first describe the hallmark features of brain aging and early-onset neurodegeneration in DS. We then explore the genetic and biochemical mechanisms underlying mitochondrial dysfunction, focusing on disrupted mitochondrial dynamics, impaired mitophagy, and oxidative stress, which we collectively refer to as "mitochondrial imbalance". Finally, we discuss emerging therapeutic strategies for neurodegeneration aimed at restoring mitochondrial homeostasis in DS. By examining mitochondrial imbalance as a key factor in DS pathology, we integrate insights from mitochondrial biology, neurodegeneration, and aging to advance our understanding of how mitochondrial dysfunction drives cognitive decline and brain aging in DS.

## 2. Early-Onset Neurodegeneration and Accelerated Brain Aging in DS

Clinically, individuals with DS exhibit accelerated aging across multiple organ systems, including muscle hypotonia, osteoporosis, early-onset skin wrinkling, and sensory impairments (e.g., vision and hearing loss) [13]. DS is associated with an increased prevalence of endocrine dysfunction, including thyroid abnormalities, premature menopause, and diabetes, and immunodeficiency, characterized by reduced T and B lymphocyte counts and increased susceptibility to autoimmune disorders.

Aging is driven by interconnected cellular and molecular mechanisms—the "hallmarks of aging". A pivotal 2023 review identified 12 key hallmarks that drive age-related decline, including genomic instability, telomere attrition, epigenetic alterations, proteostasis dysfunction, and mitochondrial impairment [14]. In DS, these hallmarks manifest with heightened severity, contributing to early-onset neurodegeneration and accelerated brain aging (Table 1).

At the genomic level, T21 is destabilizing, leading to excessive DNA damage and impaired repair mechanisms. Accelerated telomere attrition in DS suggests that cellular aging may begin as early as fetal development [15]. Widespread epigenetic abnormalities, including altered DNA methylation and histone modifications, exacerbate premature aging by dysregulating gene expression [16, 17]. Epigenetic clocks indicate that individuals with DS have an accelerated DNA methylation age, with blood and brain tissues appearing, on average, 6.6 years older than those of age-matched controls [18].

At the cellular level, proteostasis, the maintenance of protein homeostasis, is profoundly disrupted [19]. Aβ and hyperphosphorylated tau accumulation begins early in life, mirroring AD pathology while overwhelming already impaired macroautophagy and proteasomal degradation systems. Dysregulated nutrient-sensing pathways, particularly mTOR signaling cascade hyperactivity, exacerbate metabolic dysfunction and neuronal vulnerability [20]. Mitochondrial dysfunction, another key hallmark, manifests as deficient oxidative phosphorylation, increased oxidative stress, and unstable mitochondrial DNA [9]. These impairments are detectable as early as the fetal stage and persist throughout life, compounding energy deficits and oxidative damage that progressively impair neuronal function.

Systemically, DS is characterized by "inflammaging," chronic low-grade inflammation and immune dysregulation that amplify neuroinflammation and neurodegeneration [13]. Alterations in both innate and adaptive immunity heighten susceptibility to infections and sustain neuroinflammation. Evidence also

implicates gut microbiota imbalances in the link between systemic inflammation and brain aging. These mechanisms exacerbate intercellular signaling dysfunction and increase the vulnerability of DS brains to accelerate neurodegeneration.

**Table 1.** Changes in Molecular Mechanisms in Normal vs. DS Aging.

| | Normal aging | DS aging |
|---|---|---|
| Genomic Instability | DNA damage accumulates gradually with age; mtDNA mutations and replication errors emerge later in life. | T21 leads to gene dosage effects (e.g., *APP*, *SOD1*, *DYRK1A*), causing increased ROS, replication stress, and impaired DNA repair. |
| Telomere Attrition | Telomere length shortens progressively over the lifespan, influenced by genetics and environmental factors. | Substantial telomere shortening occurs early, driven by oxidative stress and increased cell division rates. |
| Epigenetic Alterations | Gradual accumulation of epigenetic alterations, such as DNA methylation and histone modifications. | Abnormal DNA methylation and histone modifications occur as early as the prenatal period, disrupting gene expression related to brain development and function. |
| Loss of Proteostasis | Protein misfolding and aggregation emerge later, contributing to aging-related diseases such as AD. | Increased protein misfolding and aggregation, including early Aβ and tau accumulation, drive neurotoxicity. |
| Disabled Macroautophagy | Autophagy declines gradually with age, primarily associated with inflammation and metabolic dysregulation. | Impaired autophagy reduces clearance of damaged mitochondria and proteins, accelerating neurodegeneration. |
| Deregulated Nutrient-Sensing | Dysregulation occurs progressively with aging, leading to reduced metabolic efficiency and chronic inflammation. | mTOR hyperactivity and disrupted insulin signaling exacerbate metabolic imbalances and energy deficits in neurons. |
| Mitochondrial Dysfunction | Mitochondrial dysfunction develops gradually, contributing to energy deficits and oxidative stress. | Early mitochondrial dysfunction is characterized by reduced ATP production, elevated ROS, and disrupted dynamics. |
| Cellular Senescence | Senescent cells accumulate slowly, causing chronic inflammation and tissue dysfunction over time. | Premature senescence is induced by oxidative stress and telomere shortening; SASP amplifies inflammation and neurodegeneration. |
| Stem Cell Exhaustion | Stem cell function declines gradually, reducing tissue repair and regeneration capacity. | Neural and hematopoietic stem cell depletion occurs early, impairing regeneration and immune modulation. |
| Altered Intercellular Communication | Dysregulation emerges later, accompanied by chronic inflammation and metabolic disturbances. | Elevated inflammatory cytokines (e.g., IL-6) and hyperactive microglia/astrocytes exacerbate neuroinflammation. |
| Chronic Inflammation | Chronic inflammation develops gradually, often associated with metabolic syndrome and chronic diseases. | Persistent low-grade inflammation driven by ROS, SASP, and immune dysregulation amplifies tissue damage. |
| Dysbiosis | Microbial dysbiosis accumulates with age, influencing immune regulation and systemic inflammation. | Gut microbiota imbalance exacerbates systemic inflammation and affects brain–gut signaling and neuronal function. |

DS, Down syndrome; mtDNA, mitochondrial DNA; T21, trisomy 21; APP, amyloid precursor protein; SOD1, superoxide dismutase 1; DYRK1A, dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A; ROS, reactive oxygen species; AD, Alzheimer's disease; Aβ, amyloid-beta; mTOR, mechanistic target of rapamycin; SASP, senescence-associated secretory phenotype; IL-6, interleukin 6.

While multiple biomarkers and molecular signatures of aging are altered in DS, their precise relationships with aging remain unclear. Few studies have systematically explored these changes across different age cohorts or through longitudinal analyses; thus, it is difficult to distinguish aging-related alterations inherent to DS from those reflective of broader aging. Addressing these gaps is essential to our understanding of how DS intersects with aging biology. Although accelerated aging in DS affects multiple physiological systems (e.g., dermatological, sensory, endocrine, musculoskeletal), neurological decline has the most profound impact on quality of life [21]. Other progeroid syndromes such as Werner syndrome (WS) and Hutchinson-Gilford progeria syndrome (HGPS) also exhibit features of accelerated systemic aging, they differ markedly from DS in their impact on the brain. In WS, cognitive decline is uncommon and AD-like neuropathology is rarely observed, despite significant peripheral aging and shortened lifespan [21]. Similarly, HGPS patients display severe multisystem deterioration but typically retain normal cognitive function [21]. The strong association between DS and AD emphasizes the brain as a crucial site of premature aging. We focus on neurodegeneration and

brain aging in DS, aiming to elucidate the mechanistic underpinnings and broader implications for aging-related diseases.

## 3. Mitochondrial Imbalance in the DS Brain

In the DS brain, mitochondrial dysfunction impairs bioenergetics, disrupts mitophagy, and causes excessive oxidative stress and abnormal mitochondrial dynamics, contributing to neuronal vulnerability and accelerated aging. These disruptions reveal a broader underlying theme, which we conceptualize as mitochondrial imbalance to capture the pervasive disequilibrium in mitochondrial homeostasis spanning molecular, structural, and systemic levels. This concept highlights the dynamic and interconnected nature of these disturbances, offering a broader perspective on their roles in premature aging and neural decline in DS. Next, we examine key dimensions of mitochondrial imbalance in detail, elucidate molecular mechanisms and explore implications for DS pathophysiology and therapeutic development.

### 3.1 Gene Dosage Imbalance: The Foundation of Mitochondrial Imbalance in DS

#### 3.1.1 Trisomy 21

DS, first documented by Dr. John Langdon Down in 1862, is the most prevalent chromosomal condition linked to intellectual disability [22]. The cause, inheritance of three (vs. two) copies of HSA21, was determined nearly a century later by Jérôme Lejeune and colleagues [23]. As the smallest human chromosome, HSA21 has been extensively sequenced, and a nearly complete, high-quality assembly of its long arm (21q) was published in 2000 [24]. Spanning approximately 33.6 Mb and constituting ~1% of the human genome, HSA21 harbors an estimated 233 protein-coding genes, 423 non-protein-coding genes, and 188 pseudogenes according to GENCODE/ENSEMBL annotations [11].

Most individuals with DS (95%) have a complete T21 (extra full copy in all cells). Less common variants (3%–4%) include mosaic DS, where a subset of cells carries T21 while others have a typical karyotype, and partial trisomy, where only part of HSA21 is triplicated. As DS primarily arises from this genetic imbalance, extensive research has focused on HSA21-encoded genes. *SOD1* was the first HSA21 gene studied in a transgenic mouse model of overexpression [25]. In 1990, Myriel Davisson at the Jackson Laboratory developed Ts65Dn, a viable mouse with partial trisomy 16 carrying a chromosomal segment homologous to a large portion of HSA21 (~132 genes) and exhibiting cognitive deficits and neurophysiological abnormalities [26]. Ts65Dn mice have since been widely used to study the molecular basis of DS.

Gene dosage imbalance is the key driver of the complex DS phenotype. While triplicated genes on HSA21 are generally upregulated, expression levels vary due to compensatory mechanisms, regulatory networks, and tissue-specific factors. In Ts65Dn mice, quantitative RT-PCR revealed that only ~37% of triplicated genes reached the expected 1.5-fold increase; ~45% were expressed below this level, and ~18% exceeded it [27, 28]. Regional differences were observed, with more pronounced gene overexpression in the cortex (~1.63-fold) than the cerebellum (~1.37-fold) and midbrain (~1.30-fold), reflecting varying molecular complexity [28]. Human transcriptome studies further confirmed that not all HSA21 genes follow the anticipated dosage effect. Among 255 genes analyzed, only 77 consistently showed increased expression, while others (e.g., mitochondrial ribosomal protein S6 [*MRPS6*], cystathionine-beta-synthase [*CBS*]) exhibited tissue- and species-specific variability. *MRPS6* was upregulated in the brain but downregulated elsewhere, whereas *CBS* showed opposing trends in humans and mouse models, suggesting species-specific regulatory differences [29]. Dosage-sensitive genes are enriched in some regions (e.g., chr21q22, chr21q21) indicating spatial heterogeneity. Trisomy-induced dysregulation also causes genome-wide regulatory disruptions. These findings underscore the complexity of gene dosage effects, revealing how trisomy affects gene expression in a context-dependent manner to shape brain development and function.

Gene dosage effects in T21 influence chromatin function through two primary mechanisms: (1) direct overexpression of HSA21 genes (coding and non-coding elements), and (2) dysregulation of gene expression across non-HSA21 chromosomes [30]. Chromatin alterations are not DS-exclusive and may arise in other aneuploidies or under cellular stress. Thus, DS is a valuable model for studying how aneuploidy disrupts chromatin dynamics and gene regulation and the interplay between genetic imbalance, chromatin architecture, and cellular function.

#### 3.1.2 HSA21-encoded Mitochondrial-Related Genes

Recent advancements have deepened our understanding of genotype–phenotype relationships in DS, specifically interactions between HSA21 gene overexpression and genome-wide dysregulation as key drivers of pathology. Several HSA21-encoded genes, including *APP*, *SOD1*, *RCAN1*, *DYRK1A*, *CBS*, nuclear receptor interacting protein 1 (*NRIP1*), and small ubiquitin-related modifier 3

(*SUMO3*), are linked to mitochondrial function, making mitochondrial dysfunction a central feature of DS.

Impaired mitochondrial dynamics, structural abnormalities, and bioenergetic deficits, including OXPHOS deficiencies and reduced ATP production, contribute to hallmark DS traits such as accelerated aging and neurodegeneration. HSA21 mitochondrial gene overexpression disrupts cellular energy homeostasis, impairs neuronal development, and promotes neurodegeneration, emphasizing mitochondrial dysfunction as a key contributor to DS pathophysiology and linking gene dosage imbalance with complex phenotypic manifestations (Fig. 1). Overexpression of HSA21 mitochondrial-related genes has profound implications for mitochondrial function. *SOD1* is overexpressed in DS, leading to hydrogen peroxide ($H_2O_2$) accumulation [31]; this damages mitochondria, exacerbating oxidative stress and impairing mitochondrial dynamics if not decomposed by catalase (CAT) or glutathione peroxidase (GPx). Redox imbalance is pervasive in DS tissues, contributing to chronic oxidative stress. *APP* is another dosage-sensitive gene. Its overexpression leads to Aβ42 accumulation within the mitochondrial matrix, impairing electron transport, reducing OXPHOS efficiency, and triggering apoptosis [32, 33]. Subsequently, Aβ-mediated mitochondrial dysfunction amplifies oxidative stress and neuronal damage. *RCAN1* (*DSCR1*), a dosage-sensitive gene, maintains mitochondrial function and integrity [34]. Its overexpression disrupts mitochondrial permeability transition pore (mPTP) function, causing calcium overload, impaired $Ca^{2+}$ retention, mitochondrial swelling, and outer membrane rupture [35]. DYRK1A contributes to mitochondrial dysfunction in DS by phosphorylating the import receptor TOM70 at Ser91, enhancing its interaction with the TOM core complex and the import of nuclear-encoded mitochondrial proteins essential for mitochondrial maintenance [36]. ETS2 exacerbates mitochondrial dysfunction by activating mitochondrial-dependent apoptosis. *ETS2* overexpression in DS neurons induces cytochrome c and apoptosis-inducing factor release, leading to caspase activation and neuronal death [37].

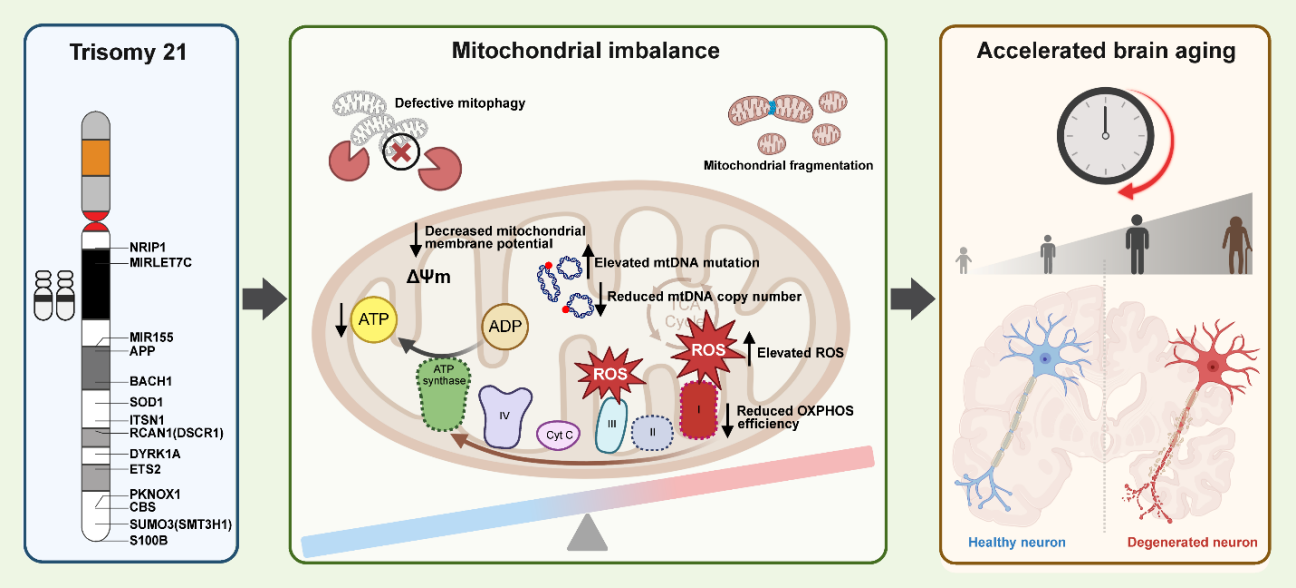


**Figure 1. HSA21 gene overexpression disrupts mitochondrial balance and accelerates brain aging in DS.** T21 leads to the overexpression of multiple HSA21-encoded genes involved in mitochondrial function, including *SOD1*, *APP*, *RCAN1*, *NRIP1*, *SUMO3*, *DYRK1A*, and *CBS*. These genes collectively affect redox balance, mitochondrial dynamics, and biogenesis. Gene dosage imbalance disrupts mitochondrial homeostasis by increasing reactive oxygen species (ROS), impairing mitophagy, and promoting mitochondrial fragmentation. Mitochondrial bioenergetic dysfunction is marked by reduced mitochondrial membrane potential (MMP, ΔΨm), elevated mtDNA mutations, reduced mtDNA copy number, and decreased OXPHOS efficiency. These alterations result in ATP depletion and contribute to neurodevelopmental deficits, neurodegeneration, and hallmark features of DS, including early-onset Alzheimer's disease-like pathology. Together, they establish a trajectory of mitochondrial vulnerability that underlies and accelerates brain aging in individuals with DS.

### 3.1.3 Genome-Wide Dysregulation of Mitochondrial Function

T21 also leads to global transcriptional dysregulation, exacerbating mitochondrial dysfunction and impacting expression of more than 90 NEMGs in DS brain tissues

[29]. These changes affect key processes such as OXPHOS, mitochondrial biogenesis, and stress responses. Upregulation of *MRPS6* in the brain indicates compensatory mechanisms for mitochondrial protein synthesis. Downregulation of *NDUFB8*, a key OXPHOS complex I gene, impairs energy production. *HSPA5*, a mitochondrial stress response gene, is consistently upregulated, while *DNAJB1*, a mitochondrial chaperone gene, is downregulated, contributing to protein-folding deficiencies. In summary, T21 both upregulates and downregulates mitochondrial pathways, with broad implications for brain development and neurodegeneration in DS. In DS-induced pluripotent stem cells (DS-iPSCs), mitochondrial dysfunction is linked to mitochondrial gene downregulation and widespread alterations in long noncoding RNA (lncRNA) expression. Functional enrichment analysis indicated that differentially expressed lncRNAs influence mitochondrial processes such as ATP synthesis and membrane organization, indicating potential regulation of DS-related mitochondrial dysfunction [38].

Upregulation of chromosome 21-derived microRNAs (miRNAs), including miR-155 and let-7c, further disrupts mitochondrial function by suppressing key NEMGs. When upregulated, miR-155 suppress mitochondrial transcription factor A (TFAM), a key regulator of mitochondrial DNA replication and transcription, disrupting mitochondrial biogenesis [39]. Increased let-7c expression targets solute carrier family 25 member 4 (SLC25A4/ANT1), a crucial regulator of ADP/ATP translocation, disrupting energy metabolism [40]. These imbalances highlight the extensive impact of gene dosage effects on mitochondrial dysfunction in DS.

### 3.2 Oxidative Stress and Redox Imbalance

ROS are generated during cellular metabolism and are essential for maintaining homeostasis and mediating cell signaling under normal conditions. In excess, they can induce oxidative stress, damaging lipids, proteins, and nucleic acids and compromising cellular integrity and function [41]. In DS, elevated oxidative biomarkers, including protein carbonylation, lipid peroxidation, and antioxidant system impairment, have been identified in the amniotic fluid of DS fetuses, underscoring mitochondrial dysfunction and oxidative stress as key contributors to DS pathogenesis [42].

#### 3.2.1 Excessive ROS Production in DS

ROS from endogenous and exogenous sources contribute to the cellular oxidative burden. Endogenously, mitochondria generate approximately 90% of total cellular ROS [7]. Other intracellular sources include NADPH oxidases (NOX) during immune responses and signal transduction, and peroxisomes during fatty acid oxidation [43, 44]. Mitochondrial ROS formation is a byproduct of OXPHOS, the central process driving ATP synthesis. OXPHOS relies on regulated NADH and FADH oxidation to drive proton transport across the mitochondrial inner membrane and establish an electrochemical gradient that powers ATP synthesis via F1-F0 ATPase (Complex V), catalyzing ADP phosphorylation to yield ATP [45]. OXPHOS includes the electron transport chain (ETC) and ATP synthase, both within the mitochondrial inner membrane. The ETC comprises Complexes I–IV (CI–CIV), coenzyme Q (Q), and cytochrome c. Electron leakage at CI and CIII produces superoxide anions, the predominant mitochondrial ROS.

The brain is highly susceptible to oxidative stress due to high oxygen consumption, abundant polyunsaturated fatty acids, and limited antioxidant defenses. This susceptibility is further heightened in DS due to overexpression of HSA21 genes such as *SOD1* and *APP*, which contribute to mitochondrial redox imbalance and oxidative damage [4, 46]. Triplication of other HSA21 genes, such as *BACH1* and *S100B*, also enhances oxidative stress in DS. In the brain, increased BACH1 expression and suppressed heme oxygenase-1 (HO-1) activation impair the antioxidant response by disrupting the Bach1/HO-1/BVR-A axis, leading to early oxidative stress [47]. S100B overexpression in DS NPCs amplifies ROS production, triggering oxidative stress and activating stress response pathways [48].

#### 3.2.2 Antioxidant Deficiencies and Systemic Vulnerability

In DS, antioxidant defenses cannot compensate for oxidative stress driven by T21-induced *SOD1* overexpression. Despite normal or slightly upregulated CAT and GPx levels in some tissues, these remain insufficient to neutralize excess $H_2O_2$ generated by SOD1 [49, 50], overwhelming mitochondrial redox regulation as mitochondria are both a primary source and target of ROS.

Redox homeostasis requires various antioxidant molecules, including GSH, amino acids (arginine, taurine, creatine), trace metals (selenium, zinc), and vitamins (E, C) [51]. In DS, disruptions of these antioxidant systems exacerbate oxidative stress. The GSH system is particularly affected, with fetal DS fibroblasts showing reduced levels of GSH and an increased oxidized-to-reduced glutathione ratio (GSSG/GSH) [52, 53]. The fetal DS brain exhibits decreased expression of peroxiredoxin 2, a crucial enzyme that protects lipids and proteins from oxidative damage [54]. Deficiencies in non-enzymatic

antioxidants further compromise the redox balance. Both children and adults with DS often exhibit reduced blood or plasma vitamin E, vitamin C, selenium, and zinc levels [55-57]. Taurine, a key antioxidant amino acid, is significantly depleted in the frontal cortex of DS fetal brains [58]. These deficiencies weaken endogenous antioxidant defenses, increasing susceptibility to oxidative stress and contributing to systemic vulnerability.

#### 3.2.3 Oxidative Damage and Cellular Consequences

Excessive ROS production in DS drives widespread oxidative damage across cellular components, generating highly reactive byproducts such as 4-hydroxynonenal (HNE), which propagate free radical formation [59]. In the fetal brain, lipid peroxidation markers, including significantly elevated malondialdehyde levels, indicate early oxidative stress [49]. In DS neurons, increased intracellular ROS and lipid peroxidation precede neuronal apoptosis in neurodegeneration [60]. Oxidative protein damage disrupts receptors, hormone, and enzyme functions, impairing intracellular degradation and promoting dysfunctional protein accumulation. A redox proteomics study of the frontal cortex in individuals younger than 40 with DS revealed elevated protein carbonylation, particularly affecting cellular quality control proteins such as cathepsin D, V0-ATPase, GRP78, and GFAP [61]. Oxidative damage impairs proteasome function and autophagosome formation, accelerating the Aβ and hyperphosphorylated tau accumulation, a key hallmark of DS-associated neurodegeneration.

DS pathology is complicated by ROS-induced DNA damage, including base modifications, strand breaks, and DNA–protein crosslinks. Fibroblasts and lymphocytes from individuals with DS exhibit elevated oxidative DNA damage, defective base excision repair (BER) mechanisms, and heightened oxidative stress sensitivity [62, 63]. RNA oxidation, indicated by upregulated 8-hydroxyguanine (8-OH-G), is highly elevated in DS neurons, particularly in early life. Aβ deposition appears to temporally follow oxidative stress, suggesting a potential compensatory response to mitigate oxidative damage [64].

However, not all studies have consistently reported elevated oxidative stress markers in DS. While some indicators such as 3-nitrotyrosine and HNE are reliably increased, others like TBARS and 15-F(2t)-isoprostanes have yielded variable results [65]. In adults with DS, oxidative DNA damage is not always elevated, suggesting possible age-related adaptations [66]. These inconsistencies highlight the need for stratified analysis by age, tissue type, and oxidative marker when interpreting redox imbalance in DS.

### 3.3 Structural and Functional Imbalance in Mitochondrial Dynamics

Mitochondria are double-membraned organelles with a specialized structure crucial for bioenergetics and cellular signaling. The outer mitochondrial membrane (OMM) interfaces with the cytosol, facilitating interactions with other organelles (e.g., endoplasmic reticulum [ER], peroxisomes, endosomes). The tightly folded and selectively permeable inner mitochondrial membrane (IMM) forms cristae that embed electron transport chain (ETC) complexes, facilitating OXPHOS [67]. In DS cells, mitochondrial morphology is abnormal, characterized by fragmentation, swelling, and cristae disorganization that impair mitochondrial function [68].

#### 3.3.1 Disrupted Fission and Fusion

Mitochondrial dynamics encompass fission and fusion and are crucial for mitochondrial integrity and cellular homeostasis [69]. Fusion, regulated by GTPases such as optic atrophy 1 (OPA1) in the IMM and mitofusins (MFN1/2) in the OMM, enables damaged mitochondria to merge and recover. Fission, controlled by dynamin-related protein 1 (DRP1), isolates dysfunctional mitochondrial fragments for degradation. In DS, this balance is disrupted, leading to excessive mitochondrial fragmentation and impaired mitochondrial function.

Mitochondrial dysfunction in DS appears to begin early in development. In DS fetal fibroblasts, reduced PGC-1α expression is associated with lower OPA1 and MFN2 levels, fragmented mitochondria, intra-mitochondrial edema, and cristae abnormalities [70]. Hippocampal NPCs in Ts65Dn mice exhibit excessive mitochondrial fragmentation, driven by increased DRP1 and reduced MFN2 and OPA1 expression [71]. In DS neurons and astrocytes, fragmented mitochondrial networks are linked to oxidative stress, elevated mitochondrial ROS, and decreased MMP and ATP synthesis, exacerbating cellular dysfunction [12].

Regulator of calcineurin 1 (RCAN1) overexpression is a hallmark of gene dosage imbalance in DS and a key contributor. RCAN1 upregulation enhances mitochondrial ROS production, disrupts mitochondrial repair mechanisms, and promotes mPTP opening, leading to $Ca^{2+}$ dysregulation, mitochondrial swelling, OMM rupture, and increased susceptibility to cell death [35]. RCAN1 interferes with DRP1 activity, amplifying mitochondrial fragmentation, bioenergetic deficits, and oxidative stress and contributing to age-related neurodegeneration, including AD [72].

### 3.3.2 Impaired Mitophagy and Mitochondrial Quality Control

Mitophagy, the selective removal of damaged mitochondria, is essential for mitochondrial integrity and preventing apoptosis [20]. Dysfunctional mitochondria are encapsulated by mitophagosomes, transported to lysosomes, and degraded, ensuring appropriate turnover. Mitophagy is impaired in DS, leading to mitochondrial accumulation, increased oxidative stress, and progressive dysfunction. Several HSA21-encoded gene products have been implicated in mitophagy dysregulation. ETS2 overexpression in DS neurons disrupts mitochondrial integrity by promoting Bax upregulation, cytochrome c release, and apoptosis, suggesting failed mitophagy-mediated quality control [37]. Intersectin 1 (ITSN1), an endocytic scaffold protein, regulates mitophagy; its deficiency leads to mitochondrial accumulation and cytochrome c-mediated apoptosis, partly through impaired MEK/ERK signaling [73].

Autophagy, including mitophagy, is inhibited by mTOR signaling, a key cell growth and metabolism regulator. In DS cells, mTOR complex 1 (mTORC1) hyperactivation disrupts autophagic flux, impairing mitochondrial clearance. DS fibroblasts, particularly fetal-derived cells, exhibit persistent mTORC1 hyperactivation as early as gestational week 19, which continues postnatally [74]. This dysregulation hinders autophagy initiation, autophagosome formation, and mitophagy, exacerbating mitochondrial dysfunction. A key mitophagy component, the ULK1 complex, is suppressed by mTORC1 phosphorylation, preventing autophagy initiation. ULK1 phosphorylates FUNDC1, an OMM protein, at Ser-17, enhancing its binding to LC3 and facilitating recruitment of damaged mitochondria into autophagosomes [75]. In DS fibroblasts, mTORC1 hyperactivation suppresses ULK1 activity, impairing autophagy and mitochondrial turnover [20].

The PINK1/Parkin pathway, essential for mitophagy, is also disrupted in DS. Under mitochondrial stress, PINK1 accumulates on the OMM and recruits the E3 ubiquitin ligase Parkin, which ubiquitinates damaged mitochondria to mark them for degradation [76, 77]. In DS fibroblasts, impaired PINK1/Parkin signaling is characterized by reduced Parkin expression and delayed PINK1 activation, leading to mitochondrial depolarization, ROS accumulation, and defective mitophagy [20].

## 3.4 Genetic and Biochemical Instability of mtDNA

MtDNA is a 16.5-kb, double-stranded circular genome essential for cellular energy production. It encodes 13 polypeptides crucial for OXPHOS, two ribosomal RNAs (rRNAs), and 22 transfer RNAs (tRNAs) necessary for mitochondrial protein synthesis [78]. Each mitochondrion contains multiple mtDNA copies. However, the majority of mitochondrial proteins, including those involved in mtDNA replication, transcription, translation, and OXPHOS complex assembly, are nuclear-encoded, reflecting the intricate nuclear–mitochondrial interaction required to maintain mitochondrial function.

### 3.4.1 mtDNA Damage and OXPHOS Deficiencies

MtDNA is particularly vulnerable to oxidative damage due to its proximity to ROS production sites and limited repair capacity. In DS, this vulnerability is exacerbated by systemic mitochondrial dysfunction, leading to cumulative mtDNA alterations—a process that mirrors the mitochondrial cascade hypothesis proposed in AD, wherein early mtDNA damage is thought to initiate and accelerate neurodegenerative progression [79].

In DS brains, mitochondrial CI subunits (24-kDa and 75-kDa) are significantly reduced in the temporal and occipital cortices and caudate nucleus, impairing energy metabolism and neuronal function [80]. In Ts65Dn mice, oxygen consumption, CI and CIV activity, ATP production, and mtDNA levels are decreased in NPCs. These defects are linked to impaired neuronal proliferation and differentiation, contributing to reduced neuronal density [81].

In human iPSC-derived neurons from individuals with T21, mitochondrial dysfunction is marked by decreased MMP, structural abnormalities, and increased Ab accumulation. These changes correlate with increased DNA double-strand breakage, suggesting a connection between mitochondrial dysfunction and genomic instability [82]. Brain samples from DS fetuses (gestation week 22) and patients with DS-associated AD (DS-AD) exhibit reduced mtDNA copy numbers, increased somatic mtDNA mutations in the control region, and lower L-strand transcript levels, further linking mitochondrial dysfunction to neurodegeneration [83].

Proteomic analysis of DS fibroblasts revealed significant reductions in OXPHOS complex subunits and other mitochondrial proteins, with functional assays confirming defective mitochondrial respiration and ATP synthesis, reinforcing mitochondrial dysfunction as a hallmark of DS [84].

### 3.4.2 HSA21 Gene-Mediated Dysregulation of Bioenergetics and Mitochondrial Biogenesis

Mitochondrial biogenesis, a highly coordinated process, integrates nuclear and mitochondrial genome expression to sustain cellular energy demands via multiple transcriptional networks. Nuclear respiratory factors

(NRF-1 and NRF-2) regulate genes encoding OXPHOS complexes, mitochondrial import machinery, and heme biosynthesis while activating the mitochondrial transcription factors TFAM, TFB1M, and TFB2M required for mtDNA transcription [85]. Nuclear hormone receptors, including peroxisome proliferator-activated receptors (PPARs) and estrogen-related receptors (ERRs), regulate mitochondrial metabolism, dynamics, and lipid utilization. Central to this regulatory network is PGC-1α, a key transcriptional coactivator that integrates environmental and metabolic cues to enhance mitochondrial gene expression [86]. By interacting with NRFs, ERRs, and other transcription factors, PGC-1α coordinates mitochondrial adaptation to physiological stressors (e.g., caloric restriction, exercise, oxidative stress).

In DS, overexpression of HSA21 genes disrupts mitochondrial homeostasis by impairing bioenergetics and biogenesis. DYRK1A, an HSA21 gene product, phosphorylates nuclear factor of activated T cells (NFATc), preventing its nuclear translocation and suppressing *PPARGC1A*, which encodes PGC-1α, a key regulator of OXPHOS and mitochondrial biogenesis [87]. Overexpression of RCAN1, the human homolog of *Drosophila nebula*, contributes to mitochondrial dysfunction by reducing mitochondrial CIV activity, mtDNA content, and ATP levels. In ST14A rat striatal neurons and SH-SY5Y neuroblastoma cells, RCAN1 overexpression decreases mitochondrial mass and oxygen consumption, impairing NFATc activity [88, 89]. NRIP1, a transcriptional corepressor encoded on HSA21, negatively regulates oxidative metabolism and mitochondrial biogenesis. In DS fetal fibroblasts, NRIP1 overexpression suppresses PGC-1α, downregulating NEMG expression and exacerbating mitochondrial dysfunction [90]. SUMO3, another HSA21 gene product, modulates NRIP1 nuclear localization, enhancing its corepressor activity and inhibiting PGC-1α-dependent mitochondrial biogenesis [91]. SUMOylation of PGC-1α promotes nuclear export, attenuating its transcriptional activity and impairing mitochondrial adaptation [92]. *PKNOX1*, which encodes encoding homeodomain transcription factor PREP1, influences mitochondrial function. Muscle-specific PREP1 ablation enhances OXPHOS subunit expression, mitochondrial enzyme activity, and endurance capacity partly through upregulation of PGC-1α and reduced inhibition by p160 Mybbp1a, a PGC-1α inhibitor [93]. Finally, BACH1, a heme-binding transcription factor encoded on HSA21, suppresses electron transport chain (ETC) genes, reducing mitochondrial respiration. Its inhibition may improve mitochondrial function and metabolic reprogramming, possibly via PPARGC1A and NRF2, although the precise mechanisms remain unclear [94].

## 4. Mitochondrial Mechanisms Driving Accelerated Brain Aging in DS

### 4.1 AD-Like Pathology in DS

Individuals with DS have a markedly increased risk of developing AD. This strong association is evident in the presence of AD pathological hallmarks, including senile plaques, NFTs, and the progressive loss of cholinergic, noradrenergic, and serotonergic neurons. Nearly all individuals with DS exhibit AD-like neuropathology by age 40 [95], and the prevalence of dementia escalates with age, affecting approximately 8%, 55%, and 75% of individuals aged 35–49, 50–59, and 60 or older, respectively [96]. This trend suggests that DS and AD share common pathological mechanisms, which are probably driven by genetic factors linked to HSA21.

Despite these shared features, DS-AD and sporadic AD differ in onset, etiology, and clinical trajectory [97]. In DS, APP triplication due to trisomy 21 results in early and robust Aβ accumulation, often initiating in adolescence and preceding overt dementia by decades. Cognitive decline in DS unfolds on the background of lifelong intellectual disability, leading to an insidious and gradual deterioration. In contrast, sporadic AD typically presents in late adulthood with new-onset memory impairment in previously cognitively intact individuals, and Aβ deposition develops later in life under the influence of aging and genetic risk factors such as APOE ε4 [98]. Thus, DS-AD exemplifies a genetically determined, developmentally primed model of early-onset AD, whereas sporadic AD reflects a complex, age-dependent, and multifactorial disorder.

#### 4.1.1 Oxidative Stress and the "Two-Hit" Hypothesis

The "two-hit" hypothesis of AD posits that while oxidative stress and mitotic signaling abnormalities are independent initiators of neurodegeneration, their convergence is necessary and sufficient to drive AD pathogenesis [99, 100]. This hypothesis suggests that particularly in people with a genetic predisposition, neurons under chronic stress divert their cellular resources toward compensatory mechanisms, leaving them vulnerable to subsequent pathological insults. An initial oxidative burden weakens neuronal defenses, heightening susceptibility to further neurodegenerative processes.

This hypothesis is particularly relevant to DS, where oxidative stress emerges early due to the gene dosage effects of T21. The early and persistent overexpression of *SOD1* and *APP* in DS establishes a pro-oxidative cellular environment, lowering neuronal resilience to additional neurodegenerative insults [65, 96]. The accumulation of oxidative damage in DS neurons parallels that in AD,

reinforcing the role of oxidative stress as a central driver of neurodegeneration in both conditions.

While oxidative stress is generally viewed as a driver of neuronal dysfunction in DS, some studies suggest that mitochondrial suppression may also represent an adaptive response to chronic redox imbalance. In vitro experiments have shown that DS neurons downregulate mitochondrial respiration and ATP production to limit ROS generation, and that forced enhancement of mitochondrial activity can paradoxically exacerbate oxidative damage and trigger apoptosis [12]. These findings suggest that not all mitochondrial deficits in DS are purely maladaptive but may instead reflect a compensatory shift in cellular metabolism aimed at preserving redox homeostasis under constitutive stress conditions.

#### 4.1.2 A Converging Pathway: The Role of APP Gene Dose

Triplication of HSA21, which includes *APP*, is among the most compelling links between DS and AD. The gene dosage effect results in a 1.5-fold increase in APP expression, leading to excessive production of Aβ, a key pathological hallmark of AD [101]. In DS, amyloid pathology develops significantly earlier than in sporadic AD. Intracellular Aβ accumulation begins within enlarged endosomes, preceding the formation of extracellular plaques. This amyloid deposition follows a spatiotemporal pattern similar to that in AD but occurs decades earlier, with Aβ aggregation beginning in adolescence and NFT formation becoming apparent by the fourth decade of life [97].

Aβ oligomers are particularly neurotoxic, contributing to cognitive decline by impairing synaptic transmission, disrupting neurotransmitter signaling, and inducing synaptic loss [102, 103]. Overproduction of the aggregation-prone Aβ42 variant accelerates amyloid deposition, and DS brains exhibit denser Aβ plaques than those seen in sporadic AD [104]. However, Aβ toxicity is not isolated but catalyzes a cascade of pathological processes that drive neurodegeneration.

Mitochondrial dysfunction is the key downstream effects of *APP* overexpression and Aβ accumulation. Aβ disrupts electron transport chain activity, increases ROS production, and impairs ATP generation, leading to severe neuronal energy deficits and creating a self-perpetuating cycle of oxidative stress and neuronal damage, further exacerbating AD-like pathology. Notably, targeting *APP* expression with antisense oligonucleotides (ASOs) has been shown to restore mitochondrial function in DS astrocytes, highlighting *APP* dosage as a key upstream driver of mitochondrial and neurodegenerative pathology—and a promising therapeutic target for both DS and AD [105].

#### 4.1.3 Additional Chromosome 21 Genes Contributing to AD Pathology in DS

Other HSA21 genes also contribute to neurodegeneration. Chronic *RCAN1* overexpression inhibits calcineurin, leading to tau hyperphosphorylation and early NFT formation [106]. Additionally, *RCAN1* has been implicated in upregulating expression of GSK-3β, a key kinase involved in tau pathology to exacerbate NFT formation, though additional studies of this relationship are needed. Aβ can directly induce *RCAN1* expression, reinforcing a vicious cycle of Aβ toxicity, tau dysregulation, and neuronal damage [107]. Another key contributor is S100B, a calcium-binding protein aberrantly overexpressed in DS astrocytes. Elevated S100B levels correlate with age and are associated with increased Aβ plaque formation, suggesting a role in AD-like pathology [108]. *DYRK1A* has been implicated in tau hyperphosphorylation and abnormal cell cycle re-entry, further linking DS with AD pathogenesis [109].

### 4.2 Mitochondrial Dysfunction as a Driver of Early Cellular Senescence in DS

Cellular senescence, first described by Hayflick in the 1960s, refers to the limited proliferative potential of human fibroblasts cultured in vitro, ultimately leading to irreversible cell cycle arrest [110]. It is now recognized as a homeostatic biological process triggered by environmental stress, with crucial roles in development, tissue remodeling, and tumor suppression. However, dysregulated senescence contributes to tissue regenerative decline, chronic disease, and aging [111]. The accumulation of senescent cells is a hallmark of aging implicated in the onset and progression of age-associated diseases [112].

Mitochondria are central regulators of cellular senescence, sustaining ROS production, amplifying DNA damage, and modulating pro-inflammatory signaling. The ATM–Akt–mTORC1–PGC-1β signaling axis plays a key role in mitochondrial biogenesis, which reinforces SASP, a major driver of age-related pathology, under chronic oxidative stress. Reducing mitochondrial content via mTORC1 inhibition or PGC-1β deletion mitigates senescence in aging tissues, highlighting mitochondria as a crucial regulatory hub in senescence progression. Recent evidence suggests that, like mitotic cells, post-mitotic neurons can acquire a senescence-like state, further implicating senescence in DS-associated neurodegeneration [113, 114].

#### 4.2.1 Cellular Senescence in DS

Features of accelerated cellular senescence are evident in DS pathology and parallel those in early-onset AD. Leukocytes from individuals with DS exhibit significantly elevated senescence-associated β-galactosidase (SA-β-gal) activity, indicating widespread lysosomal dysfunction and premature cellular aging [115]. Hippocampal tissue from Ts65Dn DS mouse models shows an increased presence of SA-β-gal-positive cells and elevated levels of pro-inflammatory cytokines such as interleukin-17A, interleukin-1β, and interferon-γ, further linking chronic inflammation and senescence [116]. DS fibroblasts are deficient in DNA polymerase β, a key enzyme involved in BER, which compromises genomic integrity and exacerbates premature senescence [117]. NPCs derived from DS-iPSCs display substantial nuclear architectural alterations, including chromosomal introversion, disrupted lamina-associated domains (LADs), and global chromatin accessibility changes. These alterations correlate with the transcriptional dysregulation characteristic of senescent cells, evidenced by upregulated senescence markers (p16, p21), downregulated proliferation-associated genes, and enriched pro-inflammatory pathways [118]. DS mouse models also exhibit accelerated senescence across multiple stem cell lineages, further contributing to age-related functional decline. In Ts65Dn mice, overexpression of Usp16, a deubiquitinase regulating chromatin remodeling and cell cycle progression, leads to impaired hematopoietic stem cell self-renewal, a threefold reduction in stem cell frequency, and defective multilineage engraftment [119]. Skeletal muscle stem cells in DS exhibit increased DNA damage and diminished regenerative capacity, further demonstrating the widespread impact of senescence on tissue function [120].

#### 4.2.2 Interplay Between Oxidative Stress, Mitochondrial Dysfunction, and Early Cellular Senescence in DS

Evidence suggests that senescence-associated defects arise early in DS development, significantly impacting neurogenesis and overall cellular homeostasis. In DS fetuses, NPCs exhibit impaired neurogenesis due to delayed cell cycle progression and reduced proliferation. Accumulation of cells in the G2 phase, which indicates a premature senescence-like state, has been observed in both DS fetal brains and Ts65Dn mice [121]. Telomere attrition further exacerbates this phenomenon: DS fetal amniocytes display significantly shorter telomeres and upregulation of *TERC*, which encodes the RNA component of telomerase. This dysregulation suggests an inherent predisposition to genomic instability, which may underlie both hematopoietic malignancies and neurodegeneration in DS [122]. DS placental trophoblasts exhibit an increased prevalence of senescence-associated heterochromatin foci, an epigenetic marker of cellular senescence, as early as the second trimester, suggesting that trophoblast senescence could be a potential early biomarker of T21 during pregnancy [123].

Premature senescence is centered around oxidative stress, which is particularly pronounced in DS due to impaired mitochondrial function. DS-derived fibroblasts exhibit excessive ROS accumulation, increased protein oxidation, and ATP depletion, which collectively activate key senescence markers, including lysosomal SA-β-gal and p21. These cellular stressors contribute to accelerated aging, reinforcing the premature senescence observed in DS [124]. In DS mouse models, hippocampal oxidative stress correlates with heightened Aβ expression, tau hyperphosphorylation, and widespread cellular senescence across key brain regions such as the dentate gyrus, CA1, CA3, and hilus [116].

Beginning in the prenatal stage, oxidative stress, mitochondrial dysfunction, and impaired antioxidant defenses synergistically drive premature cellular senescence, establishing a trajectory that accelerates neurodegenerative pathology. Accumulated senescent cells foster a proinflammatory environment through the SASP, leading to chronic neuroinflammation and impairing neurogenesis (Fig. 2). As individuals with DS age, persistent oxidative stress and mitochondrial deficits exacerbate senescence, coinciding with the emergence of AD pathology and progressive cognitive decline. This intricate interplay between oxidative stress, mitochondrial dysfunction, and cellular senescence highlights a critical pathogenic axis in DS, underscoring the urgent need for targeted therapeutic strategies aimed at restoring mitochondrial homeostasis and mitigating oxidative damage.

## 5. Therapeutic Strategies Targeting Mitochondrial Dysfunction in DS

Mitochondrial dysfunction is a central driver of accelerated aging and neurodegeneration in DS. Dysregulated mitochondrial energy metabolism lead to increased oxidative stress, chronic inflammation, and neuronal damage, contributing to systemic aging and cognitive decline. Therapeutic interventions targeting mitochondrial function may be potential strategies to mitigate neurodegenerative processes and improve cognitive outcomes in DS. In the following sections, we summarize major mechanistic targets and highlight representative agents with preclinical or early translational relevance.

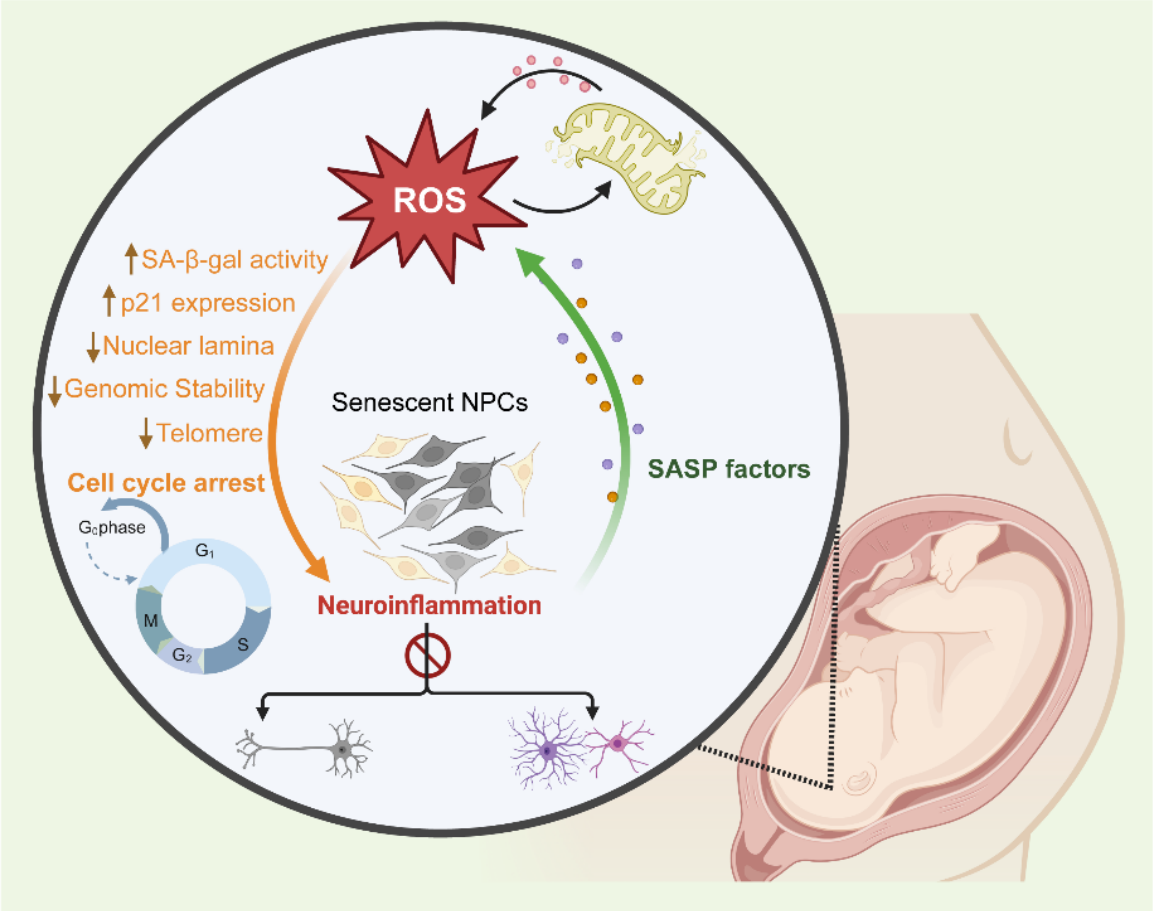


**Figure 2. Early Onset of Cellular Senescence and Neuroinflammation in DS.** Mitochondrial dysfunction and ROS drive the premature onset of cellular senescence as early as the prenatal stage, particularly in neural progenitor cells (NPCs). Hallmarks of senescence include heightened lysosomal SA-β-gal activity, genomic instability, elevated p21 expression, severe deficits in antioxidant defenses, mitochondrial impairment, nuclear lamina disruption, telomere shortening, and cell cycle arrest. The accumulation of senescent cells triggers a proinflammatory environment through the senescence-associated secretory phenotype (SASP), leading to chronic neuroinflammation and impaired neurogenesis. This persistent inflammatory state contributes to the progression of brain aging and neurodegeneration in DS.

### 5.1 Antioxidant Therapies

Oxidative stress is an early, persistent feature of DS that negatively impacts brain development and worsens with age, ultimately contributing to AD-like neuropathology and accelerated aging. Antioxidant therapies have been explored as potential interventions to counteract oxidative stress, restore mitochondrial function, and improve cognition in individuals with DS.

Vitamin E, a potent lipid-soluble antioxidant, protects cellular membranes from lipid peroxidation. Studies in DS mouse models have shown that long-term vitamin E supplementation reduces oxidative stress, improves cognitive performance, and prevents cholinergic neuronal degeneration, suggesting a potential role in mitigating age-related neuropathology [125]. However, clinical trials in older adults with DS have not demonstrated significant cognitive benefits, possibly due to limited Central Nervous System (CNS) penetration and the insufficient potency of α-tocopherol alone, a commonly used isoform of vitamin E [126, 127].

Vitamin C, a water-soluble antioxidant, complements vitamin E by regenerating its reduced form, enhancing its overall antioxidant efficacy. Clinical trials involving children and adolescents with DS have demonstrated that combined vitamin E and C supplementation reduces systemic oxidative stress, restores glutathione levels, and improves biomarkers of oxidative damage such as thiobarbituric acid reactive substances [128, 129].

Coenzyme Q10 (CoQ10), a key mitochondrial electron transport chain component, is a potent antioxidant that facilitates electron transfer. In children and adolescents with DS, long-term CoQ10 supplementation (4 mg/kg/day for 20 months) significantly reduced oxidative DNA damage in peripheral leukocytes, particularly in younger individuals

[130]. However, extended supplementation (4 years) at the same dose had no significant impact on overall DNA and RNA oxidation, suggesting that further optimization of CoQ10 formulations and dosages is needed [131].

Children with DS have a high prevalence (60%–95%) of obstructive sleep apnea (OSA), which exacerbates cognitive impairment and behavioral deficits [132]. These children have lower plasma concentrations of melatonin, a hormone traditionally associated with sleep regulation, increasing their vulnerability to oxidative damage [133]. In Ts65Dn DS mice, chronic melatonin administration reduced hippocampal lipid peroxidation and protein carbonylation while normalizing SA-β-gal-positive cell density, indicating reduced cellular senescence [134, 135]. Melatonin was found to improve spatial learning and memory, suggesting its neuroprotective potential [135]. Given its established use in clinical settings for sleep disturbances and its favorable safety record in humans, melatonin holds promise as a candidate for future DS-targeted clinical trials.

EGCG, a polyphenol from green tea, exhibits stronger antioxidant properties than vitamins E and C due to its ability to stabilize phenoxy radicals through multiple resonance structures. Unlike other antioxidants, EGCG selectively accumulates in mitochondria, scavenging free radicals at the source of oxidative damage [136, 137]. In DS cellular models, EGCG enhances mitochondrial oxidative phosphorylation by activating the cAMP/PKA and Sirtuin 1 (Sirt1)/PGC-1α signaling pathways, rescuing CI and ATP synthase activities while reducing excessive ROS production [138]. In a phase II randomized controlled trial (TESDAD), 12-month EGCG supplementation improved visual recognition memory and adaptive behavior in young adults with DS, suggesting translational potential for early intervention [139].

Notably, some studies have reported inconsistent outcomes across antioxidant trials and biomarker analyses in DS, with variability linked to age, cellular context, and the specific oxidative pathways assessed [65]. These inconsistencies highlight the need for larger, well-controlled trials to confirm efficacy, define optimal formulations, and assess long-term safety across age groups.

### 5.2 Inducers of Mitochondrial Biogenesis

Mitochondrial function requires efficient mitochondrial biogenesis, a process regulated by key transcriptional and metabolic pathways. Enhancing mitochondrial biogenesis is a promising therapeutic strategy for restoring mitochondrial homeostasis and improving neuronal function in DS. Mitochondrial biogenesis is controlled by the AMP-activated protein kinase (AMPK)–Sirt1–PGC-1α axis. Activation of AMPK, a key energy sensor, leads to downstream phosphorylation events, promoting ATP synthesis while inhibiting ATP-consuming processes. Activated AMPK enhances Sirt1 activity, which in turn stimulates PGC-1α, a master regulator of mitochondrial biogenesis.

EGCG can enhance mitochondrial respiratory chain function and promote mitochondrial biogenesis in DS models. In Ts65Dn mice, EGCG treatment (20 μM) improved NPC proliferation by restoring mitochondrial bioenergetics [140]. EGCG enhances CI activity in fibroblasts from individuals with DS by modulating cAMP levels, activating PKA, and restoring NDUFS4 subunit function, ultimately improving mitochondrial efficiency [138].

Resveratrol, a stilbenoid-class polyphenol, similarly rescues mitochondrial dysfunction in DS. In DS models, resveratrol (10 μM) restores OXPHOS and mitochondrial biogenesis by activating the AMPK–Sirt1–PGC-1α axis to improve neurogenesis and cognitive function [140]. Resveratrol supplementation for 4 weeks has been shown to decrease oxidative stress and ameliorate age-related metabolic dysfunction in patients with type 2 diabetes mellitus (T2DM) [141]. However, these drugs have not yet been validated in DS-specific clinical trials, and their safety profiles, especially in pediatric populations, warrant careful consideration.

Metformin, a widely used medication for diabetes, has emerged as a candidate anti-aging intervention due to its ability to modulate key longevity pathways. Notably, large-scale clinical trials such as the Targeting Aging with Metformin (TAME) study aim to evaluate its efficacy in delaying multiple age-related diseases and promoting healthy aging [142]. Mechanistically, metformin enhances PGC-1α expression and promotes mitochondrial biogenesis. Studies in DS fibroblasts suggest that metformin restores mitochondrial homeostasis, positioning it as a promising candidate for repurposing in DS therapy [70].

### 5.3 Modulators of Mitochondrial Dynamics

Mitochondrial homeostasis depends on the balance between fusion and fission, which are disrupted in DS. Excessive mitochondrial fission and reduced fusion lead to mitochondrial fragmentation, impaired energy production, and increased oxidative stress [143]. Enhancing mitochondrial fusion by upregulating mitofusins (MFN1 and MFN2) can restore mitochondrial integrity, improve respiratory efficiency, and reduce apoptosis. Inhibiting excessive fission by targeting dynamin-related protein 1 (DRP1) can help preserve mitochondrial function and neuronal survival [144].

Metformin was shown to rescue mitochondrial dynamics in DS fetal fibroblasts by upregulating OPA1 and MFN2, restoring mitochondrial fusion, and reducing fragmentation [70]. Similarly, Mdivi-1, a selective DRP1 inhibitor, rescued mitochondrial network integrity in hippocampal NPCs from Ts65Dn mice, mitigating excessive fission and improving mitochondrial bioenergetics [71]. While Mdivi-1 is currently limited to preclinical research, DRP1 remains a pharmacologically tractable target under investigation in broader neurodegenerative contexts such as AD and PD [142].

Pioglitazone (PGZ), a PPARγ agonist, restores mitochondrial organization in DS fibroblasts by modulating mitochondrial dynamics. PGZ increases OPA1 and MFN1 expression while downregulating DRP1, increasing mitochondrial network interconnectivity [145]. EGCG also restored mitochondrial dynamics by reducing calcium overload, balancing fission and fusion, and improving mitochondrial morphology and function in hippocampal neurons from DS models [146].

### 5.4 Enhancers of Mitophagy

Enhancing mitophagy is a promising therapeutic strategy for alleviating mitochondrial dysfunction in DS. Rapamycin, a potent mTOR inhibitor, is a well-established autophagy inducer that promotes cellular homeostasis by suppressing mTORC1 activity, enhancing autophagosome formation and mitigating age-related and disease-associated cellular dysfunction [147]. In Ts65Dn mice, 12-week rapamycin treatment restored mTOR signaling, increased LC3-II levels, and reduced oxidative stress markers, suggesting improved autophagy and mitophagy regulation [148]. However, systemic administration of rapamycin is associated with side effects such as immunosuppression and metabolic disturbance, limiting its long-term use in vulnerable populations like DS.

Beyond classical autophagy inducers, partial inhibition of DRP1 has also been shown to enhance mitophagy and improve mitochondrial quality in AD models [149]. Additional compounds such as Urolithin A and Tomatidine have demonstrated mitophagy-promoting effects via the PINK1–Parkin and AMPK–mTOR pathways, respectively, in aging and AD models [150]. Urolithin A has completed early-phase human trials and was shown to induce mitophagy-related gene expression in skeletal muscle [151], suggesting translational potential for conditions involving CNS mitochondrial dysfunction. These observations are consistent with broader findings showing that defective mitophagy driven by oxidative stress, impaired DNA repair, and telomere shortening contributes to neurodegeneration in aging and AD [152]. While these agents have not yet been tested in DS, their mechanisms may be relevant given the shared mitochondrial defects, warranting further investigation in DS-specific systems.

### 5.5 Summary and Clinical Outlook

Together, these therapeutic strategies reflect the multifaceted nature of mitochondrial dysfunction in DS and highlight diverse molecular routes for intervention, including antioxidant supplementation, mitochondrial biogenesis inducers, dynamics modulators, and mitophagy enhancers. Most candidates remain at the preclinical stage, and translational challenges persist, including the scarcity of DS-focused clinical studies, age-related variability in treatment response, and the need for CNS-penetrant compounds and robust biomarkers. Addressing these barriers will be essential for advancing mitochondrial-targeted therapies toward clinical application in DS.

Senolytic therapies, which selectively eliminate senescent cells, have emerged as a novel strategy to target mitochondrial-driven aging processes [153]. Agents such as dasatinib plus quercetin (D+Q) and Navitoclax (ABT-263) act through mitochondrial apoptotic pathways or inhibit anti-apoptotic BCL-2 proteins [151]. In DS models, D+Q has been shown to alleviate transcriptional and cellular dysfunction in neural progenitor cells, suggesting potential therapeutic relevance [118]. However, Navitoclax's hematologic toxicity, particularly thrombocytopenia [154], raises safety concerns for clinical application, especially in pediatric or vulnerable DS populations. To overcome such limitations, mitochondria-targeted senolytics like MitoTam have recently been developed, demonstrating high selectivity for senescent cells and no major toxicity observed in preclinical models [155].

In addition to age, sex-based biological differences may influence mitochondrial function, neuroinflammation, and treatment response. Recent studies in DS-AD suggest that although overall AD penetrance and biomarker trajectories are largely similar between sexes, females carrying the APOE ε4 allele tend to exhibit earlier symptom onset, poorer episodic memory, and reduced hippocampal volume compared to males, indicating a potential interaction between sex and APOE genotype [156]. Transcriptomic profiling also reveals consistent upregulation of inflammatory and glial genes in DS-AD females, particularly in late-stage disease, suggesting heightened neuroinflammatory vulnerability [157]. These findings underscore the need to incorporate sex as a biological variable in future DS-specific clinical trials to improve therapeutic stratification and precision.

## 6. Conclusion

Mitochondrial imbalance is a defining feature of DS that fundamentally disrupts OXPHOS, mitochondrial dynamics, and quality control systems. These imbalances arise from HSA21 gene dosage effects and widespread transcriptional dysregulation, leading to persistent oxidative stress, energy deficits, and accumulation of dysfunctional mitochondria. Such impairments not only increase neuronal vulnerability but also exacerbate cellular senescence and neuroinflammation, reinforcing a pathological cycle that accelerates AD-like neurodegeneration in DS.

Beyond DS, the concept of mitochondrial imbalance represents a broader mechanism underlying neurodegenerative disorders. In conditions such as AD, amyotrophic lateral sclerosis, Parkinson's disease, and Huntington's disease, similar disruption of mitochondrial homeostasis underscores its role in neurodegenerative diseases [158-161]. Given its fundamental role in neuronal function and aging, therapeutic interventions targeting mitochondrial imbalance through strategies that enhance biogenesis, stabilize dynamics, and promote mitophagy are promising.

As a model for early-onset neurodegeneration, DS provides a unique window into mitochondrial pathology, offering insights applicable to other neurological disorders [97]. Addressing both systemic- and cellular-level mitochondrial imbalance will be essential for developing precision therapies that restore cellular resilience. Interdisciplinary collaboration will be crucial for translating these mechanistic insights into effective treatments for DS and a wider array of neurodegenerative diseases.

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## Competing interests

The authors declare that they have no competing interests.

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