Neurodegenerative diseases and aging
Neurodegenerative diseases

• Neurodegenerative diseases are defined as hereditary and sporadic conditions which are characterized by progressive nervous system dysfunction.

• These disorders are often associated with atrophy of the affected central or peripheral structures of the nervous system and include: Alzheimer's Disease and other dementias, Parkinson's Disease, Multiple Sclerosis, Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's Disease), Huntington's Disease, Prion Diseases, and others.

• These diseases rob people of their ability to remember, speak, write, ambulate, and control their lives. There is no cure for these diseases.
Neurodegenerative diseases

- Much progress has been made in identifying genes involved in familial, or inherited, forms of different neurodegenerative diseases, including Alzheimer’s disease, Parkinson’s disease and Amyotrophic Lateral Sclerosis (ALS).

- However the majority of these disease cases are sporadic (not inherited), where the origin(s) of sporadic neurodegeneration remain undetermined.

- Gene candidates, susceptibility factors (environmental insults and epigenetic alterations)
Cell death and neurodegeneration

Among the different modes of cell death, apoptosis (programmed cell death) has been suggested to occur most frequently in neurodegenerative disease.

- Parkinson's disease (PD) - dopaminergic cell death
  - Familial forms of PD are associated with mutations in α-synuclein genes.
  - Sporadic PD ~ mitochondrial/environmental toxins (paraquat, MPP+)
  - Upregulation of caspase 3 and Bcl-2 protein members

- Alzheimer's disease (AD) - hippocampal/cortical neurons
  - APP, apolipoprotein E, presenilins
  - Tau and amyloid β (Aβ)
  - DNA fragmentation, caspase and Bcl-2 upregulation

Redox signaling, cell death and neurodegeneration

- Oxidative stress is a common event in the pathogenesis of neurodegenerative diseases
  - Parkinson's disease (PD)
    - Mitochondrial toxins, dopamine oxidation
    - Decreased antioxidant levels (GSH)
    - Lipid peroxidation, protein (carbonyls and nitrotyrosines) and nucleic acid oxidation
  - Alzheimer's disease (AD) and mild cognitive impairment.
    - Increased lipid-peroxidation (CSF), protein (carbonyls and nitrotyrosines) and nucleic acid oxidation
    - Oxidative stress influences Aβ formation and Aβ has pro-oxidant effects
  - Huntington's disease (HD) – Energy metabolism
### Table II. Diverse molecular modifications observed in Alzheimer’s diseased brains.

<table>
<thead>
<tr>
<th>Modifications in Alzheimer’s disease</th>
<th>Observation</th>
</tr>
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<tr>
<td>Oxidative protein modifications</td>
<td>Increases in protein carbonyls and other protein oxidation products (glutamic and aminoacidic semi-aldehydes), increased levels of methionine sulfoxide oxidized SOD, creatine kinase and glutamine synthetase UCHL1 is heavily oxidized</td>
</tr>
<tr>
<td>Nitrosative protein modifications</td>
<td>Increased levels of nitrotyrosine neurofibrillary tangles Other nitratred proteins are β-actin, α-enolase and triosephosphate isomerase</td>
</tr>
<tr>
<td>Lipid peroxidation</td>
<td>Increased levels of HNE</td>
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<tr>
<td>Oxidative DNA damage</td>
<td>Increases in 8OHdG and other base oxidation products in mitochondria and nucleus</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>Decreased activities of complex IV, α-ketoglutarate dehydrogenase, pyruvate dehydrogenase</td>
</tr>
<tr>
<td>Proteasome dysfunction</td>
<td>Decreased proteasomal activity, abnormal accumulation of proteins containing polyubiquitin</td>
</tr>
</tbody>
</table>

### Table III. Diverse molecular modifications observed in Parkinson’s diseased brains.

<table>
<thead>
<tr>
<th>Modifications in Parkinson’s disease</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative protein modifications</td>
<td>Increased levels of protein carbonyls in substantia nigra, oxidized SOD1 Increased levels of oxidized dopamine (cysteinyl-DOPA and cysteinyl-dopamine)</td>
</tr>
<tr>
<td>Nitrosative protein modifications</td>
<td>Increased levels of nitrotyrosine in α-synuclein and Lewy bodies</td>
</tr>
<tr>
<td>Lipid peroxidation</td>
<td>HNE-products in Lewy bodies and increased peroxides</td>
</tr>
<tr>
<td>Oxidative DNA damage</td>
<td>Increased levels of DNA oxidation product 8OHdG in mitochondrial and total DNA</td>
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<tr>
<td>Glutathione</td>
<td>Decreased levels of GSH</td>
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<td>Mitochondrial dysfunction</td>
<td>Decreased activities of complex I and α-ketoglutarate dehydrogenase</td>
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<tr>
<td>Proteasome dysfunction</td>
<td>Genetic defects in inherited Parkinson’s disease, decreased activities in sporadic Parkinson’s disease, decrease UCHL1 activity</td>
</tr>
<tr>
<td>Oxidized dopamine</td>
<td>Auto-oxidation of free non-vesicle dopamine to quinone</td>
</tr>
</tbody>
</table>
**Alzheimer’s disease**

- An estimated 24 million people worldwide have dementia, the majority of whom are thought to have Alzheimer's disease.
- The two core pathological hallmarks of Alzheimer's disease are **amyloid plaques and neurofibrillary tangles**.
- The amyloid cascade hypothesis suggests that deposition of amyloid β (Aβ) triggers neuronal dysfunction and death in the brain.
- Established genetic causes of Alzheimer's disease include dominant mutations of the genes encoding amyloid precursor protein (APP) and presenilin 1 (PSEN1) and PSEN2 (5% or early onset). PSEN1 and PSEN2 mutations affect concentrations of Aβ₁₋₄₂ because presenilin proteins form part of γ secretase, which cleaves APP to produce Aβ.
- Environmental risk factors for Alzheimer's disease include cognitive reserve (a concept combining the benefits of education, occupation, and mental activities), physical activity and exercise, midlife obesity, alcohol intake, and smoking.
- **Many treatable medical conditions are also associated with an increased risk of Alzheimer's disease, including stroke, diabetes, TBI.**
Amyloid beta

- Amyloid precursor protein (APP) is an integral membrane protein expressed in many tissues and concentrated in the synapses of neurons. Its primary function is not known, though it has been implicated as a regulator of synapse formation, neural plasticity and iron export.

- Non-amyloidogenic cleavage of the β-amyloid peptide (Aβ) is mediated by α-secretase. A large amyloid precursor protein (sAPPα) and the C83 fragment are generated.

- Amyloidogenic processing is initiated by β-secretase beta-site amyloid precursor protein–cleaving enzyme 1 (BACE-1), releasing a shortened sAPPβ. The C99 fragment is a γ-secretase substrate, generating Aβ and AICD (amyloid precursor protein intracellular domain).

- Soluble Aβ is prone to aggregation. Protofibrils (upper) and annular or pore-like profiles (lower) are intermediate aggregates.

- Self-association of Aβ monomers into oligomers is dependent on concentration (left immunoblot) and is promoted by oxidizing conditions (lane 2) and divalent metal conditions (lane 3).

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**Tau hyperphosphorylation**

- **Tau proteins are proteins that stabilize microtubules.** Four repeat sequences (R1-R4) make up the microtubule-binding domain (MBD).

- **Normal phosphorylation of tau occurs on serine and threonine residues.**

- When followed by **proline (P)**, these amino acids are phosphorylated by glycogen synthase kinase 3 (GSK-3β), cyclin-dependent kinase (cdk5), or mitogen-activated protein kinase (MAPK).

  **Nonproline-directed kinases phophorylating tau** are Akt, Fyn, protein kinase A (PKA), calcium–calmodulin protein kinase 2 (CaMKII), and microtubule affinity-regulating kinase (MARK).

- **Excessive kinase, reduced phosphatase activities,** or both cause hyperphosphorylated tau to **detach, self-aggregate,** and to **destabilize microtubules.**
Alzheimer’s disease and oxidative stress

- Amyloid β shows **peroxidative activity** on cell and organelle membrane lipids yields the mitochondrial toxins hydroxynonenal (HNE) and malondialdehyde.

- Cellular Aβ directly attacks electron transport complex IV (cytochrome c oxidase) and key Krebs-cycle enzymes (α-ketoglutarate and pyruvate dehydrogenase) and damage to mitochondrial DNA (mtDNA), leading to fragmentation.

- Lipid peroxidation products also promote tau phosphorylation and aggregation, which in turn inhibit complex I.

- Contradictory results have been found with respect to the effect of dietary intake of antioxidants, such as vitamin E in reducing the risk or the rate of progression of Alzheimer's disease.
Alzheimer’s disease and RNS

- NMDAR hyperactivation triggers generation of NO and subsequent S-nitrosylation of neuronal proteins, contributing to synaptic damage and eventually neuronal death.

- Soluble oligomers of Aβ, can facilitate neuronal NO production in both NMDAR-dependent and -independent manners.

- S-Nitrosylation of the fission-inducing protein Drp1 (forming SNO-Drp1) can contribute to synaptic damage and neuronal cell death by triggering excessive mitochondrial fission and bioenergetic impairment.
Oxidative stress in triple transgenic AD mouse model

- Tangle formation has been reproduced in P301L tau transgenic pR5 mice, whereas APP<sub>swPS2<sup>N141I</sup></sub> double-transgenic APP152 mice develop Aβ plaques. Cross-breeding generates triple transgenic (triple AD) mice that combine both pathologies in one model.

- Functional analysis of the consequences of the combined Aβ and tau pathologies, using proteomic analysis followed it was found a massive deregulation of 24 proteins, of which one-third were mitochondrial proteins mainly related to complexes I and IV of the oxidative phosphorylation (OXPHOS) system.

- Deregulation of complex I was tau dependent, whereas deregulation of complex IV was Aβ dependent, both at the protein and activity levels.

- Synergistic effects of Aβ and tau were evident in 8-month-old triple AD mice as only they showed a reduction of the mitochondrial membrane potential at this early age. At the age of 12 months, the strongest defects on OXPHOS, synthesis of ATP, and reactive oxygen species were exhibited in the triple AD mice, again emphasizing synergistic, age-associated effects of Aβ and tau in perishing mitochondria.

Oxidative damage in brain, including elevated levels of protein oxidation and lipid peroxidation, was completely prevented in transgenic AD mouse mice with a M631L mutation in APP. APP mice contains mutations in human APP corresponding to the Swedish and Indiana familial forms of AD are expressed (APP_{Sw,In}), resulting in Aβ accumulation, plaque formation, and memory deficits.

**Oxidative modifications and amyloid β toxicity**

Met^{35} in amyloid β-protein (Aβ) is prone to participating in redox reactions, and therefore is believed to contribute significantly Aβ-induced toxicity. Aβ40 and Aβ42 analogues containing Met^{35}→Nle (norleucine) or Met^{35}→Val substitutions had no significant effect in neurotoxicity.


Parkinson’s disease

- Parkinson's disease is a neurodegenerative process characterized by numerous motor and nonmotor clinical manifestations for which effective, mechanism-based treatments remain elusive.
- It is characterized by the presence of severe pars-compacta nigral-cell loss, and accumulation of aggregated α-synuclein in specific brain stem, spinal cord, and cortical regions.
- The main known risk factor is age. However, gene-environment interactions play a significant role.
- After decades of research, a single cause for Parkinson's disease has not been found and is unlikely to emerge. Whereas some forms of Parkinson's disease are genetic, most cases are idiopathic, and the underlying environmental causes (if any) remain to be discovered.
- An emerging concept is that SNc homeostasis is vulnerable to different genetic, cellular and environmental factors that independently or concomitantly cause cell death over time by mitochondrial dysfunction and oxidative stress, abnormal protein degradation.
- Dopamine metabolism is considered to be critical for the preferential susceptibility of ventrolateral SNc cells to damage in Parkinson's disease. Dopamine metabolism produces highly reactive species that oxidize lipids and other compounds, increase oxidative stress and impair mitochondrial function.
Rare inherited mutations in genes encoding electron transport chain components have been associated with parkinsonism.

- Parkin is partially localized to the outer mitochondrial membrane,
- PINK1 is a mitochondrial serine–threonine kinase that affords protection against oxidative stress and acts with Parkin to regulate the balance of mitochondrial fission and fusion.
- LRRK2 associates, at least in part, with the outer mitochondrial membrane
- HTRA2 is a mitochondrial serine protease, the release of which might be involved in apoptotic cell death.
- DJ-1 is relocated to mitochondria under conditions of oxidative stress and is thought to be neuroprotective under such conditions.
- The α-synuclein protein has an amino-terminal mitochondrial targeting sequence and, when overexpressed or under conditions of acidification, is at least partially associated with the inner mitochondrial membrane, where it might cause direct damage.
Experimental models of PD

- 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a by-product of the chemical synthesis of a meperidine analogue with potent heroin-like effects that can induce a parkinsonian syndrome in humans almost indistinguishable from Parkinson's disease (PD).

- It has been used extensively as a model of PD. MPTP administration causes damage to the nigrostriatal dopamine (DA) pathway identical to that seen in PD, with the exception of Lewy bodies.

- MPTP, crosses the blood–brain barrier and is metabolized to 1-methyl-4-phenylpyridinium (MPP+) by the enzyme monoamine oxidase B (MAO-B) in non-DA cells. MPP+ is then taken up by DA transporters, for which it has high affinity. MPP+ impairs mitochondrial respiration by inhibiting complex I of the electron transport chain, resulting in an increased production of free radicals, which causes oxidative stress.
Paraquat-induced neuronal cell death
Redox signaling, cell death and PD

Intrinsic Pathways

Transcription of pro-apoptotic genes

Feedback loop

Cellular substrates
PARP, α-fodrin

Membrane blebbing
and cell fragmentation

Endonucleases
DNA degradation
DJ-1 in Parkinson’s disease

Chemical Exposure → Oxidative Stress Insult

Age

SH

DJ-1

SH

SOx

Over-oxidation of key cysteine & increase in acidic isoforms

Decreased protective activity

Loss of function mutation in DJ-1

Increased sensitivity to oxidative stress

Accelerated death of DA neurons in SNpc

Parkinson’s Disease
Oxidative stress in substantia nigra

- Using transgenic mice that expressed a redox-sensitive variant of green fluorescent protein targeted to the mitochondrial matrix, it was demonstrated that normal autonomous pacemaking (responsible for the sustained release of dopamine necessary for the proper functioning of target structures, such as the striatum) created an oxidant stress that was specific to vulnerable SNC dopaminergic neurons but not in neurons in the ventral tegmental area.

- The oxidant stress engaged induced transient, mild mitochondrial depolarization or uncoupling.

- Knocking out DJ-1 (PARK7), which is a gene associated with an early-onset form of Parkinson's disease, down-regulated the expression of two uncoupling proteins (UCP4 (SLC25A27) and UCP5 (SLC25A14)), compromised Ca2+-induced uncoupling and increased oxidation of matrix proteins specifically in SNC dopaminergic neurons.
Peroxisiredoxins in PD

- Prx2 is the most abundant in mammalian neurons, making it a prime candidate to defend against oxidative stress.
- Prx2 is S-nitrosylated (forming SNO-Prx2) by reaction with NO• at two critical cysteine residues (C51 and C172), preventing its reaction with peroxides.
- Increased SNO-Prx2 in human Parkinson's disease (PD) brains, and S-nitrosylation of Prx2 inhibited both its enzymatic activity and protective function from oxidative stress.

Proc Natl Acad Sci U S A. 2007 Nov 20;104(47):18742-7
Huntington’s disease and oxidative stress

- Huntington disease (HD) is an autosomal dominant neurodegenerative disease.
- **HD is caused by a CAG (glutamine) repeat expansion in the first exon of the gene that encodes huntingtin (Htt).**
- γ-Aminobutyric acid (GABAergic) medium spiny neurons of the striatum that contain enkephalin or substance P and project to the globus pallidus and substantia nigra are particularly vulnerable in HD.
- **Defects in energy metabolism, particularly mitochondrial function,** represent a common thread in studies of HD pathogenesis in humans and animal models.
- **Impaired oxidative phosphorylation, oxidative stress,** impaired mitochondrial calcium handling, abnormal mitochondria trafficking, deregulation of key factors of mitochondrial biogenesis, such as the transcriptional coactivator PPARγ coactivator-1α (PGC-1α), and decreased glycolysis.

Huntington’s disease and oxidative stress

- Mitochondrial toxins such as malonate and 3-nitropropionic acid (3-NP) inhibit succinate dehydrogenase (SDH), which is part of complex II of the electron transport chain.
- Neuroprotection: Coenzyme Q$_{10}$ is an electron acceptor from complex I and complex II that also has antioxidant activity. Creatine and triacetyluridine can buffer intracellular energy stores.

Huntington’s disease, oxidative stress and antioxidant deficiency

- HD knock-in mice (HD^{140Q/140Q}), which have human huntingtin exon 1 with 140 CAG repeats inserted into the endogenous mouse huntingtin gene.
- Elevated ROS in HD neurons
- HD neurons had lower cell surface levels of the glutamate/cysteine transporter EAAC1 and were deficient in taking up cysteine.
- Constitutive trafficking of EAAC1 from recycling endosomes relies on Rab11 (Ras-related GTP-binding proteins) activity, which is defective in the brain of HD^{140Q/140Q} mice.
- Enhancement of Rab11 activity by expression of a dominant-active Rab11 mutant in primary HD neurons ameliorated the deficit in cysteine uptake, increased levels of intracellular glutathione, normalized clearance of ROS, and improved neuronal survival.

Huntington’s disease and oxidative DNA damage

- Neurodegenerative disorders are characterized by the accumulation of 8-oxo-7,8-dihydroguanine (8-oxodG).
- Through direct oxidation of DNA guanine or via incorporation of the oxidized nucleotide during replication.
- hMTH1 is the major human hydrolase that degrades oxidized purine nucleoside triphosphates.
- hMTH1 transgene expression conferred a dramatic protection against Huntington's disease-like symptoms, including striatal degeneration, and death induced by 3-NP.
- hMTH1 expression protected striatal cells containing an expanded CAG repeat of the huntingtin gene (mutant HdhQ111/Q111) from toxicity associated with expression of the mutant huntingtin.

Amyotrophic lateral sclerosis

• Amyotrophic lateral sclerosis (ALS) is a paralytic disorder caused by motor neuron degeneration in the brain and spinal cord.
• The causes of most cases of ALS are as yet undefined. Excessive excitatory tone, protein misfolding, impaired energy production, abnormal calcium metabolism, altered axonal transport and activation of proteases and nucleases.
• Several factors are proposed to instigate these phenomena, including latent infections by viral and non-viral agents, toxins (for example, pesticides) and autoimmune reactions.
• Five Mendelian gene defects have been reported to cause ALS. The protein products of these mutated genes are cytosolic Cu/Zn superoxide dismutase (SOD1), alsin, senataxin (SETX), synaptobrevin/VAMP (vesicle-associated membrane protein)-associated protein B (VAPB) and dynactin.
• About 20–25% of all familial ALS cases arise because of mutations in SOD1, the protein product of which accounts for 0.1–0.2% of the cellular proteins in the CNS.
• Abnormal TDP-43 (Trans-activation response [TAR] DNA-binding protein) accumulation in the cytoplasm is found in familial ALS. Mutations in the TARDBP gene that codes for the TDP-43 protein have been shown to account for ~2-6% of all familial ALS cases. TDP-43 is also involved in Frontotemporal lobar dementia with ubiquitin (FTLD-U). Abnormal TDP-43 is not present in cases of ALS with SOD1 mutations.
Amyotrophic lateral sclerosis

- The instability of the mutant SOD1 protein contributes to its toxicity, enhanced by the release of Zn.
- In the aberrant redox chemistry model, mutant superoxide dismutase 1 (SOD1) is unstable and aberrant chemistry is mediated by promiscuous interaction with non-conventional substrates.
  - Hydrogen peroxide (H$_2$O$_2$) or peroxynitrite (ONOO$^-$) can react with reduced SOD1 (SOD1-Cu$^+$).
  - Molecular oxygen (O$_2$) can react aberrantly with Zn-deficient SOD1 to generate an excess of superoxide anion (O$_2^-$).
  - The unstable protein can also release free copper and/or zinc, which might be toxic.
- In the protein toxicity model, conformationally altered mutant SOD1 forms toxic, proteinaceous deposits.
  - Aggregated SOD1 inhibits chaperone and/or proteasome activity, with subsequent misfolding and insufficient clearance of numerous proteins.
  - Alternatively, these aggregates could sequester, inactivate or enhance the toxicity of other proteins crucial for cellular processes.

Nat Rev Neurosci. 2006 Sep;7(9):710-23.
Amyotrophic lateral sclerosis

- Deletion of either NADPH oxidases Nox1 and Nox2 genes significantly slowed disease progression by mutant SOD1$^{G93A}$ and improved survival.
- (B) Survival index for mice and (C) NADPH-dependent superoxide production in spinal cords of hemizygous SOD1$^{G93A}$ transgenic mice with WT, HET, and KO Nox2 genotypes.
- Enhanced survival of ALS Nox2-KO mice correlated with higher motor neuron counts in the lumbar region of the spinal cord and reduced inflammatory response (microglial marker).

Redox control of prion and disease pathogenesis

- The underlying cause of brain pathology in all prion disorders is PrP-scrapie (PrP(Sc)), a beta-sheet-rich conformation of a normal glycoprotein, the prion protein (PrP(C)).
- In prion disorders, imbalance of brain-iron homeostasis is observed before end-stage disease and worsens with disease progression, implicating iron-induced oxidative stress in disease pathogenesis.
Multiple sclerosis and oxidative stress

- Multiple sclerosis is a chronic inflammatory disease of the central nervous system, associated with demyelination and neurodegeneration. The mechanisms of tissue injury are currently poorly understood, but recent data suggest that mitochondrial injury may play an important role in this process.

- Both in MS and in neurodegenerative diseases, inflammation initiates microglial activation.

- In MS, inflammation is immune-mediated but in neurodegenerative diseases the primary causes of inflammation remain speculative.

- Activated microglia produce $\text{O}_2^\cdot$ and $\cdot\text{NO}$ reactive species that combine to induce primary synthesis of peroxynitrite.

- Peroxynitrite inhibits glutamate transporters and/or activates glutamate receptors causing glutamate overload.

- Excitotoxicity entails mitochondrial dysfunction, calcium overload.
Ageing and oxidative stress

- The incidence in many diseases increases with age.
- Ageing can be defined as a progressive decline in the efficiency of physiological processes after the reproductive phase of life.
- The ability of cells and organisms to recover from an insult such as oxidative stress decreases with age, while the risk of disease increases.
Is the oxidative stress theory of aging dead?
Effect of genetic manipulation of antioxidant defenses on age-related disease in challenged animal models

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Gene altered</th>
<th>Description of animal model</th>
<th>Effect</th>
<th>Refs</th>
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<tr>
<td><strong>Neurodegenerative diseases</strong></td>
<td></td>
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<tr>
<td>Cu/Zn-Superoxide Dismutase</td>
<td>CD-1 mice overexpressing human SOD1.</td>
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<td>Protection against neuronal cell death after transient focal ischemia.</td>
<td>[220]</td>
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<td></td>
<td>APP TG mice overexpressing human SOD1 (APP TG/Sod1 TG)</td>
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<td>Increased lifespan of APP TG mice</td>
<td>[206]</td>
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<td></td>
<td>Sod1 TG in PD models (MPTP, PQ+mane6)</td>
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<td>Reduced neural death and loss of dopamine, improved locomotion</td>
<td>[207,208]</td>
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<tr>
<td>Mn-Superoxide Dismutase</td>
<td>APP TG mice heterozygous for Sod2 (APP TG/Sod2+/−)</td>
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<td>Increased Aβ plaques, neurodegeneration</td>
<td>[200–202]</td>
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<td></td>
<td>APP TG mice overexpressing Sod2 (APP TG/Sod2 TG)</td>
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<td>[204,205]</td>
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<td>ALS model (SOD1^{0/0}:A10Δx) heterozygous for Sod2 (Sod2^{+/-})</td>
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<td>Increased disease progression (ALS animal model)</td>
<td>[210,211]</td>
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<td>Glutathione peroxidase 1</td>
<td>Gpx1 TG in PD model (PQ +mane6)</td>
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<tr>
<td>Glutathione peroxidase 4</td>
<td>APP heterozygous for Gpx4 (Gpx4^{+/-})</td>
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<td>Increased amyloid plaques</td>
<td>[203]</td>
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</table>
Table I. Main categories of molecular damage occurring during cellular aging.

<table>
<thead>
<tr>
<th>Macromolecule</th>
<th>Examples of damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA (nuclear and mitochondrial)</td>
<td>Mutations, epimutations, base modifications, strand breaks</td>
</tr>
<tr>
<td>RNA</td>
<td>Base modifications, miscoding, missplicing</td>
</tr>
<tr>
<td>Protein</td>
<td>Amino acid modifications, misincorporation, misfolding, aggregation</td>
</tr>
<tr>
<td>Carbohydrates, lipids, and molecular conjugates</td>
<td>Advanced glycation end-products (AGE), lipofuscin, aggresomes</td>
</tr>
</tbody>
</table>

Exogenous Factors
- environmental conditions
- lifestyle
- stress conditions

Endogenous sources of ROS
- normalization
- activation
- repair

Accumulation of molecular injury: DNA, protein, lipids
- Organelle damage (e.g., mitochondria, peroxisomes)

Cellular responses:
- inflammation, survival, proliferation, death

Systematic responses:
- aging, organ dysfunction, frailty, diseases
Impaired degradation and repair systems in aging

Figure 1. Oxidized protein degradation and repair: ROS and related pathways are damaging proteins in either reversible or irreversible ways. Depending on the nature of the modification, protein maintenance is achieved by either degradation or specific repair systems. Age-related impairment of these systems has been documented in different cellular models and organisms as well as their involvement in resistance to oxidative stress and longevity.
Calorie restriction and redox balance

- Inverse correlation between metabolic rates and lifespan.
- Mammalian NAD-dependent mitochondrial deacetylase SIRT3. Endogenous SIRT3 is a soluble protein located in the mitochondrial matrix.
- Fasting increases SIRT3 expression, which increases respiration and decreases the production of reactive oxygen species.
- Calorie restriction promotes the activity of SIRT3, which deacetylates SOD2 and isocitrate dehydrogenase (IDH2), increasing the activity of these enzymes and resulting in reduced oxidative stress. Lowered oxidative stress leads to a reduced rate of aging.
A telomere is a region of repetitive nucleotide sequences at the end of a chromosome, which protects the end of the chromosome from deterioration or from fusion with neighboring chromosomes. Telomere regions deter the degradation of genes near the ends of chromosomes by allowing chromosome ends to shorten, which necessarily occurs during chromosome replication. Over time, due to each cell division, the telomere ends do become shorter. Telomeres are consumed during cell division, and are replenished by telomerase reverse transcriptase.

Because guanine-rich sequences are more sensitive and less capable of DNA repair, telomeres are more vulnerable to oxidation.
Summary

- Neurodegenerative diseases are characterized by the selective loss of neuronal populations which is associated with oxidative stress.
- Genetic, environmental factors and aging contribute to the pathogenesis of neurodegenerative disorders.
- Oxidative stress is observed in post-mortem samples of patients. However, its relevance to the pathogenesis remains elusive. Cause or consequence?
- Neurodegenerative disorders are characterized by mitochondrial dysfunction and abnormal protein aggregation.
- Further research is necessary to clearly define the etiology of neurodegenerative disorders and the role of oxidative stress and redox signaling in disease progression.
  - Oxidative damage or redox signaling.