Converging Pathologies: Reconciling Oxidative Stress and Autophagy-Lysosomal Failure in the Etiology of Alzheimer’s Disease

1. The Crisis of Causality: Moving Beyond the Amyloid Cascade

1.1 The Stagnation of the Amyloid Paradigm

For more than three decades, the scientific discourse surrounding Alzheimer’s disease (AD) has been almost singularly dominated by the Amyloid Cascade Hypothesis. This framework, which posits that the extracellular accumulation of amyloid-beta (Aβ) peptides into senile plaques is the primary and initiating event in AD pathogenesis, has consumed the vast majority of research funding and therapeutic development efforts. The hypothesis suggests a linear progression: Aβ aggregation leads to neurofibrillary tangle (NFT) formation, which in turn causes synaptic dysfunction, neuronal loss, and ultimately, dementia. However, this model faces an existential crisis. Despite the successful development of monoclonal antibodies capable of clearing amyloid plaques from the human brain—such as aducanumab and lecanemab—the clinical benefits have been modest at best, and often negligible in terms of arresting disease progression. This disconnect between the efficient removal of the purported pathogen and the lack of meaningful clinical recovery suggests a fundamental flaw in our understanding of the disease's etiology.

The failure of anti-amyloid therapeutics to cure AD indicates that Aβ plaques may not be the root cause of neurodegeneration, but rather a downstream consequence or a "tombstone" of a pathological process that occurred much earlier. As the field grapples with these failures, alternative hypotheses that were previously marginalized are now moving to the forefront. Among the most rigorously developed of these are the Oxidative Stress Hypothesis, championed by George Perry, and the Autophagy-Lysosomal Failure Hypothesis, pioneered by Ralph Nixon. Historically, these two theories have been viewed as distinct, parallel explanations for AD. Perry has focused on the biochemical ravages of free radicals and the protective nature of amyloid, while Nixon has elucidated the structural failure of the neuron’s waste disposal system.

1.2 The Necessity of Synthesis

This report posits that these two frameworks are not mutually exclusive but are, in fact, mechanistically convergent. A rigorous analysis of biochemical, genetic, and ultrastructural data reveals a unified pathogenic pathway wherein oxidative stress acts as the upstream driver that compromises the integrity of the endosomal-lysosomal system (ELS). Specifically, reactive oxygen species (ROS) and lipid peroxidation products generated by dysfunctional mitochondria

attack the molecular machinery responsible for lysosomal acidification—the vacuolar H+-ATPase (v-ATPase). This oxidative inhibition of the proton pump mimics the genetic defects seen in familial AD, leading to the autophagy failure described by Nixon.
The recent discovery of "PANTHOS" neurons—cells exhibiting a "poisonous flower" morphology due to massive intracellular accumulation of Aβ-filled autophagic vacuoles—serves as the structural validation of this convergence. This report will demonstrate that the "inside-out" mechanism of plaque formation, where a neuron dies and releases its intracellular amyloid burden, vindicates George Perry's long-held contention that Aβ accumulates intracellularly as a response to metabolic stress, while simultaneously confirming Ralph Nixon's definition of AD as a disease of lysosomal failure. By reconciling these views, we arrive at a comprehensive etiology that redefines AD not as a proteinopathy of aggregation, but as a metabolic failure of clearance and homeostasis.

2. The Oxidative Stress Doctrine: George Perry's Framework

2.1 Oxidative Stress as the Primordial Event

George Perry's extensive body of work establishes oxidative stress not merely as a bystander or a secondary effect of neurodegeneration, but as the chronologically primary event in the pathogenesis of AD. Oxidative stress arises from a fundamental imbalance between the production of reactive oxygen species (ROS)—including superoxide anions ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), and the highly reactive hydroxyl radical ($\cdot OH$)—and the neuronal antioxidant defense systems.
The temporal precedence of oxidative damage is a cornerstone of Perry's argument. Biochemical analyses of post-mortem brains reveal that oxidative damage to RNA (specifically 8-hydroxyguanosine) and lipids is detectable in neurons decades before the formation of amyloid plaques or NFTs. This damage is not randomly distributed but is concentrated in the vulnerable neuronal populations that eventually degenerate. Crucially, Perry observed an inverse correlation between oxidative damage and the presence of mature pathology. Neurons that are heavily laden with oxidative markers often lack plaques and tangles, whereas neurons with dense aggregates show reduced levels of oxidative stress markers. This counterintuitive finding suggests that the formation of aggregates might be a compensatory mechanism—a "scar" formed in the battle against oxidative injury—rather than the injury itself.

2.2 The "Protective Amyloid" Hypothesis

Central to Perry's oxidative stress theory is a radical re-evaluation of the biological function of Aβ. In direct opposition to the view of Aβ as a purely neurotoxic peptide, Perry argues that its initial accumulation is a homeostatic, protective response to oxidative and metabolic injury. The physiological properties of Aβ support this view; the peptide possesses a high affinity for redox-active transition metals, particularly copper (Cu) and iron (Fe).
Free copper and iron are potent catalysts for the Fenton reaction, a chemical process that converts relatively stable hydrogen peroxide into the devastating hydroxyl radical. By chelating these metals, Aβ precipitates them out of solution, effectively sequestering the catalysts of oxidative stress and preventing them from driving further radical production in the cytosol.

Perry’s research indicates that the upregulation of the amyloid precursor protein (APP) and its subsequent cleavage into Aβ is a desperate cellular attempt to patch oxidative leaks and stabilize membranes compromised by lipid peroxidation. The formation of the amyloid plaque, therefore, is not an act of cellular suicide, but a mechanism of containment—a "zinc-finger-like" chelation strategy gone awry due to the sheer volume of metabolic waste.

2.3 Lipid Peroxidation and the Generation of HNE

A critical and often overlooked component of the oxidative stress model is the phenomenon of lipid peroxidation. The brain is uniquely vulnerable to this form of damage due to its high content of polyunsaturated fatty acids (PUFAs), which are the primary structural components of neuronal membranes. When free radicals attack the carbon-carbon double bonds in PUFAs, they initiate a self-propagating chain reaction that destroys membrane integrity.
This process generates reactive aldehydes, the most significant of which is **4-hydroxy-2-trans-nonenal (HNE)**. Unlike free radicals, which have half-lives measured in nanoseconds and a very limited radius of damage, HNE is a stable, amphiphilic molecule that can diffuse across the cell and covalently modify proteins far from the site of its generation. HNE modifies proteins by forming Michael adducts with cysteine, histidine, and lysine residues, often targeting the active sites of enzymes. Perry and colleagues have demonstrated that HNE-protein adducts are ubiquitous in the AD brain, particularly in association with NFTs and amyloid plaques. As we will explore in subsequent sections, HNE serves as the biochemical "bullet" that links Perry’s oxidative stress theory to Nixon’s lysosomal failure, specifically by inhibiting the enzymes required for cellular waste clearance.

3. The Autophagy-Lysosomal Failure Doctrine: Ralph Nixon’s Framework

3.1 The Endosomal-Lysosomal System (ELS) as the Epicenter

While Perry focused on the biochemical environment of the neuron, Ralph Nixon dedicated decades to mapping the structural and functional failure of the neuron’s waste management infrastructure: the endosomal-lysosomal system (ELS). Neurons are post-mitotic cells that must survive for the entire lifespan of the organism. They cannot dilute toxic waste through cell division; instead, they are strictly reliant on autophagy ("self-eating") to degrade damaged organelles, protein aggregates, and oxidized lipids.
Nixon’s research has established that ELS dysfunction is not a late-stage consequence of AD, but an invariant, early, and progressive feature of the disease. One of the earliest cytopathological markers of AD, visible even in the brains of fetuses with Down syndrome (who carry an extra copy of the *APP* gene), is the enlargement of early endosomes. This enlargement signifies a "traffic jam" in the endocytic pathway, where cargo is entering the system but failing to be processed or degraded. As the disease progresses, this congestion propagates downstream, leading to the massive accumulation of autophagic vacuoles (AVs) within the neuronal cytoplasm. In healthy neurons, AVs are rarely seen because they fuse rapidly with lysosomes and their contents are degraded efficiently. In AD, the cytoplasm becomes packed with these vacuoles, a condition Nixon describes as "autophagic stress".

3.2 The Mechanism of Failure: Lysosomal Acidification and v-ATPase

The crucial insight from Nixon's work is the identification of the specific failure point in the autophagy pathway: **lysosomal acidification**. For autophagy to function, the autophagosome must fuse with a lysosome, and the resulting autolysosome must maintain a highly acidic pH (typically 4.5–5.0) to activate the cathepsin proteases responsible for degrading the cargo. Nixon's team demonstrated that in AD neurons, lysosomes fail to acidify. Without this acidification, the proteases remain inactive, and the degradation of waste halts. The machinery responsible for maintaining this pH gradient is the **vacuolar H+-ATPase (v-ATPase)**, a massive multi-subunit protein complex that utilizes ATP hydrolysis to pump protons against their gradient into the lysosomal lumen.

Nixon's lab uncovered a direct genetic link between familial AD and v-ATPase failure. They discovered that **Presenilin-1 (PSEN1)**, the protein most commonly mutated in early-onset AD, functions as a chaperone for the V0a1 subunit of the v-ATPase complex. In the endoplasmic reticulum, PSEN1 is required for the proper N-glycosylation and maturation of V0a1. When *PSEN1* is mutated (as in familial AD) or deleted, V0a1 fails to mature and is not delivered to the lysosome. This results in a deficiency of functional proton pumps, a rise in lysosomal pH, and a catastrophic failure of autophagy. This finding was revolutionary because it ascribed a loss-of-function mechanism (loss of acidification) to *PSEN1* mutations, challenging the prevailing view that these mutations acted solely by increasing the production of toxic Aβ42.

3.3 APP-βCTF: The Toxic Intermediate

In addition to the genetic loss of v-ATPase function via *PSEN1* mutations, Nixon identified a direct toxic effect of APP metabolites on the lysosome. The beta-carboxyl terminal fragment of APP (**APP-βCTF**, or C99) was found to accumulate in AD neurons and bind directly to the v-ATPase complex. This binding sterically hinders the assembly of the V0 (membrane) and V1 (cytosolic) sectors of the ATPase, effectively inhibiting the pump.

This creates a dangerous positive feedback loop. The accumulation of APP-βCTF inhibits the lysosome; the inhibited lysosome cannot degrade APP-βCTF (which is a substrate for lysosomal clearance); consequently, APP-βCTF levels rise further, exacerbating the acidification deficit. This mechanism explains how *APP* gene duplication (in Down syndrome) or overexpression leads to lysosomal failure even in the absence of *PSEN1* mutations.

3.4 The Discovery of PANTHOS and "Inside-Out" Plaque Formation

In a landmark series of studies published in 2022 and reinforced in 2024, Nixon's team utilized advanced imaging probes (mRFP-eGFP-LC3) to visualize the consequences of this lysosomal failure in vivo. They identified a unique neurodegenerative morphology termed **PANTHOS** (from the Greek *panthos*, meaning "poisonous flower").

In PANTHOS neurons, the failure of acidification leads to the accumulation of vast numbers of Aβ-positive autophagic vacuoles. These vacuoles cluster radially around the nucleus, creating a distinct, flower-like rosette pattern. Crucially, the high concentration of Aβ within these non-acidic, stalled vesicles promotes the intracellular fibrillization of the peptide. The neuron, bloated with undigested waste and amyloid fibrils, eventually undergoes **Lysosomal Membrane Permeabilization (LMP)**. The lysosomes rupture, releasing toxic cathepsins into the cytoplasm, which triggers necrotic cell death and lysis.

The aftermath of this event is the formation of a senile plaque. Quantitative analysis confirmed that PANTHOS neurons are the direct precursors to senile plaques. The plaque is not an extracellular deposit that landed on the neuron; it is the insoluble cytoskeletal and amyloid remains of a neuron that exploded from the inside out. This finding serves as the structural unification of the intracellular and extracellular theories of AD.

4. The Convergence: Oxidative Stress as the Trigger for Lysosomal Failure

The central question of this report is how George Perry's oxidative stress theory "fits" with Ralph Nixon's autophagy theory. The answer lies in the susceptibility of the lysosomal machinery to oxidative modification. While *PSEN1* mutations explain lysosomal failure in familial AD, they do not account for the vast majority of sporadic AD cases. In sporadic AD, oxidative stress acts as the "phenocopy" of the genetic defect, biochemically disabling the v-ATPase and triggering the same cascade of autophagy failure.

4.1 The HNE-v-ATPase Axis: A Biochemical Phenocopy

The bridge between Perry and Nixon is built on the interaction between HNE (the lipid peroxidation product highlighted by Perry) and the v-ATPase complex (the proton pump highlighted by Nixon). Research has demonstrated that v-ATPase is a specific target for oxidative modification.

- **Mechanism of Inhibition:** The v-ATPase complex relies on the coordinated rotation of its subunits to pump protons. HNE, being a highly reactive electrophile, forms covalent Michael adducts with nucleophilic residues (cysteine, histidine, and lysine) on the V1A and V1B subunits of the ATPase. This carbonylation alters the tertiary structure of the subunits, preventing the necessary conformational changes for ATP hydrolysis and proton transport.
- **The Causal Chain:**
    1. **Mitochondrial Dysfunction (Perry):** Aging and metabolic stress lead to electron leakage from the mitochondrial electron transport chain, generating superoxide and hydroxyl radicals.
    2. **Lipid Peroxidation (Perry):** These radicals attack the lysosomal and mitochondrial membranes, generating high concentrations of HNE.
    3. **v-ATPase Inhibition (Convergence):** HNE binds to and inactivates the v-ATPase pump on the lysosomal surface.
    4. **Acidification Failure (Nixon):** The lysosomal pH rises, inactivating cathepsins.
    5. **Autophagy Failure (Nixon):** Autophagic vacuoles accumulate, unable to degrade their cargo (including Aβ and mitochondria).
    6. **PANTHOS Formation and Lysis:** The neuron develops the PANTHOS morphology and dies, leaving an amyloid plaque.

This mechanism explains why oxidative stress markers appear *before* plaque formation (as Perry noted) and why lysosomal acidification fails in sporadic AD (as Nixon noted). The oxidative injury is the upstream trigger that disables the waste clearance system.

4.2 The Vicious Cycle of Mitophagy Failure

The convergence of these theories is further amplified by the failure of **mitophagy** (mitochondrial autophagy). Both Perry and Nixon emphasize the role of mitochondria, but from different angles that lock together in a destructive cycle.

- **Perry's View:** Mitochondria are the primary source of ROS and the primary victims of oxidative damage. He observed increased mitochondrial degradation products in AD neurons, interpreting this as evidence of mitochondrial turnover.
- **Nixon's View:** The ELS is responsible for clearing damaged mitochondria via mitophagy. When the lysosome fails (due to v-ATPase inhibition), this clearance is blocked.
- **The Cycle:** Damaged mitochondria, which should be degraded, are instead trapped in the cytoplasm within stalled autophagosomes. These undigested, damaged mitochondria are not inert; they continue to leak electrons and generate ROS. This increased ROS production leads to further lipid peroxidation (HNE formation), which causes further inhibition of v-ATPase, which leads to further blockage of mitophagy.

This feedback loop transforms the neuron into a pressure cooker of oxidative stress and toxic waste, accelerating the trajectory toward PANTHOS formation and cell death.

4.3 APP-βCTF: The Intersection of Amyloid and Oxidation

The role of APP-βCTF (C99) provides another layer of integration. Nixon has shown that this fragment is toxic to the v-ATPase. Perry has shown that oxidative stress increases the activity of BACE1 (beta-secretase), the enzyme responsible for creating APP-βCTF.
Therefore, oxidative stress directly promotes the production of the specific amyloid fragment that inhibits the lysosome. Furthermore, the accumulation of APP-βCTF within the stalled lysosome creates a local environment that favors the aggregation of Aβ. This creates a scenario where the "protective" upregulation of APP (to chelate metals, per Perry) backfires because the oxidative environment promotes its processing into a lysosome-poisoning fragment (per Nixon).

5. PANTHOS and the "Inside-Out" Revolution

5.1 Validating the Intracellular Hypothesis

The identification of PANTHOS neurons is arguably the most significant morphological discovery in AD research in recent years, as it resolves the decades-long debate regarding the location of amyloid accumulation. George Perry was a vocal proponent of the idea that Aβ accumulates intracellularly, stating that "This inside-out view has largely been ignored for at least 30 years". His early work faced skepticism from a field fixated on extracellular plaques.
Nixon's ultrastructural data provides the definitive vindication of Perry's intuition. The PANTHOS neurons are not merely cells containing amyloid; they are cells *defined* by the massive, organized accumulation of amyloid-filled vesicles that distort the cell body. The "flower" shape is formed by the crowding of giant autophagic vacuoles around the nucleus, pushing the cytoplasm outward.

5.2 The Mechanism of Plaque Genesis

The transition from a PANTHOS neuron to a senile plaque is a violent event driven by lysosomal failure. As the intracellular burden of Aβ fibrils and lipids grows, the integrity of the lysosomal membranes is compromised.

- **Calpain Activation:** Nixon's work suggests that the disruption of calcium homeostasis (due to lysosomal dysfunction) activates calpains, proteases that can cleave lysosomal membrane proteins (like LAMP2), further weakening the organelles.
- **Lysosomal Membrane Permeabilization (LMP):** Eventually, the membranes rupture. This releases cathepsins into the cytoplasm, which digest cellular components indiscriminately, leading to necrosis.
- **The Tombstone:** Once the cell membrane lyses, the insoluble core of amyloid fibrils—which was formed inside the autophagic vacuoles—is released into the extracellular space. Glial cells (microglia and astrocytes) then migrate to the site, attacking the debris and creating the classic "neuritic plaque" architecture.

This sequence confirms that the plaque is a historical record of a neuronal death event caused by autophagy failure, rather than an external deposit that kills the neuron from the outside.

6. Reconciling the Amyloid Paradox

6.1 Protective Intent, Toxic Outcome

How can we reconcile Perry's view of amyloid as "protective" with Nixon's view of it as the agent of lysosomal destruction? The answer lies in distinguishing between the *physiological intent* of the molecule and its *pathological accumulation*.

Perry is likely correct that the initial upregulation of Aβ is a defensive maneuver. In the face of metal-induced oxidative stress, the neuron produces Aβ to chelate copper and iron, preventing immediate oxidative catastrophe. Under normal conditions, this metal-Aβ complex would be trafficked to the lysosome, the metal would be stripped and recycled, and the peptide degraded. However, in the context of the "converged model," this clearance mechanism is broken. The lysosome, disabled by HNE-mediated v-ATPase inhibition, cannot degrade the Aβ-metal complex. The protective molecule thus accumulates to pathological levels. The high concentration of Aβ within the stalled, slightly acidic (but not acidic enough) vesicles favors its aggregation into fibrils. The "protective" chelator becomes a physical obstruction, clogging the autophagy system and eventually rupturing the cell. Thus, Aβ is protective in its *function* but toxic in its *persistence* due to the failure of the ELS.

7. Therapeutic Implications and Future Directions

7.1 The Failure of Monotherapies

The converged Perry-Nixon model offers a devastatingly clear explanation for the failure of previous clinical trials.

- **Why Antioxidants Failed:** Clinical trials of Vitamin E and other antioxidants failed because they were administered too late and lacked specificity. Scavenging free radicals in a patient with established AD is akin to putting out a fire after the building has burned down. By the time symptoms appear, the v-ATPase is already carbonylated and structurally disabled. Neutralizing new ROS does not repair the broken pumps or clear the massive backlog of intracellular waste.
- **Why Anti-Amyloid Antibodies Failed:** Drugs like aducanumab target extracellular plaques. According to the "Inside-Out" theory, the plaque is merely the debris of a neuron that has already died. Removing the plaque does nothing to address the active pathology

occurring *inside* the millions of surviving PANTHOS neurons. It is treating the symptom (the tombstone) rather than the disease (the dying neuron).

7.2 A Multi-Targeted Strategy

The integration of these theories mandates a paradigm shift toward multi-targeted therapies that address the root causes of metabolic and lysosomal failure.

1. **Restoring Lysosomal Acidification:** This is the most urgent therapeutic target. Nixon's work suggests that restoring acidification can rescue neuronal function even in the presence of amyloid. Potential strategies include v-ATPase agonists or small molecules that enhance the assembly of the V1 and V0 sectors of the pump.
2. **Preventing v-ATPase Oxidation:** Antioxidants must be re-engineered to target the lysosomal membrane specifically. Agents that can scavenge HNE or prevent its Michael addition to protein residues could protect the v-ATPase from inactivation. Perry has suggested the use of **deuterated polyunsaturated fatty acids (D-PUFAs)**, which are chemically resistant to peroxidation, as a way to "fireproof" neuronal membranes against ROS.
3. **Enhancing Mitophagy:** Drugs that promote the specific clearance of damaged mitochondria (e.g., via the PINK1/Parkin pathway) could break the vicious cycle of ROS production, provided that lysosomal function is supported simultaneously.
4. **Dietary Interventions:** Perry strongly advocates for complex dietary interventions like the **MIND diet** or **Mediterranean diet**. Unlike single-molecule antioxidants, these diets provide a synergistic blend of polyphenols and lipids that may support membrane integrity and reduce the overall oxidative burden, potentially preserving lysosomal function over decades.

8. Conclusion

The scientific journey to understand Alzheimer's disease has been marked by fierce debates between competing schools of thought. However, the query "How does this fit?" reveals a profound synergy between two of the most significant alternative theories in the field. George Perry's **oxidative stress** is not a competitor to Ralph Nixon's **autophagy failure**; it is the *engine* that drives it.

The evidence overwhelmingly supports a unified model: **Oxidative stress, driven by mitochondrial aging, generates lipid peroxidation products (HNE) that irreversibly damage the lysosomal proton pump (v-ATPase). This loss of acidification disables the neuron's waste management system, converting a protective antioxidant response (amyloid) into a lethal accumulation of intracellular debris (PANTHOS).** The eventual rupture of these neurons releases the amyloid plaques that have distracted the field for a century.

By recognizing that oxidative stress drives lysosomal failure, and that lysosomal failure exacerbates oxidative stress, we can finally appreciate the true, cyclic nature of Alzheimer's pathogenesis. This unified understanding demands a shift from amyloid-centric therapies to approaches that protect neuronal metabolism and restore the integrity of the cellular waste disposal system, offering a rational path forward for a field in desperate need of success.

References:.

Works cited

1. Alzheimer's Disease Research: What Has Guided Research So Far and Why It Is High Time for a Paradigm Shift 3031315693, 9783031315695 - DOKUMEN.PUB, https://dokumen.pub/alzheimers-disease-research-what-has-guided-research-so-far-and-why-it-is-high-time-for-a-paradigm-shift-3031315693-9783031315695.html 2. (PDF) Autophagy-lysosomal dysfunction, intraneuronal amyloidosis, and selective neuron death yield senile plaques in preclinical late-onset Alzheimer's Disease - ResearchGate, https://www.researchgate.net/publication/385579463_Autophagy-lysosomal_dysfunction_intraneuronal_amyloidosis_and_selective_neuron_death_yield_senile_plaques_in_preclinical_late-onset_Alzheimer's_Disease 3. Nixon Lab Provides Further Evidence for Alternative Alzheimer's Theory, https://www.nki.rfmh.org/nixon-lab-provides-further-evidence-for-alternative-alzheimers-theory/ 4. Behold PANTHOS, a Toxic Wreath of Perinuclear Aβ That Kills Neurons, https://www.dementiaresearcher.nihr.ac.uk/behold-panthos-a-toxic-wreath-of-perinuclear-a%CE%B2-that-kills-neurons/ 5. George Perry - Google Scholar, https://scholar.google.com/citations?user=ySklo5EAAAAJ&hl=en 6. Oxidative Damage Is the Earliest Event in Alzheimer Disease - Oxford Academic, https://academic.oup.com/jnen/article/60/8/759/2916237 7. Oxidative Stress and Mitochondrial Dysfunction in Alzheimer's Disease - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC4007397/ 8. International Journal of Alzheimer's Disease Guest Editors: The Contribution of the Amyloid Hypothesis to the Understanding of Alzheimer's Disease: A Critical Overview - ResearchGate, https://www.researchgate.net/publication/230774197_International_Journal_of_Alzheimer's_Disease_Guest_Editors_The_Contribution_of_the_Amyloid_Hypothesis_to_the_Understanding_of_Alzheimer's_Disease_A_Critical_Overview 9. The role of oxidative stress in Alzheimer's disease - VJNeurology, https://www.vjneurology.com/video/65q99boq1j0-the-role-of-oxidative-stress-in-alzheimers-disease/ 10. Oxidative Damage is Correlated with Mitochondrial Autophagy | Request PDF, https://www.researchgate.net/publication/274569371_Oxidative_Damage_is_Correlated_with_Mitochondrial_Autophagy 11. Iron-Export Ferroxidase Activity of β-Amyloid Precursor Protein Is Inhibited by Zinc in Alzheimer's Disease | Request PDF - ResearchGate, https://www.researchgate.net/publication/46148641_Iron-Export_Ferroxidase_Activity_of_b-Amyloid_Precursor_Protein_Is_Inhibited_by_Zinc_in_Alzheimer's_Disease 12. BACE1 is at the crossroad of a toxic vicious cycle involving cellular stress and β-amyloid production in Alzheimer's disease - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC3507664/ 13. Mechanisms of autophagy–lysosome dysfunction in neurodegenerative diseases - PMC, https://pmc.ncbi.nlm.nih.gov/articles/PMC12239022/ 14. Oxidative Stress and 4-hydroxy-2-nonenal (4-HNE): Implications in the Pathogenesis and Treatment of Aging-related Diseases - PMC, https://pmc.ncbi.nlm.nih.gov/articles/PMC8994689/ 15. Mitochondrial Dysfunction and Oxidative Stress in Alzheimer's Disease - PMC, https://pmc.ncbi.nlm.nih.gov/articles/PMC7930231/ 16. Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease - PMC - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC5409043/ 17. Mechanisms of autophagy-lysosome dysfunction in neurodegenerative diseases - PubMed, https://pubmed.ncbi.nlm.nih.gov/39107446/ 18. Ralph A. Nixon, MD, PhD - NYU Grossman School of Medicine, https://med.nyu.edu/faculty/ralph-a-nixon 19. Amyloid precursor protein and endosomal–lysosomal dysfunction in Alzheimer's disease: inseparable partners in a

multifactorial disease - PMC - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC6137496/ 20. Autophagy-lysosomal-associated neuronal death in neurodegenerative disease - PubMed, https://pubmed.ncbi.nlm.nih.gov/39259382/ 21. Mechanisms of autophagy–lysosome dysfunction in neurodegenerative diseases - Center for Dementia Research, https://www.cdr.rfmh.org/wp-content/uploads/2025/02/Nixon-2024-Nature-Review-MCB.pdf 22. Disorders of lysosomal acidification-The emerging role of v-ATPase in aging and neurodegenerative disease - ResearchGate, https://www.researchgate.net/publication/303293439_Disorders_of_lysosomal_acidification-The_emerging_role_of_v-ATPase_in_aging_and_neurodegenerative_disease 23. Disorders of lysosomal acidification - the emerging role of v-ATPase in aging and neurodegenerative disease - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC5112157/ 24. Autophagy failure in Alzheimer's disease and the role of defective lysosomal acidification | Request PDF - ResearchGate, https://www.researchgate.net/publication/239732953_Autophagy_failure_in_Alzheimer's_disease_and_the_role_of_defective_lysosomal_acidification 25. Lysosomal dysfunction in Down Syndrome and Alzheimer mouse models is caused by selective v-ATPase inhibition by Tyr682 phosphorylated APP βCTF | bioRxiv, https://www.biorxiv.org/content/10.1101/2022.06.02.494546v1.full 26. Lysosomal dysfunction in Down syndrome and Alzheimer mouse models is caused by v-ATPase inhibition by Tyr682-phosphorylated APP βCTF - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC10371027/ 27. Necrosis Links Neurodegeneration and Neuroinflammation in Neurodegenerative Disease - MDPI, https://www.mdpi.com/1422-0067/25/7/3636 28. NeuroVoices: Ralph Nixon, MD, PhD, on Autolysosome Acidification in Alzheimer Disease and Changing Perceptions of Amyloid ß | NeurologyLive, https://www.neurologylive.com/view/neurovoices-ralph-nixon-autolysosome-acidification-alzheimer-disease-and-changing-perceptions-amyloid- 29. Lysosomal Membrane Damage in Soluble Aβ-Mediated Cell Death in Alzheimer's Disease | Request PDF - ResearchGate, https://www.researchgate.net/publication/12168056_Lysosomal_Membrane_Damage_in_Soluble_Ab-Mediated_Cell_Death_in_Alzheimer's_Disease 30. 4-Hydroxynonenal from Mitochondrial and Dietary Sources Causes Lysosomal Cell Death for Lifestyle-Related Diseases - MDPI, https://www.mdpi.com/2072-6643/16/23/4171 31. Increased autophagic degradation of mitochondria in Alzheimer disease - PubMed, https://pubmed.ncbi.nlm.nih.gov/17786024/ 32. Increased Autophagic Degradation of Mitochondria in Alzheimer Disease, https://www.tandfonline.com/doi/pdf/10.4161/auto.4872 33. Autophagy and Alzheimer's Disease: Mechanisms and Impact Beyond the Brain - MDPI, https://www.mdpi.com/2073-4409/14/12/911 34. Increased Autophagic Degradation of Mitochondria in Alzheimer Disease - ResearchGate, https://www.researchgate.net/publication/6054545_Increased_Autophagic_Degradation_of_Mitochondria_in_Alzheimer_Disease 35. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances - PMC - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC7257174/ 36. Amyloid-β in Alzheimer's disease: the horse or the cart? Pathogenic or protective? - PMC, https://pmc.ncbi.nlm.nih.gov/articles/PMC2517413/ 37. What Causes Alzheimer's? Scientists Are Rethinking the Answer. - Quanta Magazine, https://www.quantamagazine.org/what-causes-alzheimers-scientists-are-rethinking-the-answer-20221208/ 38. Autophagy–lysosomal-associated neuronal death in neurodegenerative disease -

PMC, https://pmc.ncbi.nlm.nih.gov/articles/PMC11418399/ 39. Alzheimer's Disease: A Molecular View of β-Amyloid Induced Morbific Events - MDPI, https://www.mdpi.com/2227-9059/9/9/1126 40. Rethinking of Alzheimer's disease: Lysosomal overloading and dietary therapy - Frontiers, https://www.frontiersin.org/journals/aging-neuroscience/articles/10.3389/fnagi.2023.1130658/full 41. The emerging roles of vacuolar-type ATPase-dependent Lysosomal acidification in neurodegenerative diseases - PMC - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC7212675/ 42. Autophagocytosis of Mitochondria Is Prominent in Alzheimer Disease - ResearchGate, https://www.researchgate.net/publication/6287649_Autophagocytosis_of_Mitochondria_Is_Prominent_in_Alzheimer_Disease 43. Evidence that neurones accumulating amyloid can undergo lysis to form amyloid plaques in Alzheimer's disease | Request PDF - ResearchGate, https://www.researchgate.net/publication/12123111_Evidence_that_neurones_accumulating_amyloid_can_undergo_lysis_to_form_amyloid_plaques_in_Alzheimer's_disease 44. Insights into targeted ferroptosis in mechanisms, biology, and role of Alzheimer's disease: an update - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC12319056/ 45. Hsp70.1 carbonylation induces lysosomal cell death for lifestyle-related diseases - NIH, https://pmc.ncbi.nlm.nih.gov/articles/PMC9936620/ 46. Oxidative Stress and Transcriptional Regulation in Alzheimer's Disease - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC3109432/ 47. Dysregulation of Neuronal Iron Homeostasis as an Alternative Unifying Effect of Mutations Causing Familial Alzheimer's Disease - PMC, https://pmc.ncbi.nlm.nih.gov/articles/PMC6099262/ 48. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques - PubMed Central, https://pmc.ncbi.nlm.nih.gov/articles/PMC9174056/ 49. Thirty Years After the Launch of the Amyloid Cascade Hypothesis: Is there a Shift of Gears at Last? - ResearchGate, https://www.researchgate.net/publication/372360972_Thirty_Years_After_the_Launch_of_the_Amyloid_Cascade_Hypothesis_Is_there_a_Shift_of_Gears_at_Last