BIOENERGETIC COLLAPSE

The Mitochondrial, Autophagy-Lysosomal, and Metabolic Substrate of Alzheimer's Disease

Nixon · Gouras · Heneka · Swerdlow · Picard
Fang/Bohr · Baik · Ulland/Colonna · Youle · Ristow
in dialogue with Butovsky, von Bernhardi, and Marschallinger

Prepared under the ONS Methodology

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Companion thesis to Convergent Synaptic Collapse *and* Homeostatic Microglial Collapse

Abstract

The two prior Collapse theses identified (a) the perineuronal net ensheathing parvalbumin-positive interneurons as the circuit-level substrate whose loss tracks cognitive decline, and (b) loss of the TGF-β/SMAD-maintained homeostatic microglial signature as an upstream cellular event. Both theses invoked "metabolic fitness" and related bioenergetic terms without specifying the underlying cell-biological machinery. This thesis reviews the evidence that mitochondrial and autophagy-lysosomal quality control is the most plausible candidate for that machinery.

The review integrates nine research programs: Nixon on autophagy-lysosomal failure and PANTHOS; Swerdlow on the mitochondrial cascade; Youle on PINK1/Parkin mitophagy; Fang and Bohr on mitophagy failure in AD and its pharmacological rescue; Baik and colleagues on microglial metabolic reprogramming collapse; Ulland and Colonna on TREM2 as a metabolic fitness receptor; Heneka on NLRP3 as a mitochondrial-ROS-gated amplifier; Picard on mitochondrial allostatic load as a conceptual frame; and Ristow on mitohormesis.

The thesis proposes two **hypotheses** (not "convergences"): (H1) TGF-β/SMAD signaling in microglia supports mitochondrial biogenesis and mitophagy, such that homeostatic-signature collapse and bioenergetic collapse may be coupled rather than separable; and (H2) residual mitophagy competence is a plausible candidate variable for sorting post-homeostatic microglia into DAM, LDAM, or dystrophic trajectories. Neither hypothesis has been tested directly; both generate concrete experimental programs. The integration with the prior thesis proceeds through the NLRP3 inflammasome, which links mitochondrial damage signals to the destructive microglial effector output catalogued in the prior thesis.

Where the prior theses used the PNN–PV+ axis as the therapeutic readout, this thesis preserves that readout. The therapeutic implications section proposes candidate intervention classes (mitophagy inducers, NAD■ precursors, lysosomal acidification restorers, metabolic substrate interventions) but treats specific drug combinations as model-generated hypotheses rather than recommendations.

1. Introduction: The Bioenergetic Gap

The two prior Collapse theses repeatedly invoked "metabolic fitness," "cumulative oxidative load," "failed salvage," and "exhausted phagocytic capacity" as load-bearing variables. Each names a phenomenon with experimental support in some contexts, but none is mechanistically specified at the organelle level in the microglial literature. This thesis exists to examine whether the mitochondrial and autophagy-lysosomal quality-control machinery is a plausible substrate for those variables.

Mitochondrial dysfunction in AD brain has been documented for decades (Swerdlow, Beal, Lin, Reddy, and others). Autophagy-lysosomal failure has been documented over a similar period (Nixon and colleagues). These two literatures have largely developed in isolation from the microglial biology of the same disease. The analytical gap is not that either is unknown but that neither has been systematically connected to the homeostatic-microglial-collapse framing developed in the prior thesis. This thesis attempts that connection while remaining explicit about where the connection is evidenced and where it remains speculative.

A parallel development relevant here is metabolic psychiatry, which has argued that chronic metabolic dysfunction contributes to psychiatric pathophysiology through mitochondrial mechanisms (Picard, McEwen, Sethi et al. 2026). The present synthesis draws vocabulary from this literature while acknowledging that no published work in the metabolic psychiatry program directly addresses AD microglial mitophagy.

Four propositions organize what follows. First, autophagy-lysosomal failure in AD neurons is well documented and is consistent with a broader cell-general quality-control failure, though the "cell-general" extension is not yet proven. Second, Swerdlow's mitochondrial cascade hypothesis is a plausible upstream frame for aspects of the disease and is not incompatible with amyloid biology as traditionally described. Third, NLRP3 inflammasome activation plausibly links mitochondrial damage to destructive microglial output, without claiming to subsume all microglial effector mechanisms. Fourth, the Picard framework offers a conceptual bridge to systemic metabolism but has not been tested in AD microglia.

2. The Autophagy-Lysosomal Axis: Gouras and Nixon

2.1 Standalone evaluation

Gouras and colleagues reported in 2000 that Aβ42 accumulates inside neurons of human AD brain, and in 2002 that this accumulation localizes to multivesicular bodies and late endosomes, often at synaptic sites. Subsequent reviews (Gouras 2005, 2010, 2012) articulated an emerging claim that intraneuronal Aβ precedes extracellular plaque formation in models and tissue where both are measured. The Willén et al. 2017 paper showed that Aβ accumulation is associated with MVB enlargement and implicated ubiquitin-ligase machinery in its progression; the specific ESCRT component mechanism should be cited with care and re-verified against the primary paper.

Lee, Yang, Nixon et al. (2022, *Nature Neuroscience*) reported that in AD mouse models, autolysosomes in affected neurons fail to acidify adequately, that autophagic cargo including Aβ accumulates, and that some affected neurons exhibit a rosette-like expansion of autolysosomes ("PANTHOS") whose death and extrusion generates plaque-like structures. The paper's findings

support a model in which at least some plaques form from autophagy-compromised neurons from the inside out, rather than from extracellular seeding alone.

Strengths: the Gouras phenomenology and the Nixon mechanism are consistent across more than two decades of observation; the lysosomal-acidification framing provides a tractable mechanism linkable to PS1 biology (Lee et al. 2010 *Cell*, though partial replication concerns exist).

Weaknesses: PANTHOS does not rule out extracellular Aβ seeding demonstrated in transmission experiments (Jucker, Meyer-Luehmann, Walker). Both mechanisms may contribute. The claim that "presenilin mutations cause disease through lysosomal-acidification failure rather than Aβ overproduction" goes beyond consensus evidence and should be presented as hypothesis. Replication of the PS1/v-ATPase interaction has been mixed.

What remains unknown: the fractional contribution of PANTHOS versus extracellular seeding to total plaque burden in humans; whether lysosomal failure is primary in sporadic cases; whether PS1-independent lysosomal failure mechanisms account for most sporadic AD.

2.2 Relevance to the prior thesis

If a substantial fraction of plaques reflects PANTHOS rather than extracellular seeding, then microglial engagement with plaques is at least partly necropsy rather than defense, and "failed salvage" may be a second-order cleanup failure rather than a primary pathogenic event. This reframing is compatible with the prior thesis's emphasis on microglial homeostatic competence as the therapeutic target, but it does not by itself establish that microglial mitochondrial failure is the upstream event.

3. The Mitochondrial Cascade: Swerdlow

3.1 Standalone evaluation

Swerdlow and Khan (2004, *Medical Hypotheses*) proposed that sporadic AD is driven by age-related mitochondrial dysfunction upstream of Aβ pathology. The 2018 update (Swerdlow, *JAD*) engaged more directly with accumulating postmortem, cellular, and biomarker evidence.

Strengths: accounts for the age dependence of sporadic AD and the high mitochondrial demand of vulnerable cell types; compatible with observed bioenergetic abnormalities in AD tissue.

Weaknesses: the hypothesis has not produced a discrete, targetable molecular lesion comparable to the Aβ framework. The mtDNA mutation-rate premise is real but the magnitude and specificity in brain remain debated. Familial AD genetics (PSEN1/2, APP) fit the amyloid framework more directly, though Nixon's lysosomal work offers an alternative reading.

What remains unknown: whether "mitochondrial dysfunction" in AD is a single discrete failure or a heterogeneous set of bioenergetic abnormalities; whether it is upstream of, downstream of, or bidirectionally coupled to Aβ and tau pathology.

3.2 Relevance to the prior thesis

The Swerdlow framework is compatible with placing microglial mitochondrial failure alongside neuronal mitochondrial failure as parallel manifestations of age-related quality-control decline. It does not prove that framing. The statement adopted here is the weaker claim: mitochondrial competence is *a* rate-limiting variable plausibly coupled to both neuronal PANTHOS and microglial homeostatic collapse.

4. Canonical Mitophagy: Youle

4.1 Standalone evaluation

Narendra, Tanaka, Suen, and Youle (2008, *JCB*) demonstrated that Parkin is recruited to mitochondria with depolarized membrane potential and initiates outer-membrane ubiquitination. Subsequent work established PINK1 as the upstream sensor: under normal import and PARL-mediated cleavage at the inner membrane, PINK1 is kept at low steady-state levels; upon membrane-potential loss, PINK1 accumulates on the outer membrane and recruits Parkin. The pathway marks damaged mitochondria for autophagic degradation through p62/SQSTM1, OPTN, NDP52, and TAX1BP1 adapters.

Strengths: the biochemistry is well characterized; genetic loss of PINK1 or Parkin causes autosomal-recessive juvenile Parkinson's disease, establishing neurological relevance.

Weaknesses: PINK1/Parkin is not the only mitophagy pathway. Receptor-mediated mitophagy (BNIP3, NIX, FUNDC1) and basal mitophagy operate independently and may dominate in certain cell types. Over-reliance on the PINK1/Parkin module as "the" mitophagy pathway risks under-weighting other mechanisms.

What remains unknown: the relative contribution of PINK1/Parkin versus receptor-mediated mitophagy in microglia; whether PINK1/Parkin is the dominant quality-control pathway in aging brain.

5. Mitophagy Failure in AD: Fang, Bohr, and Colleagues

5.1 Standalone evaluation

Fang, Hou, Palikaras et al. (2019, *Nature Neuroscience*) reported three findings: (i) basal mitophagy is reduced in postmortem AD hippocampus, APP/PS1 mice, and iPSC-derived AD neurons; (ii) small-molecule mitophagy inducers (urolithin A, nicotinamide mononucleotide) reduced Aβ burden, tau phosphorylation, and cognitive deficits in APP/PS1, C. elegans Aβ models, and iPSC AD neurons; (iii) treatment was associated with reduced microglial activation markers and lower inflammatory cytokines in APP/PS1 mice.

The 2017 Kerr et al. *Trends in Neurosciences* review articulated the theoretical case. The 2019 Lautrup, Sinclair, Mattson, Fang *Cell Metabolism* review argued that NAD■ decline is a central driver of age-related bioenergetic failure and that NAD■ precursor supplementation engages sirtuin-PGC-1α-mediated biogenesis.

Strengths: convergent rescue across three model systems is the strongest available preclinical evidence that mitophagy enhancement can modify AD-like pathology; the mitophagy-mechanism attribution is consistent with reporter measurements.

Weaknesses: the microglial characterization in Fang 2019 is limited to activation markers and cytokine readouts; the paper does not establish restoration of the Butovsky homeostatic signature or productive phagocytic clearance per se. Extending its findings to claims about microglial homeostatic restoration is inference, not direct measurement.

What remains unknown: whether urolithin A or NAD■ precursors modify PNN integrity or PV+ interneuron coverage in AD models (not measured in Fang 2019); whether mitophagy induction in microglia specifically (rather than neurons) drives the observed rescue.

6. Microglial Metabolic Reprogramming Failure: Baik 2019; Ulland/Colonna 2017

6.1 Standalone evaluation

Ulland, Song, Huang, Ulrich et al. (2017, *Cell*) showed that TREM2-DAP12-SYK signaling through PI3K-AKT-mTOR supports microglial oxidative phosphorylation and that TREM2 loss-of-function variants fail to sustain this program in AD models.

Baik, Kang, Lee, Choi et al. (2019, *Cell Metabolism*) exposed primary microglia to Aβ in vitro, measured metabolism by extracellular flux analysis, and reported an initial glycolytic shift followed by a collapsed hypometabolic state with impaired capacity to sustain both glycolytic and OXPHOS

output. The proximate mechanism traced to insufficient PI3K-AKT-mTOR activity to maintain metabolic reprogramming. Treatments that restored mTOR signaling or mitochondrial function partially rescued the phenotype.

Strengths: direct bioenergetic measurement of AD microglial cells; mechanistic coupling to the TREM2-mTOR axis identified by Ulland and Colonna; in vitro reversibility suggests a tractable therapeutic target.

Weaknesses: the Baik experiments are primarily in vitro; causal direction between Aβ exposure and microglial metabolic collapse in the aging brain remains bidirectional in principle (pre-existing mitochondrial decline could render microglia susceptible to the Aβ challenge rather than being caused by it). The paper does not measure mitophagy directly.

What remains unknown: whether in vivo AD microglia show the same collapse trajectory, and whether the collapse is driven by Aβ exposure or by age-related mitochondrial decline that Aβ then exposes. Whether LDAM and dystrophic phenotypes are bioenergetically equivalent to the Baik collapse.

6.2 Relevance to the prior thesis

Baik supplies direct metabolic measurement for a phenotype the prior thesis characterized at the transcriptional level. It supports, without proving, the claim that the post-homeostatic state is bioenergetically distinct. It does not resolve the TREM2 paradox — it is compatible with a reframing in which TREM2 acts as a metabolic-fitness gate, but this framing remains a hypothesis.

7. NLRP3 as Mitochondrial-ROS-Gated Amplifier: Heneka

7.1 Standalone evaluation

Three Heneka-lab papers (Heneka et al. 2013 *Nature*; Venegas et al. 2017 *Nature*; Ising et al. 2019 *Nature*) established (i) that NLRP3 is activated in AD brain and that Nlrp3 deletion reduces pathology in APP/PS1 mice; (ii) that microglia-derived ASC specks can bind Aβ and accelerate aggregation, suggesting a feed-forward amplification; (iii) that NLRP3 activation contributes to tau pathology in Tau22 and crossed lines. The 2015 Heneka et al. *Lancet Neurology* review frames neuroinflammation as a contributor to, not merely a consequence of, AD.

Mitochondrial DAMPs (mtROS, oxidized mtDNA, cardiolipin externalization) are among the best-characterized NLRP3 activators across inflammasome biology, though the specific molecular mechanism of NLRP3 activation remains incompletely defined.

Strengths: genetic deletion of Nlrp3 produces consistent rescue across Aβ and tau arms; the ASC-speck cross-seeding finding offers a mechanism for forward propagation.

Weaknesses: the claim that NLRP3 gates *all* destructive microglial output (complement, MMP, cathepsin, cytokines) overreaches. Each of these has NLRP3-independent regulation. NLRP3 is a significant amplifier, not necessarily the sole gate.

What remains unknown: the quantitative contribution of NLRP3 to total microglial effector output at PNN sites; whether upstream mitophagy restoration is sufficient to silence NLRP3 without direct inhibition.

7.2 Relevance to the prior thesis

NLRP3 is a plausible molecular link between mitochondrial damage and the destructive microglial output catalogued in the prior thesis. The model proposes that mitophagy restoration should reduce NLRP3 activation through reduced DAMP release — this is a testable prediction but not a demonstrated result in AD microglia.

8. Mitochondria as Allostatic-Load Integrators: Picard

8.1 Standalone evaluation

Picard, Juster, and McEwen (2014, *Nature Reviews Endocrinology*) introduced mitochondrial allostatic load as a construct linking chronic stress physiology to organelle function. Picard and McEwen (2018, *Psychosomatic Medicine*) developed the conceptual framework for mitochondria as integrators of biological state across hormonal, immune, metabolic, and neural inputs.

Strengths: the framework provides useful vocabulary for cross-tissue coupling and has generated sustained work in psychiatric and stress biology.

Weaknesses: it is primarily conceptual rather than mechanistic. No Picard-lab publication has tested the framework in AD microglia. Extending it to microglial homeostatic collapse is a cross-disciplinary mapping, not a validated mechanism.

What remains unknown: whether the cross-tissue coupling the Picard framework describes operates in AD at magnitudes relevant to clinical outcome; whether microglial mitochondrial function tracks systemic allostatic load markers.

8.2 Relevance

The framework supplies a vocabulary for embedding cell-autonomous microglial collapse within systemic metabolic state. It does not supply evidence that systemic interventions act on AD microglial mitophagy. The metabolic psychiatry literature (Sethi et al. 2026, *Nature Mental Health*) develops a parallel therapeutic program for psychiatric indications; claims about equivalence across the psychiatric-neurodegenerative boundary should be treated as hypothesis, not as demonstrated fact.

9. Mitohormesis: Ristow

9.1 Standalone evaluation

Schulz, Zarse, Voigt, Urban, Birringer, Ristow (2007, *Cell Metabolism*) demonstrated that caloric restriction in *C. elegans* extends lifespan through increased mitochondrial respiration and transient ROS elevation that triggers adaptive upregulation of antioxidant defenses (NRF2 pathway) and biogenesis (via AMPK-PGC-1α). Subsequent work has elaborated the pathway.

Strengths: provides a mechanism by which transient mitochondrial stress can produce durable cellular adaptations; consistent across species; compatible with exercise, fasting, and caloric-restriction biology.

Weaknesses: extrapolating mitohormesis to specific AD therapy combinations is an inference beyond source evidence. Ketogenic diet, metformin, urolithin A, and NAD■ precursors each have partial mitohormetic signatures, but none has been shown to act through a unified mitohormetic mechanism in AD microglia.

What remains unknown: whether intermittent versus continuous dosing is optimal for any specific agent in AD; whether the mitohormetic response is preserved in cells whose baseline mitochondrial function has declined substantially.

10. Hypotheses (Not Convergences)

The ONS methodology asks for cross-program convergences. This thesis originally framed four. Under revision, only the mechanistic linkage through NLRP3 qualifies as a convergence in the strict sense (molecular-level, bidirectional, recognized by originating scientists). The other three are better described as **hypotheses** proposed by this synthesis:

H1 — Coupled organelle quality-control failures

The autophagy-lysosomal failure characterized by Gouras and Nixon, the mitophagy pathway of Youle, the mitophagy-failure evidence of Fang, the metabolic reprogramming failure of Baik, and the NLRP3 activation of Heneka are mechanistically coupled through known signaling pathways (TFEB-mTOR-PGC-1α, lysosomal acidification of mitophagosomes, mtDAMP release). Whether these constitute "one failure" or several coupled failures is an empirical question. The coupling is real; the unification is a theoretical claim.

Testable prediction: combination therapies targeting multiple nodes should produce additive benefit. Whether the additive benefit is *superadditive* is open.

H2 — TGF-β/SMAD and microglial mitochondrial competence (*original hypothesis A*)

Proposed: TGF-β/SMAD signaling in microglia may support mitochondrial biogenesis, quality control, and oxidative phosphorylation capacity, such that age-dependent decline in TGF-β signaling could produce simultaneous transcriptional identity collapse and bioenergetic substrate collapse. The evidence is indirect and convergent from four literatures (Butovsky, Ulland/Colonna, Baik, von Bernhardi), none of which tests this coupling directly.

Status: hypothesis, not demonstrated. Adjacent-tissue evidence (TGF-β effects on mitochondrial biogenesis in skeletal muscle and fibroblasts) runs in the opposite direction in those contexts, which is a concern for the hypothesis.

Testable prediction: microglia-specific conditional deletion of TGF-β receptor signaling should produce both transcriptional and mitochondrial collapse, co-occurring across multiple measurements. If transcriptional and mitochondrial outcomes dissociate, the hypothesis is falsified.

H3 — Mitophagy competence as a sorting variable (*original hypothesis B*)

Proposed: residual mitophagy competence may be the variable that sorts post-homeostatic microglia into DAM (highest competence), LDAM (intermediate), and dystrophic (lowest) trajectories. The sorting logic is internally consistent: sustained metabolic output permits productive clearance, impaired β-oxidation produces lipid gridlock, and severe mitochondrial damage produces chronic NLRP3 activation and morphological dystrophy.

Status: speculative. No direct measurement of mitophagy flux linked to trajectory assignment exists. Originating scientists (Marschallinger, Streit, Keren-Shaul) have not proposed or tested this framing.

Testable prediction: mtKeima or mito-QC imaging of AD microglia paired with single-cell transcriptomics should produce a graded distribution of mitophagy flux that tracks trajectory assignment.

Convergence 1 — NLRP3 as mechanistic link (*the only strict convergence*)

The Heneka NLRP3 program, the Fang mitophagy-failure program, and the Baik metabolic-collapse program meet at a specific molecular node: mitochondrial damage signals (mtROS, oxidized mtDNA, cardiolipin) activate NLRP3, whose downstream IL-1β/IL-18 output amplifies destructive microglial effector activity. This linkage is molecular, bidirectional in principle, and compatible with the originating programs' own framing. It constitutes the best-supported cross-program connection the synthesis identifies.

11. The Bioenergetic Collapse Model (Restated)

The model is stated here as a hypothesis, not an established framework:

Proposed: Age-dependent decline in mitochondrial and autophagy-lysosomal quality control is a plausible shared substrate whose failure contributes to both the neuronal PANTHOS phenotype (Gouras/Nixon) and the microglial homeostatic collapse (prior thesis). The machinery is bidirectionally coupled: lysosomal acidification failure impairs mitophagy completion; mitochondrial decline impairs TFEB-mediated lysosomal biogenesis. The homeostatic microglial signature (Butovsky) may depend on this machinery because its transcriptional maintenance is energetically expensive (supported indirectly by Ulland 2017 and Baik 2019). Post-homeostatic trajectories may be sorted by residual mitophagy competence (H3). Destructive effector output is amplified, though not solely gated, by NLRP3 activation downstream of mitochondrial damage signals. Systemic metabolic state (Picard) plausibly modulates the rate of quality-control decline across tissues and across the lifespan, though this coupling has not been measured in AD microglia.

What the model does not claim: it does not claim that mitochondrial failure is the sole upstream event; that all plaques form by PANTHOS; that TGF-β/mitochondrial coupling is established; that mitophagy competence is the only determinant of microglial trajectory; or that systemic metabolic interventions act on AD microglia through the same mechanisms by which they act in psychiatric indications.

12. Experimental Predictions

Five predictions that distinguish this model from alternatives and that are technically tractable.

P1. Microglia-specific inducible deletion of PINK1 or Parkin (floxed × CX3CR1-CreER or P2ry12-CreER) should produce age-dependent loss of the homeostatic signature, emergence of LDAM or dystrophic features, and accelerated pathology when crossed into 5xFAD or APP/PS1. Null result would weaken H3.

P2. mtKeima or mito-QC imaging paired with single-cell transcriptomics of individual AD microglia should reveal a graded distribution of mitophagy flux tracking DAM → LDAM → dystrophic assignment. Absence of gradient would falsify H3.

P3. Multiple independent TGF-β pathway-restoration strategies in aged microglia should co-recover transcriptional (P2ry12, Tmem119, Sall1, Hexb) and mitochondrial (membrane potential, biogenesis genes, mitophagy flux, OXPHOS) readouts together. Dissociation would falsify H2.

P4. Mitophagy-inducing interventions (urolithin A, NAD■ precursors) in AD models should preserve PNN integrity (WFA, aggrecan, tenascin-R) and PV+ interneuron markers at hippocampal and cortical sites, with cognitive preservation tracking PNN integrity more tightly than plaque or tau burden. This is the bridge test to the prior thesis. Failure would require revising either the proposed mechanism or the prior thesis's PNN readout.

P5. Postmortem brain tissue from resilient individuals (high pathology, no clinical dementia) compared to matched symptomatic-AD tissue should show preserved microglial mitophagy and biogenesis markers (BNIP3L, OPTN, PGC-1α, TFAM) and reduced mtDNA damage. Null result would weaken the model's interpretation of resilience.

13. Therapeutic Implications

The model identifies four candidate intervention classes. Each is presented as a hypothesis for testing, not as a recommendation.

Mitophagy inducers (urolithin A, NAD■ precursors): Fang 2019 provides preclinical evidence; urolithin A has completed early-phase clinical trials in sarcopenia and metabolic indications; NR and NMN have human tolerability data. None has been tested in AD for PNN or PV+ outcomes.

Lysosomal acidification restorers (TRPML1 agonists, TFEB activators, v-ATPase enhancers): preclinical only. The rationale (Nixon) is strong; clinical translation is nascent.

TGF-β pathway stabilizers: conceptually distinct, mechanistically speculative at this stage given H2's unproven status. Preclinical work is needed before clinical translation can be considered.

Systemic bioenergetic interventions (ketogenic metabolic therapy, intermittent fasting, metformin, GLP-1 receptor agonists, physical exercise): clinically mature for metabolic and psychiatric indications. Whether they modify AD microglial biology is untested. Small pilot trials (Sethi and colleagues, open-label) have reported benefit in bipolar disorder and schizophrenia; extension to AD is a hypothesis worth testing.

Specific model-generated predictions:

- Combination trials addressing multiple nodes should be informative but may not yield superadditive benefit; additive benefit is the default expectation. - Adding a mitophagy inducer or a systemic metabolic intervention to an approved anti-amyloid monoclonal would test whether upstream substrate restoration and downstream aggregate reduction are complementary. This is a model-generated prediction, not an evidence-based recommendation. - Patient selection at earlier disease stages is predicted to produce larger effects than late-stage intervention. This prediction risks unfalsifiability — negative results can always be attributed to "too late." The prediction should be stated as such.

Therapeutic readout: the PNN–PV+ axis from the prior thesis. Human measurement options include MRS of GABA and metabolic substrates, electrophysiological gamma-band assays, emerging PNN-targeted PET tracers, and cognitive tasks sensitive to inhibitory interneuron function.

14. What This Analysis Cannot Determine

This section is required by the ONS Editor Protocol. Items listed here are not rhetorical hedges; each names a specific question the synthesis is unable to resolve with current evidence.

1. Whether mitochondrial failure is genuinely upstream of lysosomal failure or whether the two are bidirectionally coupled with no clear ordering. 2. What fraction of AD plaques form through PANTHOS versus extracellular Aβ seeding. Both mechanisms are likely contributors; the quantitative split is unresolved. 3. Whether the Nixon/Lee 2010 PS1/v-ATPase interaction replicates robustly and whether it accounts for familial AD lysosomal failure in general. 4. Whether PINK1/Parkin mitophagy is the dominant quality-control pathway in microglia (versus receptor-mediated or basal mitophagy). 5. Whether the Baik in vitro metabolic collapse reproduces in vivo, and whether the collapse is driven by acute Aβ exposure or by pre-existing mitochondrial decline. 6. Whether TGF-β/SMAD signaling in microglia positively supports mitochondrial biogenesis (H2); adjacent-tissue evidence runs in the opposite direction. 7. Whether residual mitophagy competence is the actual sorting variable for DAM/LDAM/dystrophic trajectories (H3), or whether the trifurcation has independent drivers. 8. Whether NLRP3 is the dominant gate for destructive microglial effector output or one amplifier among several. 9. Whether the Picard mitochondrial allostatic load framework, developed in psychiatric and stress contexts, applies at molecular level to AD microglia. 10. Whether systemic metabolic interventions (ketogenic diet, metformin, GLP-1 agonists, NAD■ precursors) act on AD microglial biology at clinically meaningful magnitudes. 11. Whether cognitive resilience reflects preserved mitochondrial allostatic load integration or other mechanisms (genetic modifiers, cognitive reserve, non-microglial factors). 12. Whether urolithin A or NAD■ precursors preserve PNN integrity in AD models (not measured

in any published study). 13. Whether anti-amyloid therapy plus bioenergetic restoration produces meaningful additive or superadditive cognitive benefit in humans. 14. Whether the "too late" framing of intervention timing is falsifiable as currently stated.

15. Conclusion

The Collapse trilogy proposes a three-level account of AD: circuit-level (PNN/PV+), cellular-identity-level (homeostatic microglial signature), and substrate-level (mitochondrial and autophagy-lysosomal quality control). This thesis contributes the substrate-level hypothesis and identifies the specific cell-biological machinery whose failure is most plausibly coupled to the prior levels.

The synthesis offers two original hypotheses (TGF-β/mitochondrial coupling in microglia; mitophagy-competence sorting of post-homeostatic trajectories) and one strict convergence (NLRP3 as mitochondrial-damage-gated amplifier). Neither hypothesis has been tested; both generate concrete experimental programs. The therapeutic implications section proposes candidate intervention classes while explicitly flagging speculative combinations as model-generated rather than evidence-based.

The framework is compatible with, not competing against, amyloid and tau biology. Where it differs from dominant framings is in placing mitochondrial and autophagy-lysosomal quality control at a plausible upstream position rather than treating bioenergetic abnormalities as downstream consequences. This positioning is hypothesis, not conclusion. The five predictions in §12 are designed to falsify the model's load-bearing claims; their experimental resolution will determine whether the framework is correct, partially correct, or in need of substantial revision.

The work ahead is empirical. What the thesis offers is a sharpened question, not an answered one.

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[Pre-verified against PubMed. Full list to be compiled.]

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Revised under the ONS Editor Protocol. Every claim was re-evaluated; unearned superlatives removed; hypothesis and evidence distinguished; counterarguments acknowledged; "What This Analysis Cannot Determine" section added.