TERMINAL COLLAPSE

The Cell Death Modalities of Alzheimer's Disease and Their Convergence at the Perineuronal Net

Olney · Lipton · Hardingham · Maher · Bush · Nixon
Heneka · Stevens · Shatz · Yuan · Dawson
in dialogue with Butovsky, Crapser, de Vries, and the Collapse trilogy

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Companion to Convergent Synaptic Collapse, Homeostatic Microglial Collapse, *and* Bioenergetic Collapse

Abstract

The three prior Collapse theses identified a coherent pathological cascade in Alzheimer's disease: age-dependent loss of the TGF-β/SMAD-maintained homeostatic microglial signature produces post-homeostatic cells whose failed salvage attempts release effector enzymes that degrade perineuronal nets, exposing parvalbumin-positive fast-spiking interneurons whose subsequent loss disrupts excitation-inhibition balance and generates the cognitive phenotype of the disease. The bioenergetic thesis supplied the upstream substrate — mitochondrial and autophagy-lysosomal quality-control failure — whose collapse powers the entire cascade. What the trilogy does not specify is the final step: by what molecular mechanisms do exposed neurons actually die? The question is not academic. Each death modality responds to different therapeutic interventions, operates through different molecular machinery, and produces different secondary consequences for surrounding tissue. A framework that cannot name the death is a framework that cannot design the rescue.

This synthesis integrates the major characterized cell death mechanisms relevant to Alzheimer's disease — excitotoxicity, ferroptosis, PANTHOS, pyroptosis, phagoptosis, necroptosis, parthanatos, and Wallerian degeneration — and examines each for its mechanistic relationship to the PNN–PV+ axis that the prior theses identified as the critical circuit-level substrate. It also examines apoptosis, the death modality most frequently assumed but least convincingly demonstrated in the Alzheimer's brain, and cuproptosis, the most recently characterized mechanism whose relevance to AD remains preliminary.

The synthesis advances three claims. First, excitotoxicity — glutamate-mediated NMDA receptor hyperactivation producing calcium overload — is the single most consequential gap in the prior trilogy, because it is the oldest and most experimentally validated mechanism for the selective death of the specific cell type the trilogy identifies as circuit-critical: the parvalbumin-positive fast-spiking interneuron, whose high firing rate, extraordinary mitochondrial demand, and expression of calcium-permeable GluR2-lacking AMPA receptors render it uniquely vulnerable to excitotoxic insult, and whose perineuronal net provides precisely the diffusion barrier and iron-chelation capacity whose loss the trilogy's microglial mechanism produces. Second, ferroptosis — iron-dependent, lipid-peroxidation-driven cell death — represents the oxidative-damage gateway that determines whether the bioenergetic failures described in the prior thesis produce recoverable stress responses or irreversible cellular destruction, and the 4-hydroxynonenal-mediated poisoning of lysosomal V-ATPase provides a second, presenilin-independent entry point into the autophagy-lysosomal failure that Nixon characterized. Third, the multiple death modalities are not competing explanations but concurrent, cell-type-specific, and stage-dependent manifestations of the same upstream quality-control collapse, and their convergence at the perineuronal net — where microglial pyroptotic IL-1β release, complement-mediated phagoptotic engulfment, excitotoxic

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calcium overload, and ferroptotic lipid peroxidation all operate simultaneously on the same exposed substrate — produces a combinatorial lethality that no single-mechanism therapeutic can address.

The integrated model predicts that effective neuroprotection in Alzheimer's disease will require simultaneous engagement with multiple death pathways, that the PNN–PV+ axis remains the most informative readout of whether such engagement succeeds, and that the excitotoxicity literature — the oldest and most pharmacologically mature of the death-modality programs — has been systematically under-integrated into the microglial and bioenergetic framings that dominate the contemporary research landscape.

1. Introduction: The Death Modality Gap

The Collapse trilogy arrived at its explanatory endpoint — the loss of perineuronal net integrity around parvalbumin-positive interneurons — through a top-down analysis that traced the causal chain from microglial homeostatic collapse through effector enzyme release to matrix degradation. The final step in that chain, the one that converts matrix loss into cognitive decline, requires the death or functional silencing of the exposed PV+ interneuron. The prior theses treated this step as self-evident: once the PNN is degraded, the interneuron loses its iron-chelation shield, its diffusion barrier, its synaptic stabilization, and its oxidative protection, and it ceases to function. The mechanism of that cessation was left unnamed.

This omission was not an oversight of detail but a structural gap in the framework's explanatory architecture. Cell death in neurodegenerative disease is not a single event but a family of molecularly distinct programs, each with its own initiating signals, its own effector machinery, its own temporal dynamics, and its own consequences for the surrounding tissue. A neuron that dies by apoptosis is quietly dismantled and phagocytosed without inflammatory spillover. A neuron that dies by pyroptosis ruptures through gasdermin pores and releases IL-1β and IL-18 into the surrounding parenchyma, amplifying the inflammatory environment. A neuron that dies by ferroptosis propagates lipid peroxidation to adjacent cells through diffusible 4-hydroxynonenal. A neuron that dies by necroptosis activates a feed-forward inflammatory cascade through RIPK1/RIPK3/MLKL-mediated membrane disruption. A neuron that is eaten alive by complement-mediated phagoptosis is eliminated before it has died at all. Each of these outcomes produces different downstream consequences, responds to different therapeutic interventions, and implies different things about what went wrong upstream.

The Alzheimer's disease field has historically been vague about which of these death programs operates in the disease, in large part because the field's attention has been consumed by the question of what initiates pathology rather than by the question of what executes it. The amyloid cascade hypothesis names the initiating signal (Aβ accumulation) without specifying the death program it

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activates. The tau hypothesis names the propagating substrate (hyperphosphorylated tau) without specifying the lethal mechanism. The neuroinflammation hypothesis names the cellular context (activated microglia) without specifying the death modality their activation produces. Even the Collapse trilogy, which is substantially more mechanistically specific than these earlier frameworks, arrives at the vulnerable cell (the PV+ interneuron) and the vulnerable substrate (the degraded perineuronal net) without naming the molecular program by which the exposed cell is eliminated.

This thesis exists to fill that gap. It surveys the major characterized cell death mechanisms, evaluates the evidence for each in Alzheimer's disease, and asks a specific question of each: does this death modality operate at the PNN–PV+ axis that the prior theses identified as the critical circuit-level substrate? The answer, as will become clear, is that multiple death modalities converge on this axis simultaneously, and that their convergence is not coincidental but mechanistically entailed by the specific vulnerabilities of PV+ interneurons and by the specific consequences of perineuronal net degradation. The therapeutic implication is that single-target neuroprotective strategies will continue to fail because they address one death pathway while leaving the others operational, and that effective neuroprotection will require a combinatorial approach whose design depends on understanding which death modalities are active, in which cells, at which disease stages.

The order of treatment that follows reflects the strength of each mechanism's connection to the PNN–PV+ axis, beginning with the one whose absence from the trilogy is most consequential.

2. Excitotoxicity: The Oldest Answer to the Trilogy's Central Question

2.1 Historical foundations

The concept of excitotoxicity — neuronal death caused by excessive stimulation by excitatory amino acids — was established by John Olney in a series of experiments beginning in 1969 that demonstrated widespread neuronal loss in neonatal mouse brains following systemic administration of monosodium glutamate. Olney observed that the pattern of damage was not random but selectively affected neurons in regions where the blood-brain barrier was developmentally immature, and that the morphology of the dying cells was consistent with excessive excitatory stimulation rather than with metabolic poisoning or ischemia. In 1974, Olney coined the term "excitotoxic" to describe amino acids that exert their toxic effects through the same receptor mechanisms that mediate their excitatory physiological functions, establishing the principle that the neurotransmitter system most essential for normal brain function is also the one most capable of destroying it.

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The ionic and molecular basis of excitotoxicity was established through the work of Dennis Choi and Steve Rothman in the 1980s. Choi demonstrated that the lethal component of glutamate toxicity in cortical cultures depends on extracellular calcium and is mediated primarily through the NMDA subtype of glutamate receptor, whose channel is uniquely permeable to calcium ions and whose gating requires both glutamate binding and membrane depolarization sufficient to relieve the voltage-dependent magnesium block. Rothman contributed complementary evidence that NMDA receptor activation produces a delayed neuronal death whose time course and pharmacology are distinct from the immediate necrotic death produced by non-NMDA receptor agonists, establishing that excitotoxicity is not a single process but at least two: an acute component driven by osmotic swelling from sodium and chloride influx, and a delayed component driven by calcium overload through NMDA receptors.

2.2 The synaptic versus extrasynaptic distinction

The most consequential advance in excitotoxicity research since its founding came from the work of Giles Hardingham and colleagues, who demonstrated in a series of papers from 2002 onward that the biological consequences of NMDA receptor activation depend critically on the subcellular location of the activated receptor. Synaptic NMDA receptors — those located within the postsynaptic density and activated by phasic glutamate release during normal neurotransmission — couple to CREB phosphorylation, BDNF transcription, and a panel of pro-survival gene programs that build a neuroprotective shield. Extrasynaptic NMDA receptors — those located outside the synaptic cleft and activated by ambient or spillover glutamate — couple to CREB dephosphorylation, FOXO activation, mitochondrial depolarization, and cell death cascades. The two receptor pools use the same channel protein (GluN1/GluN2B heteromers predominate at both locations), but they are coupled to opposing intracellular signaling machinery through distinct scaffolding complexes.

This distinction transformed the excitotoxicity field because it resolved a long-standing paradox: how can glutamate, the brain's most essential neurotransmitter, also be its most potent neurotoxin? The answer is that glutamate is neuroprotective when it activates synaptic receptors in phasic, temporally precise patterns, and neurotoxic when it activates extrasynaptic receptors through tonic, spatially diffuse elevation. The pathological transition from neuroprotection to neurotoxicity is therefore not a matter of glutamate excess per se but of the redistribution of glutamate signaling from synaptic to extrasynaptic receptor pools — a redistribution that can be produced by impaired glutamate reuptake, by excessive ambient glutamate, or by the structural remodeling of the synaptic cleft that eliminates the diffusion barriers that normally restrict glutamate to its site of release.

2.3 Stuart Lipton and the memantine paradigm

Stuart Lipton's contribution to the excitotoxicity field has been both mechanistic and translational. His laboratory established that memantine, a low-affinity, uncompetitive NMDA receptor antagonist, preferentially blocks tonically activated extrasynaptic NMDA receptors while leaving phasic synaptic transmission relatively intact. The pharmacological basis for this selectivity is memantine's open-channel blocking mechanism combined with its rapid off-rate: the drug enters the NMDA receptor channel when it is held open by sustained glutamate exposure (as occurs at extrasynaptic receptors under pathological conditions) but is expelled from the channel by the strong, brief depolarizations that characterize normal synaptic transmission. This kinetic selectivity makes memantine a "pathologically activated therapeutic" — a drug that is activated by the very state it is designed to treat.

Memantine was approved for moderate-to-severe Alzheimer's disease in 2003 in Europe and 2004 in the United States. Its clinical efficacy is modest — producing detectable but limited symptomatic benefit without modifying disease trajectory — and this modesty has been interpreted by much of the field as evidence that excitotoxicity is a peripheral rather than central mechanism in Alzheimer's disease. The Homeostatic Collapse Model suggests an alternative interpretation. If memantine addresses the extrasynaptic NMDA receptor activation that is downstream of PNN degradation and PV+ interneuron exposure, but does not prevent the upstream microglial homeostatic collapse that produces PNN degradation in the first place, then its modest efficacy reflects not the irrelevance of excitotoxicity but the futility of addressing a downstream death pathway without controlling the upstream generator of vulnerability. The drug blocks one route by which exposed PV+ interneurons die without preventing their exposure.

Lipton extended the memantine platform with NitroSynapsin, a next-generation compound that combines memantine's NMDA channel-blocking activity with S-nitrosylation chemistry to provide additional neuroprotective effects. NitroSynapsin has shown disease-modifying activity in animal models of Alzheimer's disease, protecting synapses and improving neurobehavioral deficits in ways that memantine alone does not. The improvement over memantine is consistent with the prediction that addressing multiple aspects of the excitotoxic cascade — not just NMDA receptor overactivation but also the downstream nitrosative stress it generates — should produce benefit proportional to the number of death-pathway components engaged.

2.4 Why PV+ interneurons are uniquely vulnerable to excitotoxicity

The connection between excitotoxicity and the PNN–PV+ axis identified in the prior trilogy is not generic. It is the most specific and experimentally grounded of any connection this thesis will describe, and it arises from four features of PV+ interneuron biology that together create a cell type whose vulnerability to excitotoxic insult exceeds that of any other neuron in the cortex.

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First, PV+ interneurons are fast-spiking cells whose firing rates range from 30 to 150 Hz under normal operating conditions — an order of magnitude higher than the 1 to 10 Hz typical of pyramidal neurons. Each action potential requires Na+/K+-ATPase activity to restore ionic gradients, and each synaptic event requires calcium clearance from presynaptic terminals and postsynaptic densities. The ATP cost per unit time of PV+ interneuron maintenance is therefore among the highest of any cell in the brain, and the mitochondrial output required to sustain this cost places these cells at the upper boundary of their bioenergetic capacity under normal physiological conditions. Any additional metabolic demand — from increased excitatory drive, from loss of the PNN diffusion barrier, from ambient glutamate elevation — pushes PV+ interneurons past their mitochondrial ceiling faster than any other cortical cell type.

Second, PV+ interneurons in the hippocampus and neocortex express a distinctive AMPA receptor composition characterized by high GluR3 subunit expression and low or absent GluR2 subunit expression. The GluR2 subunit, when present, renders AMPA receptor channels impermeable to calcium through an RNA-editing mechanism that introduces a positively charged arginine at the channel pore. AMPA receptors lacking GluR2 are calcium-permeable, meaning that PV+ interneurons possess a second, NMDA-independent route for excitotoxic calcium entry that most pyramidal neurons lack. Under conditions of elevated ambient glutamate — precisely the conditions that PNN degradation produces by removing the diffusion barrier around the perisomatic membrane — calcium enters PV+ interneurons through both NMDA receptors and calcium-permeable AMPA receptors simultaneously, producing a calcium load that exceeds the capacity of any intracellular buffering system.

Third, parvalbumin itself is a calcium-binding protein whose physiological function is to buffer the rapid intracellular calcium transients produced by high-frequency firing. Each spike generates a calcium transient that parvalbumin binds and releases on a timescale matched to the interspike interval, preventing calcium accumulation in the cytoplasm and protecting the mitochondria from calcium overload. This buffering system is elegantly matched to the cell's normal operating parameters but has finite capacity. Under sustained excitotoxic conditions — where calcium entry through NMDA and calcium-permeable AMPA receptors exceeds the binding capacity of parvalbumin — the excess calcium is taken up by mitochondria, which serve as the secondary calcium sink. Mitochondrial calcium overload triggers the opening of the mitochondrial permeability transition pore, collapse of the mitochondrial membrane potential, cessation of ATP production, and release of cytochrome c and other pro-apoptotic factors. The transition from parvalbumin-buffered calcium handling to mitochondrial calcium overload is the molecular moment at which excitotoxic insult becomes excitotoxic death, and PV+ interneurons reach this moment faster than any other cortical neuron because their baseline calcium load is already the highest in the circuit.

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Fourth, the perineuronal net provides two specific protections against excitotoxic insult whose loss the Collapse trilogy's microglial mechanism directly produces. The polyanionic chondroitin sulfate proteoglycans that constitute the PNN create a diffusion barrier around the perisomatic membrane that restricts the access of ambient glutamate to perisomatic receptors. Under normal conditions, glutamate released at synaptic terminals is rapidly cleared by astrocytic glutamate transporters before it can diffuse to extrasynaptic receptors; the PNN provides an additional physical barrier that limits the spatial spread of any glutamate that escapes transporter clearance. When the PNN is degraded by microglial MMP-2, MMP-9, ADAMTS-4, and cathepsin-S — the specific effector enzymes catalogued in the Homeostatic Microglial Collapse thesis — this diffusion barrier is removed, and ambient glutamate gains unrestricted access to the perisomatic AMPA and NMDA receptors of the exposed PV+ interneuron. Simultaneously, the PNN's polyanionic character enables it to chelate redox-active iron through electrostatic binding, reducing the local Fenton-reaction potential and limiting the oxidative stress that the cell experiences. When the PNN is degraded, iron is released into the perisomatic space, Fenton chemistry generates hydroxyl radicals, and the oxidative insult combines with the excitotoxic calcium load to produce a dual assault that neither mechanism alone would be lethal enough to deliver.

The 2013 PNAS paper by Cabungcal, Steullet, Morishita, and colleagues demonstrated this relationship directly. Using enzymatic degradation of perineuronal nets in adult mouse cortex, they showed that PV+ interneurons whose PNNs had been removed became acutely vulnerable to oxidative stress that PV+ interneurons with intact PNNs survived. The experiment is the most direct available demonstration that the PNN is not merely a structural support but an active neuroprotective shield, and that its removal converts PV+ interneurons from resilient cells to vulnerable ones. The Collapse trilogy's microglial mechanism does precisely what the Cabungcal experiment does: it removes the PNN through enzymatic degradation. The death modality that follows is the one that the Cabungcal experiment predicts: oxidative and excitotoxic death of the now-unprotected cell.

2.5 The excitotoxic feed-forward loop

The most consequential feature of excitotoxicity at the PNN–PV+ axis is that it is self-amplifying. PV+ interneurons provide the principal perisomatic inhibition to pyramidal neurons in local cortical circuits. When PV+ interneurons die, inhibitory output to pyramidal neurons decreases. When inhibitory output decreases, pyramidal neuron firing rates increase. When pyramidal neuron firing rates increase, glutamate release increases. When glutamate release increases, the surviving PV+ interneurons — whose PNNs are also being degraded by the same microglial process — experience elevated excitatory drive that further taxes their already-compromised calcium handling and bioenergetic capacity. The result is a feed-forward excitotoxic cascade: PV+ interneuron death reduces inhibition, which increases excitation, which kills more PV+ interneurons, which further reduces inhibition. The cascade is self-sustaining once initiated and continues until the local PV+ interneuron population is eliminated or until the excitatory drive is reduced by other means.

This feed-forward loop explains a clinical observation that has been difficult to reconcile with purely amyloid-centric models of Alzheimer's disease: the occurrence of subclinical epileptiform activity in early AD. Network hyperexcitability, detectable as increased gamma-band power and subclinical seizure activity on EEG and MEG, has been documented in early-stage AD patients and in AD mouse models, and its onset correlates with cognitive decline more tightly than amyloid burden does. Within the excitotoxic framework, this hyperexcitability is the electrophysiological signature of the PV+ interneuron loss that the Collapse trilogy predicts: the circuit has lost its inhibitory brake, and the resulting hyperexcitation is both the consequence of PV+ death and the cause of further PV+ death. Verret, Mann, and colleagues demonstrated in a 2012 Cell paper that inhibitory interneuron deficits link altered network activity to cognitive dysfunction in an Alzheimer's model, and subsequent work has shown that early restoration of PV+ interneuron activity in AD mouse models prevents memory loss and network hyperexcitability, establishing that PV+ dysfunction is causal rather than merely correlational with cognitive decline.

The de Vries resilience finding, which the prior trilogy positioned as evidence of preserved microglial homeostasis, is equally interpretable as evidence of preserved excitation-inhibition balance. Resilient individuals, who carry symptomatic-level amyloid and tau pathology without cognitive decline, show preserved PNN integrity and PV+ interneuron coverage. Within the excitotoxic framework, this preservation means that the feed-forward excitotoxic loop was never initiated: the PNN was never degraded, the PV+ interneuron was never exposed, the excitotoxic vulnerability was never generated, the inhibitory output was never compromised, and the network hyperexcitability that drives cognitive decline never developed. Resilience is the absence of the excitotoxic cascade, not merely the absence of amyloid toxicity.

2.6 Integration with the Moosmann excitatory insufficiency framework

The ONS knowledge base contains a sophisticated treatment of excitatory signaling through Bernd Moosmann's excitatory insufficiency hypothesis, which proposes that NMDA receptor hypofunction — not hyperactivation — is the upstream driver, with Aβ serving as a compensatory glutamatergic sensitizer at picomolar concentrations. This framework and the classic excitotoxicity framework are not contradictory. They describe sequential phases of the same degenerative process.

In the early, compensatory phase that Moosmann describes, age-related decline in NMDA receptor function produces excitatory insufficiency that Aβ partially compensates through glutamatergic sensitization. This phase is characterized by preserved circuit function maintained through a fragile compensatory equilibrium. In the saturation phase, the compensatory glutamate upregulation overshoots or the clearance mechanisms that normally restrict glutamate to the synaptic cleft begin to fail — a failure that PNN degradation directly accelerates by removing the perisomatic diffusion barrier. Ambient glutamate rises, extrasynaptic NMDA receptors are engaged, and the Hardingham switch flips from survival signaling (synaptic CREB activation) to death signaling (extrasynaptic CREB shutoff, FOXO activation). In the excitotoxic phase, the feed-forward loop described above initiates and becomes self-sustaining. The Moosmann framework explains why the brain produces Aβ; the excitotoxic framework explains what happens when the compensation fails. The transition from one to the other is precisely the event that PNN degradation precipitates by removing the diffusion barrier that keeps compensatory glutamate within its synaptic boundaries.

This sequential framing also explains the clinical failure of memantine to modify disease course. Memantine blocks extrasynaptic NMDA receptors but does not restore the PNN, does not reverse microglial homeostatic collapse, and does not address the other death modalities (ferroptosis, pyroptosis, phagoptosis) that operate simultaneously at the exposed PV+ interneuron. It is a partial intervention against one downstream pathway in a system where multiple pathways are active and the upstream generator is untouched. The modest clinical benefit it provides is the expected benefit of blocking one channel in a multi-channel death.

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3. Ferroptosis: The Oxidative Gateway

3.1 The Maher program: Oxytosis and the glutathione axis

Pamela Maher's research program, developed principally at the Salk Institute, established the oxytosis/ferroptosis pathway as a distinct cell death mechanism characterized by the depletion of glutathione through inhibition of the cystine/glutamate antiporter System Xc-, which leads to inactivation of glutathione peroxidase 4 (GPX4), which permits uncontrolled lipid peroxidation of polyunsaturated fatty acid-containing membrane phospholipids, which generates the toxic aldehyde 4-hydroxynonenal (4-HNE), which propagates damage to adjacent membrane compartments and to intracellular organelles.

The significance of Maher's work for the Collapse trilogy is concentrated in a single biochemical finding: 4-HNE covalently modifies and inhibits the V-ATPase proton pump that maintains lysosomal acidification. This finding provides a second, presenilin-independent entry point into the autophagy-lysosomal failure that Nixon characterized as the generator of PANTHOS. Nixon's work established that presenilin mutations impair V-ATPase assembly and therefore lysosomal acidification as the mechanistic basis of familial AD. Maher's work establishes that oxidative membrane damage, acting through the lipid peroxidation product 4-HNE, impairs V-ATPase function through a completely independent mechanism. The two entry points converge on the same organelle, produce the same functional consequence (lysosomal acidification failure), and generate the same downstream pathology (autophagic cargo accumulation, PANTHOS). That the #1 familial genetic driver (presenilin) and the dominant age-related biochemical process (lipid peroxidation) both converge on V-ATPase inhibition through independent mechanisms is among the strongest evidence that lysosomal acidification failure is the mechanistic core of the disease rather than one of many contributing pathways.

Maher's discovery of geroneuroprotective compounds — most notably J147 and CMS121 — provides pharmacological validation of the ferroptotic pathway's relevance. Both compounds work through Nrf2-AMPK-mTOR signaling to restore antioxidant gene expression and protect against glutathione depletion. Their efficacy in aging and AD models demonstrates that the ferroptotic pathway is both active and therapeutically tractable.

3.2 The Bush program: Iron accumulation and the ferroptosis theory

Ashley Bush's research program has developed the most comprehensive account of iron-dependent neurodegeneration in Alzheimer's disease. The central empirical observation is that brain iron accumulates with age, that this accumulation is accelerated in AD-vulnerable regions, and that the accumulated iron drives Fenton chemistry ($Fe^{2+} + H_2O_2 \rightarrow$ hydroxyl radicals + $Fe^{3+} + OH^-$) whose products attack polyunsaturated fatty acids in neuronal and microglial membranes, initiating the lipid peroxidation cascade that Maher characterized from the glutathione side.

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Bush's most provocative contribution is the reframing of amyloid plaques and neurofibrillary tangles as compensatory sinks for toxic lipid aldehydes and redox-active iron. On this reading, Aβ aggregation and tau hyperphosphorylation are not pathogenic events but protective responses that sequester the products of ferroptotic damage, and the removal of these aggregates without addressing the underlying ferroptotic process may paradoxically worsen outcomes by eliminating the sink while leaving the toxin source intact. This prediction received striking support from Bush's deferiprone trial, in which simple iron chelation — removing iron from the brain without restoring the iron-handling machinery that normally prevents its toxic accumulation — worsened AD outcomes rather than improving them. The result demonstrates that brain iron has essential functions (in myelination, mitochondrial function, ferroportin-mediated iron export) that crude chelation disrupts, and that the therapeutic target is not iron removal but ferroptosis inhibition — the prevention of the oxidative cascade that iron accumulation triggers, without disturbing iron's physiological roles.

Bush has further proposed that familial AD presenilin mutations impair anti-ferroptotic defenses through a Presenilin-Notch-LRP8-GPX4 signaling axis, providing a genetic link between the familial AD architecture and the ferroptotic death pathway. If correct, this means that presenilin mutations impair neuroprotection through two parallel mechanisms: V-ATPase assembly disruption (Nixon's mechanism, producing PANTHOS) and GPX4 signaling disruption (Bush's mechanism, producing ferroptosis). Both mechanisms are active in familial AD; in sporadic AD, where presenilin function is intact, the ferroptotic pathway is driven by age-dependent iron accumulation and glutathione depletion rather than by genetic disruption of the anti-ferroptotic axis.

3.3 Ferroptosis at the PNN–PV+ axis

The connection between ferroptosis and the PNN–PV+ axis is direct and has been hiding in plain sight throughout the prior trilogy. The perineuronal net's polyanionic chondroitin sulfate proteoglycans chelate redox-active iron through electrostatic binding, maintaining a low-iron microenvironment around the ensheathed PV+ interneuron. When the PNN is degraded by post-homeostatic microglial effector enzymes, the iron-chelation capacity is lost, free iron is released into the perisomatic space, and Fenton chemistry begins. The hydroxyl radicals generated attack the PUFA-rich membranes of the PV+ interneuron — whose membrane composition is enriched in docosahexaenoic acid and arachidonic acid to support the rapid ion channel kinetics required for fast spiking — and initiate the lipid peroxidation cascade whose 4-HNE product both damages the cell directly and poisons the V-ATPase in any surviving lysosomal compartments.

The PV+ interneuron is thus vulnerable to ferroptosis for the same reason it is vulnerable to excitotoxicity: its extreme metabolic demands produce high baseline ROS, its membrane composition is rich in oxidizable PUFAs, and its perineuronal net is the specific structure whose loss exposes it to the initiating insult. The Collapse trilogy described the PNN as protecting the PV+

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interneuron from oxidative damage in general terms. The ferroptosis literature supplies the specific molecular mechanism: the PNN chelates the iron whose liberation would drive lipid peroxidation of the PV+ interneuron's PUFA-rich membranes.

3.4 GPX4 as the gating variable

Maher and Bush's work converges on a single molecular gatekeeper: GPX4, the selenoprotein that reduces lipid hydroperoxides to their corresponding alcohols, preventing the propagation of lipid peroxidation through membrane compartments. As long as GPX4 is functional and supplied with glutathione as its reducing substrate, lipid peroxidation is contained and does not propagate. When GPX4 is depleted — by glutathione depletion (System Xc- inhibition), by selenium deficiency, by genetic disruption, or by the covalent modification that 4-HNE itself produces — lipid peroxidation becomes self-propagating and ferroptotic death follows.

This gating function has a critical implication for the Bioenergetic Collapse thesis. That thesis proposed, via the Ristow mitohormesis framework, that transient mitochondrial stress can produce adaptive upregulation of antioxidant defenses through the Nrf2 pathway. The ferroptosis literature reveals the condition under which mitohormesis fails: if GPX4 and glutathione are already depleted, the transient stress cannot be buffered, the adaptive response cannot be mounted, and the stress produces irreversible ferroptotic damage instead of hormetic adaptation. GPX4/glutathione status is therefore the variable that determines whether a cell responds to mitochondrial stress with adaptation or with death — the switch between the Ristow mitohormetic pathway and the Maher ferroptotic pathway.

4. PANTHOS: Death by Failed Autophagy

The PANTHOS mechanism — death through autophagy-lysosomal failure producing intracellular Aβ accumulation, organelle expansion, and inside-out plaque formation — was treated at length in the Bioenergetic Collapse thesis as the neuronal endpoint of the quality-control cascade. Its inclusion here serves to position it within the family of death modalities rather than to repeat the mechanistic analysis.

PANTHOS is distinguished from the other death modalities in this synthesis by a specific feature: it is not a death program initiated by a specific molecular trigger but the consequence of the absence of a protective process. The cell does not die because a death pathway was activated; it dies because the quality-control pathway that would have prevented cargo accumulation has failed, and the accumulating cargo eventually overwhelms the cell. This makes PANTHOS the "passive" death modality in the synthesis — the death that happens when nothing else works — and it distinguishes it from the "active" modalities (excitotoxicity, ferroptosis, pyroptosis, necroptosis) in which specific

molecular programs execute the cell.

The distinction matters therapeutically. Active death modalities can be blocked pharmacologically by inhibiting their effector machinery: memantine blocks excitotoxic NMDA receptor overactivation, GPX4 activation blocks ferroptotic lipid peroxidation, gasdermin inhibitors block pyroptotic membrane rupture, RIPK1 inhibitors block necroptotic execution. PANTHOS cannot be blocked in the same way because there is no effector to inhibit — the death results from the absence of lysosomal function, not from the presence of a death signal. The therapeutic response to PANTHOS must therefore be restorative rather than inhibitory: lysosomal acidification must be reinstated (through V-ATPase restoration, TFEB activation, or autophagosome-closure repair via the BIN1-ESCRT-III axis identified by Rubinsztein) rather than blocked.

At the PNN–PV+ axis specifically, PANTHOS is less directly relevant than excitotoxicity and ferroptosis because PV+ interneurons, which are GABAergic cells with relatively low Aβ production compared to glutamatergic pyramidal neurons, are less likely to accumulate the intraneuronal Aβ burden that drives the PANTHOS phenotype. PANTHOS is predominantly a death modality of pyramidal neurons and other glutamatergic cell types whose APP expression and Aβ generation are highest. The PV+ interneuron is more likely to die by the death modalities that are inflicted upon it from outside (excitotoxicity from elevated ambient glutamate, ferroptosis from released iron, phagoptosis from complement-tagged engulfment) than by the death modality that arises from within (PANTHOS from intracellular cargo accumulation). This cell-type specificity is an important feature of the integrated model: not all death modalities operate equally in all cells, and the PV+ interneuron's death is predominantly a consequence of its environment rather than of its own proteostasis failure.

5. Pyroptosis: The Inflammatory Execution

5.1 The Heneka NLRP3 program

Michael Heneka's research program established the NLRP3 inflammasome as a central mediator of the neuroinflammatory contribution to Alzheimer's disease through three landmark papers. The 2013 Nature paper demonstrated that NLRP3 is activated in AD brain and that Nlrp3 genetic deletion reduces pathology in APP/PS1 mice. The 2017 Nature paper by Venegas and colleagues showed that microglia-derived ASC specks — the oligomeric aggregates of the adaptor protein ASC that are released when pyroptotic cells rupture — can bind Aβ fibrils and accelerate their aggregation, establishing a feed-forward amplification loop in which inflammasome activation generates the seeds for further amyloid aggregation. The 2019 Nature paper by Ising and colleagues extended the framework to tau pathology, demonstrating that NLRP3 activation contributes to tau hyperphosphorylation and that the inflammasome therefore sits at the intersection of both hallmark pathologies.

The pyroptotic death pathway proceeds through NLRP3 inflammasome assembly → caspase-1 activation → gasdermin-D cleavage → gasdermin-D N-terminal fragment insertion into the plasma membrane → pore formation → osmotic swelling → membrane rupture → release of IL-1β, IL-18, ASC specks, and intracellular contents. The death is inflammatory by definition: the pore formation that kills the cell simultaneously releases the cytokines and damage-associated molecular patterns that activate surrounding cells and amplify the inflammatory environment.

5.2 Pyroptosis at the PNN–PV+ axis

The connection between pyroptosis and the PNN–PV+ axis is indirect but mechanistically significant. Pyroptosis operates primarily in microglia and potentially in astrocytes, not in neurons — although recent evidence suggests that neurons can also undergo pyroptotic death under some conditions. The microglial pyroptotic output most relevant to the PNN–PV+ axis is the release of IL-1β and IL-18 through gasdermin pores, which produces two downstream effects.

First, IL-1β upregulates MMP expression in surrounding cells (including other microglia and astrocytes), amplifying the enzymatic degradation of perineuronal nets that the Homeostatic Collapse thesis identified as the mechanistic link between microglial dysfunction and PV+ interneuron vulnerability. Second, IL-1β enhances glutamatergic neurotransmission through multiple mechanisms including upregulation of AMPA receptor surface expression, inhibition of astrocytic glutamate transporter function, and potentiation of NMDA receptor currents. Each of these effects increases the excitotoxic load on PV+ interneurons whose PNNs are being simultaneously degraded, creating a combinatorial assault in which pyroptotic IL-1β release both accelerates PNN degradation and amplifies the excitotoxic insult that the degradation exposes the cell to.

The Bioenergetic Collapse thesis positioned NLRP3 as the mitochondrial-ROS-gated amplifier through which failed salvage becomes destructive effector output. This thesis extends that positioning to identify the specific death modality that NLRP3 activation produces (pyroptosis) and the specific secondary consequences of that death for the PNN–PV+ axis (MMP amplification and excitotoxic potentiation).

5.3 The mitochondrial DAMP trigger

The activation of NLRP3 is not spontaneous. It requires priming (through NF-κB-mediated upregulation of NLRP3 and pro-IL-1β) and activation (through a second signal that triggers inflammasome assembly). The most well-characterized activation signals in the microglial context are mitochondrial damage-associated molecular patterns: mitochondrial ROS, oxidized mitochondrial DNA released into the cytosol, and externalized cardiolipin from damaged inner mitochondrial membranes. Each of these signals is produced when mitophagy fails and damaged mitochondria accumulate — precisely the condition that the Bioenergetic Collapse thesis described as the upstream substrate.

The causal chain is therefore: mitophagy failure → damaged mitochondria accumulate → mtROS, oxidized mtDNA, and cardiolipin externalization → NLRP3 activation → caspase-1 → gasdermin-D pore formation → IL-1β/IL-18 release → MMP upregulation + excitotoxic potentiation → PNN degradation + enhanced glutamate signaling → PV+ interneuron excitotoxic vulnerability. Pyroptosis is the molecular bridge between the bioenergetic failure described in the third thesis and the circuit-level consequences described in the first, operating through the microglial cell biology described in the second. It is the only death modality in this synthesis that mechanistically connects all three prior theses in a single causal chain.

6. Phagoptosis: Death by Engulfment

6.1 Complement-mediated elimination of live neurons

Phagoptosis — the phagocytic engulfment and elimination of viable cells — was identified as a microglial effector mechanism in the Convergent Synaptic Collapse thesis through the work of Beth Stevens and colleagues on complement-mediated synaptic pruning. The Stevens program demonstrated that C1q and C3 tag synapses for microglial engulfment through complement receptor 3 (CR3/CD11b), that this pathway is developmental in origin (mediating critical-period synaptic refinement), and that it is pathologically reactivated in AD models to drive early synaptic loss. The Shatz program identified a parallel pathway through C4d binding to LilrB2/PirB receptors on postsynaptic terminals, triggering a cell-autonomous spine withdrawal that operates independently of microglial engulfment.

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The distinction between phagoptosis and the other death modalities in this synthesis is categorical. In excitotoxicity, ferroptosis, pyroptosis, necroptosis, and parthanatos, the neuron dies from an intrinsic molecular program and is subsequently cleared by phagocytic cells. In phagoptosis, the neuron is eliminated by phagocytic engulfment while it is still alive and potentially salvageable. The complement tag that marks it for elimination is deposited on its surface by the innate immune system, and the decision to eliminate it is made by the engulfing microglial cell, not by the neuron itself. Phagoptosis is therefore the only death modality in this synthesis in which the cell does not die by its own hand but is killed by its neighbor.

6.2 Phagoptosis at the PNN–PV+ axis

The relevance of phagoptosis to the PNN–PV+ axis operates through a specific mechanism: the perineuronal net may serve as a physical barrier to complement deposition on the PV+ interneuron surface. The dense proteoglycan matrix that enwraps the perisomatic membrane of PV+ interneurons restricts access not only of glutamate to receptors (the excitotoxic protection described above) but also of complement components to the neuronal membrane. When the PNN is degraded, the neuronal surface becomes accessible to C1q, C3, and C4d deposition, and the complement tags that initiate phagoptotic engulfment can be placed. An exposed PV+ interneuron is therefore simultaneously vulnerable to excitotoxic death from glutamate access, ferroptotic death from iron release, and phagoptotic death from complement deposition — three independent death pathways all gated by the same upstream event (PNN degradation) and all operating concurrently on the same cell.

The temporal dynamics of phagoptosis are important. Complement-mediated synaptic pruning in AD models is detectable before plaque formation, suggesting that complement deposition on vulnerable synapses is among the earliest pathological events in the disease. If PNN degradation begins early — as a consequence of the gradual microglial homeostatic collapse that the prior thesis describes — then phagoptotic elimination of PV+ interneuron synapses may precede the excitotoxic and ferroptotic death of the same cells, producing functional silencing of PV+ circuits before the interneurons themselves are killed. This sequence — synaptic elimination first, somatic death later — is consistent with the clinical observation that cognitive decline in AD begins with synaptic dysfunction and progresses to neuronal loss, and it suggests that phagoptosis may be the earliest death modality to operate at the PNN–PV+ axis.

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7. Necroptosis: Programmed Necrosis

7.1 The RIPK1/RIPK3/MLKL pathway

Necroptosis is a regulated form of necrotic cell death mediated by the kinases RIPK1 and RIPK3 and the pseudokinase MLKL. The pathway is activated when death receptor signaling (through TNF-α, TRAIL, or FasL) proceeds in the context of caspase-8 inhibition, redirecting the cell from apoptosis to necroptosis. RIPK1 phosphorylates RIPK3, which phosphorylates MLKL, which oligomerizes and inserts into the plasma membrane to form pores that rupture the cell, releasing intracellular contents and damage-associated molecular patterns.

The foundational cell biology of necroptosis was established through the work of multiple laboratories, with Junying Yuan at Harvard contributing critically to the understanding of RIPK1's role in neurodegeneration. Yuan's laboratory demonstrated that RIPK1 kinase activity is elevated in human AD brain, that RIPK1 inhibition reduces neuroinflammation in AD mouse models, and that the RIPK1-RIPK3-MLKL axis represents a therapeutically tractable target for neuroprotection. RIPK1 inhibitors have entered clinical development for neurodegenerative indications, representing one of the most pharmacologically advanced death-pathway-targeted therapeutic programs in the field.

7.2 Necroptosis in Alzheimer's disease

The evidence for necroptosis in AD is substantial and growing. Elevated RIPK1, RIPK3, and phospho-MLKL have been detected in human AD brain tissue, particularly in regions of active neurodegeneration. TNF-α, the principal upstream activator of the necroptotic pathway, is among the most consistently elevated cytokines in AD brain and cerebrospinal fluid. And the conditions that promote necroptosis over apoptosis — chronic inflammatory signaling combined with impaired caspase-8 function — are precisely the conditions that prevail in the aged, neuroinflamed AD brain.

Necroptosis is inflammatory by nature: the membrane rupture that constitutes the death releases intracellular contents that activate surrounding microglia and astrocytes, amplifying the inflammatory environment. In this respect, necroptosis and pyroptosis produce similar secondary consequences despite proceeding through different molecular machinery. The practical distinction is that necroptosis is primarily a neuronal death pathway activated by microglial TNF-α release, while pyroptosis is primarily a microglial death pathway whose inflammatory output damages neurons secondarily. Both contribute to the self-amplifying inflammatory cascade, and both are therapeutically targetable through distinct pharmacological interventions (RIPK1 inhibitors for necroptosis, NLRP3 inhibitors for pyroptosis).

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7.3 Necroptosis at the PNN–PV+ axis

The specific relevance of necroptosis to PV+ interneuron death has not been experimentally tested. The prediction from the integrated model is that PV+ interneurons exposed by PNN degradation to the TNF-α-rich inflammatory environment produced by post-homeostatic microglia should be susceptible to necroptotic death through TNF receptor activation. Whether this susceptibility is greater or lesser than their susceptibility to excitotoxic or ferroptotic death is an empirical question that the model cannot currently resolve. What the model does predict is that RIPK1 inhibition alone will be insufficient to prevent PV+ interneuron loss because the other death modalities (excitotoxicity, ferroptosis, phagoptosis) will continue to operate on the same exposed cells.

8. Parthanatos: The NAD+ Catastrophe

8.1 PARP-1 hyperactivation

Parthanatos is a cell death pathway mediated by hyperactivation of poly(ADP-ribose) polymerase 1 (PARP-1), a nuclear enzyme that detects and initiates repair of single-strand DNA breaks. Under conditions of massive DNA damage — such as that produced by oxidative stress from Fenton chemistry, by excitotoxic calcium-activated endonucleases, or by mitochondrial ROS — PARP-1 activity increases dramatically, consuming NAD+ as a substrate for poly(ADP-ribose) polymer synthesis. The resulting NAD+ depletion collapses the cellular energy economy because NAD+ is required for glycolysis, the tricarboxylic acid cycle, and mitochondrial oxidative phosphorylation. The depleted cell cannot produce ATP, its ion gradients collapse, and it dies.

The foundational work on parthanatos as a distinct death pathway was contributed by Ted Dawson and Valina Dawson at Johns Hopkins, who identified the pathway through which PARP-1 hyperactivation leads to the nuclear translocation of apoptosis-inducing factor (AIF) from mitochondria, producing a chromatinolysis that is morphologically and biochemically distinct from apoptotic DNA fragmentation.

8.2 The connection to the Bioenergetic Collapse thesis

Parthanatos connects to the Collapse trilogy through a specific biochemical node: NAD+ depletion. The Bioenergetic Collapse thesis, through the Fang/Bohr program, identified NAD+ decline as a central driver of age-related bioenergetic failure and NAD+ precursor supplementation (nicotinamide riboside, nicotinamide mononucleotide) as a promising therapeutic strategy for AD. What the Bioenergetic thesis did not specify is the mechanism by which NAD+ is depleted in the AD brain. Parthanatos supplies one such mechanism: PARP-1 hyperactivation driven by the oxidative DNA damage that Fenton chemistry and mitochondrial ROS produce.

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The causal chain is: iron release (from PNN degradation) + mitochondrial ROS (from quality-control failure) → oxidative DNA damage → PARP-1 hyperactivation → NAD+ depletion → energy collapse → cell death. This chain reveals that NAD+ depletion is not merely a background age-related process but an active death pathway whose rate is accelerated by the specific molecular events that the Collapse trilogy describes. NAD+ precursor therapy, on this reading, is not merely a substrate-restoration strategy but a parthanatos-prevention strategy, and its efficacy should be greatest in cells experiencing the highest oxidative DNA damage load — which, for the reasons described in the excitotoxicity and ferroptosis sections, are the PV+ interneurons whose PNNs have been degraded.

9. Wallerian Degeneration: Axonal Self-Destruction

9.1 The SARM1 pathway

Wallerian degeneration is the programmed self-destruction of axons distal to a site of injury or metabolic failure. The central executioner of Wallerian degeneration is SARM1 (sterile alpha and TIR motif-containing 1), an NAD+ hydrolase that, when activated, cleaves NAD+ to produce nicotinamide and cyclic ADP-ribose, collapsing the axonal NAD+ pool and triggering rapid axonal fragmentation. SARM1 is normally maintained in an inactive state by the NAD+ biosynthetic enzyme NMNAT2, whose continuous supply of NAD+ keeps SARM1's autoinhibitory domain engaged. When NMNAT2 delivery is interrupted — by axonal transport failure, by metabolic stress, or by the depletion of the NAD+ pool that NMNAT2 requires as substrate — SARM1 becomes active and destroys the axon.

9.2 Wallerian degeneration in Alzheimer's disease

Axonal degeneration is among the earliest neuropathological features of Alzheimer's disease. Dystrophic neurites — swollen, fragmented axonal segments — are a defining feature of AD neuropathology that precedes somatic neuronal death in many brain regions. The SARM1 pathway provides a molecular mechanism for this axonal degeneration: axonal transport failure (produced by tau hyperphosphorylation, by mitochondrial dysfunction along the axon, or by the loss of trophic support from demyelinating oligodendrocytes) interrupts NMNAT2 delivery to the distal axon, SARM1 activates, NAD+ is destroyed, and the axon degenerates.

The connection to parthanatos is through NAD+: both pathways destroy NAD+, one in the soma (PARP-1) and one in the axon (SARM1), and both are activated by the same upstream events (oxidative stress, energy failure). The connection to the PNN–PV+ axis is through the inhibitory axonal arbor of the PV+ interneuron, which provides perisomatic inhibition to hundreds of pyramidal neurons through extensive axonal branching. If the PV+ interneuron's axon degenerates through the SARM1 pathway before the soma dies through excitotoxicity or ferroptosis, the

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functional consequence — loss of inhibitory output — is the same. Wallerian degeneration may therefore contribute to the excitotoxic feed-forward loop not by killing PV+ interneurons outright but by silencing their inhibitory output through axonal destruction, which reduces inhibition and increases excitation even while the soma is still alive.

10. Apoptosis: The Dog That Didn't Bark

Apoptosis — caspase-mediated programmed cell death proceeding through either the intrinsic (mitochondrial cytochrome-c/Apaf-1/caspase-9) or extrinsic (death receptor/caspase-8) pathway — is the cell death mechanism most frequently assumed to operate in Alzheimer's disease and the one for which the evidence is, paradoxically, least convincing.

The expectation that apoptosis should be the dominant death modality in AD arose from the general association of apoptosis with programmed cell death in disease and from the observation that caspase activation, cytochrome-c release, and TUNEL-positive nuclei can be detected in AD brain tissue. However, the quantitative evidence has never matched the expectation. The fraction of neurons showing definitive apoptotic morphology (chromatin condensation, nuclear fragmentation, apoptotic body formation) in AD tissue is vanishingly small — far too small to account for the magnitude of neuronal loss observed over the disease course. The TUNEL-positive nuclei that were initially interpreted as apoptotic may reflect DNA damage from other sources (oxidative damage, PARP-1 activation, necroptotic chromatinolysis). And the caspase activation detected in AD tissue may reflect non-lethal caspase functions, including the caspase-mediated cleavage of tau that produces neurotoxic tau fragments without proceeding to apoptotic execution.

The most informative feature of apoptosis for the integrated model is its relative absence. Apoptosis is immunologically silent: apoptotic cells expose phosphatidylserine as an "eat me" signal, are phagocytosed by surrounding cells before membrane integrity is lost, and do not release inflammatory intracellular contents. If apoptosis were the dominant death modality in AD, the neuroinflammatory component of the disease would be minimal. The fact that neuroinflammation is among the most prominent and consistent features of AD pathology is itself evidence that the dominant death modalities are inflammatory — pyroptosis, necroptosis, and the failed phagocytic attempts that the Homeostatic Collapse thesis catalogued — rather than immunologically silent. The dog that didn't bark, in this case, is the anti-inflammatory death program that would have prevented the neuroinflammation the field has spent decades studying.

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11. Cuproptosis: The Newest Entry

Cuproptosis — copper-dependent cell death mediated by copper binding to lipoylated mitochondrial enzymes, producing proteotoxic stress and cell death — was characterized in 2022 and represents the most recently identified cell death mechanism with potential relevance to neurodegeneration. Copper dysregulation has been documented in AD brain (elevated copper in senile plaques, altered ceruloplasmin and ATP7B expression), and the mitochondrial proteins targeted by cuproptosis (dihydrolipoamide S-acetyltransferase, DLAT, a component of the pyruvate dehydrogenase complex) are among those whose dysfunction has been documented in AD tissue.

The evidence for cuproptosis as a significant contributor to neuronal death in AD is preliminary. No studies have demonstrated cuproptotic death in neurons in vivo in AD models, and the pathway's relevance may be limited to specific cell populations with high copper exposure. Its inclusion here is for completeness and to flag it as an area where future evidence may alter the landscape. At present, the death modalities with established relevance to the PNN–PV+ axis — excitotoxicity, ferroptosis, pyroptosis, phagoptosis — are far better supported.

12. Convergences: Where the Death Modalities Meet

12.1 The PNN as the master vulnerability switch

The single most important insight of this synthesis is that the perineuronal net functions as a multi-modal neuroprotective shield whose degradation simultaneously exposes the PV+ interneuron to every death modality described above. The PNN is not merely a structural scaffold. It is:

- A **glutamate diffusion barrier** whose loss exposes perisomatic NMDA and calcium-permeable AMPA receptors to ambient glutamate, enabling excitotoxic death. - An **iron chelator** whose loss releases redox-active iron into the perisomatic space, enabling ferroptotic death through Fenton chemistry and lipid peroxidation. - A **complement access barrier** whose loss exposes the neuronal surface to C1q, C3, and C4d deposition, enabling phagoptotic elimination. - A **cytokine diffusion buffer** whose loss allows direct IL-1β and TNF-α access to neuronal receptors, potentiating pyroptosis-adjacent inflammatory signaling and necroptotic TNF receptor activation. - An **oxidative shield** whose polyanionic matrix scavenges reactive oxygen species and limits the oxidative potential of the perisomatic microenvironment, whose loss accelerates every oxidative death pathway simultaneously.

No other structure in the brain serves as the convergent protection against this many independent death modalities simultaneously. This is why PNN integrity, as the prior theses argued, is the most informative readout of therapeutic success: a preserved PNN indicates that none of the death modalities have been activated at that site, while a degraded PNN indicates that all of them may be.

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12.2 Temporal ordering of death modalities

The death modalities do not operate simultaneously from disease onset. The integrated model predicts a temporal ordering:

Phase 1 — Synaptic elimination (phagoptosis): Complement deposition on PV+ interneuron synapses begins as microglial homeostasis declines and complement-mediated pruning reactivates. Synaptic contacts are eliminated while the soma is still viable. Circuit dysfunction begins before neuronal death.

Phase 2 — Axonal silencing (Wallerian degeneration): Axonal transport failure, driven by tau hyperphosphorylation and metabolic stress, activates SARM1 in the PV+ interneuron axon. Inhibitory output is further reduced without somatic death.

Phase 3 — PNN degradation (microglial effector release): Post-homeostatic microglia release MMP-2, MMP-9, ADAMTS-4, and cathepsin-S, degrading the perineuronal net and exposing the PV+ interneuron to multiple death modalities simultaneously.

Phase 4 — Combinatorial death (excitotoxicity + ferroptosis + inflammatory potentiation): The exposed PV+ interneuron faces excitotoxic calcium overload through de-shielded receptors, ferroptotic lipid peroxidation from released iron, IL-1β-potentiated glutamatergic signaling from microglial pyroptotic output, and TNF-α-mediated necroptotic signaling. These pathways operate concurrently, and the cell likely dies from their combination rather than from any single one.

Phase 5 — Cascade amplification: PV+ interneuron death reduces inhibitory output, increasing network excitability, which increases glutamate release, which accelerates excitotoxic death of remaining PV+ interneurons. Simultaneously, the inflammatory death of PV+ interneurons (through necroptotic or secondary necrotic mechanisms) releases intracellular contents that further activate surrounding microglia, amplifying the post-homeostatic microglial response and accelerating PNN degradation at adjacent sites. The cascade becomes self-sustaining.

Phase 6 — Pyramidal neuron death (PANTHOS + secondary excitotoxicity): With the inhibitory brake removed, pyramidal neurons face sustained hyperexcitation. Those whose autophagy-lysosomal capacity has been compromised (by presenilin-mediated V-ATPase failure, by 4-HNE-mediated V-ATPase poisoning, or by BIN1-mediated autophagosome closure failure) undergo PANTHOS. Others die through the same excitotoxic and ferroptotic mechanisms that killed the PV+ interneurons, but at a slower rate because their baseline metabolic demand is lower and their AMPA receptors are GluR2-containing and therefore calcium-impermeable.

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12.3 The NAD+ convergence

A striking feature of the death modality landscape is that three independent pathways converge on NAD+ depletion as their lethal mechanism or accelerating factor:

- **Parthanatos** depletes somatic NAD+ through PARP-1 hyperactivation driven by oxidative DNA damage. - **Wallerian degeneration** depletes axonal NAD+ through SARM1 hydrolytic activity when NMNAT2 delivery fails. - **Bioenergetic collapse** depletes cellular NAD+ through the age-related decline in NAD+ biosynthetic capacity that the Fang/Bohr program documented.

All three pathways are accelerated by the specific events the Collapse trilogy describes (oxidative stress from PNN loss, axonal transport failure from tau pathology, mitochondrial quality-control failure from age-dependent mitophagy decline), and all three are potentially addressable by NAD+ precursor supplementation. The convergence of three independent death pathways on a single depletable substrate (NAD+) explains the broad therapeutic potential of NAD+ precursors and predicts that their efficacy should be measured not only by bioenergetic readouts but by death-pathway-specific endpoints (PARP-1 activity, SARM1 activation, axonal integrity).

12.4 The ferroptosis-excitotoxicity amplification loop

Ferroptosis and excitotoxicity are not merely concurrent but mutually amplifying at the PNN–PV+ axis. Excitotoxic calcium overload increases mitochondrial ROS production (through mitochondrial calcium overload and electron transport chain disruption), which initiates lipid peroxidation (the ferroptotic entry point). Lipid peroxidation damages mitochondrial inner membranes, further reducing the mitochondrial calcium buffering capacity that is the PV+ interneuron's last defense against excitotoxic death. Simultaneously, 4-HNE produced by lipid peroxidation poisons V-ATPase, impairing the lysosomal degradation of damaged mitochondria (preventing mitophagic clearance), and PARP-1 hyperactivation from oxidative DNA damage depletes the NAD+ required for both energy production and SIRT1-mediated antioxidant gene expression. The result is a death spiral in which excitotoxicity drives ferroptosis, ferroptosis impairs the mitochondrial and lysosomal systems that would otherwise contain excitotoxic damage, and the two pathways escalate each other until the cell is destroyed.

This amplification loop is the molecular content of what the prior theses called "failed salvage." A post-homeostatic microglial cell that releases effector enzymes at the PNN does not merely produce matrix degradation; it initiates a coupled excitotoxic-ferroptotic cascade in the exposed PV+ interneuron that is self-amplifying and irreversible once the cell's antioxidant and calcium-buffering capacities are exceeded. The GPX4/glutathione status of the PV+ interneuron determines how quickly this threshold is reached, which is why the Maher program's identification of GPX4 as the ferroptotic gatekeeper is not merely a finding about lipid peroxidation but a finding about the threshold at which excitotoxic-ferroptotic coupling becomes lethal.

13. The Integrated Model: Terminal Collapse at the Perineuronal Net

The integrated model may now be stated. Alzheimer's disease produces neuronal death through multiple concurrent, mechanistically distinct cell death pathways whose convergence at the perineuronal net–parvalbumin interneuron axis generates the circuit-level dysfunction that constitutes the cognitive phenotype of the disease. The convergence is not coincidental but mechanistically entailed: the perineuronal net is the single structure whose integrity simultaneously gates excitotoxic vulnerability (through its glutamate diffusion barrier function), ferroptotic vulnerability (through its iron-chelation function), phagoptotic vulnerability (through its complement-access-barrier function), and inflammatory vulnerability (through its cytokine-diffusion-buffer function). The degradation of the PNN by post-homeostatic microglial effector enzymes is therefore not merely a structural event but a multi-modal vulnerability event that simultaneously exposes the ensheathed PV+ interneuron to every characterized death pathway relevant to Alzheimer's disease.

The death modalities operate in a predicted temporal sequence — phagoptotic synaptic elimination, then Wallerian axonal silencing, then PNN degradation, then combinatorial somatic death through coupled excitotoxic-ferroptotic cascades amplified by pyroptotic and necroptotic inflammatory signaling — whose progression from functional impairment to neuronal loss matches the clinical progression of Alzheimer's disease from mild cognitive impairment to dementia.

The model resolves the longstanding question of why single-target neuroprotective strategies have consistently failed in Alzheimer's disease clinical trials. Memantine addresses excitotoxicity but not ferroptosis, phagoptosis, or pyroptosis. Anti-inflammatory agents address the inflammatory amplification but not the excitotoxic or ferroptotic death pathways. Complement inhibitors address phagoptosis but not the other death modalities. Each intervention captures one death pathway while the others continue to operate, and the net neuroprotective effect is therefore modest at best and unmeasurable at worst. Effective neuroprotection, the model predicts, will require simultaneous engagement with multiple death pathways — which in turn requires the upstream intervention that prevents the PNN degradation generating vulnerability to all of them simultaneously: the restoration of microglial homeostasis that the prior trilogy identified as the master therapeutic target.

The perineuronal net remains, as the prior theses argued, the most informative readout of whether a given intervention succeeds at the level that matters. A preserved PNN indicates that the multi-modal death cascade was never initiated. A degraded PNN with preserved PV+ interneurons indicates that the death pathways were pharmacologically blocked despite ongoing vulnerability. A degraded PNN with PV+ interneuron loss indicates that the intervention failed. The hierarchy of

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therapeutic ambition is therefore: homeostatic restoration (prevents PNN degradation, addresses all death pathways simultaneously) > PNN preservation (prevents vulnerability to all death pathways) > multi-modal death pathway inhibition (blocks death despite ongoing vulnerability) > single-pathway inhibition (blocks one death modality, others continue).

14. Therapeutic Implications

The integrated death-modality model generates specific therapeutic predictions that extend the Collapse trilogy's therapeutic framework.

Multi-modal neuroprotective combinations. The model predicts that combinations addressing multiple death pathways simultaneously should produce superadditive benefit relative to single-pathway interventions. The most pharmacologically mature combination would pair memantine (excitotoxicity) with a GPX4 activator or glutathione precursor (ferroptosis) and a RIPK1 inhibitor (necroptosis), with the rationale that all three death pathways converge on the exposed PV+ interneuron after PNN degradation. Whether this combination should be administered alongside or instead of anti-amyloid therapy depends on whether the amyloid-as-compensatory-sink hypothesis (Bush) is correct — if it is, amyloid removal without ferroptosis inhibition may worsen outcomes.

NAD+ precursor therapy as multi-pathway intervention. The convergence of parthanatos, Wallerian degeneration, and bioenergetic collapse on NAD+ depletion suggests that NAD+ precursor supplementation (NR, NMN) addresses three death pathways through a single substrate, making it the most efficient multi-target intervention currently available. The model predicts that NAD+ precursors should preserve axonal integrity (through SARM1 suppression), reduce somatic parthanatos (through PARP-1 substrate provision), and sustain mitochondrial function (through bioenergetic substrate provision) — three distinct endpoints measurable in the same clinical trial.

Ferroptosis inhibition as a gating intervention. The identification of GPX4/glutathione as the switch between recoverable stress and irreversible death suggests that ferroptosis inhibition should be administered before or concurrently with any intervention that increases mitochondrial stress (including mitohormetic interventions). Without intact GPX4, the transient ROS elevation that mitohormesis requires cannot be contained, and the intervention produces ferroptotic death rather than adaptive upregulation.

Memantine reconsidered. The model predicts that memantine's clinical efficacy should be substantially greater when combined with PNN-preserving interventions than when administered alone. The failure of memantine to modify disease course reflects not the irrelevance of excitotoxicity but the continued generation of vulnerability through PNN degradation. Block the

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death pathway and the vulnerability pathway simultaneously, and the benefit should be greater than either alone.

Patient stratification by death-pathway biomarkers. Different patients at different disease stages may have different dominant death pathways, and therapeutic selection should reflect this. Biomarkers of ferroptotic activity (4-HNE, oxidized phospholipid species), excitotoxic activity (glutamate levels in CSF, gamma-band hyperexcitability on EEG), necroptotic activity (phospho-MLKL), and parthanatos activity (poly-ADP-ribose levels) could in principle be used to identify which death pathways are most active in a given patient and to select the combination most likely to provide benefit.

15. Conclusion

The Collapse trilogy described the upstream cascade — microglial homeostatic collapse, effector enzyme release, perineuronal net degradation — and identified the vulnerable cell (the PV+ interneuron) and the vulnerable substrate (the degraded PNN). This thesis supplies the final step: the molecular mechanisms by which the exposed cell actually dies. The answer is not one mechanism but many, operating concurrently and synergistically, each contributing to and amplifying the others.

Excitotoxicity is the most consequential gap the thesis fills, because it is the oldest, most pharmacologically mature, and most experimentally validated mechanism for the selective death of the specific cell type the trilogy identifies as circuit-critical. The PV+ interneuron's unique biophysical properties — its extreme firing rate, its calcium-permeable AMPA receptors, its dependence on parvalbumin calcium buffering, and its reliance on the perineuronal net for glutamate diffusion restriction — render it maximally vulnerable to excitotoxic insult following PNN loss. Ferroptosis is the second most consequential gap, because it supplies the oxidative-damage gateway that determines whether stress produces adaptation or death, and because the 4-HNE-mediated V-ATPase poisoning it produces provides a presenilin-independent entry point into the autophagy-lysosomal failure at the center of the Bioenergetic Collapse thesis.

The convergence of multiple death modalities at the PNN–PV+ axis is the deepest structural finding of this synthesis. The perineuronal net is not merely a scaffold but a multi-modal neuroprotective shield whose degradation simultaneously initiates excitotoxic, ferroptotic, phagoptotic, and inflammatory death cascades in the ensheathed cell. This convergence explains why single-target neuroprotective strategies fail (they address one pathway while others operate), why the PNN is the most informative therapeutic readout (its integrity indicates that no death pathways are active), and why upstream homeostatic restoration remains the master therapeutic target (it prevents the PNN degradation that generates vulnerability to all death pathways simultaneously).

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The Collapse trilogy described how the brain's myeloid immune system turns against its most metabolically demanding circuits. This thesis describes how those circuits die when the immune system succeeds. The two accounts are one story, and the story ends not with a single death but with a convergent, self-amplifying, multi-modal execution whose prevention requires the same thing the trilogy has argued from its first page: the restoration of the homeostatic state whose collapse set the entire cascade in motion.

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Prepared under the Organic Network Synthesis methodology as a companion analysis to the Collapse trilogy. This work identifies the cell death modalities that execute the terminal step of the pathological cascade the trilogy describes, and argues that their convergence at the perineuronal net is the mechanistic basis for the multi-modal vulnerability of the PV+ interneuron in Alzheimer's disease.

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