ONE SENSOR, TWO COLLAPSES

The Aggregative and Proteolytic Arms of the Microglial NLRP3 Inflammasome in Alzheimer's Disease — A Graded Adjudication

The Shared Root · The Aggregative Arm · The Proteolytic Arm
The Pincer on Tau · The Weighing · The Grades of the Evidence

A Capstone Adjudication Prepared under the Organic Network Synthesis Methodology

AdultCognitiveDisease.com

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The synthesis that stands over The Sensor and the Speck and The Net and the Speck: one inflammasome, two effector arms — one building pathological protein, one dismantling protective matrix — placed in a single frame, weighed, and graded on one scale.

"One activation, two destructions. The inflammasome matures a single cytokine, and the cytokine goes two ways at once — to build the aggregate and to dissolve the shield. To ask which of the two matters more is to ask which blade of the scissors does the cutting."

— ONS Methodology Working Notes, 2026

For Michael Heneka and Kim Green, whose laboratories built the two arms of this argument — for the most part without citing one another.

A CAPSTONE THE ADJUDICATION OF TWO ARMS

The papers this volume weighs against each other:

The Sensor and the Speck — the aggregative arm

the inflammasome that seeds amyloid and relays tau

The Net and the Speck — the proteolytic arm

the inflammasome that strips the perineuronal net

This volume — One Sensor, Two Collapses the weighing of both

The two prior papers looked incompatible — one a story of building pathological protein, the other of tearing down protective structure — because they followed one sensor into two literatures that do not cite each other. This volume shows they are two branches of one node: it places both in a single frame, maps how they interact (the pincer on tau, the shared phenotype axis, the cross-amplification), weighs their relative importance under three distinct lenses, and grades the evidence for every arc of both on one explicit scale.

Contents

Abstract

Two prior papers of this corpus traced the microglial NLRP3 inflammasome down two different roads. *The Sensor and the Speck* followed it into the proteinopathy of Alzheimer's disease: the inflammasome as the innate-immune amplifier that seeds amyloid-β through the released ASC speck, relays the injury to tau, and impairs the clearance of the amyloid that activated it. *The Net and the Speck* followed the same sensor into the extracellular matrix: the inflammasome as the engine that, through interleukin-1β, induces the aggrecanases that strip the perineuronal net from the parvalbumin interneuron. Read side by side, the two papers seemed mechanistically far apart — one a story of aggregation and accumulation, the other of proteolysis and dissolution — and the question arose whether they were even compatible. This paper answers that they are not merely compatible but two branches of a single trunk, and it does the work the two prior papers left undone: it places both pathways in one frame, maps their relationship, weighs their relative importance, and grades the evidence for every arc of both on a single explicit scale.

The unifying observation is simple and, at the level of basic inflammasome biology, uncontested: a microglion activates its NLRP3 inflammasome once, but the output of that single activation — mature interleukin-1β and interleukin-18, the released ASC speck, the gasdermin-D pore — is pleiotropic, and it drives two distinct effector programmes at the same time. The *aggregative arm* (Branch A) builds pathological protein: the speck cross-seeds amyloid, interleukin-1β shifts neuronal tau kinases toward hyperphosphorylation, and inflammasome activity suppresses the microglial phagocytosis that would clear the aggregate. The *proteolytic arm* (Branch B) dismantles protective structure: interleukin-1β, by the best-characterised cytokine-to-protease mechanism in matrix biology, induces the ADAMTS aggrecanases and matrix metalloproteinases that cleave the aggrecan core of the perineuronal net, exposing the parvalbumin interneuron the net had shielded. The two arms are not independent. They are co-secreted from one activation; they converge on tau from opposite directions — Branch A building the seed, Branch B removing the net's tau-exclusion barrier, a pincer on the same protein; they share a single microglial phenotype axis, on which inflammasome activation simultaneously lowers phagocytic clearance and raises secretory proteolysis; and Branch B's degradation products feed back to re-prime the inflammasome that drives Branch A.

The adjudication is deliberately layered, because the honest answer to "which arm matters more" has more than one part. By weight of evidence, Branch A is materially stronger: its spine — amyloid activates NLRP3, genetic deletion of the sensor rescues amyloid mice, the pathway is engaged in the human brain — reaches the highest grade this paper awards, while Branch B's decisive steps in the Alzheimer brain reach only the middle grades and its central loop is, as yet, conjecture. But evidence weight is not disease importance, and the paper refuses to conflate them: Branch B acts directly on the parvalbumin interneuron, network inhibition, and the tau-permissiveness that track cognition more tightly than amyloid burden does, so its *potential*

proximity to the cognitive endpoint may exceed its *demonstrated* standing — the best-lit arm is not certainly the most important one. The practical resolution is that the two arms share the druggable node, so that a single selective inflammasome inhibitor interdicts both, and the relative-importance question converts from a debate to be settled in advance into an empirical readout of whether such an inhibitor's benefit tracks the proteinopathy, the matrix, or both. The paper closes with the discriminating experiments that would move the ranking, and with the standing concession both prior papers share: that the inflammasome, on either arm, is an amplifier and not the initiator of a disease that begins upstream of it.

Keywords: NLRP3 inflammasome, interleukin-1β, ASC speck, aggrecanase, ADAMTS-4, perineuronal net, tau, amyloid-β, parvalbumin interneuron, pyroptosis, microglia, evidence grading, mechanistic adjudication, neuroinflammation, Alzheimer's disease

1. Introduction

1.1 The Problem: Two Pathways, One Node

This corpus has produced two accounts of the microglial NLRP3 inflammasome in Alzheimer's disease, and they do not obviously belong to the same organism. The first, *The Sensor and the Speck*, is an account of proteinopathy: the inflammasome reads aggregated amyloid-β as a danger signal, matures interleukin-1β and interleukin-18 through caspase-1, disgorges the ASC speck that cross-seeds further amyloid, relays the injury to tau, and, by suppressing the phagocytic phenotype of the microglion, impairs the clearance of the amyloid it senses. Its verdict is that the inflammasome is a validated amplifier of the amyloid–tau proteinopathy. The second, *The Net and the Speck*, is an account of proteolysis: the same inflammasome, through the same interleukin-1β, induces the aggrecan-specific ADAMTS proteases and the matrix metalloproteinases that cleave the perineuronal net, stripping the parvalbumin interneuron of the extracellular shield on which its survival depends. Its verdict is that the inflammasome is the specific molecular engine of the "microglial activation" that the perineuronal-net literature had left as a placeholder.

Placed together, the two accounts create a genuine perplexity, and this paper begins from it rather than around it. One account is about the brain accumulating too much of the wrong protein; the other is about the brain losing a protective structure. One is a story of building up, the other of tearing down. The literatures they draw on scarcely cite one another — the amyloid-and-tau inflammasome literature of Heneka, Latz, and Golenbock on one side, the extracellular-matrix literature of Crapser, Fawcett, and the cartilage biologists on the other — and the two papers, written faithful to their separate sources, inherited that separation. The reasonable reader is entitled to ask whether the two mechanisms are even compatible, and, if they are, which of them is the more

important, and how much of either is actually known rather than surmised. This paper exists to answer those three questions in order: whether, how much, and which.

1.2 The Apparent Incompatibility and Its Dissolution

The apparent incompatibility dissolves at the first mechanistic step, and the dissolution is the premise of everything that follows. The two arms are not two hypotheses competing to explain one fact; they are two consequences of one node. A microglion activates its NLRP3 inflammasome once — through the assembly of the sensor, the nucleation of ASC, and the autoactivation of caspase-1 — but the products of that single activation are several, and they are pleiotropic. Mature interleukin-1β is not a single-purpose molecule; it is among the most broadly acting cytokines in the body, and its transcriptional programme, run through the interleukin-1 receptor and NF-κB, includes both the suppression of reparative microglial phenotypes and the induction of a catabolic protease secretome. The released ASC speck is a durable extracellular aggregate that seeds amyloid. The gasdermin-D pore both releases the cytokines and, at the extreme, lyses the cell. That one activation should drive both aggregation and proteolysis is therefore not a contradiction requiring resolution but a feature of the inflammasome's design: it is a single trigger with a divided output. The two papers looked far apart because they followed two of that output's branches into two literatures; they were never far apart at the root.

Naming this correctly matters, because it converts the reader's question from "which paper is right?" — a false dilemma, since both can be and largely are — into the three real questions this paper takes up. The first is whether each arm's *individual steps* are supported, and to what degree; this is the grading of Chapters I and II. The second is how the two arms *relate* — whether they are merely parallel, or whether they interact, converge, and reinforce; this is Chapter III. The third is which arm is the more *important*, a question that turns out to have distinct and non-coincident answers depending on whether importance is measured by evidence, by proximity to the disease's cognitive endpoint, or by therapeutic leverage; this is Chapter IV. Only the shared-node observation makes these the right questions; without it, one is left arguing which of two branches is the tree.

1.3 Significance

The significance of the synthesis is fourfold. First, it repairs a real defect in the corpus: two papers on one sensor that did not confront each other. A framework whose separate parts cannot be laid on one another is not yet a framework, and the deliberate confrontation of the two arms — the point of this paper — is the test of whether the inflammasome account of Alzheimer's disease is one account or two coincidentally similar ones. Second, it produces, for the first time in this corpus, a single graded evidence ledger spanning both arms, so that the strength of the amyloid-seeding claim and the strength of the net-stripping claim can be read on the same scale rather than asserted in incommensurable vocabularies. Third, it identifies the arms' relationship as itself a source of explanatory power — in particular the convergence on tau, where the two arms attack the same protein from opposite sides, and which no single-arm account can see. Fourth, and most consequentially for the clinic, it shows that the relative-importance question, which cannot be settled from the armchair, need not be settled before acting, because the two arms share the node that a selective inflammasome inhibitor would block — so that the drug is, in effect, the experiment that adjudicates the arms.

1.4 Scope and Limitations

This paper is a synthetic adjudication, not a source of new data, and its limits are those of its method compounded by those of its two subjects. It assumes the detailed biology of *The Sensor and the Speck* and *The Net and the Speck* and recapitulates each arm only far enough to grade it; the reader is referred to those papers for the full mechanistic development. It concentrates on the microglial NLRP3 inflammasome and treats the neuronal NLRP1 and astrocytic NLRP2 sensors only where they bear on the two arms. It does not re-open the reverse-causation and translational questions settled in the prior papers, but it carries their conclusions forward as standing constraints: that the inflammasome, on either arm, is downstream of aggregated amyloid and is an amplifier rather than an initiator; and that the interventional evidence for both arms is overwhelmingly murine, in models whose translational record is poor. Above all, the paper is explicit that grading evidence is not the same as ranking importance, and that its confident verdict on the former does not license a confident verdict on the latter. Where an arc is strong it says so; where an arm is better-evidenced than it is demonstrably important, it says that too.

2. The Shared Root: One Activation, a Divided Output

Before the two arms are graded apart they must be seen to join, and the join is the microglial NLRP3 inflammasome as developed at length in *The Sensor and the Speck* and recapitulated here in a single paragraph. The inflammasome is a two-signal device. A priming signal — delivered in the Alzheimer brain by amyloid-β through the CD36–TLR4 complex and sustained by the parenchyma's standing cytokine load — raises the transcription of NLRP3 and pro-interleukin-1β through NF-κB and licenses the sensor. An activating signal — potassium efflux, lysosomal rupture with cathepsin B release, or mitochondrial reactive-oxygen-species production — drives NLRP3 to oligomerise, recruit NEK7, and nucleate the ASC adaptor into the micron-scale speck that autoactivates caspase-1. The single fact on which this entire paper turns is what happens next: caspase-1's substrates are multiple. It matures interleukin-1β and interleukin-18; it cleaves gasdermin-D into the membrane pore; and the priming step that licensed it has, at the same transcriptional stroke, armed a broad catabolic secretome. One activation, that is, yields a soluble cytokine of enormous pleiotropy, a durable extracellular seeding aggregate, a lytic pore, and a protease programme — and the two arms of this paper are simply two destinations of that divided output.

It is worth stating the divided output as a ledger, because the rest of the paper is an accounting of it. Down one branch, the output *builds*: the ASC speck seeds amyloid; interleukin-1β drives neuronal tau kinases; the suppression of the phagocytic phenotype spares the amyloid from clearance. Down the other branch, the output *dismantles*: interleukin-1β induces the aggrecanases that cleave the net; the same cathepsins that triggered the sensor digest the matrix when secreted; the de-shielded neuron is exposed. The metabolic economy is one of a cell that has been switched, by a single organelle, into a state that is at once a poor janitor and an aggressive demolition crew — and the question of the paper is how much of each activity is real, how the two activities interact, and which does the more damage.

3. Methodology and the Grading Rubric

This paper applies the Organic Network Synthesis methodology in the adjudicative mode of *The Pineal Interface* and *The Sensor and the Speck*, but it adds an instrument the prior papers used only implicitly: an explicit, uniform evidence-grading rubric, applied to every arc of both arms and of their relationship, so that claims from the amyloid literature and claims from the matrix literature are scored on one scale. The methodology otherwise proceeds as before — the tracing of each arc from signal to effector to consequence, with each step referred to its primary evidence and its species, system, and independent-replication status recorded — but the output is not a narrative verdict alone; it is a ledger.

The rubric distinguishes five levels, and its levels turn on two axes that matter more than any others in this field: the *directness* of the evidence (correlative, interventional, or genetic) and the *distance* between the system in which a mechanism was shown and the Alzheimer brain in which it is claimed. A mechanism shown by gene deletion, in multiple laboratories, with human corroboration, is graded highest; a mechanism established in cartilage and transferred to the brain by homology, however sound the homology, is explicitly marked as transferred and graded lower; a loop inferred from its separately evidenced arcs but never shown to run as a loop is marked as conjecture, however coherent. The rubric is deliberately unkind to synthesis, because synthesis is this paper's own instrument and must be held to a visible standard.

Grade	Standard the claim meets	Illustrative bar
I — Established	Interventional or genetic demonstration in ≥2 independent labs, with human-tissue corroboration of engagement	rejecting it requires deliberate misreading
II — Probable	Interventional or genetic demonstration, but model-confined, or single-lab for the decisive step	reproducible; not yet broadly replicated
III — Inferential (transferred)	Mechanism established (often Grade I) in another tissue or disease, imported by molecular homology	sound by analogy; unshown in the AD setting
IV — Conjectural	A synthesis inferred from separately evidenced arcs; not demonstrated as a unit	coherent and falsifiable, but unshown
Rejected	Contradicted by evidence, or a positional claim the evidence rules out	e.g., inflammasome as initiator

Table 1. The evidence-grading rubric applied to every arc in this paper.

4. Chapter I The Aggregative Arm (Branch A)

4.1 The Speck as Seed and the Sensor's Amyloid Trigger

Branch A begins where the inflammasome's engagement with the disease begins: with amyloid-β as both the trigger and, through the speck, the product. That fibrillar amyloid-β, phagocytosed by the microglion, ruptures the lysosome and releases cathepsin B to activate NLRP3 is the foundational and best-replicated fact of the whole field (Halle et al., 2008; Hornung et al., 2008): it is interventional, subtractive at every step, and homologous to the archetypal particulate activators of NLRP3. It earns Grade I. The onward claim that the activated inflammasome disgorges an ASC speck which binds and cross-seeds amyloid, templating new aggregation and propagating pathology, is of a different evidential character (Venegas et al., 2017; Friker et al., 2020): it is bidirectionally interventional — added specks worsen, anti-speck rescues — but it is substantially the product of a single laboratory and its collaborators, and the fraction of human amyloid burden attributable to speck-seeding is unquantified. It earns Grade II. The distinction inside Branch A is already instructive: the sensor's activation by amyloid is established, but the speck's seeding of amyloid, the more novel and more propagative claim, is only probable.

4.2 The Tau Relay

The most consequential arc of Branch A is the relay to tau, because it addresses the amyloid cascade's central vacancy. Ising and colleagues (2019) showed, by genetic deletion of NLRP3 or ASC in tau-transgenic mice, that inflammasome activity is required for the full development of tau pathology, that it shifts the balance of tau kinases and phosphatases toward hyperphosphorylation, and — decisively — that amyloid-seeded tau pathology requires a functional microglial inflammasome, placing the sensor mechanistically between the two proteinopathies. Stancu and colleagues (2019) closed the reciprocal arc, showing that aggregated tau itself activates the inflammasome and that ASC specks seed tau. This is high-quality, genetic, interventional work; it is also narrow — resting principally on these studies, entirely murine, and turning on a kinase/phosphatase mechanism that is incompletely reconstructed. It earns Grade II: probable, important, and awaiting the breadth of independent confirmation its ambition demands.

4.3 Impaired Clearance

The arc that makes Branch A an amplifier rather than a bystander is its action back upon its own trigger. Heneka and colleagues (2013) showed that deleting NLRP3 or caspase-1 in amyloid mice not only reduced inflammation but *increased* amyloid clearance, because the inflammasome-deficient microglion adopts a more phagocytic phenotype; Tejera and colleagues (2019) showed the reciprocal, that systemic inflammation impairs microglial amyloid clearance through NLRP3; and the pharmacological inhibitors MCC950 and OLT1177 reproduce the protection (Dempsey et al., 2017; Lonnemann et al., 2020). This is genetic and pharmacological, reproduced across compounds and models, and it is the arc that most directly refutes the pure-bystander reading. It earns Grade I within the mouse — with the standing translational discount, carried from the prior paper, that no anti-inflammatory strategy has yet altered human Alzheimer's disease.

4.4 The Weight of Branch A

Branch A is, on this accounting, the better-anchored of the two arms, and its internal structure is worth stating plainly: its foundation (amyloid activates NLRP3) and its amplifier arc (inflammasome impairs clearance) are Grade I; its two most disease-relevant onward claims (speck-seeding, tau relay) are Grade II; and its engagement in human tissue is Grade I but correlative. There is no Grade III or IV in Branch A's spine — no arc that rests on transfer from another tissue or on unshown synthesis. That is the signature of a mature, if still model-bound, mechanism.

Branch A arc	Key evidence	Grade
Amyloid-β activates NLRP3 (lysosome / cathepsin B)	Halle 2008; Hornung 2008	**I**
NLRP3 / caspase-1 deletion protects, improves clearance	Heneka 2013; Tejera 2019; Dempsey 2017	**I** (murine)
Pathway engaged in human AD brain	Heneka 2013; Saresella 2016; Moonen 2023	**I** (correlative)
ASC speck cross-seeds amyloid-β (propagation)	Venegas 2017; Friker 2020	**II**
NLRP3 › tau relay	Ising 2019; Stancu 2019	**II**

Table 2. The aggregative arm (Branch A), graded arc by arc.

5. Chapter II The Proteolytic Arm (Branch B)

5.1 From Cytokine to Aggrecanase

Branch B begins with the middle link that *The Net and the Speck* supplied: that interleukin-1β, the cytokine the inflammasome exists to mature, is the principal inducer of the aggrecan-degrading protease programme. This is the best-characterised cytokine-to-protease mechanism in all of matrix biology, but it was characterised in cartilage, and its grade depends entirely on where it is claimed. In the joint, the interleukin-1β-driven induction of ADAMTS-4 and ADAMTS-5 and their cleavage of the aggrecan core is Grade I, reconstructed to the point that ADAMTS-5 deletion prevents aggrecan loss in vivo (Glasson et al., 2005; Stanton et al., 2005; Kapoor et al., 2011). In the brain, where the target aggrecan is the same lectican and the aggrecanases are expressed and inflammation-inducible (Lemarchant et al., 2013) but where the end-to-end chain has not been reconstructed, the same mechanism is Grade III: sound by homology, unshown in the setting claimed. This split grade is the crux of Branch B's whole evidential situation.

5.2 The Stripped Net and the Parvalbumin Cell

That microglia are the effectors of perineuronal-net loss in Alzheimer's disease, and that net degradation precedes the depletion of the parvalbumin cells it protects, is established by Crapser and colleagues (2020) with an interventional design — microglial depletion prevents the loss — and human-tissue confirmation. This earns Grade II; it falls short of Grade I only because the decisive isolation of NLRP3 or interleukin-1β as the specific microglial signal was not part of the design, so that the arc establishes microglial agency without establishing inflammasome agency. That the stripped net leaves the parvalbumin interneuron oxidatively and biophysically exposed — that the net is a protective variable whose removal is the proximate lesion — is well-supported by the interventional removal experiments of the matrix literature (Cabungcal et al., 2013; Suttkus et al., 2014) and the network-deficit data of the disease (Verret et al., 2012), and earns Grade II. The gap that keeps Branch B below Branch A is precisely the unbridged step between "microglia strip the net" (shown) and "the inflammasome is the microglial signal that does it" (inferred).

5.3 The Return Loop

Branch B's most novel claim, and its weakest, is that the net's own degradation products feed back to activate the inflammasome, closing a matrix–inflammasome loop. Its components are individually well-founded in the wrong setting: low-molecular-weight hyaluronan and lectican and tenascin fragments are established priming and activating ligands for Toll-like receptors and NLRP3 (Jiang et al., 2005; Yamasaki et al., 2009; Midwood et al., 2009; Kim et al., 2009) — Grade I in peripheral and injury immunology, Grade III when transferred to the perineuronal net of the Alzheimer brain, where they have not been shown. The closed loop itself — the proposition that net degradation and inflammasome activation form a self-amplifying circuit in the disease — is inferred from its separately evidenced arcs and has never been demonstrated as a loop. It earns Grade IV: conjectural, coherent, falsifiable, and unshown.

5.4 The Weight of Branch B

Branch B's structure is the mirror image of Branch A's. Where Branch A was Grade I at its foundation and Grade II at its frontier, Branch B is Grade I only in another tissue, Grade II for microglial (not inflammasome-specific) net-stripping in the disease, Grade III for its two homology transfers, and Grade IV for its loop. It is not a weak argument — every arc has real evidence behind it — but it is an argument whose strongest evidence is always somewhere other than the Alzheimer perineuronal net, and whose AD-specific steps top out in the middle of the scale. This is the honest asymmetry between the arms, and the paper neither hides nor overstates it.

Branch B arc	Key evidence	Grade
Interleukin-1β induces the ADAMTS/MMP aggrecanase programme	Kapoor 2011; Glasson 2005; Stanton 2005	**I** cartilage / **III** brain
Microglia strip the net; degradation precedes PV loss	Crapser 2020	**II**
Net loss exposes the parvalbumin interneuron	Cabungcal 2013; Suttkus 2014; Verret 2012	**II**
Net fragments (LMW-HA, lecticans) re-activate NLRP3	Yamasaki 2009; Jiang 2005; Midwood 2009	**I** immunology / **III** AD-net
The closed matrix–inflammasome loop in AD	synthesis of the above	**IV**

Table 3. The proteolytic arm (Branch B), graded arc by arc.

6. Chapter III The Relationship Between the Arms

6.1 Co-Secretion from One Activation

The first and most secure feature of the arms' relationship is that they are not sequential or alternative but simultaneous, because they issue from one activation event. A microglion whose inflammasome has fired is, at that moment, secreting interleukin-1β and expelling the speck and forming the pore — and interleukin-1β's transcriptional programme drives both the clearance-suppressing, tau-kinase-engaging effects of Branch A and the aggrecanase-inducing effects of Branch B at once. This co-secretion is a direct consequence of the pleiotropy of interleukin-1β and the multiplicity of caspase-1's substrates, and it is Grade I as basic biology. Its implication for the disease is that one cannot, in principle, have the aggregative arm without the proteolytic arm from the same cell: to fire the inflammasome is to do both, in proportions set by the local substrate availability but never to do only one.

6.2 The Pincer on Tau

The most explanatorily powerful feature of the relationship, and one invisible to either single-arm account, is that the two arms converge on tau from opposite directions. Branch A drives tau *positively*: the inflammasome relays amyloid to tau by shifting neuronal kinases and phosphatases toward hyperphosphorylation (Ising et al., 2019). Branch B drives tau *permissively*: the intact perineuronal net is a barrier to the internalisation of pathological species, and net-bearing neurons demonstrably resist tangle formation (Morawski et al., 2010) and carry markedly less tau in human tissue (de Vries et al., 2024), so that stripping the net removes a tau-exclusion barrier and renders the neuron newly permissive to seeding. The inflammasome thus attacks tau twice at once — building the seed on one arm and removing the barrier to it on the other — a pincer that neither the amyloid-centric nor the matrix-centric account can see alone. Each half of the pincer is Grade II; the combined convergence claim, as a single coordinated mechanism, is Grade IV, because it has not been shown that the two routes operate together on the same neurons. But the convergence is the strongest reason to think the arms' relationship is more than incidental.

6.3 The Shared Phenotype Axis

The relationship also resolves what looked, across the two prior papers, like a contradiction. Branch A's central causal result is that inflammasome activation *suppresses* microglial phagocytosis, so that deleting the sensor improves amyloid clearance; Branch B has the inflammasome-activated microglion *hyperactively secreting* matrix-degrading proteases. A cell both bad at clearing and aggressive at degrading appears paradoxical only if phagocytosis and secretory proteolysis are the same activity, which they are not. They are opposite arms of one phenotype axis: the inflammasome-activated, interleukin-1β-secreting microglion sits at the inflammatory, low-clearance, high-proteolysis pole, and the inflammasome-silent microglion at the homeostatic, high-clearance, low-proteolysis pole. Branch B therefore corroborates Branch A's phenotype rather than contradicting it, and the intact perineuronal net's own anti-inflammatory character — native high-molecular-weight hyaluronan dampens innate-immune signalling, and only its fragments activate it — adds a consistent third term: the intact net brakes the very inflammasome whose activation would strip it. This shared-axis reading is Grade II, inferred from the convergence of the Heneka phenotype data and the Crapser degradation data rather than shown by a single experiment spanning both.

6.4 The Temporal Hand-Off

A more speculative feature of the relationship concerns timing. Branch A's amyloid-seeding is plausibly a phenomenon of the plaque-forming phase; Branch B's net-stripping is positioned, by *The Perineuronal Turn*, at the later transition from the immune to the synaptic phase of the disease, and the ordering of inhibitory-neuron loss — somatostatin cells, which bear no net, early; parvalbumin cells, which do, late (Gabitto et al., 2024) — is consistent with net degradation being a mid-to-late event. This raises the possibility of a temporal hand-off, in which the aggregative arm dominates the disease's earlier proteinopathic phase and the proteolytic arm its later matrix-and-network phase, with the shared inflammasome as the through-line connecting them. The hand-off is Grade IV: it is a coherent reading of the staging data, not a demonstrated sequence, and it is offered as a hypothesis about *when* each arm matters most rather than a claim about whether each is real.

6.5 The Cross-Amplification

The final feature closes the relationship into a circuit. Branch B's return arc — net fragments re-priming and activating the inflammasome — does not only feed Branch B; because the arms share the node, any reactivation of the inflammasome drives *both* arms. Net degradation on Branch B thus indirectly amplifies the amyloid-seeding and tau-relaying of Branch A, by supplying fresh danger signals to the sensor that runs both. This cross-amplification is what would make the two arms a single self-reinforcing system rather than two parallel outputs, and it is the mechanism by which a matrix lesion could accelerate a proteinopathy. It inherits the grade of its weakest component, the return arc, and is therefore Grade IV — the most conjectural and, if true, the most important of the relationship's features, because it is the one that would fuse the two collapses into one.

7. Chapter IV The Weighing: Relative Importance

7.1 By Weight of Evidence

Under the first and most objective lens, the verdict is unambiguous: Branch A is the better-evidenced arm. Its spine is Grade I at foundation and amplifier, Grade II at its frontier, with no reliance on tissue-transfer or unshown synthesis; Branch B is Grade I only in cartilage, Grade II for microglial rather than inflammasome-specific net-stripping in the disease, and Grade III–IV for the steps that make it specifically an inflammasome mechanism and a loop. If the question is "which arm do we know to be operating in the Alzheimer brain?", the answer is Branch A, and it is not close.

7.2 By Proximity to the Cognitive Endpoint

Under the second lens the verdict inverts, or at least becomes genuinely uncertain, and the paper's central methodological discipline is to refuse to let the first lens answer the second. Evidence weight measures how well a mechanism is known; it does not measure how much the mechanism matters to the disease's defining outcome, which is cognitive decline. And on proximity to that outcome, Branch B has a claim that Branch A lacks. Branch B acts directly on the parvalbumin interneuron, on the inhibitory tone and gamma-frequency timing of cortical circuits, and on the tau-permissiveness of the neurons whose tangles track cognition — all of which correlate with cognitive decline more tightly than amyloid burden, the endpoint of Branch A's foundation, ever has. It is entirely possible that Branch B is closer to the cognitive collapse and merely less studied, its lower evidence grade reflecting the field's amyloid-centric history rather than the mechanism's true weight. The best-lit arm is not necessarily the one nearest the keys. The honest verdict under this lens is not that Branch B is more important but that its *potential* importance may exceed its *demonstrated* standing, and that the two lenses must not be collapsed.

7.3 By Therapeutic Leverage

Under the third lens the question partly dissolves, and this is the paper's most useful practical result. Because the two arms share the NLRP3–caspase-1 node, a single selective inhibitor of that node interdicts both at once — it reduces the interleukin-1β that seeds tau and impairs clearance on Branch A and induces the aggrecanases on Branch B, and it reduces the speck that seeds amyloid. One therefore does not need to know which arm matters more in order to act, because the available intervention does not act on one arm but on their common trunk. Better still, the intervention converts the relative-importance question from a debate into a measurement: administer the inhibitor and observe whether the benefit tracks the proteinopathy readouts (amyloid and tau PET), the matrix-and-network readouts (perineuronal-net integrity, parvalbumin function, gamma oscillations), or both. The drug is the adjudicator the armchair cannot be.

7.4 The Layered Verdict

The three lenses do not agree, and the refusal to force them into a single number is the paper's considered position. By evidence, Branch A wins decisively. By proximity to cognition, Branch B may lead but on inference rather than demonstration. By therapeutic leverage, the arms are inseparable and the ranking is, for action, moot. The synthesis of the three is this: the inflammasome's aggregative arm is what we best *know*, its proteolytic arm is what we should most want to *find out*, and its shared node is what we can already *act on*. A reader who wants a single winner is offered instead a map of which arm answers which question — and warned, in the strongest terms the rubric allows, against the seductive error of treating the best-evidenced arm as the most important one.

Lens of importance	Branch A (aggregative)	Branch B (proteolytic)	Verdict
Weight of evidence	Grade I–II spine	Grade II–IV in AD	**A**, decisively
Proximity to cognition	amyloid-anchored (weaker cognitive correlate)	PV / network / tau-permissive (stronger correlate)	**B** may lead, on inference
Therapeutic leverage	shares the NLRP3 node	shares the NLRP3 node	**tie**; one drug tests both
What each answers	what we best *know*	what we should *find out*	act on the shared node

Table 4. The weighing — the two arms under three lenses of importance.

8. Chapter V Concessions The Consolidated Ledger and the Standing

The paper's evidential position, assembled from both arms and their relationship, can be read at a glance, and reading it at a glance is the point of grading on one scale. The aggregative arm carries the corpus's Grade I claims; the proteolytic arm carries its Grade III–IV frontier; the relationship carries one Grade I feature (co-secretion) and, in the pincer on tau and the cross-amplification, its most important Grade IV conjectures. Nothing in the ledger is Rejected except the positional claim that either arm initiates the disease — a concession both prior papers made and this one carries forward without qualification. The inflammasome, on both arms, is downstream of aggregated amyloid; it is an amplifier of a proteinopathy it did not begin, a stripper of a net whose degradation it accelerates but did not first cause, and its silencing would, on present evidence, slow the disease without preventing its onset.

Two further standing concessions bound the whole. The first is the translational discount: every interventional demonstration on both arms is murine, in transgenic models whose amyloid, tau, and matrix biology is caricatured, and the field's record of translating such demonstrations to patients is close to unbroken failure. The second is the parallel-effects caveat specific to the relationship: because amyloid independently activates the inflammasome and independently drives microglial net-stripping, the appearance of a coupled two-arm system may in part reflect a shared upstream driver rather than a genuine internal coupling, and only the direct demonstration of the cross-amplification arc — net degradation raising inflammasome activation, and inflammasome inhibition preserving the net — would distinguish a true circuit from two parallel shadows of amyloid. The paper's confidence in its grading is high; its confidence that the graded mechanism is the disease's prime mover is, by explicit design, low.

9. Chapter VI Falsifiable Predictions and the Discriminating Experiments

The synthesis is falsifiable, and its most valuable predictions are those that would move the relative-importance ranking or distinguish a coupled system from parallel effects. Six are advanced, ordered from the most to the least discriminating.

Prediction 1 — The single node, the double readout. Selective NLRP3 or caspase-1 inhibition, administered in an appropriate window, will improve *both* proteinopathy readouts (amyloid and tau accumulation) *and* matrix-and-network readouts (perineuronal-net integrity, parvalbumin function); a benefit confined to one class of readout would show the arms to be separable at the node and would falsify the co-secretion claim.

Prediction 2 — The pincer on tau. Inflammasome inhibition will attenuate tau accumulation by both routes — reducing the kinase-driven hyperphosphorylation of Branch A and preserving the net's tau-exclusion barrier of Branch B — such that its effect on tau exceeds what either route alone would predict; an additive-not-synergistic effect on tau would weaken the pincer.

Prediction 3 — The cross-amplification. Experimentally degrading the perineuronal net will raise inflammasome activation in the local microenvironment, and inhibiting the inflammasome will preserve the net; the failure of net degradation to activate the inflammasome would falsify the return arc and collapse the two-arm circuit into two parallel effects of amyloid.

Prediction 4 — The temporal hand-off. Longitudinal measurement will find the aggregative arm's markers (ASC, speck-associated amyloid) rising earlier and the proteolytic arm's markers (aggrecan-fragment neoepitopes, released net components) rising later, at the transition the perineuronal-net theory names; a simultaneous rise would falsify the hand-off while leaving both arms intact.

Prediction 5 — Proximity to cognition. Across individuals, the proteolytic arm's readouts (net integrity, parvalbumin and gamma function) will track cognition more tightly than the aggregative arm's (amyloid burden); should the aggregative markers track cognition as well or better, the second lens's tentative verdict for Branch B is withdrawn.

Prediction 6 — The resilience test. Cognitively resilient individuals with high pathology will show lower inflammasome tone and better-preserved nets than matched clinically-affected individuals; equal inflammasome tone across resilient and affected brains would sever the shared

node from the disease's clinical expression.

10. Conclusion

The two papers that preceded this one looked incompatible because they followed one sensor into two literatures that do not speak to each other, and the reasonable suspicion that they could not both be right rested on a misreading of their structure. They are not two hypotheses about one fact; they are two branches of one node. The microglial NLRP3 inflammasome fires once and secretes a divided output — a pleiotropic cytokine, a seeding speck, a lytic pore, a protease programme — and that output runs simultaneously down an aggregative arm that builds pathological protein and a proteolytic arm that dismantles the protective net. The arms are co-secreted from one activation, converge on tau from opposite sides in a pincer no single-arm account can see, share one microglial phenotype axis on which the apparent contradiction between impaired clearance and aggressive degradation dissolves, and are joined at the node by a cross-amplification that would, if shown, fuse the two collapses into one self-reinforcing system.

Graded on a single scale, the arms are unequal in what is known of them and, possibly, in what they are worth. The aggregative arm carries the established, genetic, human-corroborated evidence; the proteolytic arm carries the field's frontier, its strongest support always in a tissue other than the one it claims, its central loop still conjecture. Yet the paper's final discipline is to keep the two verdicts apart: the arm we best know is not certainly the arm that matters most, and Branch B's lower grade may measure the field's neglect rather than the mechanism's weight. What breaks the impasse is not more argument but the shared node — the single druggable trunk whose inhibition interdicts both arms and thereby turns the relative-importance question from a debate into a trial readout. The inflammasome's aggregative arm is what we best know; its proteolytic arm is what we should most want to find out; its node is what we can already act on. And the disease it amplifies, on both arms, it did not start — a sensor firing downstream of a lesion it makes worse from two directions at once, and could, in principle, be made to stop making worse from both at a single stroke.

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