THE NET AND THE SPECK

The NLRP Inflammasome as the Engine of Perineuronal-Net Degradation — and the Matrix Fragments That Feed It Back — in Alzheimer's Disease

The Vacancy in the Stripping · The Forward Arc · The Return Arc
The Matrix–Inflammasome Loop · The Resilience Switch · The Grading of the Arcs

A Convergence Paper Prepared under the Organic Network Synthesis Methodology

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The edge between The Sensor and the Speck (the NLRP3 inflammasome) and The Perineuronal Turn (the perineuronal net): interleukin-1β-driven aggrecanase induction as the engine of the stripping, and the net's own fragments as the signals that feed the inflammasome back.

"The net is stripped by an enzyme; the enzyme is called by a cytokine; and the cytokine is made by the speck. If that chain holds, the structure whose loss defines the transition and the organelle whose activation defines the disease are the same lesion, read from two ends."

— ONS Methodology Working Notes, 2026

For Joshua Crapser and Kim Green, who showed that microglia strip the net, and for the arthritis biologists who first traced interleukin-1β to the aggrecanase — a chain this paper only carries across a border.

A CONVERGENCE PAPER THE EDGE BETWEEN TWO AXES

Axis A — The Innate-Immune Engine

The Sensor and the Speck · Homeostatic Microglial Collapse

Axis B — The Extracellular Matrix

The Perineuronal Turn · the Perineuronal-Nets concept article (the 7th, ECM-matrisome axis)

This paper — The Net and the Speck the edge A ↔ B

The Perineuronal Turn names, in a single clause, "the inflammasome-primed microglion" that shifts its output toward the proteases that strip the net, but does not develop it. This paper takes that clause as its subject: it traces the forward arc — interleukin-1β to the ADAMTS aggrecanases that cleave the aggrecan core — and the return arc — the net's hyaluronan and lectican fragments back to the NLRP3 inflammasome — and grades the loop they close.

Contents

Abstract

Two of this corpus's axes have been developed in near-isolation from one another. The first is the inflammasome axis of *The Sensor and the Speck*: the NLRP3 inflammasome of the microglion as the innate-immune amplifier that reads aggregated amyloid-β as danger, matures interleukin-1β and interleukin-18 through caspase-1, and disgorges the ASC speck. The second is the extracellular-matrix axis of *The Perineuronal Turn* and its supporting concept article: the perineuronal net as a protective variable whose microglial "stripping" is the proximate lesion of the transition from the immune to the synaptic phase of the disease. This paper joins them, and argues that the join is not a loose analogy but a specific and, in places, well-anchored molecular coupling — one the existing formulation gestures at but does not develop. *The Perineuronal Turn* names, in a single clause, "the lipid-burdened, inflammasome-primed microglion" that shifts its output toward matrix-degrading enzymes; the present paper takes that clause as its subject and asks what the inflammasome actually contributes to the stripping of the net, and what the stripped net contributes back to the inflammasome.

The coupling is bidirectional, and each direction is graded. The *forward arc* — the inflammasome as the engine of the stripping — is the better anchored. The current formulation attributes net loss to "microglial activation" and to the matrix metalloproteinases and ADAMTS aggrecanases it elaborates, but it does not name the switch that redirects the microglion's secretory programme toward those enzymes. The inflammasome names it: caspase-1-matured interleukin-1β is, in the best-characterised catabolic system in all of matrix biology — the cytokine-driven destruction of cartilage aggrecan in arthritis — the principal transcriptional inducer of exactly the ADAMTS-4, ADAMTS-5, and MMP-3/MMP-9 program that cleaves the aggrecan core of the perineuronal net; and the cathepsin B whose lysosomal release activates NLRP3 is itself a matrix protease. The *return arc* — the net's own fragments as inflammasome signals — is the more novel and more inferential. The hyaluronan backbone of the net, once fragmented, is a canonical activator of the NLRP3 inflammasome; the lectican and tenascin fragments generated by aggrecanase cleavage are Toll-like-receptor priming ligands; and the de-shielded, oxidatively stressed parvalbumin neuron the net once protected becomes a local source of the mitochondrial and purinergic danger signals that fire NLRP3 anew. The two arcs close a loop — matrix degradation begets inflammasome activation begets matrix degradation — that is tighter than, and nested within, the circuit-level self-sustaining loop of *The Perineuronal Turn*, because it need not detour through the excitatory cortex to feed itself.

The paper grades this coupling honestly. The forward cytokine-to-protease arc is strong in cartilage and moderate in the specific setting of the Alzheimer perineuronal net; the microglial agency of net loss is strong (Crapser); the return arc is strong in peripheral immunology and inferential in the AD-net context; and the closed loop is a novel synthesis, not a demonstrated mechanism. Above all, the paper concedes the parallel-effects alternative: amyloid-β independently activates the inflammasome and independently drives net loss, so that

inflammasome activation and net stripping may be parallel consequences of a shared upstream cause rather than a coupled loop. What survives that concession is the paper's robust contribution — that the inflammasome supplies the specific, druggable molecular identity of the "microglial activation" that the perineuronal-net formulation has until now left as a placeholder — and its reframing of the resilience finding of de Vries: that the difference between the net's homeostatic remodeling and its pathological stripping may be, in the end, a difference of inflammasome tone.

Keywords: NLRP3 inflammasome, interleukin-1β, ADAMTS-4, ADAMTS-5, aggrecan, perineuronal net, hyaluronan, matrix metalloproteinase, cathepsin B, parvalbumin interneuron, microglia, extracellular matrix, DAMP, Toll-like receptor, cognitive resilience, Alzheimer's disease

1. Introduction

1.1 The Vacancy in the Stripping

The Perineuronal Turn locates the irreversible passage of Alzheimer's disease at the degradation of one structure and names the agent of that degradation with care. "The structure that protects the parvalbumin interneuron is, in the transition, dismantled, and the agent of its dismantling is the microglion that has, in the preceding phase, lost its homeostatic restraint." The account then specifies three "chemistries" of the stripping — a proteolytic one (the matrix metalloproteinases and the aggrecan-specific ADAMTS proteases), an oxidative one (iron-driven Fenton fragmentation), and an opsonic one (complement-licensed phagocytic removal). It is a precise account of *how* the net is degraded. What it does not specify — what it names only in passing, in the single phrase "the lipid-burdened, inflammasome-primed microglion" — is the switch that throws the microglion from its homeostatic programme into the matrix-degrading one. The proteases are named; the signal that induces them is not.

This is the vacancy the present paper fills. It is the same species of vacancy that motivated *The Sensor and the Speck*: there, the amyloid cascade named amyloid and tau as the endpoints of a relay without naming the relay; here, the perineuronal-net formulation names "microglial activation" and its downstream proteases without naming the transcriptional switch that couples the two. In both cases the inflammasome is the candidate filler, and for the same reason — it is the best-characterised device by which a microglion converts the sensing of danger into a stereotyped secretory programme. The proposition of this paper is that the inflammasome is the molecular engine of the stripping: that the interleukin-1β matured by caspase-1 on the ASC scaffold is the principal signal that redirects the microglion's output toward the aggrecanases and metalloproteinases that

dismantle the net; and, further, that the fragments liberated by that dismantling feed back to activate the inflammasome, closing a loop that the current formulation approaches from the circuit level but does not close at the level of the matrix itself.

1.2 Significance

The significance of joining these two axes is threefold. First, it supplies the perineuronal-net formulation with a molecular mechanism it currently lacks and, with it, a pharmacology. "Microglial activation" is not a drug target; the NLRP3 inflammasome, its effector caspase-1, and the interleukin-1 receptor are. If the inflammasome is the engine of the stripping, then the selective inflammasome inhibitors developed against amyloid pathology in *The Sensor and the Speck* become, without modification, candidate net-preserving agents — and the net-integrity readout that *The Perineuronal Turn* nominates as its biomarker becomes a pharmacodynamic readout for inflammasome-directed therapy.

Second, it tightens the disease's central feed-forward loop. *The Perineuronal Turn*'s self-sustaining loop is a circuit-level one: net stripping disinhibits the excitatory cortex, the disinhibited cortex releases more amyloid and tau, the rising pathology sustains the matrix-degrading microglion, and the microglion strips further net. The coupling proposed here adds a shorter inner loop that does not require the excitatory detour: net-degradation products activate the inflammasome directly, the activated inflammasome drives the aggrecanases, and the aggrecanases generate more net-degradation products. A loop with a shorter path length is a loop with a higher gain, and its existence would help explain why the transition, once begun, is so difficult to arrest.

Third, it reframes the resilience finding on which the perineuronal-net axis stakes its therapeutic optimism. De Vries and colleagues found that cognitively resilient individuals — those with high amyloid and tau burden but preserved cognition — show *homeostatic* perineuronal-net remodeling rather than the *pathological*, protease-driven degradation seen in clinical disease. The matrix biology offers no account of what distinguishes the two fates of the net, because ADAMTS and MMP activity is also the normal machinery of physiological matrix turnover and plasticity. The inflammasome offers one: the difference between remodeling and stripping may be the difference between an inflammasome held below its activation threshold and one driven past it — between a matrix turned over under homeostatic control and a matrix digested under inflammatory command.

1.3 Scope and Limitations

This is a focused convergence paper, not a general treatment of either axis. It assumes the inflammasome biology of *The Sensor and the Speck* and the perineuronal-net biology of *The Perineuronal Turn* and the perineuronal-net concept article, recapitulating each only far enough to establish the point of contact. It does not re-derive the amyloid-activation, ASC-seeding, or tau-relay arcs of the inflammasome thesis, nor the protective-variable, somatostatin-control, or latent-interval propositions of the perineuronal-net theory; it takes them as given and builds the edge between them.

The paper makes a bounded and explicitly graded claim. It does not claim that the inflammasome–matrix loop initiates Alzheimer's disease; both the inflammasome and net loss are downstream of aggregated amyloid-β, and the paper concedes throughout that they may be parallel consequences of that upstream cause rather than a coupled loop. It claims, more modestly, that the inflammasome supplies the specific molecular identity of the microglial signal that strips the net (the forward arc, well-anchored), that the stripped net supplies danger signals that reactivate the inflammasome (the return arc, inferential in this setting), and that together these convert two parallel effects into a self-amplifying loop (a novel synthesis, ungraded by direct evidence). Where an arc rests on cartilage biology extrapolated to brain, on peripheral immunology extrapolated to the perineuronal net, or on a loop inferred rather than demonstrated, the paper says so. Chapter V grades every arc, and Chapter VI states the conditions under which the coupling would be falsified.

2. The Two Formulations to Be Joined

2.1 The Inflammasome, in Brief

The NLRP3 inflammasome, as developed in *The Sensor and the Speck*, is a two-signal device of the microglion. A priming signal — delivered in the Alzheimer brain by amyloid-β through the CD36–TLR4 receptor complex, and sustained by the standing cytokine elevation of the inflamed parenchyma — raises the transcription of NLRP3 and of 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. Active caspase-1 matures interleukin-1β and interleukin-18 and cleaves gasdermin-D, whose membrane pore releases the cytokines and, at the extreme, lyses the cell in pyroptosis. The single feature of this device that matters most for the present paper is one it shares with all NF-κB-driven inflammatory programmes: the priming signal that licenses the inflammasome is also the signal that induces a broad catabolic secretome, of which the matrix-degrading proteases are a part. To prime the inflammasome is, at the same transcriptional stroke, to arm the microglion's proteolytic machinery.

2.2 The Perineuronal Net, as Currently Formulated

The perineuronal net, as formulated across the concept article and *The Perineuronal Turn*, is a condensed extracellular-matrix lattice that ensheaths the soma and proximal dendrites of predominantly parvalbumin-positive, fast-spiking interneurons. Its architecture is a hyaluronan backbone, tethered at the neuronal surface, decorated with the lectican chondroitin-sulfate proteoglycans — aggrecan foremost, the obligatory and highest-density component, with brevican, neurocan, and versican — which are stabilised by the HAPLN link proteins and cross-linked into a reticular mesh by tenascin-R. Its offices are precisely those a metabolically extravagant, fast-firing, oxidatively exposed cell requires: cation buffering for high-frequency firing, an antioxidant and iron-chelating shield, the stabilisation of perisomatic synapses, the restraint of plasticity, and a barrier to the internalisation of pathological species including tau and amyloid.

Three empirical pillars fix the net's role in the disease. Crapser and colleagues showed that perineuronal nets are lost in the 5xFAD model and the human Alzheimer cortex, that microglia are the effectors of that loss — pharmacological microglial depletion prevents it — and, critically, that net degradation *precedes* the depletion of the parvalbumin population it protects. De Vries and colleagues showed that cognitively resilient individuals preserve their nets and their perisomatic synapses, and that net-bearing neurons carry markedly less tau, reframing net integrity as a substrate of resilience. And the reviews of Fawcett, van 't Spijker and Kwok, and Auer synthesise the net's roles in memory, oxidative defense, and disease. *The Perineuronal Turn* organises these into a theory of the transition: the net as protective variable, its microglial stripping as the proximate lesion, the silenced-but-living parvalbumin cell as a latent casualty, and the interval before its death

as the disease's window of rescue.

2.3 The Point of Contact the Two Formulations Leave Implicit

The two formulations already touch, at exactly one point, and the touch is left undeveloped. The perineuronal-net concept article names the mechanistic chain as "Aβ-induced microglial activation › MMP-2/MMP-9, ADAMTS-1/4/5, and cathepsin upregulation › enzymatic cleavage of aggrecan/brevican and tenascin-R › PNN thinning/loss." *The Perineuronal Turn* refines the agent to "the lipid-burdened, inflammasome-primed microglion." Both, that is, place a microglion in the causal chain and attribute to it a proteolytic output, and both leave the interior of that microglion — the signal that couples "activation" to "protease" — unspecified. The inflammasome thesis, meanwhile, develops that interior in full but stops at the cytokine and the speck, never following interleukin-1β to its matrix consequences. The point of contact is thus a shared blind spot: the perineuronal-net axis sees the protease but not the signal, and the inflammasome axis sees the signal but not the protease. This paper looks directly at the seam.

3. Methodology

This paper employs the Organic Network Synthesis methodology in its adjudicative mode, as applied in *The Sensor and the Speck* and *The Pineal Interface*. It treats the two axes as networks of mechanistic claims and seeks the specific molecular edges at which they make contact, on the premise that a demonstrated edge between two independently supported frameworks carries more explanatory weight than either alone. Because the central edge is proposed rather than established, the assembly is followed by an explicit grading of each arc, weighted toward disconfirmation, and the parallel-effects alternative — that the two axes are co-driven by amyloid rather than coupled to each other — is treated not as an objection to be rebutted but as a hypothesis to be weighed.

The method proceeds in four steps. First, *edge identification*: the isolation of the two directional arcs — inflammasome-to-matrix and matrix-to-inflammasome — that would, if both operative, close a loop. Second, *cross-literature triangulation*: the assembly of three literatures that do not ordinarily cite one another — the neuro-inflammasome literature of the first thesis, the perineuronal-net literature of the second, and, as the load-bearing bridge, the cytokine-driven matrix-catabolism literature of cartilage and joint biology, in which the interleukin-1β-to-aggrecanase axis is the single best-characterised mechanism in all of matrix pathology. Third, *arc construction*: the tracing of each direction from signal to enzyme to substrate (forward) and from fragment to receptor to sensor (return), with each step referred to its primary

evidence and its species and system of origin recorded. Fourth, *grading and prediction*: the assignment of an evidential verdict to each arc and the derivation of predictions weighted toward those that discriminate a coupled loop from parallel effects.

The methodology carries two limitations specific to this subject. The forward arc's strongest evidence comes from cartilage, a tissue whose aggrecan catabolism is mechanistically homologous to the net's but whose cellular and regulatory context differs; the extrapolation is principled but is an extrapolation. And the return arc's strongest evidence comes from peripheral sterile inflammation, in which hyaluronan and lectican fragments are established inflammasome and Toll-like-receptor ligands, but which has not been demonstrated for the specific fragments of the specific net in the specific setting of Alzheimer's disease. The paper foregrounds both extrapolations rather than concealing them.

4. Chapter I The Forward Arc: The Inflammasome as the Engine of the Stripping

4.1 From Caspase to Cytokine to Protease

The forward arc is a chain of three links, of which the inflammasome thesis develops the first and the perineuronal-net thesis the third, leaving the middle link — the one that joins them — undeveloped by both. The first link is the maturation of interleukin-1β: the assembled NLRP3 inflammasome autoactivates caspase-1, which cleaves pro-interleukin-1β to its secreted, bioactive form. The third link is the degradation of the net: the aggrecan-specific ADAMTS proteases and the matrix metalloproteinases cleave the proteoglycan core and disassemble the mesh. The middle link, which this chapter supplies, is that the second is a principal transcriptional consequence of the first. Interleukin-1β, signalling through the interleukin-1 receptor and MyD88 to NF-κB, is among the most potent known inducers of the matrix-catabolic secretome — of MMP-1, MMP-3, MMP-9, and MMP-13, and of the aggrecanases ADAMTS-4 and ADAMTS-5. The cytokine that the inflammasome exists to produce is, in system after system, the cytokine that commands the destruction of aggrecan.

This is not a speculative coupling in general; it is textbook in the tissue where it was first and best characterised. It becomes an extrapolation only in its transfer to the brain — but the extrapolation is unusually well-motivated, because the molecular target is, at its core, the same molecule.

4.2 The Aggrecanase Program and Its Cartilage Anchor

The destruction of articular cartilage in osteoarthritis and rheumatoid arthritis is, molecularly, the interleukin-1β-driven catabolism of aggrecan, and it is the most thoroughly reconstructed matrix-degradation pathway in biology. Proinflammatory cytokines, interleukin-1β foremost, drive chondrocytes and synovial cells to express ADAMTS-4 and ADAMTS-5, the two aggrecanases, which cleave the aggrecan core protein at specific sites in its interglobular domain; ADAMTS-5 is the dominant aggrecanase in vivo, and its genetic deletion prevents cartilage aggrecan loss in murine osteoarthritis (Glasson et al., 2005; Stanton et al., 2005). The same cytokines induce the matrix metalloproteinases that cleave aggrecan at a distinct site and degrade the collagen and link-protein scaffold, and MMP-3 (stromelysin) activates other pro-MMPs in a proteolytic cascade (Kapoor et al., 2011). The point of transfer to the brain is that the aggrecan of the perineuronal net is the same lectican, cleaved by the same aggrecanases at homologous sites, and that ADAMTS-4, ADAMTS-5, and MMP-3/MMP-9 are all expressed in the central nervous system and upregulated in reactive glia under inflammatory conditions (Lemarchant et al., 2013). The perineuronal-net concept article already names MMP-2/9 and ADAMTS-1/4/5 as the effectors of net loss; what the cartilage literature adds is the identity of their master inducer, and the inflammasome supplies it.

Inflammasome output	Induced protease	Perineuronal-net substrate	Consequence of cleavage
Interleukin-1β (caspase-1)	ADAMTS-4, ADAMTS-5 (aggrecanases)	aggrecan core, interglobular domain	loss of the highest-density, obligatory net component
Interleukin-1β / TNF via NF-κB	MMP-3, MMP-9	aggrecan, brevican, HAPLN link proteins	disassembly of the reticular mesh; MMP-3 activates further MMPs
Lysosomal rupture (NLRP3 signal 2)	cathepsin B, cathepsin S	proteoglycan core, tenascin	one protease both triggers NLRP3 and digests the matrix
Pyroptosis (gasdermin-D pore)	bolus of proteases + DAMPs	—	catabolic enzymes released at the microglion's death

Table 1. The forward arc — from the inflammasome's cytokine output to the proteases that cleave the perineuronal net.

4.3 The Cathepsin Double Duty

A second, more direct thread ties the inflammasome's activation to matrix proteolysis, and it runs through the cathepsins. The activating signal of the amyloid-triggered NLRP3 inflammasome, as established by Halle and colleagues and developed in *The Sensor and the Speck*, is lysosomal rupture and the release of cathepsin B into the cytosol. But cathepsin B and its relative cathepsin S are not only intracellular inflammasome triggers; they are secreted matrix proteases, and cathepsin S is already named in the perineuronal-net concept article's degradation chain. The same lysosomal-protease machinery whose escape signals danger to NLRP3 is machinery capable, when secreted, of digesting the proteoglycan core of the net. The cathepsins thus perform a double duty that tightens the forward arc: they are at once a trigger of the inflammasome and an effector of the stripping, so that the act of inflammasome activation and the act of matrix degradation share, in part, a common enzymatic currency.

4.4 What the Forward Arc Adds to the Current Formulation

The forward arc's contribution is not to overturn the current formulation but to complete it. The perineuronal-net axis has always held that microglia strip the net by proteolysis; the inflammasome axis has always held that microglia mature interleukin-1β; the forward arc observes that these are two ends of one chain. Its value is specificity and, through specificity, tractability. "Microglial activation" admits no intervention; "the interleukin-1β-driven induction of ADAMTS-4/5" admits several — inflammasome inhibition upstream, interleukin-1-receptor blockade at the cytokine, and aggrecanase inhibition at the protease. The forward arc converts a placeholder into a pathway, and it does so on the strength of the best-anchored cytokine-to-protease mechanism in matrix biology, with the single, honestly-stated caveat that its transfer from cartilage to cortex, though homologous at the level of the substrate, has not been reconstructed in full in the Alzheimer brain.

5. Chapter II The Return Arc: The Net's Fragments as Inflammasome Signals

5.1 The Hyaluronan Backbone as a Danger Signal

If the forward arc is the better anchored, the return arc is the more novel, and it begins with the net's own backbone. Hyaluronan, in its native high-molecular-weight form, is immunologically quiet; fragmented into low-molecular-weight oligomers — by hyaluronidases, by reactive oxygen species, or as collateral of the very proteolysis that strips the net — it becomes one of the archetypal endogenous danger signals of sterile inflammation. Low-molecular-weight hyaluronan signals through Toll-like receptors 2 and 4 to activate NF-κB, delivering precisely the priming signal that licenses the NLRP3 inflammasome (Jiang et al., 2005; Scheibner et al., 2006); and, more directly, hyaluronan is a demonstrated activator of the NLRP3 inflammasome itself, required for interleukin-1β release in response to tissue injury (Yamasaki et al., 2009). The implication for the perineuronal net is immediate and, to the author's knowledge, undeveloped in the AD literature: the degradation of the net does not merely remove a protection but generates, from the net's own dismantled backbone, a ligand that both primes and activates the inflammasome which drove the degradation. The net, in dying, arms its executioner.

5.2 The Lectican and Tenascin Fragmentome

The hyaluronan backbone is not the only fragment with danger-signal properties; the proteoglycan and glycoprotein components generate their own. The lecticans, cleaved by the ADAMTS aggrecanases, yield a "fragmentome" of matrikines with signalling activity: versican, a lectican of the same family, is a Toll-like-receptor-2 ligand that primes myeloid cells (Kim et al., 2009), and chondroitin-sulfate fragments engage Toll-like receptor 4 and bias microglia toward a proinflammatory phenotype. The tenascins compound the effect. Tenascin-C — an inducible matrix glycoprotein that rises in inflamed tissue and is a well-established endogenous activator of Toll-like receptor 4, sufficient to sustain inflammation in arthritic joints (Midwood et al., 2009) — is upregulated in the same inflammatory conditions that degrade the net, adding a further priming ligand to the local milieu. The composite picture is of a degrading net that releases, more or less simultaneously, a backbone fragment that activates NLRP3, lectican and chondroitin-sulfate fragments that prime through Toll-like receptors, and an inducible tenascin that primes through another — a fragmentome whose net effect is to prime and fire the inflammasome. Each of these ligand–receptor relationships is established in peripheral or injury immunology; none has been demonstrated for the specific fragments of the perineuronal net in the Alzheimer brain, and the return arc is inferential to exactly that degree.

PNN degradation product	Innate-immune receptor	Inflammasome consequence	Evidential status
Low-MW hyaluronan (backbone fragments)	TLR2 / TLR4 (prime); NLRP3 (activate)	primes and fires NLRP3 › interleukin-1β	established in sterile inflammation; inferential in AD-net
Chondroitin-sulfate / lectican fragments	TLR4	proinflammatory microglial priming	moderate
Versican fragments (matrikines)	TLR2	myeloid priming	moderate (tumour / inflammation)
Tenascin-C (co-induced)	TLR4	sustained inflammatory priming	established in arthritis; inferential in AD
ATP from the de-shielded PV neuron	P2X7	K+ efflux › NLRP3 activation	established mechanism; contextual inference

Table 2. The return arc — perineuronal-net degradation products as priming and activating signals for the microglial inflammasome.

5.3 The Oxidative Coupling at the Parvalbumin Cell

There is a third strand to the return arc, and it runs not through the matrix fragments but through the neuron the matrix protected. The perineuronal net's antioxidant and iron-chelating office is among its best-evidenced functions: its experimental removal renders the enclosed parvalbumin interneuron measurably more vulnerable to oxidative insult, and aggrecan, link protein, and tenascin-R are each required for that protection (Cabungcal et al., 2013; Suttkus et al., 2014). A stripped parvalbumin cell is therefore an oxidatively stressed one — and mitochondrial reactive oxygen species are a canonical activating signal of the NLRP3 inflammasome (Zhou et al., 2011). The oxidative consequence of net loss thus feeds the same sensor as the matrix fragments do, from a different direction: the de-shielded neuron becomes a local generator of the redox danger signals that fire the microglial inflammasome in its vicinity, and, should it release ATP as it decompensates, of the purinergic P2X7 signal that drives the potassium efflux underlying NLRP3 activation. The parvalbumin cell, on this reading, does not merely suffer the loss of its net; its suffering becomes an input to the loop that took it.

6. Chapter III The Matrix Inflammasome Loop

6.1 The Inner Loop Nested in the Perineuronal Turn

The forward and return arcs, joined, describe a loop, and the loop is the paper's central synthetic claim. The inflammasome, primed by amyloid and by the standing inflammation of the disease, matures interleukin-1β; interleukin-1β induces the aggrecanases and metalloproteinases that cleave the net; the cleavage liberates hyaluronan, lectican, and tenascin fragments and oxidatively exposes the parvalbumin cell; and these products prime and fire the inflammasome anew. Each output returns as an input, and the loop is positive.

Its significance is best seen against the self-sustaining loop of *The Perineuronal Turn*. That loop is real and circuit-level: net stripping disinhibits the excitatory cortex, the disinhibited cortex releases more amyloid and tau in an activity-dependent manner, the rising pathology sustains the matrix-degrading microglion, and the microglion strips further net. It is a loop whose shortest path runs from the matrix, out through the pyramidal population and the proteins it releases, and back to the matrix. The matrix–inflammasome loop proposed here is nested inside it and shorter: it runs from the matrix to the microglial inflammasome and back to the matrix, without the excitatory detour. A degrading net generates fragments that fire the inflammasome that drives the proteases that degrade the net — a self-contained catabolic circuit local to the perineuronal space. A shorter loop has a higher gain and a lower activation threshold, and its presence would mean that the transition's feed-forward character does not depend entirely on the excitatory cascade to sustain itself, but has, in the inflammasome, a tighter engine running underneath.

6.2 The Threshold and the Latent Interval

The inner loop inherits, and sharpens, the threshold behaviour that *The Perineuronal Turn* attributes to the transition. Early, the loop's gain is low: the net is intact, few fragments are generated, the inflammasome fires only transiently on the amyloid signal, and the matrix turns over under homeostatic control. As stripping begins, fragments accumulate, the oxidative burden on the parvalbumin cell rises, priming becomes chronic, and the loop's gain climbs past unity — beyond which the degradation of the net sustains the inflammasome that sustains the degradation, independent of the original amyloid stimulus. This is the molecular reading of the transition's irreversibility: past the tipping point, removing the upstream amyloid trigger no longer arrests a loop that now supplies its own inputs from the matrix.

The reading maps directly onto the latent interval, the window of rescue on which the perineuronal-net theory stakes its therapeutic claim. The interval between the loss of the net and the loss of the parvalbumin neuron is, in inflammasome terms, the interval during which the inner loop is running but the neuron it will kill still lives — and it is therefore the interval during which interrupting the loop, by silencing the inflammasome, could break the feed-forward before the cell is lost. The perineuronal-net theory identifies *what* to preserve (the net) and *when* (the latent interval); the inflammasome coupling adds *how* (interrupt the loop at the sensor, the cytokine, or the protease).

The two theories are, in this, complementary halves of one therapeutic proposition.

7. Chapter IV The Resilience Switch and the Reconciliation

7.1 Homeostatic Remodeling versus Pathological Stripping

The resilience finding of de Vries and colleagues poses a question the matrix biology alone cannot answer. Resilient individuals, carrying the molecular pathology of the disease without its cognitive expression, preserve their perineuronal nets and show homeostatic net remodeling rather than the protease-driven degradation of clinical disease. But ADAMTS and MMP activity is not intrinsically pathological — it is also the ordinary machinery of physiological matrix turnover, of developmental plasticity, and of the net remodeling that normal learning requires. The same enzymes, then, subserve both the net's healthy plasticity and its diseased destruction, and nothing in the enzymology distinguishes the two fates. What sets a net that is being remodeled apart from a net that is being stripped?

The inflammasome coupling proposes an answer: the difference is one of inflammasome tone. Under homeostatic conditions, aggrecanase and metalloproteinase activity is transient, local, and stimulus-bounded — turnover under control. When the inflammasome is chronically driven, the same enzymes are induced continuously and at high amplitude, and their activity crosses from controlled turnover into runaway catabolism. The switch between the net's two fates, on this reading, is not a switch between two sets of enzymes but between two levels of the signal that commands them; and the resilient brain is the brain in which that signal is held below its threshold — whether by lower amyloid-driven priming, by a more restrained microglial phenotype, by protective genetics of the innate-immune axis, or by whatever combination the resilience literature will eventually resolve. Resilience, in inflammasome terms, is the net never entering the loop.

7.2 Why the Inflammasome Predicts Core-Directed Degradation

The coupling makes a second, more specific contribution to the perineuronal-net theory: it predicts the exact molecular signature on which *The Perineuronal Turn* stakes its reconciliation of the loss-versus-preservation debate. That theory resolves the apparent contradiction — nets reported lost by some methods and preserved by others — by proposing that the net is "stage- and compartment-specifically stripped at its aggrecan core," a degradation visible to antibodies against the proteoglycan core but maskable to the lectin stains that report only the sulfated-glycan coat. The inflammasome mechanism predicts precisely this signature. The ADAMTS aggrecanases induced by interleukin-1β cleave the aggrecan *core protein*, at its interglobular domain, liberating the glycosaminoglycan-bearing portion while the core is severed; the immediate readout of aggrecanase activity is therefore a loss of core integrity that can precede, and dissociate from, any change in the glycan coat that the lectin recognises. A net whose core is being cut by inflammasome-driven ADAMTS would read as functionally stripped by core-directed antibody and as partially preserved by lectin — exactly the dissociation the perineuronal-net theory invokes. The coupling thus does not merely borrow the theory's central prediction; it supplies the mechanism that generates it.

8. Chapter V An Assessment of Validity: Grading the Arcs

8.1 The Strong Arcs

Three arcs are strong. That interleukin-1β induces the ADAMTS aggrecanases and matrix metalloproteinases that cleave aggrecan is among the best-established mechanisms in matrix biology, reconstructed in exhaustive detail in cartilage, with ADAMTS-5 deletion preventing aggrecan loss in vivo (Glasson et al., 2005; Stanton et al., 2005; Kapoor et al., 2011); its strength as a *general* cytokine-to-protease mechanism is not in doubt. That microglia are the effectors of perineuronal-net loss in Alzheimer's disease, and that net degradation precedes parvalbumin depletion, is established by Crapser and colleagues (2020). And that low-molecular-weight hyaluronan primes through Toll-like receptors and activates the NLRP3 inflammasome is established in sterile-inflammation immunology (Jiang et al., 2005; Yamasaki et al., 2009). These three arcs — cytokine-to-aggrecanase in general, microglia-to-net in AD, and hyaluronan-to-inflammasome in general — are each individually well-founded.

8.2 The Moderate Arcs

Two arcs are moderate: strong in their system of origin, inferential in their transfer to the Alzheimer perineuronal net. The forward cytokine-to-protease arc, though textbook in cartilage, has not been reconstructed end-to-end in the AD brain — that interleukin-1β, specifically, is the principal inducer of the specific ADAMTS activity that strips the specific net is a well-motivated extrapolation rather than a demonstrated fact, because the brain's ADAMTS regulation and cellular context differ from cartilage's even where the substrate is shared. The return fragmentome arc — that the specific hyaluronan, lectican, and tenascin fragments of the degrading net prime and fire the microglial inflammasome in situ — rests entirely on the transfer of peripheral and injury immunology to a setting in which it has not been directly shown. Both arcs are load-bearing for the coupling and both await their reconstruction in the correct tissue.

8.3 The Contested Arcs and the Parallel-Effects Problem

Two claims are contested or unproven. The closed matrix–inflammasome loop is a novel synthesis, not a demonstrated mechanism: no study has shown the loop operating as a loop in Alzheimer's disease, and its existence is inferred from the separate evidence for its two arcs. And the initiating role is rejected outright — both the inflammasome and net loss are downstream of aggregated amyloid, and neither the coupling nor its loop is proposed to begin the disease.

The gravest objection is the parallel-effects alternative, and it must be stated at full strength. Amyloid-β independently activates the NLRP3 inflammasome (Halle et al., 2008) and independently drives microglial net degradation; inflammasome activation and net stripping may therefore be two parallel consequences of a shared upstream cause, temporally coincident but not causally coupled, and the appearance of a loop may be an artefact of their common driver. The paper cannot exclude this alternative, and it does not pretend to. What it offers against the alternative is the forward arc's mechanistic directness — interleukin-1β does not merely accompany aggrecanase induction but is its known inducer, which is a coupling and not a coincidence — and the return arc's demonstration, in other tissues, that matrix fragments genuinely activate the inflammasome, which supplies a real and not merely hypothetical feedback. Even were the loop to fail, however, the paper's robust residue survives: the inflammasome supplies the specific molecular identity of the "microglial activation" that the perineuronal-net formulation leaves as a placeholder, and that contribution stands whether or not the return arc closes the loop.

Arc	Claim under assessment	Verdict
Forward (general)	interleukin-1β induces the ADAMTS/MMP aggrecanase program	Strong in cartilage; Moderate in the AD net
Forward (microglial agency)	microglia strip the net; degradation precedes PV loss	Strong (Crapser 2020)
Return (backbone)	low-MW hyaluronan primes and activates NLRP3	Strong in immunology; Inferential in the AD net
Return (fragmentome)	lectican / tenascin fragments prime the inflammasome	Moderate; Inferential in the AD net
The closed loop	net loss and inflammasome form a self-amplifying loop	Contested; novel synthesis, undemonstrated
The resilience switch	inflammasome tone distinguishes remodeling from stripping	Speculative but testable
Initiation	the loop initiates the disease	Rejected (downstream of amyloid)

Table 3. Grading the arcs of the inflammasome–matrix coupling.

9. Chapter VI Therapeutic Implications and Falsifiable Predictions

9.1 The Prediction the Coupling Makes

The coupling makes one therapeutic prediction that neither parent axis makes alone, and it is the paper's most consequential and most testable claim: that selective inflammasome inhibition should *preserve the perineuronal net*. If interleukin-1β is the principal inducer of the aggrecanase program that strips the net, then blocking the inflammasome, or the interleukin-1 receptor, should reduce ADAMTS and MMP activity in the perineuronal space and slow net degradation — and, because net degradation precedes parvalbumin loss, should do so within the latent interval, before the cells are lost. This is a prediction that unites the therapeutic surfaces of both axes: the selective NLRP3 inhibitors (MCC950, OLT1177) and caspase-1 inhibitors (VX-765) of *The Sensor and the Speck* become candidate net-preserving agents, and the net-integrity readout nominated as a biomarker by *The Perineuronal Turn* becomes their pharmacodynamic endpoint. An inflammasome inhibitor that reduces amyloid but leaves net degradation untouched would falsify the forward arc; one that preserves the net would confirm the coupling in the one experiment that matters.

9.2 Falsifiable Predictions

The coupling is falsifiable, and its value depends on the predictions that would confirm or refute it. Five are advanced, ordered from the most to the least discriminating.

Prediction 1 — Inflammasome inhibition preserves the net. Selective NLRP3 or caspase-1 inhibition, administered before or during the stripping, will reduce perineuronal-aggrecanase activity and preserve the aggrecan core of the parvalbumin net; failure to preserve the net despite adequate inflammasome inhibition falsifies the forward arc as the operative mechanism of the stripping.

Prediction 2 — Interleukin-1β drives the aggrecanases in the net. Conditional loss of interleukin-1 signalling, or of NLRP3, in the microglia of an amyloid model will lower ADAMTS-4/ADAMTS-5 expression in the perineuronal space and delay net loss, dissociating net stripping from the residual amyloid that a parallel-effects model predicts would strip it regardless.

Prediction 3 — Net fragments activate the microglial inflammasome. Low-molecular-weight hyaluronan and defined lectican fragments derived from perineuronal aggrecan will prime and activate the NLRP3 inflammasome in microglia, and net degradation in vivo will be accompanied by a rise in inflammasome activation in the immediate perineuronal microenvironment. Absence of such activation despite net degradation falsifies the return arc.

Prediction 4 — The signature is core-directed. The net degradation driven by the coupling will present as aggrecan-core cleavage with relative glycan-coat retention — the dissociation *The Perineuronal Turn* predicts — and inflammasome inhibition will preserve the core specifically; a purely coat-directed or inflammasome-independent degradation would not fit the mechanism.

Prediction 5 — Resilience tracks inflammasome tone. Cognitively resilient individuals with high pathology and preserved nets will show lower perineuronal inflammasome activation than clinically affected individuals with matched pathology; if resilient and affected brains show equal inflammasome tone despite divergent net integrity, the resilience-switch hypothesis is not supported.

9.3 The Honest Therapeutic Summary

The coupling's therapeutic promise is real and specific — a mechanistic rationale for repurposing the inflammasome inhibitors of one axis as the net-preserving agents of another — but it inherits the discounts of both parents. The inflammasome interventions are mouse-validated in a field whose anti-inflammatory translational record is close to unbroken failure; the perineuronal-net target is human-anchored but pharmacologically unproven; and the coupling itself is, at the loop level, undemonstrated. The paper's contribution is not a therapy but a testable unification: it names a single experiment — does inflammasome inhibition preserve the net? — whose outcome would confirm or refute the edge between the two axes, and it specifies the readout by which that experiment should be judged.

10. Conclusion

This paper set out to join two axes of the corpus that had been developed apart — the NLRP3 inflammasome of *The Sensor and the Speck* and the perineuronal net of *The Perineuronal Turn* — and to do so at the level of specific molecules rather than loose analogy. It found the join already half-named. The perineuronal-net formulation attributes the stripping of the net to an "inflammasome-primed microglion" and to the aggrecanases and metalloproteinases it secretes, but leaves unspecified the signal that couples the activation to the proteolysis; the inflammasome formulation develops that signal in full but stops at the cytokine. The forward arc of this paper closes the gap between them: interleukin-1β, the cytokine the inflammasome exists to mature, is the best-characterised inducer of the aggrecanase program that cleaves the net's aggrecan core, in a mechanism transplanted, with due caution, from the cartilage biology in which it is textbook. The return arc, more novel and more inferential, observes that the net's own fragments — its hyaluronan backbone above all — are established activators of the inflammasome, so that the degrading net arms the sensor that degrades it; and the two arcs close a loop nested inside, and tighter than, the circuit-level loop the perineuronal-net theory already describes.

The paper grades this coupling without indulgence. The forward cytokine-to-aggrecanase mechanism is strong in cartilage and moderate in the brain; the microglial agency of net loss is

strong; the return arc is strong in immunology and inferential in the perineuronal net; the closed loop is a novel synthesis awaiting its demonstration; and the whole is conceded to be downstream of amyloid and vulnerable to the parallel-effects alternative, which the paper cannot exclude. What survives every discount is the robust contribution and the single prediction that carries it: the inflammasome supplies the specific, druggable molecular identity of the "microglial activation" that the perineuronal-net axis has left as a placeholder, and if it does, then inhibiting the inflammasome should preserve the net. The perineuronal-net theory said what to protect and when; this paper says how — and names the experiment that would prove it right or wrong. The net is stripped by an enzyme, the enzyme is called by a cytokine, and the cytokine is made by the speck. If that chain holds, then the structure whose loss defines the transition and the organelle whose activation defines the innate-immune disease are the same lesion, read from two ends.

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