ORGANIC NETWORK SYNTHESIS

A Comprehensive Evaluation of the C4d-LilrB2 Axis in the Pathogenesis of Alzheimer’s Disease

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Synaptic Loss in Alzheimer's Disease: Evaluation of the C4d-LilrB2 Axis

Abstract

Cognitive decline in Alzheimer's disease (AD) correlates most strongly with loss of excitatory synapses in the hippocampus, neocortex, and entorhinal cortex—more robustly than with fibrillar amyloid plaque burden or neurofibrillary tangle load. Recent research by Barbara K. Brott, Carla J. Shatz, and colleagues identifies the complement cleavage product C4d as a high-affinity ligand for the neuronal receptor Leukocyte immunoglobulin-like receptor subfamily B member 2 (LilrB2), and its murine ortholog, Paired immunoglobulin-like receptor B (PirB). This analysis evaluates the biochemical, biophysical, and spatial evidence for C4d-LilrB2 binding and traces the downstream cofilin-actin signaling cascade that leads to dendritic spine collapse. The work integrates human genomic, fluid biomarker, and functional data to assess the mechanism's relevance to neurodegeneration. While the C4d-LilrB2 pathway provides a coherent mechanistic account of complement-mediated synaptic loss, critical questions remain about its relative contribution to overall AD pathology, the determinants of synapse-specific vulnerability, and the therapeutic efficacy of pathway antagonism in human patients.

Introduction

Alzheimer's disease represents a major global health burden, with dementia prevalence projected to rise substantially by mid-century[1]. Despite decades of investigation and billions in pharmaceutical investment, only modestly effective disease-modifying therapies exist[2].

The Amyloid Cascade Hypothesis and Its Limitations

For much of the modern research era, the Amyloid Cascade Hypothesis dominated AD research: fibrillar amyloid-beta (Aβ) accumulates, triggering tau hyperphosphorylation[4], neuronal death, and cognitive decline[4]. However, several observations have complicated this model:

- Up to 44% of cognitively normal older adults possess amyloid burdens equivalent to those in advanced AD[5]
- Individuals with minimal plaque pathology can exhibit severe dementia if synaptic loss is prominent[5]
- Modern neuropathological analysis consistently shows that synaptic density, not plaque burden, predicts cognitive status[6]

This evidence has shifted focus toward understanding the specific mechanisms targeting synapses for destruction.

Complement-Mediated Pruning and Neuronal Receptors

Two partly separate research directions emerged:

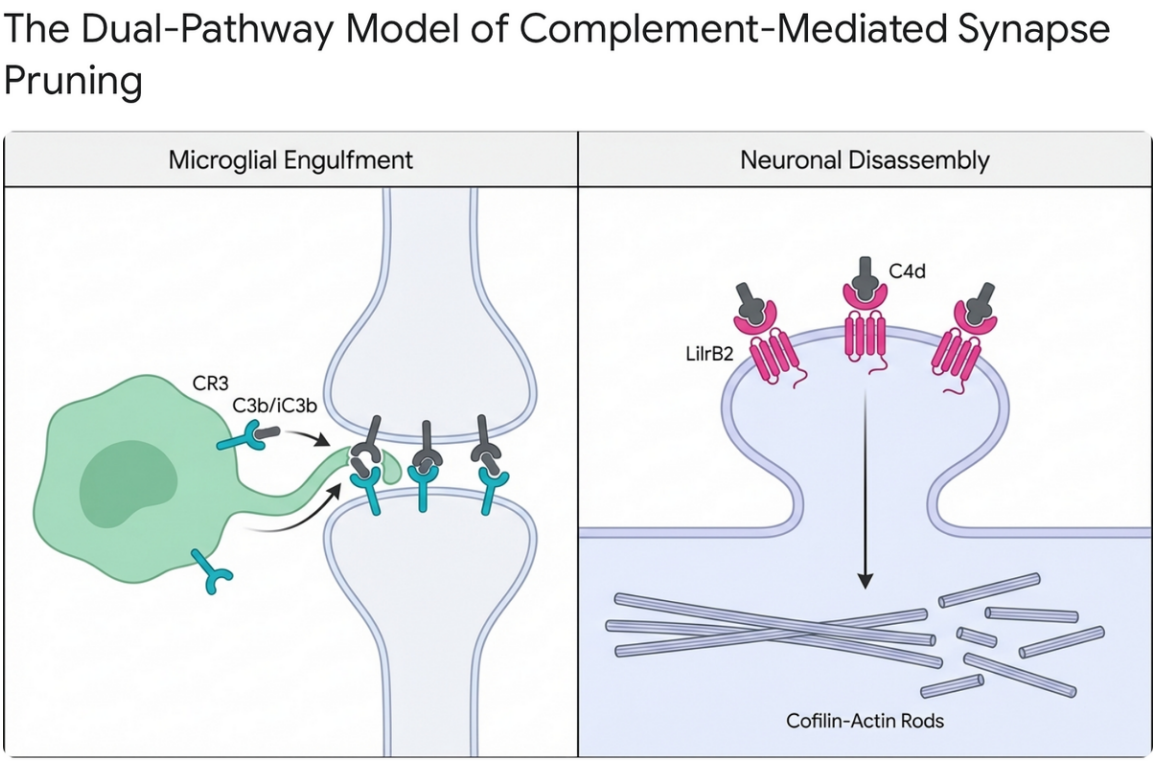
1. **Microglial Engulfment (External Mechanism)**: The classical complement cascade—specifically the C1q-C3-CR3 axis—is upregulated in AD brains[7] and recruits resident microglia to engulf synapses. Soluble Aβ oligomers activate C1q, initiating this cascade.

2. **Neuronal Receptor Signaling (Internal Mechanism)**: The Shatz laboratory identified PirB (and its human ortholog LilrB2)—an MHC Class I receptor—as highly expressed on CNS pyramidal neurons[27]. In 2013, they demonstrated that PirB/LilrB2 binds soluble Aβ oligomers with high affinity, triggering cofilin hyperactivation and dendritic spine collapse[15]. Genetic deletion of PirB in AD transgenic mice rescued synaptic plasticity and memory deficits.

The Unifying Discovery: C4d as a LilrB2 Ligand

The 2025 PNAS publication by Brott, Shatz, and colleagues provides evidence that C4d—a terminal cleavage product of complement C4—acts as a high-affinity ligand for LilrB2/PirB[16]. This finding potentially unifies external and internal mechanisms: the same complement cascade that tags synapses for microglial removal also generates a signal that instructs neurons to dismantle their own dendritic spines.

Analytical Framework



Activated complement protein C4 is cleaved to produce multiple fragments. C4b contributes to the activation of C3, leading to the tagging of synapses by iC3b and subsequent engulfment by microglia via the CR3 receptor. Concurrently, the terminal cleavage product C4d binds to the neuronal LilrB2 receptor, initiating an intracellular cascade that hyperactivates cofilin, leading to the destabilization of the actin cytoskeleton and the autonomous shrinkage of the dendritic spine.

Evaluating these claims requires integration of:

- **High-Resolution Spatial Validation**: Array Tomography (AT)[38] permits precise colocalization of LilrB2, C4d, and Aβ at individual synapses without the z-axis blurring of standard microscopy

- **Biophysical Kinetics**: Surface Plasmon Resonance (SPR) quantifies binding affinity (dissociation constants); mutant domain analysis maps binding sites
- **In Vivo Functional Validation**: Osmotic minipump infusions of C4d into mouse cortex, combined with PirB-knockout controls, test causality
- **Human Genomics**: Genome-Wide Association Studies and cerebrospinal fluid proteomics establish clinical relevance

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Chapter 1: The Molecular Architecture of the C4d-LilrB2 Axis

Complement Cascade Basics

The classical complement pathway is initiated by the C1 complex. Upon activation, C1s protease cleaves C4 into C4a (soluble) and C4b (membrane-tetherable). Factor I subsequently cleaves membrane-bound C4b into C4c and C4d; C4d remains covalently attached to the original surface.

C4d as a Previously "Orphan" Ligand

Historically, C4d has been viewed as a stable byproduct of complement activation—a clinical biomarker for antibody-mediated rejection or autoimmune activity[46]. It lacked an identified physiological receptor or known CNS signaling function.

The C4d-LilrB2 Interaction

The Brott-Shatz study identified LilrB2 as the receptor for C4d through:

- **Dot blot analysis**: LilrB2 (as an Fc-tagged extracellular domain) binds C4d intensely but shows negligible affinity for C4, C4a, or C4b
- **Surface Plasmon Resonance**: C4d binds LilrB2 with a dissociation constant (Kd) of ~3 nM (cell-free), 37 nM (HEK293 cells), 56 nM (murine PirB), and 380 nM (primary neuronal cultures)—all consistent with high-affinity binding
- **Domain Mapping**: Using truncated Fc-tagged mutants, binding maps to the N-terminal D1D2 immunoglobulin domains—the same domains that bind Aβ oligomers and MHC Class I

This makes LilrB2 a convergence receptor: it integrates signals from pathogenic protein aggregates (Aβ), neuroinflammation (C4d), and developmental/immune status (MHC-I).

Spatial Colocalization at Human Synapses

Using Array Tomography on post-mortem tissue from temporal and prefrontal cortices:

- In normal tissue, LilrB2 overlaps with C4d puncta in the neuropil
- Approximately 60% of excitatory synapses (identified by VGlut1/PSD95) show colocalized C4 or LilrB2 signal; ~30% contain explicit C4d
- In AD brains, C4d-LilrB2 colocalization is enriched near amyloid plaques
- Oligomeric Aβ, LilrB2, and C4d are frequently detected together at individual synapses showing signs of distress

This spatial evidence places the molecular machinery at sites of maximal pathology and cognitive decline.

Chapter 2: Signal Transduction and Structural Collapse

Actin Dynamics and Cofilin

Dendritic spine architecture depends on a dynamic network of filamentous actin (F-actin). Cofilin—an actin-severing protein—regulates this balance:

- **Phosphorylated cofilin** (inactive): F-actin networks remain stable; the spine maintains structural integrity[17]
- **Dephosphorylated cofilin** (active): Severing F-actin monomers increases structural fluidity; brief activation supports normal synaptic plasticity

The balance is maintained by kinases (e.g., LIMK) that phosphorylate cofilin and phosphatases (e.g., Slingshot/SSH1) that dephosphorylate it.

Pathological Hyperactivation

Upon binding of Aβ oligomers or C4d to LilrB2/PirB, intracellular signaling recruits phosphatases via the receptor's immunoreceptor tyrosine-based inhibitory motifs (ITIMs)[52], driving massive cofilin dephosphorylation. At pathologically elevated concentrations, active cofilin shifts from severing to bundling F-actin, forming rigid, insoluble cofilin-actin rods.

These rods:

- Occlude the dendritic spine neck[11]
- Disrupt intracellular vesicular trafficking
- Impede delivery of post-synaptic receptors (AMPA, NMDA) and mitochondria[11]
- Lead to structural spine collapse and synaptic disconnection

In Vivo Functional Evidence

Osmotic minipump infusion of recombinant C4d into adult mouse primary visual cortex resulted in:

- Rapid, statistically significant decrease in dendritic spine density on basolateral dendrites of layer 5 pyramidal neurons in wild-type mice[16]
- **Complete prevention of spine loss in PirB-knockout mice**, with spine density indistinguishable from control BSA-infused animals[16]

This demonstrates that C4d is sufficient to drive structural pruning in living mammalian brain, and that PirB receptor is the necessary conduit for this effect.

Dual-Pathway Pruning Model

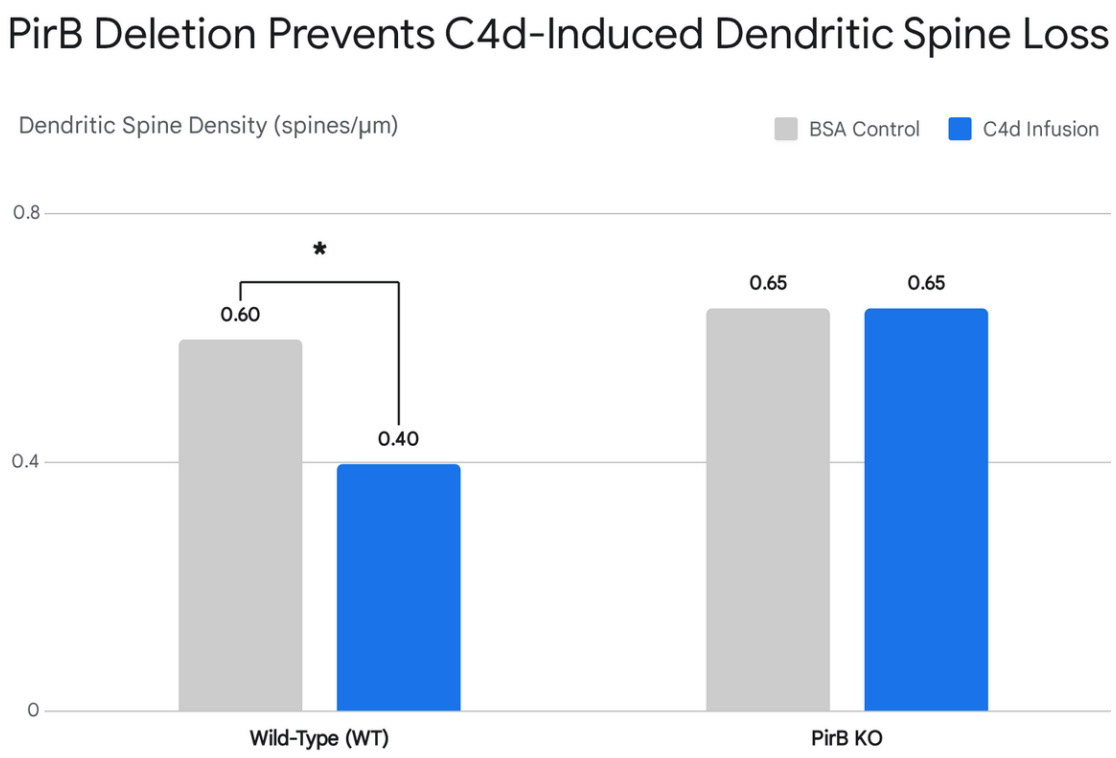
The convergent evidence suggests a unified mechanism:

1. **External (Glial) Axis**: C4b facilitates C3 cleavage into C3b/iC3b, which opsonizes the synapse and recruits CR3+ microglia for phagocytosis[48]
2. **Internal (Neuronal) Axis**: C4d remains tethered and binds post-synaptic LilrB2, triggering cofilin hyperactivation and structural collapse[16]

These processes are synergistic: a synapse that is internally destabilized, functionally silent, and shrinking via the C4d-LilrB2-cofilin axis becomes a more attractive target for microglial engulfment. Targeting only the glial component (e.g., anti-C1q, anti-CR3) may be insufficient if neuronal structural collapse proceeds

unchecked.

Chapter 3: Human Genetics, Biomarkers, and Clinical Relevance



In vivo infusion of C4d into the visual cortex of adult mice results in a significant reduction of dendritic spine density on layer 5 pyramidal neurons in Wild-Type (WT) mice. In contrast, mice lacking the PirB receptor (PirB KO) show no reduction in spine density when exposed to identical C4d levels, indicating that the PirB receptor is strictly required for C4d-mediated synaptic elimination.

Data sources: Brott et al., PNAS (2025)

Genome-Wide Association Studies

Recent large-scale GWAS (hundreds of thousands of participants) have identified over 75 AD risk loci[19]. Among the most significant novel findings is the LILRB2 locus.

Ethnic-Specific Effects: Genetic variation at LILRB2-LILRB5 shows opposite associations across populations[42]. For example, a lead variant (rs587709-T) is associated with decreased AD risk and altered LILRB5 expression in European cohorts but increased AD risk and elevated LILRB2 expression in East Asian populations. This highlights the necessity of cross-ancestry genetic studies.

Convergence with Schizophrenia Genetics

The genetic locus encoding complement C4 shows strong associations with schizophrenia—a disorder characterized by aberrant synaptic pruning in the prefrontal cortex during late adolescence. The finding that

C4d binds LilrB2 suggests a shared pathophysiological mechanism: regardless of whether the initial trigger is amyloid-driven (aging, AD) or C4 overexpression (schizophrenia), the terminal event may be C4d-LilrB2-mediated synapse elimination. **This remains speculative and requires direct experimental validation.**

C4d as a Fluid Biomarker

- Proteomic analysis of human brain tissue shows C4d is elevated ~4-fold in prefrontal cortex of AD patients versus cognitively normal controls[16]
- C4d possesses a robust plasma half-life[46] (unlike highly transient fragments C3a, C5a)
- Higher plasma C4d correlates with memory impairment, active amyloid PET accumulation, and accelerated progression from Mild Cognitive Impairment to dementia[10]
- C4d may provide a window into real-time neuroimmune activation intensity, facilitating earlier intervention and trial stratification

Unknown: The specificity of C4d for AD-related pathology versus other neuroinflammatory conditions, and whether C4d levels are better predictors of cognitive decline than existing biomarkers.

Therapeutic Targeting

LilrB2 Antagonism

Monoclonal antibodies engineered to block the D1D2 domains of LilrB2 aim to:

- Shield synapses from both Aβ-driven and C4d-driven toxicity[3]
- Preserve dendritic spine integrity and cofilin-actin architecture

Microglial Disinhibition via TREM2

LilrB2 is heavily expressed on microglia[69], where it functions as an inhibitory immune receptor that suppresses activation. TREM2 is a beneficial sensor that activates microglia to phagocytose plaques and clear debris.

Recent evidence indicates that LILRB2 acts as a molecular brake on TREM2 signaling[69]. Consequently, a LILRB2-blocking antibody may achieve dual effects:

- **Direct neuroprotection**: Prevents neurotoxic signaling at the synapse
- **Enhanced plaque clearance**: By relieving ITIM-mediated inhibition on microglia, it hyperactivates beneficial TREM2 signaling and increases microglial phagocytosis[42]

Status: This mechanism is supported by preclinical evidence; clinical efficacy in human patients remains untested.

What This Analysis Cannot Determine

Outstanding Mechanistic Questions

1. **Relative Contribution to Overall Pathology**: What proportion of AD synaptic loss is attributable to the C4d-LilrB2 axis versus other complement fragments, Aβ receptors, or tau-related mechanisms? This cannot be determined from current evidence.

2. **Synapse-Specific Vulnerability**: Why do certain synapses within the same local microcircuit become targets for C4d-LilrB2 engagement while others are spared? The spatial proximity to plaques is documented, but the determinants of selective vulnerability remain unknown.

3. **Threshold Effects and Kinetics**: Is there a minimum C4d concentration required to trigger spine loss? What is the temporal lag between receptor engagement and structural collapse in intact tissue? These remain untested in human brain.

4. **Interaction with Other Pathways**: How do Aβ oligomers, tau, and C4d signaling interact at individual synapses? Do they compete, cooperate, or activate distinct populations of spines?

Translational Uncertainties

1. **Clinical Efficacy of LilrB2 Antagonism**: Preclinical evidence supports the mechanism, but Phase 1/2a clinical trials in human AD patients have not yet reported final efficacy endpoints. The safety profile in central nervous system pathology is unknown.

2. **Biomarker Specificity**: While C4d elevation correlates with AD pathology, specificity for AD-related mechanisms (versus, for example, microglial activation from infection, stroke, or other inflammatory conditions) is not established.

3. **Ethnic-Specific Therapeutic Response**: The opposing genetic associations at LILRB2 across populations suggest that antagonism may benefit some ancestry groups while potentially worsening disease in others. This critical question requires prospective, diversified clinical research.

4. **Long-Term Safety of Complement Inhibition**: Chronic inhibition of complement pathways—already implicated in healthy synaptic pruning during development and neural circuit refinement—could alter normal plasticity, learning capacity, or immune surveillance. Duration and reversibility of these effects are unknown.

Model Limitations

1. **Species Translation**: The primary experimental evidence derives from murine models and post-mortem human tissue. Acute C4d infusion in mouse cortex differs from chronic, system-wide complement dysregulation in aging human brain.

2. **Cell-Type Specificity**: While LilrB2 is expressed on neurons and microglia, contributions from glial cells, astrocytes, and other CNS cell types have not been fully characterized.

3. **Genetic Background**: AD transgenic mouse models may not recapitulate the full complexity of late-onset AD, where amyloid accumulation is often asymptomatic and multiple parallel pathologies contribute to decline.

Conclusion

The identification of C4d as a high-affinity LilrB2 ligand provides a mechanistic account of how the complement cascade—a system evolved for pathogen opsonization—can drive pathological synapse elimination in AD. The evidence integrates structural biology, neuroanatomy, transcriptomics, and in vivo physiology. Spatial colocalization at vulnerable synapses, high-affinity binding kinetics, and functional rescue in PirB-knockout mice establish the C4d-LilrB2 axis as one contributory mechanism in AD pathogenesis.

However, the scope of this mechanism's contribution to overall cognitive decline remains incompletely defined. The convergence of evidence from multiple disciplines is suggestive rather than definitive.

Therapeutic antagonism of LilrB2 represents a rational next step, with dual benefits for synaptic preservation and microglial plaque clearance. But clinical efficacy, optimal patient selection, and long-term safety in human patients remain to be determined through rigorous prospective trials.

The work of Brott and Shatz illuminates a specific molecular node—C4d-LilrB2-cofilin—in the neuroimmune cascade. It advances mechanistic understanding but does not resolve the fundamental paradox of AD: why some individuals accumulate pathology without cognitive decline, why some decline without pathology, and how to intervene safely and effectively in an aging system that depends on many of these same mechanisms for normal function.

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