

Alzheimer's Disease as a Failure of Immune Resolution

An Infection-Triggered Neuroimmune Cascade Model and Therapeutic Rationale for IgG3 Immunotherapy

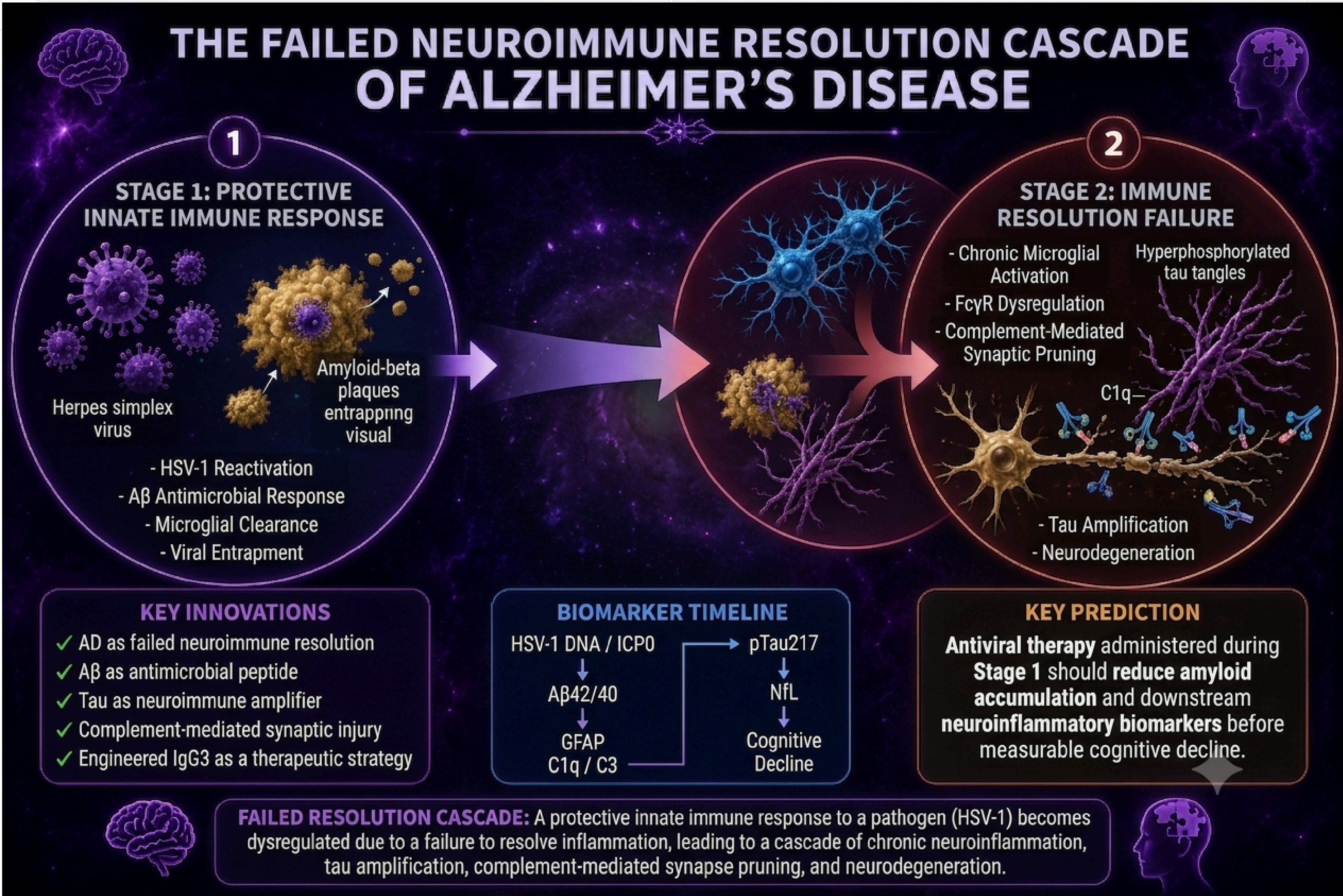


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INTRODUCTION	QUESTION & OBJECTIVES	METHODOLOGY	WHY THIS MATTERS
- Alzheimer's disease is characterized by amyloid-β plaques and tau neurofibrillary tangles.¹ - Current anti-amyloid therapies remove plaques but provide only modest clinical benefit.²⁻³ - Amyloid-β may function as an antimicrobial peptide within innate immunity.⁴⁻⁵ - Chronic neuroinflammation is increasingly recognized as a major driver of disease progression.⁶ - IgG3 exhibits the strongest Fc-mediated immune effector functions and may help restore immune resolution and enhance pathological clearance.⁷⁻⁸	QUESTION Can Alzheimer's disease originate from a failure of immune resolution rather than amyloid accumulation alone? OBJECTIVE Evaluate evidence linking infection and AD Examine immune-resolution pathways Develop an integrated disease model	METHODOLOGY Literature-Based Conceptual Framework Development Databases: PubMed, Scopus, Google Scholar Topics Reviewed: Infection • Amyloid Biology • Neuroinflammation • Complement • Tau • Immunotherapy Outcome: Development of an integrated neuroimmune disease model.	Current therapies target plaques. This model explores whether chronic immune dysfunction drives disease progression and whether IgG3-based approaches could restore immune balance.

EVIDENCE SUPPORTING THE MODEL

- Pathogens Linked to AD: HSV-1, HHV-6, and P. gingivalis consistently detected in AD brains.⁹**
- Antimicrobial Amyloid: A β peptide functions as an innate trap for micro-organisms.⁴**
- Neuroinflammation: Chronic microglial activation directly predicts cognitive decline rates.⁶**
- Synaptic Loss: Complement cascade activation drives aberrant microglial pruning.¹⁰**



THERAPEUTIC RATIONALE FOR IgG3

- Strongest Fc γ receptor binding profile
- Potent classic complement activation
- Enhanced microglial phagocytosis kinetics
- Rapid immune-complex clearance
- High-affinity microglial engagement

PROPOSED BIOMODULATORY ROLE:

- Restore active immune resolution
- Accelerate pathological clearance
- Dampen chronic neuroinflammation

TESTABLE PREDICTIONS	CLINICAL IMPLICATIONS		NOVEL CONTRIBUTION
- Biomarkers: Microbial and inflammatory markers trackably precede plaque presentation. - Kinetics: Local complement activation occurs prior to regional tau spread. - Prognosis: Neuroinflammation dynamics dictate absolute clinical velocity. - Therapeutics: Early resolution therapy yields superior efficacy over late-stage ablation.	Current Strategy	Proposed Strategy	Unifies infection biology, antimicrobial amyloid function, complement-mediated synaptic injury, neuroinflammation, and tau amplification into a testable neuroimmune-resolution framework for Alzheimer's disease.
	Remove plaques	Restore immune resolution	
	Target amyloid	Target neuroimmune dysfunction	
	Late intervention	Earlier intervention	

TAKE-HOME MESSAGE

What if Alzheimer's disease is not primarily a disease of plaque accumulation, but a disease of failed immune resolution? This framework proposes that amyloid- β begins as a protective response, while chronic neuroinflammation becomes the true driver of neurodegeneration. Targeting immune resolution may therefore be as important as targeting plaques themselves.

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