

Alzheimer's Disease As A Disorder Of The Innate Immunity: A Unifying Mechanistic Framework

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Amyloid and tau are not toxins but innate immune effectors driven in parallel by one MyD88-biased signal and ApoE4 is a broken brake that lets the response become self sustaining

INTRODUCTION

For three decades, Alzheimer's disease has been treated as a primary proteinopathy, amyloid- β and tau as direct toxins driving neurodegeneration. But the model leaves core observations unexplained, while genetic risk clusters around innate-immune genes (APOE, TREM2, CD33, CR1) rather than protein-handling genes.

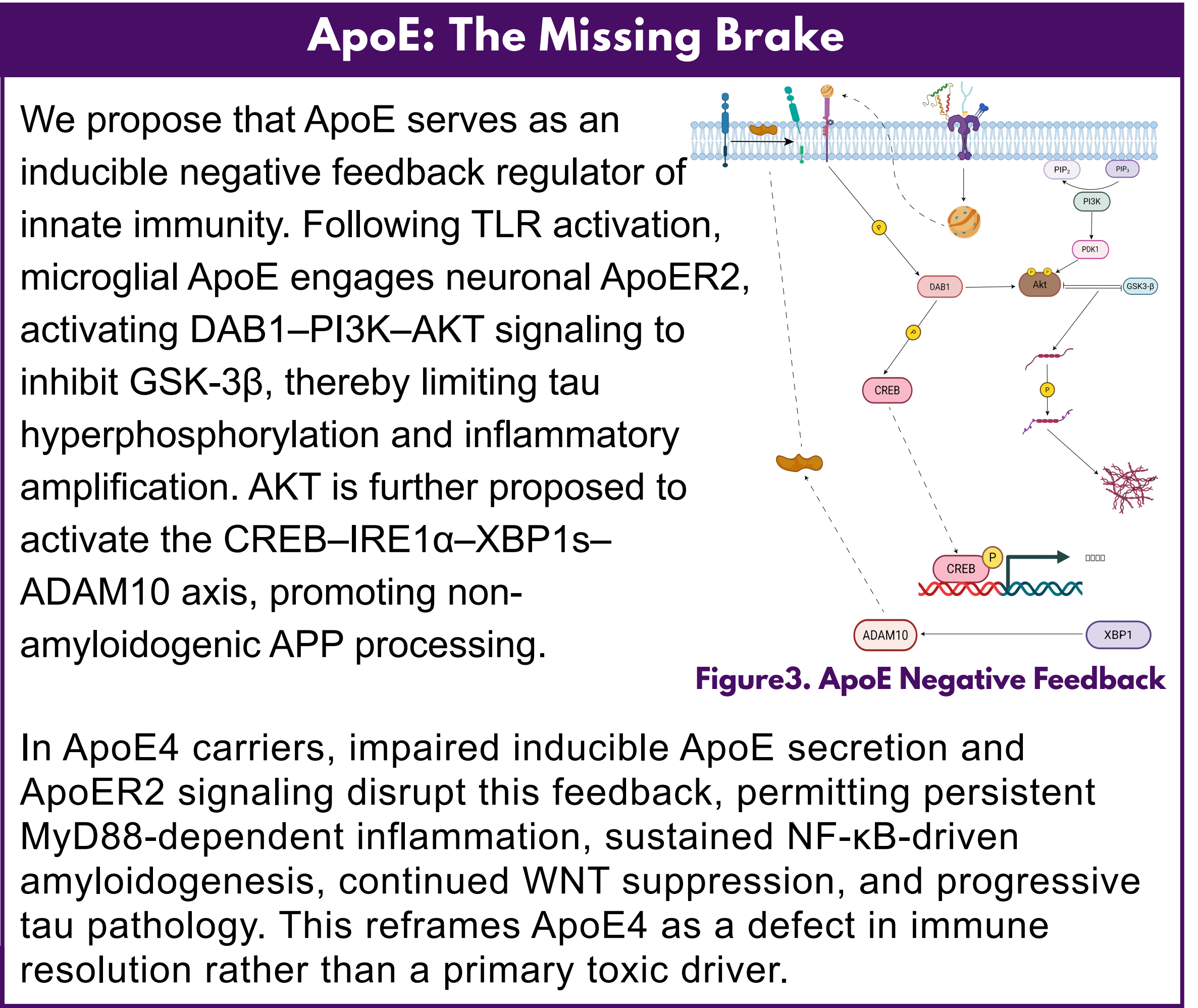
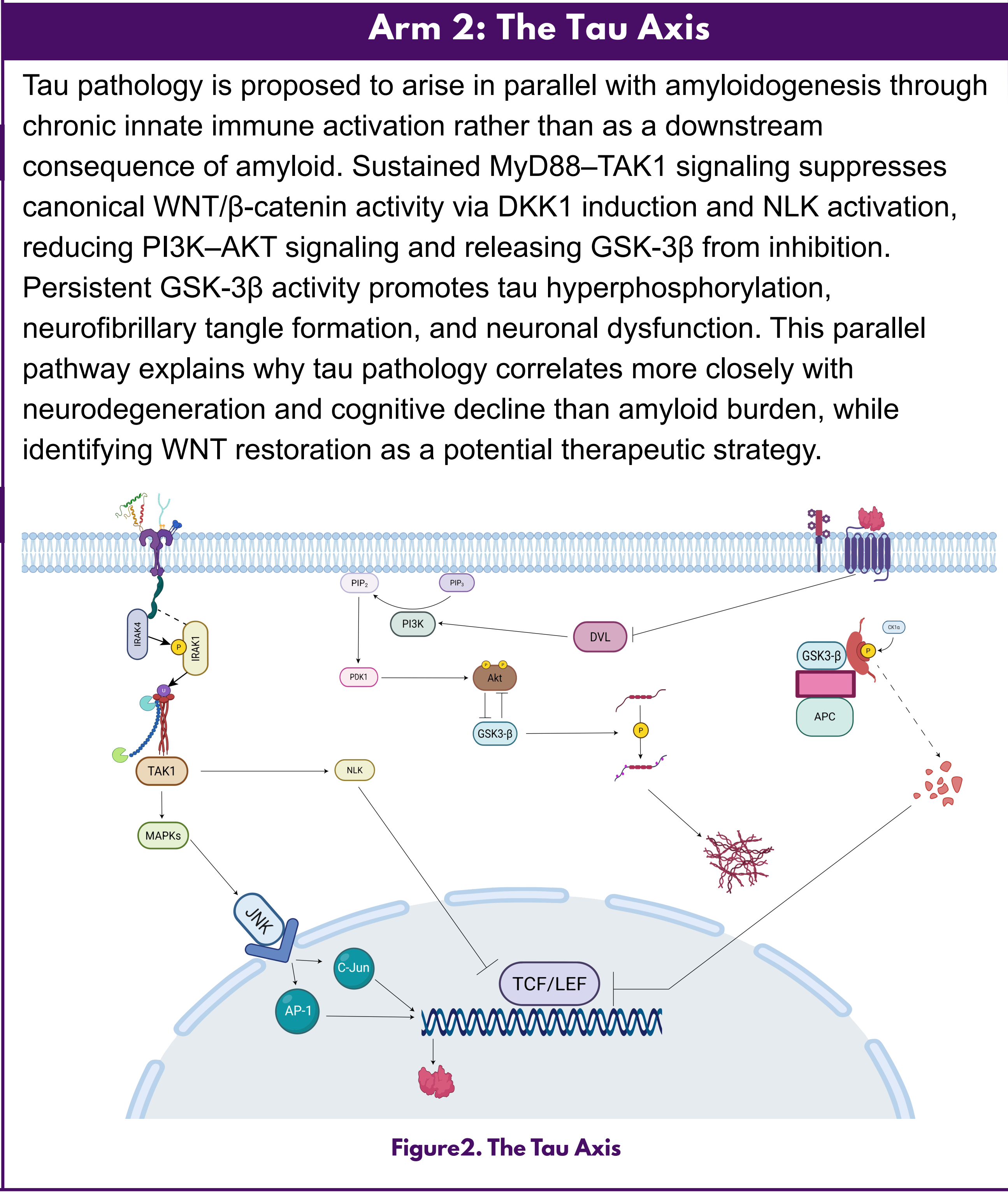
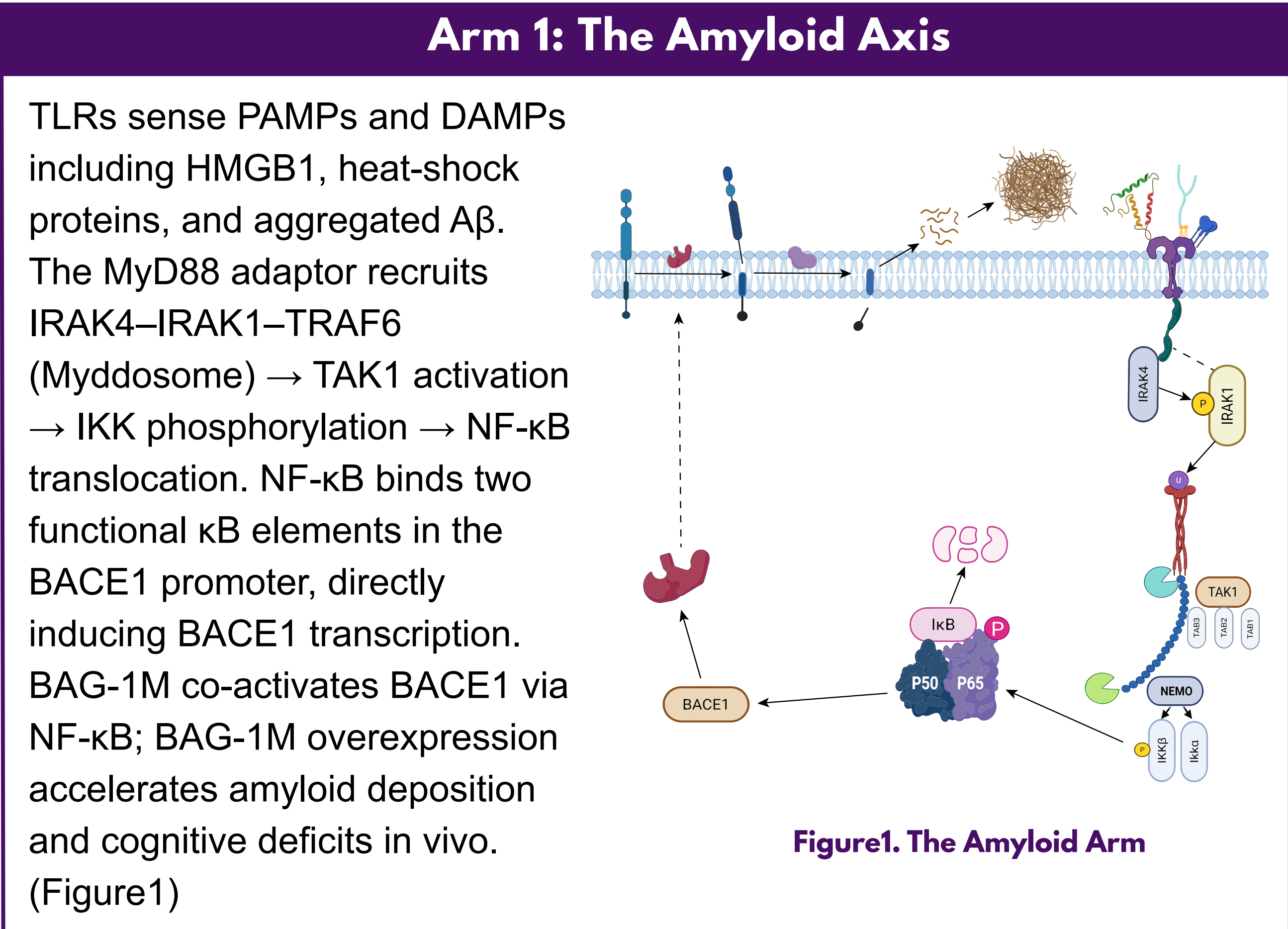
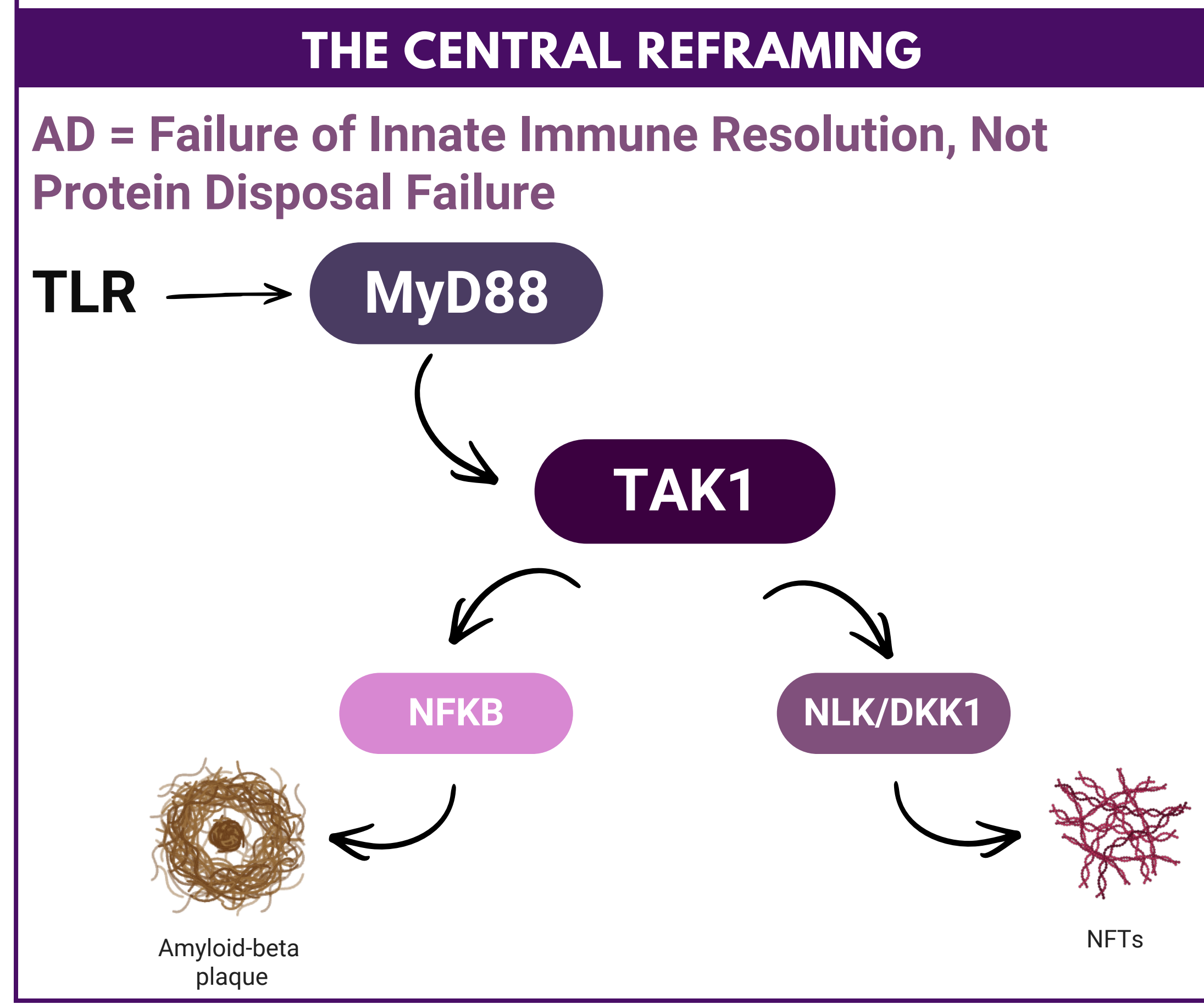
This framework reframes amyloid- β and tau as innate-immune effectors whose chronic persistence, not their existence, is the disease.

Four paradoxes the amyloid hypothesis can't resolve:

- Amyloid burden tracks poorly with cognition, tau tracks it far more closely
- Cognitively normal people can carry substantial amyloid loads
- Anti-amyloid drugs clear plaque but give only modest clinical benefit
- APOE ϵ 4 risk is non-linear (2–4 $\times$ het, 8–12 $\times$ homozygous), not explained by clearance alone

METHODS

We integrated epidemiological, genetic, and molecular evidence to construct a unified mechanistic model centered on innate immune signaling in the brain. This framework synthesizes data on Toll-like receptor (TLR) signaling bias, MyD88-dependent inflammatory cascades, NF- κ B-mediated amyloidogenic processing, suppression of canonical WNT/ β -catenin signaling, and apolipoprotein E (ApoE) biology.



CONCLUSION

This framework redefines Alzheimer's disease as a disorder of dysregulated innate immunity rather than a primary proteinopathy. Chronic MyD88-biased signaling drives two parallel pathological axes : NF- κ B-mediated amyloidogenesis and WNT/ β -catenin suppression–mediated tau pathology. We propose that ApoE functions as an inducible negative feedback regulator of this response, with ApoE4-mediated feedback failure permitting chronic self-sustaining neuroinflammation. This unifying model integrates genetic risk, amyloid, tau, and neuroinflammation into a single mechanistic architecture, generating experimentally testable predictions and highlighting upstream restoration of immune homeostasis as a promising therapeutic strategy.

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