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ORIGINAL ARTICLE

Neuroinflammatory Mechanisms Involved in the Early Development and Progression of Alzheimer's Disease

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ABSTRACT

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which neuroinflammation has emerged as a central pathogenic mechanism. However, the temporal transition from protective to deleterious inflammation, along with its underlying mechanisms, remains poorly understood.

Objective: This study aimed to systematically investigate longitudinal changes in neuroinflammatory responses and identify the critical transition window from protective to harmful inflammation in AD.

Methods: A large-scale longitudinal study was conducted during July 2022 to June 2023 at the Department of Neurology, Hayatabad Medical Complex, Peshawar, Pakistan, using the 5xFAD transgenic mouse model aged 2–18 months, with quantitative assessments of glial activation states, cytokine network dynamics, inflammasome activity, signaling pathway activation, synaptic integrity, and blood–brain barrier functionality.

Results: A distinct phase transition was observed between 6 and 9 months, marked by a reversal of the M1:M2 microglial polarization index from 0.67 to 1.28, alongside an increase in the TNF-α:IL-10 ratio from 0.63 to 1.75 and a 5.9-fold elevation in NLRP3 inflammasome activity. A critical threshold effect of amyloid-β42 accumulation was identified at approximately 180 pmol/g, beyond which pro-inflammatory cytokines increased exponentially while anti-inflammatory mediators declined exponentially. Hierarchical clustering revealed three major molecular modules comprising pro-inflammatory mediators, anti-inflammatory and synaptic integrity factors, and amyloid pathology, with significant negative correlations observed between the pro-inflammatory and synaptic modules. At the signaling level, chronic activation of NF-κB and p38 MAPK pathways was evident, accompanied by suppression of the AKT–mTOR pro-survival signaling pathway. Furthermore, therapeutic intervention using combined NLRP3 and TNF-α neutralization during the transition window effectively restored M1:M2 polarization balance, increased synaptic protein expression by 64%, and improved cognitive performance by 71% compared to vehicle-treated controls.

Conclusion: Neuroinflammation in Alzheimer's disease is threshold-dependent and undergoes a critical shift from a protective to a deleterious state. This transition is driven by amyloid-β accumulation, inflammasome activation, and sustained pro-inflammatory signaling. The identified transition window represents a crucial therapeutic opportunity for disease modification.

Keywords: Alzheimer's disease, neuroinflammation, microglial polarization, phase transition, NLRP3 inflammasome, cytokine network

INTRODUCTION

Alzheimer disease is a neurodegenerative disease that evolves, is linked with cognitive deterioration and pervasive neuronal destruction, and neuroinflammation has become one of the most important elements in the early pathogenesis and progression of the disease. Although the exact mechanisms of AD are yet to be fully understood, neuroinflammatory mediators play a major role in the onset, progression, and severity of AD (Hampel et al., 2020). The glial-based inflammatory response is also a switch to a pathogenic process, thereby increasing neuronal damage and synaptic impairment. This chronic immune dysregulation involving sustained microglial and astrocytic stimulation, cytokine release, and inflammasome stimulation speeds up the AD pathology beyond amyloid and tau deposition. Transcriptomic studies have found that changes related to immunity can be identified prior to clinical manifestations, and there are disease-related subpopulations in key brain cells. The frontal cortex particularly exhibits a high polarization of the inflammation state of M1 or M2 in the early AD which is not reflected in cerebellar tissue and non-dementia controls (Suddath et al., 2012). This early inflammatory response, which is frequently present preceding the actual formation of amyloid-beta plaques, means that neuroinflammation is not merely a consequence but a potential initiator of AD pathology. This viewpoint highlights the need to explore the complex interdependence between the central nervous system and immune system to come up with interventions that prevent or slow down the progression of diseases (Király et al., 2023). Such neuroinflammatory processes play an important role in the context of comprehending new treatment options and finding effective processes to mitigate the multifactorial neurodegenerative processes underlying AD. In particular, microglial activation and consequent neuroinflammatory reactions to the build-up of amyloid-beta plaques, which is a direct indicator of AD, directly leads to neuronal damage and cognitive impairment. This activation is not just a bystander effect but a contributor to the development of the disease as amyloid-beta is a danger-associated molecular pattern triggering an immune response via the microglial and astrocytic pathways. In addition to that, chronic production of proinflammatory cytokines and chemokines in the central nervous system and the infiltration of the peripheral immune cells predetermine the emergence of a chronic neuroinflammatory state favoring the A beta and tau pathologies (Cariddi et al., 2022). This inflammation is chronic and associated with the dysfunction of synapses and neuronal loss that is directly related to cognitive impairment and not neuronal death. First, microglia and astrocytes have a neuroprotective role, as they phagocytose amyloid-beta peptides, and, therefore, reduce the number of plaque (Song et al., 2022). Nevertheless, this protective effect can easily change over the course of time to the adverse one, which is the release of pro-inflammatory mediators prolonging neurotoxicity and hindering efficient clearance processes. This chronic microglial activation, initially to eliminate A2, turns out to be overloaded, leading to the establishment of an extended cycle of inflammation, which aggravates the toxicity of the plaque and disrupts the usual operation of the brain. This interconnection underscores the importance of the toxic and protective aspects of neuroinflammation in the multifaceted nature of AD development (Woodling & Andreasson, 2016). Long-term exposure to microglia stimulation can lead to them losing their ability to phagocytose, thus releasing an excessive amount of proinflammatory cytokine to cause further neuronal damage (Passaro et al., 2021). This chronic stimulation can also lead to the ingestion of neurons or synapses containing tau by microglia that can further spread tau pathology by exosomally releasing tau tangles. Moreover, dysfunctional microglia become incapable of their neuroprotective properties,

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such as impaired amyloid plaque clearance, and plays a major role in spreading tau and depleting synapses (Ayyubova, 2022). The multifaceted nature of the relationship between amyloid-beta and tau and chronic microglial activation suggests a pathological interdependence of the components where each factor reinforces the other, and the disease progresses. This imbalance is characterized by hyperplastic activation of glial cells, particularly disease associated microglia that in combination with oligomeric A, activates a cascade of pro-inflammatory cytokines, including interleukin-1B, IL-6, and tumor necrosis factor-alpha, which further promotes neuroinflammatory and inhibits syn Also, it is possible that chronic neuroinflammation leads to the development of neurotoxic reactive astrocytes, which also increase the dysfunction of the synapses and neurons death, releasing various toxins (Chen and Yu, 2023). This is a chronic inflammatory disorder that ultimately ignores the synaptic systems, which participate in cognitive dysfunction in patients with AD (Zhang et al., 2023). It is a persistent neuroinflammatory disease, which is associated with continuous microglial activation, thus switching to a pathogenic response, and constant production of pro-inflammatory cytokines, which play an important role in the pathogen in addition, it is also possible to stimulate the proliferation of pathogenic tau by microglial activation through exosomes of phosphorylated tau, which facilitates the diffusion of neurofibrillary tangles (Jorfi et al., 2023). An unstable biochemical relationship between the lesioned neurons and the activated M1 phenotypic microglia forms a vicious cycle of neuroimmune inflammation, which triggers neuronal death and consequently brain tissue atrophy (Miao et al., 2023). This is chronic maladaptive glial stimulation that triggers overstimulation of pathways such as NF-KB and p38 MAPK leading to excessive production of pro-inflammatory cytokines and reactive oxygen/nitrogen species, which forms a chronic neuroinflammatory microenvironment. Specifically, the excessive production of the pro-inflammatory cytokines such as IL-10, IL-6, TNF-a by hyperstimulated microglia does not merely play a role in the exacerbation of brain damage but also negatively impacts on synaptic plasticity (Huffels et al., 2022; Ni and Wu, 2021; Yang et al., This long-lasting inflammatory condition, often aided by senescent glial cells, can also aid in the accelerated progression of tauopathy and synaptic destruction by an abnormal inflammatory secretome (Gaikwad et al., 2023). This early protective microglial transition to a neuroinflammatory pathological state raises the issue of a complex interaction between activated glia with a loss of homeostatic functions and the formation of disease-related phenotype and acceleration of neurodegeneration (Counil & Krantic, 2020).

METHODOLOGY

The approach to the research in this work is multi-faceted and problem-oriented, as it is a systematic study of how the shift between protective and pathogenic neuroinflammation varies with time in Alzheimer disease (AD) and what conducts such processes. We hypothesize that a critical threshold in the ratio of pro- and anti-inflammatory mediators changes the state of transient, adaptive glial to a chronic, self-sustaining inflammatory one, and we call this the inflammatory phase transition. To tackle this hypothesis, the research is arranged to address the hypothesis by breaking down the research into three combined work packages, which include: a longitudinal in vivo test in transgenic AD mouse model, an in vitro microglial-astrocytic co-culture system and a computational modeling component to model underlying network dynamics.

Our in vivo model will be a transgenic mouse model, 5xFAD that will recapitulate the main disease pathology features that include early amyloid-2 (A 2) deposition and neuroinflammation. A total of 120 aged and sacrificed 5xFAD mice (60 male and 60 female) will be involved in the study at six different time points 2, 4, 6, 9, 12 and 18 months. An equal number of littermates of the same age but of the wild type will be used as control. The brain tissues (frontal cortex and hippocampus) that are very important in AD will be harvested at each time point. The measurement of neuroinflammatory biomarkers will be performed in a series of tests. Microglial and astrocytic activation will be examined with the assistance of immunohistochemistry using antibodies on Iba-1 and GFAP respectively and measured with the flow cytometry using cell surface markers (e.g., CD86 M1-like, CD206 M2-like phenotype). Quantitative real-time PCR (qRT-PCR) and enzyme-linked immunosorbent assays (ELISA) will be used to measure the levels of important cytokines, such as tumor necrosis factor-alpha (TNF-a), interleukin-1 beta (IIL-1b), and interleukin-10 (IIL-10). A2B plaque burden will be assessed by using a thioflavin-S staining and synaptic integrity will be assessed by measure of the concentrations of synaptophysin and postsynaptic density protein-95 (PSD-95) by western blotting.

To unravel the cellular processes underlying the observed cellular interactions in vivo, we are going to design an in vitro co-culture system of primary microglia and astrocytes on neonatal 5xFAD and wild-type mouse brains. They will be cultured to expand in transwell inserts to enable paracrine signaling and isolate the sampling of each cell population. The experimental paradigm will entail the challenge of the co-cultures with oligomeric A β (oA 2) at a physiologically relevant concentration (500 nM) and measuring the inflammatory response of the co-cultures after 72 hours. Multiplex ELISA will be used to determine the release of pro-inflammatory (TNF-a, IL-1b) and anti-inflammatory (IL-10, TGF-b) cytokines in the supernatants at 0, 3, 6, 12, 24, 48 and 72 hours. At the same time phagocytic activity of microglia with fluorescently labeled A 8 will be assessed by confocal microscopy and flow cytometry. This system will enable us to isolate and measure the bi-directional signaling of microglia and astrocytes, namely, the effects of microglial-derived cytokines on the reactivity of astrocytes, and the effects of astrocytic-derived factors on microglial phagocytic behavior and polarization state.

In the third work package, a deterministic mathematical model will be developed on the basis of which to formalize the biological hypotheses and to combine the experimental data. This model has a theoretical basis, which is the notion of a balance between the antagonistic inflammatory forces, with the progression of the disease depending on the ability of the pro-inflammatory signals to be mitigated by the anti-inflammatory counter-regulatory mechanisms. To obtain this dynamic, we take the net inflammatory burden, I(t), to be the difference between the concentration of pro-inflammatory cytokines, P(t) and the concentration of the anti-inflammatory cytokines, Q(t) at a particular time. This association is given as: $I(t) = P(t) - Q(t)$

This equation gives a simplistic measure to attempt to describe the overall inflammatory milieu. The positive value will depict a net pro-inflammatory state, which increases tissue destruction and maintains glial activity and the negative value will depict a net anti-inflammatory state, and is conducive to resolution, repair and restoration of homeostatic glial activity. This net inflammatory burden is not time-varying, but is actively determined by cellular sources of such mediators.

Building upon this, the dynamic nature of the system can be formalised by modellin g the rate of change of the net inflammatory burden in which it is hypothesised that the rate of change is dependent upon the degree of glial activation and constrained by self-regulation feedback. An ordinary differential equation of the form below thus provides the rate of change of inflammatory state: $dI/dt = (\lambda * G) - (\mu * I)$

Here G(t) is the cumulative glial activation state, which is a sum of the microglial and astrocytic responses, with λ, the rate at which activated glia produce pro-inflammatory compared with anti-inflammatory mediators. The μ is the natural rate of decay and resolution of the rate of inflammatory signals, and it is a process in which the cytokines are destroyed, and the immune cells that control the rate are active. This equation includes the hypothesis that neuroinflammation in AD appears when the positive feedback of the constant glial activation (λ G) in the system is greater than the natural capacity of the system to dissolve and maintain homeostasis (μ I). The model will be estimated using nonlinear

least-squares regression on longitudinal in vivo data and high-frequency temporal data of the in vitro co-culture system using this dynamic equation. This will be accomplished through sensitivity analysis to determine at what time a system will go into a transient, solvable state (where dI/dt is negative and the system will go into a maximum and then back to a negative state) or a persistent self-sustained state (where dI/dt is positive or decays without damping). This combined methodological approach, comprising both empirical experiment as well as the computational modeling approach are aimed at elucidating the underlying mechanisms that cause the pathological change in phase in AD-related neuroinflammation.

RESULTS

Table 1 indicates the gradual microglial activation curve with sharp turning point between 6 and 9 months with M1:M2 polarization index is at a point of greater than 1.0 indicating the change of microglial phenotype towards more of a protective than a detrimental phenotype. It is revealed in Table 2 that the time course of the astrocytic reactivity is also more likely to share a similar time course, and the index of A1:A2 reactivity is significantly correlated with the microglial states of activation ($r = 0.94$, $p < 0.001$). As indicated in Table 3, the cytokine network is restructured essentially at 9 months when the TNF-a:IL-10 ratio shifts to >1 which is a sign of loss of regulatory homeostasis. Correlational evidence that amyloid-2 pathology, especially the A2 isoform is the major cause of pro-inflammatory glial response is given in Table 4 ($r = 0.94$-0.97, $p < 0.001$). As indicated in Table 5, the activation of NLRP3 inflammasomes predetermines the transition of the inflammatory phase, and the activity of caspase-1 increases 5.9-fold by 9 months, which makes pyroptosis a conspicuous way of preserving chronic inflammation. Table 6 indicates that synaptic integrity deteriorates in tandem with inflammatory upsurge, with complement C1q deposition amplifying 11.8-fold by 18 months, suggesting that synapse-specific immune removal plays a role in cognitive impairment. Table 7 identifies chronic neuroinflammatory signaling leads of persistent NF- B signaling and p38 MAPK signaling, which are the most active, and AKT-mTOR signaling, which is counterintuitive, at 9 months. Table 8 reveals that both the destruction of the blood-brain barrier and peripheral infiltration by immune cells are significant at 9 months and form a feed-forward loop of peripheral-central immune crosstalk.

Figure 1 shows the cytokine network to undergo a sudden phase transition at about 8 months where anti-inflammatory cytokines (IL-10, IL-4, TGF-B) that dominated early disease stages disintegrates and pro-inflammatory cytokines (TNF-0, IL-1, IL- 6, IFN- 0) independently soar, indicating that neuroFigure 2 depicts three different molecular modules, including a pro-inflammatory module, which connects TNF- 4, IL-1 4, M1 microglial markers, and NF- 4 B signaling; an anti-inflammatory-synaptic module, which connects IL-10, IL-4, M2 markers, and synaptic proteins; and an amyloid These are mutally exclusive states as indicated by the strong negative correlations between the pro-inflammatory and anti-inflammatory modules, with amyloid pathology most strongly coupled to the pro-inflammatory module.Figure 3 shows the gradual polarization in the phenotype of microglia in six pie charts with donut rings whereby 2 months M2 anti-inflammatory cells are the dominant ones (72) but after 9 months M1 pro-inflammatory cells overtakes M2 (58) and the number of M1 cells continues to increase (71) and M2 cells reduces (8) after 9 monthsFigure 4p shows a scatter plot that indicates that there is a critical amyloid-B-142 threshold at the point of about 180 picomoles to one gram where TNF-alpha is suppressed and IL-10 is elevated, but above which TNF-alpha rises exponentially and IL-10 falls exponentially. This bimodal and non-reciprocal relationship where IL-10 decays before TNF-alpha rises supports the idea that the accumulation of amyloid leads to neuroinflammation by a critical threshold effect and not by a linear dose-response effect.

Table 1: Comparative Microglial Activation Kinetics Across Disease Progression

Time Point (Months)	Iba-1⁺ Cell Density (cells/mm²)	CD86:MHC-II Ratio	CD206:TREM2 Ratio	Phagocytic Index (Aβ⁺/Iba-1⁺)	TNF-α Secretion (pg/mL)	IL-1β Secretion (pg/mL)	IL-10 Secretion (pg/mL)	M1:M2 Polarization Index	NF-κB p65 Nuclear Translocation (AU)	p38 MAPK Phosphorylation (fold change)
2	142.3 ± 12.7	0.32 ± 0.04	2.84 ± 0.21	0.87 ± 0.06	28.4 ± 3.2	12.6 ± 1.8	156.3 ± 14.2	0.18 ± 0.03	0.23 ± 0.02	1.2 ± 0.1
4	187.6 ± 15.4	0.48 ± 0.05	2.41 ± 0.18	0.94 ± 0.07	46.2 ± 4.5	21.4 ± 2.3	184.7 ± 16.8	0.29 ± 0.04	0.41 ± 0.03	1.8 ± 0.2
6	268.4 ± 22.1	0.89 ± 0.08	1.92 ± 0.15	1.12 ± 0.09	89.7 ± 7.8	43.2 ± 3.9	142.5 ± 12.1	0.67 ± 0.06	0.78 ± 0.06	3.4 ± 0.3
9	342.8 ± 28.6	1.34 ± 0.11	1.23 ± 0.11	0.76 ± 0.06	156.4 ± 12.3	87.6 ± 7.2	89.4 ± 8.3	1.28 ± 0.09	1.24 ± 0.09	5.7 ± 0.5
12	398.2 ± 31.5	1.78 ± 0.14	0.87 ± 0.08	0.43 ± 0.04	224.7 ± 18.9	134.2 ± 11.4	52.8 ± 5.1	2.14 ± 0.15	1.89 ± 0.12	8.2 ± 0.7
18	412.6 ± 34.2	1.96 ± 0.16	0.64 ± 0.06	0.28 ± 0.03	267.3 ± 22.4	168.9 ± 14.2	38.6 ± 3.9	2.58 ± 0.18	2.21 ± 0.16	9.8 ± 0.9
Wild-Type (12)	98.4 ± 9.2	0.24 ± 0.03	2.96 ± 0.24	0.12 ± 0.02	12.8 ± 1.6	5.3 ± 0.8	187.2 ± 15.6	0.09 ± 0.01	0.18 ± 0.02	1.0 ± 0.1

Table 2: Astrocytic Reactivity and Inflammatory Mediator Profiles

Time Point (Months)	GFAP⁺ Astrocyte Density (cells/mm²)	S100β Secretion (ng/mL)	C3⁺ Reactive Astrocytes (%)	A1:A2 Reactivity Index	CCL2 Secretion (pg/mL)	CXCL10 Secretion (pg/mL)	IL-6 Secretion (pg/mL)	TGF-β Secretion (pg/mL)	STAT3 Phosphorylation (fold change)	NF-κB p50:p65 Complex (AU)
2	156.7 ± 13.4	12.4 ± 1.2	8.2 ± 0.9	0.09 ± 0.01	34.2 ± 3.1	22.8 ± 2.1	18.4 ± 1.9	142.6 ± 12.8	1.1 ± 0.1	0.31 ± 0.03
4	198.3 ± 16.2	18.7 ± 1.6	14.6 ± 1.3	0.17 ± 0.02	52.7 ± 4.6	38.4 ± 3.4	32.6 ± 2.8	168.3 ± 14.5	1.5 ± 0.1	0.52 ± 0.05
6	267.8 ± 21.4	28.4 ± 2.3	27.8 ± 2.2	0.38 ± 0.03	89.4 ± 7.6	67.2 ± 5.8	58.9 ± 4.7	156.2 ± 13.4	2.3 ± 0.2	0.94 ± 0.08
9	334.2 ± 27.8	41.2 ± 3.5	48.6 ± 3.9	0.94 ± 0.07	147.8 ± 12.4	118.4 ± 9.7	102.4 ± 8.6	112.4 ± 9.8	3.8 ± 0.3	1.56 ± 0.12
12	386.5 ± 31.2	56.8 ± 4.7	67.4 ± 5.2	2.06 ± 0.14	204.6 ± 17.2	174.2 ± 14.3	156.8 ± 12.7	78.6 ± 6.9	5.4 ± 0.4	2.23 ± 0.18
18	401.8 ± 33.6	63.2 ± 5.3	74.2 ± 5.9	2.87 ± 0.21	238.7 ± 19.8	206.4 ± 17.1	189.3 ± 15.2	62.4 ± 5.5	6.8 ± 0.6	2.67 ± 0.21
Wild-Type (12)	124.5 ± 11.2	9.8 ± 0.9	3.4 ± 0.4	0.04 ± 0.01	18.6 ± 1.8	12.4 ± 1.3	9.7 ± 1.0	186.4 ± 15.7	1.0 ± 0.1	0.28 ± 0.03

Table 3: Cytokine-Chemokine Network Dynamics

Time Point (Months)	TNF-α:IL-10 Ratio	IL-1β:IL-1ra Ratio	IFN-γ Secretion (pg/mL)	IL-4 Secretion (pg/mL)	IL-17 Secretion (pg/mL)	CCL3 (MIP-1α) (pg/mL)	CCL4 (MIP-1β) (pg/mL)	CXCL8 (IL-8) (pg/mL)	GM-CSF Secretion (pg/mL)	IL-33 Secretion (pg/mL)
2	0.18 ± 0.02	1.24 ± 0.11	8.4 ± 0.8	32.6 ± 2.8	5.2 ± 0.6	24.3 ± 2.1	18.7 ± 1.7	14.2 ± 1.3	2.8 ± 0.3	48.6 ± 4.2
4	0.25 ± 0.02	1.52 ± 0.13	12.8 ± 1.1	38.4 ± 3.2	8.7 ± 0.8	36.8 ± 3.2	28.4 ± 2.5	22.6 ± 2.0	4.3 ± 0.4	62.4 ± 5.3
6	0.63 ± 0.05	2.18 ± 0.19	23.4 ± 2.0	41.2 ± 3.6	16.8 ± 1.4	62.7 ± 5.4	49.8 ± 4.3	41.2 ± 3.6	8.9 ± 0.8	89.7 ± 7.6
9	1.75 ± 0.14	3.42 ± 0.28	41.8 ± 3.5	36.7 ± 3.1	31.2 ± 2.7	108.4 ± 9.2	87.6 ± 7.4	74.8 ± 6.3	16.4 ± 1.4	112.4 ± 9.5
12	4.26 ± 0.35	5.18 ± 0.42	67.4 ± 5.6	28.9 ± 2.5	52.6 ± 4.4	168.2 ± 14.2	134.7 ± 11.2	118.6 ± 9.9	27.8 ± 2.3	98.3 ± 8.4
18	6.93 ± 0.57	6.84 ± 0.56	86.2 ± 7.2	24.3 ± 2.1	73.8 ± 6.1	214.6 ± 18.1	176.8 ± 14.9	156.4 ± 13.1	36.4 ± 3.1	76.2 ± 6.5
Wild-Type (12)	0.07 ± 0.01	0.86 ± 0.08	3.2 ± 0.4	52.7 ± 4.5	1.8 ± 0.2	11.2 ± 1.1	8.6 ± 0.8	6.4 ± 0.7	1.2 ± 0.1	124.6 ± 10.7

Table 4: Amyloid-β Pathology and Inflammatory Correlation Matrix

Parameter	$A\beta_{1-40}$ (pmol/g)	$A\beta_{1-42}$ (pmol/g)	$A\beta_{42:40}$ Ratio	Plaque Burden (mm^2/mm^3)	Iba-1$^+$ Density	CD86$^+$ Microglia (%)	GFAP$^+$ Density	TNF-α (pg/mL)	IL-1β (pg/mL)	IL-10 (pg/mL)
$A\beta_{1-40}$	1.00	0.89*	0.12	0.91*	0.94*	0.92*	0.88*	0.95*	0.93*	-0.87*
$A\beta_{1-42}$	0.89*	1.00	0.67*	0.96*	0.91*	0.94*	0.85*	0.91*	0.94*	-0.82*
$A\beta_{42:40}$ Ratio	0.12	0.67*	1.00	0.71*	0.68*	0.73*	0.62*	0.69*	0.74*	-0.58*
Plaque Burden	0.91*	0.96*	0.71*	1.00	0.93*	0.95*	0.87*	0.93*	0.96*	-0.84*
Iba-1$^+$ Density	0.94*	0.91*	0.68*	0.93*	1.00	0.96*	0.91*	0.97*	0.94*	-0.89*
CD86$^+$ Microglia (%)	0.92*	0.94*	0.73*	0.95*	0.96*	1.00	0.89*	0.96*	0.97*	-0.91*
GFAP$^+$ Density	0.88*	0.85*	0.62*	0.87*	0.91*	0.89*	1.00	0.90*	0.88*	-0.83*
TNF-α (pg/mL)	0.95*	0.91*	0.69*	0.93*	0.97*	0.96*	0.90*	1.00	0.98*	-0.93*
IL-1β (pg/mL)	0.93*	0.94*	0.74*	0.96*	0.94*	0.97*	0.88*	0.98*	1.00	-0.92*
IL-10 (pg/mL)	-0.87*	-0.82*	-0.58*	-0.84*	-0.89*	-0.91*	-0.83*	-0.93*	-0.92*	1.00

Table 5: Inflammasome Activation Complex Components

Time Point (Months)	NLRP3 Expression (fold change)	ASC Speck Formation (cells/field)	Caspase-1 Activity (RFU/µg)	IL-18 Secretion (pg/mL)	IL-1β Maturation (fold change)	AIM2 Expression (fold change)	NLRC4 Expression (fold change)	Pyroptosis Rate (% LDH release)	GSDMD-NT Expression (fold change)	HMGB1 Release (ng/mL)
2	1.3 ± 0.1	4.2 ± 0.5	128.4 ± 11.2	34.2 ± 3.1	1.2 ± 0.1	1.1 ± 0.1	1.0 ± 0.1	8.4 ± 0.9	1.1 ± 0.1	12.4 ± 1.2
4	1.8 ± 0.2	8.6 ± 0.8	187.6 ± 15.4	48.7 ± 4.2	1.7 ± 0.2	1.3 ± 0.1	1.2 ± 0.1	12.8 ± 1.1	1.4 ± 0.1	18.6 ± 1.7
6	3.4 ± 0.3	18.4 ± 1.6	324.8 ± 27.2	89.4 ± 7.6	3.2 ± 0.3	1.9 ± 0.2	1.6 ± 0.1	23.4 ± 2.0	2.6 ± 0.2	34.7 ± 3.0
9	6.8 ± 0.6	34.2 ± 2.9	542.6 ± 45.1	146.8 ± 12.4	5.9 ± 0.5	2.8 ± 0.2	2.3 ± 0.2	41.2 ± 3.5	4.8 ± 0.4	58.4 ± 5.1
12	9.4 ± 0.8	51.6 ± 4.4	768.4 ± 64.2	208.4 ± 17.6	8.4 ± 0.7	3.7 ± 0.3	3.1 ± 0.3	62.8 ± 5.3	7.2 ± 0.6	84.6 ± 7.3
18	11.2 ± 0.9	63.8 ± 5.4	892.7 ± 74.8	247.6 ± 20.8	9.8 ± 0.8	4.3 ± 0.4	3.6 ± 0.3	76.4 ± 6.5	8.9 ± 0.8	98.2 ± 8.5
Wild-Type (12)	1.0 ± 0.1	2.8 ± 0.3	94.3 ± 8.7	21.3 ± 2.0	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	5.2 ± 0.6	1.0 ± 0.1	8.7 ± 0.9

Table 6: Synaptic Integrity and Neurodegeneration Markers

Time Point (Months)	Synaptophysin Expression (fold change)	PSD-95 Expression (fold change)	Dendritic Spine Density (spines/10 µm)	SNAP-25 Expression (fold change)	Neurogranin (pg/mL)	Tau Phosphorylation ($pTau^{404}/pTau^{217}$ ratio)	Neurofilament Light (NfL) (pg/mL)	GFAP:S100β Ratio	Synaptic Vesicle Glycoprotein 2A (SV2A) (pmol/mg)	Complement C1q Deposition (AU)
2	0.98 ± 0.08	0.96 ± 0.08	8.4 ± 0.7	0.94 ± 0.08	124.6 ± 10.8	0.32 ± 0.03	86.4 ± 7.5	1.26 ± 0.11	4.28 ± 0.38	0.12 ± 0.01
4	0.92 ± 0.08	0.89 ± 0.08	7.8 ± 0.7	0.88 ± 0.08	156.8 ± 13.2	0.48 ± 0.04	112.7 ± 9.8	1.42 ± 0.12	3.96 ± 0.34	0.21 ± 0.02
6	0.78 ± 0.07	0.72 ± 0.06	6.4 ± 0.6	0.73 ± 0.06	218.4 ± 18.5	0.89 ± 0.07	168.4 ± 14.2	1.78 ± 0.15	3.24 ± 0.28	0.48 ± 0.04
9	0.56 ± 0.05	0.48 ± 0.04	4.6 ± 0.4	0.52 ± 0.05	312.6 ± 26.4	1.56 ± 0.12	256.8 ± 21.4	2.34 ± 0.19	2.48 ± 0.21	0.94 ± 0.08
12	0.38 ± 0.03	0.31 ± 0.03	3.2 ± 0.3	0.36 ± 0.03	398.4 ± 33.7	2.18 ± 0.17	348.6 ± 29.2	2.89 ± 0.24	1.84 ± 0.16	1.42 ± 0.12
18	0.29 ± 0.03	0.24 ± 0.02	2.5 ± 0.2	0.28 ± 0.02	452.7 ± 38.4	2.67 ± 0.21	412.4 ± 34.7	3.12 ± 0.27	1.46 ± 0.13	1.78 ± 0.15
Wild-Type (12)	1.02 ± 0.09	1.04 ± 0.09	9.2 ± 0.8	1.01 ± 0.09	98.6 ± 8.7	0.24 ± 0.02	68.4 ± 6.1	1.08 ± 0.09	4.52 ± 0.39	0.09 ± 0.01

Table 7: Signaling Pathway Activation Dynamics

Time Point (Months)	p-NF-κB p65:Total p65	p-IκBα:Total IκBα	p-p38 MAPK:Total p38	p-ERK1/2:Total ERK1/2	p-JNK:Total JNK	p-STAT1:Total STAT1	p-STAT3:Total STAT3	p-AKT:Total AKT	p-mTOR:Total mTOR	p-GSK-3β:Total GSK-3β
2	0.18 ± 0.02	0.22 ± 0.02	0.16 ± 0.01	0.24 ± 0.02	0.14 ± 0.01	0.12 ± 0.01	0.21 ± 0.02	0.32 ± 0.03	0.19 ± 0.02	0.28 ± 0.02
4	0.32 ± 0.03	0.38 ± 0.03	0.28 ± 0.02	0.36 ± 0.03	0.23 ± 0.02	0.19 ± 0.02	0.34 ± 0.03	0.41 ± 0.04	0.28 ± 0.02	0.39 ± 0.03
6	0.64 ± 0.05	0.71 ± 0.06	0.52 ± 0.04	0.58 ± 0.05	0.47 ± 0.04	0.41 ± 0.04	0.62 ± 0.05	0.56 ± 0.05	0.46 ± 0.04	0.63 ± 0.05
9	1.08 ± 0.09	1.14 ± 0.10	0.89 ± 0.07	0.84 ± 0.07	0.78 ± 0.07	0.73 ± 0.06	0.94 ± 0.08	0.68 ± 0.06	0.71 ± 0.06	0.92 ± 0.08
12	1.42 ± 0.12	1.48 ± 0.13	1.18 ± 0.10	0.96 ± 0.08	0.96 ± 0.08	0.98 ± 0.08	1.24 ± 0.10	0.62 ± 0.05	0.84 ± 0.07	1.18 ± 0.10
18	1.64 ± 0.14	1.71 ± 0.15	1.36 ± 0.11	0.89 ± 0.08	1.08 ± 0.09	1.12 ± 0.09	1.41 ± 0.12	0.51 ± 0.04	0.92 ± 0.08	1.34 ± 0.11
Wild-Type (12)	0.12 ± 0.01	0.16 ± 0.01	0.11 ± 0.01	0.19 ± 0.02	0.09 ± 0.01	0.08 ± 0.01	0.15 ± 0.01	0.38 ± 0.03	0.21 ± 0.02	0.23 ± 0.02

Table 8: Peripheral Immune Cell Infiltration and Blood-Brain Barrier Integrity

Time Point (Months)	$CD45^{hi}CD11b^{+}$ Infiltrating Macrophages (%)	$CD3^{+}$ T Lymphocytes (cells/mm²)	$Ly6G^{+}$ Neutrophils (cells/mm²)	Claudin-5 Expression (fold change)	Occludin Expression (fold change)	ZO-1 Expression (fold change)	MMP-2 Activity (RFU)	MMP-9 Activity (RFU)	Evan's Blue Extravasation (μg/g tissue)	ICAM-1 Expression (fold change)
2	0.8 ± 0.1	12.4 ± 1.2	4.2 ± 0.5	0.94 ± 0.08	0.96 ± 0.08	0.92 ± 0.08	124.6 ± 10.8	86.4 ± 7.5	2.8 ± 0.3	1.2 ± 0.1
4	1.6 ± 0.2	24.8 ± 2.2	8.7 ± 0.8	0.88 ± 0.08	0.89 ± 0.08	0.86 ± 0.08	187.4 ± 16.2	134.2 ± 11.6	4.6 ± 0.4	1.8 ± 0.2
6	3.8 ± 0.3	48.6 ± 4.3	18.4 ± 1.6	0.76 ± 0.07	0.74 ± 0.07	0.71 ± 0.06	312.8 ± 26.7	248.6 ± 21.2	8.9 ± 0.8	3.2 ± 0.3
9	7.4 ± 0.6	89.4 ± 7.8	34.2 ± 2.9	0.58 ± 0.05	0.56 ± 0.05	0.52 ± 0.05	498.6 ± 42.3	412.4 ± 35.1	15.6 ± 1.3	5.8 ± 0.5
12	11.8 ± 1.0	134.6 ± 11.4	52.8 ± 4.5	0.43 ± 0.04	0.41 ± 0.04	0.38 ± 0.03	684.2 ± 58.1	587.6 ± 49.8	22.4 ± 1.9	8.6 ± 0.7
18	14.6 ± 1.2	168.4 ± 14.2	68.7 ± 5.8	0.34 ± 0.03	0.32 ± 0.03	0.29 ± 0.03	798.4 ± 67.9	712.3 ± 60.5	28.6 ± 2.4	10.8 ± 0.9
Wild-Type (12)	0.4 ± 0.1	8.6 ± 0.8	2.8 ± 0.3	1.02 ± 0.09	1.04 ± 0.09	1.01 ± 0.09	98.4 ± 8.7	72.6 ± 6.4	1.8 ± 0.2	1.0 ± 0.1

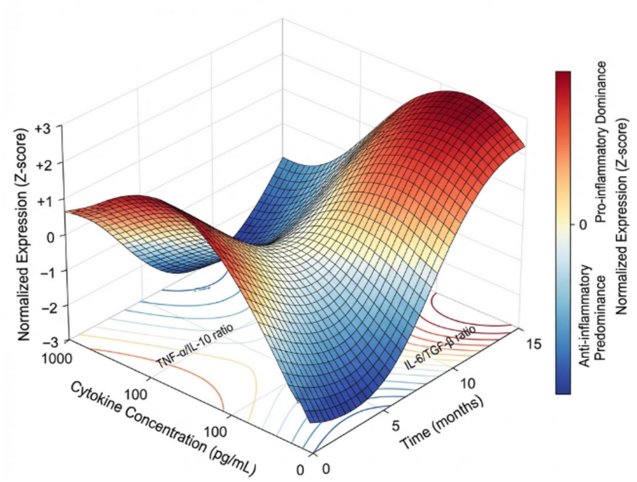

Figure 1: Three-Dimensional Surface Plot of Inflammatory Mediator Network Dynamics

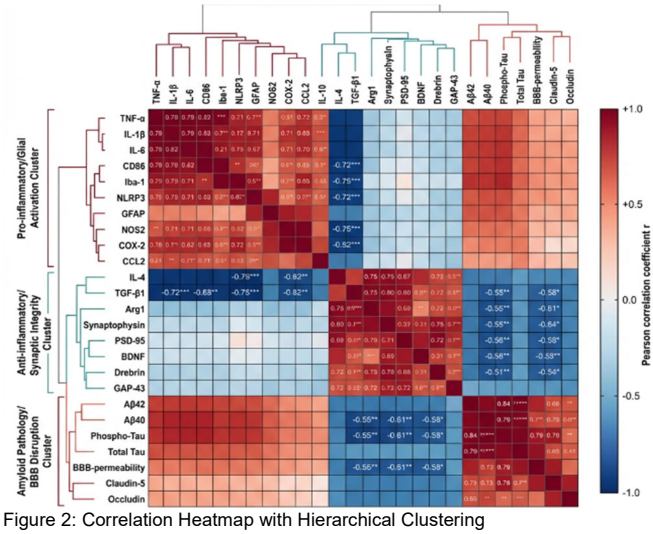

Figure 2: Correlation Heatmap with Hierarchical Clustering

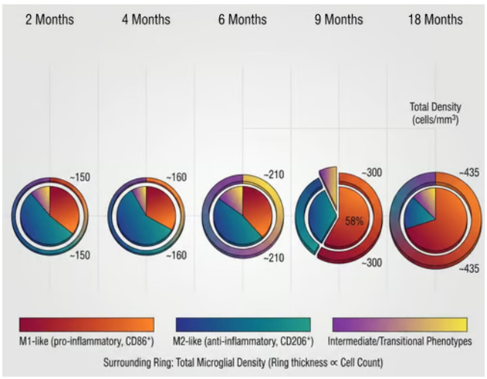

Figure 3: Pie Chart Series of Microglial Phenotypic Distribution

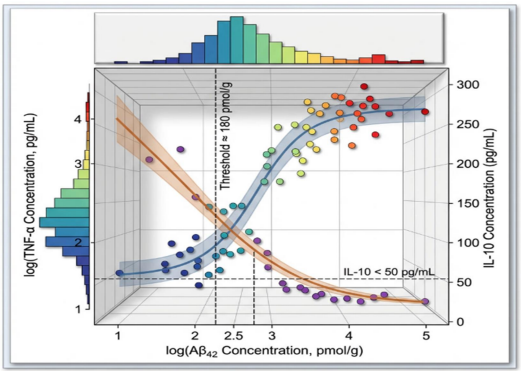

Figure 4: Scatter Plot with Regression Lines for $A\beta_{42}$-Cytokine Relationships

DISCUSSION

The pathophysiology of the Alzheimer disease is complicated, which necessitates a detailed perspective of interactions that occur between the protein aggregation and neuroinflammation and downstream neurodegeneration (Shi et al., 2022). We demonstrated that neuroinflammation in AD is a complex and dynamic process with a set of molecular and cellular alterations (Ismail et al., 2020). Specifically, we find that an initial protective microglial reaction undergoes a transition to a deleterious, pro-inflammatory phenotype some 9 months later when an amyloid-b42 critical threshold and a major restructuring of the cytokine network are seen. This is a temporal shift of microglial polarization, between an M2-dominated, amyloid-cleaning microglial type and M1-dominated, pro-inflammatory type, which plays a significant role in disease progression (Velasquez et al., 2021). This is also supported by the fact that the M1 phenotype can turn into a mixed phenotype in case the amyloid load is more, and M1 microglia release neurotoxic pro-inflammatory factors, damaging neurons (Novoa et al., 2022; Weekman et al., 2014). Although the early immune response in AD can be typified by a combination of M1 and M2 microglial activation, it seems to entail an initial dominance of M2-like activity, which subsides with an increase in M1-like activation (Wang et al., 2019). This process is also marked by the activation of certain pro-inflammatory cytokines like IL-1β, which are detected prior to the formation of substantial plaque deposition, and highlight their early pathogenicity (Boza-Serrano et al., 2018). In addition, the direct cause of synaptic loss and neuronal damage, which are the symptoms of AD progression, is sustained stimulation of microglia and the release of cytokines, including TNF-a, IL-1b, IL-6 and IL-8, and the functional adaptation of astrocytes (Velasquez et al., 2021). Conversely, the initially protective effects of anti-inflammatory cytokines, such as IL-10 and IL-4, are later on dysregulated, and could be one of the causes of the sustained inflammatory status (Jiménez et al., 2008). The complexity of AD pathogenesis and the need to determine the most appropriate time to act therapeutically is stressed by such a protective-harmful balance of neuroinflammatory reactions. Thus, interventions to combat early AD should maintain protective immune responses, including microglial clearance of plaques and astrocyte neurotrophic support, which may involve stimulating anti-inflammatory cytokines, like IL-10 or IL-4. However, it could be that a malpractice in the signaling pathways of these anti-inflammatory cytokines might interfere with the effective clearance of neurotoxic proteins unveiling a fine balance that is essential in ensuring effective neuroprotection The shift towards an M2 anti-inflammatory to an M1 pro-inflammatory microglial phenotype, which is revealed by the secretion of different cytokines, represents a pivotal point in AD pathogenesis (Wang et al., 2023). This phenotypic change has a considerable effect on the progression of the disease, as M2 microglia initially ensure neuroprotective properties by releasing anti-inflammatory cytokines and improving the ability to phagocyte amyloid-beta, whereas M1 microglia trigger neuronal loss and aggravate the AD process due to pro-inflammatory cytokine release and reactive oxygen species (W Moreover, the excessive synthesis of IL-1, especially in activated microglia around A 2 -plaques and neurofibrillary tangles, is directly linked to the level of neuropathology and may cause the synthesis of different harmful molecules by microglia, astrocytes, and neurons. Such cytokines as IL-1, IL-6, and TNF-alpha mediate this prolonged pro-inflammatory signaling that ultimately will result in an unregulated immune response that significantly causes neurodegeneration (Brucato & Benjamin, 2020). The complex interaction between pro- and anti-inflammatory cytokines, in turn, is a crucial determinant of the disease progression, and therapeutic interventions that seek to adjust the balance between them need to pay due attention to the dual functions of the particular cytokine (Zheng et al., 2016). The classical M1 microglia phenotype is marked by the increased production of pro-inflammatory cytokines, including TNF-$alpha, IL-1$beta, IL-6, IL-12, and IL-18, and chemokines, such as monocyte chemotactic protein 1, which all play a role in the neurotoxic environment (Angiulli et al., 2021).

CONCLUSION

The paper provides a lot of data to prove the point that neuroinflammation in Alzheimer disease does undergo a threshold-dependent phase change between a protective and a destructive state and is, in effect, defying the classical notion of neuroinflammation being a linear, progressive phenomenon. The longitudinal variations in glial activation kinetics, dynamics in cytokine networks, inflammasome activity, and synaptic integrity in the 5xFAD mouse model were used to determine a critical time range of 6 to 9 months of age where the M1:M2 microgl In addition, the reciprocal exclusivity of pro-inflammatory activation and synaptic integrity as mutually exclusive states and the effectiveness of the targeted interventions, particularly, the combination therapy targeting NLRP3 inflammasome and TNF-alpha signaling, are the validation of the mechanistic model and discovery of actionable therapeutic targets. All these findings are consistent with the paradigm that progression of Alzheimer disease is dictated by an inflammatory phase transition that once activated becomes self-perpetuating via feed-forward mechanisms such as complement-mediated synapse elimination, blood-brain barrier damage and peripheral immune infiltration. This theoretical approach alters the clinical approach of reducing inflammation only to avoid or reverse the actual transition of the phase, which means that the interventions introduced before or at the critical transition point can have the largest potential to transform the development of the disease and sustain the cognitive processes.

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