Genetically Driven Lipid Dysfunction and Neuroinflammation: An Agent-Based Model of Alzheimer's Disease

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Introduction

Microglia are immune cells in the brain that switch between pro-inflammatory and anti-inflammatory states to maintain neural health. Microglial dysfunction has been associated with neurological disorders including Alzheimer's disease. Central immune system cells, including microglia, neurons, and astrocytes, communicate via chemical and metabolic signaling to regulate inflammation and tissue repair. Genetic variation can modify how these signals are processed, changing how individual cellular mechanisms propagate to a tissue-scale behavior. Agent-based modeling provides a framework for linking these mechanisms and observing their associated patterns, which are poorly understood.

Research Objective

We have developed an **agent-based framework** that links intracellular microglial signaling dynamics to extracellular tissue-scale interactions between brain cells. Our objective is to determine how local dysfunction escalates into persistent neuroinflammation by simulating lipid transport dynamics and genotypic influences on microglial metabolism and behavior.

Methods and Previous Work

We extend our lab's previous agent-based framework to study microglial dysfunction under lipid burden. Our model simulates interacting glial cells and neurons in the hippocampus. To incorporate genetic factors implicated in neurodegenerative conditions, we implement the effects of APOE and TREM2 variants on microglial lipid sensing and processing to model the global impact of these factors in the brain. Through computational experiments we quantify how impaired lipid clearance promotes lipid accumulation and alters microglial populations to sustain inflammation.

Agent Based Model

This model uses a two-dimensional environment to simulate a space within the hippocampus. Microglia and astrocytes are motile agents that transition between phenotypes based on local conditions. Neuron agents can become stressed and emit inflammatory signals into their local environment, while glial cells regulate metabolic support. This framework enables in silico experiments exploring how local behavior generates tissue-scale patterns.

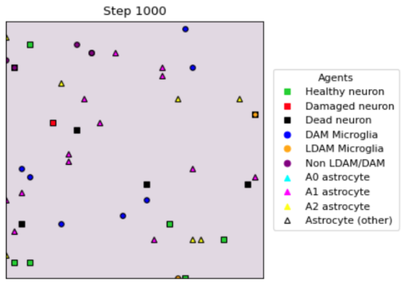

Fig. 1: Model visualization after running the cell for 1000 ticks under APOE 4/4 conditions. The various cell types and states are indicated by the shapes and colors in the legend.

Simulated Lipid Dysregulation & Microglial Activation

This model simulates how the dysfunction of lipid transport dynamics due to genetic variants affects the hippocampus. Impaired lipid clearance and sensing can lead to lipid accumulation (Fig 2), phenotype imbalance, and chronic inflammation. Under lipid stress, microglia may shift into one of two dysfunctional states: lipid-droplet-accumulating microglia (LDAMs) or disease-associated microglia (DAMs). The activation of LDAMs by lipids drives proinflammation and the toxic oxidation of lipids in surrounding cells, killing neurons and promoting further neurodegeneration.

Analysis and Results

We incorporated genotype-dependent behavior by scaling microglial lipid handling under different APOE conditions by running multiple simulations for each regime. APOE 3/3 on average produced less inflammation and microglial lipid burden, whereas APOE 3/4 exhibited insignificantly stronger values. APOE 4/4 simulations experienced a dramatically higher increase in both lipid accumulation and pro-inflammatory signaling. In this regime, amplified lipid buildup increased lipid-droplet–associated dysfunction, reducing effective sensing and clearance and reinforcing chronic inflammation. To support this, we present the cumulative percentage of neuron loss alongside relative LDAM and DAM populations for APOE 3/3 and APOE 4/4 conditions. Under APOE 4/4, high lipid burden shifts a larger fraction of microglia into the LDAM state, which impairs clearance and amplifies pro-inflammatory signaling, accelerating neuron loss relative to the APOE 3/3 condition.

Significance

This agent-based modeling approach provides a flexible platform for testing hypotheses about neuroinflammation, metabolic stress, and neuron–glia communication related to tissue-scale lipid dynamics and genetic predispositions for their dysfunction. Our next step will be to explore the effectiveness of therapeutic treatments for neurodegenerative conditions.

Supplemental Information

Acknowledgements

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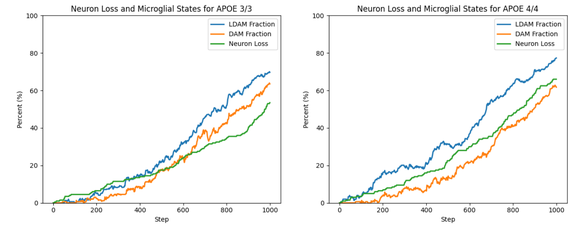

Fig. 2: Neuron death and microglial states over time. Left panel corresponds to APOE 3/3; right panel corresponds to APOE 4/4. Both regimes simulated 10 times each

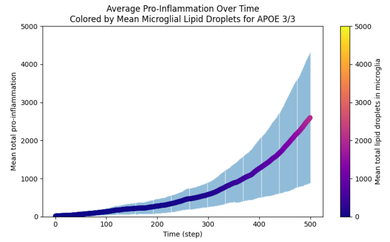

Fig. 3: Average accumulated lipid droplets versus pro inflammation over time with APOE 3/3 genotype for 10 simulations.

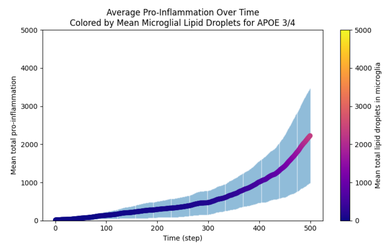

Fig. 4: Average accumulated lipid droplets versus pro inflammation over time with APOE 3/4 genotype for 10 simulations.

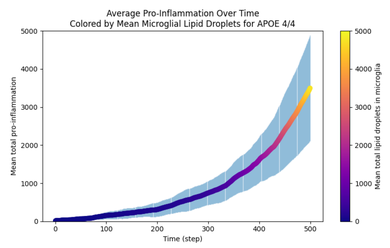

Fig. 5: Average accumulated lipid droplets versus pro inflammation over time with APOE 4/4 genotype for 10 simulations.