A Dynamic Model of the PI3K/AKT/PTEN Axis in Pathological Microglial Phenotype

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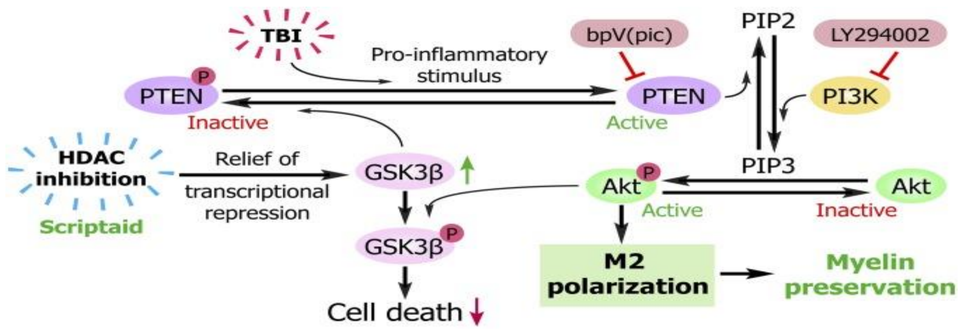
Abstract

Neurodegenerative disorders like Alzheimer's disease often involve progressive damage and eventually death of neuronal cells in the central nervous system (CNS). This often leads to the irreversible loss of various CNS-dependent cognitive and physical functions. Microglia, which are immune cells of the CNS, are critical to maintaining the integrity of nervous system and are stimulated into action after detection of damaged/dying cells and foreign pathogens. Microglia patrol and alter the CNS by fluctuating between generally two states: M1 (inflammatory or classical) and M2 (anti-inflammatory or alternative). The PI3K/AKT pathway is a highly versatile pathway that has recently been shown to be an imperative mechanism by which microglia modulate the switch between inflammatory and anti-inflammatory microglia phenotype. Recent literature has implicated the role of dysregulated PI3K/AKT dynamics in promoting hyperactive M1 microglia that chronically promote damaging neuroinflammation in neurodegenerative disease. This vicious cycle speeds up the progression of some neurodegenerative diseases and is critical to dampen for protection of CNS functionality as unfortunately there have not been many meaningful therapeutics that can fight this disease. In this project, I will design a computational model that can elucidate the intrinsic biochemical mechanisms and kinetics of the PI3K/AKT pathway that govern the microglial states. Considering the recent findings of PI3K/AKT pathway's role in neuroinflammation, I plan to use the in-silico model I design to study the therapeutic potential of manipulating this pathway's biochemical kinetics to slow neurodegenerative disease progression.

Research Questions

1. Will microglia return back to their original steady state after a pro-inflammatory stimulus, or adopt a new one in response to CNS insult? Is a trigger needed to return to the original homeostatic state?
2. How might these rates influence the phagocytosis phenotype of microglia?
3. Can we reliably predict microglial response to Ca^{2+}, inhibitors, agonists, etc?

Methods and Design



$$\frac{d[Akt]}{dt} = r3[pAkt] - k3\left(\frac{[PIP3]^2}{[PIP3]^2 + 1}\right)[Akt]$$

$$\frac{d[pAkt]}{dt} = k3\left(\frac{[PIP3]^2}{[PIP3]^2 + 1}\right)[Akt] - r3[pAkt]$$

$$\frac{d[PI3K]}{dt} = k1 - r1[PI3K]$$

$$\frac{d[nNFkB]}{dt} = k12[cNFkB] - k11[nNFkB][pAkt] + i3[LPS]$$

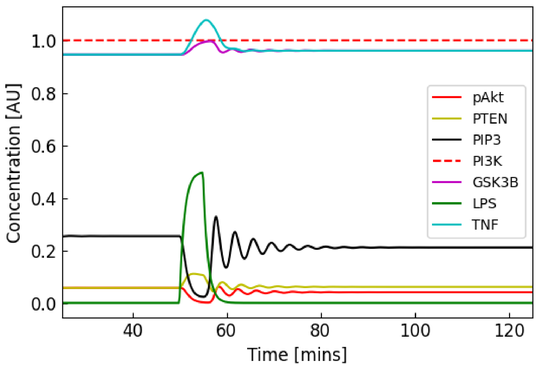
$$\frac{d[TNF]}{dt} = k13[nNFkB] - k14[TNF]$$

Above are a sample of equations we have devised based on extensive literature review. We implemented some mathematically formulations like Goodwin's oscillator to capture the feedback mechanisms as well as implemented rates with a steady state assumption in the rates expressions.

We are interested in the pathway presented in the figure above by [2]. We believe that analyzing the dynamics of this axis will provide insights into how microglia switch phenotypes in results to CNS insults. To model these interactions we implemented, fit and studied the ODE rates expressions in python and generated simulations as demonstrated below. Repository for the code and the simulation can be found here: https://github.com/rsethi21/genericInteractionNetwork.git

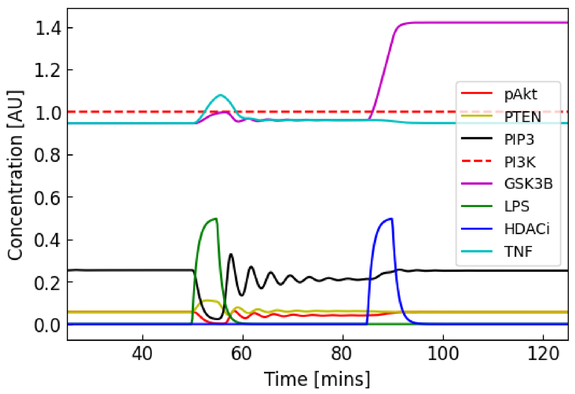
Preliminary Results

The following results are preliminary as we are in the process of fitting the rates to experimental data. The ligands are allowed to reach a steady state before and after the application of the stimulus in the simulation



Here you can see that after stimulation by lipopolysaccharide (LPS), and inflammatory stimulus, the PI3K/Akt pathway adopts are new steady state and remains that is slightly more favoring to inflammation (measured by TNFa).

Here you can see that after stimulation by LPS we apply an antagonist stimulus that restores the kinetics of the PTEN/pAkt signalling enzymes, demonstrating the need for an external stimulus to return to a semi-original homeostatic state.



Discussion/Conclusions

Preliminary results suggest that microglia adopt a new and slightly more inflammatory homeostatic states after removal of a proinflammatory insult. We demonstrate of incorporation of a anti-inflammatory stimulus partially restores the steady state of these microglial cells. This indicates the need for an external trigger in order to restore microglia to an M2 anti-inflammatory state in neuroinflammatory disorders as intrinsic mechanisms are not enough to protect the CNS from inflammatory damage.

Next Steps

1. Fitting and validating rate kinetics using the genetic algorithm to experimental data collected by the PKH lab
2. Expand network to incorporate ligands associated with phagocytosis
3. Train and develop an ML model that can predict microglial phagocytosis from various ligand states. This will be supervised learning and will use predictions from the model to label data and train it.
4. Explore the effects of the isoforms of AKT and differences in resulting phenotypes.

References

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