QSP model describing the dynamics of microglial phenotypes: Effect on treatments targeting microglia

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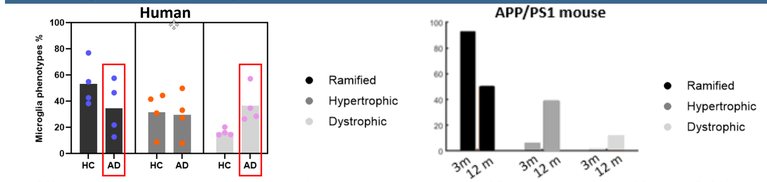
Abstract

During Alzheimer's disease (AD) pathogenesis microglia transition into different phenotypes (ramified-homeostatic, hypertrophic-active and dystrophic-senescent) while removing various toxic deposits [1-4]. Activating microglia and retaining them in hypertrophic state, as well as ablating dystrophic microglia has been postulated as promising therapeutic strategies in neuroinflammatory diseases [5]. We developed a quantitative systems pharmacology (QSP) model approach to capture the pathology driven longitudinal changes in microglial phenotypic states as a part of AD neuroinflammation model [6], the implementation of which we will explain in detail in this poster. The model was calibrated with pre-clinical [7] and clinical data [8-11] to capture the dynamic changes in fraction of microglial phenotypes. The model explored pharmacological strategies to (i) activate and retain hypertrophic state and (ii) ablate dystrophic phenotype. Our simulations suggest-subjects with certain combinations of phenotype fractions would respond more efficiently to microglia activating therapies. As far as we are aware, this is the first QSP model that mechanistically captures longitudinal, diseases driven, changes in microglial phenotypes that will have potential applications in therapies targeting specific cellular phenotypes.

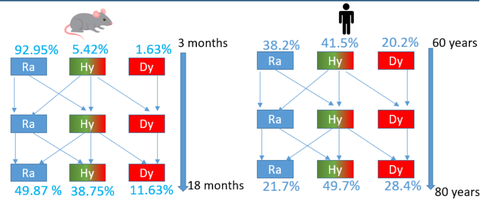
Microglial phenotypic fractions



- Microglial phenotypic fractions are distinct between healthy and AD, observed in both Human [8-11] and mouse [7].
- AD patients have less Ramified (Ra) and more Dystrophic (Dy) microglia when compared to HC.
- In APP/PS1 mouse model of AD, a more dramatic change in all the phenotypic fractions is observed, especially a ~ 7-fold increase in both Hy and Dy cell fractions by 12 months.
- We utilized the above information to build and constrain the microglial phenotype transition model.

Implementing microglial phenotype transition

- Initial phenotypic fractions were assigned based on the data.
- Next, probability of transition from each starting phenotypic state to the other is assigned.
- The transition probabilities are then iteratively improved to quantitatively match the data.



In Human/Mouse

If Phenotype is **Ra** at simulation time t = 0

$=> P_{(Ra \rightarrow Hy \rightarrow Dy)} = p1$

$=> P_{(Ra \rightarrow Hy \rightarrow Hy)} = p2$

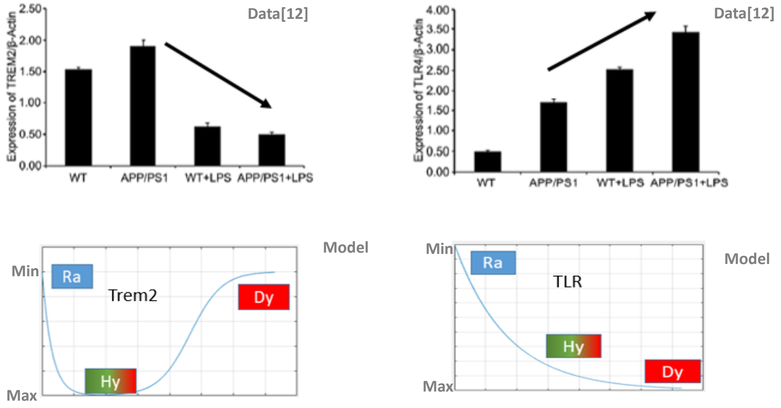
$=> P_{(Ra \rightarrow Hy \rightarrow Ra)} = p3$

$=> P_{(Ra \rightarrow Ra \rightarrow Ra)} = 1 - (p1+p2+p3)$

Here, p1-p3 are probabilities of occurrence of each transition pathways starting from Ra (similarly implemented for Hy).
The Dy phenotype is a terminal/senescent cell state and hence phenotypic transition from Dy back to Hy or Ra was not considered

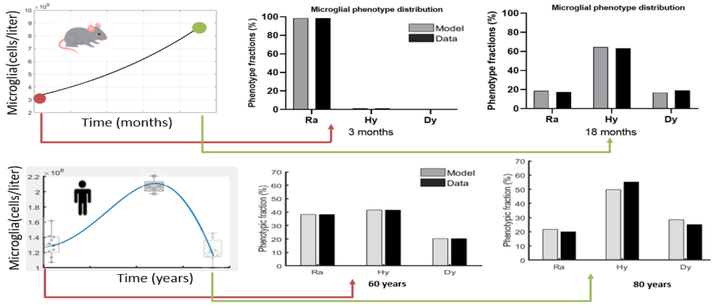
Microglial phenotypic changes & Trem2/TLR expression

Pathology driven changes in Trem2 and TLR expression



- Studies in APP/PS1 mice shows Trem2 and TLR4 receptor expression is pathology (LPS challenge) driven [12].
- Several studies have shown that TLR4 counter regulates TREM2, and hence we assumed similar direction of change in Trem2 and TLR4 expressions from Ra to Dy phenotype.

Model calibration: Microglial count and phenotype fractions



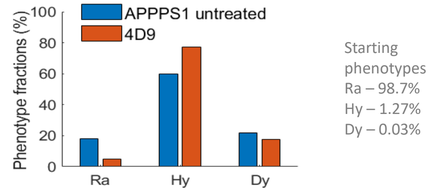
- Mouse model calibration: The model is calibrated to the phenotypic fraction distribution for 3- and 18-months old APP/PS1 mice while also capturing the microglial proliferation dynamics in the timespan [7].
- Human model calibration: In Human, microglial proliferation follows a bell-shaped pattern from early to late stage of the disease as has been observed from autopsy material [9]. Age-matched healthy is considered as 60 years old and 80 years corresponds to terminal stage in AD pathology, respectively.

Microglial phenotypic fractions can impact drug-response

Model predictions (APP/PS1 mice)

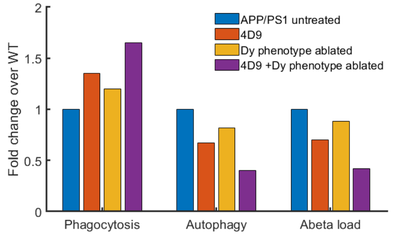
- Drug response depend on starting microglial phenotypes (see [6])
- TREM2 antibody accelerates Ra->Hy transition and delays Hy->Dy transition (i.e. retain Hy state longer)

Terminal phenotypic fraction distribution



Starting phenotypes
Ra – 98.7%
Hy – 1.27%
Dy – 0.03%

- The effect of activating Ra/Hy microglia or ablating Dy microglia on microglial processes and amyloid load.



Future directions

- Despite the availability of several macrophage/microglial phenotype transition model in the literature, the mechanistic link of phenotype transition to disease dynamics has not been well established. This data-driven and data-constrained mechanistic model captures the phenotypic transition of microglia as the disease progresses and shows that the effect of drug can differ based on pre-treatment phenotypic status of microglia.
- The model can have potential applications in therapies targeting cells that can assume multiple phenotypes, for examples, microglia/macrophages, heterogenic tumor cells

References

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