Evaluating the therapeutic potential of Neuregulin-1 for myelin repair in Multiple Sclerosis

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Background

- Multiple Sclerosis (MS), a chronically immune-mediated condition, manifests itself as a demyelinating, neuronal/axonal degenerating, and inflammatory disease in the central nervous system (CNS).
- Over 80,000 Canadian adults are living with MS, i.e. 1 in every 385 Canadians.
- There are currently four identifiable phenotypes of MS: Clinically isolated syndrome (CIS), Relapsing-remitting MS (RRMS), Primary progressive MS (PPMS), Secondary progressive MS (SPMS).
- CIS refers to the first inflammatory instance of demyelination within the CNS.
- Currently approved treatments are not effective against progressive MS.
- The Karimi lab has shown that Neuregulin-1 (Nrg-1) is dysregulated in active MS lesions and preclinical EAE (brain inflammation disease model). Also, Nrg-1 has been shown to promote oligodendrogenesis and remyelination in other animal models (LPC, SCI).
- Karimi lab has also shown that Nrg-1 modulates innate immune cells (microglia and monocyte derived macrophages) towards a pro-regenerative response in EAE and increase phagocytosis.
- However, there is still a significant gap present about the impact of Nrg-1 on microglia and monocyte derived macrophages to regulate the oligodendrocyte cell population during the chronic demyelination and remyelination phase of MS.

Hypothesis and Objectives

We hypothesize that Nrg-1 augments reparative properties of microglia/macrophages to facilitate repair of demyelinated lesions within the MS mouse model of Cuprizone.

Objective 1: To characterize the chronic demyelination and remyelination in the Cuprizone Mouse Model.

Objective 2: To evaluate the role of Nrg-1 in regulation of microglia and monocyte derived macrophages in myelination in vitro models.

Methods

Cuprizone (CZ) mouse model (in vivo)

Start Cuprizone diet

Cuprizone withdrawal; Begin Normal Chows/Diet

End-point

OPCs in vitro study

PDGFR-Cre mice

Number of Weeks

Demyelination

Remyelination

1 2 3 4 5 6 7 8 9 10 11 12

Nrg-1 is dysregulated during chronic remyelination in the Cuprizone Mouse Model

Markers:

MBP (Myelin-based Protein) = mature/myelinating oligodendrocytes

Edu = thymidine analogue that incorporates into DNA and is used to identify proliferating cells in tissue

Olig2 = Neural progenitor cells mature oligodendrocytes marker for entire oligodendrocyte lineage

Iba1 = Microglia (macrophages that reside in CNS) and/or Macrophages (reside in PNS/outside CNS)

TME/M119 = Only Microglia

DAPI = nuclear marker 4',6-diamidino-2-phenylindole

GFP = PDGFRα expressing OPCs

NG2 = OPCs (Oligodendrocyte progenitor cells) + Pre-OLs (Pre-mature oligodendrocytes)

LPS + INFγ = microglia and MDMs activated with lipopolysachharide (LPS) and interferon-γ (INFγ)

M1 = LPS+INFγ

Microglia

Characterization of Cuprizone Chronic Demyelination Model (CPZ 12wk)

Optimization of conditions to study myelination under microglia/macrophage conditioned media

Microglia

Note: Sample size too small (N=2) to conduct statistical analysis; further experiments need to conducted. Furthermore, from the 3 day timepoint it was determined that OPCs are still immature hence, 7 day timepoint experimentation is also required.

Conclusions

- Have established the criteria to characterize the Cuprizone Mouse Model and in vitro myelination assay.
- Following year, will look to see the impact of Nrg-1 in remyelination.
- Being an FDA approved drug, Nrg-1 offers high translational feasibility as a new therapeutic approach for MS.

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