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

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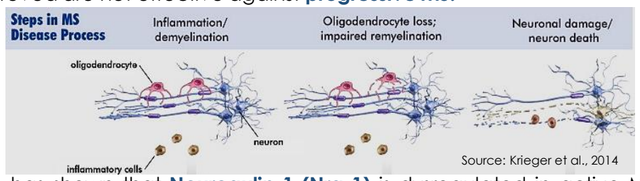
Background

- **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 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 modulate 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

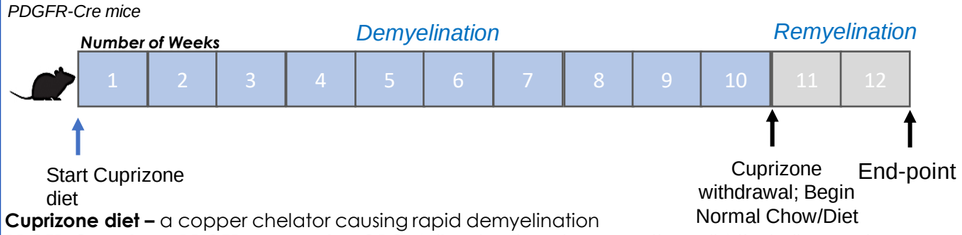
We **hypothesize** that Nrg-1 augments reparative properties of microglia/macrophages to facilitate repair of demyelinated lesions within the MS mouse model of Cuprizone.

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 using in vitro models.

Methods

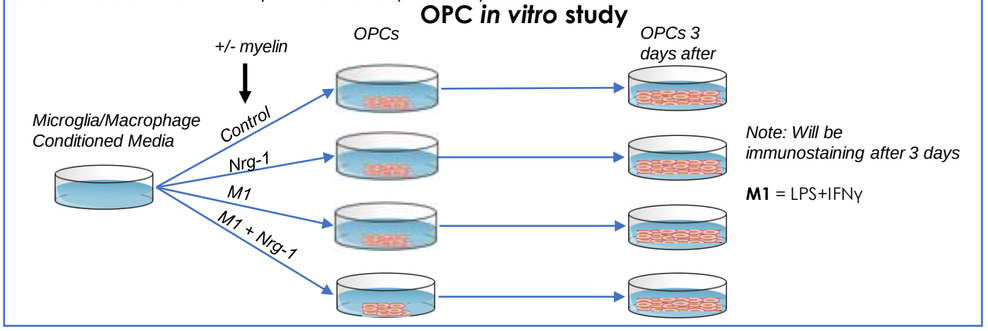
Cuprizone (CZ) mouse model (*in vivo*)



Cuprizone diet – a copper chelator causing rapid demyelination

PDGFR-Cre mice – PDGFRa expressing OPCs (oligodendrocyte progenitor cells) that allows us to differentiate between newly formed and spared myelin

OPC *in vitro* study

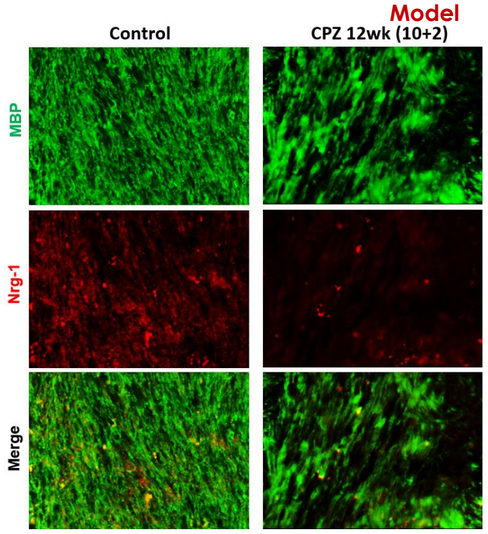


Note: Will be immunostaining after 3 days

M1 = LPS+IFNγ

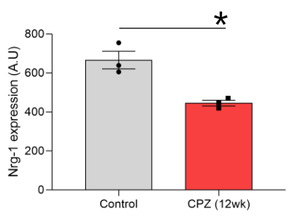
Results

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



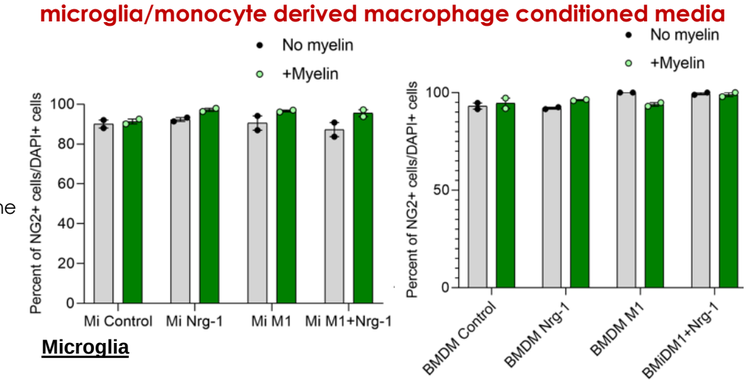
Control = age-matched wildtype control

CPZ 12wk = 10 week (Cuprizone diet) + 2 week (normal diet)

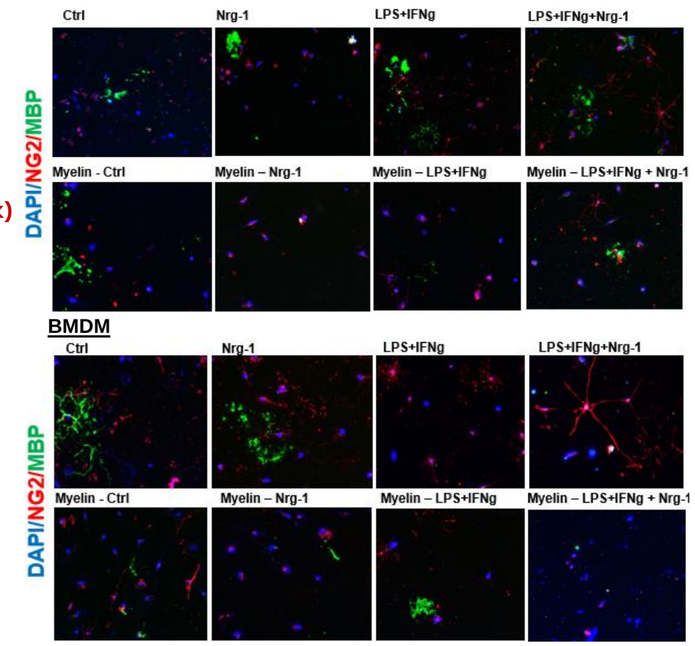


N=3, *p<0.05. student t-test

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



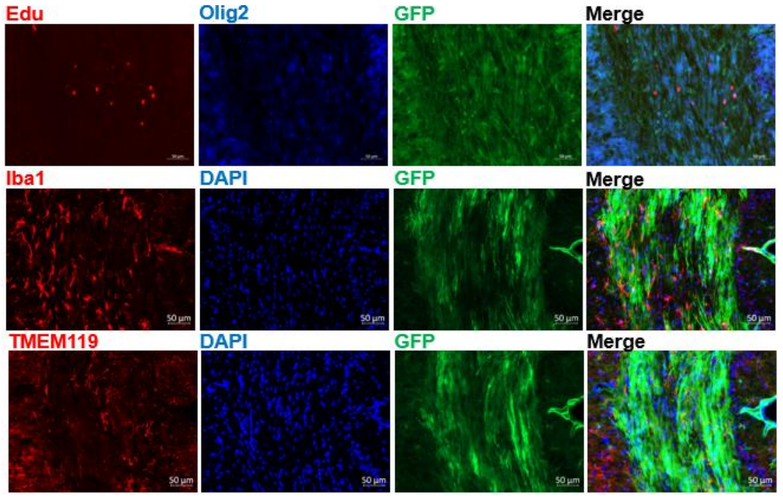
Microglia



BMDM

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

Characterization of Cuprizone Chronic Demyelination Model (CPZ 12wk)



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)

TMEM119 = Only Microglia

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

GFP = PDGFRa expressing OPCs

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

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

M1 = LPS+IFNg

Mi = Microglia Conditioned Media

BMDM = Macrophage Conditioned Media

Conclusion

- 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.

Karimi Lab

Lab website: https://home.cc.umanitoba.ca/~karimis/index.html

Funding Acknowledgement:

Acknowledging the Max Rady of College of Medicine and in accordance the BSc Med program, The University of Manitoba, the Multiple Sclerosis Society of Canada, and members of the Karimi Lab.