A transcriptional Approach to Myelin Repair

Ben Emery
Jungers Center for Neurosciences Research
Oregon Health & Science University
For any individual, the exact cause of MS is still unknown, but at the population level risk factors may include:

- Genetics
- Infections (e.g., Epstein-Barr virus)
- Climate (latitude)
- Smoking

MS involves an autoimmune attack on myelin:

From Ross et al. Front Neurol. 2013 4:21
Axonal damage in MS

Remyelination in MS

Remyelination vs. Axonal Loss

Remyelination therapies in MS

• Relatively new idea, and remyelination/neuroprotective therapies still lag behind immunomodulatory treatments

• Excitingly, the first few clinical trials of remyelination treatments have been underway over past several years:
  • Anti-Lingo1 therapy (Phase 1 and 2, Biogen Idec)
  • Clemastine (Dr. Ari Green and Dr. Jonah Chan, UCSF)
  • rHlgM22 (Phase 1, Mayo Clinic/Acorda)

• There is a clear need for additional targets for pro-remyelination therapies
Development of oligodendrocytes

Neural Precursor → Oligodendrocyte Progenitor (OPC) → Immature/Pre-myelinating Oligodendrocyte → Myelinating Oligodendrocyte
Development of oligodendrocytes

Neural Precursor

Oligodendrocyte Progenitor (OPC)

Immature/Pre-myelinating Oligodendrocyte

Myelinating Oligodendrocyte

Neural Precursor Cells in developing mouse spinal cord
Development of oligodendrocytes

Mouse OPCs in culture
Development of oligodendrocytes

Myelin Basic Protein (MBP): young mouse brain
Development of oligodendrocytes
Failure of remyelination

- As MS progresses, many demyelinated lesions fail to remyelinate

- Oligodendrocytes within these regions often “stall” in their development:

The fundamental questions in my lab

• What controls the development of oligodendrocytes?

• How do oligodendrocytes and neurons communicate with each other?

• How is the expression of genes regulated in oligodendrocytes?
Screen for genes with pro-myelination function in mouse development

Adapted from Cahoy et al. 2008 J Neurosci 28, 264-278
Myelin Regulatory Factor

An essentially unknown gene, now named Myelin Regulatory Factor (Myrf)

Highly specific to oligodendrocyte lineage:

Cahoy, Emery, Kaushal et al. 2008 J Neurosci 28, 264-278
Zhang, Chen, Sloan et al. 2014 J Neurosci 36, 11929-47
Myelin Regulatory Factor (Myrf): Essential for CNS myelination

Emery et al. 2009 *Cell* 138, 172-185
Forced expression of Myrf accelerates oligodendrocyte differentiation

Emery et al. 2009 *Cell* 138, 172-185
How does Myrf turn on the myelination program?
How does the Myrf gene promote myelination?

Myrf protein:

- Predicted domain for binding DNA
- Domain related to bacteriophages
- Transmembrane domain
How does the Myrf gene promote myelination?
Use of Myrf knockout mice as a novel model of myelin loss
Aims of our current NMSS grant

• What usually turns on the expression of Myrf in oligodendrocytes (and how can we make use of this to turn it on ourselves)?

• Does increased expression of Myrf in mouse models of demyelination improve remyelination?

• What does Myrf look like in the brains of MS patients?
Expression of Myrf in MS (with Ranjan Dutta from Cleveland Clinic)

- Myrf is down-regulated in MS brains and within MS lesions

- Is it expressed within “stalled” oligodendrocytes?

- Is it in its active or inactive form?

B: RNA expression of Myrf in normal appearing white matter, active lesion border and demyelinated white matter lesion. **Data courtesy of Dr Ranjan Dutta, Cleveland Clinic.**
Thanks…

**Emery lab**
Biliana Rotse
AeSoon Bensen
Antoinette Foster
Helena Bujalka
Matthias Koenning
Stacey Jackson
Melanie Willingham
Curtis Hay
Stan Mitew