Improving Remyelination of the Central Nervous System in Multiple Sclerosis

Garry Richard and Clark Ramsey*
Department of Neurology, Rise College of Medical Research, Italy

Corresponding Author*
Clark Ramsey
Department of Neurology
Rise College of Medical Research,
Italy
E mail:ramsey4214@gmail.com

Received date: 07-January-2023, Manuscript No: JMSO-23-96456; **Editor assigned:** 10-January-2023, PreQC No. JMSO-23-96456(PQ); **Reviewed:** 24-Januray-2023, QC No. JMSO-22-96456(Q); **Revised date**: 26-January-2023, Manuscript No: JMSO-23- 96456 (R); **Published date:** 29-January-2023, DOI: 10.35248/2376-0389.23.10.1.484

Abstract

The idea is that neural precursors can restore the injured central nervous system of multiple sclerosis patients where the endogenous remyelination process has failed, as a result of recent studies on adult neural stem cells and the embryonic biology of myelination. As a result, numerous labs are working on translational studies with the aim of developing strategies to encourage remyelination and repair.

Here, we bring forth concerns raised by earlier experimental and human work that should be taken into account to avoid having these research "lost in translation."

Keywords: Multiple sclerosis ● Epigenetics ● Vitamin D● Smoking

Introduction

Epigenetic regulatory mechanisms

The amazing evolutionary development of myelination of nerve fibres in vertebrates allows for quick "saltatory" conduction of action potentials by limiting voltage-dependent sodium channels to the node of Ranvier between myelin internodes. Multiple Sclerosis (MS), the most prevalent myelin disease, is an inflammatory demyelinating disease that frequently begins in young adults and can proceed chronically over several decades, resulting in severe disability. While anti-inflammatory medications help lessen the severity of the condition, they do not directly address the issue of myelin repair in chronic disease. The amazing evolutionary development of myelination of nerve fibres in vertebrates allows for quick "saltatory" conduction of action potentials by limiting voltage-dependent sodium channels to the node of Ranvier between myelin internodes. Multiple Sclerosis (MS), the most prevalent myelin disease, is an inflammatory demyelinating disease that frequently begins in young adults and can proceed chronically over several decades, resulting in severe disability. While anti-inflammatory medications help lessen the severity of the condition, they do not directly address the issue of myelin repair in chronic disease.

The improvement in conduction efficiency brought about by the change from nonsaltatory conduction along demyelinated axons to saltatory conduction along a remyelinated axon historically served as the basis for encouraging remyelination. An even stronger argument has been made, nevertheless, with the more recent recognition of axon loss as the primary pathogenic cause of MS's progressive functional decline. Axon damage can occur during the disease's initial inflammatory phase or as a result of chronic demyelination. Knockout mice deficient in oligodendrocyte-specific genes provide evidence for the critical part played by the myelin sheath in long-term axon survival.

The phenotype of mice lacking Cyclic Nucleotide Phosphodiesterase (CNP) is more unexpected. Oligodendrocytes express this gene. The underlying axons experience significant degeneration, build up amyloid precursor protein, and result in a motor impairment at 7 months, but the phenotypic effects are not in these cells, which produce myelin that appears to be normal [1]. These investigations demonstrate the necessity of molecularly "fit" oligodendrocytes for the integrity maintenance of axons in myelinated circuits. A crucial problem to be overcome is figuring out the particular chemical mechanisms, which almost certainly include the points of contact between the myelin sheath and the axons at the paranode [2,3].

This work has a significant implication that remyelination should prioritise long-term axon protection. Unknown amount of remyelination is needed to do this. It seems sense to think that the axon's susceptibility to degeneration will depend on the number of missing internodes and the amount of time it is demyelinated. Due to the relative sparing of axons in areas of remyelination compared to areas of demyelination, efficient remyelination will therefore diminish chronic axonal loss [4]. The new myelin sheaths are typically shorter and thinner than the original myelin sheath, which is a distinguishing property of endogenous remyelination. The composition of the myelinated and remyelinated myelin sheath does not appear to be fundamentally different, for unknown reasons, and its decreased dimensions only slightly affect the conduction characteristics of the axon. It is still unclear, nevertheless, whether a myelin sheath's lower volume affects how susceptible an axon is to degeneration. If this is the case, exciting new information from Michaelov et al. (2004) on the involvement of neuregulins in controlling myelin sheath thickness in the PNS would have significant ramifications for analogous mechanisms in the CNS [5,6].

Which animals should we use as MS models?

Animal models can be utilised to research MS regeneration processes in at least two different ways. The models that provide a replica of the human disease in the absence of an animal disease similar to MS are the most immediately pertinent. Even though there is no proof that MS is brought on by a comparable mechanism, the Experimental Allergic Encephalitis (EAE), which is brought on by immunisation against a specific myelin antigen, is the most frequently utilised model [7]. It is obvious that such "disease models" are required for the last preclinical testing of proremyelination therapies. However, in order to thoroughly deconstruct particular disease pathways, an initial, more reductionist sort of model is needed when dealing with a complex and varied disease. The extensive usage of "mechanism models" based on the direct injection of lysolecithin or ethidium bromide into white matter to destroy myelin-forming glia serves as an example of how beneficial these models are for studying the cell and molecular biology of remyelination. These models clearly distinguish between the acute demyelination phase and the subsequent repair process, allowing researchers to examine the precise roles that various molecules play in repair. Contrarily, in EAE, the two processes take place concurrently in the CNS, making it challenging to distinguish between an influence that makes remyelination more effective in the sense of making the environment less hostile to it. Despite how varied these models are, they do not encompass the entire range of problematic. The necessity for a model of oligodendrocyte apoptosis within the category of mechanism models is underscored by the knowledge that this can be a significant contributor to disease in some subgroups of MS [8]. The use of the demyelinating poisons mimics this type of demyelination to some extent. Recombinant syncitin, a Human Endogenous Retrovirus (HERV) glycoprotein that was recently

discovered in MS lesions, is an alternative and potentially extremely relevant inducer of oligodendrocyte death when injected in the corpus callosum. Following stereotaxic injection of a Cre-expressing virus, anatomically targeted oligodendrocyte death can also be induced by recombination in transgenic mice carrying a floxed Cholera toxin (fragment A) gene under the CNP promoter [9,10]. These recently developed genetic strategies may also be useful in creating models of the neuronal apoptosis also seen in cortical MS lesions. New models that more effectively bridge the gap between disease pathology and the clinical assessments utilized in MS are also urgently needed. Optic neuritis makes sense because it frequently manifests as the initial MS symptom and because it may be linked to lesions that show inflammation on MRI scans enriched with gadolinium [11-14]. Additionally, anatomically localized EAE model may be useful, particularly if they can be applied to primates. Applying imaging methods like serial magnetization transfer, which can provide information on demyelination, axonal loss, and/or nerve atrophy in MS, and diffusion tensor imaging, which can distinguish between axon loss and myelin damage, to these rodent and primate models would provide an excellent translational system for the evaluation of both drug- and cell-based proremyelination therapies.

Are Cell-Based Therapies Effective for MS?

Bill Blakemore and Madeleine Gumpel were the first to successfully transplant myelinogenic cells, and additional research using oligodendrocyte precursor cells, Schwann cells, olfactory ensheathing cells, and neural stem cells have since been conducted for 20 years.

This comprehensive research has shown that this strategy offers a fantastic experimental tool for researching the biology of remyelination. The hypothesis that cell transplantation also offers a potential therapeutic strategy to remyelination in MS has been reinforced by the broad myelination that can occur in animal models. Two recent research have given this idea more momentum. First, the finding that the adult human brain contains many cells that resemble rodent OPCs, can be separated during neurosurgery procedures, and heavily myelinate shiverer axons following grafting [15-16].

Second, the grafting of autologous Schwann cells restored myelination to a focal demyelinated lesion in the spinal cord of rhesus monkeys. But there are some glaring issues with this strategy. How will cells be distributed, first? A multifocal illness will necessitate many injection sites (each requiring an expensive neurosurgery procedure and carrying a modest but real danger of intracerebral hemorrage), unless transplanted cells can move extensive distances within the CNS. The amount to which the cells migrate away from their entrance points needs to be addressed, even though the entry of neurosphere-derived neural precursors into the CNS from the bloodstream seen in mice EAE offers a potential remedy Second, what will be the benefit of transplanting new myelin-forming precursors into an environment where OPCs are already abundant and apparently unable to contribute to repair? It might be possible to engineer ES cell-derived OPCs to overcome putative inhibitory cues, but will such engineered cells then be safe over the subsequent years? Short-acting and self-limiting treatments, such as Polysialic Acid (PSA) mimetic peptides shown to promote migration, might be a safer method of manipulating cells prior to transplantation, but the optimum strategy would then be to use these small molecules to alter the behavior of endogenous cell populations. Further concerns over safety would also be raised if neural cell grafting requires immunosuppression, as this may release the inhibition of a dormant virus. Thus, cell therapies alone seem unlikely to contribute to remyelination on the scale required in MS, although their use to induce temporary immunoregulation and exert a neuroprotective effect as observed in chronic EAE or as a means of delivering therapeutic factors into the CNS holds considerable potential [17].

References

1. Brockschnieder, Damian, et al. "Cell depletion due to diphtheria toxin fragment A after Cre-mediated recombination." *Mol. cell. biol.* 24.17 (2004): 7636-7642.
2. Feil, Robert. "Environmental and nutritional effects on the epigenetic regulation of genes." *Mutat. Res./Fundam. Mol. Mech. Mutagen.* 600.1-2 (2006): 46-57.
3. Holliday R. "A historical overview." *Epigenetics*. 2006;1:76—80
4. Kornek, Barbara, et al. "Multiple sclerosis and chronic autoimmune encephalomyelitis: a comparative quantitative study of axonal injury in active, inactive, and remyelinated lesions." Am. j. pathol. 157.1 (2000): 267-276.
5. Michailov, Galin V., et al. "Axonal neuregulin-1 regulates myelin sheath thickness." *Science* 304.5671 (2004): 700-703.
6. Baker, David, et al. "Critical appraisal of animal models of multiple sclerosis." *Mult. Scler. J.* 17.6 (2011): 647-657.
7. Ma, Y. T., et al. "Smoking initiation is followed by the early acquisition of epigenetic change in cervical epithelium: a longitudinal study." *Br. J. Cancer* 104.9 (2011): 1500-1504.
8. Brockschnieder, Damian, et al. "Cell depletion due to diphtheria toxin fragment A after Cre-mediated recombination." *Mol. cell. biol.* 24.17 (2004): 7636-7642.
9. Sugden, C. "One-carbon metabolism in psychiatric illness." *Nutr. res. rev.* 19.1 (2006): 117-136.
10. Huynh, Jimmy L., et al. "Epigenome-wide differences in pathology-free regions of multiple sclerosis–affected brains." *Nat. neurosci.* 17.1 (2014): 121-130.
11. Liggett, Thomas, et al. "Methylation patterns of cell-free plasma DNA in relapsing–remitting multiple sclerosis." *J. neurol. sci.* 290.1-2 (2010): 16-21.
12. Janson, Peter CJ, et al. "Profiling of CD4+ T cells with epigenetic immune lineage analysis." *J. Immunol.* 186.1 (2011): 92-102.
13. Graves, Moira C., et al. "Methylation differences at the HLA-DRB1 locus in CD4+ T-Cells are associated with multiple sclerosis." *Mult. Scler. J.* 20.8 (2014): 1033-1041.
14. Spence, Rory D., and Rhonda R. Voskuhl. "Neuroprotective effects of estrogens and androgens in CNS inflammation and neurodegeneration." *Front. neuroendocrinol.* 33.1 (2012): 105-115.
15. Alonso, Alvaro, and Cari Jo Clark. "Oral contraceptives and the risk of multiple sclerosis: a review of the epidemiologic evidence." *J. neurol. sci.* 286.1-2 (2009): 73-75.
16. Portaccio, E., et al. "Breastfeeding is not related to postpartum relapses in multiple sclerosis." *Neurology* 77.2 (2011): 145-150.
17. Tuohy, Orla, et al. "Alemtuzumab treatment of multiple sclerosis: long-term safety and efficacy." *J. Neurol. Neurosurg. Psychiatry* 86.2 (2015):208-215.

Cite this article: Ramsey, C., Richard, G. Improving Remyelination of the Central Nervous System in Multiple Sclerosis. J Mult Scler 2023, 10(1), 484