Expectations and Result on Regenerative Medicines for Remyelination

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Introduction

The adult mammalian Central Nervous System (CNS), according to conventional knowledge, is not a good regenerator. While this is unquestionably true for neurons, which seldom regenerate from scratch after injury and do not easily repair damaged axons, it cannot be said for glia and, in particular, oligodendrocytes. The myelinating oligodendrocytes of the Central Nervous System (CNS) preserve and support neuronal function. Loss of these cells, for example in conditions like Multiple Sclerosis (MS), leads to demyelination of axons, which impairs their activity and survival. Axons need an intact myelin sheath to maintain their integrity, and ongoing demyelination makes them susceptible to cumulative degeneration that is both irreversible and progressive. Replacement oligodendrocytes are produced after injury-induced activation, recruitment, and differentiation of a large population of multipotent adult neural stem cells, also known as Oligodendrocyte Progenitor Cells (OPCs). This process is in many ways a paradigmatic example of regeneration. These freshly formed oligodendrocytes repair the injured tissue's original structure and function.

Remyelination, as it is known, is a genuine regeneration process. If remyelination is effective, why is there such a pressing demand for remyelination enhancing medications? And why is a recent study by Najm and colleagues' discovery of two small molecules with such action such a significant step towards satisfying this need?

With time, remyelination becomes less effective [1]. Remyelination's effectiveness decreases to the point where it essentially fails in chronic demyelinating illnesses like MS. Therefore, encouraging remyelination should also result in axon priming in addition to restoring lost function. In areas of chronic demyelination in MS patients, undifferentiated oligodendrocyte lineage cells are frequently seen. This failure of re- cruited oligodendrocyte lineage cells to develop into new oligodendrocytes is the main bottleneck in remyelination that occurs with ageing. The consequences of ageing can be reversed, and aged adult OPCs can remyelinate just as well as young adult OPCs when given the right environmental signals, according to earlier research utilising the hetero-chronic parabiosis paradigm [2,3]. This suggests that reversing the aging-related decline in remyelination efficiency can be accomplished in theory through pharmacological methods as opposed to cell treatment, motivating numerous teams to identify the targets that promote OPC differentiation.

Similar to numerous other recent research, Tesar and colleagues performed phenotypic screens utilising small chemical libraries to identify drugs that stimulate oligodendrocyte development [1]. To find molecules that promote differentiation of mouse epiblast-derived OPCs, Najm et al. examined a library of bioactive small compounds with a history of safe use in clinical trials, hence giving immediate translational value [1]. This method found two topical medications with FDA approval, mi-conazole and clobestasol, which may both pass the blood-brain barrier. The first is a topical antifungal agent, while the second is a strong topical corticosteroid. The two drugs were then tested in what may very well become a standard hierarchical series of experimental models of myelination/remyelination of increasing complexity. The initial screen was based on the ability of tested compounds to enhance production of membrane sheet-forming oligodendrocytes in vitro. Ex vivo slice preparations of developmental myelination, toxin-induced demyelination in adult rodent spinal cord, and Experimental Autoimmune Encephalomyelitis (EAE), an immune-mediated model of CNS inflammation thought to most closely mimic the pathology of MS, all demonstrated activity in both compounds. Finally, both medications were discovered to induce differentiation of human OPCs obtained from hESCs and hiPSCs, demonstrating the translational significance of findings generated from rodents.

The use of EAE models for remyelination assessment is not without significant challenges. The therapeutic intervention being investigated may directly affect the adaptive immune response that the EAE model is predicated, while having been shown to be beneficial for understanding the immunopathogenesis of MS. The degree of demyelination may be decreased, which may be interpreted as increased re-myelination, if the intervention were to repress this response. Additionally, remyelination may proceed at its normal rate without necessarily being accelerated if the treatment eliminates a reaction that is hostile to the oligodendrocyte lineage (like to allowing a car to travel quicker by removing the hand brake rather than pressing the accelerator). Aware of these possibilities, Najm and colleagues take great care to demonstrate that their treatments have no effect on the adaptive immune response and that, as a result, the positive effects of miconazole and clobestasol on EAE are probably caused by a direct increase in re-myelination. The fact that only a small portion of the several EAE models include genuine initial demyelination in which undamaged but demyelinated axons are still available for remyelination increases the likelihood of inconsistent interpretation of results. Given these concerns, the requirement of the EAE model, which was created to understand CNS autoimmunity, as part of the remyelination validation pipeline to support regenerative neurobiology, should always be subject to careful scrutiny.

Remyelination biology has advanced quickly in recent years and is almost ready for clinical use. The possibility of clinical trials is now a reality thanks to the discovery that approved drugs, in addition to the two identified by Najm and colleagues, can also enhance remyelination in pre-clinical models [4-6]. In fact, encouraging findings from the first of these, a phase 2 trial utilising antibodies against Lingo-1, were just presented at the American Academy of Neurology Annual Meeting this year [7].

While a better understanding of the biology underpinning remyelination and the discovery of additional possible targets will continue to be crucial areas of future research, clinical translation issues may currently be the most significant and pressing ones. What patient populations and illness stages are most likely to benefit from remyelination therapies? What are the most trustworthy metrics for these treatments' results? How should immunosuppression and remyelination therapy be coordinated for best results?

These are only a few of the numerous queries that demand prompt solutions. We are now in a position to be even asking such clinically relevant issues, which is a credit to the advancement and excitement in the MS regenerative medicine field as well as the significant gains that studies like those of Najm and colleagues have made.

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