Central nervous system regeneration—where are we?

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Summary

Until relatively recently, we thought that the human central nervous system (CNS) was unable to regenerate. However, with the initial discovery of remyelination within the brain and the spinal cord in cat (Bunge, Bunge and Ris. Ultrastructural study of remyelination in an experimental lesion in adult cat spinal cord. J Biophys Biochem Cytol 1961;10:67–94.) and later in human (Prineas and Connell. Remyelination in multiple sclerosis. Ann Neurol 1979;5:22–31.), we know that regeneration can be quite extensive. This review will concentrate on CNS remyelination, indicating why it is important for various human neurodegenerative diseases including multiple sclerosis and spinal cord injury, and relate how stem cells may be involved—both in endogenous repair and in proposed therapies.

Inefficiency of human CNS regeneration

Compared to other organisms, humans are remarkably poor at regeneration of the central nervous system (CNS). Zebrafish are able to successfully regenerate the spinal cord and remyelinate very efficiently,1–3 and even rodents will restore myelin sheaths to virtually all demyelinated axons.4 However, in humans, axonal regeneration is poor, and even remyelination is limited.5,6 So, is there a benefit to not regenerating the CNS in humans? It is hard to imagine that wild zebrafish with a spinal cord injury will survive to regenerate, but perhaps the mechanisms of regeneration were designed originally as an advantageous method of plasticity to adapt to the environment. Zebrafish in small tanks remain small, but if put into a bigger tank, grow bigger, even if moved in (early) adulthood, and perhaps this need for plasticity determines their better apparent regeneration in the laboratory environment. Have humans evolved to avoid CNS regeneration, or have we just lost this as a consequence of acquiring some other benefit? It may be that the complexity of the human brain, compared to rodents and zebrafish means that regeneration might be deleterious, by confusing neural pathways and networks, and developing foci of unstable electrical activity, leading to seizures. Putting a new wire into a highly organized network of wires may be more risky than helpful, as finding the correct connections may be impossible. Poor regeneration in all tissues is not a human trait, as skin7 and liver8 are very capable of fast regeneration.

However, to lessen the burden of human disease and trauma, due to the increased longevity of humans, repair of the brain and spinal cord is now an important research goal. Regrowing neurons and axons (which are correctly connected) is a higher aim, but currently extremely difficult. However, regeneration of a myelin sheath around an axon is possible and desirable. Myelin abnormalities or damage (demyelination) can occur in many diseases including multiple sclerosis (MS), trauma, perinatal...
leukomalacia and leukodystrophies. Regeneration of myelin sheaths (remyelination) is therefore a key research aim.

Why is remyelination important?
Myelin is formed by oligodendrocytes, which produce a vast quantity of membrane which is wrapped around axons forming a spiral of closely opposed membranes held together by myelin proteins. Each oligodendrocyte can wrap several or even many different segments of different axons. Each spiral of wraps is called an internode, which is separated from the next wrap by the node of Ranvier where sodium channels lie and where propagation of the saltatory impulse occurs. Not only is myelin an electrical insulator, but the oligodendrocyte provides metabolic support for the axon by passing it nutrients through channels.9,10 This is the basis for the hypothesis that remyelination after injury is helpful for axons, not only restoring electrical conduction, as seen by direct neurophysiology in animal models,11 but protecting the nerve from neurodegeneration. The evidence for neuroprotection in animal models is strong: neurophysiology in transgenic mice with disordered myelination (through mutations in the myelin proteins or oligodendrocyte ablation) show axonal degeneration,12–14 there is reduced axonal pathology and degeneration after remyelination compared to when this is prevented,15 and there is evidence of direct metabolic support.9,10 In humans, this is more difficult to prove as there are not yet robust ways of directly measuring remyelination or neuroprotection in vivo, but by association from post-mortem studies, those MS lesions which successfully remyelinate are also those with less axonal pathology.16

How is remyelination achieved?
To achieve remyelination, new myelinating oligodendrocytes are generated from their precursor cells—oligodendrocyte precursor cells (OPCs). These cells may be thought of as our endogenous tissue stem cells in the CNS, and reside both in the subventricular zone as well as dispersed throughout the CNS. It is not clear what these cells do in normality. They may be the pool of cells available for myelin turnover, which does occur (albeit at a slow rate17), but after injury, they proliferate, migrate to areas of damage and mature into myelinating oligodendrocytes to replace myelin sheaths. So why is this repair then limited if all the components are present? In fact, in some patients with MS, remyelination may be extensive,5,6 though never sufficient and complete. In addition, patients with a single episode of demyelination, such as in acute demyelinating encephalomyelitis can recover to near normal function,18 with normalization of many of the changes seen on magnetic resonance brain scans.19 Remyelination (as with all regeneration) seems less successful with increasing age (both in humans20 and rodents21). The reason for this disparity of regeneration between individual humans is not well understood, and may be related to either differences in the inherent repair capacity of OPCs, or the varying inflammatory/toxic environment that the repairing cells are required to work in, in disease.

How can we manipulate remyelination?
Whatever the cause of limitation of remyelination capacity in humans, it is not sufficient, and therefore means to improve its efficiency are being actively sought as therapies for MS and other diseases involving demyelination, e.g. traumatic spinal cord injury. There are two approaches to this—either to promote the efficiency of the endogenous repair system—‘tweaking your own stem cells’ or to transplant in exogenous OPCs that may repair better—‘stem cell transplants’ (Figure 1).

There does not appear to be a reduction in number of total OPCs in humans (even after MS for many years), suggesting that OPC depletion is not a rate-limiting step for remyelination—although we know that OPCs in adult rodent brains are slower to be recruited to demyelinated lesions and slower to differentiate into myelinating oligodendrocytes compared to ones from younger brains.22 Around 30% of MS lesions examined from post-mortem human brains show a lack/insufficiency of OPCs

![Figure 1. Possible strategies for pro-remyelination therapies in the CNS.](image-url)
within the lesion.\textsuperscript{23,24} The other 70% contain a normal number of OPCs (compared to white matter) but these are stuck as immature cells, and not able to remyelinate axons. Therefore, therapeutically improving both OPC migration and maturation may be ways of improving remyelination. Using rodent models, potential druggable target receptors and pathways have been identified that improve remyelination by acting on these two mechanisms and are summarized in Figure 2. Only one of these, anti-LINGO-1 antibody therapy has reached clinical trial (NCT01244139), but others will no doubt follow.

The idea of stem cell transplants is strangely attractive to patients and doctors alike, with the promise of regeneration through a new approach. In terms of generating new myelin sheaths from transplanted cells, we can now produce human OPCs \textit{in vitro} either from embryonic stem cells or induced pluripotent stem cells, albeit rather slowly, as culture to OPC stage takes 90 days.\textsuperscript{25} These cells are capable of myelinating mouse brain.\textsuperscript{26} However, whether they are better at repair than endogenous OPCs is not possible yet to test in humans. Injection of cultured OPCs into the CNS may be useful in traumatic spinal cord injury when there is a single event with damage in a single place, but seems much less practical in a MS patient who has multifocal demyelinating lesions which continue to appear over many years. A clinical trial (NCT01217008), initiated by Geron, to treat acute spinal cord injury patients with OPCs transplanted into the lesion site passed regulatory bodies, but was terminated early, with entry of only four patients, apparently for financial reasons. However, if OPCs could be manipulated to make them better at remyelination—perhaps by ignoring chemorepellent cues produced by some MS lesions, or being more likely to mature properly, then they may achieve a therapeutic advantage in MS patients. Equally, if we find that some MS patients have OPCs which are inherently poor at remyelination, then these patients may benefit from transplantation with more potent OPCs obtained from elsewhere or manipulated to work better.

Delivery of these cells deserves some thought—how to get them into the CNS, to the correct place within the CNS, and also when to give them in the course of a chronic disease such as MS. Delivery by stereotactic injection directly into the CNS guarantees that cells are close to the area of damage, but carries risk of surgery. Whether cells delivered in one place of the CNS can migrate to other areas of need is not known in human. In rodent models, the evidence is divided: neural stem cells (NSCs) can disperse widely, particularly in abnormal brain,\textsuperscript{26} but other studies have shown that OPCs migrate more slowly.\textsuperscript{27} This may be related to whether the CNS is diseased or not, as only with damage will migration cues be active. Delivery into the cerebrospinal fluid (CSF) may also allow penetration into the CNS parenchyma but there is no evidence that OPCs or NSCs given intravenously will reach the brain. However,
mesenchymal stem cells have been given intravenously in animal models and in humans in trials (and at some private clinics), with the initial hope that these would home to areas of damage and form the appropriate cell for the situation. These cells do appear to home to CNS damaged areas, but unfortunately, they convert into CNS cells extremely rarely. However, they still seem to show a pro-regenerative action, which is hypothesized to be related to a variety of immunomodulatory and pro-regenerative factors released from these cells. For this reason, trials of treatment with mesenchymal stem cells in MS have begun, and there are 14 currently registered with clinicaltrials.gov. Delivery of cells intranasally has also been proposed and in rodents, mesenchymal stem cells or neural stem cells can apparently pass through into the CNS, resulting in widespread dispersal of cells through both the parenchyma and the CSF, providing an interesting possible alternative delivery route.

The timing of administration of ‘stem cell transplants’ is also difficult. Some MS lesions remyelinate spontaneously, whereas others do not, and predicting as to which is impossible currently. Should we be giving regenerative therapy early in the relapsing–remitting phase of the disease, when the patient is well, so that lesions are repaired quickly, or is this too risky for the potential side effects? If we wait until the patient is more disabled (in a progressive phase) then will therapy to promote remyelination still be effective, or will it be too late? Again, as yet, we do not have the biomarker tools available to determine whether axons in lesions have lost the ability to be remyelinated and which are degenerating inexorably. It seems likely that regenerative therapies will co-exist alongside immunomodulatory therapies for MS treatment but the timing of this needs work.

Will we ever be able to regrow parts of the CNS? Recent work has shown that three-dimensional structures resembling brain may be grown from human iPS cells in culture, and these organoids contain layered cortex. These cultures are likely to be very important in research to understand brain development and ultimately regeneration, however, using them to replace chunks of injured brain in this manner is currently science fiction.

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References


