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Harnessing therapeutic potential of induced pluripotent stem cell-derived endothelial cells for remyelination in the central nervous system

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Myelin is the protective sheath surrounding nerve fibers, and its damage (demyelination) occurs in many central nervous system (CNS) diseases, including multiple sclerosis (MS), traumatic injury, neurodegenerative diseases such as Alzheimer's disease, and mental disorders such as schizophrenia (Barateiro et al., 2016). Repair of damaged myelin sheaths (remyelination) often fails in MS, leading to neuronal loss and irreversible functional deficits. Remyelination involves the activation and recruitment of adult oligodendrocyte progenitor cells (OPCs), the residential stem cells in CNS, which eventually differentiate into new mature oligodendrocytes and form new myelin sheaths on demyelinated axons. Promoting remyelination emerges as a potentially effective clinical intervention for a broad range of demyelinating diseases such as progressive MS (Franklin and Ffrench-Constant, 2017). Currently, there is no treatment directly promoting remyelination in the clinic.

In recent years, advances in stem cell research have paved the way for innovative approaches to treating neurological disorders. One promising avenue involves the use of human induced pluripotent stem cell (iPSC)-derived cells to promote remyelination in the CNS. iPSCs have the potential to differentiate into almost all cell types, making them a promising source of cells for conditions requiring tissue graft. Patient-specific iPSC-derived cells have not only been widely used to model various diseases in research, but they also have shown potential for clinical application in a wide variety of devastating diseases.

iPSC-derived cells for remyelination: Several human cell types have been explored in cell therapy for enhancing remyelination in animal models, including embryonic stem cells-derived neural stem cells and OPCs, embryonic neural stem cells and neural precursor cells, embryonic OPCs and bone marrow mesenchymal stromal cells (Christodoulou et al., 2024). Exogenously administered cells exert a beneficial effect following demyelination through cell replacement or/and cell modulation such as immunomodulation, extracellular matrix remodeling, nutritional support, neuroprotection, and stimulating endogenous remyelination. These cell modulation effects are predominantly attributed to the secretome of the transplanted cells, which consists of all soluble factors and extracellular vesicles (Daneshmandi et al., 2020). For iPSC-derived cells, current research mainly focuses on iPSC-derived myelin-producing cells. iPSCs-derived OPCs and oligodendrocytes generated by varying induction protocols are capable of myelinating host axons in mouse models of congenital hypomyelination, CNS demyelination, and spinal cord injury (McCaughey-Chapman and Connor, 2023). The challenge remains in obtaining a progenitor population from iPSCs with high efficiency. Currently, the iPSC-derived oligodendrocyte lineage cells used for transplantation are mostly of the $O4^+$ population, which consists of mainly immature pre-myelinating oligodendrocytes (preOLs). PreOLs are post-mitotic and not able to expand *in vitro*, and their use as a source of cell therapy is limited compared with progenitors. Nevertheless, transplantation of iPSC-derived OPCs or/and preOLs has been shown to have the therapeutic potential for myelin loss in the CNS (**Figure 1**). Whether iPSC-derived OPCs/preOLs can remyelinate demyelinated axons after transplantation in the adult human brain is unknown.

In addition to replacing myelinating cells, astrocytic-fated iPSC-derived progenitors increase endogenous oligodendrogenesis and remyelination via the release of growth factors in mice with white matter stroke (Llorente et al., 2021). Recently it has been reported that human iPSC-derived long-term neuroepithelial stem cells can produce bona fide oligodendrocytes, these cells myelinate long-term neuroepithelial stem cell-derived axons in culture, host axons in rat stroke-injured cortex and human cortex in organotypic cultures (Martinez-Curiel et al., 2023). These findings provide encouraging evidence for the future use of human iPSC-derived cell lines to promote effective clinical recovery following brain injuries.

Remyelination is associated with multiple cell types in a dynamic microenvironment. The current success in the generation of iPSC-derived cells has provided a practical source for obtaining specific cell types. It is expected that there are more efforts in exploring other iPSC-derived cell types for remyelination therapy.

iPSC-derived endothelial cells for remyelination: Endothelial cells (ECs) from cerebral blood vessels secrete trophic factors such as FGF and brain-derived neurotrophic factor (BDNF) to sustain OPC proliferation, survival, and differentiation (Arai and Lo, 2009). Human iPSC-derived ECs (iPSC-ECs) have been shown to be able to improve tissue restoration after ischemic damage in the heart, limb, and brain, and in wound healing either by direct cell replacement or by cell interaction (Jang et al., 2019). Recently, Ishizaki's lab and our lab have reported that iPSC-ECs promote remyelination in different mouse demyelinating models. Transplantation of iPSC-ECs improves white matter recovery from ischemic damage; this is via increased number of oligodendrocyte lineage cells, suppressed inflammatory response, and recruitment of regulatory T cells (Xu et al., 2023). We tested the effects of exogenous iPSC-ECs on remyelination in toxin-induced CNS demyelination mouse model and showed that transplantation of iPSC-ECs promoted myelin repair through soluble factors such as BDNF, which enhanced oligodendrocyte linage progression by activating mTORC1 signaling pathway. In addition, iPSC-ECs also promoted the M2 polarization of microglia, which synergistically promoted regeneration (Ma et al., 2024). The exact cellular and molecular mechanisms underlying the therapeutic properties of iPSC-ECs are yet to be fully elucidated. However, the results further substantiate the suggestion that iPSC-ECs hold therapeutic potential for myelin damage in diseases and injuries in the CNS.

Dynamic effect of iPSC-ECs on oligodendrocyte lineage progression: The therapeutic effects of iPSC-ECs on promoting remyelination can be attributed to their multifaceted impact on the CNS microenvironment. Remyelination occurs in a dynamic tissue environment, contributed by factors not only produced locally, but also from circulation. Within the local microenvironment, multiple cell types in demyelinated areas orchestrate the remyelination process. Microglia and astrocytes release cytokines and growth factors, secret extracellular matrix molecules, and clear myelin debris, which create a conducive environment for the generation of new oligodendrocytes from OPCs. The lineage progression of oligodendrocytes during remyelination correlates with a switch from proinflammatory M1 microglia/A1 astrocyte to pro-regenerative M2/A2 phenotypes. The transition of this local neuroinflammation profile facilitates stage-specific microenvironment required for recruitment and maturation of OPCs for successful remyelination.

The biologically active factors secreted by ECs, which come from either soluble factors or/and extracellular vehicles, contain a cocktail of growth factors and cytokines which have been proved to exert different effects on OPC proliferation and differentiation. Among them, FGF and BDNF have been well known to support OPC survival and proliferation, whereas BDNF and transforming growth factor β individually enhance OPC differentiation and oligodendrocyte maturation. Since OPC proliferation and differentiation are two inversely related cellular processes and differentiation usually coincides with proliferation arrest, their enhancement by exposure to iPSC-ECs likely occurs sequentially and is mediated by activation of different pathways. Moreover, some of the factors may play their roles in a context-dependent manner, thereby modulating OPC proliferation then differentiation by interacting with additional factors. Hence, EC's secretome holds a therapeutic potential for myelin repair. In the past decade, secretome-based therapies have emerged as a promising approach to overcome the limitations associated with cell-based therapies for tissue and organ regeneration (Daneshmandi et al., 2020). However, the exact dynamic signature of EC secretome and their importance in remyelination is still to be established.

Furthermore, it is reasonable to speculate that the EC secretome may be affected by OPCs and oligodendrocytes. ECs and OPCs interact via both released factors and direct physical contact which regulate their functions mutually (Chavali et al., 2020). It is conceivable that iPSC-ECs switch their status with changing secretome following interactions with OPCs and oligodendrocytes. In addition, the iPSC-ECs present more pre-maturation characteristics (Jang et al., 2019), therefore are expected to resemble more nascent while less specialized ECs. This may enable them to be more effective in oligodendrocyte lineage progression compared to mature ECs.

Thus, the dynamic interaction between different cell types by different factors shapes the remyelinating environment. ECs play essential roles in not only rebuilding the vasculature following the tissue damage, but also promoting cellular progression towards successful repair. In demyelination situations, functional impairment occurs in various cell types due to pathological factors or ageing, application of healthy iPSC-ECs will help restore a functional network, therefore, promote a successful remyelination in the CNS (**Figure 2**). Furthermore, these cells might provide additional benefits such as enhancing blood-brain barrier stability, modulating inflammation, and immune cell infiltration.

Therapeutic potential of iPSC-EC for myelin related CNS diseases: Demyelinating diseases are a group of disorders that cause myelin damage leading to progressive and irreversible neurological deficits. MS is the most common demyelinating disease caused by autoimmune attack. Others include optic neuritis, neuromyelitis optica spectrum disorder, and myelin oligodendrocyte glycoprotein antibody-associated disease. Recently, it has been revealed that many other CNS diseases are associated with myelin damage. For example, recent research suggested that the breakdown

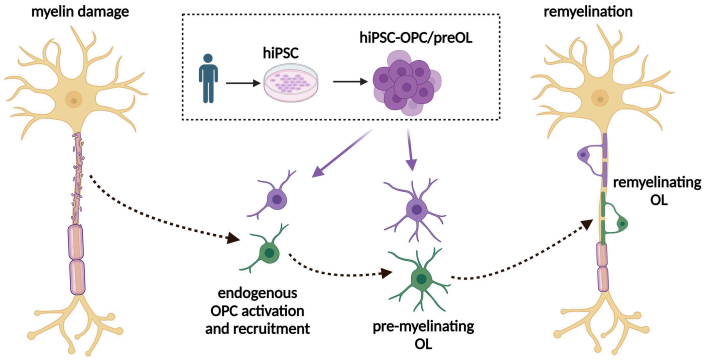

Figure 1 | iPSC-derived myelin-producing cells hold therapeutic potential for myelin loss in the central nervous system.
iPSC-derived OPCs and preOLs are capable of remyelinating host axons in demyelination models, together with endogenous remyelination. Created with BioRender.com. hiPSC: Human induced pluripotent stem cell; OL: oligodendrocyte; OPC: oligodendrocyte precursor cell.

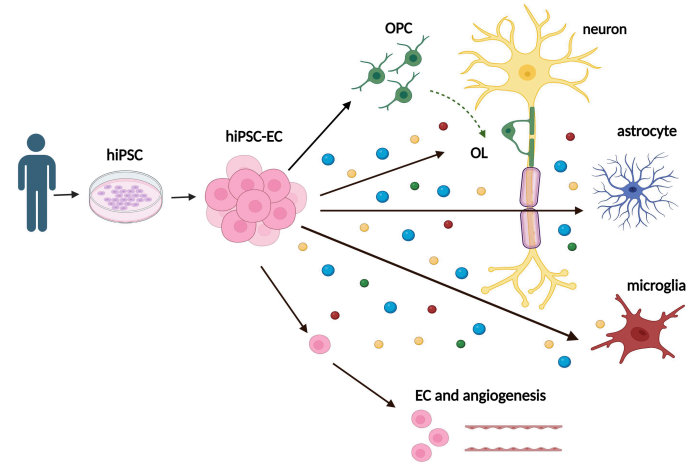

Figure 2 | iPSC-ECs hold therapeutic potential for myelin damage in diseases and injuries in the CNS.
iPSC-EC secretome, including extracellular vesicles, affects multiple cell types to restore a local functional network for CNS remyelination. iPSC-ECs are also involved in rebuilding the vasculature following tissue damage. Created with BioRender.com. CNS: Central nervous system; EC: endothelial cell; hiPSC: human induced pluripotent stem cell; hiPSC-EC: hiPSC-derived EC; OL: oligodendrocyte; OPC: oligodendrocyte precursor cell. ●: Extracellular vesicles; •••: molecules/soluble factors.

of myelin plays a role in the development of Alzheimer's disease. It has also been found that myelin dysfunction may be a component of Schizophrenia. In CNS ischemia/stroke and injury, myelin regeneration after damage contributes to functional recovery. These represent a wide yet complex pathological context in different myelin-related diseases. Therefore, the application of iPSC-ECs should be fully assessed according to the individual diseases on their pathological and treatment characteristics. Although compared to iPSC-OPCs ECs can be derived faster from iPSCs with higher efficiency, there are still challenges existing. As transplanted iPSC-derived OPCs can replace endogenous OPCs, a combination of iPSC-OPCs with iPSC-ECs might obtain further advantages for therapeutic purposes, to increase the integration of them into the existing neural network (Li et al., 2024).

Overall, studies suggest that iPSC-ECs may benefit both myelin protection and regeneration, providing a potential source of cell therapy for a wide range of diseases and injuries associated with myelin damage. Developing interventions using iPSC-ECs presents a promising direction for clinical translation. iPSC technology has enabled the generation of a scalable and consistent source of patient-specific endothelial cells, offering a renewable and precision therapeutic platform.

Challenges and considerations: Despite great promise, several challenges have been associated with iPSC-EC therapy in clinical settings. iPSC-ECs will still need to be tested for several safety measures, including their propensity to form teratomas *in vivo*, especially in a remyelination environment. Safe, efficient, functional, and scalable protocols to differentiate iPSC-ECs will also need to be thoroughly tested before reaching a clinical trial. Immunogenicity should be considered when using differentiated and ready-to-go iPSC-ECs for allogeneic transplantations (Jang et al., 2019). Another challenge is the effective cell delivery. Many CNS diseases involving demyelination exhibit myelin damage in multiple regions or disseminated form, making cell grafting into the injury sites extremely challenging. Other delivery routes such as intraventricular or intranasal have yet to be tested. Furthermore, cell delivery timing, frequency, treatment duration, and cell dosage should all be optimized.

Overall, harnessing the regenerative potential of iPSC-ECs will help unlock transformative treatments that potentially target the underlying causes of disability affecting the CNS. Future studies will likely focus on refining the transplantation protocols, exploring combinatorial approaches with other regenerative strategies, and conducting preclinical trials to validate the safety and efficacy of this innovative therapeutic approach.

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