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REVIEW ARTICLE

Direct Conversion to Achieve Glial Cell Fates: Oligodendrocytes and Schwann Cells

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Glia have been known for its pivotal roles in physiological and pathological conditions in the nervous system. To study glial biology, multiple approaches have been applied to utilize glial cells for research, including stem cell-based technologies. Human glial cells differentiated from pluripotent stem cells are now available, allowing us to study the structural and functional roles of glia in the nervous system, although the efficiency is still low. Direct conversion is an advanced strategy governing fate conversion of diverse cell types directly into the desired lineage. This novel strategy stands as a promising approach for preliminary research and regenerative medicine. Direct conversion employs genetic and environmental cues to change cell fate to that with the required functional cell properties while retaining maturity-related molecular features. As an alternative method, it is now possible to obtain a variety of mature cell populations that could not be obtained using conventional differentiation methods. This review summarizes current achievements in obtaining glia, particularly oligodendrocytes and Schwann cells.

Keywords: Direct conversion, Differentiation, Oligodendrocyte, Schwann cell, Disease modeling

Introduction

Glial cells, including astrocytes, oligodendrocytes, Schwann cells, ependymal cells, and microglia, are non-neuronal cells in the nervous system, which are more abundant than neurons (1). They support the morphological and functional features of neurons, and maintain the homeostasis in the nervous system (2). The abnormal activation of astrocytes, which are the most abundant cell type in the central nervous system (CNS), has been regarded as a cellular feature of pathological conditions (3). Likewise, oligodendrocytes and Schwann cells are also thought to be involved in the pathogenesis of several neurological diseases (4). Since deriving glial cells from individual patients is extremely difficult, it is now believed that obtaining glial cells from human pluripotent stem cells (hPSCs) is more feasible and efficient (5-7). However, as glial cells, particularly oligodendrocytes and Schwann cells, naturally develop during the late stage of nervous development through neurogenesis-to-gliogenesis switch, these developmental characteristics are considered as obstacles for complete differentiation of glial cells from hPSCs, and even the differ-

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entiated glial cells have functionally immature features. While human neuronal development begins at 6∼8 gestational week (8), oligodendrocytes differentiation begins around 18∼20 gestational week (9), and Schwann cells are observed after 7th week (10). Moreover, the myelination process continues until after the postnatal stage (11). Hence, hPSC-derived glial cells have not been adequately applied to study many neurological diseases associated with the impaired functions of these glial types (12).

Advances in stem cell and direct conversion technology have provided invaluable research models that describe the pathophysiology of human neurological diseases (13). In addition to the already mentioned limitations of differentiating glial cells, concerns related to cellular defects, such as the lack of functionalities based on the immature states of differentiated cells, are being raised. Direct conversion, which bypasses the pluripotent stage and irreversibly converts a certain cell type into a desired cell types (14), is one of the innovations in stem cell field. Numerous studies have shown that the cell fate can be switched to neuronal or glial cells by introducing lineage-specific transcription factors that regulate cellular plasticity and lineage flexibility (15, 16). This newly developed methodology is designed to transfer the cellular and molecular maturity of native cells intact to their converted counterparts. Additionally, it is considered as a promising alternative to avoid the biological or technical obstacles of conventional cell fate reprogramming, namely the necessity of reprogramming cells to the pluripotent state or embryonic stage. Cell fate conversion technique has been used in recent studies to improve the understanding of neurological diseases and to propose novel potential therapeutic approaches (17).

In this review, we discuss the recent progress in the utilization of myelinating glial cells, represented by oligodendrocytes and Schwann cells. This article covers both differentiation and direct conversion to obtain these cell types and provides prospects for future directions in light of current interest in the role and importance of glial cells in the nervous system.

Glia in the Nervous System

Glial cells in the CNS include astrocytes, oligodendrocytes, ependymal cells and microglia; whereas glial cells in the peripheral nervous system (PNS) include Schwann and satellite cells (18). These cells are responsible for maintaining the homeostasis and function of the nervous system, which includes providing physical and metabolic support to neurons and insulating neuronal axons (19). In the brain, glial cells exert various roles such as cerebrospinal fluid (CSF) production and distribution, blood-brain barrier regulation, neuro transmitter and ATP uptake and release, and myelin sheath formation depending on the cell type and anatomical location (20). In contrast, in spinal nerves and peripheral nerves, glial cells are known to be involved in efficient transmission of electrical signals and protection of neurons, mainly through the myelination (21).

Recently, in addition to their physiological functions, the role of glial cells in various pathological conditions has been suggested (22). Astrocytes and microglia are known to be related to the activation of inflammatory responses involved in the progression of brain diseases due to ischemic injury, infections, and genetic causes, and their cellular changes are recognized as markers of acute or chronic pathological conditions (23). Another type of glial cells, ependymal cells, form a cellular lining, control CSF production, and prevent CSF leakage (24, 25). Although previous studies have reported the differentiation of ependymal cells into new neurons in various pathological environments, whether they are neural stem cells with self-renewal capacity remains unclear (26-28). While the aforementioned types of glial cells have properties that are attributed to organ-specific features of the brain, oligodendrocytes and Schwann cells have similar functions despite their distinct anatomical location (29). Although Schwann cells include a non-myelinating subpopulation (30), both types of glial cells myelinate neuronal axons. Histological analyses of various neurological diseases have reported demyelination as a pathological hallmark (31); however, it is unclear whether intrinsic factors within glial cells cause demyelination triggering the development of the disease or it is only an intermediate phenotype of disease progression. Defects of these cells due to genetic factors or unknown pathogenesis cause serious clinical symptoms, and in many cases, immunological response is also involved. Denaturation of the myelin sheath is often observed in various hyper-immunity diseases (32, 33). Additionally, oligodendrocytes and Schwann cells have been reported to be involved in neuroinflammatory mechanisms (34, 35). Therefore, identifying the cellular mechanisms of oligodendrocytes and Schwann cells in pathological environments may contribute to the understanding of a variety of demyelinating diseases.

Differentiation of Glial Cells from Pluripotent Stem Cells

During embryonic development, oligodendrocyte pro-

genitor cells (OPCs) are produced from the motor neuron progenitor domain in the ventral neuroepithelium of the spinal cord and differentiate into oligodendrocytes, whereas Schwann cell precursors (SCPs) originate from neural crest cells migrating along the dorsoventral tract and differentiate into Schwann cells. In this context, protocols for differentiating each cell type have been established to mimic the developmental processes along the developmental lineage (CNS or PNS).

Developmental pathways differ depending on the anatomical location of oligodendrocytes in the nervous system (36), and distinct pathways towards the ventral spinal cord or forebrain fates have been proposed as pathways for the differentiation of oligodendrocytes from hPSCs (Table 1).

Table 1. Summary of oligodendrocyte differentiation

Species	Cell sources	Regional identity	Target cell type (Efficiency)	Duration (Days)	Self-renewal	*In vitro* disease modeling	*In vivo* transplantation	References
Human	hESCs	Spinal Cord	PDGFRα^+ OPCs (>80%) MBP^+ OLs (Not shown)	>90 days >120 days	Not shown	Not shown	Newborn shiverer mice	Hu et al., 2009
Mouse	EpiSCs	Spinal Cord	PDGFRα^+ OPCs (~90%) MBP^+ OLs (Not shown)	>10 days >13 days	>passage 8	Not shown	Newborn shiverer mice	Najm et al., 2011
Human	hESCs hiPSCs	Spinal Cord	PDGFRα^+ OPCs (>30%) MBP^+ OLs (Not shown)	>120 days ~200 days	Not shown	Not shown (Schizophrenia, as shown in Windrem et al., 2017; Huntington's Disease, as shown in Osipovitch et al., 2019)	Newborn shiverer mice	Wang et al., 2013
Human	hESCs	Forebrain Spinal Cord	$NG2^+$ OPCs (~87%) MBP^+ OLs (~5%)	>120 days >135 days	Not shown	Not shown (As shown in Djelloul et al., 2015)	Not shown	Stacpoole et al., 2013
Human	hESCs hiPSCs	Spinal Cord	$O4^+$ OPCs (~70%) MBP^+ OLs (~20%)	>50 days ~75 days	Not shown	Not shown (Pelizaeus-Merzbacher Disease, as shown in Nevin., 2017; Schizophrenias, as shown in McPhie et al., 2018; Alexander disease, as shown in Li et al., 2018)	Newborn shiverer mice	Douvaras et al., 2014 and 2015
Human	hESCs hiPSCs	Forebrain	PDGFRα^+ OPCs (25%) MBP^+ OLs (Not shown)	>50 days >85 days	Not shown	Not shown	Irradiated rats	Piao et al., 2015
Monkey Human	mESCs hiPSCs	Spinal Cord	PDGFRα^+ OPCs (>10%) MBP^+ OLs (~4%)	>57 days >73 days	Not shown	Not shown	Newborn C57BL6/J mice	Yamashita et al., 2017
Human	hESCs	Not shown	PDGFRα^+ OPCs (>90%)	>28 days	Not shown	Not shown	Adult rat spinal cord	Kim et al., 2017
Human	hESCs hiPSCs	Hindbrain	PDGFRα^+ OPCs (>20%) MBP^+ OLs (>3%)	>65 days ~120 days	Not shown	Not shown	Adult shiverer mice	Yun et al., 2019

Differentiation into the ventral spinal cord is mimicked by ventralization and caudalization, which are stimulated by the activation of the retinoic acid and sonic hedgehog signaling pathways that induce the expression of OLIG2 (5, 37-39); forebrain (39, 40) and hindbrain (41) patterning can be achieved by rostralization through inhibition of the Wnt signaling pathway. Most studies on subsequent differentiation have adopted stepwise methods through sphere formation under appropriate culture conditions including platelet-derived growth factor (PDGF), neurotrophin-3, cyclic adenosine monophosphate, and triiodothyronine that promote the development of oligodendrocytes. Using stepwise strategies, Wang et al. (38) reported large-scale production of hPSC-derived OPCs expressing OLIG2, PDGFRa, NKX2.2 and SOX10. Since conventional methods require much time (more than 100 days), subsequent studies have attempted to improve protocols to overcome the long-term period of differentiation (40, 42-45). Recently, Douvaras et al. successfully established a straightforward, rapid, and efficient differentiation method that enables the generation of oligodendrocytes within 70 days (42); however, whether the protocol facilitates the large-scale expansion of clinically compatible progenitor cells remains unknown. Moreover, attempts have been made to reduce the differentiation period using the strong fate commitment role of transcription factors (46-48). SOX10, discovered in the screening of transcription factors involved in the fate decision of OPCs, was sufficient to differentiate neural progenitor cells into oligodendrocytes expressing mature oligodendrocyte markers O4 or myelin basic protein (MBP) rapidly within 3 weeks of its introduction (47, 48). Furthermore, the combined expression of SOX10, OLIG2 and NKX6.2 increased the efficiency of O4-expressing oligodendrocytes to 70% (46). Although the generation of mature oligodendrocytes expressing MBP can be achieved in a relatively short period by the introduction of certain transcription factors, the effect of artificially shortening the differentiation period on the reconstruction of pathophysiological features of differentiated cells is still unknown.

Schwann cells originate from multipotent migratory neural crest cells that are specified at the neural plate border region and differentiate into neurons and glia in the PNS. Most of the early developmental studies on neural crest cells and Schwann cells have been primarily conducted in different organisms because of the spatiotemporal properties of neural crest cells during embryonic development (49, 50). Developmental mouse embryos have been sacrificed to study neural crest biology (51, 52) and avian models such as quail and chick that are capable of tracking live neural crest cells also have been commonly used (53). Lee et al. (54, 55), showed that human neural crest cells can be isolated from the periphery of hPSC-derived neural rosettes representing the early developing neuroepithelium and established feeder-free reliable protocols to establish for neural crest lineages, including peripheral neurons and Schwann cells. The differentiation and maturation processes of Schwann cells have not yet been studied in detail. Multiple studies have attempted to differentiate Schwann cells by administrating factors secreted by peripheral neurons, such as PDGF and neuregulin-1, since Schwann cells directly contact with peripheral neuronal axons (56). Subsequent studies developed direct protocols for the differentiation of Schwann cells through the intermediate stage of SOX10- and p75-positive neural crest cells, which required approximately 50 days, depending on the specific protocol (Table 2) (57-62). While GFAP expression is uniquely found in astrocytes not oligodendrocytes in the CNS, differentiated Schwann cells expressed GFAP as well as S100β representing functional overlap of the CNS and PNS glia besides myelination. Most studies have commonly used S100β, GFAP or MPZ as markers for differentiated Schwann cells (63). The regenerative capacity of the resulting cells has been validated and shown to be comparable to that of primary human Schwann cells in peripheral nerve injury models (60, 62, 64). In addition, the method developed by Kim et al. (62) not only enables differentiation into Schwann cells within 32 days but also allows the stable expansion of SCPs for more than 35 passages, providing insight into possible cell-based therapeutic strategies for peripheral nerve injury. Recently, Mukherjee-Clavin et al. (7) obtained a population of pure Schwann cell precursors (SCPs) from neural crest cells that differentiated as a result of natural interactions with peripheral neurons. Furthermore, Schwann cells differentiated from Charcot-Marie-Tooth (CMT) 1A patient- induced pluripotent stem cells (iPSCs) and preimplantation genetic diagnosis-human embryonic stem cells (hESCs) have contributed to reveal the pathological mechanisms of CMT and other diseases, thereby providing a promising research tool for disease modeling. Although the protocol reported in this study is longer (more than 80 days) than that of other studies, it is still considered that the resulting differentiated Schwann cells are insufficient to represent the mature patient's PNS, as the myelination efficiency *in vitro* was comparably low, but effective nerve regeneration was achieved when transplanted into animal models.

Both oligodendrocytes and Schwann cells develop continuously at the postnatal stage and are known to require

Table 2. Summary of Schwann cell differentiation

Species	Cell sources	Target cell type (Efficiency)	Duration (Days)	*In vitro* disease modeling	*In vivo* transplantation	References
Human	hESCs hiPSCs	$p75^+$ NCSCs (~30%)	>28 days	Not shown	Chick embryos and adult NOD/SCID mice	Lee et al., 2007 Lee et al., 2010
		$GFAP^+$ or $S100\beta^+$ SCs (>5%)	>109 days			
Human	hESCs	$GFAP^+$ or $S100\beta^+$ SCs (~60%)	~84 days	Not shown	Not shown	Ziegler et al., 2011
Human	hESCs hiPSCs	$p75^+$ NCSCs (Not shown)	>22 days	Not shown	Adult rat sciatic nerve	Wang et al., 2011
		$GFAP^+$ or $S100\beta^+$ SCs (Not shown)	>34 days			
Human	hESCs hiPSCs	$p75^+$ NCSCs (~46%)	>14 days	Not shown	In Ovo NCSC Injection	Liu et al., 2012
		$GFAP^+$ or $S100\beta^+$ SCs (Not shown)	>54 days			
Human	hESCs hiPSCs	$p75^+$ NCSCs (~80%)	>8 days	Not shown	Not shown	Kreitzer et al., 2013
		$GFAP^+$ SCs (Not shown)	Not mentioned			
Human	hESCs hiPSCs	$SOX10^+$ SCPs (~99%)	>24 days	Not shown	C57BL/6 mice sciatic nerve injury model	Kim et al., 2017
		$S100\beta^+$ or MPZ^+ SCs (Not shown)	>31 days			
Human	hiPSCs	$p75^+$ NCSCs (Not shown)	>20 days	Not shown	Adult athymic nude rat sciatic nerve	Huang et al., 2017
		$GFAP^+$ or $S100\beta^+$ SCs (Not shown)	>41 days			
Human	hESCs hiPSCs PGD−hESCs	CD49d+ SCPs (~18%) $GFAP^+$ or $S100\beta^+$ SCs (Not shown)	>21 days ~101 days	CMT1A pathogenesis	Mouse tibial nerve and rat models of chronic peripheral nerve denervation	Mukherjee-Clavin et al., 2019

time-consuming differentiation strategies *in vitro*. Moreover, in all differentiation methods from hPSCs developed to date, cells undergo epigenetic reprogramming. (65, 66). Epigenetic state of the hESCs is immature and thus maintains the euchromatin state in whole chromosome (67). In the process of establishing iPSCs from adult fibroblasts, it is known that OCT4, which regulates epigenetic regulatory mechanisms, reconstructs the mature epigenetic state of fibroblasts similar to that of embryonic stem cells (68). It is known that the initialized epigenetic characteristics change in the direction of limiting cell lineage and increasing cellular maturity as cell differentiation progresses (69). Therefore, the relatively short developmental period compared to that of living organs, the absence of stimuli for cellular aging, and the lack of a clear understanding of epigenetic changes that induce cellular maturation are still obstacles to obtaining biologically reliable cells. Current challenges to obtain functional myelinating cells from hPSCs may hamper studying myelination-related diseases. Despite extensive studies on differentiation, very little is known about the genetic control of the transition from hPSCs to myelination competent cells. Understanding the intrinsic and extrinsic factors including transcription factors governing functional myelinating cells will lead to acquiring authentic oligodendrocytes and Schwann cells.

Direct Conversion as an Alternative to Differentiation

To overcome the limitations arising from stem cell reprogramming and differentiation procedures, recent studies have shown promising results for the direct conversion of fibroblasts into oligodendrocytes (Table 3) and Schwann cells (Table 4).

The reporter cell line expressing green fluorescent protein along with PLP1 identified lineage-specific transcription factors for OPCs. Additionally, induced expression of OLIG2, SOX10, and NKX6.2 or ZFP536 which are involved in OPC development, led to rodent fibro-

Table 3. Summary of oligodendrocyte conversion

Species	Cell source	Reprogramming factors	Target cell type (Efficiency)	Duration (Days)	Self-renewal	*In vitro* disease modeling	*In vivo* transplantation	References
Mouse	Fibroblasts	SOX10, OLIG2, NKX6.2	PLP1$^+$ iOPCs (>20%) MBP$^+$ iOLs (Not shown)	>21 days >24 days	>passage 5	Not shown	Newborn shiverer mice	Najm et al., 2013
Mouse	Fibroblasts	SOX10, OLIG2, ZFP536	O4$^+$ iOPCs (>15%) MBP$^+$ iOLs (>10%)	>21 days >24 days	Not shown	Not shown	Newborn shiverer mice	Yang et al., 2013
Mouse	Fibroblasts	OCT4	A2B5$^+$ iOPCs (>90%) MBP$^+$ iOLs (Not shown)	>35 days >63 days	>passage 31	Not shown	Adult rat SCI models	Kim et al., 2015
Mouse	Astrocytes	SOX10	NG2$^+$ iOPCs (>80%)	>16 days	Not shown	Not shown	In vivo conversion in cuprizone-induced demyelinated mice	Khanghahi et al., 2018
Mouse	Astrocytes	SOX2	PDGFRα^+ iOPCs (>70%)	>14 days	Not shown	Not shown	In vivo conversion in cuprizone-induced demyelinated mice	Farhangi et al., 2019
Mouse	Fibroblasts	Chemical condition (M9)	A2B5$^+$ iOPCs (>60%) MBP$^+$ iOLs (Not shown)	>18 days >28 days	>passage 8	Not shown	Not shown	Chang Liu et al., 2019
Human	Fibroblasts	OCT4	A2B5$^+$ iOPCs (~10%) MBP$^+$ iOLs (~3%)	>14 days >50 days	>passage 10	Not shown	Adult shiverer mice and EAE-induced model	Yun et al., 2022

blasts developing into induced OPCs (iOPCs) within 3 weeks (70, 71). The obtained cells exhibited typical bipolar morphology and not only expressed various OPC markers including NG2, A2B5, and S100β presenting gene expression profiles consistent with those in bona fide OPCs but also could give rise to mature O4 and MBP-positive oligodendrocytes *in vitro* and successfully generated myelin structures for neuronal axons when transplanted into hypomyelinated Shiverer mice *in vivo*. In addition, the combination of SOX10, OLIG2, and NKX6.2 has been reported to provide an enhanced driving force for fate conversion towards OPCs through differentiation (46) and direct conversion (70) demonstrating relatively straightforward set of genes. Previous studies have attempted to minimize the number of transcription factors utilized for direct conversion (72-75). OCT4 has been proposed as a single factor sufficient for converting rodent fibroblasts into proliferative iOPCs, which promote extensive remyelination by retaining locomotor activity that facilitates access to the wound site when transplanted into an animal model of spinal cord injury (72). Similarly, the generation of iOPCs was achieved by introducing a single transcription factor, SOX2 or SOX10, into rodent astrocytes in an *in vitro* and *in vivo* manner (73, 74). Weider et al. (76) reported that overexpression of SOX10 drives the cellular properties of peripheral satellite glia to resemble those of oligodendrocytes *in vivo*. Recent attempts to convert human fibroblasts into iOPCs has been also successful (77). Ectopic expression of OCT4, along with small molecules, directly converts human fibroblasts into expandable iOPCs. These cells exhibit not only *in vitro* differentiation potential into oligodendrocytes, but also *in vivo* differentiation potential when transplanted into experimental autoimmune encephalomyelitis mice, providing insight into whether iOPCs can be a useful population for cell-based therapies.

Despite the great efforts aimed to successfully generate

Table 4. Summary of Schwann cell conversion

Species	Cell source	Reprogramming factors	Target cell type (Efficiency)	Duration (Days)	*In vitro* disease modeling	*In vivo* transplantation	References
Human	Fibroblasts	SOX10	$SOX10^+$ NCSCs (~2%) MPZ^+ or $S100\beta^+$ SCs (Not shown)	>14 days ~35 days	Not shown (CMT1A pathogenesis, as shown in Mukherjee-Clavin et al., 2019)	Chick embryos	Kim et al., 2014
Human	Fibroblasts	Chemical condition	$GFAP^+$ or $S100\beta^+$ SCs (Not shown)	>27 days	Not shown	Not shown	Thoma et al., 2014
Human	Fibroblasts	SOX10, EGR2	$S100\beta^+$ SCs (~43%)	>10 days	Not shown	The sciatic nerve of nude and NOD/SCID mice	Sowa et al., 2017
Human (mouse)	Fibroblasts	SOX10, EGR2	$S100\beta^+$ SCs (>5%) MPZ^+ SCs (Not available)	>14 days >21 days	Not shown	Not shown	Mazzara et al., 2017
Human	Fibroblasts	Chemical condition	$GFAP^+$ or $S100\beta^+$ SCs (Not shown)	>9 days	Not shown	The sciatic nerve injury rat model	Kiada et al., 2019
Human	Fibroblasts	OCT4, SOX2, KLF4, MYCL1, and LIN28 and p53 shRNA	$SOX10^+$ SCPs (~97%) $S100\beta^+$ or $NGFR^+$ SCs (>95%)	>18 days >25 days	Not shown	The sciatic nerve injury mouse model	Kim et al., 2020

human iOPCs, the mechanism of the transcription factors used in the conversion process is still not clearly understood. Yun et al. (77) employed OCT4 as a pioneer factor governing the opening of chromatin regions otherwise generally inaccessible in differentiated cells (78, 79). In line with this, Dehghan et al. (80) reported that the forced expression of OCT4 in combination with the administration of valproic acid to the demyelinated mouse brain enhanced myelin sheath repair, providing evidence for functional link between an OCT4 and the regulation of myelin related factors. However, OCT4 alone-driven methods exhibit low efficiency in converting ratio of SOX10-expressing cells and induce uncharacterized heterogeneous populations (77). By contrast, the combined use of SOX10, OLIG2, and NKX6.2 strongly favored commitment to the specific OPC lineage from hPSCs-derived neural progenitor cells (differentiation) (46) and rodent fibroblasts (direct conversion) (70, 81), suggesting that cell fate conversion to OPCs can be achieved with SOX10-combined methods in a more favorable manner.

In contrast to oligodendrocytes, which express SOX10 only at the beginning of OPC specification after neural tube formation, Schwann cells retain the expression of SOX10 throughout the entire differentiation process ranging from the migrating neural crest stage to becoming fully differentiated myelinating Schwann cells. Kim et al. (16) reported the generation of induced neural crest cells with SOX10 overexpression in combination with small molecules that activated the Wnt signaling pathway, and mature Schwann cells expressing endogenous SOX10 were acquired by a subsequent differentiation process. To obtain a more specific Schwann cell fate, EGR2 and SOX10 were employed to rapidly convert cells into Schwann cells expressing MPZ (82, 83). EGR2 is known to be involved in the myelination process as well as in the initiation of the terminal differentiation of Schwann cells into the MBP- and MPZ-positive mature state (84, 85). Hence, the combination of SOX10 and EGR2 allows rapid and efficient conversion into Schwann cells; however, whether these cells harbor functional myelin-competent capacity, comparable to that of bona fide Schwann cells *in vivo*, remains elusive. As shown in a recent study by Mukherjee-Clavin et al. (7), Schwann cells derived from SOX10-induced neural crest cells (16) can be effectively applied to model specific diseases, such as CMT1A. Therefore, it may be more promising to identify additional transcription factors involved in Schwann cell development in human systems, such as SOX9, TFAP2A, and PAX3, as shown in rodent oligodendrocyte studies (46, 70), and it would be effective to employ genes used in oligoden-

drocyte studies to achieve a better efficiency. Indeed, a recent study reported the successful generation of induced SCPs (iSCPs) using pluripotency factors (OCT4, SOX2, KLF4, L-MYC, LIN28, and p53-shRNA) under appropriate culture conditions (86). This is a feasible approach for the application into a clinical setting in terms of large-scale expansion and permitting differentiation into mature Schwann cells while maintaining the identity of iSCPs. However, the introduction of pluripotency factors has raised concerns about the risks of residual expression. In fact, OCT4, SOX2, KLF4, L-MYC, and LIN28 are all known as oncogenes or proto-oncogenes (87-89). In particular, strong expression of OCT4 and SOX2 was confirmed in Schwannoma (90), and LIN28 also contributes to embryonal tumor progression in the CNS (91). Moreover, inhibition of p53, a potent tumor suppressor, further amplifies concerns about tumor development (92). As aforementioned, determining the transcription machinery of the myelination process among the complete pool of candidate genes has been made in oligodendrocytes through direct conversion study, whereas only a few transcription factors involving SCs development have been tested and screened for inducing SCs. Furthermore, converted human iSCs still exhibited incomplete myelination compared to rodent counterpart, suggesting necessity of additional transcription factors screening for functional myelinating SCs.

Perspectives

Transcription factor-mediated direct conversion is accomplished by the reactivation of epigenetically repressed state of target genes and successful reprogramming largely depends on native cell types, whereas the differentiation process differentiates the desired cells by applying the developmentally established procedures from cells in a pluripotent state. Thus, it is difficult to establish a consensus regarding protocol and optimal conditions such as the driving transcription factors and the duration of the protocol. Although direct conversion from cell types of the same lineage can be efficiently conducted, it is considered more feasible to utilize cell sources that are readily accessible. For example, direct conversion of human fibroblasts to OPCs and SCPs has been achieved (7, 16, 77, 86). However, fibroblasts, in particular, are heterogenous and considered to have significant differences in properties depending on the anatomical locations and tissue types from which they are derived (93-95). Therefore, it is necessary to verify the applicability of the protocol in fibroblasts obtained from different parts of the human body and to clarify the molecular mechanisms of the introduced transcription factors and the role of environmental factors regulated by small molecules in more detail. Moreover, direct conversion is recognized as an artificial process that does not follow the natural stages of development and utilizes the strong driving forces of ectopic transcription factors. Accordingly, concerns have been raised regarding the unpredictable risks posed by the use and retention of such transcription factors. However, many studies showed that ectopic expression of transcription factors enable achievement of self-renewal ability in iOPCs and iSCPs transiently that would otherwise be inaccessible through conventional differentiation methods in human (Table 3, 4). The use of transcription factors for establishing expandable cells may facilitate clinical-based studies requiring large numbers of cells and reveal the precise mechanisms for intrinsic cues governing self-renewal ability. Interestingly, chemical- or small molecule-based approaches have been reported to enable the generation of iOPCs or iSCPs without the aid of transcription factors (75, 96, 97). However, further elucidation of the molecular mechanisms and functional validation of these cells will be required. Recently, the establishment of organoids which mimic natural stimuli for tissue development, including cell-cell interactions, are at the forefront of stem cell research. Obtaining functional brain organoids in which mature glial cells are present is an extremely difficult challenge that is drawing considerable attention nowadays within the stem cell field (98). As mentioned earlier, the limitation of the glial differentiation, which appears late in development, is still not overcome, even in brain organoids. Brain organoids do not contain qualified glial cells even after hundreds of days of differentiation, even though the neuronal cells are observed in the early stages of organoids (99). Although long-term cultivation of brain organoids has reported the appearance of oligodendrocytes, these are often atypical populations that are not present in normal brain condition such oligodendrocyte spheroids (100). This highlights the feasibility of the direct conversion method as an alternative to overcome the difficulties of the differentiation methods. Therefore, future studies that combine direct conversion-derived mature glial cells with organoids will provide diverse understanding and new insights across the fields of development, aging, physiology, and pathology (101). However, of course, how to combine the brain organoids generated by the development process and the glia with relative maturity is still challenging.

Conclusions

Since glia are one of the major populations of the nervous system and exert a variety of roles that support the structural and functional homeostasis of nervous tissue, it is crucial to include the roles of glial cells to understand in physiological neurobiology and pathological studies in neural system. A direct conversion method has been proposed as an alternative to the differentiation from hPSCs. Although the direct conversion method still has multiple challenges requiring methodological improvements, it provides an opportunity to understand the pathophysiology of the nervous system with advantages of mature and functional oligodendrocytes and Schwann cells.

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Potential Conflict of Interest

The authors have no conflicting financial interest.

Author Contributions

W.Y., Y.J.K.: collecting data, writing manuscript, G.L.: conception, collecting data, and writing manuscript.

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