Heterogeneity of Oligodendrocytes and Their Precursor Cells

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Abstract

While oligodendrocytes have been thought to be homogenous, a number of reports have indicated evidences of the heterogeneity of oligodendrocytes and their precursor cells, OPCs. Almost a century ago, Del Río Hortega found three and four types of oligodendrocytes with regions where they exist and their morphologies, respectively. Interfascicular oligodendrocytes are one of the three regional dependent types and are the most typical oligodendendroglial cells that myelinate axonal fibers in the white matter tracts. In the other two, perineuronal oligodendrocyes function as reserve cells for remyelination and regulate neuronal excitability, whereas perivascular oligodendrocytes may play a role in metabolic support of axons. Among the four morphological categories, type I and II oligodendrocytes form many myelin sheaths on small-diameter axons and specific signal is required for the myelination of small-diameter axons. Type III and IV oligodendrocytes myelinate a few number of axons/or one axon, whose diameters are large. A recent comprehensive gene expression analysis with single-cell RNA sequencing identifies six different populations in mature oligodendrocytes and only one population in OPCs. However, OPCs are not uniformed developmentally and regionally. Further, the capacity of OPC differentiation depends on the environments and conditions of the tissues. Taken together, oligodendrocytes and OPCs are diverse as the other cell types in the CNS. The orchestration of these cells with their specialized functions is critical for proper functioning of the CNS.

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5.1 Introduction

Oligodendrocytes have been thought that they consist of a homogenous population, although many neuronal subtypes are morphologically and functionally identified. However, almost a century ago, Del Río Hortega already well-described regional and morphological differences of oligodendrocytes in the CNS (Del Río Hortega 1922, 1928). He found three distinct localizations of oligodendrocytes: (1) interfascicular oligodendrocytes that exist in between axonal fiber tracts; (2) perineuronal oligodendrocytes, alternatively called satellite oligodendrocytes that are localized just beside neuronal cell bodies; and (3) perivascular oligodendrocytes that attach blood vessels (Fig. 5.1). Further, he categorized four different subtypes of oligodendrocytes (type I–IV) with morphology and the size and number of axons that they myelinate. Recently, there has been a quantity of evidences that indicate the heterogeneous populations of oligodendrocytes and their progenitor cells (oligodendrocyte precursor cells, OPCs). In this chapter, we review the heterogeneity of oligodendrocytes and OPCs.
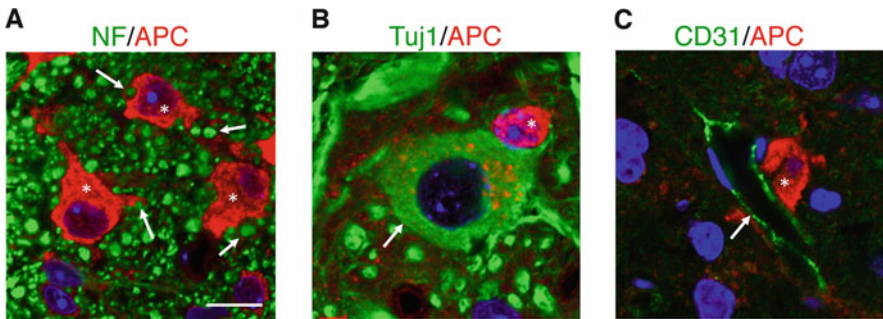
Fig. 5.1 Regionally different oligodendrocytes in the mouse spinal cord. (**a**) Myelinating oligodendrocytes among the axonal fiber tracts in the anterior funiculus of the white matter at P7. Asterisks: APC (Adenomatous Polyposis Coli) (red) positive interfascicular oligodendrocyte; allows: NF (neurofilament) (green) positive axon that is ensheathed or wrapped by an oligodendrocyte process. (**b**) Oligodendrocyte adhering to a neuronal cell body in the anterior horn of the gray matter in adult mice. Asterisks: APC (red) positive perineuronal oligodendrocyte; allow: Tuj1 (green) positive anterior horn neuron. (**c**) Oligodendrocyte attaching to a blood vessel in the gray matter at P7. Asterisks: APC (red) positive perivascular oligodendrocyte; allow: CD31 (green) positive endothelial cell. Nuclei are labeled by DAPI (blue). Scale bar, 10 μm

5.2   Heterogeneity of Oligodendrocytes

5.2.1   Regional Differences of Oligodendrocytes in the CNS

As mentioned previously, Del Río Hortega described three distinct localizations of oligodendroglial cells (Del Río Hortega 1928). First, the interfascicular oligodendrocytes localized in the axonal fiber tracts of the white matter are the most typical and well-characterized type among the three (Fig. 5.1a). These typical oligodendrocytes in the axonal fibers seem to be homogenous, however, several studies using gene-manipulated animals indicate that loss of gene expression exhibit regionally different phenotypes in the oligodendrocytes. Ablation of WAVE1 [WASP (Wkiskott-Aldrich syndrome proteins) family verprolin homologue-1] or B-Raf, an upstream kinase of MEK and ERK, causes hypomyelination of axonal tracts in the corpus callosum and the optic nerve, but not in the spinal cord (Kim et al. 2006; Galabova-Kovacs et al. 2008). On the other hand, knockout of mTOR (mammalian target of rapamycin) in oligodendrocytes results in myelination defect only in the white matter of the spinal cord (Wahl et al. 2014). In addition, more severe hypomyelination is observed in the spinal cord, compared with in the corpus callosum, of the transmembrane protein teneurin-4 (Ten-4) deficient mice (Suzuki et al. 2012). These observations represent region-specific signaling and mechanisms in CNS myelination. Further, analyzes of CNS tissues and using microfibers uncovered that oligodendrocytes in the spinal cord form longer internodes of myelin sheaths than those in the brain (Hildebrand et al. 1993; Bechler et al. 2015). Elongation of myelin internodes increases velocity of action potential (Stassart et al. 2018), therefore axonal tracts in the white matter of the spinal cord achieve more rapid conduction of action potential than those in the brain as "express way" of descending and ascending electrical signals between the brain and peripheral tissues. From these investigations, oligodendrocytes give rise to the region-specific features for each requirement in their locations.

The second perineuronal oligodendrocytes, called satellite oligodendrocytes, neighbor neuronal cell bodies in the gray matter and rarely form myelin (Fig. 5.1b). They are thought as reserve cells since they exert myelination ability after demyelination (Ludwin 1979). Furthermore, it has become clear that they regulate neuronal excitability by uptaking the extracellular potassium ion surrounding an active neuronal soma (Battefeld et al. 2016). Third, the perivascular oligodendrocytes are located around blood vessels in the CNS tissues (Fig. 5.1c). Their functions have not been characterized yet. However, perivascular oligodendrocytes may be a key player in metabolic support of axons, since there is a report demonstrating that oligodendrocytes transport pyruvate and lactate, which are probably derived from glucose secreted by blood vessels, to axons through MCT1, a monocarboxylate transporter localized in the most inner oligodendroglial cytoplasm inside myelin (Lee et al. 2012a). The latter two types of oligodendrocytes may possess more distinct functions from normal myelin formation. Further investigations are required for understanding them.

5.2.2   Morphological Differences of Oligodendrocytes in the CNS

Del Río Hortega categorized four different subclasses of oligodendrocytes with their morphologies and size/number of axons to form myelin (Del Río Hortega 1928). Type I oligodendrocytes have round and small cell body and form a lot of cell processes to myelinate many axons with small caliber sizes. The directions of these axons myelinated by type I cells are diverse. Type I oligodendrocytes exist in both white and gray matters. Type II oligodendrocytes are similar to type I cells, but their cell bodies are more cuboidal and axons they myelinate direct in parallel. These type II cells are found in the white matter, but not in the gray matter. Type III oligodendrocytes are located in both white and gray matters and the number of type III cells is less than type I and II cells. Type III oligodendrocytes have fewer cell processes forming myelin on larger diameter axons. Type IV oligodendrocytes are called Schwannoid oligodendrocytes alternatively. Their cell bodies are long and lie along large-diameter axons. Type IV cells myelinate only one large axon, like Schwann cells, and are usually observed in the white matter. After Del Río Hortega's report, several groups have demonstrated more defined characteristics of the four subtypes of oligodendrocytes. Butt et al. identified a couple of expression markers for the subtypes [CAII (carbonic anhydrase II) and long- and short-isoforms of MAG (myelin associated glycoprotein)] and a difference in internodal length among type I–IV oligodendrocytes in rat anterior medullary velum (Butt et al. 1995, 1998a, b).

5.2.3   Selectivity of Axonal Sizes in Myelination by Oligodendrocytes

One of the interesting aspects in the features of type I–IV oligodendrocytes is the difference in axonal diameters that they myelinate. A study using engineered nanofibers revealed that oligodendrocytes form myelin-like structures on the nanofibers and suggested that oligodendrocytes do not require axonal adhesion molecules, which is different from Schwann cells (Lee et al. 2012b). However, nanofibers whose diameter is less than 0.4 μm are not myelinated by oligodendrocytes, indicating that myelination of the smaller diameter fibers requires additional signaling, as it from axonal surface molecules.

There are several studies that indicate key molecules in myelination of small-diameter axons. Inhibiting integrin β1 signaling and conditional knockout of FAK (focal adhesion kinase), which is a downstream effector of integrin β1, in oligodendrocytes result in temporal hypomyelination during myelinating stage, while inhibition of integrin β3 signaling does not (Câmara et al. 2009). Further, the spontaneous null mutation of the laminin α2 chain, a component of laminin-211 that is a ligand of integrin β1, reduces myelination of small-diameter axon (Chun et al. 2003). These results suggest that the signaling of laminin α2-integrin β1-FAK may play an important role in myelination by type I/II oligodendrocytes. Further, the transmembrane protein Ten-4 is required for myelination of small-diameter axons through FAK activation (Suzuki et al. 2012) (Figs. 5.2 and 5.3). The
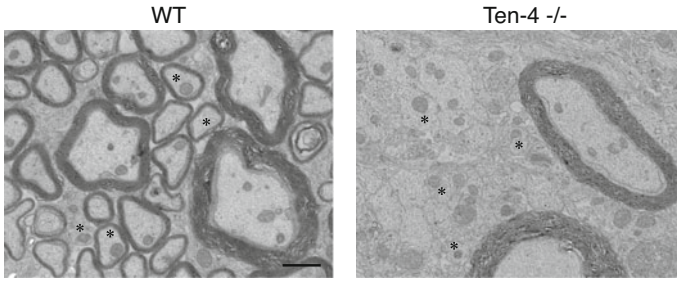
Fig. 5.2 Hypomyelination of small-diameter axons in the spinal cord of Ten-4 (teneurin-4)-deficient (−/−) mice. EM images in the lateral funiculus of 7-week-old WT and Ten-4 −/− mice are represented. Asterisks: Small-diameter axon. Scale bar, 1 μm
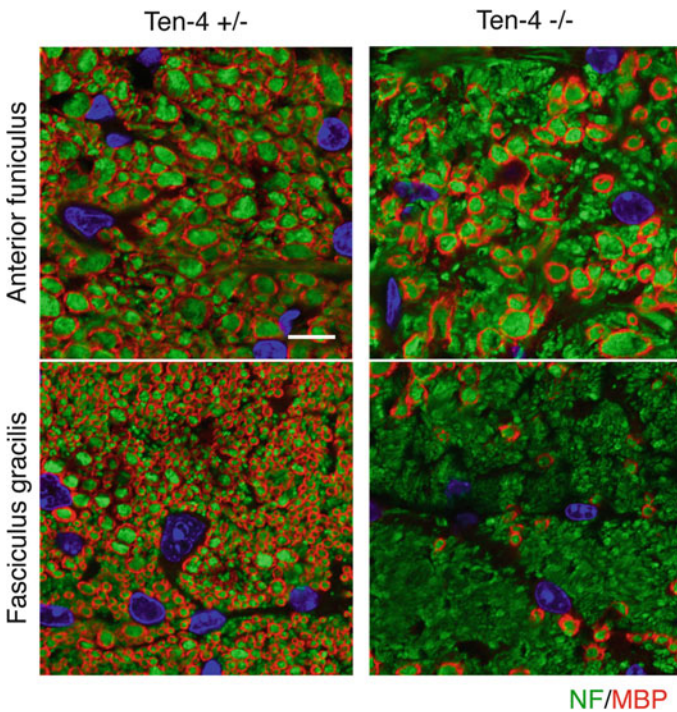
Fig. 5.3 Reduced myelination on small-diameter axons in the spinal cord of Ten-4 (teneurin-4)-deficient (−/−) mice. Immunohistochemical images of MBP (red) and neurofilament (NF) (green) in the anterior funiculus and fasciculus gracilis of 5-week-old Ten-4 heterozygous (+/−) and −/− mice are shown. Nuclei are labeled by DAPI (blue). Scale bar, 10 μm

hypomyelination of small axons and the neurological phenotype in Ten-4-deficient mice are more severe than those in the mutant mice of integrin β1, FAK, and laminin α2. Ten-4 may be a critical upstream molecule to regulate the signaling in type I/II oligodendrocyte myelination. Another regulator of myelination on small-diameter

axon is phosphatidylinositol 3,5-bisphosphate phosphatase Fig4. Interestingly, ectopic expression of Fig4 in neurons is sufficient to rescue the phenotype with hypomyelination of small-diameter axons in Fig4 null mice, whereas Fig4 is an intracellular protein (Winters et al. 2011). Neuronal Fig4 signaling presumably regulates the myelination through the expression of neuronal surface and/or secreted proteins for axon–oligodendrocyte interaction. These studies tell us that myelination of small-diameter axons by oligodendrocytes (type I and II) requires specific signaling, which is orchestrated by these molecules.

5.2.4   Oligodendrocyte Heterogeneity from Comprehensive Single-Cell RNA Sequencing

Recently, a comprehensive single-cell RNA sequencing analysis of oligodendrocyte lineage cells was reported and revealed the heterogeneity of these cells, particularly mature oligodendrocytes (Marques et al. 2016). In this report, a total of 5072 cells from 10 different regions of juvenile and adult CNS in mice were analyzed, and as a result, one population of OPCs, one population of differentiation-committed OPCs, two populations of newly formed oligodendrocytes, two populations of myelin-forming oligodendrocytes, and six populations of mature oligodendrocytes were identified. It is interesting to note that OPCs consist of the homogenous population according to the comprehensive analysis of single-cell gene expression, while OPCs are developmentally originated from a couple of distinct regions and timings, as reviewed below. Their data show that oligodendrocyte lineage cells are more homogenous during the sequential differentiation steps anywhere in the CNS, however, terminally differentiated oligodendrocytes consist of the heterogenous populations in a CNS region- and age-specific manner. Four of the six populations of mature oligodendrocytes are more abundant at the juvenile stage and express genes related to lipid synthesis and myelination at higher levels, compared with the other two populations. In contrast, one population of the six is specifically found in adult CNS and more highly express synapse-related genes, such as Grm3, a metabotropic glutamate receptor. The remaining population in the six is the most common throughout all the regions and ages. Functions of the oligodendrocytes in each population should be elucidated in near future.

5.3   Heterogeneity of OPCs

5.3.1   OPCs from Distinct Regions in the CNS

The single-cell RNA sequencing analysis shows that OPCs are composed of the homogenous population at the comprehensive gene expression level (Marques et al. 2016). However, there are a number of evidence that indicate OPCs are not uniformed. During development in the murine spinal cord, Shh (sonic hedgehog) and BMPs (bone morphogenetic proteins) are expressed in the ventricular zone of

the neural tube and function as morphogens in the regulation of specification and generation of OPCs. Shh plays a key role in determining cell fate toward OPCs, while BMPs suppress the production of OPCs. Regional differences in the expression of Shh and BMPs give rise to distinct OPC populations during development (Rowitch and Kriegstein 2010). Around embryonic day (E) 12, the first wave of OPC production occurs in the motor neuron progenitor domain of the ventral spinal cord. The second OPCs emerge from the dorsal region in the spinal cord around E16 (Kessaris et al. 2006; Rowitch and Kriegstein 2010). The OPCs derived from the dorsal region specifically express transcription factors, Pax7 and Mash1 (Cai et al. 2005). The expression of Olig1 is induced by the stimulation of Shh signaling in the ventrally derived OPCs, however, OPCs from the dorsal region develop normally without the Shh signaling (Cai et al. 2005). Instead, the development of dorsally derived OPCs is dependent on signaling induced by FGF (fibroblast growth factor) (Fogarty et al. 2005). The functional difference between these two populations has not been clearly elucidated yet, except for the ability of remyelination is higher in the OPCs from the dorsal spinal cord (Crawford et al. 2016).

5.3.2 OPCs in the Gray and White Matters

OPCs migrate and spread throughout CNS tissues, including both the gray and white matters. The characteristics of OPCs in the gray and white matters are different. For instance, white matter OPCs proliferate more rapidly than those in the gray matter, since OPCs in the white matter are more susceptible to PDGF (platelet-derived growth factor), which is widely used for OPC proliferation in culture (Chen et al. 2007; Hill et al. 2013; Viganò et al. 2013). Further, direct synaptic inputs to OPCs are reported and OPCs react with neuronal activity. However, white and gray matters OPCs possess sets of synapses with distinct neurotransmitters, glutamate and glutamate/GABA, respectively (Kukley et al. 2007; Ziskin et al. 2007). These evidence tell us that expression patterns of these proteins and biological roles in OPCs are distinguishable between in the white and gray matters. Finally, transplantation experiments in adult mouse brain demonstrated that white matter OPCs can differentiate to mature oligodendrocytes after transplantation into the gray matter, whereas gray matter OPCs are unable (Viganò et al. 2013). This suggests an intrinsic difference between these OPCs, which is not altered by their environmental factors.

5.3.3 Region-Specific Differentiation of OPCs

OPCs can differentiate to astrocytes, which are specifically called type II astrocytes, in the presence of a high concentration of serum in culture (Raff et al. 1983). In vivo, the differentiation from OPCs to type II astrocytes is region restrictedly observed in the ventral cortex (Zhu et al. 2008; Suzuki et al. 2017). This observation indicates that the differentiation capacity of OPCs is also different, although a mechanism of the regional difference in OPC differentiation is still unknown. In addition, OPCs

can differentiate not only into oligodendrocytes and astrocytes but also Schwann cells during the process of tissue regeneration in the CNS (Zawadzka et al. 2010). From these evidence, the fate of OPCs is altered by environmental factors in each region or condition, which may be important to control OPCs' behavior for the therapy of demyelinating diseases.

5.4   Conclusion

While sets of subtypes in neurons have been defined well, those in glial cells are still under discussion. One of the reasons is that glia cells are more flexible with their multipotency, compared with neurons. OPCs are able to differentiate into not only oligodendrocytes but also astrocytes as mentioned, furthermore, there is a report that demonstrates OPC differentiation to neurons (Rivers et al. 2008). In addition, differentiated oligodendrocytes can transdifferentiate into astrocytes under a pathological condition (Kohyama et al. 2008), and vice versa with an ectopic Sox10 expression (Mokhtarzadeh Khanghahi et al. 2018). However, many phenotypic differences of glia cells are clearly characterized and there are the evidence that indicate the heterogeneity of oligodendrocytes and OPCs in morphology, localization, and gene expression as described in this chapter. The specialized functions in each population of oligodendrocytes and OPCs need to be disclosed, and these discoveries will facilitate a better understanding of their biology, as well as the development of diagnostic and therapeutic reagents for dysmyelinating diseases and other related disorders.

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