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Minireview

Molecules and Cells

Olig2 Transcription Factor in the Developing and Injured Forebrain; Cell Lineage and Glial Development

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Olig2 transcription factor is widely expressed throughout the central nervous system; therefore, it is considered to have multiple functions in the developing, mature and injured brain. In this mini-review, we focus on Olig2 in the forebrain (telencephalon and diencephalon) and discuss the functional significance of Olig2 and the differentiation properties of Olig2-expressing progenitors in the development and injured states. Short- and long-term lineage analysis in the developing forebrain elucidated that not all late Olig2+ cells are direct cohorts of early cells and that Olig2 lineage cells differentiate into neurons or glial cells in a region- and stage-dependent manner. Olig2-deficient mice revealed large elimination of oligodendrocyte precursor cells and a decreased number of astrocyte progenitors in the dorsal cortex, whereas no reduction in the number of GABAergic neurons. In addition to Olig2 function in the developing cortex, Olig2 is also reported to be important for glial scar formation after injury. Thus, Olig2 can be essential for glial differentiation during development and after injury.

INTRODUCTION

Transcription factors regulate cell-type-specific differentiation during animal development, including the nervous system. Olig1 and Olig2 are sonic hedgehog (Shh)-responsible basic helix-loop-helix (bHLH) transcription factors, and are initially identified as oligodendrocyte lineage-specific transcription factors (Lu et al., 2000; Takebayashi et al., 2000; Zhou et al., 2000). Indeed, a considerable number of mature oligodendrocytes (such as *PLP*+ cells) are immunoreactive for Olig2 in the adult brain (Figs. 1A-1C). Loss-of-function studies by independent groups have elucidated that Olig2 is essential not only for oligodendrocyte development but also for motoneuron development, as Olig2-deficient mice and *olig2*-knockdown zebrafish are devoid of both cell types in the spinal cord and hindbrain (Lu et al., 2002; Park et al., 2002; Takebayashi et al., 2002; Zhou and Anderson, 2002), while Olig1 is reported to be important for myelination in the central nervous system (CNS) (Lu et al., 2002; Xin et al., 2005). Olig2 is widely expressed throughout the CNS during and after development, which suggests that Olig2 plays multiple roles in all regions of the CNS. Indeed, accumulated evidence suggests that Olig2 has multiple functions in both neuronal and glial cell differentiation in normal development (Cai et al., 2007; Furusho et al., 2006; Marshall et al., 2005; Ono et al., 2008) and also in glial scar formation after injury (Chen et al., 2008). In this mini-review, we focus on Olig2 in the forebrain (telencephalon and diencephalon) in developing and injured states, and discuss the functional significance of Olig2 and the differentiation properties of Olig2-expressing progenitors in the rostral CNS.

Initial localization and subsequent gradual dispersal of Olig2+ cells in the forebrain

Olig2 is initially localized in a relatively restricted region of the ventral forebrain (Figs. 2A-2H). In the telencephalon, Olig2 high+ cells show overlapping distribution of the Nkx2.1 domain in the medial ganglionic eminence (MGE) (Miyoshi et al., 2008; Nery et al., 2001; Parras et al., 2007; Petryniak et al., 2007; Takebayashi et al., 2000) and also in the ventricular zone (VZ) of the septum and anterior entopeduncular area (AEP) (Ono et al., 2008; Petryniak et al., 2007). Olig2+ cells in the diencephalon first appear around the zona limitans intrathalamica (ZLI) and VZ of the caudal hypothalamus (Ono et al., 2008). All of these areas are adjacent to Shh-expressing zones (Marti et al., 1995; Naruse et al., 2006; Ono et al., 2008), which is consistent with the fact that Olig2 is initially induced by Shh. Subsequently, Olig2+ cells leave the VZ and disperse to parenchymal regions in a ventral-to-dorsal manner, and are finally distributed throughout the forebrain. This spacio-temporal continuity of Olig2+

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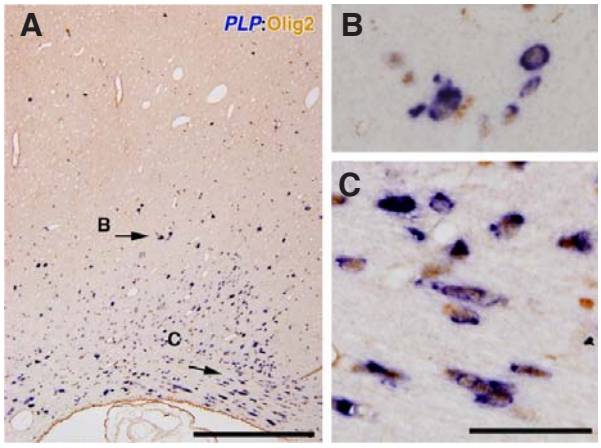

Fig. 1. Double staining of adult dorsal cortex with *PLP* (proteolipid protein) *in situ* hybridization (deep blue) and Olig2 immunohistochemistry (brown). A majority of *PLP*+ oligodendrocytes express Olig2 while not all cortical Olig2+ cells express *PLP*. Bars in (A) = 500 μm; in (B, C) = 50 μm.

cell distribution raises two possible explanations. One is that sequential dispersal of Olig2+ cells is a reflection of the migration of this cell type. The other is that this may be an Olig2 expression wave; resident Olig2-negative (Olig2(-)) cells would become Olig2+ sequentially without vigorous migration. Our short-term lineage tracing study demonstrated that early, such as E9.5, Olig2+ cells, cease Olig2 expression within a few days after tamoxifen-inducible Cre-mediated recombination; no or few recombined cells expressed Olig2 (Ono et al., 2008). Even in the later stages, approximately two thirds of Olig2 lineage GFP+ cells, recombined at E13.5 or E14.5, ceased Olig2 expression within a three-day survival period. GFP+/Olig2(-) cells include Glast+ astrocyte progenitors, PDGFRα+ OPCs and Tuj1+ immature neurons; therefore, a majority of glial progenitors, including OPCs, cease Olig2 expression during their development (Ono et al., 2008). This implies that the gradual dispersal of Olig2+ cells in the developing CNS is not always a reflection of Olig2 progenitor migration, although migrating OPCs express Olig2 (Kessaris et al., 2006; Nakahira et al., 2006), and not all late Olig2+ OPCs are direct descendants of early Olig2+ OPCs in the forebrain. These observations are consistent with the report on the dynamic view of oligodendrogenesis in the forebrain that early-generated ventral OPCs are replaced with late-generated dorsal OPCs (Kessaris et al., 2006). Indeed, OPCs derived from cortical VZ (dorsal OPCs) are mostly Olig2(-) when they are localized in the VZ (Ivanova et al., 2003; Kessaris et al., 2006). These results suggest that most OPCs, including late OPCs (at E13.5, E14.5), cease Olig2 expression in the progenitor stage, and then re-express Olig2 during myelination in the postnatal stage, because Olig2 also have a role in myelination (Yue et al., 2006). It is of note that a very limited number of OPCs possibly continue to show Olig2 expression.

Neuron and glial cell production from fetal Olig2 progenitor cells

Initial localization of Olig2+ cells in the Nkx2.1 domain of the MGE strongly suggests that early Olig2+ cells in the VZ are GABAergic neuron progenitors (Anderson et al., 1997; Fogarty et al., 2007; Petryniak et al., 2007). In addition, cholinergic neurons in the basal forebrain were also shown to be derived from MGE and lateral ganglionic eminence (LGE) by a grafting experiment (Olsson et al., 1998). Our long-term lineage tracing demonstrates that Olig2+ cells in the GE differentiate into cholinergic neurons in the basal forebrain (Furusho et al., 2006) and GABAergic neurons in both the cortex and basal forebrain (Miyoshi et al., 2008; Ono et al., 2008). In particular, we observed that approximately 60% of recombined cells induced at E12.5 are GABA immunoreactive and over 80% expressed *GAD65* or*GAD67* mRNA in the adult cortex (Ono et al., 2008), which apparently suggests that nearly all Olig2 lineage neurons in the cortex are GABAergic neurons. Miyoshi and colleagues elucidated that the physiological subtype of cortical GABAergic interneurons depends on the date of generation (or recombination). Thus, the time point of origin may be an important factor for cortical interneuron differentiation (Miyoshi et al., 2008).

Although Olig2+ cells around the ZLI in the diencephalon differentiate into GABAergic neurons in the ventral thalamus, as observed in the cortex (Ono et al., 2008; Takebayashi et al., 2008), those in the caudal hypothalamus give rise to *VGluT2*+ neurons, probably excitatory neurons (Ono et al., 2008). It is possible that other transcription factors expressed in Olig2 lineage cells play a major role in the differentiation of neuronal subtypes. Indeed, Olig2+ VZ cells in the caudal hypothalamus expressed Ngn2 mRNA, which is also expressed in the VZ of the dorsal telencephalon where excitatory neurons originate (Figs. 3C and 3D). In the caudal diencephalon, Olig2 is also expressed dorsally to the ZLI (Figs. 3A and 3B; Vue et al., 2007), which is a future thalamus. The adult rodent thalamus is mostly composed of glutamatergic excitatory neurons. Currently, it is not clear whether Olig2+ cells differentiate into thalamic excitatory neurons. Olig2 lineage neurons recombined at E16.5 or later are mostly localized in the olfactory bulb of the adult brain, although a few are still observed in the striatum, but not in the cortex. Olfactory neurons are the latest neurons originating from embryonic Olig2+ progenitors (Ono et al., 2008).

Cells in the early MGE also give rise to oligodendrocyte precursor cells (OPCs) (Nakahira et al., 2006; Nery et al., 2008; Parras et al., 2007; Petryniak et al., 2007; Tekki-Kessaris et al., 2001), and these early-generated ventral OPCs are reported to be replaced with late-generated dorsal OPCs (Kessaris et al., 2006). In accordance with these observations, our long-term lineage tracing study demonstrated that early Olig2+ cells generate a relatively lower proportion of oligodendrocytes in the adult forebrain. Neuron generation from Olig2+ cells gradually decreases while gliogenesis increases as the forebrain develops (Ono et al., 2008). In the diencephalon, as well as in the spinal cord and hindbrain, oligodendrocytes are the most abundant cell types generated from relatively late Olig2+ progenitors (Masahira et al., 2006; Ono et al., 2008), although Olig2 lineage cells also differentiate into astrocytes in these regions. The production of oligodendrocytes and astrocytes from oligodendrocyte progenitors in the developmental forebrain is consistent with an early lineage tracing experiment using a retrovirus (Levison and Goldman, 1993) and a recent study using NG2-CreBAC;Z/EG mice (Zhu et al., 2008), which show NG2+ oligodendrocyte progenitors. It is surprising that the most common type of recombined cells induced on E16.5 or E17.5 in the cortex or telencephalon showed busy astrocytic morphology and some were immunoreactive for GFAP, an astrocyte marker. Therefore, Olig2+ cells in the telencephalon at a later stage give rise to astrocytes most abundantly, suggesting that the differentiation property of Olig2+ cells in the telencephalon is different from that in other regions of the CNS (Ono et al., 2008).

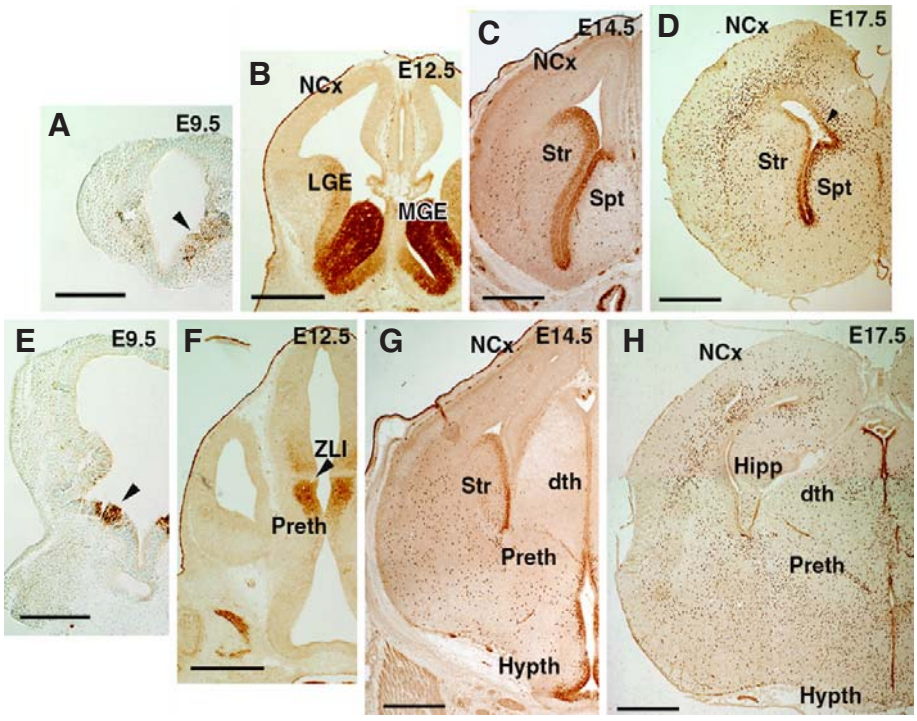

Fig. 2. Restricted origin and gradual dispersal of Olig2+ cells in the forebrain. Olig2 is initially localized in the ventricular zone of the medial ganglionic eminence (MGE) (B) and the prethalamus (Preth) ventral to the zona limintance intrathalamica (ZLI) (F). Olig2+ cells are gradually distributed throughout the forebrain by E17.5 (D, H). dth, dorsal thalamus; Hipp, hippo-campus; Hypth, hypothalamus; LGE, lateral ganglionic eminence; NCx, neocortex; Spt, septum; Str, striatum. From Fig. 1 in Ono et al. (2008), with permission. Bars in (A, E) = 100 μm; (B-D) and (F-H) = 500 μm.

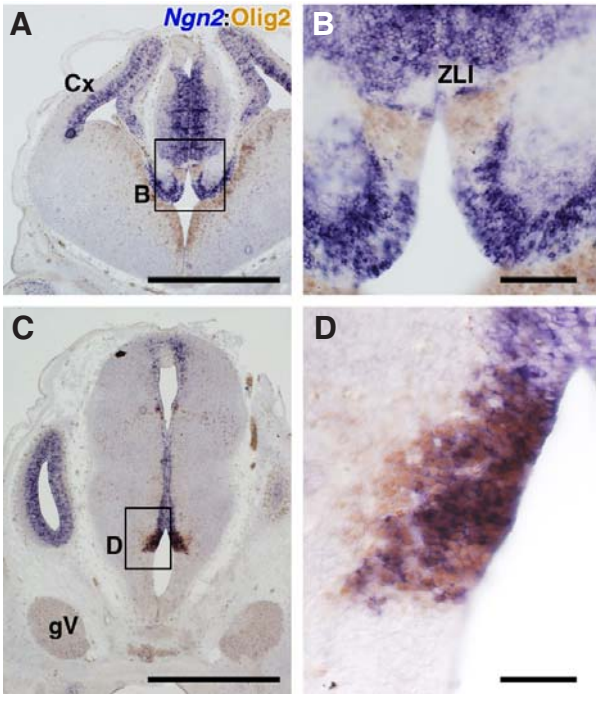

Fig. 3. Double staining of E13.5 forebrain with *Ngn2* (neurogenin2) in situ hybridization (deep blue) and Olig2 immunohistochemistry (brown). (A, B) Rostral level of the diencephalon. Boxed area in (A) is magnified in (B). Note that Olig2+ cells ventral to the ZLI (zone limitans intrathalamica) do not express *Ngn2*. (C, D) Caudal level of the diencephalon. The boxed area in (C) is magnified in (D). Note that Olig2+ cells in the ventricular zone also express *Ngn2*. Cx, cortex. gV, trigeminal ganglion. Bars in (A, C) = 1 mm; in (B) = 100 μm; in (D) = 50 μm.

Involvement of Olig2 in corticogenesis

Although Olig2 in the telencephalon is vigorously expressed in the Nkx2.1+ MGE at early stages, from which GABAergic neurons are generated, Olig2-deficient mice do not show any obvious defects in the generation of GABAergic neurons in the cortex and in the subcortical regions (Miyoshi et al., 2008; Ono et al., 2008; Takebayashi et al., 2008). These data suggest that Olig2 function is compensated for by other transcription factors or that Olig2 is not essential for GABAergic neuron differentiation; however, microarray analysis demonstrated that *GAD1* expression is slightly elevated in the absence of Olig2 (supplemental data in Ligon et al., 2007). Therefore, further analysis may demonstrate the involvement of Olig2 in GABAergic neuron development, including subtype specification.

As mentioned above, a lineage tracing experiment using Olig2-CreER mice demonstrated that Olig2+ precursor cells differentiate into both oligodendrocytes and astrocytes in the telencephalon (Ono et al., 2008). Olig2 deficient mouse is devoid of oligodendrocyte or OPCs throughout the CNS including the cortex although reminiscent OPCs can be seen in restricted regions in the Olig2 knockout brain, which suggests that Olig2 positively regulates oligodendrogenesis in all regions of the CNS, including the cortex (Fig. 4.; Lu et al., 2002; Takebayashi et al., 2002). In addition, Marshall and colleagues demonstrated that, in early postnatal SVZ, inhibition of Olig2 function by Olig2-VP16, a dominant negative form of Olig2, led to the generation of olfactory interneurons, whereas the expression of Olig2 generates astrocytes and oligodendrocytes (Marshall et al., 2005). Recently, Cai and colleagues demonstrated that conditional knockout of *Olig2* in the radial glia resulted in loss of astrocyte in the cortical white matter (Cai et al., 2007). We also discovered that a lack of Olig2 function resulted in a decrease of cortical astrocytes or their precursors in the late fetal stage; *Glast*+ and *FGFR3*+ astrocyte progenitors decreased in the E18.5 dorsal cortex in Olig2 knockout mice compared with age-

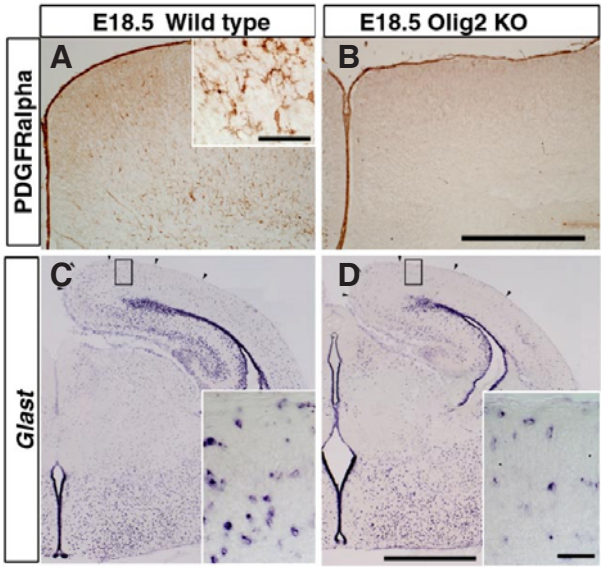

Fig. 4. Retardation of glial development in the Olig2-deficient cortex. (A, C) E18.5 wild-type animals. (B, D) E18.5 Olig2 knockout mice. PDGF receptor alpha immunopositive oligodendrocyte precursors are widely distributed in the E18.5 forebrain (A) while they are devoid of Olig2 knockout cortex (B). *Glast*-mRNA+ astrocytes decreased in the E18.5 dorsal cortex of E18.5 Olig2 knockout mice (D) compared with age-matched wild-type animals (C). Bars in (A, B) = 500 μm; (C, D) = 1 mm; inset = 50 μm.

matched wild-type or heterozygous animals (Figs. 4A-4D), while astrocytes normally developed in the late fetal basal forebrain region in Olig2-deficient mice. Therefore, it is apparent that Olig2 also positively regulates astrocytogenesis in late fetal and newborn cortical development, which may be specific to the dorsal cortex (Ono et al., 2008). Together with these observations, Olig2 can be an important determinant factor for gliogenesis in the forebrain, especially the dorsal cortex.

Role of Olig2 in the injured adult brain

Olig2+ cells persist until the brain has matured, and NG2+ cells mostly correspond to Olig2+ cells (Ligon et al., 2006). NG2 glial cells in the adult brain are a population of CNS glial cells distinct from mature oligodendrocytes, astrocytes and microglia in the adult brain (Nishiyama et al., 2009), and they proliferate and respond rapidly after brain injury (Levine et al., 2001; Lytle et al., 2009; Tan et al., 2005). Lineage tracing experiments in the normal brain revealed that adult NG2+/Olig2+ cells give rise to oligodendrocyte in the white matter (Dimou et al., 2008; Rivers et al., 2008). It is of note that the expression of Olig2-VP16 results in an increased number of immature neurons in the injured brain (Buffo et al., 2005) and postnatal SVZ (Marshall et al., 2005). Recently, Chen and colleagues directly demonstrated that Olig2 is involved in cortical gliogenesis after injury using astrocyte-specific Olig2 conditional knockout mice; they showed that astrocytes in the adult cortex become Olig2 positive, and give rise to reactive astrocytes (Chen et al., 2008). Tatsumi and her colleagues observed that Olig2+ cells before injury, possibly NG2+ glial cells, give rise to reactive astrocytes or myelinating oligodendrocytes after cryo-injury or demyelinating insult, respectively (Islam et al., 2009; Tatsumi et al., 2008). At present, the extent to which adult NG2+ glial cells or mature astrocytes give rise to reactive astrocytes is not well defined and further investigations are required; however, it is obvious that Olig2 transcription factor is involved in gliogenesis after injury.

Concluding remarks and future perspective

We conclude by summarizing the putative functions of Olig2 in the developing and injured forebrain. Olig2 may have multiple functions in cellular differentiation and exert them in a stage- and region-specific manner in CNS development and repair. Currently, a major issue to be elucidated is the differentiation potency of single Olig2+ cells. Our group demonstrated that the Olig2+ cell population differentiates into neurons and two types of macroglial cells as well as ependymal cells (Masahira et al., 2006). Mukouyama and colleagues reported the lineage restriction of Olig2+ cells in the developing ventral spinal cord (Mukouyama et al., 2006). Wu et al. suggested that motoneurons and oligodendrocytes do not share a common lineage of restricted progenitors (Wu et al., 2006); however, it is still unclear whether there are multipotential Olig2+ progenitors in the early CNS, which gives rise to three main cell types, neurons, oligodendrocytes and astrocytes during development, although they may be a minor population. Further analysis will elucidate the detailed differentiation properties of Olig2+ precursor cells and the mechanisms by which Olig2 lineage cell differentiation is regulated *in vivo*, which could lead to the regeneration of neurons in the mammalian CNS. In conclusion, Olig2+ cells undergo cellular differentiation in a spatio-temporal specific manner, which apparently reflects the multiple functions of Olig2 in the developing and adult CNS.

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