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Najate Benamer, Marie Vidal, Maria Cecilia Angulo

Mini-Review

The cerebral cortex is a substrate of multiple interactions between GABAergic interneurons and oligodendrocyte lineage cells

Najate Benamer[1,2], Marie Vidal[1,2], Maria Cecilia Angulo[1,2]

[1] *Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, Paris, France*

[2] *Université de Paris, Paris, France*

Corresponding author

María Cecilia Angulo, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM 1266, 102, rue de la Santé, 75014 Paris, FRANCE. Tel: 33-1-40789243. e-mail address: maria-cecilia.angulo@parisdescartes.fr

HIGHLIGHTS

- Oligodendrocyte precursor cells (OPCs) are active partners of GABAergic interneurons in the developing cerebral cortex
- Comprehensive review of interneuron-oligodendroglia interactions in the cerebral cortex
- Presenting future directions on the study of interneuron-oligodendroglia interactions in health and disease

ABSTRACT

In the cerebral cortex, GABAergic interneurons and oligodendrocyte lineage cells share different characteristics and interact despite being neurons and glial cells, respectively. These two distinct cell types share common embryonic origins and are born from precursors expressing similar transcription factors. Moreover, they highly interact with each other through different communication mechanisms during development. Notably, cortical oligodendrocyte precursor cells (OPCs) receive a major and transient GABAergic synaptic input, preferentially from parvalbumin-expressing interneurons, a specific interneuron subtype recently recognized as highly myelinated. In this review, we highlight the similarities and interactions between GABAergic interneurons and oligodendrocyte lineage cells in the cerebral cortex and suggest potential roles of this intimate interneuron-oligodendroglia relationship in cortical construction. We also propose new lines of research to understand the role of the close link between interneurons and oligodendroglia during cortical development and in pathological conditions such as schizophrenia.

Key words : interneurons, oligodendrocyte precursor cells, oligodendrocytes, myelination, parvalbumin, synapses, GABA, cortical development, medial ganglionic eminence

1. Introduction

In the central nervous system (CNS) of vertebrates, neuronal myelination by oligodendrocytes (OLs) is determinant to speed up the conduction of action potentials -*via* saltatory conduction- and to provide neuronal metabolic support. Myelination in the CNS relies on the generation, proliferation and differentiation of oligodendrocyte precursor cells (OPCs) during development. Interestingly, all these processes are most probably influenced by neuronal activity and neuron-OL lineage cell interactions. OPCs and OLs sense their environment through an array of different neurotransmitter receptors and channels, and respond to neuronal activity through different communication mechanisms by modulating their properties and function [1,2]. While OPCs are the only glial cell type that receive synaptic inputs from neurons, non-synaptic modes of neuron-to-oligodendroglia communication such as extrasynaptic transmission or mechanical interactions influence oligodendroglia function and myelination [1,2]. In this context, the cerebral cortex represents an important region of study that has allowed to reveal multiple types of interactions between neurons, especially GABAergic interneurons, and OL lineage cells. In fact, cortical GABAergic interneurons and oligodendroglia share different characteristics: 1) both cell types are born from the same germinal regions and their precursors can express the same transcription factors [3,4]; 2) these cells follow similar migratory routes to the cortex and 3) subpopulations of both interneurons and OL lineage cells are initially over-produced and then significantly demised early at postnatal stages [3,5,6,7]. Beyond their common features, different modes of interactions between interneurons and OPCs have been described during development: 1) migrating interneurons release paracrine factors that promote OPC differentiation [8,9]; 2) cortical OPCs receive a major and transient synaptic input from interneurons, preferentially from parvalbumin (PV)-expressing interneurons, prior to the peak of OPC differentiation [10,11]; 3) PV interneurons represent the largest proportion of myelinated GABAergic axons in the cortex

[12,13,14]. Furthermore, a recent report showed that OPCs have a more accessible chromatin environment around key interneuron transcription factor genes than astrocytes or fibroblasts and lack repressive marks, suggesting that these progenitors could more easily switch their fate onto interneurons [15].

In this review, we describe the different types of communication between cortical GABAergic interneurons and oligodendroglia and discuss the possible functions of their shared properties and interactions, both during normal development and in neurodevelopmental disorders such as schizophrenia.

2. **Common origins of cortical interneurons and OPCs**

The developmental origins of cortical interneurons and OL lineage cells remained under debate for several years. However, their different origins are now fairly well-established and, by connecting information reported separately for each of these two cell types, it can be deduced that interneurons and OPCs arise from overlapping germinal regions in rodents and primates [3,4,16,17] (Fig. 1). Using Cre-lox fate mapping studies during mouse forebrain development, Kessaris et al. (2016) [3] demonstrated that OPCs are generated from three waves that emerge from distinct periventricular areas following a ventro-dorsal temporal progression. The first wave of OPCs arises from Nkx2.1-expressing precursors of the medial ganglionic eminence (MGE), and Nkx2.1- and Dbx1-expressing precursors of the embryonic preoptic area (POA) around the embryonic day 12.5 (E12.5), and start to migrate into the dorsal pallium around E14.5 [3,18] (Fig. 1). Interestingly, almost 70% of interneurons are also generated from Nkx2.1-expressing precursors of the MGE, which accounts for about 60% of them [4] and from Nkx2.1- and Dbx1-expressing precursors of the POA, which accounts for the remaining 10% [4,19]. While the MGE produces PV- and somatostatin (SST)-positive interneurons [20,21,22],

the POA covers a very heterogeneous population including mainly PV-, SST- and reelin-positive cells [4,19]. Although the massive MGE-derived interneuron production occurs before the generation of the first wave of OPCs, around E10.5 [23], this common embryonic origin suggests a specific relationship between these two cell types. In fact, it has even been suggested that MGE-derived progenitors expressing both NG2 and Olig2, two markers of OL lineage cells, directly generate a subpopulation of interneurons at embryonic stage E14.5 in mice [24], underlining the complexity of interneuron and OPC specification and identification during early development. In line with this, Olig2 which is highly expressed in the Nkx2.1-expressing MGE domain, has also been reported to be expressed in interneuron progenitors [22].

Later on, a second wave of OPCs starts to be produced at E14.5 from the lateral (LGE) and caudal (CGE) ganglionic eminence in mice (Fig. 1) [3]. The production of this second wave of OPCs partially overlaps with the production of another major interneuron population arising from the CGE between E12.5 and E16.5 and that constitutes around 30% of the total number of interneurons [25] (Fig. 1). CGE-derived interneurons are highly diverse, expressing mainly either reelin or the vasoactive intestinal peptide (VIP) [25]. Unlike interneurons generated from the POA, whose final destination is to occupy deep cortical layers, this interneuron population preferentially invades superficial layers. Whether similar differential distributions of OPCs from these two subpallial embryonic regions occur across cortical layers is unknown.

Finally, a third migratory wave of OPCs derived from Emx1-expressing precursors from the dorsal pallial region arises at perinatal stages in mice. Although it was initially proposed that this dorsal wave of OPCs is produced postnatally [3], a recent report argues that it starts to be generated at E17.5 [9]. Unlike OPCs derived from ventral regions, dorsal OPCs share less characteristics with GABAergic interneurons since most of these neurons arise outside the Emx1-expressing lineage. Nevertheless, it has been described that a subpopulation of 5HT3A-positive interneurons is produced from the subventricular zone around birth [26] (Fig. 1). It is

thus not excluded that this interneuron subpopulation invades the postnatal neocortex in concomitance with dorsal OPCs.

The lineage relationship, the convergent germinal regions and the similar migratory routes of interneurons and OPCs, especially OPCs from ventral sources, suggest possible developmental interactions between these two cell types. Of note, a large proportion of OPCs from the first wave disappears in the cerebral cortex during the first two postnatal weeks in mice [3,27]. Interestingly, 30-40% of GABAergic interneurons also die during the same period [5]. Although the meaning of these massive cortical cell deaths is not completely understood [28], our recent report suggests that interactions between lineage-related interneurons and OPCs from the first wave may influence the construction of the cerebral cortex during embryonic and early postnatal development [29]. Similarly, the second and third waves of OPCs also play a crucial role in cortical development, as they are considered the main sources of OL lineage cells in the postnatal neocortex. Interestingly, it seems that functional differences in OPCs from distinct origins emerge during development. Indeed, although the gene expression profile determined by RNA-sequencing is not different for the three OPC populations at postnatal stages [30], differences in their functional roles have been identified. In demyelinated lesions of adult mice, ventral OPCs display a reduced capacity to proliferate and differentiate into mature OLs compared to those of dorsal regions [31]. Therefore, the study of interneuron-OPC interactions and functional analyses of specific OPC populations are now required to assess potentially different properties and functions across postnatal stages.

3. **Interactions between GABAergic interneurons and OPCs in the cerebral cortex**

OL lineage cells have been reported to express metabotropic $GABA_B$ receptors ($GABA_B$Rs) and ionotropic $GABA_A$ receptors ($GABA_A$Rs) in different brain regions [32]. Although global immunohistochemical assays revealed intense $GABA_{B1a/b}$ labelling in the

cerebral cortex [33], the extent to which $GABA_BR$ expression is present in cortical OL lineage cells is still unclear. Interestingly, however, $GABA_BRs$ were shown to play a positive role in the migration of both OPCs cultured from the CG-4 line [33] and MGE-derived interneurons of organotypic slice cultures of rat brains [34], raising the possibility that a convergent $GABA_BR$-mediated mechanism of migration exists for developing interneurons and ventral OPCs tangentially migrating to the neocortex. It would also be of interest to evaluate whether migration of interneurons and ventral OPCs sharing a common embryonic origin (Fig. 1) occurs through dynamically interacting mechanisms implicating GABAergic signaling.

Concerning $GABA_ARs$, single cell RT-PCR and pharmacological analyses on OPCs recorded in acute slices of mouse somatosensory cortex have revealed a highly heterogeneous expression of subunits, some of which are dramatically down-regulated during postnatal development [35]. While $\alpha1$ and $\beta2/\beta3$ subunits expression remains constant at different ages, $\alpha5$ and $\gamma2$ subunits expression highly decreases in the fourth postnatal week [35]. Mature OLs from rat forebrain cultures also express $GABA_ARs$ that contain $\alpha1$, $\alpha3$ and $\beta2/\beta3$ subunits, but lack $\gamma2$ subunits [36]. Therefore, the subunit composition and the functional properties of these receptors differ according to the maturation stage of OLs and the age of the animals, suggesting different roles of these receptors during cortical development.

On a similar note, Lin & Bergles (2004) [37] were the first to record spontaneous and evoked $GABA_AR$-mediated currents in hippocampal OPCs whose fast kinetics were consistent with a direct GABAergic synaptic signaling. Since then, GABAergic synaptic activity has been described in OPCs of various CNS regions, including the cerebral cortex and cerebellum [10,38,39]. In the somatosensory cortex, OPCs display high frequency GABAergic synaptic currents during the first two postnatal weeks (although variable, it can reach up to 4 Hz around postnatal day 10 in standard recording conditions, a value larger than the one reported for

glutamatergic synaptic currents in various regions [10]). However, this activity declines with age [10]. The GABAergic synaptic connectivity of OPCs is therefore transient in the neocortex during the critical developmental period of oligodendrogenesis. However, although a postnatal loss of GABAergic synapses should result in a strong reduction of the amplitude of evoked currents in older mice, the extracellular stimulation of GABAergic fibers revealed the presence of evoked GABAergic currents in adult OPCs that are solely mediated by local GABA spillover from nearby interneurons [1,10]. $GABA_A$Rs in OPCs are activated directly by GABAergic synaptic transmission at a young age and indirectly by local GABA spillover from nearby interneurons at more mature stages [10,35]. A switch in GABAergic transmission, from synaptic to extrasynaptic, thus occurs between interneurons and OPCs during postnatal development. Interestingly, this switch in transmission mode is concomitant with the loss of expression of the γ2 subunit of $GABA_A$Rs, a downregulation consistent with the loss of OPC synapses and the synaptic nature of this subunit [13,40].

Compared to neurons, little is known about the dynamics of individual synapses of OPCs, the specific rules that govern neuron-OPC synaptic connectivity and their integration in different neuronal networks. Moreover, the function of neuron-glia synapses is still controversial and it is unclear whether they play a role in oligodendrogenesis, myelination and myelin repair [2]. Some aspects, however, are already characterized. In the developing somatosensory cortex, it has been shown that interneurons and OPCs form highly organized transient networks [11]. In these networks, PV-expressing fast-spiking interneurons (FSI), highly connected to OPCs, target proximal subcellular domains while non-fast spiking interneurons (NFSI), that constitute a highly heterogeneous interneuron population (when considering the expression of biochemical markers and the firing properties [4]) and are poorly connected with these progenitors, target distal sites [11]. This compartmentalization of FSI and NFSI inputs onto OPCs suggests specific functions for each type of synapse which need to be

tested in the future. Using Cre-loxP fate mapping in transgenic mice, we recently examined whether the anatomical proximity and the temporally and spatially organized synaptic connectivity between interneurons and OPCs is influenced by their common embryonic origin [29]. We found that a subpopulation of the first wave of OPCs from the MGE and POA survives at postnatal stages, forms spatial anatomical clusters and displays a privileged synaptic connectivity with its ontogenetically-related interneurons compared to OPCs from different sources during cortical development [29]. Furthermore, this preferential connectivity constitutes a highly specific and regulated process that cannot be promoted by preventing the death of MGE- and POA-derived interneurons (that mainly comprises PV^+ FSI and SST^+ NFSI [4]) and OPCs committed to die during the first postnatal week [29]. These findings reveal a unique anatomical and functional interplay between neurons and glia that is favored by a common embryonic origin. Further investigation is needed to evaluate whether a preferential synaptic connectivity between interneurons and OPCs generated from CGE and/or dorsal regions also exists (see Fig. 1). Another study using stereological analyses in the mature mouse dorsal neocortex showed that 40% of cortical OPCs form anatomical pairs with neurons, mainly GABAergic interneurons expressing PV, calbindin and calretinin, showing that a different type of anatomical association exists between interneurons and OPCs in the adult brain [41].

Concerning neuron-OPC synapses, a main hypothesis in the field suggests that GABAergic synaptic signaling represents a mechanism tuning OPC proliferation and differentiation in the normal brain. However, opposing results came from recent studies identifying the neurotransmitter GABA as a potential modulator of OL lineage cell development. Zonouzi et al. (2015) [39] observed that a reduced GABAergic signaling in OPCs induces an increase of OPC proliferation and a delayed OL maturation in the immature mouse cerebellum. In contrast, another work using organotypic cortical slices revealed that the pharmacological block of $GABA_A$Rs increases the number of both OPCs and mature OLs [42].

While Zonouzi et al. (2015) [39] propose a positive effect of GABA on OL lineage cell progression, Hamilton et al. (2017) [42] suggest that $GABA_AR$ signaling promotes OL lineage cell death. In both cases, however, GABAergic synapses of OPCs were not specifically targeted. To directly assess the role of $GABA_AR$-mediated synapses in the somatosensory cortex, we recently inactivated the γ2 subunit of GABAergic synapses of OPCs [13]. We found no impact on OPC proliferation and differentiation in young mice in line with the absence of effect on OPC proliferation upon in vivo optogenetic stimulation of cortical interneurons in mouse pups [29]. However, a significant decrease of OPC density during later stages of cortical development suggests that γ2-mediated synapses finely tune OPC self-maintenance capacity rather than oligodendrogenesis [13]. Since these data were obtained in the cortex, it would be interesting to analyze the impact of this specific GABAergic synapse on oligodendroglia dynamics of the developing cerebellum to assess whether its role differs according to the brain region. We also cannot exclude that other interneuron-OPC synapses, distinct to γ2-mediated synapses, play different roles in OPC function.

Beyond GABAergic synapses, other forms of interneuron-OPC interactions exist in the developing cerebral cortex. A recent report showed that migrating MGE-derived interneurons secrete the cytokine fraktaline which promotes oligodendrogenesis *via* the fraktaline receptor CX3CR1 expressed in OPCs [8]. Furthermore, interneurons are the primary source of Sonic Hedgehog ligand that promotes oligodendrogenesis from dorsal forebrain progenitors at late embryonic stages [9]. These examples of factors promoting OPC differentiation into OLs extend the communication potential of interneurons to interact with OPCs.

Altogether, these studies have revealed that interneurons and OPCs are anatomical and functional partners and suggest a potential role of interneuron-OPC interactions in the formation of inhibitory neuronal networks and cortical myelination.

4. Myelination of cortical parvalbumin-expressing interneurons

Myelination is a developmental process during which OLs ensheath the axons of neurons, providing them with metabolic support and the electric insulation needed for the fast conduction of action potentials. In the cerebral cortex, a large proportion of myelinated cells are GABAergic interneurons, of which a large majority corresponds to fast-spiking, PV-positive basket cells that make contact on the soma and proximal dendrites of neurons, particularly pyramidal cells [12,14]. Surprisingly, other types of interneurons that play important roles in the cortex, such as VIP- and SST-positive interneurons, are much less myelinated [12,14], considering both the proportion of myelinated cells and the coverage of myelin around the axon [43]. Of note, it was recently proposed that OLs are specialized in the myelination of cortical interneurons with respect to glutamatergic neurons [43], although this point needs further investigation. Although PV interneurons are highly connected with OPCs compared to other interneuron subtypes during postnatal development, this preferential synaptic connectivity does not seem to be essential to initiate the myelination process of this interneuron population for several reasons: 1) OPCs are also synaptically contacted by PV-negative interneurons that are not myelinated [11,12,14,29]; 2) PV interneurons remain myelinated when PV interneuron-OPC synapses are inactivated [13]; 3) surviving OPCs from the first wave differentiate into myelinating oligodendrocytes in cell clusters formed with their lineage-related interneurons, independently of the interneuron identity, and myelinate both glutamatergic and GABAergic axons [29] and 4) forcing the survival of lineage-related interneurons and OPCs from the first wave causes a large increase in the density of other oligodendroglia populations which induces a global hyper-myelination. These data do not exclude, however, that the impairment of PV interneuron-OPC synaptic interactions causes an abnormal myelination of these interneurons in terms of internode formation and myelin distribution.

Recently, the myelination of PV interneurons has been gaining more and more attention, and so for two reasons: 1) PV interneurons and OPCs preferentially communicate during development [11], and 2) PV myelination defects might play a role in the etiology of psychiatric disorders such as schizophrenia [44]. The myelination of these GABAergic, PV-positive cells has been reliably found both cortically [12,13,14,43,45,46,47] and subcortically [14,48,49,50], and so, in different mammal species including mice [12,13,14,47,43], primates [46] and humans [14,47, 50], showing the strong cross-species conservation of this phenotype. Interestingly, it has been suggested that myelination of GABAergic interneurons is different from that of non-GABAergic neurons in terms of myelin composition and morphology in both rodents and humans. Indeed, their myelin contains more myelin basic protein (MBP), one of the major proteins in myelin, than non-GABAergic cells, although they share similar levels of proteolipid protein (PLP), the other main component of myelin [12,47]. Their axon structure also presents interesting differences: GABAergic axons are enriched in neurofilaments and contain lower levels of microtubules than non-GABAergic ones [12,47]. These axons also contain more mitochondria as shown by higher levels of malate dehydrogenase 2 (MDH2), translocase of outer mitochondrial membrane 20 (TOMM20) and voltage-dependent anion channel 1 (VDAC1) (i.e., mitochondrial proteins), as well as more 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP) in their myelin [12,47], which probably participates in providing trophic support to the axon through the maintenance of cytoplasmic channels [51]. These results are consistent with the higher metabolic demands of fast-spiking, PV interneurons whose firing frequency can exceed several hundreds of hertz, as seen both in brain slices [52] and in vivo [53]. To go further, it would also be interesting to assess whether surface molecules specific to GABAergic neurons are capable of promoting axon-oligodendroglia interactions that initiate and guide the myelination process of interneurons. GABAergic cells also present morphological differences in their myelination, which is biased towards the proximal segments

of axons [14]. These myelinated cells also tend to have shorter nodes and internodes, and myelin segments starting closer to the axonal initial segment than their non-GABAergic counterparts [12]. Moreover, these axons possess prenodes (i.e., clusters where NaV channels and ankyrin G co-localize prior to myelination), which are only found in GABAergic axons and require OL lineage cells cues for their assembly [54]. This prenode clustering increases AP conduction velocity in GABAergic axons, and so, even in their pre-myelinated state, providing evidence for a role of OL lineage cells in the optimization of AP propagation even before the onset of myelination [54]. Furthermore, the activity of PV interneurons induces specific changes in their axonal morphology and myelination pattern. Indeed, active PV interneurons possess longer axons, more internodes and exhibit a more ramified morphology, compared to inactive PV cells [55]. In conclusion, although PV interneuron-OPC synaptic communication does not seem to be determinant to drive oligodendrogenesis [13], PV interneuron-oligodendroglia interactions may play important roles in the development, maturation and myelination of these GABAergic neurons.

5. Implications for schizophrenia

An accumulating number of studies, based on both mouse models and human patients, point to PV interneurons as a recurrent locus of dysfunctions in neurodevelopmental disorders such as schizophrenia. Levels of PV and glutamic acid decarboxylase (GAD) 67 are consistently reduced in this disorder at both mRNA and protein levels [56,57,58,59], although there is no decrease in PV interneuron density [60,59], which hints at functional deficits rather than a simple loss of these cells. Notably, oscillations in the gamma range frequency (i.e., from 30 to 120 Hz), which are obtained through the synchronous activity of populations of PV interneurons [61,62], are commonly altered in schizophrenia. These impairments mostly arise

over frontal regions while patients perform higher-order cognitive tasks [63,64], and are considered a hallmark feature of the disease.

However, PV interneuron dysfunction is not the only major alteration in schizophrenia. Defects in myelin and OL lineage cells have also been found in this disease [65]. It is now widely known that cortical and subcortical myelination is reduced in this disorder [66,67,68,69], both in first-episode [66,67] and long-term patients [66,69]. These myelination abnormalities are particularly pronounced in the frontal cortex [66,70,67,68,69], and can even be detected before the onset of schizophrenia [70]. Furthermore, a number of OL lineage cells dysfunctions have been detected in this disorder. Specifically, the prefrontal cortex of schizophrenia patients contains significantly less differentiated OLs and less CNP than controls [66,71]. Genetic studies have also provided evidence that a wide number of genes related to oligodendroglia development and function are affected in this disease [72,69]. A recent study showed the existence of mutations of the Chondroitin Sulfate Proteoglycan 4 (CSPG4) gene, also known as NG2, a common OPC marker, that show familial segregation with schizophrenia [69]. These mutations are associated with several dysfunctions of OPCs derived from human induced pluripotent stem cells (hiPSC) obtained from schizophrenia patients [69]. They display aberrant morphology (e.g. smaller cells), viability and maturation into myelin-producing OLs, characteristics that correlate with a reduced white matter integrity in patients compared to controls [69]. Consistently, neonatal implantation of OPCs derived from hiPSCs from patients with schizophrenia in mice lacking MBP reduces the myelination capacity and impairs glia differentiation gene expression [73]. Together, these observations provide evidence in support of OPC dysfunction and abnormal myelin defects as novel candidate mechanisms in schizophrenia.

Although evidence for specific myelination defects in PV interneurons has yet to be provided, there has been accumulating evidence for the colocalization of both PV interneuron

and OL lineage cells dysfunctions in schizophrenia. Indeed, these neurons, which are the major type of myelinated GABAergic interneuron, are particularly altered in this disease. Given the essential role of myelin in the rapid conduction of action potentials, and the high firing frequency of PV interneurons, myelination defects might play a role in the functional impairments of PV interneurons found in this disorder. The suboptimal functioning of PV cells, notably the production of altered oscillations in the gamma band frequency, might in turn contribute to cognitive deficits associated with such impaired oscillations (e.g., executive dysfunctions). Although myelination defects may not be restricted to PV interneurons, the impaired myelination of these cells might still play a crucial role in the etiology of schizophrenia. Over the last decades, many hypotheses on the etiology of the disease have been formulated, but no theory has yet managed to integrate these different results. Aberrant interactions between PV interneurons and OL lineage cells could thus offer the opportunity to link interneuron dysfunction and myelin alterations, reconciling findings at the molecular, cellular and behavioral levels, and might provide us with an integrative pathophysiological target.

6. Conclusion

This review summarizes various evidence showing common features and different modes of interactions between cortical interneurons and OL lineage cells. It is particularly interesting that a neuronal population as complex as that of GABAergic interneurons [4] shares several characteristics and constitutes a true partner of oligodendroglia during cortical embryonic and postnatal development. It is very likely that the proper functioning of these two distinct cell types depends on each other, at least during the early phases of circuit formation and maturation. For this reason, a dysfunction of interneuron-oligodendroglia interactions may play a role in the etiology of neurodevelopmental disorders such as schizophrenia.

Conflict of interest

None

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Figure Legend

Figure 1. Overlapping origins of OPCs and Interneurons during development of the cerebral cortex.

Schematic representation of coronal embryonic brain sections showing the common origin of OPCs and interneurons from ventral and dorsal regions during embryonic development. OPCs are generated by three successive waves emerging from different areas of the periventricular zone: (i) the first wave from Nkx2.1- and Dbx1-expressing precursors emerges from MGE and POA; (ii) the second wave from Gsh2-derived precursors originates from CGE and LGE; and (iii) the third wave from Emx1-expressing cortical precursors from the dorsal pallium. Interneurons are generated from partially overlapping germinal regions to those of OPCs: around 60% arise from the Nkx2.1-expressing precursors of MGE, around 10% from Dbx1-expressing precursors of POA and around 30% from CGE. A subpopulation is also generated from the subventricular zone.

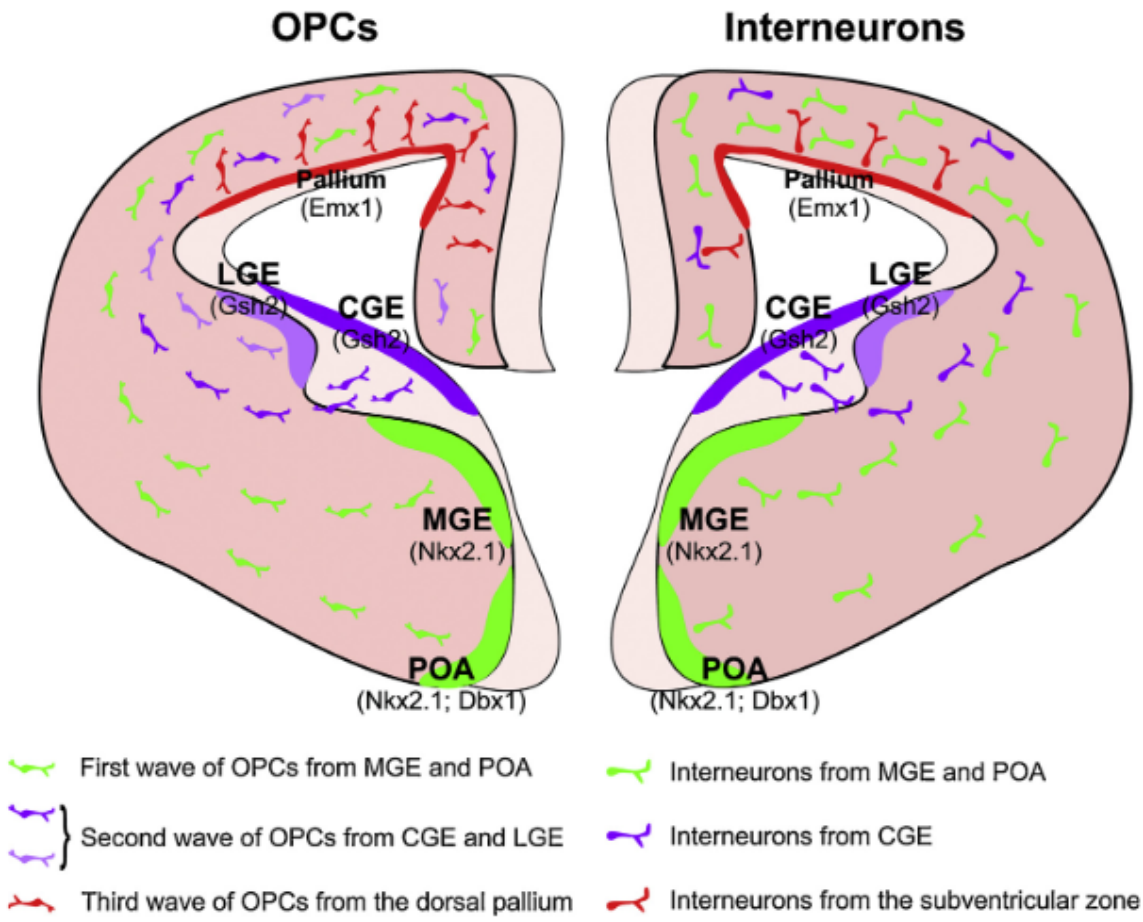
OPCs
Interneurons
Pallium
(Emx1)
LGE
(Gsh2)
CGE
(Gsh2)
MGE
(Nkx2.1)
POA
(Nkx2.1; Dbx1)
Pallium
(Emx1)
LGE
(Gsh2)
CGE
(Gsh2)
MGE
(Nkx2.1)
POA
(Nkx2.1; Dbx1)
First wave of OPCs from MGE and POA
Second wave of OPCs from CGE and LGE
Third wave of OPCs from the dorsal pallium
Interneurons from MGE and POA
Interneurons from CGE
Interneurons from the subventricular zone

Figure 1