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Tuning neural circuits by turning the interneuron knob

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Interneurons play a critical role in sculpting neuronal circuit activity and their dysfunction can result in neurological and neuropsychiatric disorders. To temporally structure and balance neuronal activity in the adult brain interneurons display a remarkable degree of subclass-specific plasticity, of which the underlying molecular mechanisms have recently begun to be elucidated. Grafting new interneurons to pre-existing neuronal networks allows for amelioration of circuit dysfunction in rodent models of neurological disease and can reopen critical windows for circuit plasticity. The crucial contribution of specific classes of interneurons to circuit homeostasis and plasticity in health and disease underscores their generation as an important objective for emerging strategies of lineage reprogramming *in vivo*.

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Introduction

Cortical GABAergic interneurons exert a crucial influence on the computations performed by microcircuits of the cerebral cortex by gating signal flow and sculpting activity patterns [1]. Dysfunction of inhibitory circuits can lead to neurological and neuropsychiatric disease, very typically linked to abnormalities in the development and plasticity of cortical interneurons [2]. Interneurons come in many flavors and have traditionally been classified on the basis of their molecular, anatomical and physiological

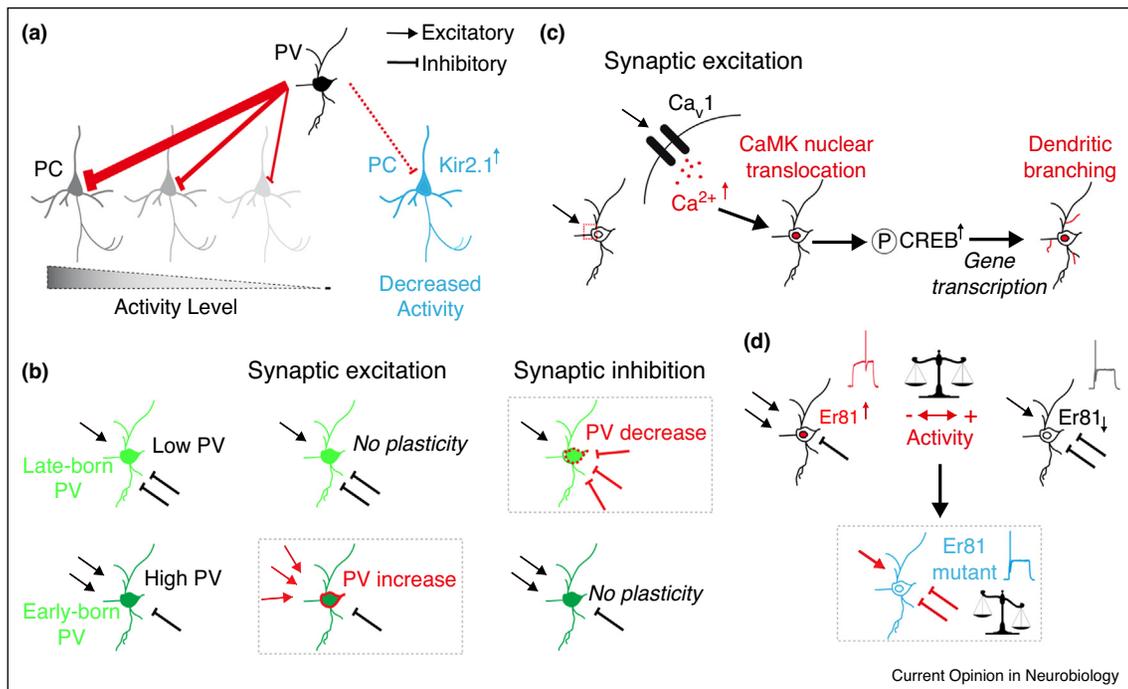
properties [3]. While early genetic specification seems to determine the cardinal properties of these interneurons [4], it is increasingly recognized that their final specification is subject to regulation by neuronal activity [5,6]. In this review, we discuss how interneurons contribute to neuronal plasticity of adult cortical circuits in a subclass-specific fashion and highlight new insights into the molecular mechanisms that underlie these physiological adaptations. We also review how network dysfunction can be ameliorated and plasticity reactivated by grafting specific classes of interneurons. Finally, we consider new opportunities for rebuilding inhibitory circuits by the emerging strategy of direct lineage reprogramming *in vivo*.

Modulation of neuronal plasticity by fast-spiking interneurons

The balance between synaptic excitation and inhibition is critical for cortical function, and its disruption has been associated with several developmental neuropsychiatric conditions such as autism or schizophrenia [7,8]. For instance, temporally locked excitation and inhibition is fundamental for the generation of oscillatory rhythms underlying high-order functions, and defects in these rhythms are strongly linked to neurological and psychiatric disorders [9]. Although pyramidal cells may have very different levels of activity depending on the behavioral state and their specific engagement into particular neural assemblies, individual neurons show relatively stable ratios of excitation and inhibition caused by the prominent capability of interneurons to compensate for changes in the firing of pyramidal cells [10,11[•],12[•]].

Inhibitory neurons regulate the adaptation of neural circuits to experience by controlling the connectivity between neurons. In particular, somatostatin-expressing (SST) interneurons mediate different forms of plasticity and memory formation by providing state-dependent inhibition at multiple levels and timescales in the cortex. These interneurons are involved in feedback and feed-forward inhibitory and disinhibitory circuits, thereby integrating different streams of sensory information [13,14]. Inhibitory plasticity seems to be mediated by parvalbumin-expressing (PV+), fast-spiking basket cells, which primarily target the soma of pyramidal cells. These cells are able to adjust their synapses onto pyramidal cells in response to changes in their activity (Figure 1a). For instance, experimental suppression of the firing of individual pyramidal cells reduces their inhibition but not their excitatory drive [11[•]], whereas enhancing the discharge of pyramidal cells potentiates perisomatic

Figure 1



Activity-dependent regulation of PV+ interneuron plasticity. **(a)** Pyramidal cells received inhibitory inputs from PV cells that match their corresponding levels of activity (light to dark colors indicate low to high activity). When the activity of pyramidal cells is suppressed by expression of Kir2.1 (blue), the inhibition that these cells receive from PV interneurons is reduced and the variability of synaptic inputs in Kir2.1-expressing neurons is reduced. **(b)** Cell-specific plasticity on PV interneurons. The plasticity of early-born PV interneurons is primarily regulated through excitation whereas the plasticity of late-born PV interneurons is regulated through inhibition. PV+ fast-spiking interneurons are largely segregated in two main classes based on their birthdates, level of PV and synaptic inputs. Early-born basket cells (E9.5-E11.5; lower panel) preferentially allocate in deep layers of the cortex, express relatively high PV levels and receive strong excitatory inputs. Late-born basket cells (E13.5-E15.5; upper panel) preferentially allocate in superficial layers of the cortex, express relatively low PV levels and receive strong inhibitory inputs. In response to excitation, early-born PV basket cells specifically exhibit cell plasticity with enhanced excitatory inputs and increased PV levels. In response to inhibition, late-born PV basket cells specifically exhibit cell plasticity with enhanced inhibitory inputs and decreased PV levels. **(c)** Activity regulates CaMKI trafficking between the cytoplasm and the nucleus, thereby coupling excitation to gene expression in PV+ fast-spiking interneurons. Depolarizing stimuli induce Ca²⁺ influx via CaV1 channels, which signals CaMKI to translocate to the nucleus, induce CREB phosphorylation (P-CREB) and specific gene transcription and, ultimately, morphological changes in PV+ interneurons, including enhanced dendritic branching (red). **(d)** Activity-dependent transcriptional control of PV+ fast-spiking basket cell excitability. Expression of Er81 segregates PV+ fast-spiking basket cells in at least two major subtypes based on their intrinsic properties, including the latency to firing at near threshold potential and synaptic inputs. PV+/Er81+ basket cells display delay to the first spike and strong excitatory inputs whereas PV+/Er81- basket cells show no delay and strong inhibitory inputs. In the absence of Er81 all PV+ interneurons show limited delay or become non-delayed, and exhibit reduced excitatory but enhanced inhibitory inputs (blue). PV, parvalbumin-expressing interneuron; PC, pyramidal Cell; ↑, increase in activity; ↓, decrease in activity; P, phosphorylation. Modified from Refs. [11**] (a); [19,20*] (b), [24**] (c); and [18**] (d).

inhibition [11**,15]. These synaptic changes can be induced through different mechanisms. For example, sensory deprivation experiments have revealed that weakening of feedforward inhibition in layer (L) 4 → L2/3 connections contributes to compensate for the reduction in sensory drive, thereby maintaining excitatory-inhibitory balance in L2/3 pyramidal neurons [16]. Conversely, the responses induced by the direct modification of L2/3 pyramidal cells (either increasing or decreasing their firing) suggest that feedback circuits also contribute to this form of inhibitory plasticity [11**]. In addition to synaptic mechanisms, other studies have shown that fast-spiking interneurons contribute to

maintain the excitatory-inhibitory balance by dynamically adjusting their intrinsic neuronal excitability in an activity-dependent manner [17,18**].

The dynamic reconfiguration of PV+ fast-spiking basket cells in response to dynamic changes in network conditions has attracted much attention recently. Work from the Caroni laboratory suggests that PV+ fast-spiking basket cells may contribute to neural plasticity by dynamically oscillating between two main states in response to recent experience [19]. These cell states are characterized by specific neurochemical properties and synaptic-density ratios, and are differentially modulated by experience

(Figure 1b). For example, environmental enrichment increased the fraction of basket cells with low levels of PV and GAD67 and relatively low excitatory inputs, whereas fear conditioning increases the fraction of basket cells with high PV and GAD67 levels and that receive a relatively high number of excitatory synapses [19]. The switch from low-PV to high-PV state also involves changes in the number inhibitory synapses received by basket cells [19], which suggest that plasticity mechanisms involve adjustments in very different types of synapses. Intriguingly, recent studies have revealed that low-PV and high-PV basket cells are born at different times during neurogenesis [20[•]], and therefore are likely engaged in different neuronal assemblies. Since the laminar location of interneurons derived from the medial ganglionic eminence (MGE) is directly linked to their neurogenesis [21], low-PV and high-PV basket cells should be largely segregated in deep and superficial layers of the neocortex [22]. This later finding makes difficult to reconcile the idea of state oscillations, as originally described in the hippocampus [19], with the organization of interneurons in the neocortex. One possibility is that early-born and late-born PV+ interneurons are fated to exhibit different forms of plasticity. For example, low-PV basket cells are particularly abundant in L2/3, where they would contribute to the acquisition of new information through adult circuit plasticity [18^{••},20[•]].

Molecular mechanisms controlling inhibitory neuronal plasticity

It is now well established that activity does not simply promote the maturation of interneuron populations that are already pre-specified, but also directs differentiation in the adult. The effects of neuronal activity are mediated through the regulation of transcription factors that set in motion programs of gene expression controlling specific features of these cells [23]. Recent studies have focused on transcription factors that are targets of specific Ca²⁺-dependent signaling pathways in various classes of interneurons. For instance, it has been shown that PV+ fast-spiking basket cells rely specifically on the Ca²⁺/calmodulin-dependent kinase 1 (CaMKI) pathway to drive gene expression in response to the opening of Ca^v1 channels by excitatory inputs from pyramidal cells [24^{••}]. CaMKI promotes the expression of CREB target genes in PV+ fast-spiking basket cells, including *Pvalb* (PV) and *Gad1* (GAD67) [24^{••}]. One of the genes that might be activated downstream of CaMKI is *Er81* (*Etv1*), an activity-dependent ETS transcription factor that interacts with the transcriptional coactivator CREB-binding protein [25,26]. *Er81* regulates the intrinsic properties of PV+ fast-spiking basket cells, including the expression of *Kv1.1* channel subunits, and neural activity in turn regulates the expression (and probably the nuclear translocation) of *Er81* [18^{••}]. This mechanism allows PV+ fast-spiking basket cells to dynamically adjust their excitability in response to changes in network activity. It remains

to be determined how this mechanism of neural plasticity influences the function of PV+ fast-spiking basket cells [27–29], as it is clear now that they comprise a heterogeneous population of cells.

The mechanisms regulating activity-dependent changes in gene expression have also begun to unveil for other types of interneurons. For instance, the transcription factor *Npas4* is an early-response transcription factor that is induced in response to activity in both somatostatin-expressing (SST+) interneurons and pyramidal cells. Interestingly, *Npas4* drives different gene expression programs in both cell types, reinforcing the view that activity-dependent transcriptional responses are regulated in a cell-class specific manner [30[•]]. Another major class of interneurons is characterized by the expression of vasoactive intestinal peptide (VIP). It has been recently shown that sensory experience promotes the expression of *Igf1* specifically in VIP+ interneurons, which in turn enhances the inhibitory synaptic input onto these neurons [31^{••}].

How does the timing of different forms of activity-dependent plasticity influence their impact on neuronal circuits? Neural activity induces gene expression changes in cortical circuits, but it is unclear how these modifications impact neural circuits in the long term. A recent study has shown that activity-dependent plasticity of PV+ fast-spiking basket cells is specifically required for long-term, but not short or intermediate forms of memory consolidation [32[•]]. This form of plasticity relies on dopamine signaling through D1/D5 receptors, and underlies the contribution of PV+ fast-spiking basket cells to fast oscillatory events during memory consolidation, including sharp-wave ripples. Similarly, transient disinhibition contributes to map stabilization following whisker deprivation, which suggest that inhibitory plasticity temporally precedes more classical forms of Hebbian plasticity during sensory map formation and stabilization [33]. The signaling pathways underlying this form of homeostatic plasticity are currently unknown, but they should be distinct from synapse-specific plasticity as they operate on different temporal and spatial scales [34]. Determining the molecular nature of this process from a temporal perspective will certainly aid to segregate interneurons based on their experience-dependent functions.

Altogether, these studies suggest that activity-induced transcriptional responses are triggered in a cell type-specific manner to achieve circuit homeostasis. In some cases, activity-dependent responses modified cardinal features in specific classes of interneurons, revealing a prominent role of neural activity in the specification of neuronal fate [18^{••}]. Future studies should aim to link global patterns of gene expression with specific neuronal fates, for example through approaches such as the recently developed ‘patch-seq’ method [35[•]].

Cell-based tuning of cortical inhibitory circuits

Given the emerging significance of inhibitory plasticity for experience-dependent circuit remodeling, a fascinating avenue for tinkering with neuronal circuits consists in the addition of new interneurons by grafting their precursors into the brain. Nearly two decades of transplantation experiments [36,37] have unveiled that precursors from the MGE and the caudal ganglionic eminence (CGE) have a remarkable capacity to disperse within the postnatal and adult mouse cerebral cortex (as well as other CNS areas), settle within appropriate cortical layers, differentiate into lineage-specific interneurons, and functionally integrate. This has yielded interesting insights not only into the mechanisms regulating interneuron specification, migration, survival and integration, but also allowed the modification of diseased circuits and the reactivation of cortical plasticity [38].

For example, transplantation of varying numbers of interneuron precursors into the postnatal mouse cortex revealed that apoptotic cell death of interneurons is intrinsically determined and apparently not dependent on the limited supply of trophic support as posed by the neurotrophic hypothesis [39]. Another important finding of this study was that the frequency of inhibitory synaptic events observed in surrounding pyramidal neurons did not linearly scale with interneuron density. This is suggestive of the operation of homeostatic mechanisms that adjust synaptic strength and number, and bears important implications for the interpretation of the functional consequences of interneuron addition to neural circuits. Bearing this in mind, several studies have shown that despite heterochronic transplantation into the cortex, interneuron precursors differentiate into their cognate interneuron lineages acquiring appropriate morphologies, laminar positions, neurochemical signatures and electrophysiological properties dependent on from which progenitor domain they originate. For instance, MGE-derived precursors gave rise to PV+ and SST+ interneurons [40], while VIP+ interneurons were only present in CGE transplants [37].

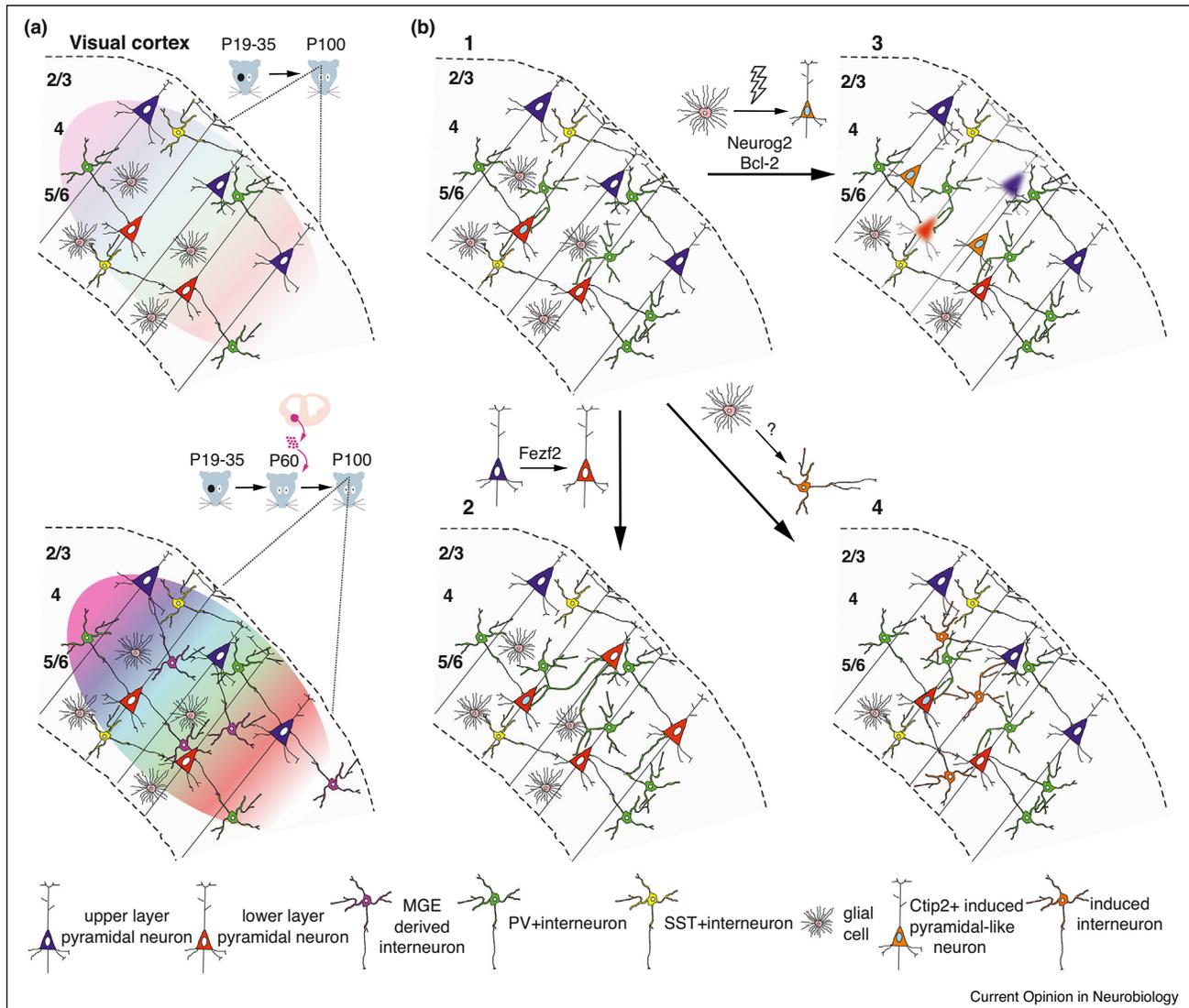
Based on such findings, transplantation of MGE precursors has been assessed for their ability to modify diseased neural circuits. Prime candidates for a cell-based therapy via addition of new interneurons are epilepsies [41]. Indeed, transplantation of MGE precursors into the cortex of Kv1.1 mutant mice simulating a human channelopathy before the appearance of seizures resulted in reduced seizure activity [42]. Interestingly, the disease-modifying effect of transplantation can be observed even after manifestation of seizures. When MGE precursors were grafted into the hippocampus of mice that had undergone pilocarpine-induced status epilepticus, there was a marked reduction in seizure occurrence and behavioral comorbidities of epilepsy compared to non-grafted controls [43]. While the earlier study showed that there

was a significant increase in inhibitory input into pyramidal neurons, it would be worth repeating these studies with MGE precursors expressing optogenetic actuators to dissect the functional importance of inhibition in suppressing the epileptic activity, as recently shown for transplantation experiments in models of Parkinson's disease [44].

Grafting of MGE-derived interneuron precursors into the adult striatum has also shown to bring about functional improvements in a rat model of Parkinson's disease [45] and reverse mechanical hypersensitivity produced by peripheral nerve injury upon grafting into the adult mouse spinal cord [46]. These effects are not restricted to rodent MGE precursors. When human embryonic stem cells were differentiated into MGE-like precursors and transplanted into the injured mouse spinal cord, a relieve of injury-related symptoms was observed [47]. These experiments highlight the remarkable capacity of interneurons derived from MGE grafts or generated from stem cells for integrating throughout the CNS and inducing functional circuit remodeling.

One of the most remarkable effects of MGE grafts is the reopening of a critical window of cortical plasticity (Figure 2a). Cortical plasticity can be probed by closure of one eye (monocular deprivation, MD) and subsequent assessment of the resulting reorganization of connectivity between the open and closed eyes, respectively, and the primary visual cortex [48]. If MD is induced during a critical period of cortical development, then the closed eye will exhibit a reduced ability of activating neurons in the primary visual cortex compared to the open eye (a phenomenon referred to as ocular dominance plasticity, ODP). Intriguingly, the end of this critical period is closely associated with the maturation of PV+ and SST+ interneurons which in mice peaks at postnatal day 35 [49]. Southwell and colleagues have tested the hypothesis whether transplantation of MGE-derived precursors would result in the induction of a new window of ODP when MD was performed after the end of this critical window [50]. MGE grafts induced a new critical window the closure of which coincided with the maturation of the grafted interneurons. Remarkably, the time course of maturation of the grafted interneurons matched the pace of endogenous interneuron differentiation suggestive of an intrinsic maturational program. More recently, the Gandhi lab has shown that the capacity of MGE grafts for reactivating ODP is not limited to early postnatal life but extends into adult [51**]. Importantly, such reopened ODP allows for the reversal of visual deficits induced by visual deprivation during the earlier critical period at both circuit and behavioral levels. In keeping with the subclass-specific function of interneurons in experience-dependent function discussed above, the ODP re-opening effect is restricted to interneurons derived from MGE grafts (PV+ and SST+), while CGE grafts fail to induce a

Figure 2



Cell-based remodeling of inhibitory circuits. **(a)** Grafting of MGE-derived interneuron precursors reactivates cortical plasticity. Monocular deprivation during a critical period of visual cortical plasticity (P19-35) results in the weakening of retinotopic inputs from the deprived eye (illustrated by the weak color grading) by P100. Grafting of interneuron precursors from the MGE into the visual cortex at P60 induces a new critical period that allows for cortical remapping of the input originating from the formerly closed and then reopened eye (illustrated by the enhanced color grading). **(b)** Circuit remodeling induced by lineage reprogramming. (1 → 2) Lineage reprogramming of layer 2/3 projection neurons into layer 5-like neurons by the transcription factor *Fezf2* induces functional redistribution of perisomatic inhibitory inputs arising from PV+ interneurons to these cells. (1 → 3) Forced expression of *Neurog2* and *Bcl2* following brain injury (illustrated by the thunderbolt and the diffuse silhouette of the degenerated neurons) *in vivo* induces conversion of local glia into *Ctip2+* pyramidal-like neurons. (1 → 4) Selection of appropriate reprogramming factors may allow for lineage reprogramming of local glia into induced interneurons.

new critical window despite their successful dispersion and integration in the primary visual cortex [37,52].

The possibility of generating MGE-like progenitors from human induced pluripotent stem cells (hiPSC), which can mature into functional interneurons following grafting into the mouse cortex [53,54], allows addressing now

the exciting question whether human MGE-like interneurons possess the same capacity for reactivating ODP as their rodent counterparts. Even more thrilling is the prospect that the duration of such induced critical window would be substantially prolonged along with the protracted maturation pace specific to human interneurons [55].

Prospects of inhibitory circuit remodeling by lineage reprogramming

In line with the subclass-and state-specific distribution of interneurons, it has been shown that during development the laminar distribution of cortical interneurons is under strong influence of the excitatory projection neuron subtypes they normally innervate [56–58]. Even more striking, when early postmitotic layer 2/3 callosal projection neurons were lineage-reprogrammed into layer 5-type of corticofugal projection neurons by forced expression of the transcription factor *Fezf2*, the reprogrammed neurons received inhibitory synaptic input akin to endogenous layer 5 projection neurons [59**] (Figure 2b). It will be interesting to learn whether such remodeling of interneuron distribution and synaptic innervation is limited to the intrinsic window of interneuron maturation or represents a form of circuit plasticity extending into adulthood.

Direct lineage reprogramming of brain-resident cells into induced neurons has gained enormous momentum as novel means towards repairing the diseased brain [60,61]. Earlier *in vitro* studies discovered the possibility of reprogramming mouse astroglia into inhibitory neurons exhibiting firing properties of MGE-derived interneurons by forced expression of the transcription factors *Ascl1* and *Dlx2* [62]. Subsequent work revealed the feasibility of converting adult human brain pericytes into functional GABAergic neurons via two reprogramming factors *Sox2* and *Ascl1* [63], which also constitute the core of a reprogramming cocktail for mouse and human fibroblasts into GABAergic neurons [64*]. Remarkably, these fibroblast-derived interneurons can functionally integrate when transplanted into the hippocampus. Most excitingly, direct lineage conversion of glia into neurons can be induced *in vivo* (Figure 2b). However, evidence for specification of a defined subtype identity of the neurons induced via reprogramming is currently scarce. Consistent with the role of *Neurog2* during the development of the cerebral cortex, neurons induced from glia *in vivo* by co-expression of *Neurog2* and *Bcl2* acquired a pyramidal neuron-like morphology and have a transcriptional profile characteristic of deep-layer projection neurons (*Ctip2+*, *FoxP2+*, *Satb2-* and *Cux1-*) [65**]. Likewise, *NeuroD1*-induced neurons were found to be *Tbr1+* and *Ctip2+*, again suggesting some degree of subtype specification [66]. In contrast, conversion of glia into subtype-specific interneurons has not yet been achieved in the cerebral cortex *in vivo*, though induced GABA-immunoreactive neurons have been observed in the lesioned spinal cord following reprogramming by *Sox2* [67]. Given the unique effects of different classes of interneurons on circuit function and plasticity, the development of robust strategies to induce the conversion of local glia into subtype-specific interneurons is of outstanding interest to unleash the full potential of these cells as disease-modifying agents.

Conclusions

Owing to their plasticity well into adulthood, interneurons are an emerging target for interventional circuit remodeling in the treatment of neurological and neuropsychiatric disease. To fully unleash such potential, it will be critical to uncover the molecular mechanisms that account for the remarkable flexibility of these neurons and their class-specific differences. Similarly, only a full grasp of the biology of grafted or lineage-reprogrammed interneurons will allow us to recruit these cells as means for re-tuning diseased cortical microcircuits to their healthy function.

Conflict of interest statement

Nothing declared.

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