Review

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GABAergic interneuron transplants to study development and treat disease

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Advances in stem cell technology have engendered keen interest in cell-based therapies for neurological disorders. Postnatal engraftments of most neuronal precursors result in little cellular migration, a crucial prerequisite for transplants to integrate within the host circuitry. This may occur because most neurons migrate along substrates, such as radial glial processes, that are not abundant in adults. However, cortical GABAergic interneurons migrate tangentially from the subcortical forebrain into the cerebral cortex. Accordingly, transplants of cortical interneuron precursors migrate extensively after engraftment into a variety of CNS tissues, where they can become synaptically connected with host circuitry. We review how this remarkable ability to integrate post-transplant is being applied to the development of cell-based therapies for a variety of CNS disorders.

Tangential (non-radial) migration of cortical GABAergic interneurons, and initial transplantation studies

GABAergic interneurons represent about 20% of the neurons in the cerebral cortex [1]. In most instances, GABA hyperpolarizes target cells largely via postsynaptic chloride-permeable receptors. In addition to an inhibitory effect on cortical activity, a single interneuron can synchronize the firing of projection neuron ensembles, which is crucial for normal cerebral cortical function. Accordingly, cortical interneuron dysfunction is associated with a variety of neuropathologies, including epilepsy, schizophrenia, and autism.

Multiple studies have demonstrated that cortical interneurons in rodents are born in subcortical regions and migrate tangentially (non-radially) over long distances to populate both the neocortex and the hippocampus [2,3] (Figure 1). Similar migrations were also identified in gyrencephalic mammals, including ferrets and humans [4,5]. Although a cortical source of cortical interneurons has also been suggested to occur in primates [5–7], two recent studies found that the vast majority of GABAergic interneurons in primate cortex arrive there via non-radial migration from subcortical origins [8,9] (Figure 1).

The discovery of this remarkable capacity for cortical interneurons to migrate substantial distances, across the radial-glial scaffold, led Alvarez-Buylla and colleagues to test the idea that this capacity would permit their dispersion following engraftment into adult brain. Indeed, transplantation of interneuron progenitors from the medial ganglionic eminence (MGE; Figure 2) into the adult striatum resulted in widespread migration and survival [10] (Figure 2). Neither transplants of progenitors of striatal GABAergic projection neurons (from the lateral ganglionic eminence; LGE), nor transplants of neocortical glutamatergic projection neurons, showed a significant capacity to migrate into host brain tissues. This differential capacity to migrate post-transplantation into the adult brain may relate to the general tendency for forebrain projection neuron populations to migrate radially, in contrast to forebrain interneuron populations [11]. These results suggested that MGE-derived interneuron precursors may be especially suited for use in cell-based therapies [10], a notion supported by the finding that MGE transplants into postnatal cortex differentiate into GABAergic interneurons that enhance local synaptic inhibition [12] (Figure 3A).

MGE transplants to study interneuron fate

Although analysis of transgenic mice and genetic fate-mapping have made invaluable contributions to understanding cortical interneuron development, the migration and differentiation of MGE-derived cortical interneurons post-transplant has enabled a variety of studies on interneuron migration, fate determination, and function. Embryonic transplantation studies revealed that MGE interneurons will migrate into the overlying cortex, and differentiate into parvalbumin (PV)- or somatostatin (SST)-expressing interneuron subgroups when transplanted heterotopically into more caudal regions of the basal forebrain [13]. In addition, MGE interneurons lacking reelin signaling, transplanted homotopically into the wild type MGE *in utero*, still migrate into the temporally appropriate layers of cortex [14]. This study and others led to the important conclusion that cortical pyramidal neurons have a major influence on the layer-specific targeting of temporally defined cohorts of MGE-derived interneurons [14–16].

Transplantations of MGE-derived interneuron progenitors into postnatal cortex have also been used to study

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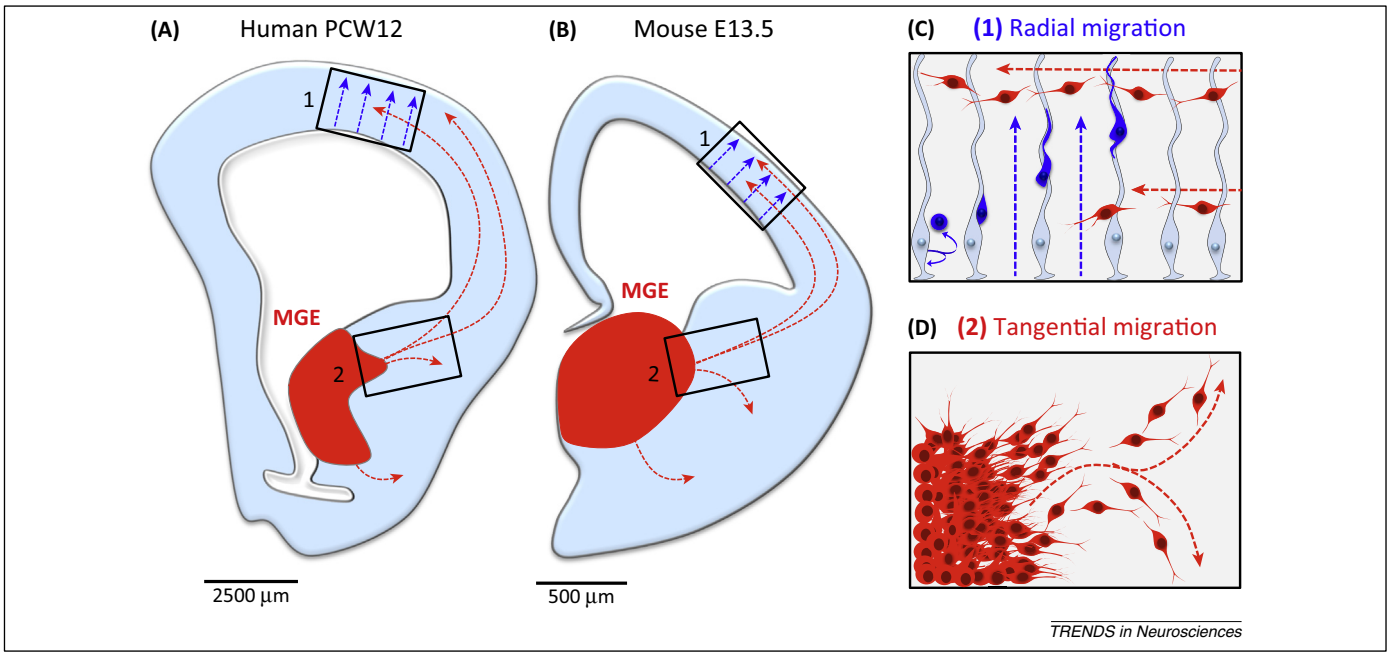

Figure 1. Subcortical origins and migration of mouse and human neocortical interneurons. Cortical interneurons in rodents and primates originate embryonically in subcortical structures, then migrate non-radially into the cerebral cortex (MGE in red); **(A)** human post-conception week 12; **(B)** mouse embryonic (E) day 13.5. Unlike radially migrating pyramidal cells born in the cortical ventricular zone (VZ) **(C)** (blue cells), the movement of interneurons is not restricted to radial glial scaffolds **(C,D)** (red cells). Mouse interneuron migration routes schematized as reviewed in [2], human interneuron migratory routes schematized from data in [8,9]. Abbreviations: MGE, medial ganglionic eminence; PCW, weeks post-conception.

interneuron subgroup origins. Neonatal cortical transplantation of different regions of the MGE (dorsal vs ventral), revealed a strong bias for SST-expressing interneurons to originate early from the dorsal-most region of the MGE, and a weaker bias for PV-expressing interneurons to originate in the ventral two thirds of the MGE later in neurogenesis [17–19]. This approach also revealed a remarkable bias for a subtype of cortical interneuron, the axo-initial segment targeting Chandelier cell, to be generated from the ventral-most region of the MGE at the latest stages of cortical neurogenesis [18,20]. This latter finding is spurring follow-up studies to discover the fate determination of Chandelier cells, a neuron whose dysfunction is implicated in epilepsy and schizophrenia [21–23].

In addition to their utility for studying interneuron origins, MGE transplantation methods, by allowing the examination of chemically or genetically manipulated cells developing within an otherwise wild type cortex, have also been invaluable for studying interneuron fate. For example, addition of the morphogen sonic hedgehog to slice cultures, followed by transplantation of the MGE region into wild type cortex, can convert ventral MGE progenitors from the generation of PV to the generation of SST-expressing fates [24]. The approach can also be used to study the transcriptional regulation of interneuron fate. Electroporation of Lhx6 (LIM homeobox protein 6), a target of the interneuron-fate determining transcription factor Nkx2.1 (NK2 homeobox 1), into the MGE-like region of slices cultures from Nkx2.1 nulls, can rescue the ability of these cells to express PV or SST after transplantation into neonatal neocortex [25].

In addition to the study of early aspects of interneuron development, MGE transplantation approaches can also be used to study the regulation of interneuron maturation and survival. For example, Dlx1 is required for the dendritic maturation and survival of interneuron subclasses [26]. Remarkably, interneuron survival both *in vivo* and in transplantation studies appears to be determined by an interneuron-intrinsic mechanism that results in the death of roughly 50% of cells, independently, in the case of transplant studies, of the number of cells transplanted [27].

MGE transplants in the study of interneuron-induced cortical plasticity.

A potential role for cortical interneuron maturation in the process of adolescent age-range cortical plasticity was posited based on the tight correlation between PV expression in a subset of cortical interneurons, and dendritic spine density on pyramidal neurons, during prefrontal cortical development in the macaque [28]. Subsequent studies using transgenic mice and visual cortical plasticity in response to monocular deprivation revealed that the maturation of GABAergic interneurons is indeed crucial in determining the temporal window of plasticity [29,30]. To examine whether the maturation of inhibition induces this type of plasticity based on cell-intrinsic aspects of inhibitory circuitry, MGE progenitors were transplanted into either neonatal [postnatal (P) days P0–2] or postnatal (P9–11) mouse cortex. The transplants were able to reopen ocular dominance plasticity in recipient cortex according to the age of the engrafted interneurons, specifically when they reached an age equivalent to when this plasticity occurs normally (P26–28) [31]. Of note, the effects of transplanted MGE on cortical plasticity probably cannot be exclusively attributed to increased inhibition because enhancing inhibition pharmacologically does not similarly