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Clonal origins of neocortical interneurons

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Once referred to as 'short-axon' neurons by Cajal, GABA (gamma-amino butyric acid)-ergic interneurons are essential components of the neocortex. They are distributed throughout the cortical laminae and are responsible for shaping circuit output through a rich array of inhibitory mechanisms. Numerous fate-mapping and transplantation studies have examined the embryonic origins of the diversity of interneurons that are defined along various parameters such as morphology, neurochemical marker expression and physiological properties, and have been extensively reviewed elsewhere. Here, we focus on discussing two recent studies that have, for the first time, examined the production and organization of neocortical interneurons originated from individual progenitors, that is, with clonal resolution, and provided important new insights into the cellular processes underlying the development of inhibitory interneurons in the neocortex.

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Introduction

GABAergic interneurons comprise ~20% of the neuronal population in the neocortex. In addition to providing local inhibition and shaping circuit output, they are crucial in generating network oscillations, thereby further influencing the response of the circuit to incoming signals. Born in the ventral regions of the developing telencephalon, neocortical interneurons are a diverse cell population and have been extensively characterized based on their morphological, neurochemical, and physiological properties [1–7]. Previous fate-mapping and transplantation studies have suggested that, similar to the dorsally derived excitatory neurons, the developmental history (i.e. place and time of birth) of inhibitory interneurons has a strong influence on their subtype specification and distribution in the mature neocortex [8–16]. In the case of excitatory neurons, lineage history not only contributes to the spatial/structural organization, but also influences the functional development of the neocortex as excitatory cells derived from the same progenitor cell exhibit preferential (both electrical and chemical synapse-based) connectivity and similar physiological properties amongst each other in comparison to nearby non-lineage related cells [17–19].

However, unlike neocortical excitatory neurons, virtually nothing is known about the lineage development of interneurons at the single progenitor cell level. Thus, fundamental questions about the production, specification, and organization of interneurons that underlie the construction of functional neocortical circuits remain largely open. For instance, do individual progenitors produce the same subtype or different subtypes of interneurons? How heterogeneous are the progenitors spatially and temporally regarding their proliferative behavior and neuronal output? Does the lineage relationship of interneurons influence their spatial and functional organization? Considering the incredible diversity of interneuron subtypes that carry out distinct essential functions in the neocortex, lineage analysis of interneuron progenitors can certainly help unravel how diverse components of this fundamental cell population are produced and assembled structurally and functionally, by following the behavior of one progenitor cell at a time.

Answering these questions requires clonal analysis of interneuron production and organization. By exploiting retrovirus-mediated gene transfer in conjunction with mouse genetics, Brown *et al.* [20••] and Ciceri *et al.* [21••] specifically labeled individual progenitor cells in the embryonic medial ganglionic eminence (MGE) and preoptic area (PoA), which are responsible for producing more than 70% of neocortical interneurons, and analyzed the behavior of individual progenitors and their progeny from birth to maturation.

In the first study, the specificity is achieved by taking advantage of the exquisite fidelity of the subgroup A avian sarcoma leukosis virus (ASLV)-receptor interaction [22]. TVA, the cognate receptor for ASLV, was selectively expressed in the progenitor cells in the MGE and PoA by crossing $R26^{LSL\text{-}TVAiLacZ}$, a knock-in mouse line that expresses TVA in a Cre recombinase-dependent manner [23], with an *Nkx2.1-Cre* transgenic mouse line [15]. *Nkx2.1* encodes a homeobox transcription factor specifically expressed in the progenitor cells in the MGE and the PoA [10,15,24]. Dividing progenitors expressing TVA at the ventricular zone (VZ) surface were then labeled by

performing *in utero* intraventricular injection of low-titer RCAS (replication-competent ASLV long terminal repeat with splice acceptor) retrovirus expressing fluorescent proteins at embryonic day (E) 11–12 [20••].

In the second study, the specificity is achieved by using retroviruses carrying a reversed and double-floxed cDNA sequence encoding a fluorescent protein. Thus, while the retroviruses infect progenitors indiscriminately, only those expressing Cre recombinase are capable of inverting the cDNA sequence for expression by recombination and are subsequently labeled [21••]. It is worth noting, however, that the Cre-mediated inversion is reversible so that in the continued presence of Cre, the cDNA sequence can become reversed again, and therefore its expression is not stable until additional recombination to permanently delete a set of flox sequences [21••].

Clonal production of neocortical interneurons

While progenitors in the VZ of the dorsal telencephalon responsible for producing neocortical excitatory neurons have been extensively characterized, progenitors in the ventral telencephalon including the MGE are less understood. By labeling and characterizing individual progenitors, both studies demonstrated that progenitors in the VZ of the MGE and PoA are radial glial cells in nature. They exhibited the defining morphological characteristics including a cell body in the VZ, a short process reaching the ventricular surface with a large endfoot and a long fine radial process directed toward the pial surface [20••,21••]. They expressed astrocyte-specific glutamate transporter (GLAST) and brain-lipid-binding protein (BLBP), two proteins known to be specifically expressed in radial glial cells, as well as the neural progenitor marker, Nestin [20••].

Clonal clusters labeled in the MGE and PoA at the embryonic stages mostly contained a single mitotic radial glial progenitor (RGP) and a few short-process cells that closely associated with the long radial glial process (Figure 1, left). The progressive increase in the number of short-process cells suggests that the RGP undergoes asymmetric divisions to self-renew, and simultaneously produce short-process cells. Indeed, using time-lapse imaging in organotypic slice cultures, Brown *et al.* directly observed asymmetric divisions of RGPs. RGPs displayed interkinetic nuclear migration and divided at the VZ surface. After mitosis, while one of the two daughter cells remained as a bipolar RGP, the other daughter cell initially moved along the renewed RGP away from the VZ and then detached and migrated tangentially toward the neocortex. In some asymmetric divisions, the resulting non-radial glial daughter cell reentered the cell cycle and divided again in the subventricular zone (SVZ), likely representing intermediate progenitors (IPs) in the region.

These divisions in the SVZ appeared to be symmetric, producing two daughter cells with similar morphology and cellular behavior. Interestingly, simultaneous or synchronous symmetric divisions in the SVZ were frequently observed within a clone, suggesting that IPs in the MGE undergo multiple rounds of symmetric division. In comparison, IPs in the dorsal telencephalon mostly undergo one round of symmetric division [25]. The relative size of the SVZ compared to the VZ in the ventral telencephalon is substantially larger than that in the dorsal telencephalon [26]. Related to this, while the divisions in the dorsal telencephalon occur mostly at the VZ surface, substantial divisions in the ventral telencephalon take place in the SVZ. Together, these observations suggest that synchronous symmetric IP divisions may be a crucial feature of interneuron neurogenesis in the MGE.

MGE-originated interneurons exhibit a birth date-dependent 'inside-out' distribution in the neocortex [27]. Within a clone, asymmetric divisions of the RGP generate interneurons at different times, whereas synchronous symmetric divisions of the IP generate interneurons around the same time. Therefore, progenitor division patterns may fundamentally influence the distribution and differentiation of clonally related neocortical interneurons. A direct comparison between RGP lineages and IP lineages will provide crucial insights into this; however, this requires the identification and characterization of IP-specific markers in the MGE. It has been postulated that cyclins D1 and D2 are expressed in distinct progenitor niches, with cyclin D1 predominantly found in the VZ (likely in RGPs), and cyclin D2 in the SVZ (likely in IPs) of the cerebral cortex and the ganglionic eminence (GE) [28]. Other potential candidates for IP lineages in the MGE include Mash1/Asc1 and Dlx1/5 [29–32].

In embryonic stages, the daughter cells including IPs and differentiating interneurons appeared closely associated with the radial glial process of the RGP initially. Brown *et al.* noticed that the cells located farthest away from the VZ often acquired the typical bipolar morphology of tangentially migrating interneurons [20••]. Moreover, they were positive for TuJ1, a differentiated neuronal marker, and possessed Na^+ conductance. These observations raised the possibility that associating with the mother radial glial fiber is critical for proper interneuron differentiation and that acquiring differentiating interneuron properties is a prerequisite for commencing tangential migration. Should this be the case, the morphology and property of radial glial fibers may also play crucial roles in regulating neocortical interneuron differentiation and distribution.

Clustering of clonally related neocortical interneurons

Ventrally derived interneurons embark on a long, tangential journey to reach their destination in the neocortex. Previous studies suggest that this migration process appears to be random [33,34]. Unexpected from what

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