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The chandelier cell, form and function

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Abstract

Among γ-aminobutyric acid (GABA) interneurons, the Chandelier cell (ChC) has long captured
the interest of neuroscientists as a subtype not described by Ramon y Cajal. ChCs feature an
axonal arborization that selectively innervates the axon initial segments of pyramidal cells. Recent
studies involving transgenic mice have identified intriguing features of ChCs, including a
remarkably specific spatial and temporal origin, their capacity to have either excitatory or
inhibitory influences on pyramidal neurons, and their synaptic alterations in schizophrenia. This
review explores these and other developmental and functional aspects of this fascinating cortical
neuronal subtype.

Introduction

In the cerebral cortex, γ-aminobutyric acid (GABA) interneurons modulate cortical
excitability by feedback and feedforward inhibition, and are critical to the neuronal plasticity
[1, 2] as well as to the synchronous activity of pyramidal neurons [3]. Among GABAergic
cortical interneurons, one major subclass is defined by its property of discharging in trains of
very rapid, non-accommodating action potentials (40–200 Hz), and thus are called "fast-
spiking" (FS). Most FS interneurons are termed "basket" cells for their propensity to have
curved axon terminals that mainly target the proximal dendrites and cell soma of pyramidal
neurons. However, it is the other FS interneuron type that is arguably the most enigmatic of
cortical interneurons, the "chandelier" cell (ChC). ChCs, also referred to as axo-axonic cells,
have long captured the interest of neuroscientists as the interneuron subtype that was not
described by Ramon y Cajal [4]. More recently, a number of intriguing features of ChC have
come to light that further piques this interest, including the spatial and temporal specificity
of their origin [5*, 6**], their capacity to have either excitatory or inhibitory influences on
pyramidal neurons [7**], their remarkable elimination of axon terminals during adolescent-
age range development in primates [8–10], and their synaptic alterations in schizophrenia

[11]. This review delves into these and other developmental and functional aspects of this fascinating cortical interneuronal subtype.

Chandelier cells; initial identification and defining features

The chandelier cells (ChCs), so named because the axon terminals resembled a candelabrum, were first identified in the 1970s by Szentagothai, and independently, by Jones [12, 13]. ChCs feature a distinctive axonal arborization that includes a moderately dense weave of horizontal collaterals, from which vertically-oriented axon terminals hang (Figure 1). These terminals, also called cartridges, selectively innervate the axon initial segment (AIS) of pyramidal neurons [14]. ChCs are most abundant in layers 2 and 3, but are present in all cortical layers [15, 16]. Although originally described in neocortex [12], ChCs have also been found in the CA3 [17], CA1 [18] and dentate gyrus [19] regions of the hippocampus, and in the amygdala [20].

Chandelier cell origin and development

With respect to their origins at the subcortical forebrain, cortical interneurons can broadly be parsed into two: those that derive from Nkx2.1-expressing progenitors in the medial ganglionic eminence (MGE) or preoptic area, and those that derive from caudal ganglionic eminence (CGE). Fate-mapping studies using the Nkx2.1 Cre lines [6**, 21], *in utero* retroviral injections [22*], and transplantation studies [5*] have demonstrated that most or all ChCs originate in the MGE starting at embryonic day (E) 13.5 (Figure 2A). Studies involving MGE transplantations into mouse neonatal neocortex, as well as spatial and temporal fate mapping using Nkx2.1Cre-ERT2 mice, have indicated that ChCs are primarily generated by the most ventral region of the MGE and at the latest stages of cortical neurogenesis (Figure 2B) [5*, 6**]. In fact, tamoxifen injections in the neonatal period can label ChCs in the Nkx2.1Cre-ERT2 mice [6**]. However, this may reflect persistent expression of Nkx2.1, or the in-lineage ectopic expression of Cre that occurs in transgenic mice with Cre-poly A inserts to the Nkx2.1 gene [21, 23], rather than reflecting the neonatal neurogenesis of ChCs. While the late gestation generation of ChCs in mice is distinctive, it is not entirely unexpected since most ChCs in the mouse are found directly at the layer 1 - layer 2 boundary, and since MGE interneurons generally follow the same "inside-out" relationship of birthdate to laminar location as pyramidal neurons [24, 25].

The finding by Taniguchi and colleagues that late gestation and early postnatal administration of tamoxifen to Nkx2.1CreERT2 reporter mice labels cortical interneurons with a roughly 3:1 bias for ChCs over basket cells led to fascinating observations on ChC postnatal development. ChC precursors migrate along the lateral wall of the ventricle and follow a lateral or medial route (Figure 2B) once they reach the cortex around birth (at postnatal day (P) 0). Initially, they enter the ventricular zone and then invade the cortical plate, reaching layer 1 around P2-P3. Finally, these cells descend to their destination in the cortical plate between P3-P7. At P7, well prior to the formation of axonal cartridges, many labeled cells were present along the layer 1- layer 2 border where their processes seemed to form a dense plexus (Figure 2C) [6**]. By P20, some 90% of these cells were no longer detected, and the remaining cells were nearly all ChCs, raising the likelihood that ChCs

form this plexus transiently, which is then pruned to adult levels (Figure 2D). Interestingly, cell death of mouse cortical interneurons was reported during a similar developmental period, although with loss of about 40% of the cells [26]. At this developmental stage, just after the close of pyramidal neuron radial migration, pyramidal neurons are extending and ramifying their apical dendrites and forming their terminal tufts. P7 is also a time when the gradient for chloride across the pyramidal neuron plasma membrane favors a depolarizing response to the activation of GABA-A receptors. This raises the possibility that ChCs may be providing a transient, excitatory drive to the cortical projection neurons when they are extensively involved in axonal and dendritic maturation and synaptogenesis. In line with this possibility, conditional loss of the Neuregulin receptor ErbB4 in MGE interneurons affect ChC but not basket cell synapses, and secondarily results in reduced spine density by cortical pyramidal neurons [27**].

An additional interesting finding from the fate-mapping study based on Nkx2.1CreERT2 mice was that most ChCs that were not at the layer 1 - layer 2 boundary were present in layer 5 [6**]. A similar observation was reported for human neocortex [28] while analysis of chandelier axon terminals in monkey prefrontal cortex over postnatal development did not reveal this pattern [8]. In addition to the variations in the layer distribution of ChCs, the density of ChC terminals in different cortical regions were found to be distinct in mice, monkey and humans [9, 16, 28]. It is important to note that the differences observed in cartridge distribution may reflect the changes in the expression of synaptic markers used in each study. Still, one remaining issue is whether ChCs exist as subtypes of a general class of axo-axonic cells, as reported in the monkey [29], a possibility that is also raised by their variable expression of the calcium binding protein parvalbumin (Figure 1) [6**]. Whether layer 5 ChCs have distinct properties from those in layer 2 is not known, but within layer 2, ChCs appear to form a homogenous interneuron type as defined by dendritic or axonal morphology and various electrophysiological characteristics [7**]. In addition, these cells also show extensive electrical coupling, suggesting that their activity is coordinated [6**, 7**].

Chandelier cell targeting, physiological features, and function

ChC cartridges target the axon initial segment (AIS) of pyramidal neurons, where action potentials are generated [14, 30]. Cartridges of ChCs located at the border of layer 1 and 2 are visible by around P14, and were found to be surprisingly stable in their distribution and morphology from the P18 (late pre-weaning) to P90 (young adult) in mice [31]. The lateral span of the ChC axonal arbor and number of cartridges increases slightly with age although the average density of cartridges does not differ significantly between different ages (Figure 2E, F). Consistent with earlier findings [16, 28, 32, 33], ChC axon terminals contact an AIS with an average of 3–5 boutons per cartridge [31]. By comparing this number to the total number of putative synapses at the AIS, at least 4 ChCs are estimated to innervate each pyramidal neuron. On the other hand, the mean number of boutons innervating the AIS is reduced in ChCs of the monkey prefrontal cortex during development, and the number of boutons per cartridge is positively correlated with the AIS size [10].

In mouse somatosensory cortex, individual ChCs contact 35–50% of pyramidal neurons within the range of its axonal arbor, with clear pockets of higher or lower innervation densities (Figure 2E, F). It remains unclear how this arrangement forms or whether it reflects a previously unappreciated organizational construct in the cortical circuitry. Interestingly, AIS innervation by the cartridges was found to be highly variable also in the monkey prefrontal cortex ChCs during development [10]. Although regulation of AIS targeting is unknown in the cortex, an axo-axonic interneuron population in cerebellum has been found to initially target the axonal side of the cell soma and the AIS, then to refine this targeting to the AIS by signaling of the adhesion molecule L1CAM [34].

Both the Parvalbumin-expressing basket interneurons, and the far less common ChCs, fire high frequency, minimally adapting, "fast-spiking" trains of action potentials in response to supra-threshold current injections. Parvalbumin (PV) is an EF-hand domain containing, high affinity calcium (Ca^{2+})-binding protein [35]. In PV knockout mice, synapses with short-term depression are converted to synapses with short-term facilitation resulting in enhanced synaptic transmission [36]. Although PV is expressed in all FS basket cells, PV expression in ChCs located at different cortical areas of the Nkx2.1CreERT2 reporter line varied between 15% colabeling in the prefrontal cortex to 50% in the somatosensory cortex [6**]. It would be interesting to compare the short-term plasticity of ChCs in different cortical areas to elucidate whether PV-expressing and PV-negative ChCs have different short-term plasticity properties.

Prior to recent advances that employed transgenic mice to visualize ChC and basket cells in slice preparations and hence tremendously enhance electrophysiological studies, basket and ChCs were often seen as having similar effects on pyramidal neuron excitation. However, with the aid of transgenic reporter mice, a detailed comparison of cortical basket and ChC intrinsic firing properties, as well as more detailed analysis of ChC influences on pyramidal neuron excitability, has become possible. For example, in terms of intrinsic firing properties, basket cells have a greater latency of firing at threshold current injections [37], although this parameter varies by species [38]. Interestingly, this study also revealed that ChCs have a higher firing frequency and adaptation compared to basket cells in both rats and monkeys [38].

ChCs can have a great impact on the output of pyramidal neurons based on the localization of their synapses at the AIS, and they were proposed to be circuit switches [39]. On the other hand, the unusual location of ChC synapses at the AIS also renders them with complex physiological properties, such that whether they depolarize [37, 40] or hyperpolarize [41] their target pyramidal neurons had been controversial.

Recently, extensive analysis of the synaptic transmission of ChCs at the layer 1 and 2 border of P16- P25 mouse somatosensory cortex revealed that the effect of ChC synaptic transmission relies on the resting membrane potential (V_{rest}) of the pyramidal neuron [7**]. If the pyramidal neuron V_{rest} is more hyperpolarized than the reversal potential of GABA (E_{GABA}), ChC synaptic transmission was depolarizing and increased the spiking probability of the pyramidal neuron. However, ChC synapses were found to have a hyperpolarizing effect if the pyramidal neuron was depolarized to E_{GABA} or above. In another set of

experiments, an "*in vivo*-like" activity was induced in the pyramidal neurons. Activation of the ChCs shortly (5 ms) before the expected pyramidal neuron spike evoked reliable inhibition. On the other hand, ChC activation at earlier time points (15–40 ms) evoked both hyperpolarizing and depolarizing effects. These results are consistent with the findings that ChC synaptic response is dependent on the V_{rest} of the pyramidal neurons because shortly before the expected pyramidal neuron spike, the pyramidal neuron is already at a depolarized state whereas V_{rest} of the pyramidal neuron is expected to be variable at earlier time points.

Analyses of ChCs located at the border of layers 1 and 2 also revealed an asymmetric distribution of the dendrites that are mostly oriented towards layer 1 (Figure 2E). This finding led to the hypothesis that ChCs, similar to the apical dendrites of pyramidal neurons, may receive input from other cortical areas via axons in layer 1 and may act as circuit switches [7**]. Stimulation of layer 1 and dual recordings from both pyramidal neurons and ChCs at layer 2/3 showed that the stimulation strength necessary for activation by layer 1 inputs is significantly less for ChCs compared to pyramidal neurons. An analogous situation exists for fast-spiking interneurons and excitatory granule neurons in the hippocampus [42]. Hence, ChCs can affect pyramidal neuron responses to layer 1 input. In fact, at the stimulation strength that is sufficient to activate ChCs, pyramidal neurons were initially depolarized. However, the highest stimulation strength that activates the ChC but not the pyramidal neuron depolarized the pyramidal neuron to a value similar to E_{GABA}, leading to a shunting effect. As the layer I stimulation was increased to induce pyramidal neuron spiking, the influence of the ChC input converted from shunting to hyperpolarizing. In sum, these experiments revealed a novel top-down regulation role for the ChCs providing feed-forward inhibition onto pyramidal neurons. That said, the possibility exists that in a "quiet" circuit, multiple depolarizing ChC inputs onto a pyramidal neuron may evoke an excitatory response. This possibility can now be tested on the Nkx2.1CreERT2 line by using optogenetics to activate multiple ChCs targeting the same pyramidal neuron [43].

Finally, PV+ interneuron activity can entrain gamma frequency oscillations and contribute to their synchrony [44, 45]. The rhythmic activity of PV+ interneurons synchronizes cortical circuits by generating a narrow window for effective excitation. However, since basket cells outweigh ChCs among PV+-expressing neurons, clarification is still needed for whether ChCs have a specific role in gamma oscillations or not. Once again, Nkx2.1CreERT2 line, combined with lines that allow Cre-mediated excitation or inhibition *in vivo* by optogenetics, should be a good model system to address this question.

Chandelier cells in disease

Recent advances in mouse genetics, imaging and electrophysiology techniques have greatly advanced our efforts to understand the cortical interneuron dysfunction in neuropsychiatric disorders. Alterations in the GABAergic signaling components have been reported in the pathogenesis of these disorders such as epilepsy, schizophrenia and autism [46–48]. In particular, PV+ interneuron abnormalities are prominent [47, 49], consistent with their role in gamma oscillations that are thought to mediate or to reflect cognitive functions disrupted in these disorders [50]. In the case of ChCs, evidence exists for an association between ChC

abnormalities and schizophrenia [48, 49]. A genetic association between ChCs and schizophrenia was uncovered when the cortical interneuron-specific disruption of a candidate susceptibility gene for schizophrenia, ErbB4, decreased the number of chandelier synapses [22*]. ErbB4 is a receptor tyrosine kinase that signals via interaction with its ligand, Neuregulin, also a candidate susceptibility gene for schizophrenia [51]. Earlier studies suggested that ErbB4 signaling contributes to formation and/or stabilization of glutamatergic synapses onto PV$^+$ cortical interneurons [22*, 52–54]. Recently, analysis of a conditional knockout mouse line (ErbB4 CKO) where ErbB4 was disrupted selectively in postmitotic, MGE-derived interneurons, also showed a reduction in the excitatory synapses onto both basket and ChC interneurons [27**]. Remarkably, the ChCs, but not the basket cells, had a marked reduction of synapses onto pyramidal neurons [27**]. The same mice also had several phenotypes associated with schizophrenia, some of which include decreased cortical pyramidal neuron spine density, disrupted synchrony in gamma-range oscillations between the frontal cortex and hippocampus, and reduced prepulse inhibition. This mouse model suggests a remarkable connection between human genetics, physiology, postmortem studies of schizophrenia, and ChC function as measured in mice. However, a definitive study on ChC function at the system level and in relation to ErbB4 or putative disease genes awaits a method to selectively affect most or all cortical chandeliers, but not other interneurons.

Although these alterations in ChCs certainly affect the cortical microcircuitry, whether they could be an effect, rather than a cause, of the core pathology is still unclear. Additionally, while some of this pathology probably results from disruptions that began close to the time of symptom onset, it is also likely that symptomatic dysfunction of cortical microcircuitry evolves from abnormalities that occurred earlier during development. However, linking microcircuitry dysfunction to the disruption of their developmental trajectories has been a major challenge. To this end, generation of the Nkx2.1CreERT2 line is a major improvement to overcome this challenge. Using this line, manipulations of genes associated with neuropsychiatric disorders during development have the potential to model the cause and effect relation of ChC deficits in these disorders.

Future challenges and opportunities

Despite the considerable progress made in understanding the development and function of ChCs, a number of major questions remain. First, what is the regulation of ChC fate determination? Like other MGE-derived interneurons, the transcription factors Nkx2.1 in mitotic progenitors, and Lhx6 [55–57] and Sox6 [58, 59] in postmitotic Nkx2.1-lineage interneurons, are likely to be important. But how is the fate of these cells being established relative to other MGE-derived interneuron subtypes? The recent discovery of the spatial and temporal bias for ChC generation during late gestation in the ventral-most MGE [5*] paved the way for identifying transcriptional regulators and signaling pathways based on their enrichment in this particular spatial and temporal coordinates. These studies have the potential to identify an embryonic marker for ChCs, which can circumvent the caveat that one third of the cells that express Cre in the Nkx2.1CreERT2 line are not ChCs. On a related topic, a retroviral lineage study suggests that Somatostain and PV expressing interneurons can be generated by the same radial progenitor [60*]. This raises the question of whether

basket and chandelier interneurons related clonally and whether ChCs are generated from radial progenitors that are distinct from other MGE interneurons.

Second, how do ChCs function, *in vivo,* both at the local circuit and behavioral levels? The ability to enrich for ChC labeling via the Nkx2.1CreERT2 mouse not only allows the investigation of their postnatal development, but it also enables studying their function by expressing a) genetically encoded activity indicators, such as calcium (GCaMPs) or voltage indicators [61] b) optogenetic activators and silencers, or other proteins that alter membrane potential [62] c) selective cellular silencers or suicide mediators. Finally, genes linked to neuropsychiatric disorders, such as ErbB4, can be manipulated in ChCs by crossing the Nkx2.1CreERT2 line to the transgenic mice carrying floxed alleles of these genes. These studies will reveal which of these genes can induce disease-related endophenotypes in mice when mutated specifically in ChCs, and are, together with similar approaches targeting other cortical cell types, likely to revolutionize discovery of the etiological antecedents of neuropsychiatric disease.

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Highlights

- Chandelier cells (ChCs) have specific spatial and temporal origins.

- ChCs can depolarize or hyperpolarize the pyramidal cell based on its resting membrane potential.

- Nkx2.1CreERT2 reporter line is the first mouse line for studying a specific interneuron subtype.

- ChC-specific defects reported in interneuron-specific ErbB4 knockouts (ErbB4 CKO).

- ErbB4 CKOs have schizophrenia-like endophenotypes, providing a direct link to ChCs.
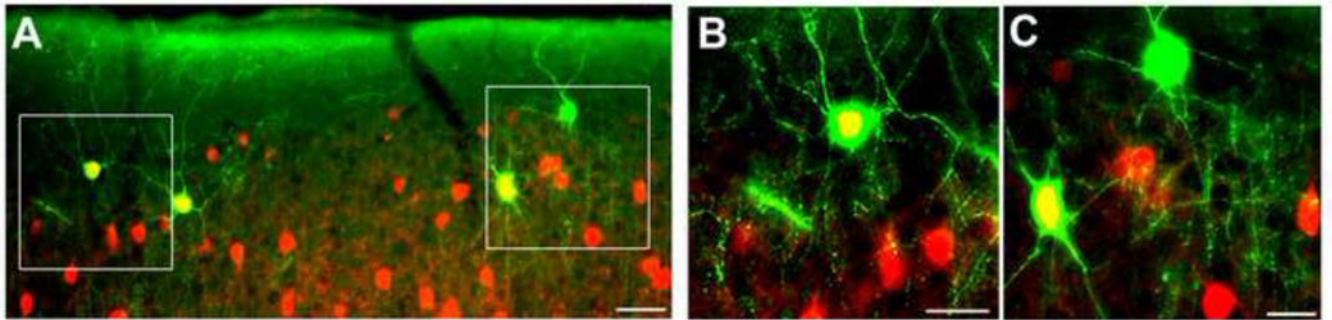
Figure 1. Variable expression of Parvalbumin in chandelier cells (ChCs)
A. Immunofluorescence staining for GFP (green) and Parvalbumin (PV; red) in the superficial layers of neocortex in an Nkx2.1-Cre reporter line [31]. **A.** In this reporter line, cortical interneurons other than ChCs are also labeled, including the PV-expressing basket cells. PV expression is not detected in all ChCs. **B.** High magnification image of the ChC expressing PV (left box in **A**). **C.** High magnification image of the ChC with no detectable PV expression (right box in **A**). Scale bars: 50μm in **A** and 25μm in **B and C**.
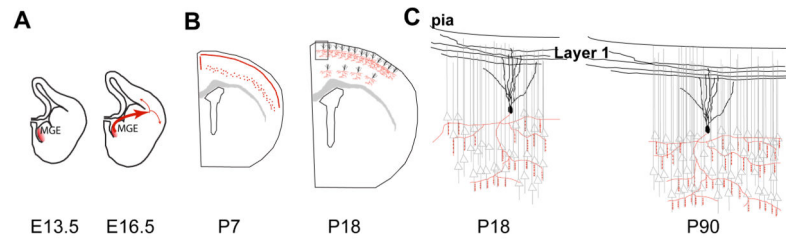
Figure 2. Origin and development of chandelier cells in mice
A, B. ChCs originate primarily from the ventral region of the Medial Ganglionic Eminence (vMGE, area in red) as early as E13.5 **(A), although** most are generated late in gestation. ChC precursors are thought to initially migrate along the periventricular region of the lateral ventricle and into the overlying cortex **(B). C, D.** Postnatal development and morphology of ChCs. At P7, immature ChCs form a dense plexus at the border of layers 2 and 1 **(C)**. Some ChCs are also detected in layer 5. By P20, the majority of immature ChCs die and their distinct dendritic (black) and axonal morphology with its cartridges (red) are formed **(D). E, F.** Morphology of ChCs during postnatal development. A significant increase in the lateral span of the ChC axonal arbor is observed with age while number of cartridges increases slightly. However, the average density of cartridges does not differ significantly between different ages. The innervation pattern of ChC axon remains similar between P18 **(E)** and P90 **(F)** with pockets of dense innervation where every pyramidal cell is targeted by ChC cartridges. Additionally, the dendrites of ChCs at the layer 2 and 1 have an asymmetric morphology and they are strongly driven by the layer 1 axons.