Interneurons: Learning on the Job

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In this issue, Wester et al. (2019) examine the obligate relationship between cortical interneurons and pyramidal neurons. By genetically converting superficial IT pyramidal cells into PT-like deep-layer pyramidal cells, they alter the position, connectivity, and gene expression within CGE-derived interneurons.

During development, neural networks composed of excitatory and inhibitory neurons must grow from a state of zero connectivity to one characterized by precise circuit connections within the adult brain. Considerable evidence suggests that, during cortical development, pyramidal cells (PCs) and interneurons (INs) intimately interact to establish canonical circuit motifs. Classical work on birthdating by Dick Sidman established that the cortex is built from the inside out, with the deep-layer PCs being born early and the superficial PCs being born late (Angeline and Sidman, 1961). Work from many labs has shown that IN populations follow a similar pattern. Cortical GABAergic INs arising from the ventral telencephalon, namely the medial and caudal ganglionic eminences (MGE and CGE, respectively), migrate tangentially to reach the cortex with a tightly defined temporal cadence.

MGE and CGE produce different types of INs at different times. MGE-derived parvalbumin- (PV) and somatostatin- (SST) expressing IN populations are born early and preferentially occupy deep cortical layers, while CGE-derived vasoactive-intestinal-peptide-expressing (VIP) and neuroglialform populations are born later.

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and come to occupy the superficial layers of the cortex. The correlation between the birthdate and final location of excitatory and inhibitory neurons suggests a temporal matching by which cells with similar birthdates are predisposed to become physically associated and synaptically connect (Batista-Brito and Fishell, 2009). But is this correlation causal? How does time of origin and identity of excitatory-neuronal-type influence the fate, location, and connectivity of their interneuronal counterparts? Pioneering work by the Ariotta laboratory tested these questions using an ingenious approach born of their discovery that the early-born/deep-layer corticofugal (so called PT, pyramidal tract) pyramidal populations rely on their expression of the zinc-finger transcription factor Fezf2 (Molyneaux et al., 2005). By combining both loss- and gain-of-function experiments (Lodato et al., 2011; Ye et al., 2015), they demonstrated that Fezf2 was both necessary and sufficient to reprogram pyramidal-cell fates. Loss of Fezf2 leads to the conversion of corticofugal (PT) PCs into late-born/callosal (or IT, intertelinecephalic) PCs, while Fezf2 gain of function had the opposite effect. This allowed them to ask the non-cell-autonomous question of whether early-born, MGE-derived INs redistributed themselves in response to changes in pyramidal-cell identity. The Ariotta laboratory showed that PV and SST IN-layer distribution is altered when the position of PT PCs is shifted (Lodato et al., 2011; Ye et al., 2015). Most strikingly, even when Fezf2 PT cells are ectopically positioned in the white matter, MGE-derived INs follow suit and cluster around them. Furthermore, they showed that PCs control the afferent inputs of PV-INs into pyramidal neurons in a non-cell-autonomous manner (Ye et al., 2015).

In this issue of Neuron, the McBain laboratory completes and extends the picture by doing the complementary experiment using Satb2 loss of function (Wester et al., 2019). Previous work from the McConnell and Tarabykin laboratories have shown that loss of Satb2 gene function results in a complementary transformation to that seen in Fezf2 mutants (Leone et al., 2008). In Satb2 mutants, IT pyramidal neurons transform their identity into their PT brethren. By using this strategy, Wester et al., 2019 were able to ask whether CGE-derived VIP and neurogliiform IN populations adjust their position, connectivity, and gene expression if the late-born IT pyramidal neurons are altered. The answer from their work turns out to be a clear yes! Using an elegant set of experiments that include genetics, careful physiology, optogenetics, and single-cell RNA-seq analysis, the authors were able to show that changing the fate of neurons from IT- to PT-like PCs leads to non-autonomous changes in CGE-derived INs. While in Satb2 mutants, CGE-derived INs still conserve their overall class identity, many ectopically express CCK. They also become mislocalized, receive reduced connectivity from trans-fated PCs, and alter their transcription profiles for synaptic proteins and cell-adhesion molecules. Specifically, CGE-INs in Satb2 mutants receive reduced connections from trans-fated PT PCs relative to the connections they normally receive from IT neurons (Figure 1). This suggests that, similar to what happens to MGE-derived INs, CGE-INs are receptive to changes in their dance partners. Wester et al. dive deeper into their analysis by showing differential effects on VIP versus reelin-expressing CGE-INs in the Satb2 mutant background. Specifically, while VIP-INs are shifted to deeper layers, reelin-expressing neurogliiform neurons are reduced in number. Interestingly, their data indicates that input onto VIP-INs is particularly affected in mutants. Once again, this suggests that different IN types are differentially receptive to the signals sent by their excitatory neuron partners. The current study is conducted in the visual cortex, but it stops short of investigating in vivo functional consequences to visual processing. Given recent evidence that developmental disruptions to VIP-IN afferents affect both cortical state and processing of visual information (Batista-Brito et al., 2017), it would be interesting to investigate the functional implications of the observed changes in the location and connectivity of CGE-INs further.

In helping to complete our understanding of the obligate relationship between INs and PCs, the McBain paper raises additional questions. For instance, would Satb1 gain of function result in CGE-INs being drawn hither by ectopic IT pyramidal neurons? Similarly, given their results, it seems likely that there is further nuance in the relationship between INs and pyramidal neurons. Recent work shows that both PT and IT pyramidal neurons come in an abundance of flavors (Tasic et al., 2018), and these types vary across cortical regions. Furthermore, CGE-INs are also much more diverse than simply VIP- and reelin-expressing types (Tasic et al., 2018). This raises the question as to whether there are more fine-grain relationships in precisely which IN types synapse on different pyramidal types. Given the differences in pyramidal neurons in different
Mitochondria Re-set Epilepsy

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Neuronal networks maintain stable activity around a given set point, an enigmatic variable in homeostatic systems. In this issue of Neuron, Styr et al. (2019) now show that set points are regulated by mitochondria and propose a potential strategy to treat refractory forms of epilepsy.

Neurons in the central nervous system are extensively interconnected to form networks. These neuronal networks have to master complex tasks: they need to be stable to store memories but also have to be plastic to allow for learning and the formation of new memories. Past research suggests that stable neuronal activity is accomplished by a homeostatic control system that regulates the properties of neuronal networks, e.g., the mean firing rate (Davis, 2013). Deviations of network properties from the norm, the set point, are monitored by sensors. Homeostatic compensatory mechanisms return the network to its original state (Figure 1). Failure of such control mechanisms will ultimately result in circuit instability, and this characterizes neurological diseases, including epilepsy (Swann and Rho, 2014). Thus, understanding how set points are regulated by mitochondria is profound and will advance our understanding of how the cerebral cortex is assembled.

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