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“Genetic dissection of cortical circuit organization and assembly - chandeliers light up the path”

Abstract

Despite its immense complexity and sophisticated operations that underlie mental functioning, the fundamental plan for the cellular organization of cerebral cortex is encoded in the genome, which directs cascades of developmental programs in each fetus. Therefore genetic approaches that engage intrinsic biological mechanisms have the potential to penetrate cortical complexity and achieve appropriate cellular and molecular specificity, and analyses of circuits assembly will facilitate deciphering their functional organization. I suggest that, similar to “genetic screens” that so powerfully identified genes and principles underlying embryonic patterning, systematic genetic targeting of cell types and their progenitors, basic units of circuit organization and construction, will not only provide experimental entry points but also establish a paradigm that coherently link molecular, developmental, and systems studies of cortical circuits. I will summarize our progress on the genetic targeting of GABAergic interneurons, an effort that has facilitated reliable identification and manipulation of cell types and enabled comprehensive analysis from cell specification, connectivity, to their functional role in networks. The chandelier cell (ChC) is arguably the most distinctive class of interneurons that may shape cortical ensembles by exerting decisive control over pyramidal cell firing. I will present results on the stringent genetic mechanisms that specify ChC identity and their laminar deployment, evidence of a massive postnatal pruning process that likely shapes their circuit integration, and on-going studies on their local and long-range synaptic connectivity. I will end with a highlight of our recent project on systematic targeting of pyramidal neuron subtypes, cellular hardware that constitute the myriad of cortical processing streams and output channels. With increasing experimental access to multiple build blocks that make up the two cardinal cellular ingredients of the cortex, we are poised to explore how stereotyped circuit motifs are assembled and organized, how they are further molded by neural activity, and how their developmental trajectory might be altered in models of mental disorders.