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POST-TRANSCRIPTIONAL REGULATORY ELEMENTS AND SPATIOTEMPORAL SPECIFICATION OF NEOCORTICAL STEM CELLS AND PROJECTION NEURONS

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Abstract—The mature neocortex is a unique six-layered mammalian brain region. It is composed of morphologically and functionally distinct subpopulations of primary projection neurons that form complex circuits across the central nervous system. The precisely-timed generation of projection neurons from neural stem cells governs their differentiation, postmitotic specification, and signaling, and is critical for cognitive and sensorimotor ability. Developmental perturbations to the birthdate, location, and connectivity of neocortical neurons are observed in neurological and psychiatric disorders. These facts are highlighting the importance of the precise spatiotemporal development of the neocortex regulated by intricate transcriptional, but also complex post-transcriptional events. Indeed, mRNA transcripts undergo many post-transcriptional regulatory steps before the production of functional proteins, which specify neocortical neural stem cells and subpopulations of neocortical neurons. Therefore, particular attention is paid to the differential post-transcriptional regulation of key transcripts by RNA-binding proteins, including splicing, localization, stability, and translation. We also present a transcriptome screen of candidate molecules associated with post-transcriptional mRNA processing that are differentially expressed at key developmental time points across neocortical prenatal neurogenesis.

Key words: neocortex, projection pyramidal neuron, neural stem cell, post-transcriptional processing, translation, RNA-binding protein.

Contents

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Abbreviations: BAC, Bacterial Artificial Chromosomes; BLBP, brain lipid-binding protein; CLIP, crosslinking-IP; coup-TF, chicken ovalbumin upstream promoter transcription factor; CP, cortical plate; CPNs, callosal projection neurons; CSMNs, corticospinal motor neurons; Ctip2, coup-TF-interacting protein 2; Emx2, Empty spiracles homolog 2; FACS, fluorescent activated cell sorting; Fezf2, family zinc finger 2; FMRP, Fragile X mental retardation protein; Fox, Forkhead box; FXS, Fragile X syndrome; GFP, green fluorescent protein; hiPSCs, human induced pluripotent stem cells; HMGA, High Mobility Group A; Hu, Human Antigen; ICN, intracellular notch receptor domain; INM, interkinetic nuclear migration; IPC, intermediate progenitor cell; IZ, intermediate zone; KH, K homology; KO, knockout; LINE1 or L1, Long interspersed element-1; MTH, maternal thyroid hormone; NECs, neuroepithelial cells; NSCs, neural stem cells; oRG, outer radial glia; oSVZ, outer subventricular zone; Pax6, Paired box 6; PD, Parkinson's disease; PFC, prefrontal neocortex; PTB, polypyrimidine-tract-binding; Ptbp2, PTB protein 2; qRT-PCR, quantitative reverse transcription polymerase chain reaction; RBD, RNA-binding domain; RBP, RNA-binding protein; RG, radial glia; RNP, ribonucleoprotein; RRM, RNA-recognition motif; Satb2, sequence-binding protein 2; SNPs, short neural precursors; SVZ, subventricular zone; TBR2, T-brain gene-2; TFs, transcription factors; TRAP, transcripts with cell types; VZ, ventricular zone; ZBP1, Zipcode-Binding Protein 1.

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INTRODUCTION

The adult neocortex is the central circuit of consciousness, complex cognition, language and the coordination of voluntary motor activity in mammals (Weiler et al., 2008; Lui et al., 2011). Throughout mammalian evolution, the neocortex is the brain region that has exhibited the greatest expansion in mass relative to body weight (i.e., encephalization) (Shultz and Dunbar, 2010). In this way, the neocortex can be thought of as the evolutionary foundation for cognitive advances, including the uniquely human ''theory of mind'' and language. However, with these advances, human-specific ailments such as schizophrenia, autism spectrum disorders, Parkinson's disease, Alzheimer's disease, and Amyotrophic Lateral Sclerosis have also developed (Garey, 2010; Wegiel et al., 2010; Morgen et al., 2011; Ozdinler et al., 2011; Rapoport and Nelson, 2011; Yang et al., 2011). Therefore, understanding the molecular and cellular mechanisms underlying neocortical formation, maintenance, and dysfunction is critical not only for furthering basic neuroscience knowledge of brain development and architecture but also for better understanding neuropsychiatric disorders. In addition, these efforts may improve current therapeutic approaches to these neocortical ailments.

Neocortical function relies on precise interactions among an array of cell types, which can be broadly divided into epithelial cells, glia and neurons. Neocortical neurons belong to two main classes: interneurons and primary projection neurons. Interneurons are inhibitory GABAergic cells that have short processes forming local circuits. Interneurons migrate tangentially into the developing neocortex from the lateral, medial and caudal ganglionic eminences and can be delineated from projection neurons based on their morphology and expression of markers such as parvalbumin, somatostatin, vasoactive intestinal peptide, neuropeptide Y and cholecystokinin (Corbin et al., 2001; Tanaka and Nakajima, 2012; DeFelipe et al., 2013; van den Berghe et al., 2013).

In contrast, primary projection neurons are excitatory glutamatergic cells which carry out the mainstay of the signaling in the neocortex and extend processes over long distances. Importantly, of all of the neurons that populate the neocortex, 75–85% are excitatory projection neurons. The earliest systematic investigation of the neocortex by Santiago Ramón y Cajal revealed that these neurons have characteristic morphological features, including a pyramidal-shaped cell body, many basal dendritic processes, a single apical dendrite oriented toward the pial surface of the neocortex that gives rise to a variable number of oblique branches, and a single axon that usually stems from the base of the cell body or proximal parts of the basal dendrites (Ramón y Cajal et al., 1988). Later seminal studies demonstrated histological differences in the density and size of neocortical cell bodies, which define what are now recognized as six distinct layers (Caviness, 1975; Ramón y Cajal et al., 1988; Brodmann, 2006; Hevner, 2006). The target of each projection neuron is related to its position within the six neocortical layers (I–VI) (Fig. 1). Lower-layer (V–VI) neurons mainly project subcortically, with axons often terminating in the thalamus, brain stem and spinal cord, although numerous collaterals for intermediate targets also exist (Floeter and Jones, 1985; Zhang and Deschenes, 1997). Upper-layer (II–IV) neurons exclusively project intracortically, either within the ipsilateral hemisphere or reaching the contralateral hemisphere via the corpus callosum.

The delineation of the neocortex into six layers arose from neuroanatomical and electrophysiological evidence. More recent work, initially in rodents, has defined subgroups of neurons based on of the expression of transcription factors (TFs) (Molyneaux et al., 2007; Leone et al., 2008; Kwan et al., 2012b; Kriegstein and Alvarez-Buylla, 2009). For example, subcortically projecting neurons selectively express Ctip2, Fezf2, and Tle4, whereas intracortically projecting neurons selectively express Cdp/Cux1 and Satb2 for full names of genes see abbreviation list (Hevner et al., 2006; Molyneaux et al., 2007). These findings were recently extended to human and non-human primates, with gestational and postnatal investigations showing that the specificity of TF expression in neocortical projection neurons is at least partially conserved across species. As particular TFs correspond to differences in dendritic complexity and axonal projections and, hence, the function of distinct neuronal subpopulations (Molyneaux et al., 2007; Leone et al., 2008; Kwan et al., 2012b), there are continuing efforts to identify additional markers of neuron subtypes. Moreover, ongoing studies continue to elucidate the molecular and cellular mechanisms underlying TF specification of neocortical neuron subpopulations.

The remaining text of this ForeFront Review will be dedicated to reviewing the current understanding of neocortical development with a focus on neural stem cells, projection neurons, the use of state-of-the-art transcriptome analyses and the emerging field of the role of post-transcriptional processing steps.

NEURAL STEM CELLS IN THE DEVELOPING NEOCORTEX

All functionally-distinct subgroups of neocortical projection neurons are generated prenatally through a highly-orchestrated set of developmental processes. Projection neurons emerge from a pool of neural stem cell progenitors called radial glia (RG) that divide at the ventricular zone (VZ) surface (Fig. 2). Lower-layer, subcortically projecting neurons are born first, followed by upper-layer, intracortically projecting neurons. The laminar organization of newborn cells results in the arrangement of distinct columns of functionally related neurons spanning different layers (Mountcastle et al., 1957; Hubel and Wiesel, 1962). According to the radial unit hypothesis (Rakic, 1988), the cytoarchitecture of these columns is the outcome of neuroblasts migrating along basal RG processes from the VZ of the prenatal neocortex. This hypothesis was later confirmed using retroviral green fluorescent protein (GFP) transfection, allowing the tracking of daughter cells from dividing RG (Kornack and Rakic, 1995). Thus, the organization of