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Review

Cellular and molecular introduction to brain development

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ABSTRACT

Advances in the study of brain development over the last decades, especially recent findings regarding the evolutionary expansion of the human neocortex, and large-scale analyses of the proteome/transcriptome in the human brain, have offered novel insights into the molecular mechanisms guiding neural maturation, and the pathophysiology of multiple forms of neurological disorders. As a preamble to reviews of this issue, we provide an overview of the cellular, molecular and genetic bases of brain development with an emphasis on the major mechanisms associated with landmarks of normal neural development in the embryonic stage and early postnatal life, including neural stem/progenitor cell proliferation, cortical neuronal migration, evolution and folding of the cerebral cortex, synaptogenesis and neural circuit development, gliogenesis and myelination. We will only briefly depict developmental disorders that result from perturbations of these cellular or molecular mechanisms, and the most common perinatal brain injuries that could disturb normal brain development.

Contents

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1. Introduction

Human brain development starts with neurulation from the ectoderm of the embryo and it takes, on average, 20 to 25 years to mature. This protracted process is presented as both physical and experience-based maturation. Building this most complex and highly organized organ involves the generation of a wide variety of specialized neural and non-neural cell types that must be produced in the correct numbers, at appropriate locations and with the right timing. Additionally, accurate connections between neurons and efficient communication between distinct cell populations are crucial for the brain to exert centralized control for behaviour, perception and higher cognitive function.

Brain develops in an intricately orchestrated sequence of stages. Neural tube, the origin of the entire central nervous system (CNS), is formed at approximately 3–4 weeks of gestation and followed by massive cell proliferation, migration and brain expansion in size, complexity and surface area (gyrification). Neurogenesis and formation of the general architecture of brain regions are largely complete at birth, while maturation of the two principal glial cells (astrocytes and oligodendrocytes), synaptogenesis and synapse pruning, and myelination represent postnatal brain growth (Giedd, 1999). Furthermore, brain constantly changes at the level of connectivity throughout the life span with environmental influences. At the cellular level, both neurons and astrocytes/oligodendrocytes are derived from the common multipotent neuroepithelial cells that line the cerebral ventricles (Davis and Temple, 1994). It is now known that neurogenesis precedes gliogenesis, which is the results of an inherent, exquisitely timed mechanism regulated by complex interactions between intrinsic factors (for example, gene epigenetic modifications) and extrinsic cues (secreted or contact-mediated factors) (Rowitch and Kriegstein, 2010). Adequate neurogenesis and timely switch of developmental program of progenitor domains to gliogenesis are critical for proper neural circuit formation and normal brain function. Disruptions in any of the mechanisms may lead to disorganization and eventually, dysfunction of the CNS.

As a preamble to the reviews of this issue, we will provide an overview of the processes that orchestrate the successive steps of normal cortical brain development, including progenitor division and production in coordination with appropriate layer neuron production, neuron migration and maturation, synaptogenesis and at last gliogenesis. We will only briefly discuss how alterations of such mechanisms can be related to some of the brain development disorders. Neurodevelopmental diseases will be reviewed in detail in the other articles of this issue.

2. Morphogenesis of the cerebral cortex

The cerebral cortex, also called the neocortex in mammals to distinguish it from the more ancient paleo-cortex and archicortex, differentiates in the dorsal telencephalon, the most anterior region of the embryonic brain (Rubenstein and Beachy, 1998). The neocortex is the seat of the higher cognitive functions and has a very complex cytoarchitecture, including projection neurons born in the same area and interneurons originating in ventral telencephalic regions (Molyneaux et al., 2007). Cortical projection neurons are organized into six layers that constitute a laminar structure called the cortical plate. Layer neurons are distinguished by the expression of specific combinations of molecular markers and distinct axonal projections. Neurons occupying the deep layers (V and VI) are predominantly composed of corticofugal neurons that project to subcortical areas, such as the thalamus, brain stem and spinal cord. In contrast, the superficial layers (IV to II) are composed of intracortical neurons that project locally or to the contralateral hemisphere (Greig et al., 2013). All these neurons are excitatory glutamatergic neurons and derive from the germinative zones of the developing neocortex: the ventricular zone (VZ), which lines the ventricle, and the subventricular zone (SVZ), which develops from the VZ and is juxtaposed to its basal surface (Angevine and Sidman, 1961; Anthony et al., 2004; Molyneaux et al., 2007; Rakic, 2009). The first phase of neurogenesis occurs in the VZ and generates pioneer neurons, including Cajal–Retzius cells that populate the preplate (Meyer et al., 1998). A second phase, resulting in a much more important output of neurons, principally occurs in the SVZ and gives rise to projection neurons. These primary neurons split the pre-plate into the marginal zone or layer I, and the subplate (Super et al., 1998; Olson, 2014), an intermediary structure in which neurons receive important informative cues during their migration to their destination layer (Molnar and Clowry, 2012; Molyneaux et al., 2007). Sequentially arising projection neurons migrate to the cortical plate in an inside-out manner, with the youngest upper-layer neurons migrating over deeper neurons born earlier (Molyneaux et al., 2007; Caviness et al., 2008). While the laminar structure of the cortical plate has been relatively well conserved, its size has expanded remarkably with respect to both volume and surface, in particular in humans and other primates, along with the evolutionary complexification of cognitive function. Because the ventricle has not increased to a matching extent, this expansion imposes the folding of the cortical plate and the formation of convolutions or gyri (Fietz et al., 2012; Borrell and Gotz, 2014; Sun and Hevner, 2014). Many genetic and functional studies in animal models, especially in the mouse, have provided valuable insights into the cellular and molecular mechanisms that underlie the complex development of the cerebral cortex (Hansen et al., 2010; Fietz et al., 2012; Betizeau et al., 2013; Gao et al., 2014; Florio et al., 2015). Nonetheless, understanding how these mechanisms have evolved and adapted to allow this increase in cortical size remains a major challenge in neurodevelopmental biology.

3. Neurogenic phases in the developing neocortex

3.1. Neurogenic phases and transitions in progenitor subtypes

In the beginning, the neural tube corresponds to a neuroepithelium, made up of highly polarized cells called neuroepithelial cells (NECs) (Lui et al., 2011; Paridaen et al., 2013). In the developing cortex, NECs extend long process throughout the entire cortical wall. Their apical and basal end feet are attached at the ventricular surface and the pial lamina, respectively (Lui et al., 2011; Borrell and Gotz, 2014; Florio and Huttner, 2014). Cadherins and catenins form adherens junctions that mediate cell–cell adhesion (Elias et al., 2007). NECs divide symmetrically to self-renew and to generate an adequate pool of founder progenitors (Fig. 1b). This initial proliferative phase affects both lateral extension and radial extension and has a significant impact on the final surface area and thickness of the neocortex (Florio and Huttner, 2014; Sun and Hevner, 2014; Dehay et al., 2015).

At the onset of neurogenesis, NECs turn into apical radial glial cells (aRGCs) (Gotz and Huttner, 2005; Kriegstein et al., 2006). aRGCs maintain neuroepithelial features with adherens junctions