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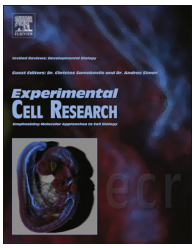

Review Article

Cell fate control in the developing central nervous system

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ABSTRACT

The principal neural cell types forming the mature central nervous system (CNS) are now understood to be diverse. This cellular subtype diversity originates to a large extent from the specification of the earlier proliferating progenitor populations during development. Here, we review the processes governing the differentiation of a common neuroepithelial cell progenitor pool into mature neurons, astrocytes, oligodendrocytes, ependymal cells and adult stem cells. We focus on studies performed in mice and involving two distinct CNS structures: the spinal cord and the cerebral cortex. Understanding the origin, specification and developmental regulators of neural cells will ultimately impact comprehension and treatments of neurological disorders and diseases.

Contents

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Introduction

The structure of the central nervous system (CNS) is highly complex, a reflection of its importance and diverse functions. In vertebrates, the CNS is derived from the neuroepithelial cells (NECs) of the neural tube. NECs are relatively homogenous during the earliest phase of CNS development, and they undergo massive proliferation to expand their population prior to cell fate specification. During patterning of the neural plate and neural tube, morphogens such as fibroblast growth factors (FGFs), retinoic acid (RA), Sonic hedgehog (Shh) and bone morphogenetic proteins (BMPs) are secreted in distinct spatial patterns. These morphogens are responsible for patterning the dorsal–ventral, anterior–posterior and medial–lateral axes of the developing neural tube, thus driving the initial specification of the main CNS regions: the forebrain, midbrain, hindbrain and spinal cord [1]. NECs begin losing some of their epithelial properties as they mature into regionally-specified CNS progenitors. One major process occurring during this NEC-to-progenitor transition is a change of proliferation mode, from symmetric to asymmetric division. The Notch signaling pathway is a central regulator of this process, repressing proneuronal gene expression while promoting the progenitor state and proliferation. During asymmetric division of progenitors, Notch is unequally distributed to the daughter cells where high Notch signaling in one daughter cell maintains self-renewal and low Notch signaling in the second daughter cell allows neuronal differentiation [2]. Here, we will provide an overview of the main processes allowing progenitor cells to generate the diversity of differentiated CNS neural cell types, focusing mainly on lessons learned from studies of the developing mouse spinal cord and cerebral cortex. Given the vast literature on these topics, and the present space limitations, it is unfortunately inevitable that many important manuscripts from our colleagues could not be referenced here.

Neurons

The spinal cord comprises the caudal region of the CNS, and is responsible for conveying motor and sensory information between the brain and the periphery, as well as for elaborating certain reflexes. During early development, NEC proliferation increases the dorso-ventral and rostro-caudal dimensions of the spinal cord. Progenitor cells are located in the ventricular zone (VZ) surrounding the nascent central canal, and they are subject to a gradient of ventrally and dorsally expressed morphogens that will dictate their fate as post-mitotic neurons, including motor, sensory and interneurons [3]. The ventral part of the spinal cord is under the influence of Shh signaling. Shh is produced by two sources, the notochord and the floor plate (FP), and both its secretion and diffusion are highly regulated [4]. Diverse transcription factors are activated or repressed by Shh, as a function of its concentration gradient, giving rise to spatially segregated progenitor domains: FP (Foxa2), p3 (Nkx 2.2), pMN (Olig2), p2 (Nkx6.1 and Irx3), p1 (Nkx6.2) and p0 (Dbx1), where the listed genes encode transcription factors that specify each domain [4]. Each progenitor domain will generate distinct neuronal subtypes: the pMN domain gives rise to motor neurons while p0–p3 domains generate specific subtypes of ventral interneurons [5]. A recent study showed that the two sources of Shh can play distinct roles in regulating progenitor specification and differentiation where FP-derived Shh is specifically essential for the generation of motor neurons at a time point when the regression of the notochord is already complete at all axial levels [6].

In the dorsal spinal cord, neurogenesis is essentially regulated by BMP signaling. The roof plate (RP) synthesizes BMP proteins which are secreted along the dorsal–ventral axis of the developing spinal cord. The effects of BMP signaling are dictated by the receptors expressed by the progenitor cells: BMPR-IA promotes proliferation while BMPR-IB induces differentiation [7]. The BMP gradient also leads to the formation of specific progenitor domains giving rise to six classes of postmitotic dorsal neurons between E10 and 12.5 [5]. Moreover, Wnt proteins are downstream targets of BMP signaling and their graded expression further stimulates the proliferation of dorsal progenitors [8]. The final localization of the mature neurons is not strictly limited to their domain of origin, as it was shown that dorsally generated $Dmrt2^{+}$ neurons migrate to the p0 ventral domain [9].

In the cerebral cortex, neuronal diversity is achieved through different strategies. The mature cerebral cortex is composed of six neuronal layers where subcortical regions of the cortex are key features of mammalian evolution regulating higher sensory, motor, emotional and cognitive functions. During embryogenesis, NECs in the dorsal telencephalon symmetrically divide until E9–E10. They then become radial glial cells (RGCs) with glial cell features and radial processes extending from the pial surface to the lateral ventricle. RGCs are connected to each other by adherence junctions forming the VZ [10]. RGCs can divide both symmetrically to expand their population and asymmetrically to generate one daughter RGC and one non-RGC daughter cell, with 10–20% of RGCs directly generating neurons. Most of the non-RGC daughter cells are known as intermediate progenitor cells (IPCs), which can undergo a few rounds of division to expand their population or directly generate two neurons. Over the course of cortical neurogenesis, IPCs migrate away from the VZ and form a new germinal layer, the subventricular zone (SVZ) [11].

The mature cerebral cortex is comprised of six layers and two major types of neurons: excitatory projection neurons (pyramidal neurons) and inhibitory interneurons. All cortical pyramidal neurons are derived from RGCs in the dorsal telencephalon VZ and IPCs in the SVZ. The first pyramidal neurons migrate to the preplate and form the nascent cortical plate, which further develops into layers II to VI. Birthdating experiments have shown that pyramidal neurons are sequentially generated and migrate to the different layers in an inside-first, outside-last manner. An important number of studies have identified several neurogenic transcription factors regulating neuronal survival, migration and layer specification, as previously reviewed in detail [12,13]. Unlike pyramidal neurons, inhibitory interneurons derive from RGCs in the medial and caudal ganglionic eminences (GE) of the ventral telencephalon. Following cell cycle exit, these interneurons migrate first tangentially to reach the dorsal telencephalon and then radially within the different cortical layers starting around E15. The laminar distribution and subtypes of interneurons depend on their gene expression, origin within the GE and birthdate [14]. Moreover, it was recently shown that subtypes of pyramidal neurons extrinsically influence the fate of interneurons by regulating their laminar fate and circuitry [15].

The six layers of the cerebral cortex consist of different subtypes of pyramidal neurons with distinct projections, functions and