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Review

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Epigenetics: major regulators of embryonic neurogenesis

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Abstract Mammalian cortical development is a dynamically and strictly regulated process orchestrated by extracellular signals and intracellular mechanisms. Recent studies show that epigenetic regulation serves as, at least in part, interfaces between genes and the environment, and also provides insight into the molecular and cellular bases of early embryonic cortical development. It is becoming increasingly clear that epigenetic regulation of cortical development occurs at multiple levels and that comprehensive knowledge of this complex regulatory landscape is essential to delineating embryonic neurogenesis.

Keywords Neural stem cell · Neurogenesis · Epigenetic · Brain development · Neuron

1 Introduction

Epigenetic is typically defined as heritable alterations in gene expression that are not due to changes in DNA sequence. With the rapid advances in epigenetics, epigenetic processes have mainly focused on three molecular bases: DNA, RNA and histones [1, 2]. Major epigenetic mechanisms can involve modifications to DNA, RNA, histone and regulatory noncoding RNAs [3–9]. Spatial and temporal heterogeneity of gene expression is crucial for the cerebral cortex development and for generating and maintaining individual-specific cortical networks, which is owing to epigenetic processes [10]. More specifically, the development of cerebral cortex is epigenetic landscape [1, 11]. Therefore, the flexibility of certain epigenetic marks between differentiated cells and their progenitor cells is tightly regulated. Accumulating evidence has outlined a framework for delineating neocortical neurogenesis and of which many epigenetic regulatory mechanisms have been shown to play critical roles in the mammalian cortical development [12], as shown in Fig. 1.

This review summarizes current knowledge of mammalian cortical development, with a particular focus on the epigenetic regulatory landscape that orchestrates neural progenitor cells (NPCs) fate decisions, as well as proper morphology of projection neuron. Finally, we summarize how the dynamics of chromatin remodeling play a role in lineage restriction and commitment.

2 Embryonic neurogenesis

The neocortical projection neurons are excitatory and are generated by neural progenitors in the embryonic cortical ventricular zone (VZ), beginning in mice at approximately E11.5 (embryonic day 11.5) and continuing through subsequent cortical development [13–15]. Neural progenitor cells, also known as radial glia cells (RGCs), can divide both symmetrically to self-renew and asymmetrically to generate intermediate progenitor cells (IPCs) or neurons [14, 16]. IPCs subsequently undergo transit-amplifying divisions to establish the subventricular zone (SVZ) and

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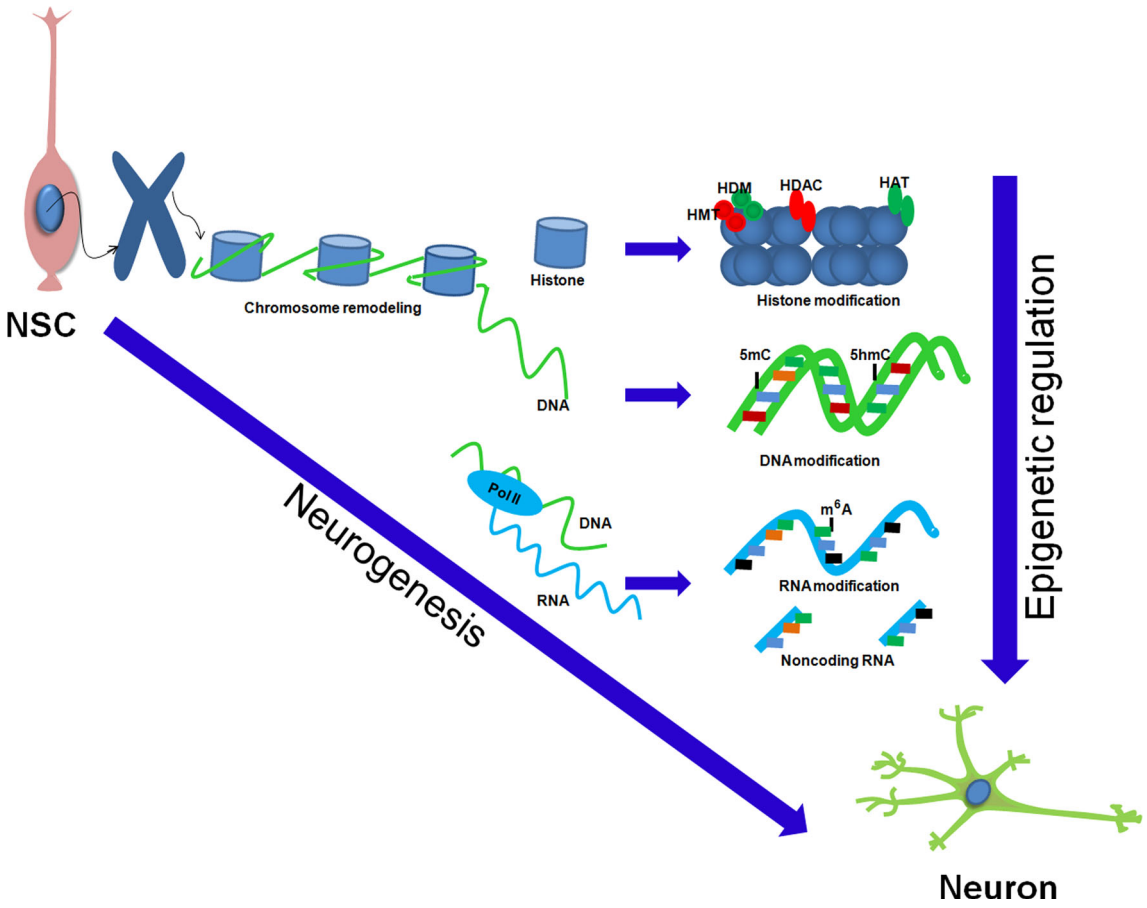

Fig. 1 Major epigenetic mechanisms of neurogenesis include chromatin remodeling via dynamic modifications of DNA and histones, and dynamic mRNA modifications and noncoding RNAs, all of which orchestrate neurogenesis by spatiotemporal epigenetic control of gene expression

increase neuronal production indirectly [16, 17]. These postmitotic neurons migrate radially away from their birthplace to populate progressively within the cortical plate [18, 19]. Importantly, the consecutive migration of distinct projection neurons leads to the formation of cortical layers in an "inside-out" manner [20]. All in all, neocortical development involves many complex time-dependent processes which entail the proliferation and fate determination of NPCs, and subsequent positioning, maturation and functional integration of newborn neuron.

3 The role of embryonic neurogenesis

During the cortical development, proper neurogenesis is critical for brain organization. Any disturbance of neurogenesis is associated with brain malformation or neuropsychiatric disorders, including schizophrenia, autism, depression and epilepsy [21–28]. Further, abnormal embryonic neurogenesis caused by dysfunction of genes may affect the postnatal life [21–26, 29]. Unlike adult neurogenesis regulated by their microenvironment, maternal effecters such as alcohol, lipopolysaccharide (LPS) and IL-6 primarily contribute to embryonic neurogenesis because of the asynchronous development of astrocytes [10, 30–32].

In addition, symmetric mitotic division of NPCs plays an important role in self-renewing of progenitors to maintain the NPC pool. Disruption of the symmetric division can lead to the depletion of the pool of NPCs during embryonic brain development, the subsequent reduction in neuronal generation and, in turn, decreased brain size characterized by microcephaly. Various gene mutations have been proposed recently to cause microcephaly such as *ZNF335*, *Dicer*, *WDR62*, *MCPH1*, *KAT2A* and *Trrap* [33–39]. It is worth noting that miRNAs and histone modifications are crucial for maintaining the size of the NPC pool [34, 37–41]. On the other side, megalencephaly and gyrencephaly are caused by brain overgrowth because of expansion of the IPCs pool. Recent progresses have shed light on the molecular mechanisms underlying the cortical growth and folding. Interestingly, the PI3K–AKT pathway, cell cycle regulators, *PTEN*