Neuroscience 253 (2013) 256–273

NEUROSCIENCE FOREFRONT REVIEW

PRONEURAL GENES IN NEOCORTICAL DEVELOPMENT

G. WILKINSON, D. DENNIS AND C. SCHUURMANS *

Hotchkiss Brain Institute, Alberta Children's Hospital Research Institute, University of Calgary, Calgary, Alberta, Canada

Abstract—Neurons, astrocytes and oligodendrocytes arise from CNS progenitor cells at defined times and locations during development, with transcription factors serving as key determinants of these different neural cell fates. An emerging theme is that the transcription factors that specify CNS cell fates function in a context-dependent manner, regulated by post-translational modifications and epigenetic alterations that partition the genome (and hence target genes) into active or silent domains. Here we profile the critical roles of the proneural genes, which encode basic-helix–loop–helix (bHLH) transcription factors, in specifying neural cell identities in the developing neocortex. In particular, we focus on the proneural genes *Neurogenin 1* (*Neurog1*), *Neurog2* and *Achaete scute-like 1* (*Ascl1*), which are each expressed in a distinct fashion in the progenitor cell pools that give rise to all of the neuronal and glial cell types of the mature neocortex. Notably, while the basic functions of these proneural genes have been elucidated, it is becoming increasingly evident that tight regulatory controls dictate when, where and how they function. Current efforts to better understand how proneural gene function is regulated will not only improve our understanding of neocortical development, but are also critical to the future development of regenerative therapies for the treatment of neuronal degeneration or disease.

Key words: proneural genes, basic-helix–loop–helix transcription factors, neocortex, Neurog1, Neurog2, Ascl1, GABAergic and glutamatergic neuronal fates, astrocyte and oligodendrocyte cell fates.

Contents

GENERAL INTRODUCTION

A short primer on neocortical development

During fetal and early postnatal development, the human brain produces 250,000 new cells per minute, giving rise to 160 billion neurons and glia, all with precise cellular phenotypes (Azevedo et al., 2009). Deciphering how such striking diversity is created is a major challenge in developmental biology. Here we review the roles of the proneural genes in controlling neural cell fate decisions in the developing murine neocortex.

The neocortex is comprised of four main neural cell types, including two classes of neurons – glutamatergic (glu$^+$) pyramidal neurons and GABAergic (GABA$^+$)

*Corresponding author. Tel: +1-403-220-3025; fax: +1-403-283-2700.
E-mail address: cschuurm@ucalgary.ca (C. Schuurmans).

Abbreviations: Ascl1, *Achaete scute-like 1*; AS–C, *achaete–scute* complex; BAF, Brahma-associated factors; bHLH, basic-helix–loop–helix; CGE, caudal ganglionic eminences; GABA$^+$, GABAergic; glu$^+$, glutamatergic; GSK3, glycogen synthase kinase 3; Hes1, *hairy and enhancer of split* 1; HMGA, high mobility group A; LGE, lateral ganglionic eminences; MGE, medial ganglionic eminences; NICD, Notch intracellular domain; *Neurog*, *Neurogenin*; OPCs, oligodendrocyte precursor cells; PcG, polycomb; PRC, PcG repressive complex; RGCs, radial glial cells; SP, serine–proline; STAT, Signal transducers and activators of transcription; SVZ, subventricular zone; VZ, ventricular zone.

0306-4522/13 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2013.08.029

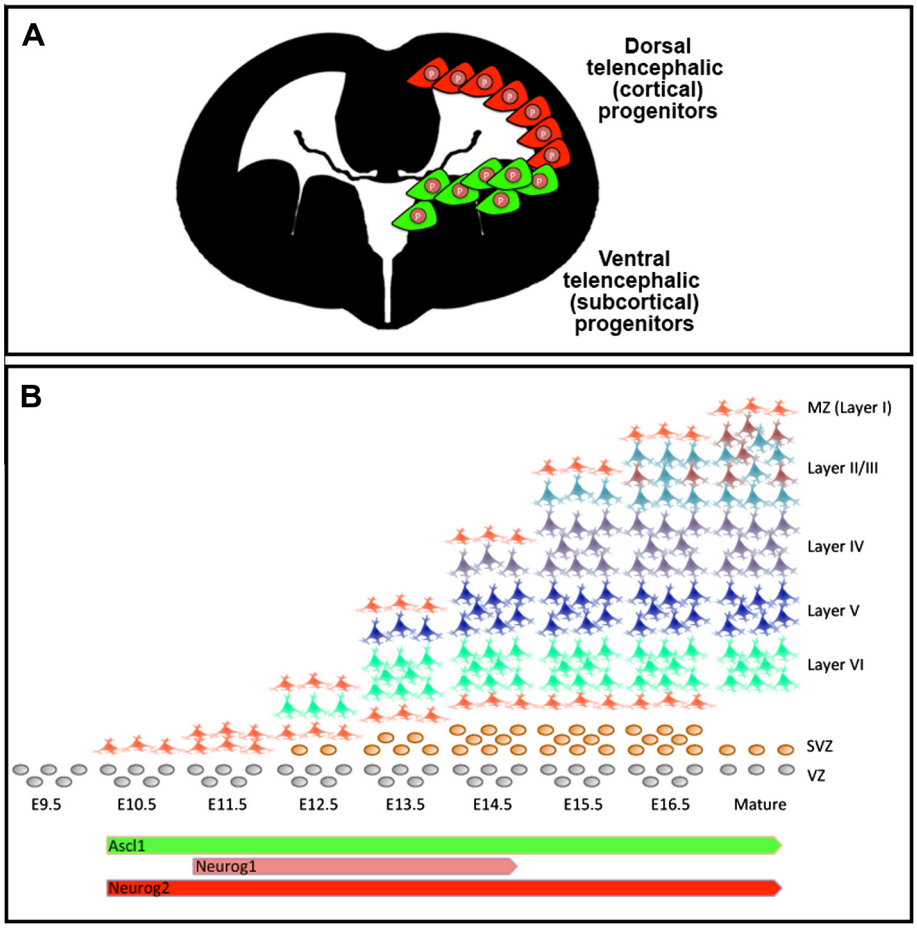

Fig. 1. Neocortical development occurs through temporal identity transitions in cortical progenitor cells. The neocortex (cortex) is comprised of just four cell types – glu$^+$ and (GABAergic) GABA$^+$ neurons, astrocytes and oligodendrocytes (oligodendrocyte precursor cells – OPCs). (A) Glu$^+$ neurons are derived from embryonic Neurog2$^+$ cortical progenitors in the dorsal telencephalon. Embryonic GABA$^+$ neurons and OPCs are derived from embryonic Ascl1$^+$ subcortical progenitors in the ventral telencephalon, some of which migrate tangentially into the cortex. Astrocytes are generated from cortical and subcortical progenitors in late embryogenesis (i.e., not lineage restricted, not depicted). In the postnatal period, cortical progenitors switch their cellular output, giving rise to OPCs (postnatal period not depicted). (B) As neocortical projection neurons differentiate, they migrate radially outward toward the pial surface of the brain, forming the layers of the cortex. Layers I and VII are generated first, followed by layer VI, then V, IV, and finally layers III/II, which are fused in mice, following an inside-out sequence, such that later-born neurons migrate past the previous cohort of neurons toward the pial or basal surface (layer VII neurons are transient and die postnatally). The expression of Neurog1, Neurog2 and Ascl1 is also temporally regulated in cortical progenitors.

interneurons, as well as two glial cell types – oligodendrocytes and astrocytes (Fig. 1). During development, these four cell types are derived from two pools of multipotent neural progenitors located in the dorsal and ventral telencephalon (Fig. 1). *Cortical* progenitors in the *dorsal* telencephalon first differentiate into glu$^+$ pyramidal neurons between mouse embryonic day (E) 10 to E17 (Fig. 1) (Smart and Smart, 1977; Caviness, 1982; Caviness et al., 1995; Super et al., 1998; Takahashi et al., 1999). As they differentiate, glu$^+$ neurons exit the ventricular zone (VZ) and migrate radially toward the pial surface, forming the six neuronal layers of the mature neocortex in an inside-out manner (Caviness, 1982; Caviness et al., 1995; Takahashi et al., 1999). That is, layer I (and transient layer VII) neurons are generated first, followed by layer VI, then V, IV, and finally layers II/III, which are fused in mice (Fig. 1) (Smart and Smart, 1977; Super et al., 1998). At later developmental stages, cortical progenitors switch to gliogenesis, first giving rise to astrocytes in late embryogenesis, and then oligodendrocyte precursor cells (OPCs) in the early postnatal period (Kessaris et al., 2006; Piper et al., 2010; Subramanian et al., 2011). Similarly, embryonic *subcortical* progenitors in the *ventral* telencephalon differentiate sequentially, forming GABA$^+$ neurons, then astrocytes and finally OPCs. Notably, a subset of ventrally derived GABA$^+$ interneurons and OPCs then enter the neocortex via tangential migration (Anderson et al., 1997a, 2001, 2002; Tamamaki et al., 1997; Marin and Rubenstein, 2001; Nery et al., 2002; Xu et al., 2003, 2004; Butt et al., 2005; Kessaris et al., 2006).

Thus, as development proceeds, dorsal (i.e., cortical) and ventral (i.e., subcortical) telencephalic progenitors undergo temporal identity transitions, such that they first give rise to neurons and later to glia. This review summarizes our knowledge of how the proneural basic-helix–loop–helix (bHLH) transcription factors contribute