SnapShot: Cortical Development

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This SnapShot summarizes current knowledge of mammalian cortical development, with a particular focus on the molecular controls that orchestrate the stepwise decisions leading from multiple types of undifferentiated forebrain progenitors to fully mature projection neurons with correctly-targeted axons and carefully-elaborated dendritic trees, as well as appropriate electrophysiology and gene expression, reflective of precise subtype and area identity.

Neocortical Progenitors

Early in development, the telencephalic wall is composed of undifferentiated neuroepithelial (NE) cells, which give rise to diverse progenitor populations. Radial glial cells (RG) divide asymmetrically to self-renew and generate intermediate progenitor (IP) cells or neurons. IP cells divide symmetrically to produce two neurons. In the mouse, small numbers of neurons are produced by radial glia-like (oRG) cells, but oRG cells are abundant in the outer SVZ of human fetal cortex where they generate transit amplifying cells that in turn produce most cortical neurons.

Projection Neuron Diversity

Specific subtypes of neocortical projection neurons are generated by neural progenitors during distinct temporal windows, beginning in mice at approximately E11.5, and continuing through late embryonic development. These young postmitotic neurons migrate away from the ventricular zone to populate progressively more superficial positions in the cortical plate. Projection neurons can be classified on the basis of their mature axonal projections: corticothalamic projection neurons (CThPN) are located in layer VI and send axons to thalamus; subcerebral projection neurons (SCPN) are located in layer V and send axons to optic tectum, brainstem, or spinal cord; and callosal projection neurons (CPN) are located in layers II/III, V, and VI and send axons to contralateral cortex. Importantly, neurons of each subtype are further specialized based on their positions in specific cortical areas. For example, CThPN establish area-specific connections with thalamic nuclei (motor cortex CThPN with VL; sensory cortex CThPN with VP; visual cortex CThPN with dLG).

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Molecular Controls over Subtype and Area Identity

Both subtype and area identity are specified in a stepwise fashion, with early overlapping expression of critical controls resolving over the course of development to specific subtypes and areas. Area identity begins to be imparted embryonically by smooth gradients of transcription factors in progenitors and postmitotic neurons, but during the first postnatal week, expression of critical controls, such as *Lmo4* and *Bhlhb5*, becomes restricted to domains that sharply delineate cortical areas. Similarly, subtype identity is progressively specified, as molecular controls that are initially co-expressed by newly-generated postmitotic neurons later refine to a single subtype, or to high levels in some subtypes and low levels in others. Several central identified controls over subtype development, including *Fezf2*, *Ctip2*, *Satb2*, and *Tbr1*, interact combinatorially (although not linearly) as part of a broader molecular network and nested molecular logic that directs subtype identity acquisition.

Abbreviations

A1	primary auditory cortex
Bhlhb5	basic helix-loop-helix domain-containing, class B5
Btg1	B cell translocation gene 1, anti-proliferative
Cdh6	cadherin 6
Cdh8	cadherin 8
Cdh13	cadherin 13
Clim1	carboxyl-terminal LIM domain-binding protein 1
Couptf1	chicken ovalbumin upstream transcription factor I
CC	corpus callosum
CP	cortical plate
CPN	callosal projection neuron(s)
CR	Cajal-Retzius cell(s)
Crym	mu crystallin
CSMN	corticospinal motor neuron(s)
Csmn1	zinc finger protein 703
CThPN	corticothalamic projection neuron(s)
CTPN	corticotectal projection neuron(s)
Ctip2	Couptf-interacting protein 2
Cux1	cut-like homeobox 1
Cux2	cut-like homeobox 2
Darpp32	dopamine- and cAMP-regulated neuronal phosphoprotein
Diap3	diaphanous homolog 3
Dkk3	dickkopf homolog 3
DL	deep-layer (layers V and VI)
dLG	dorsal lateral geniculate nucleus of thalamus

E	embryonic day
Emx2	empty spiracles homeobox 2
Epha7	Eph receptor A7
Fezf2	Fez family zinc finger 2
Fog2	friend of GATA 2
FoxP2	forkhead box P2
GC	granule cell(s)
Gfra2	glial cell line derived neurotrophic factor family receptor alpha 2
Hspb3	heat shock protein 3
Id2	inhibitor of DNA binding 2
Igfbp4	insulin-like growth factor binding protein 4
Inhba	inhibin beta-A
IP	intermediate progenitor
Lhx2	LIM homeobox protein 2
Limch1	LIM and calponin homology domains 1
Lix1	limb expression homolog 1
Lmo4	LIM domain only 4
Lpl	lipoprotein lipase
M1	primary motor cortex
MZ	marginal zone
NE	neuroepithelial cell
Nfib	nuclear factor IB
Ngn2	neurogenin 2
Odz3	odd Oz/ten-m homolog 3
oRG	outer radial glia
OT	optic tectum (superior colliculus)
Otx1	orthodenticle homolog 1
P	postnatal day
Pax6	paired box gene 6
Plxnd1	plexin D1
PP	preplate
RG	radial glia
Rorb	RAR-related orphan receptor beta
S1	primary sensory cortex
S100a10	S100 calcium binding protein A10
Satb2	special AT-rich sequence binding protein 2

SC	spinal cord
SCPN	subcerebral projection neuron(s)
Sox5	SRY box-containing gene 5
Sox6	SRY box-containing gene 6
SP	subplate neuron(s)
Sp8	trans-acting transcription factor 8
SVZ	subventricular zone
Tbr1	T-box brain gene 1
Tbr2	T-box brain gene 2
Tcrb	T cell receptor beta chain
Tle4	transducin-like enhancer of split 4
UL	upper-layer (layers II/III and IV)
V1	primary visual cortex
VL	ventral lateral nucleus of thalamus
VP	ventral posterior nucleus of thalamus
VZ	ventricular zone
WM	white matter

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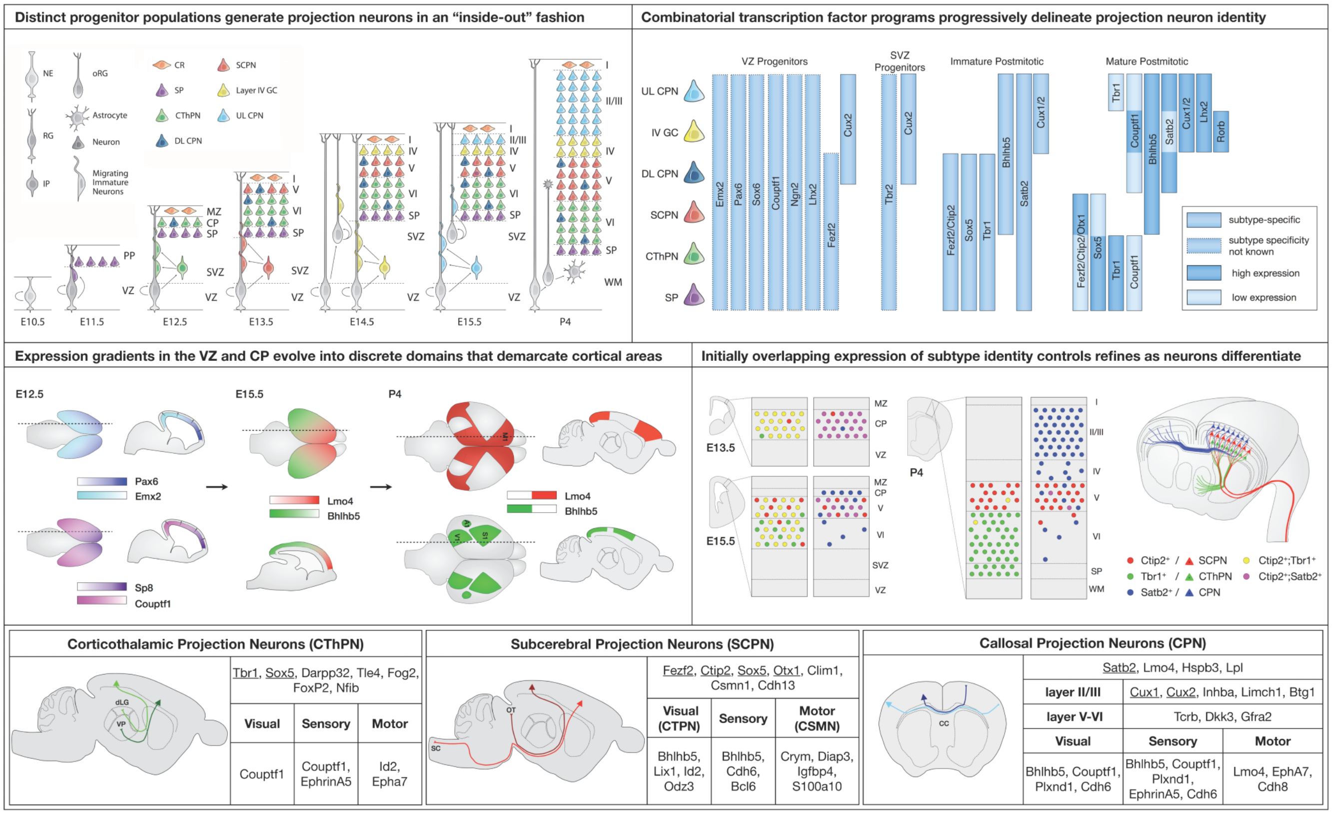

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