Preface

Neural differentiation is an early embryonic event that occurs soon after germ layer specification. In vertebrates, the early ectoderm undergoes further patterning to separate into two identifiable components: the presumptive neural ectoderm and the presumptive epidermis. Neural ectoderm tissue segregates as a clearly demarcated epithelium termed the neuropeithelium (or neuroectoderm). This neuroepithelium generates all of the major components of the central nervous system (CNS) and the peripheral nervous system (PNS), including the neural crest. As development progresses the neuroepithelium forms the neural tube which ultimately forms the CNS. Two transient cell populations contribute to the PNS: the neural crest that differentiates at the neuroectodermal/epithelial junction and placodal precursors that differentiate from cranial ectoderm. The neural crest contributes to both neural and non-neural structures therefore, precursors that generate the PNS also contribute to non-neural structures that include pigment cells of the skin as well as craniofacial mesenchyme.

As the CNS develops, neural stem cells (NSCs) generated from neuroepithelium produce more specified neural restricted precursors cells and glial restricted prcursor cells as shown in Fig. 1.

Undifferentiated neural precursor cells, whether in the CNS, neural crest or the placodes, proliferate, differentiate and migrate to appropriate locations. Cells undergo further maturation, neuro-glial cells become postmitotic, and neuronal cells send projections to appropriate targets and make synapses while acquiring the correct rostro-caudal and dorso-ventral identity. An accumulating body of evidence suggests that neurogenesis follows a pattern of development that is similar to developmental patterns described in other systems such as the liver, skin and hematopoietic system. In each of these systems, tissue specific stem cells are generated and these cells undergo a series of developmental restrictions to generate proliferative progeny that are more restricted in their developmental potential to ultimately give rise to fully differentiated cells.

As development proceeds the number of NSCs is much diminished and by birth these cells represent a small fraction of dividing cells present in restricted regions of the brain. Coincident with this decrease, the number of progenitor cells

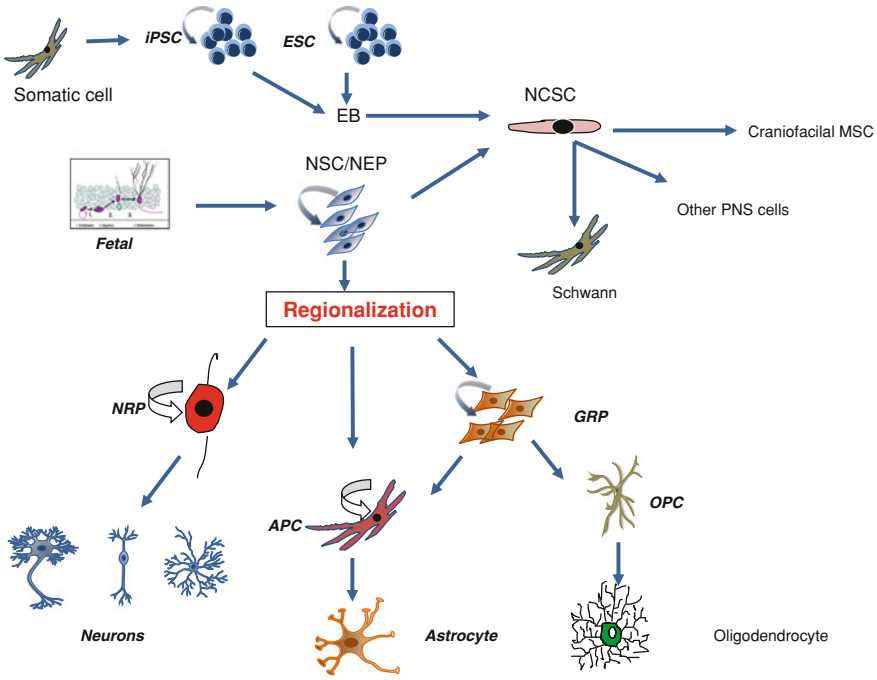

Fig. 1 Lineage restricted neural progenitors from Pluripotent and Somatic cells (*iPSC* = induced pluripotent stem cells; *ESC* = embryonic stem cells; *NCSC* = neural crest stem cells; *EB* = embryoid body; *NSC* = neural stem cells; *NEP* = neural epithelial precursors; *MSC* = mesenchymal stem cells; *PNS* = peripheral nervous system; *NRP* = neural restricted precursors; *GRP* = glial restricted precursors; *APC* = astrocyte precursor cells; *OPC* = oligodendrocyte precursor cells)

increases dramatically and mature differentiated cells can be identified as they migrate from the proliferating zones to their terminal locations. Throughout the CNS, neurogenesis is followed by gliogenesis which is followed by the development of neuronal connections and subsequent myelination of axons. The total cell number in the CNS is regulated at different stages of development as is the density and spread of interneuronal connections.

These complex changes ultimately result in the formation of the adult brain which undergoes little new neuronal augmentation, except in the hippocampus and olfactory regions. In contrast, glial cells continue to be replaced throughout life at a low but measurable rate. In the adult brain neither acute neural damage nor chronic neurodegenerative disorders are repaired by regeneration or activation of endogenous stem cell populations. Rather, restitution of function is generally engendered by reorganization of connections or repurposing of brain regions to a new function or to glial proliferation. Although endogenous stem cells and precursor or progenitor cells exist in the adult it appears that the endogenous cellular response is inadequate in promoting functional regeneration and repair of the damaged central nervous system (CNS).

Research in the stem cell field has therefore focused on mobilizing existing endogenous stem cell or progenitor cell populations or replacing damaged or dead cells using stem cells propagated in culture as a potential cell source. Stem cells have been isolated from a variety of sources, expanded in culture and differentiated into appropriate cells types. These cells can be used to replace the missing neurons and glia and the factors that they release or to deliver factors to the damaged tissues to augment the endogenous repair process.

In this third edition of *Neural Development and Stem Cells* we have asked leaders in the field to describe neural stem and progenitor cell behavior in development and in disease. We hope that readers will see how basic biology and its understanding has guided therapeutic intervention and dictated which cell types are best suited for therapy. We encourage the reader to explore these issues in greater detail by reading the references listed within each chapter. We welcome comments and recommendations for additions and deletions and hope you will find this book useful.

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