New Horizons for the Subplate Zone and Its Pioneering Neurons

Transitionional neuronal layers are a hallmark of the prenatal and neonatal brain yet their contribution to the development of higher functions is not clear. Evidence accumulated over the last 3 decades shows that early connectivity and functional activity start in a transitional layer called the subplate zone (SPZ). The SPZ is host to a heterogenous population of neurons and its evolutionary complexity peaked in the human brain. In this issue of Cerebral Cortex, three reports (Hoerder-Suabedissen et al., 2008; McKellar and Shatz, 2008; Moore et al., 2008) present new data and evidence in three species (mouse, rat, human) as to the function of the SPZ, to the heterogeneity of its cellular composition, and to the genetic basis of its development.

Keywords: evolution, gene chip, neocortex, subplate zone, synaptogenesis

The subplate zone (SPZ) is one of the few new structures in the central nervous system defined in the last 35 years. The SPZ was overlooked by the generation of great neuroanatomists at the onset of the 20th century, perhaps because of the common belief that transitional neuronal layers coalesce with neighboring layers or altogether disappear (His 1874; Campbell 1905; Brodmann 1909; Economo and Koskinas 1925; Cajal 1952). It was first described as a separate region between the cortical plate and the intermediate zone in the human fetal cortex (Kostovic and Molliver 1974) and then in the fetal macaque (Rakic 1977) and carnivores (Luskin and Shatz 1985). It is much smaller but nevertheless clearly defined in rodents (Molnar 2000). In spite of its biomedical significance and enormous evolutionary expansion that culminates in human evolution, gene chip, neocortex, subplate zone, synaptogenesis complexity peaked in the human brain. In this issue of Cerebral Cortex, three reports (Hoerder-Suabedissen et al., 2008; McKellar and Shatz, 2008; Moore et al., 2008) present new data and evidence in three species (mouse, rat, human) as to the function of the SPZ, to the heterogeneity of its cellular composition, and to the genetic basis of its development.

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(2008) from early postnatal embryos. Age-related differences apart, confirmation of gene expression reported by Osheroff and Hatten, by real-time quantitative polymerase chain reaction and in situ hybridization, is necessary after Genench hybridization. At first inspection, the difference between the SPZ and layer 6 neurons seems miniscule, considering the difference in their function and morphology (Hoerder-Suabedissen et al. 2008). Sorting out spatiotemporal gene expression is necessary to affirm specificity and contribution of identified genes to neuronal subtype specification, axonal guidance, dendritogenesis, synaptogenesis and, in a broader sense, the evolution of the human brain. Furthermore, one cannot expect a complete picture without a comparative genomic analysis to uncover mutations in coding and noncoding regulatory sequences of SPZ-specific genes responsible for the expansion and cellular elaboration of the SPZ during evolution.

Biophysical and immunohistochemical properties of embryonic neurons were studied by Moore et al. (2008) in slices of human fetal brain at different gestational ages. The advanced maturation and electrical excitability of SPZ neurons as reported by Moore et al. (2008) lend support to the proposition that the earliest functional circuit forms in the SPZ by midgestation in the human and rodent neocortex (Allendoerfer and Shatz 1994). The size and prolonged period of SPZ development in the human brain, with respect to the increased number of connections (Kostovic and Rakic 1990) and presence in specific cortical areas, require further studies from the neurological point of view. In this vein, identifying heterotopic cells, which have been observed in several neuropathological conditions, based on their expression of SPZ-specific genes (Cplx3, Nurr1/Nr 4a2, Mox D1, CTGF, and F-spondin) or other cortical markers may help resolve the issue of the source of these cells, as mislocalized cortical plate neurons or remnants of the SPZ, and the time window when the pathology ensued. Studies on the human SPZ using a variety of physiological and molecular genetic approaches (Bayatti et al. 2008; Moore et al. 2008) are essential if we are to understand the etiology of neocortical abnormalities.

The 3 reports published herein confirm the initial findings that the SPZ is composed of 2 basic classes of neuronal phenotypes, glutamatergic and γ-aminobutyric acid (GABA)ergic (Antonini and Shatz 1990; Meinecke and Rakic 1992), serving different functions due to their differential gene expression. Postmigratory GABAergic neurons may coexist with different peptides (somatostatin [Kostovic et al. 1991]; neuropeptide-γ [Delalle et al. 1997]), calbindin and calretinin. Laminar shifts of different markers during development (Ina et al. 2007; Stumm et al. 2007; Bayatti et al. 2008) may pose a problem when analyzing different developmental stages in 1 species or comparing different species (Kostovic and Rakic 1990). The most prominent differences in comparative studies were observed in the size and fiber content of the SPZ between primates and rodents (Kostovic and Rakic 1990; Bystrom et al. 2008). The primate has a higher activity of extracellular matrix (ECM) production because this extracellular component forms the largest portion of the SPZ (Kostovic et al. 2002). Some of the ECM molecules are putative synaptic genes (McKellar and Shatz 2008) or may represent axon guidance molecules (Kostovic et al. 2002). Functional studies involving in utero overexpression or misexpression of select genes have proved invaluable in explaining the molecular mechanisms underlying the formation of deep cortical layers (Kwan et al. 2008; Voss et al. 2008). Similarly, future molecular genetic analyses should characterize the function of SPZ-specific genes (Cplx3, Nurr1/Nr 4a2, Mox D1, CTGF, and F-spondin) as well as the diversity of cells within this layer during development.

Studies of SPZ development are necessary to assess the perinatal origin of cognitive disorders and shed light on the transient functions of preterm cortex (Kostovic and Judas 2006; Bayatti et al. 2008). Recent advances in magnetic resonance imaging technology allow imaging and assessment of the SPZ in the human fetus in utero (Kostovic et al. 2002; Staudt et al. 2006). The SPZ may be a crucial structure for understanding early functional interactions in the human preterm cerebral cortex (Kostovic and Judas 2006) and essential elements of structural plasticity that are necessary for the development of higher brain function in the human brain (Staudt et al. 2006). The 3 reports published in this issue of Cerebral Cortex and other recently published evidence (Bayatti et al. 2008; Kwan et al. 2008) provide support for earlier hypotheses, which were based primarily on anatomical data, that the SPZ is a substrate for the formation of early molecular and functional neuronal interactions, synaptogenesis, growth, and patterning of thalamocortical pathways and their termination in the cerebral cortex (Rakic 1977; Kostovic and Rakic 1980, 1990; Shatz et al. 1988). Furthermore, the identification of new genes and development of new experimental paradigms are bound to pave the way for exiting new discoveries and deeper understanding of species-specific differences between humans and rodents.

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