Results and Problems in Cell Differentiation

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Christine F. Hohmann (Ed.)

Cortical Development

From Specification to Differentiation

With 28 Figures, 5 in Color

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Preface

The cerebral neocortex, unique to mammals, is regarded as the prerequisite for higher cognitive function and is the structure most closely associated with the idea of the "mind". Expansion of mental capacity between mammals is most typically associated with an evolutionary increase in neocortical volume that culminates in the intricately folded configuration of sulci and gyri so characteristic of the primate cerebral cortex. Yet, the basic unit structure and fundamental connectivity of cortex appears to have been preserved from the smooth cortex of the mouse or rat to the highly convoluted cortical mantle of the human that, if stretched out as a sheet, would be large enough to wrap the entire human brain multiple times. The basic similarity in structure and function has made it possible to conduct studies in the relatively simple cortices of rat or mouse and have the results pertain to the understanding of the primate, including human, cortex.

The neocortex is an intriguing structure for the study of cell differentiation. Its dozens of neuronal cell types and small handful of different glial types have their origin in a pseudostratified germinal epithelium lining the ventricular surface of the forebrain. In its mature form, neocortex is a six-layered structure; five of its layers contain multiple different but characteristic neuronal types with the sixth occupied by neuronal processes. Various glial cells are dispersed throughout all six layers. Its precise stratification is essential for the proper function of neocortex. Postmitotic, undifferentiated cells must migrate to their proper position within the developing cortex. Once arrived in their correct cortical stratum, neurons must elaborate their differentiated characteristics while simultaneously establishing appropriate synaptic connections with their axonal targets and the afferent axons of other neurons of cortical as well as diencephalic and brainstem origin. Moreover, specific morphological and neurochemical relationships between neurons and glia must evolve during the course of morphogenesis. Mishaps during any of these steps can result in cascades of developmental alterations, leading to functional changes, as has been learned from the study of mouse mutations and the pathologies of human developmental disorders.

While the first glimpse into the complexities of neocortical development was allowed us by Ramon y Cajal, a century ago, the study of cortical morphogenesis came into its own in the early 1960s. Studies by Angevine, Racik, Sidman, Bayer and colleagues described the time line of "birth" among cortical cells, their basic modes of migration along the scaffolding of radial glia cells and

elucidated the fundamental "inside-out" pattern of cortical development whereby the earliest wave of neurons forms the deepest cortical layer and subsequent waves of neurons will migrate past earlier ones to become situated in more superficial positions. Mutant mice with various abnormalities in cortical formation helped to reveal a plethora of cell–cell and cell–matrix interactions instrumental in the proper assembly of the neocortex. Many of the cell surface and diffusible signals involved in altered migration and subsequent abnormal differentiation in these mutants have since been identified, while others are still under study.

Along with the description of these basic rules of neocortical ontogeny, research began to reveal the fundamental plasticity of the developing neocortex. Like no other brain structure, cortical morphogenesis has shown itself amenable to molding by sensory inputs from the periphery as well as motor feedback. Such plasticity was demonstrated early on in the kitten visual system by experiments that would eventually help D. Hubel and T. Wiesel earn the Nobel Prize for Medicine. Many studies since have shown that use-dependent plasticity is a universal feature of neocortex. The elaboration of cortical neuronal fine structure (dendrites, their spines, synapses), and the resulting perceptual and behavioral outcomes, is shaped by activity patterns in afferent axons onto cortical neurons. These activity patterns, in turn, are representative of patterns of peripheral sensory inputs and/or motor feedback.

Thus, understanding the ontogeny of cerebral cortex requires us to understand not just the step-by-step "readout" of a developmental program, but also the manner in which this program is designed to interact with environmental influences. While this might appear to some a daunting task, perhaps to be abandoned for simpler systems, the reward of understanding cortical differentiation on a functional level will be to understand how a thinking and learning, cognitive brain is assembled and continues to evolve. In other words, understanding the cortex is to understand how we understand! On a biomedical level, such knowledge eventually will enable us to prevent and/or remedy numerous disorders of the brain and "mind".

Contemporary research into cortical differentiation has at its disposal the new tools of molecular biology that, combined with a systems approach to the study of the nervous system, will eventually reveal the full picture of the functional assembly of the cerebral cortex. Exciting new insights into cortical development are uncovered on both the molecular and systems level with increasing frequency and have recently been augmented by computational approaches as well. In this first volume of a two-volume issue on cortical development, we will concentrate on "early" events in ontogeny, namely, issues related to cortical cell generation/specification, migration, and early differentiation. Many of the questions before us in this arena are of a molecular nature. The second volume will concentrate, to a larger degree, on issues involved in cortical plasticity and associated function and, thus, will feature models using a systems approach.

The chapters assembled here have been selected to show a cross section of what I personally regard as the most pertinent and exciting areas in current research on early cortical ontogeny. I have made an attempt to generate a diversity of voices, although, for reasons of practical limitations, not every area of research could be sampled and not every opinion represented. I will leave it to readers of this volume to "dig deeper" into areas of interest and uncover the debates and controversies that may exist, as they do in any field of scientific inquiry.

Chronologically, the earliest questions we encounter in cortical morphogenesis are: How does the germinal epithelium of the ventricular lining control the generation of the many different kinds of neurons and glia emerging during the days or weeks of cortical cell generation? Are selected populations of precursor cells generated first, which later will give rise to limited populations of differentiated cells or is the germinal epithelium composed of pluripotent stem cells responding to timed signals with differentiated responses? In any case, what are the molecular signals that interact with such stem cell or precursor cell populations to specify their future differentiation?

The chapters by Richard Nowakowski and colleagues and Mark Mehler address these questions from very different angles. R. Nowakowski et al. look at patterns of postmitotic cell emergence and the changes in cell cycle regulation that accompany their generation as a source for controlling differences in cell populations. Mehler reviews and investigates a number of different growth factors and like molecules in the specification of postmitotic neuronal and glial lineages. As different as these approaches seem, they are intimately connected as cell cycle activity is clearly subject to regulation by many of the growth factors at issue. Bernd Sutor introduces us to another perspective on neuronal genesis, the role of Gap junctions which exist between clusters of cells of the germinal epithelium and allow for communications between these cells concerning internal (e.g., cell cycle) as well as external (e.g., receptor-mediated) signals. Studies discussed in this chapter furthermore address the early stages of cortical neuronal differentiation and the role of Gap junctions as well as the emergence of synaptic communication in these differentiation steps.

There has been considerable speculation for some time that differentiating cortical neurons and glia depend on each other, as well as on certain afferent axons, to generate their appropriate differentiated morphologies and circuits. The chapter by Juliano and Gierdalski revisits neuronal-glia interactions during the migratory phase that sets up cortical lamination. Her work suggests that focal disruptions of neuronal genesis will alter molecular signaling between the remaining glial and neuronal populations in ways that suggest a profoundly complex information exchange between the maturing cellular elements of the emerging neocortex. Juliano et al.'s data moreover indicate that normal afferent thalamocortical ingrowth can proceed despite profoundly altered cortical morphogenesis.

Bernd Sutor proceeds to gives us some insights into how direct neuronal communication, via Gap junctions and/or excitatory and inhibitory chemical

synapses, may shape cortical differentiation. Kimberly McAllister, on the other hand, illuminates the role of diffusible neurotrophins in the differentiation of neuronal processes and elaboration of synaptic contacts. Her chapter allows us a glimpse of the intricate relationship between these neurotrophic factors and synaptic activity in shaping cortical ontogeny as well as use-dependent plasticity.

Katrin Andreasson and Walter Kaufmann take us inside the differentiating cortical neuron by exploring the intracellular signaling pathways and "immediate, early" gene activation that occur in response to both synaptic and neurotrophic signaling in the developing cortex. Here, we can begin to see how synaptic activity mediated and neurotrophin mediated intracellular responses might converge on signaling chains leading to gene activation. Once more, as in the chapter by McAllister, parallels between the regulation of morphogenesis and plasticity become evident.

While much of the current focus in cortical development is directed towards molecular and cellular studies, many questions continue to require a look at the "larger picture". We have known for centuries that the neocortex is subdivided into clearly delineated functional areas. Research during the last few decades has detailed the synaptic circuitry of several such functional areas, in particular, the different sensory areas, and has shown that substantial differences exist, for instance, in how visual and auditory synaptic processing occurs. There has been a long-standing debate as to whether such structural and functional differences are the result of intrinsic cortical signals or the consequence of information conveyed to cortex by afferents of different sensory modalities. Several laboratories have recently identified genes that are expressed at appropriate developmental times, marking specific cortical fields. The implication has been that the products of these genes guide afferent target finding and the establishment of functional cortical areas. However, studies presented here by Alvin Lyckman and Mriganka Sur present a powerful argument for the important role of sensory afferents in shaping the functional innervation of neocortex; simultaneously, their data concede that some secondary specifications of cortical circuitry are apparently intrinsically programmed. The independence of thalamocortical afferents from intrinsic cortical differentiation signals does echo the findings communicated earlier in this volume by Juliano and Gierdalski.

I am concluding this volume with a second chapter by Mark Mehler. I share with him a profound interest in the clinical relevance of current research into cortical morphogenesis and plasticity. This final chapter reviews recent data concerning the origin and morphogenetic regulation of cortical cells from the ventral telencephalic eminence, an area viewed in the past as giving rise to deeper forebrain structures. Most importantly, however, this chapter makes the provocative claim that disruptions of early events in cortical cell generation, migration, and differentiation may be at the root of pathogenesis in neurodegenerative diseases by creating latent vulnerabilities. Degenerative disorders then arise in later life in response to otherwise nonlethal stressors of cell physiology that expose the underlying weakness.

In conclusion, I hope that this volume will update the initiated reader in regards to the current "hot spots" regarding studies of early cortical development while simultaneously raising interest among developmental biologists not currently familiar with this fascinating area of research. Increasingly, successful inquiry in the neurosciences depends on a strongly interdisciplinary approach. I believe this volume shows that, as we diversify in our research questions, we simultaneously, collectively, begin to approach the answers that will reveal the entire complicated mosaic of events.

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