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Cortical Development: New Concepts

Overview

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Progress in understanding development of the cerebral cortex has made significant leaps in recent years in areas including neurogenesis, fate determination, migration, and differentiation—all finally culminating in the establishment of cortical architecture and circuitry. From May 12–15, on the Greek Island of Santorini, groups studying each of these aspects of cortical development will come together to discuss the present state of understanding of how this enormous complexity is achieved. An emphasis of this meeting will be on the earliest steps of neurogenesis, with the idea that an understanding of these formative events will help direct strategies for neural repair. In the following minireviews, each of the key events involved in cortical formation will be examined.

The cortex, like all CNS structures, arises from the symmetric divisions of neuroepithelial cells, the stem cell from which all neural cells derive. Fiona Doetsch, Li-Chun Cheng, and Masoud Tavazoie discuss progress in our views of stem cells, their modes of division leading to self-renewal versus differentiation, their developmental progression and components of the environmental niche that maintains them. Their minireview also considers the specific molecular mechanisms underlying these processes. These range from the extrinsic signals such as Notch, ephrins, and Shh that maintain stem cell population to the intrinsic effectors such as noncoding RNAs and chromatin remodeling that act at the transcriptional or translation level.

Stem cells and the progenitors that they give rise to appear to take multiple forms as cortical development progresses. In the embryonic cortex, radial glia are the predominant form of neural progenitor cell, giving rise to both neurons and the secondary progenitors that populate the subventricular zone. Magdalena Götz and Yves-Alain Barde discuss this intriguing population. Evidence suggests that the linear relationship between radial glia and the neurons that they give rise to in the cortex may be unique to this structure, as, unlike what appears to occur in ventral regions of the brain, cortical radial glia give rise both to subventricular cells as well as directly to neurons. In the cortex, the transcription factor Pax6 appears to be causally linked to neurogenesis, and the relationship of Pax6 to radial glia will be considered. Finally, they examine the question of how cortical radial glia resemble ES cells. This question is pertinent to understanding the extent to which certain commonalities exist between different stem cell populations.

What distinguishes the cerebral cortex from other brain regions is its remarkable diversity of cellular subtypes arrayed in a stereotyped laminar and radial organization. Kenneth Campbell will discuss how the temporally controlled expression of different transcription factors progressively restricts cortical progenitor fate. One of the first cell types generated in the cortex is the Cajal Retzius cell, which has an important role in cortical lamination, at least partially due to its expression of the matrix protein Reelin. Eduardo Soriano and Jose Antonio Del Rio discuss recent work concerning the Reelin pathway and will examine the broader role of Cajal Retzius cells in cortical development.

The great majority of cortical neurons fall into one of two broad categories: pyramidal cells that form cortical projections and cortical interneurons that regulate cortical function through local circuits. Recent work suggests that these two populations have spatially distinct sites of origin, with the pyramidal cells being generated within the cortex, while most of the cortical interneurons arise from subcortical structures. This latter category is known to contain considerable diversity. Nuria Flames and Oscar Marín discuss the developmental origins of interneuron subtypes and molecules that guide this population during their tangential migration to the cortex. These studies hold the promise that developmental genetics will hold the key to understanding how the diversity of this important class of neurons is generated.

Unlike interneurons, pyramidal cells arise from cortical progenitor zones near the ventricle and migrate radially into the cortex. Our understanding of the molecular basis for cellular motion during radial migration has come from a multitude of sources, including human genetic disorders, analysis of mouse mutants, and studies of nuclear movement in yeast. In their minireview, Li-Huei Tsai and Joesph Gleeson discuss how the molecules implicated in each of these systems contribute to the intracellular mechanisms of radial migration by mediating nuclear translocation and positioning of the microtubule organizer. These studies not only have relevance for radial migration in the cortex, but are important for cytokinesis and interkinetic nuclear movements in general.

Once they have obtained their laminar position, cortical pyramidal cells must make and receive efferent and afferent projections. Franck Polleux discusses how the interplay between intrinsic transcriptional determinants and extrinsic signaling factors results in the establishment of both appropriate topographic intercortical connections and proper connectivity with the thalamus. Complementing the growth of axonal afferents is the elaboration of dendritic branches and spines. The re-

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view by Sila Konur and Anirvan Ghosh highlights how activity-dependent growth and refinement utilizes signals that are also involved in multiple other processes. These include extrinsic developmental signals such as Notch and Wnt signaling, axonal guidance cues including semaphorin and slits, trophic factors such as BDNF, and finally the neurotransmitters GABA and glutamate. In turn, dendrites respond through intracellular effectors such as the calcium-activated Crest and CREB.

Finally, Pat Levitt considers how developmental mechanisms can inform thinking about the pathophysiology of neurodevelopmental disorders such as autism and schizophrenia. It is known that many neurobehavioral disorders arise as a consequence of subtle developmental abnormalities. In his minireview, Pat Levitt discusses both the problems and promise in correlating genetic abnormalities to behavior disorders. At its heart, the problem is two fold. First, cognitive brain disorders are typically pleotropic, with estimates of 5 to 15 genes underlying autism and 10 to 50 genes acting in schizophrenia. Second, gene actions are context specific. Gene mutations causing mental retardation in humans do not necessarily present the same phenotype in model organisms. Sorting through the subtle interactions of such a large number of genetic effectors across species will not be easy. To do so will require interactions between neuroscientists studying all levels of development and neuronal function.

The predecessor of the Santorini meeting occurred in Delphi three years ago and brought together neuroscientists from a similar range of disciplines. During this short window of time, considerable strides have been made in our understanding of the molecular basis of key processes underlying cortical development. Quite a bit more is now understood concerning the molecular cues that direct the migration of neurons both to and within the cortex, as well as the means by which cortical regions obtain their laminar and areal specificity. Complementing this are advances in our understanding of the mechanisms by which stem cells acquire specific neuronal identities. Over three thousand years ago, a cataclysmic volcanic eruption originated in Santorini, and the impact spread rapidly throughout the Mediterranean. Possibly, the development of neural stem cell strategies will be accelerated by a better understanding of the process of normal cortical development as discussed in Santorini. The minireviews in this issue and the talks in Santorini reflect our present state of knowledge and suggest that molecular, developmental, and systems neuroscientists will by necessity begin to learn each others' language. Perhaps by becoming multilingual, neuroscientists will make the promise of brain repair a reality in the not so distant future.