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Introduction

The development of complex neural circuitry with a capacity to elicit robust and diverse animal behavior remains one of the most remarkable events in biology. The central questions in developmental neuroscience have changed little in the past fifty years. How is cell diversity established and controlled? How do neurons and glia migrate to their appropriate positions? How do neurons establish specific synaptic connections with appropriate neuronal partners and how are the functional properties of these connections regulated? As development proceeds, how are relatively crude wiring diagrams refined both anatomically and physiologically? How is flexibility achieved? How does the development of neural circuitry specify unique behavior in different organisms, including differences in male versus female organisms of the same species? And finally, do abnormalities or variations in neural development predispose an organism to neurological disease? Developmental neuroscience, as with many fields of biology, has benefited tremendously from the explosion of modern molecular and genetic tools. With these new reagents, we are gaining insight into these age-old questions of neural development, with implications for how we may one day treat neurological injury or disease, and with potentially profound insight into the acquisition of robust and nuanced animal behavior. This issue covers a range of topics highlighting recent advances in these diverse areas.

Glial Signaling and Neurogenesis

Interactions between glia and neurons are increasingly recognized as an essential form of cellular communication during neural development. Glial cells and glia-derived signaling participates in the patterning the early nervous system, influences the anatomical and functional maturation of synaptic connections and participates at various levels in developmental and neurodegenerative elimination of neural processes. An emerging question surrounds the diversification of cell types in the developing nervous system, both glia and neuronal. The diversification of cell types, the generation of appropriate cell numbers of each type, and the migration of cells to defined sites represent challenging developmental problems. While previous research has mostly focused on neuronal diversification, the discovery of distinct glial fates has opened a new avenue of exploration. Schlegelmilch et al. review recent literature on function and activity of microglia in the

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nervous system, with a particular emphasis on their role during development and under physiological conditions, previously underexplored topics. Unlike most other cells in the nervous system, microglia are derived from the hematopoietic cell lineage and are considered the resident macrophages of the brain. Surprisingly, microglia are not only of importance during pathological conditions, but also play key roles in dynamically clearing debris during development and indirectly influencing synaptic function and animal behavior.

Drosophila has emerged as a system in which the study of specific populations of glial cells can be advanced using a combination of forward genetics and molecular manipulation. Advances in understanding adhesion and intercellular signaling between glia and neurons in *Drosophila* is reviewed by Silies and Klambt. The signaling systems discussed include adhesive interactions and secreted factors controlling cell proliferation and survival. In some respects, parallels can be drawn to the intercellular signaling event that are involved in the regulation of migrating neural crest cells in mammalian systems, summarized by Clay and Halloran. In this review, work is summarized that examines the delamination of migrating neural crest cells, which require precise regulation of adhesive interactions and linkage to intracellular cytoskeletal components.

Another system that has become a focus for developmental studies on cell proliferation is the developing mammalian neocortex, reviewed Fietz and Huttner. This review examines the mechanisms that control cell proliferation and diversification in this system. The neocortex is a very unique structure with high demands for increased proliferation, especially in species with comparatively large neocortices. Neocortical cell types fall into different principle classes depending on the location of mitosis (apical vs basal) and cell polarity during mitosis (bipolar, monopolar, and nonpolar). The review also includes a very interesting evolutionary comparison of cortex development in different species. Clearly, the requirement for precise control of cell proliferation is not restricted to the neocortex. As Weng and Lee describe, this problem has also been studied extensively in the fruit fly *Drosophila* larval brain, where progenitor cells with restricted developmental potential generate a defined pedigree of postmitotic offspring. Insight in signaling pathways with evolutionary conservation and involved the control of proliferation may allow for comparative analysis of restriction and expansion in cell proliferation.

Neuronal Specification and Axon Targeting

Programs involved in neuronal specification also control the establishment of precise axonal trajectories and synaptic targeting to defined areas of the nervous system. Recent studies have provided insight into the mechanisms of how transcriptional programs are linked to the expression of cell surface molecules involved in the direct control of these cellular processes. Peljto and Wichterle summarize recent progress in using knowledge on genetic pathways specifying neuronal subpopulations *in vivo* to program embryonic stem (ES) cell differentiation. They describe how knowing intrinsic and extrinsic cues involved in the specification of neuronal populations *in vivo* can be used to instruct ES cells towards specific subpopulations of spinal or cortical motor neurons, highlighting the importance of understanding developmental events also for translational research. Next, Liu and Ma describe the developmental programs involved in the specification of the many distinct classes of dorsal root ganglia sensory neurons, a process influenced by transcriptional and neurotrophic receptor signaling, as well as retrograde specification by target-derived factors. Da Silva and Wang, then, provide a summary of recent studies describing the influence of target-derived signaling on circuit assembly at late developmental stages. For many of the peripherally projecting neuronal populations, target-derived specification appears to be of key importance for circuit assembly, and it will be interesting to know in how far this principle also applies to circuits in the brain.

The next series of reviews in this area highlights advances in axon guidance and the early stages of circuit assembly more specifically. For example, commissural neurons establish communication and balance between the left and right side of the nervous system, and as a consequence, insight into the molecular mechanisms controlling the elaboration of these projections is very important. Chedotal describes recent progress in understanding the complex signaling interactions axonal growth cones encounter when they decide whether to cross or not to cross the midline, including many signaling molecules accumulating at the midline and their receptor interactions, as well as regulation, translation and cell surface presentation of corresponding receptors. Next, Hadjiconomou et al. highlight molecular strategies employed by the developing *Drosophila* visual system to establish precise axonal projections to their target area. A combinatorial strategy with anterograde and autocrine signaling processes, interactions between neurons and glia cells, as well as activity of homophilic cell surface molecules is used to achieve precision in axonal targeting in this system. Finally, Bochtrop and Hummel provide another example of how cell-intrinsic neuronal differentiation programs interact with context-dependent cellular interactions to sculpt a precise map in another sensory system in *Drosophila*, the olfactory system. While axonal trajectories of olfactory receptor neurons are highly stereotypic in their target choice, recent work also revealed a high degree of diversity at the level of olfactory interneurons, establishing local microcircuits.

Circuit Assembly

Neural circuits assemble in a step-wise fashion, but connected circuit elements initiate activity at early stages. As a consequence, the developmental hierarchy as well as the activity of associated circuits may contribute in a significant way to the later functioning of the mature circuits, a topic highlighted in the next set of reviews. In the first review, Maeder and Shen review recent evidence demonstrating the potent role for morphogen signaling in the development of synapse specificity. Of particular interest are data demonstrating that morphogens can impose both positive and negative influence on synapse formation. These data represent a remarkable advance in the logic involved in synapse formation, which previously emphasized highly localized synaptotrophic signaling events such as inter-cellular adhesion. The next two reviews examine the assembly and emerging function of motor circuits in different species. Motor circuits need to function at early developmental stages, a time during which there is ongoing plasticity and maturation of neural circuitry. Kiehn describes the genetic programs involved in specification of neuronal subpopulations and their connectivity in the circuits contributing to the generation of left-right and extensor-flexor alternations of motor bursts in the spinal cord, with emphasis on neonatal mice. Specifically, progress on interneurons derived from ventral spinal progenitor domains has allowed insight into the process of how developmental ontogeny contributes to the generation of distinct neuronal subtypes in the spinal cord. McLean and Fetcho highlight the use of optogenetic and imaging approaches to study the control of movement in zebra fish, allowing insight in the process of neuronal migration, network connectivity as well as behavior.

The next two reviews highlight the important influence of gender and environment on the specification of the motor circuitry underlying complex, yet well defined, motor behavior. Wu and Shah review the literature examining the influence of gender on circuit development. The influence of circulating androgens on the development of neural circuits has been known for some time. However, new advances enabled by cutting edge mouse molecular genetics has demonstrated surprising twists regarding how testosterone and estrogen specify the development of neural circuits in the male and female brain, with profound effects on reproductive behavior. Next, Olveczky and Gardner describe recent progress in the field of song bird circuit development. These circuits are under the control of

both genetic elements and powerful environmental influences. Song birds provide an excellent model system to assess how perturbations of circuit assembly during development have an immediate consequence in a behavioral output.

Synapse Assembly and Specificity

The neuronal synapse is characterized by pre- and postsynaptic specializations that appear as electron densities at the ultrastructural level. The postsynaptic density contains the scaffolding and stabilizing systems that control neurotransmitter receptor abundance. The presynaptic density includes numerous molecules that achieve high fidelity synaptic vesicle exo- and endocytosis. The molecular complexity of the pre- and postsynaptic elements and the specificity with which synapses are assembled in the developing nervous system implies a remarkable level of regulation. The review by Siddiqui and Craig reviews the literature examining the protein complexes that organize pre- and postsynaptic differentiation. The review highlights not only mechanisms of protein scaffolding, but essential signaling systems including those derived from surrounding glia. The review by Sigrist and Schmitz focuses more specifically on the developmental assembly and plasticity of the presynaptic active zone. The authors review both the identity of the molecules that are assembled at the active zone and how they are organized into a macro-molecular complex capable of regulated synaptic vesicle recycling. Finally, intercellular signaling is one of the cues that controls the placement, maturation and plasticity of synaptic connections and Wnt signaling has emerged as a major player in this regard. The review by Budnik and Salinas examines the increasingly complex function of Wnt signaling during synapse development and plasticity. The authors cover data derived from studies in diverse organisms including *C. elegans*, *Drosophila* and the mammalian nervous system. Among the most important advances covered in the review are data describing a function for Wnts during activity-dependent plasticity of synaptic connections.

Mechanisms of Development and Plasticity

Once synaptic connections are assembled, mechanisms of neural plasticity refine both neuronal connectivity and functionality. Reviews in this section span a range of literature from developmental plasticity within complex neural circuitry to cell biological studies that examine the control of neuronal actin and microtubule cytoskeleton as a basis for morphological plasticity. First, Cossart reviews how the functional diversity of GABAergic interneurons is established during development and how these neurons interface with the development of proper neural network function. A diversity of GABAergic interneurons has recently been established and the implications for the development of precise neurological circuitry is now being explored. This review highlights recent advances and then places these studies within the context of development plasticity, with implications for neurological disease. Next, Yu and Zuo review the literature surrounding the plasticity of dendritic spines in the motor cortex. There is remarkable spine plasticity in the motor cortex in response to motor learning and following injury. The review begins by placing current advances in the context of prior research and moves into exciting new studies following the plasticity of dendritic spines with two-photon microscopy in the motor cortex in living animals. Finally, it is now well established that dendritic spines are highly dynamic structures and changes in spine size and density have been correlated with functional plasticity throughout the nervous system. Spine dynamics are driven by regulation of the actin cytoskeleton. Dent and colleagues take a cell biological perspective and discuss advances in our understanding of actin organization and regulation within dendritic spines. The authors also highlight recent work demonstrating microtubule invasion into dendritic spine, a new insight that may lead to a better understanding of regulated spine dynamics and functional plasticity.

Developmental Links to Disease

The elaboration of precise neurological circuitry requires sequential stages of cell fate specification, morphological transitions such as cell migration and axon path-finding, and mechanisms of neural plasticity that refine neuronal connectivity. It is becoming clear that defects at different stages of neural development not only cause developmental abnormalities associated with specific syndromes but can predispose the nervous system to the emergence of neurological and neurodegenerative disorders later in life. The Bone Morphogenetic Protein (BMP) signaling system is both a potent morphogen involved in cell fate specification and a juxtacrine signal involved in synapse development and neural plasticity at later stages of development. Bayat and Bellen review an emerging literature that links mutations in BMP signaling molecules to the cause and progression of neurodegenerative disease. The review draws from research in fields as diverse as the *Drosophila* neuromuscular junction and human genetics. In so doing, the review highlights the importance of both unbiased forward genetic approaches in model genetic organisms as well as human genetics. At the intersection is an increasingly rich understanding of developmental neurobiology and its relevance to our understanding of neurodegenerative disease.

The repair of neural circuitry following injury or disease has been a focus of cellular and developmental neuroscience for decades. In particular, the limited regeneration of axons within the mammalian central nervous system has been a longstanding challenge for experimental neuroscience. Here, Wang and Jin review new developments in the field of axon regeneration being achieved in the model genetic organisms *C. elegans* and *Drosophila*. In these systems, the combined use of laser-based axotomy, live imaging and forward genetics have led to the identification of molecular pathways that are required for nerve terminal sprouting and functional regeneration following axotomy. These studies may lay the foundation for future translational work between these model organisms and the vertebrate central nervous system.

Finally, clear association of developmental signaling with neurological disease will require identification of disease causing mutations. Kevin Mitchell specifically addresses the literature and approaches toward identifying disease related genes in human genetic studies. The authors detail, “a paradigm shift in our conception of the genetic architecture of common neurodevelopmental disease, highlighting the importance of individual, rare mutations and overlapping genetic etiology of various disorders.”

Conclusions

This issue highlights advances in our understanding of genetic programs involved in the specification of neuronal and glial identity. In addition, the assembled reviews show how early events of neuronal specification not only define the initial events of nervous system assembly including the migratory routes of nascent neurons, but also how these events influence circuit assembly more broadly by controlling axonal and dendritic targeting, choice of synaptic partners, as well as the precision and plasticity of synaptic connections. From the reviews highlighted here, it can also be seen that signaling systems and molecular mechanisms are reutilized not only at different stages of early development, but also during processes of developmental plasticity and disease. For example, potent, early developmental signaling pathways have emerged as essential contributors to both neurodegeneration and the regenerative capacity of nerve cells following injury. It seems increasingly likely, as the field moves forward, that the boundaries will be blurred between early neural development and the lifelong maintenance of flexible neural circuitry. Thus, as the age-old mysteries of neural development gradually yield to the powers of new molecular and genetic

technologies, we are learning not only about how the nervous system is assembled, but how it is maintained throughout life and how it fails during disease.

Biographies

Silvia Arber is a professor of Neurobiology and Cell Biology at the Biozentrum and the Friedrich Miescher Institute. Her laboratory studies the molecular and cellular mechanisms involved in the assembly and connectivity of neuronal circuits during development, with a particular emphasis on circuits controlling movement in the developing spinal cord.

Graeme Davis is a professor and chairman of the department of Biochemistry and Biophysics at UCSF. He holds the Albert Bowers Endowed Chair and is a member of graduate programs in Neuroscience, Cell Biology and Developmental Biology. His laboratory studies the mechanisms that are required to stabilize neural circuitry with an emphasis on the homeostatic control of synaptic transmission and neuronal excitability.