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Development of neurons and glia

Editorial overview

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Sam Pfaff is an investigator with the Howard Hughes Medical Institute and Professor in the Gene Expression Laboratory at the Salk Institute for Biological Studies. His group studies the development, function, and degeneration of spinal neurons involved in motor control. Sam and his colleagues have made seminal contributions to understanding how combinatorial sets of transcription factors specify neuronal subtypes, and the identification of spatial and temporal mechanisms that gate the activity of axon guidance receptors. His recent work uses optical imaging of neuronal activity and locomotor behavior in mice to probe the development and function of spinal motor circuits.

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Shai Shaham is a Professor and Head of Laboratory at The Rockefeller University. His lab discovered the first example of a nonapoptotic developmental cell death program in animals, and its similarities to neurodegenerative processes. He and his colleagues also developed the model organism *C. elegans* as a unique setting to study glia, the major cellular components of vertebrate nervous systems, revealing essential and dynamic roles for these cells in the development and function of the nervous system.

The process by which a mature animal is produced from a single cell has fascinated and puzzled scientists and non-scientists alike for centuries. The nervous system took center stage in many of the pioneering studies on animal development, and neurodevelopment can trace its modern origins back to studies by Wilhem His and Ramon y Cajal in the 1800s. The stereotyped nature of developmental processes led to the notion that these must, in some way, be programmed within the animal — a remarkable feat given the cellular complexity of the brain. Nevertheless, this hypothesis is now taken for granted due to the pioneering work done with genetically tractable model organisms in which developmental defects have been linked to specific genes and signaling pathways. Despite the anatomical and functional differences between vertebrate and invertebrate nervous systems, there is a remarkable degree of conservation in the signaling pathways and cellular processes across evolution. This feature has been exploited in many labs to uncover general principles in neurodevelopment ranging from gene regulation and specification of cell identity, to signaling pathways for growth, differentiation and morphogenesis of neural tissue, to identification of cellular processes and genetic components that establish proper patterns of neuronal connectivity.

Given the tremendous and rapid progress in defining cellular, molecular and genetic features of brain development, it is perhaps not surprising that as we entered the 21st century a general sense that the major questions in neurodevelopment had been addressed began to permeate the biological community. While the vast degree to which cellular diversification occurs during development was still acknowledged together with the immense complexity of establishing trillions of neural connections, it was thought that simple explanations would emerge by applying and reapplying general paradigms that were already known.

However, cracks in this intellectual edifice have emerged. As with other basic scientific endeavors, studies of neurodevelopment have turned to the practical application of the knowledge. The realization that stem cells may be used to cure disease became popular, and it was logically predicted that application of developmental paradigms would provide a means for rationally finding ways to repair the nervous system as a new form of regenerative medicine. Unfortunately it became rapidly clear, that despite the accrued information on animal development, many of the field's most basic questions remained poorly understood, leaving its application wanting. General questions of development such as: ''What is a differentiated cell? How do cells switch from one state to another? How are precise single-cell borders established between adjacent cellular compartments? What limits the scope of action of developmental cues to achieve local morphogenesis?'', are answered only incompletely even today.

While the same general questions also apply to the nervous system, unique aspects of nervous tissue presented additional fundamental conundrums. For example, while some vertebrate tissues exhibit robust regeneration and wound healing in response to injury, the brain is generally loathe to reprogram and repair. Why? Even more remarkable is the realization that our brain consists primarily of cells that are not neurons. The steadfast march to catalog the molecular components and functions of every cell in animals seemed to have passed glia by. Indeed, unlike any other tissue, the most abundant cell class in the nervous system is the least studied.

In this issue, we have compiled a set of reviews that reflect on many of the emerging and unresolved problems concerning development of the nervous system. Importantly, the issue is roughly equally divided in its attention to neurons and glia, reflecting the many emerging roles these non-neuronal cells have been found to play in the nervous system. As development and neuroscience both encompasses large fields, the reviews likewise cover a broad set of topics, from gene regulation, viewed from the perspective of epigenetics and post-transcriptional processes, to the cellular interactions that influence axons and synapses, to the intimate relationship between neurons and glia.

The question of what cell differentiation means is discussed by Staahl and Crabtree, who explain the role of chromatin in defining what makes a neuron a neuron; Barres and Nakashima review the developmental biology of oligodendrocytes and astrocytes, respectively, discussing the molecules that impart identity to these cell types. Sun, examines the role of newly discovered microRNAs in neuronal and glial cell fate determination, revealing remarkable mechanistic complexity in the assignment of cell fate. Doetsch reviews our current state of understanding of adult neuronal stem cells, which may eventually provide a means of applying developmental principles to solve human disease.

Once differentiated, neurons often migrate to their final positions. Prince and Reiner describe novel molecular insights into the mechanisms of neuronal migration in the periphery and CNS, respectively. Gotoh connects the question of migration and differentiation and reviews how these processes are coupled.

How neuronal processes reach their targets is explored by Charron, describing novel axon guidance cues, Marquardt, who describes axon–axon signaling in fascicles, and Schmucker, who reflects on the roles of self-avoidance in wiring the nervous system. Yaron examines the intimate connection between neuronal pruning and cell death in sculpting the nervous system; and Cline examines possible roles for exosomes, extracellular signaling vesicles, in cellular communication in the developing brain.

Other aspects of neuronal morphogenesis are tackled by Heiman, who discusses intriguing similarities in the machineries controlling dendrite and epithelial shapes; and Jin, who discusses a conserved and important pathway for neurite regrowth following injury.

Once neurons are in the vicinity of their targets, synapse formation must ensue to connect them. Colón-Ramos describes recent advances in understanding how synaptic specificity is achieved; while Allen and Stevens describe how glia promote and remodel synaptic contacts, respectively.

To function properly once wired, many neurons require glial partners. The developmental biology of ensheating glia is explored by Talbot, who examines neuron–Schwann cell interactions in the peripheral nervous system; Peles, who delineates the rules of node of Ranvier formation; Daneman, who describes formation and control of the blood–brain barrier; and Nave, who looks at the metabolic support of neurons by glia.

The exploitation of model systems to reveal general principles of neuronal development and morphogenesis has only recently been emulated to begin to map out conserved principles governing glial form and function. Freeman, explores our current state of understanding of glia in invertebrate systems; and an evolutionary perspective on nervous system development, compiled by comparing expression of key genes controlling development of the nervous system in pre-bilaterian animals and the hypothalamus of bilaterians by Arendt.

Finally, many of the studies reviewed here utilized a wide set of imaging techniques with ever increasing spatial and temporal resolution, allowing finer and finer details of developmental processes to be identified and studied. These methods are reviewed by Shroff.

Reading through the collection of essays in this issue, it is hard to imagine that neurodevelopment was ever considered passé. Although most of the topics selected in this review were identified because of their fundamental importance to normal development, it is striking that most reports identify important links between normal development processes and pathways that are relevant to nervous system diseases or injuries in post natal stages of life. The papers reveal a rich set of mysteries in various states of exploration, and remind us that problems in science can rarely be considered truly solved.