Neuronal and glial cell biology

Editorial overview

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Abbreviations
bHLH basic helix-loop-helix
ETS extracellular signal-regulated kinase

Introduction

The reviews in this year’s section on ‘Neuronal and glial cell biology’ focus on recent advances in development, function, and disease. One set of reviews highlights advances in our understanding of the nuclear mechanisms that control the specification of neurons and glia, as well as how extracellular signals regulate these intracellular mechanisms. A second set of reviews describes studies of the neural cytoskeleton that have led to a new understanding of how neuronal structure is molded and how it is rapidly modified in response to external stimuli. A third set of reviews focuses on recent advances in our understanding of the pathophysiology of genetic triplet repeat diseases (which affect a variety of cellular organelles leading to neuronal cell death) and of prion proteins, which are involved in spongiform encephalopathies. This issue also contains a Commentary highlighting the new gene chip methodology, which promises to revolutionize cell biological research in neurobiology during the coming decade.

Specification of neural fate

One of the fundamental goals for cell biologists is determining the molecular basis of cell diversification. How are the thousands of unique neuronal and glial cell fates established during development? Three reviews in this section address this issue and discuss some recent steps forward in understanding the intrinsic mechanisms that regulate the specification of neural identity and in identifying the signaling pathways that control cell fate by regulating these intrinsic diversification mechanisms.

In his review, Anderson (pp 517–524) addresses the question of how neuronal fate is specified by focusing on the roles of major classes of transcription factors in sensory neurogenesis. This review is of interest for several reasons. First, it provides a wonderful example of how transcription factor cascades with striking similarities to those that direct neurogenesis in Drosophila lead to the expression of different combinations of terminal neuronal differentiation genes that result in the generation of sensory neurons with different axonal projections and functions. In particular, he describes recent work on two basic helix-loop-helix (bHLH) transcription factors, neurogenin-1 and -2, which are homologues of Drosophila ATONAL-related bHLH factors. These transcription factors have recently been shown to be essential for sensory neurogenesis and appear to help specify different sensory neuronal fates. He discusses how these transcription factors, in turn, regulate other downstream transcription factors that control expression of trk receptors and other genes important in specifying sensory neuron identity. Second, he describes how these transcription factors have made it possible to elucidate the steps and lineages in sensory neuron generation, from multipotential neural crest stem cells to immature neurons committed to the sensory pathway to specific sensory neuron types. Third, he describes preliminary, but exciting work aimed at understanding how proprioceptive sensory neurons become assembled into functional circuits with motor neurons. Recent studies have identified specific ETS-domain transcription factors found in proprioceptive sensory neurons that are also expressed in the motor neurons they innervate. In motor neurons, expression is highly restricted initially, but in sensory neurons, these factors are initially expressed widely and become restricted to specific pools as development proceeds. Thus, these ETS-domain transcription factors may provide the coding information necessary to establish the classic sensori-motor reflex arc.

How are different types of sensory neurons, such as proprioceptors, nociceptors, and mechanoreceptors, specialized to detect different types of sensory stimuli? Caterina and Julius (pp 525–530) review a variety of recently identified terminal neuronal differentiation genes specifically expressed by nociceptive sensory neurons that encode receptors and channels involved in the detection of painful stimuli. For example, the VR1 receptor for capsaicin, the substance that makes hot peppers burn, has now been identified and cloned. Its expression is limited to the thermal and acid response physiology of C fibers and Type II Aδ nociceptors. A related protein, VRL-1, has recently been identified, and, however, it is not activated by capsaicin or acid, but is activated by temperatures above 52°C, and, therefore, appears likely to underlie the physiological responses of Type I Aδ nociceptors. As their review makes clear, identification of these new receptors and channels has revealed an unsuspected heterogeneity of nociceptive neuronal subtypes. In addition, unexpectedly, the specific biophysical properties of some of these new pain-detecting receptors have provided insight into the pathophysiological bases of chronic pain states, including...
neuropathies and inflammatory pain. For example, acidification or temperature elevation greatly reduce the threshold for activation of VR1 receptors.

A great number of transcription factors that help to specify neuronal fate have now been identified. But how is glial fate specified? Although glia are the predominant cell type in mammalian brain, transcription factors that specify glial fate have not yet been identified. Recent progress has been made, however, in understanding how glial cells in Drosophila are specified, as reviewed by Grandcherath and Klamkin (pp 531–536). Interestingly, cascades of transcription factors, similar to those that control neuronal fate, also direct development of glia. Some of the extrinsic signals that induce the expression of these transcription factors have also been identified. These transcription factors include glial cells missing (gcm), repo and pointed. Although many of the transcription factors that specify neuronal fate in Drosophila are highly conserved and have homologues with very similar functions in vertebrates, there is much less conservation of function in glia. It has been disappointing, for instance, to find that gom, which commits neural precursor cells to glial fates in Drosophila, does not appear to have the same function in mammals. Fortunately, HHLH proteins that specify glial fate in mammals are beginning to be identified and may be ready for review in time for next year’s issue.

**Signaling pathways that regulate neural development**

How is expression of the genes that induce neurogenesis regulated? Whereas proneural genes are transcription factors that endow cells with the potential to become neural cells, neurogenic genes are involved in the cell–cell interactions that select the subset of cells that actually become neurons. The prototypical neurogenic genes are those encoding the Notch receptor and its ligands Delta and Serrate (Jagged), which, among many functions, limit the generation of neurons by transmitting inhibitory signals from neural cells to surrounding cells, which otherwise would also become neural. In other contexts, these same interactions actually induce glial fate. Importantly, modulators of Notch signaling have been found to regulate boundaries of gene expression in developing tissues such as has been observed at the limb–bud apex and during the segmentation of mesoderm into somites. Wu and Rao (pp 537–543) review how Notch function is regulated by the fringe gene to make borders in developing regions, including the neural tube, eye, and limb. Genetic evidence suggests that Fringe may modulate the Notch signaling pathway by controlling differentially activation of Notch by different ligands. The fringe gene may encode a glycosyltransferase, but it is still puzzling how it acts on itself.

In their review, Grewal, York, and Stork (pp 544–553) provide another example of how extracellular signals regulate neuronal survival and differentiation. They focus on extra-cellular-signal-regulated kinases (ERKs), also known as MAP kinases), which are emerging as important regulators of activity-dependent neuronal survival, development, and plasticity. ERKs are activated by various receptor tyrosine kinases and are thought to mediate the ability of nerve growth factor (NGF) to induce differentiation of PC12 cells into sympathetic neuron-like cells. Within neurons, novel pathways have been identified that allow second-messenger signals such as calcium, cAMP, and diacylglycerol to regulate ERK signaling independent of protein kinases A and C. These pathways involve the activation of small G proteins such as ras, which has already been shown to mediate receptor tyrosine kinase activation of ERKs. Activation of ras results in either cell proliferation or differentiation, depending on the cellular context.

Grewal and colleagues summarize recent work addressing how the complement of intracellular signaling proteins within a cell controls the duration of ras activation and the induction of the proliferative versus the differentiative response. The mechanisms for ensuring specificity have been obscure because so many pathways are activated by ras and other signaling molecules. Recent work has suggested that adapter proteins that localize one or more constituents of a signaling pathway are crucial for assuring specificity. It has also been found that neurotransmitters such as glutamate can directly regulate ras activation. Here, adapter proteins that target proteins controlling ras activity to the vicinity of glutamate receptors appear to be important. Thus, activity-dependent mechanisms can synergize with tyrosine kinases in a variety of ways to activate ERKs. Once activated, ERKs are relocated from neuronal processes to the cytoplasm and, ultimately, enter the nucleus, where they activate transcription. These findings have raised many questions. What are all the targets of ERKs? How is signal specificity generated given the many different pathways that can lead to activation of ERKs? The answers to these and other signaling questions has been hindered by the difficulty in doing systematic cell genetics. The new gene chip technology promises to provide a powerful tool for understanding the signaling pathways that regulate the development and function of neurons. These chips consist of high-density oligonucleotide arrays (also known as cDNA arrays) that allow the mRNA levels of thousands of genes to be quantified. To understand how signaling regulates gene expression, mRNA levels in a cell or tissue type of interest can be compared before and after stimulation. This provides information on how various signaling pathways can quantitatively and qualitatively affect transcription. Although this new methodology has only recently become available, its use is already leading to new insights into how signaling pathways achieve their different transcriptional outputs. Among other uses, the availability of these chips is likely to stimulate new initiatives in somatic cell genetics as they greatly facilitate analyses of mutant cell phenotypes. In his Commentary, Serafini (pp 641–644) reviews this new methodology and describes how it may be useful for future
studies in neurobiology. His article makes it clear that oligonucleotide and DNA arrays provide a powerful new tool for neural cell and developmental biologists.

**Functional roles for the neuronal cytoskeleton**

The neuronal cytoskeleton is composed of three intercon-
nected filaments: actin microfilaments, microtubules, and intermediate filaments called neurofilaments. Neuro-
filaments consist of heavy, medium, and light subunits that assemble into 10 nm filaments. Neurofilament proteins are unique to the nervous system, suggesting an important functional significance in neurons, but these functions have been surprisingly difficult to identify.

In his review, Julien (pp 554–560) discusses recent evi-
dence demonstrating that neurofilaments can control the caliber of axons. Though not required for dendritic growth or axonogenesis, neurofilaments are required for the radial enlargement of axons in response to myelination. (It appears that it is both actin filaments and microtubules that are crucial for dendritic growth and axonogenesis, as well as for imparting neuronal polarity; see [1] for a recent review.) Transgenic mice have now been generated that are deficient in each neurofilament subunit, and they each yield a different axonal phenotype. Together, these studies have begun to give rise to tentative models for how these filaments are organized to control axon diameter.

Julien also summarizes the evidence that neurofilament mutations, as well as abnormal secondary modifications of neurofilaments, can result in neurodegenerative disease. These mutations cause abnormal accumulation of neurofil-
aments or disorganization of the cytoskeleton that may lead to neuronal death. Familial amyotrophic lateral scle-
rosis (ALS) is often caused by mutations in Cu/Zn superoxide dismutase (SOD1), which leads to abnormal accumulation of neurofilaments and appears to be caused less frequently by mutations in the neurofilament subunit, though it is not yet clear how or why they end up there. Surprisingly, new evidence indicates that accumulation within the nucleus is required, but aggregation within the nucleus of these proteins is not always required for disease pathogenesis. Nonetheless, pharmacological blockade of the caspase-mediated cleavages can attenuate neuronal death of cells induced by pathogenic triplet repeat proteins. As there are a great variety of triplet repeat diseases that affect many different types of neurons, this is an important advance. Many issues remain to be addressed, including identification of the targets affected by the path-
ogenic repeat fragments and the aggregation process itself.

Spongiform encephalopathies are a group of transmissible diseases include Creutzfeldt-Jakob disease (CJD), a human dementing illness, also bovine spongiform encephalopathy (BSE), which affects primarily cattle (and is also known as mad cow disease), as well as a similar disease called scrapie that affects sheep and goats.

Many previous reviews have focused on aspects of pathogen-
ess and infectivity, but in his review, Brookes (pp 571–577)
discusses recent advances in our understanding of the cell biological aspects of prions, including PrPc location, structure and topology within the cell and its normal physiological role, as well as new insights about prion phenomenon from studies of fungi. Only recently has it been realized that PrPc is synthesized in two alternative topological forms across the plasma membrane. Certain mutations can alter the balance of these topological forms, producing the typical neuropathological features of prion disease in transgenic mice. The normal role of PrPc has been a mystery, but, remarkably, it turns out that PC12 cells selected for resistance to copper toxicity express elevated levels of PrPc, suggesting a role in copper metabolism. Finally, filamentous fungi have provided an interesting new system for studying propagation and transfer of prion-like states by proteins, suggesting new models of how prions and other infectious proteinaceous particles may be generated. As this review makes clear, however, there is a long road left to travel before we understand either the normal function of PrPc in neural cells or how it leads to disease.

References