Neuronal and glial cell biology

Editorial overview

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Neurons and glial cells evolved long after the molecules, organelles and metabolic processes necessary for the survival of eukaryotic cells had appeared. Accordingly, most of the molecules, organelles and mechanisms involved in the function of neurons and glial cells are common to other cells. Indeed, it is generally accepted that the many specialized functions of the nervous system are simply the result of the unique way in which neurons and glial cells use common cell features. The reviews of neuronal and glial cell biology that focus on those aspects of cellular anatomy, chemistry and physiology that give neurons and glial cells their distinctive properties. The themes covered here unavoidably overlap with those in reviews on other topics in this series, particularly those concerning mechanisms involved in neuronal development and in intercellular signalling; the reader is referred to them for extended coverage. We have chosen to discuss the reviews under four headings: vesicle traffic and exocytosis; cytoskeletal structure and function; adhesive interactions and growth cone dynamics; and specialized interactions of glial cells with neurons and endothelial cells. All are topics currently attracting much research interest in cellular neurobiology.

Vesicle traffic and exocytosis

The reviews by Huttner and Dotti (pp 388–392) and Linecsted and Kelly (pp 382–387) cover in detail several important aspects of these interrelated topics. It is made clear that directed vesicle traffic plays a crucial role in establishing the polarity in neurons, as manifest in the structural and functional differences between axons and dendrites, just as it does in establishing polarity in other cell types. Moreover, the signalling involved in establishing neuronal polarity seems to be much the same as that for other cells. Expression studies indicate, for example, that the same targeting signals that are used to direct vesicles to particular compartments in epithelial cells, and thus account for the apical/basal polarity of such cells, are also involved in the development of neuronal polarity. Two neuronal organelles that do not appear to have specific counterparts in many other cell types, large dense-core vesicles and small synaptic vesicles, are also discussed. Both vesicle types contain neurotransmitters and are found together in axon terminals from which they release the transmitters by exocytosis. Until recently, differences in the regulation of the two types of vesicles were unknown. It now seems likely that each vesicle type is generated by a different cellular pathway and that their participation in exocytosis can be independently regulated.

A large family of small GTP-binding proteins, rabs, has recently been identified in a variety of cells. The current view is that the individual members of this family associate with subsets of organelles to help regulate organelle trafficking in the cells. The above reviews describe properties of these proteins, a model providing a role for the proteins in membrane trafficking, and experiments suggesting that one such protein, rab 3A, plays an important role in Ca2+-regulated exocytosis of synaptic vesicles. Although the sites of exocytosis in nerve terminals, active zones, have long been known, the mechanisms directly involved in exocytosis are poorly understood. Of much interest in this regard are the results of recent studies that lead to the conclusion that synapsins, a family of phosphoproteins that interact with synaptic vesicles and cytoskeleton, regulate both synaptic vesicle clustering at active zones and exocytosis. Also of interest are kinetic measurements indicating that vesicles must be docked to the plasma membrane of the axon terminal in fusion-competent complexes which include pores that can be rapidly and reversibly opened. Progress in defining the molecular composition of these pores is discussed; such knowledge is requisite for detailed studies on how the opening and closing of the pores are regulated.

Cytoskeletal organization and function

Recent progress in understanding functions of the major cytoskeletal proteins in the nervous system has been dramatic. Cleveland and Hoffman (pp 546–555), focusing primarily on microtubules, review interesting new studies in this area. Among these are studies suggesting that two microtubule-associated proteins, MAP-2 and tau, are directly involved in neuronal morphogenesis, studies aimed at identifying specific modifications that make brain tubulin heterogeneous biochemically, and studies indicating that tubulin is a substrate for phosphorylation by src and possibly additional protein tyrosine kinases. New methods have made it possible to observe directly the behavior of single microtubules and other cytoskeletal elements in active growth cones. Such observations indicate that microtubules are prominent constituents of the leading edges of elongating neurites, where their distributions and dynamics suggest that they have an important role in neurite guidance. Tyrosine-phosphorylated tubulin is preferentially incorporated into microtubules,
suggesting a mechanism by which signalling molecules, such as NGF, may influence the rate and direction of axon growth.

Sheetz and Martenson (pp 393–398) review the recent explosion of work on fast intracellular transport, focusing on possible mechanisms by which directionality may be regulated, including the microtubule-based motors, kinesin and dynein. They also review recent work on slow transport which indicates that the cytosol does not move continuously as one mass down the axon. Instead, different elements move discontinuously, and movement seems likely to depend on unidentified motor proteins.

Adhesive interactions and growth cone dynamics
Many steps in the differentiation of neurons, including myelination and axon growth, require adhesive interactions mediated by receptors on neurons and ligands immobilized on other cells or present in the extracellular matrix. Grumet (pp 370–376) and Tomaselli and Neugebauer (pp 364–369) review progress in characterizing these receptors and ligands. Two prominent classes of cell adhesion molecule have been identified in the nervous system — the cadherins and members of the immunoglobulin superfamily. These molecules are believed to play crucial roles in guiding axons to establish correct connections during embryogenesis, among other functions. Some new evidence in support of this proposal has been obtained from studies on Drosophila embryos. The number of identified members of the immunoglobulin superfamily in vertebrates has approximately doubled in the past two years. Many have been characterized by sequence analysis of clones encoding neural antigens which were shown by immunohistochemistry to have intriguing distributions. When expressed, each member has been shown to function as an adhesion molecule, and the majority, as substrates, promote neurite outgrowth. The limited distributions of several of these molecules suggests that they may have roles in axon guidance. The more widespread distributions of others, such as NCAM, suggest that they have additional important functions. During the past few years, the number of cadherins identified in the vertebrate nervous system has increased from one, N-cadherin, to approximately 15. The majority of these have been discovered using the polymerase chain reaction. The distributions and functions of the novel cadherins are at present not well characterized, but they seem likely to function in axon guidance and other aspects of neural development.

The majority of extracellular matrix molecules interact with cells via specific receptors. In the past few years, several matrix molecules, including thrombospondin, fibronectin, and vitronectin, have been shown to promote neurite outgrowth in vitro and have been identified in the embryonic nervous system in vivo. Antibodies to several of these have been shown to perturb neural development. Members of a large class of protein heterodimers, named integrins, have been shown to function as receptors for these matrix proteins. Integrins are assembled using one each of several possible α- and β-subunits. Thus this family includes many more receptors than genes (14α, 8β). Recent work has identified ligands for these receptors including both matrix proteins and cell adhesion molecules. Of particular interest is that many of the α- and β-subunits are expressed in the nervous system where they are differentially localized and developmentally regulated.

Adhesive interactions and the cytoskeleton are both required for growth cone motility. In their review, Heidemann and Buxbaum (pp 339–345) focus on recent experiments elucidating the biophysical basis of growth cone movement. Direct observations of Ca2+ levels, microtubules, microfilaments, and surface proteins in growth cones during responses to guidance cues have made it possible to develop and test more detailed molecular models for growth cone motility.

Specialized interactions of glial cells with neurons and endothelial cells
In this set of reviews, only a subset of the specialized interactions between cells in the nervous system is considered. Rubin (pp 360–363) reports on progress in the understanding of how the tight endothelial cell junctions that constitute the blood-brain barrier are formed. There is now good evidence that astroglia induce vascular endothelial cells to make unusually tight junctions and that several second messenger systems regulate the permeability of these junctions.

That there must be an interaction between neurons and glial cells (oligodendrocytes and Schwann cells) to produce the glial sheaths of neurons, including myelin, has been recognized for more than 30 years, yet the discovery of the mechanisms underlying such an interaction still proves difficult. Colman (pp 377–381) discusses cell adhesion molecules, including L1, myelin associated glycoprotein and P0, that appear to have distinct roles in ensheathment or myelination of axons. Indeed, the functional role of individual adhesion molecules are much better understood in these cases than they are for other cellular interactions in the nervous system.

Early electrophysiological studies on glial cells in situ revealed that they respond to neuronal electrical activity. A variety of elegant experiments indicated that the response was simply passive. Barres (pp 354–359) discusses recent experiments that have extended these studies by using techniques that permit a higher degree of resolution of the electrical properties of glial cells than previously possible. In particular, glial cells are now known to express voltage-regulated and transmitter-gated ion channels. There is also evidence of signalling in both directions between neurons and glia. Such findings raise the possibility that glial cells actively and rapidly modulate neuronal function.

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