Glial cells have long been considered to play roles in the nervous system that are unexciting compared with those of neurons. They provide neurons with nutrients, guide migrating neurons and their precursors during development, and dispose of the brain’s “waste.” Recent evidence, however, suggests that glial cells play more sophisticated, neuronlike roles. They integrate neuronal input, modulate synaptic activity, and process signals related to learning and memory. These findings have significant implications for humans with neurodegenerative diseases. In addition to activation on nervous system injury and during neuronal degeneration, glial cells also degenerate in several neurodegenerative diseases. Therefore, glial cell loss may contribute to the impairment of learning and memory. Therapeutic approaches to combat human neurodegenerative diseases thus need to restore the function of both neurons and glial cells.

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NEURONAL PROPERTIES OF GLIAL CELLS

Additional, more elaborate functions were recently assigned to glial cells. In the mature nervous system, examination at the ultrastructural level reveals a tripartite structure involving the astrocyte that can be intimately associated with the synapse and that literally enwraps many presynaptic and postsynaptic terminals (Figure 1). This close physical relationship probably provides an opportunity for many functional interactions between astrocytes and neurons. As an astrocyte can make contacts with a neuron and a capillary, it has the potential to shuttle nutrients and metabolites between the blood supply and the active neuron (Figure 1). Furthermore, as a single astrocyte can make contacts with multiple neurons, these nonneuronal cells are positioned to provide information transfer between neighboring neurons.

In the stratum radiatum hippocampi, for example, about 50% of the synapses have astrocytic processes, and in 30% of the synapses, an astrocyte process separates 2 neighboring synapses (Figure 1). In addition, astrocytes almost exclusively surround synapses that have a high probability of neurotransmitter release.

Astrocytes express functional receptors for many different neurotransmitters. Binding to these receptors leads to changes in intracellular calcium levels and even to oscillations in internal calcium levels. Many of the initial studies that demonstrate calcium excitability of astrocytes were performed in cell culture, but studies using acutely isolated brain slices and later acutely isolated hippocampi have supported the calcium excitatory property of astrocytes. As astrocytes possess a number of neurotransmitter receptors coupled to intracellular calcium mobilization, neuronal activity may regulate astrocytic calcium levels. Indeed, several laboratories have demonstrated that astrocytes and perisynaptic Schwann cells respond to synaptic activity through the activation of glial receptors.

In addition to integration of neurotransmitter input, astrocytes release their own transmitters that act on neighboring neurons and modulate their function, suggesting a bidirectional signaling pathway between astrocytes and neurons (Figure 1). If glial cells can release neurotransmitters in a regulated manner, this process must be a fundamental component of their dialogue with neurons during synaptic activity.

A compartmentalization reminiscent of that of neurons has been demonstrated for the cerebellar Bergmann glia. These highly ramified glial cells consist of hundreds of independent compartments, called microdomains, that are capable of autonomous interactions with the particular group of synapses they enwrap. Stimulation of adjacent parallel fibers induces localized elevations of intracellular calcium levels in the Bergmann glia.

ROLE IN MEMORY AND LEARNING

What is the role of glial cells in memory and learning? Studies in brain slices showed that activation of astrocytes increased miniature inhibitory postsynaptic currents in hippocampal pyramidal neurons. Astrocytes may therefore be necessary in the activity-dependent modulation of inhibitory synapses in the hippocampus. A role of astrocytes in synaptic function is also supported by results of studies in mice lacking the intermediate-filament glial fibrillary acidic protein (GFAP), a protein found predominantly in astrocytes of the CNS. Although astrocytes were present in the CNS of the mutant mice, they contained a severely reduced number of intermediate filaments. Since astrocytic processes contact synapses and may modulate synaptic function, McCall et al examined whether the hippocampal CA1 region of GFAP-deficient mice was altered in long-term potentiation (the increase in synaptic potential after brief high-frequency trains of stimulation). The mutant mice indeed displayed enhanced long-term potentiation compared with control mice. Therefore,
Figure 2. Gial cells under pathologic conditions in the adult brain. A, Reactive astrocystosis as a vigorous response to diverse neurological insults, including viral infections, acute, chronic, and traumatic brain injuries, and neurodegenerative diseases such as Alzheimer disease (AD). The key histopathological hallmarks of AD, tau-containing neurofibrillary tangles and amyloid plaques, induce astrocystosis and the activation of microglia, which subsequently release cytokines. B, In many tauopathies, tau aggregates are numerous in neurons and gial cells. In some brain regions of affected individuals, the glial abnormalities outnumber the neuronal abnormalities. Functional impairment of gial cells as a consequence of the deposits is likely to affect gial-glia and gial-neuron interactions. C, Glial abnormalities of Alexander disease. Eosinophilic deposits of gial fibrillary acidic protein (Rosenthal fibers) are the key pathological hallmark of Alexander disease. Again, functional impairment as a consequence of the deposits is likely to affect gial-mediated interactions.

these mice demonstrate that a primary defect in gial cystoses influences neuronal physiology. In a related study using another GFAP-deficient mouse strain, excitatory synaptic transmission from parallel or climbing fibers to Purkinje cells was unaltered in the cerebellum, and these synapses displayed normal short-term synaptic plasticity to paired stimuli. In contrast, long-term depression at parallel-fiber Purkinje cell synapses was clearly deficient, suggesting a role for gial cystoses in induction and maintenance of long-term depression in the cerebellum.

GLIAL CELLS IN DISEASE

Results of a recent quantitative postmortem investigation of the cerebral cortex have convincingly demonstrated cortical gial cell loss in patients with major depression. Evidence is also mounting that gial cell loss may be a feature of schizophrenia. In addition, gial cells are heavily affected in diseases with cognitive dysfunction related to Alzheimer disease. Hallmark lesions of Alzheimer disease are extracellular amyloid plaques and intracellular neurofibrillary tangles that are composed of hyperphosphorylated, filamentous microtubule-associated tau protein. In the absence of amyloid plaques, neurofibrillary tangles are also abundant in additional neurodegenerative diseases, including Pick disease, progressive supranuclear palsy, corticobasal degeneration, argyrophilic grain disease, and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). In contrast to Alzheimer disease, in which hyperphosphorylated tau protein forms filaments only in neurons, numerous tau filament-containing glial cells are present in many of these diseases that are collectively termed tauopathies. These disease entities, all of which were previously defined as neurodegenerative diseases, are now better considered glaneuronal disorders. A recent analysis of 2 patients with the disease-causing FTDP-17–linked tau mutation N279K showed widespread neuronal and gial tau accumulation in the cortex, basal ganglia, brainstem nuclei, and white matter. In the neocortex, tau-immunoreactive gial cells outnumbered immunoreactive neurons. The glial abnormalities of corticobasal degeneration include astrocytic plaques and numerous tau-immunoreactive inclusions in the white matter (Table).

Although it is likely that the glial abnormalities affect neuronal degeneration, it is at present unknown whether they are required for a progression of the disease and its clinical features. Aspects of the glial tau abnormalities have been reproduced in a mouse model that expresses the FTDP-17–associated tau mutation G272V under control of a prion protein promoter–driven transactivator system. Transgenic tau expression in oligodendrocytes was much higher than that in neurons. Oligodendroglial G272V tau formed filaments and was phosphorylated at the tau phosphoepitope AT8 that is diagnostic for Alzheimer disease. In related transgenic models that express wild-type or FTDP-17–associated mutant forms of tau in neurons, the tau abnormalities were restricted to neurons, but microglial and astrocytic cells were activated. In some of these transgenic mouse models, microglia with phagocytosed myelin debris and myelin ovoids were present, indicating wallerian degeneration. Together, these animal models are useful to study the pathophysiology and prevention of tau filament formation in neurons and gial cells.

The only known late-onset neurodegenerative disease in which gial cell inclusions constitute the predominant lesion is multiple system atrophy. Clinically, multiple system atrophy includes olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome. The cytoplasmic inclusions are strongly immunoreactive for α-synuclein and are found mainly in the cytoplasm and, to a lesser extent, in the nucleus of oligodendrocytes (Table). The formation of gial cytoplasmic inclusions might be the primary lesion that will eventually impair nerve cell function. Nerve cell loss and clinical symptoms of multiple system atrophy in the presence of only cytoplasmic inclusions have been described. Physiologic expression of tau and α-synuclein proteins occur predominantly by neurons.
Associated with the accumulation of insoluble protein aggregates in various disorders, but also with injury in the nervous system, is the morphologic activation of astrocytes and microglial cells, a process called reactive gliosis (Figure 2A). After injury, brain macrophages proliferate and function in tissue repair, including removal of dead tissue and debris through phagocytosis. In addition, cytokines produced by reactive microglia initiate a cascade of cellular responses that greatly influence astrocytes. During this process, GFAP is up-regulated in astrocytes. In a variety of conditions, including injury and neurodegenerative diseases, the GFAP content of astrocytes at the site of injury or activation increases until the astrocyte cell body and its processes are completely filled. These reactive astrocytes repair damaged brain tissue and function in the reestablishment of the integrity of the microenvironment surrounding the lesion.

In addition to degeneration during disease and reaction to injury of the nervous system, glial alterations are the primary cause of the neuropathological changes in some cases. Alexander disease is a rare disorder of the CNS of unknown etiology. Infants with Alexander disease usually die within the first decade of life; patients with juvenile or adult forms typically experience ataxia, bulbar signs, spasticity, and a more slowly progressive course (Table). The pathological hallmark of all forms of Alexander disease is the presence of Rosenthal fibers, ie, cytoplasmic inclusions in astrocytes that contain GFAP in association with small heat shock proteins (Figure 2C). Overexpression of human GFAP in astrocytes of transgenic mice is fatal and accompanied by the presence of inclusion bodies indistinguishable from human Rosenthal fibers. These results suggest that a primary alteration in the GFAP may be responsible for Alexander disease. Indeed, results of sequence analysis of DNA samples from patients representing different phenotypes of Alexander disease showed that most cases are associated with nonconservative mutations in the coding region of the GFAP. Alexander disease therefore represents the first example of a primary genetic disorder of astrocytes.15

<table>
<thead>
<tr>
<th>Disease</th>
<th>Affected Cell Type</th>
<th>Cell Abnormalities</th>
<th>Clinical Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Astrocytes and oligodendrocytes</td>
<td>Astrocytes: thorn-shaped with tau deposits, strongly GFAP-positive; oligodendrocytes: coiled bodies with tau inclusions</td>
<td>Early signs of vertical gaze paresis and progression to total external ophthalmoplegia; progressive dementia; parkinsonism</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>Astrocytes and oligodendrocytes</td>
<td>Astrocytes: thorn-shaped with tau deposits, astrocytic plaques positive for tau; oligodendrocytes: coiled bodies with tau inclusions</td>
<td>Cognitive disturbances, cortical sensory loss, extrapyramidal motor dysfunction, and unilateral rigidity</td>
</tr>
<tr>
<td>Pick disease</td>
<td>Astrocytes and oligodendrocytes</td>
<td>Astrocytes: ramified inclusions and Pick body−like tau inclusions; oligodendrocytes: coiled bodies with tau inclusions are less frequent</td>
<td>Progressive dementia and personality deterioration, associated with verbal and behavioral stereotypes; extreme form of frontotemporal dementia</td>
</tr>
<tr>
<td>Alexander disease</td>
<td>Astrocytes</td>
<td>Contain eosinophilic inclusion bodies called Rosenthal fibers; cytoplasmic inclusions contain GFAP in association with small heat shock proteins</td>
<td>Rare, progressive leukoencephalopathy; infants die within the first decade of life; patients with juvenile or adult forms typically experience ataxia, bulbar signs, and spasticity</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>Oligodendrocytes</td>
<td>Cytoplasmic and, to a lesser extent, nuclear inclusions of α-synuclein</td>
<td>Orthostatic hypotension, impotence, incontinence, and parkinsonism; clinically often mistaken for Parkinson disease</td>
</tr>
</tbody>
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*GFAP indicates glial fibrillary acidic protein.

**Glia Cells in Neurodegenerative Diseases**

Associated with the accumulation of insoluble protein aggregates in various disorders, but also with injury in the nervous system, is the morphologic activation of astrocytes and microglial cells, a process called reactive gliosis (Figure 2A). After injury, brain macrophages proliferate and function in tissue repair, including removal of dead tissue and debris through phagocytosis. In addition, cytokines produced by reactive microglia initiate a cascade of cellular responses that greatly influence astrocytes. During this process, GFAP is up-regulated in astrocytes. In a variety of conditions, including injury and neurodegenerative diseases, the GFAP content of astrocytes at the site of injury or activation increases until the astrocyte cell body and its processes are completely filled. These reactive astrocytes repair damaged brain tissue and function in the reestablishment of the integrity of the microenvironment surrounding the lesion.

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**TRANSPLANTATION APPROACHES TO TREAT HUMAN DISEASES**

A common neuropathological feature of neurodegenerative diseases is neuronal cell loss. In addition to pharmacological treatments, cellular grafting approaches are currently undergoing evaluation for their therapeutic potential. These approaches should appreciate the substantial cell loss in the glial compartment in many of these diseases, but also that the cells that are routinely used in grafting protocols have the potential to differentiate into neurons and gliallike cells. Cell replacement therapies are currently used to treat Huntington disease or Parkinson disease.16,17 For the latter, clinical trials have been initiated already by transplanting human fetal brain tissue to substitute for the loss of dopaminergic neurons. However, several aborted fetuses are required for the therapy in a single patient, which causes practical and ethical problems. Another approach is the use of engineered murine embryonal stem cells, or human cell lines. One of the best established human cell lines is the embryonal carcinoma cell line NT2. This cell line is transflectable, capable of differentiating into postmitotic neuronlike cells (NT2N cells) after treatment with retinoic acid, and transplantable into the brain or the spinal cord of immunocompetent and immunodeficient rodents.18 Intracerebral grafting of NT2N cells has been used successfully to promote functional recovery of ischemic rats, and NT2N cells have been used also as replacement therapy for Parkinson disease. Undifferentiated human NT2 cells grafted into brains of newborn immunocompetent mice migrate over distances of several millimeters and differentiate into neuronlike and oligodendrogiallike cell types.19 These findings emphasize the usefulness of NT2 cells in therapeutic approaches. The NT2 cells are particularly valuable, as they may be used
as vehicles for the release of neurotrophic factors into the host brain environment.

Intrauterine transplantation of murine embryonal stem cells into the brain generated chimeras composed of embryonal stem cell–derived neurons, oligodendrocytes, and astrocytes. These cells can thus serve also as a valuable source of cell type–specific somatic precursors for neural transplantation.

Although the field of neural transplantation has been dominated experimentally and clinically by the transplantation of neuronal cells or their progenitors, recent glial cell transplantations suggest that such an approach may be on the verge of therapeutic application in human myelin diseases. As a cell source, neural stem cells have been exploited as a potential source of oligodendrocyte precursors. These cells can be isolated from the CNS throughout life and grown as neurospheres by means of conditioned media. Transplantation of oligodendrocyte precursors into the spinal cords of rats has shown that these cells can migrate up to 3 to 4 mm from the injection site, although most of these cells die, mainly by apoptosis. Surviving cells, however, persist for up to 18 months after transplantation, depending on the host strain used. It is also possible to promote an oligodendrocytic differentiation from embryonic stem cells in vitro. Grafting of these cells into rat induced myelination of axons.

These advances are promising and suggest that treatment of human neurodegenerative diseases needs to restore the function of neurons and glial cells. As more insight is gained into the role of glial cells in brain function, the importance of these cells in disease processes will become even more apparent. At the same time, pharmacological and cell transplantation treatments will pay credit to the therapeutic potential of glial cells.

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