What Is a Glial Cell?

BEN A. BARRES*
Stanford University School of Medicine, Department of Neurobiology, Fairchild D235, Stanford, California

The last few years has seen a revolution in our understanding of glial cells. We now know that astrocytes, in addition to mopping up transmitters and maintaining extracellular ion levels, actively control synaptogenesis, synapse number, synapse function, and synaptic plasticity. Even oligodendrocytes and Schwann cells, are active participants in nervous system function. In addition to providing insulation and trophic support to neurons, they sculpt the structure and electrical properties of axons by controlling their diameter, the spacing and clustering of ion channels at the node and paranode. Schwann cells also control the regeneration of axons and the function of synapses at the neuromuscular junction. Neurons and glia divide metabolic labor in a way that, though still poorly understood, no doubt underlies an interaction vital to proper nervous system function and perhaps much of the brain's response to ischemia. In short, virtually every aspect of brain development and function involves a neuron-glial partnership. It is no longer tenable to consider glia as passive support cells.

There are an endless number of important questions about neuron-glial interactions. Exactly how is metabolic labor divided between neurons and glia and what is the point of this? What is the identity of the signals flowing between neurons and glia and what is their purpose? Might astrocytes be the primary synthesizers of neurotransmitters or their immediate biochemical precursors, rather than neurons? Do astrocytes play a role in inducing and maintaining the blood-brain barrier, or is another cell type responsible? Do astrocytes actually help to signal neuronal survival in vivo? And what is the point of reactive astrocytes; are they good, bad, or both? I know of little convincing data that addresses most of these questions, but newly developed methods for genomics, proteomics, RNA interference, neural cell purification and culture, all offer a way forward. These new methods provide powerful new ways to better characterize glia and their interactions with neurons, and to perform question-oriented, hypothesis-driven research about glial function.

An important, closely related set of questions is raised by recent studies on neural stem cells and gliogenesis reviewed in this special issue. These papers review the amazing findings of the last few years that some "glia" can actually behave as multipotent neural stem cells that can generate neurons, both in vitro and in vivo. Radial glia and subventricular zone astrocytes have all been shown to do this in developing and adult brains, respectively. A subset of ependymal cells also appears to have the capacity to generate new neurons, although they now appear to lack the self-renewing ability of a true stem cell. In addition, in the adult chick, Muller glial cells in the retina and supporting glial cells in the inner ear can be induced after injury or growth factor stimulation to generate new neurons. Even oligodendrocyte precursor cells in culture can be induced with certain growth factors to become multipotent neural stem cells. It is quite important to note, however, that most glial cells in the CNS are not neural stem cells, but rather a distinct subset.

The new findings that glia can be neural stem cells raise a difficult question. When should a cell be called a glial cell? Several papers in this issue will review the astounding recent discovery that in developing rodent brains, radial glia give rise to the majority of pyramidal neurons. So, are these radial glia actually glial cells after all? This question is especially thorny given that radial glia also subserve a traditional "glial" function of guiding the migration of developing neurons. Nonetheless I would argue that they should no longer be called glial cells because we now know that their most important function is to be neural stem cells. That radial glia also guide migration does not sway me, because I believe that all cell classes in the brain, including neurons and glia, simultaneously perform both passive support roles and more active roles. For instance, considerable evidence now indicates that neurons provide trophic support for glia. In fact, the evidence that neurons support glia in the brain in vivo is far stronger than the evidence that glia support neurons. Thus, I see no reason why we shouldn't return to the nomenclature of the early neurohistologists and refer to radial glial cells as neuroepithelial cells, just as we do in the developing retina.

*Correspondence to: Dr. Ben A. Barres, Stanford University School of Medicine, Department of Neurobiology, Fairchild D235, 299 Campus Drive, Stanford, CA 94305-5125.E- mail barres@stanford.edu

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Similarly, should the subventricular zone astrocytes that generate neurons be referred to as "astrocytes"? I once again have considerable reservation. Though these cells may express a few proteins such as GFAP or S100β, this alone is clearly insufficient to make them deserving of the name astrocyte. Though strongly expressed by white matter astrocytes, GFAP is hardly expressed by most protoplasmic astrocytes, and is strongly expressed by a number of non-neural cell types outside the nervous system. Similarly, S100β is expressed by cell types besides astrocytes such as oligodendrocyte precursor cells. Until there is convincing evidence that they share important astrocyte functions, I propose that we call them arturocytes in honor of the person who discovered them and so beautifully demonstrated their function as neural stem cells. It is far past time to stop calling every neural cell in the brain that is not a neuron, a glial cell.

Finally, the exciting advances reviewed in this special issue, raise many important questions. First of all, how are white matter (fibrous) and grey matter (protoplasmic) astrocytes normally generated? Both radial glia and SVZ stem cells have been shown to generate primarily protoplasmic astrocytes, so it is still very mystical how the bulk of fibrous astrocytes arise, and how their functions compare to those of protoplasmic astrocytes. Radial glia are intrinsically different in their neurogenic potential from region to region; how are these intrinsic differences specified? Why do radial glia and Muller cells maintain their ability to behave as stem cells in some organisms but not others? Do aberrantly persisting "glial" stem cells in some cases lead to gliomas, and is their failure to persist in mammals relevant to understanding the evolutionary loss of regenerative ability in our CNS? Most importantly, how can we harness the stem cell abilities of some glia to generate new neurons to rebuild damaged brains? One thing is certain; there has never been a better time for young neuroscientists to enter this field.