Do Your Glial Cells Make You Clever?

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The cellular basis for cognition is generally believed to derive from neurons. In this issue of *Cell Stem Cell*, Han et al. (2013) transplant human glial progenitors into mouse brains and thereby improve their learning and memory and implicate a previously unknown role for glial cells in contributing to cognition.

Few neuroscientists would deny that their subject has, by and large, been a neuron-centric one, with the neurons fulfilling the primary functions of the nervous system, helped along by the surrounding glial cells. Indeed, this notion of glial subordinance is encapsulated in the very term glia, which, translated from the original Greek, means "glue." This is an understandable position—it has been apparent from the time of Galvani in the eighteenth century that the nervous system is bioelectrical and that electrical impulse conduction by nerve fibers is central to brain function. Moreover, an undoubted correlation exists between brain size (with its accompanying complexity of neuronal connections) and an increasing sophistication of neurological function, seemingly culminating in the human brain, with its staggering 10^{15} synapses. Yet a growing body of data elevates the role of glia beyond that of simply gluing neurons together, and makes a concerted challenge to the centuries-old dominance of the idea of neurons as the aristocrats of the nervous system. In this issue of *Cell Stem Cell*, Han and colleagues report a remarkable study that assigns a role of previously unexpected importance to glial cells in higher cognitive functions, such as learning, that will come as a surprise to many in the neuroscience community (Han et al., 2013).

Glial cells comprise several distinct populations. In the central nervous system (CNS) these are astrocytes and oligodendrocytes, both of which share a neuroepithelial origin with neurons, as well as microglia, CNS-resident cells of the innate immune system. There is in addition an abundant population of progenitor cells commonly called oligodendrocyte progenitor cells (or OPCs, a term that belies their multipotency). So why are glial cells more than simply brain glue? Without reviewing all the evidence, here are a few examples. (1) As brain size and information processing capacity increases, one would predict a corresponding increase in glia. Yet the increase is disproportionate: on ascending the phylogenetic tree the proportion of glia to neurons increases—this is apparent even within the primates (including humans—Albert Einstein had an especially large number of glia within the brain region responsible for higher-level cognition) (Fields, 2004). (2) In addition to facilitating rapid impulse conduction, oligodendrocytes also provide trophic support for the axons they myelinate, allowing axons to attain longer lengths and hence vertebrates to achieve much greater sizes than would otherwise be possible (Nave, 2010). (3) OPCs can generate action potentials, previously thought to be the sole preserve of neurons and a key function that distinguished them from glia (Káradóttir et al., 2008). This OPC property strongly hints at important physiological functions in the normal CNS in addition to their role in the regenerative process of remyelination (Zawadzka et al., 2010). (4) Astrocytes, a diverse population of cells with multiple functions, maintain and sculpt the synaptic contacts on which CNS function depends (Ullian et al., 2001). All of these relatively recently revealed properties of glia demand an updated concept of brain function in which neurons and glia work as equal partners, interacting in a mutually dependent manner. But what evidence is there that glia might be in the driver's seat?

Human astrocytes are larger and have a greater morphological diversity than those of rodents, with distinctive subtypes uniquely present in hominids. Thus, there is a correlation between more complex information processing and astrocyte complexity that might be causal. In their current report, Han and colleagues test this theory using an ingenious stem cell (or more specifically progenitor cell) -based approach. Previously, the laboratory of Steven Goldman (one of this study's senior authors) produced adult mice with a chimeric CNS consisting of mouse neurons (and oligodendrocytes) and human astrocytes and progenitor cells, achieved by engrafting human glial progenitors into the neonatal mouse CNS (Windrem et al., 2008). Large regions of the CNS in these mice, including the hippocampus, consist of mouse neurons surrounded by human astrocytes, thus providing a configuration with which to compare with wild-type mice.

Using this transplantation model in the current study, Han and colleagues addressed the critical question of whether the increasing complexity of human astrocytes confers greater *functional* abilities. The authors tested the mice on a battery of learning and memory tasks (including Barnes maze navigation, object-location memory, and contextual and tone fear conditioning tasks) and found that the chimeric mice showed enhanced performance on all tests compared to their entirely murine controls. Furthermore, long-term potentiation (LTP), a long-lasting enhancement in signal transmission between two

neurons thought to underlie the plasticity necessary for certain types of learning and memory, was enhanced in these animals. These results provide compelling evidence that the greater cognitive sophistication of humans compared to mice is at least in part due to differences in their glia.

By beginning to explore a role for glia in higher cognitive function, this study raises intriguing questions about exactly what, and how extensive, these roles might be; for example, are other domains of cognition affected? Furthermore, it would be of interest to examine the effects of engrafting human glia on other important forms of plasticity, such as long-term depression (LTD). Further exploration of exactly what role glia play in these and in other processes would ultimately be fascinating.

This paper, which promises to be a landmark for glial cell biology, provides a wonderful example of how stem cell biology can be used to address fundamental questions of physiology. In a sense, this study harks back to the early days of glial cell transplantation, where this procedure represented a powerful experimental tool to study how glia interacted with each other and with neurons (Blakemore and Franklin, 1991). The finding that transplanted glial progenitors were able to remyelinate demyelinated axons meant that the technique quickly became diverted toward possible therapeutic objectives, a route which has now crossed the translational chasm, with the publication of the outcome of initial cell therapies for inherited disorders of myelination (Gupta et al., 2012). While these developments are immensely encouraging, it is nevertheless important that the research community fully harness the power of stem cells to explore physiology: this paper provides just such an example, elegantly revealing the functional interplay between neurons and glia. Perhaps, after all, it is neither your neurons nor your glia that make you clever, but both, working in tandem.

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An Inflammatory Situation: SOX2 and STAT3 Cooperate in Squamous Cell Carcinoma Initiation

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Although SOX2 has been identified as a squamous cell carcinoma oncogene, mechanisms of SOX2-induce oncogenesis have remained elusive. In this issue of *Cell Stem Cell*, Li et al. (2013) show that SOX2 synergizes with inflammation-induced STAT3 activation to transform basal progenitors and initiate squamous cell carcinoma.

The genes and pathways that are essential for the maintenance of stem and progenitor cell populations seem ideally suited to being hijacked by developing cancers. Indeed, cancer genomes commonly contain alterations leading to aberrant activation or inactivation of members of key developmental transcription factors and key developmental signaling pathways, such as WNT, notch, and hedgehog. An important but little understood example of this phenomenon is that of *SOX2*, which is a transcription factor recently recognized to be essential for development and maintenance of epithelial tissues (Arnold et al., 2011) that has also been noted to be a frequently amplified oncogene across a variety of