The American Society for Cell Biology

8120 Woodmont Avenue, Suite 750
Bethesda, MD 20814-2762
Tel: (301) 347-9300
Fax: (301) 347-9310
ascbinfo@ascb.org, www.ascb.org

Joan R. Goldberg
Executive Director

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At the Frontier between Cell Biology and Neuroscience

This column was written by Michael D. Ehlers, Duke University, at the request of Brigid Hogan.


Brigid Hogan

News Flash: *The brain is composed of individual separated cells!* Well, OK, this headline might have appeared in the late 19th century. But it is still quite remarkable that it was only a century ago when debate raged about whether the brain was composed of individual separated cells or by units connected through protoplasmic bridges (resolution: Cajal was right). Some 200 years after van Leeuwenhoek observed cells under the microscope, brain science was taking its first bold steps toward cell biology. Although a surprisingly large gap still exists between neuroscience and cell biology, never has there been a more compelling time for cell biologists intrigued by the brain.

Frontier or Candy Shop

Brigid Hogan asked me to recount my experience at the frontier between neuroscience and cell biology, and the first "frontier" image that came to mind was one of being caught in the crossfire in the OK Corral. A large part of the research in my lab has focused on membrane trafficking and protein dynamics (the cell biology) and how these influence synapses and neural circuits (the neuroscience). Over the course of the last decade, my lab has worked on how specific neurotransmitter receptors are transported, how organelles and trafficking machinery become positioned in dendritic spines, and how this organization influences synapse function and plasticity. These all end up being important topics for fundamental brain function and for an amazingly large number of brain disorders, including autism, epilepsy, addiction, and Alzheimer's disease to name a few.

Yet, there *is* a frontier between the all-too-frequently grumpy neuroscientist (who seeks the source of consciousness and may have little interest in subclasses of endosomes) and the purist cell biologist (for whom neurons are just an oddly shaped fibroblast cell line far too distant from *Saccharomyces* and much too difficult to transfect). Scientific life at the interface between neuroscience and cell biology requires a *lot* of explanation to colleagues and students alike. Witness the neurobiology student studying brain-derived neurotrophic factor (a very common secreted neuronal growth factor) who has trouble remembering whether the ER comes before or after the Golgi. Or consider the well-seasoned cell biology professor interested in studying a brain-enriched actin binding protein in learning-related synaptic plasticity without knowledge of what kinds of synapses there are or where in the brain to look for them (let alone what form of learning they underlie).

In reality, the crossfire analogy overemphasizes the potential for criticism from both sides and obscures what is, in fact, a simple lack of understanding. I think that a much better (and more positive) analogy is that of being a kid in an uncrowded candy shop. Neuronal cell biology contains many goodies with little need to share. We are still at early stages in understanding the cellular interactions that occur during brain development, the rich internal workings of cytoskeleton and organelle machinery in enormous compartmentalized neurons, and the varied function of the large number of brain-specific genes. Indeed, neuroscientists really have no idea how many different cell types there are in the brain! It's a fertile ground for cell biologists indeed.

Mobbed or Solitary

I vividly recall one of my early experiences attending an ASCB Annual Meeting, my second or third. I was a young assistant professor, doing a lot of bench work myself (yes, this does happen). I decided to present my results describing the regulated endocytic sorting of AMPA-type glutamate receptors in neuronal dendrites. These receptors (AMPA receptors for short) are the glutamate-gated ion channels present at glutamatergic synapses that mediate

most rapid excitatory synaptic transmission in the brain.

At the time (eight or nine years ago), it was a quite new phenomenon to observe that AMPA receptors undergo regulated endocytosis and endosomal sorting controlled by signaling pathways important for synaptic plasticity. I was excited by these results and had presented a poster at the Society for Neuroscience meeting just a month before. There my poster was mobbed by the throngs interested in excitatory synaptic transmission and plasticity (a big and important field). My experience presenting the same results at the ASCB Annual Meeting was somewhat different.

My poster was placed in the neuroscience ghetto, somewhere near the restrooms at the farthest reaches of the cavernous conference hall, far away from the meat and potatoes of cell biology. A few cautious individuals meandered by over the course of the day. Two or three people asked me to take them through my poster. Still, there were times of unexpected solitude where I could have sworn that I heard crickets chirping and saw tumbleweeds blowing by. Walking around the posters later, I could not help but notice that there were more posters on Arp2/3 than on all of neuroscience combined (perhaps attributable to the clear importance of Arp2/3).

But seriously, why this difference between scientific audiences? Weren't the topics of endocytosis and endosomes and signaling smack dab in the sweet spot of cell biology, even if conducted on a neuronal receptor? In one sense, I suspected the difference was due to the tendency of cell biologists (or at least the ASCB Annual Meeting) to lump all things neuroscience into one or two categories that invariably acquire the veneer of "other." Or, perhaps there is enough neuroscience-specific jargon and techniques (think electrophysiology…currents and channels and voltage, oh my!) that comes across as exotic and foreign.

A New Day

Fortunately, times have changed. More and more neuroscientists are staying abreast of traditional cell biology and attending the ASCB Annual Meeting. In addition, an ever increasing number of cell biologists are branching out into the neuroscience. Given this, I anticipate more and more integration of neuronal and glial cell biology into the mainstream of cell biological thought, journals, and meetings.

Of course, there are classic areas of neuroscience that have long been in the domain and parlance of cell biologists—areas such as synaptic vesicle exocytosis and endocytosis, axon transport, and neuromuscular synaptogenesis. These areas, centered firmly in neuroscience, have informed cell biology more broadly, and have thrived and greatly benefited from the cell biological perspective.

The areas of neuroscience where cell biologists are needed are ever-expanding. My own field of postsynaptic plasticity is an excellent example of how a problem initially defined and framed by synaptic electrophysiology has become increasingly a problem for cell biologists. In addition, areas such as neuronal migration, neuronal stem cells, protein misfolding in neurodegeneration, and synapse formation are all areas where the cell biologist's perspective is crucial.

There is little doubt that cell biology will continue to move beyond the view that highly specialized cells and tissues somehow represent a form of "applied" cell biology of incremental value beyond what we have learned in model systems (didn't we already know that in yeast or a COS cell?). As fundamental as the latter systems are to cell biological discovery, there is clearly an enormous range of untapped cell biology in highly differentiated cells and tissues, and nowhere is this more apparent than the brain.

The future for neuronal cell biology is one of amazing advances. In my view, this frontier will increasingly be the place where important breakthroughs emerge in both neuroscience *and* cell biology. Neurons in their diversity will hold a lot of surprises for cell biologists. The discoveries and tools of basic cell biology will continue to inform the complexity of neurons and their interconnected circuits. From the developmental programs of brain connectivity, to the cellular basis of neural circuitry, to the function of genes associated with disorders such as schizophrenia, autism, and Alzheimer's disease, there has never been a better time for cell biologists young and old to take a close look at the cells that compose our brains.

For those of you yet to marvel at the cells of the brain, I encourage you to take a moment to think about the cells that allow us to think. ■

—Michael D. Ehlers, Howard Hughes Medical Institute/Duke University Medical Center

Comments are welcome and should be sent to president@ascb.org.

Michael D. Ehlers

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