Developmental Cell
Previews

The Soothing Touch: Microglial Contact Influences Neuronal Excitability

Aude Panatier[1,2,*] and Richard Robitaille[3,4,*]
[1]INSERM U862, Neurocentre Magendie, 33077 Bordeaux, France
[2]Université de Bordeaux, 33077 Bordeaux, France
[3]Département de Physiologie
[4]Groupe de Recherche sur le Système Nerveux Central
Université de Montréal, Montréal, Québec H3C 3J7, Canada
*Correspondence: aude.panatier@inserm.fr (A.P.), richard.robitaille@umontreal.ca (R.R.)
http://dx.doi.org/10.1016/j.devcel.2012.11.015

Resting microglial cells in the brain scan their environment with their processes, primed to react to injury and disease. In this issue of *Developmental Cell*, Li and colleagues (2012) report that resting microglia also react to physiological neuronal activity, sending their processes toward highly active neurons to regulate their excitability.

Neurons are considered to be the principal cells implicated in the processing and transmission of information in the brain. Although glial cells are as numerous as neurons, their role in information processing was ignored for a long time. Initially, the main role of glial cells was considered to be limited to "sticking" together principal cells in the brain, i.e., neurons. However, a growing body of evidence has emerged over the last decade to suggest that glial cells, in particular astrocytes, regulate neuronal communication (Panatier et al., 2011; Perea and Araque, 2007) and synaptic plasticity (Henneberger et al., 2010; Parpura et al., 2012). Glial cells are principally classified in three groups: oligodendrocytes, astrocytes, and microglial cells. Whereas oligodendrocytes and astrocytes are known to play active role in the transmission of information of the brain, the role of microglia under physiological conditions was still elusive until recently (Tremblay et al., 2011).

For a long time, microglia were only considered to be the immune cells of the brain, playing key roles only in brain injury and disease (Ransohoff and Cardona, 2010). During local damage, this cell type has the incredible faculty to extend processes to the injured site (Davalos et al., 2005; Nimmerjahn et al., 2005). Interestingly, this macrophage of the brain is "highly motile" under physiological, normal conditions. Microglia continuously scan the surrounding environment with processes, in a timescale of minutes (Davalos et al., 2005; Nimmerjahn et al., 2005). Studies have suggested that neuronal activity could play a role in regulating resting microglial motility; however, whether these movements are oriented to specific targets, the possible mechanisms regulating these movements, and the consequences of such contacts in neuronal function were still unclear until the work by Li and colleagues (2012), published in this issue of *Developmental Cell*.

Li and colleagues (2012) now carefully explore the role of microglia in the regulation of neuronal excitability, using the zebrafish larvae as a model system. Experiments were performed in the neuronal soma layer of the optic tectum between 5 and 8 days postfertilization, a time window in which the larvae already exhibit relatively mature visual functions and behaviors. The authors took advantage of a large number of tools, including genetic approaches, in vivo and FRET imaging, in vivo electrophysiology (whole-cell recordings), glutamate uncaging (local activation), and electron microscopy.

The authors propose that resting microglia play an active role in the homeostatic regulation of neuronal activity under physiological conditions. They show that microglial processes continuously contact the soma of surrounding neurons. During their dynamic movement, stick-like ending of processes frequently expand into a bulbous ending, which enwrapped nearby neuronal soma for several minutes before retracting to explore another area. Although this activity may appear random at first, Li et al. (2012) describe that when a neuron is highly active, a "find-me" signal corresponding to ATP released through pannexin-1 hemichannels is sent and detected by nearby microglia processes. Within a short period of time (less than 10 min), the distribution of an active small Rho GTPase (Rac) in microglial processes is reorganized, and the process movement becomes oriented toward the highly activated neuron. The migroglial process then enwraps the neuron soma for several minutes, and the activity of the targeted neuron subsequently decreases within about 5 min of contact. This decrease persists for several minutes after the removal of the microglial process (Figure 1). As a whole, microglia could act as a controller that defines the proper activity window for the brain to work under physiological conditions. Importantly, the work of Li and colleagues (2012) continues to help us in building the real story of brain processing in physiological conditions to include glial cells in the cast of players.

While this study provides exciting insights, it also raises additional important questions. For instance, it takes several minutes for resting microglial processes to discriminate the position of the highly active neuron. How does the signal travel to the nearby process in a space window of tens of microns? It is also still unclear whether ATP is acting directly on microglial processes or whether another step is required. Moreover, does this oriented movement guided by neuronal activity also take place around synapses? What is the microglial signal that interacts with neurons to reduce their activity? Finally,

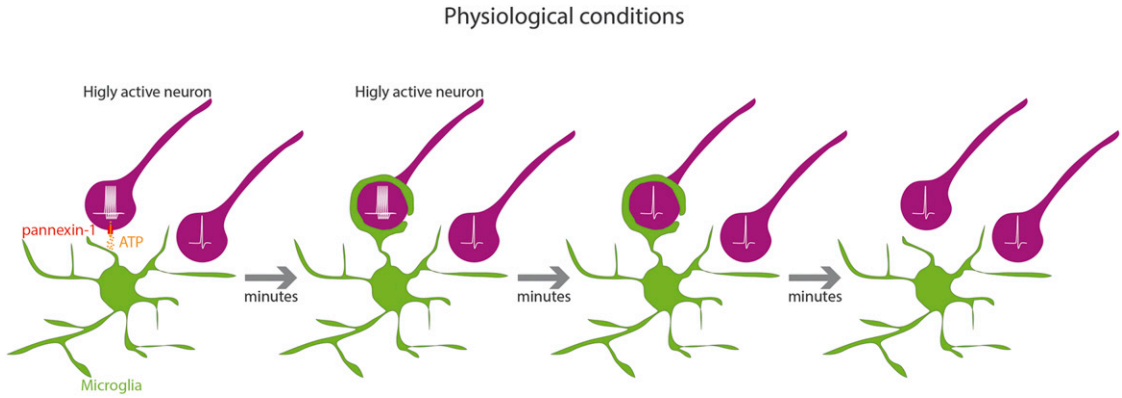

Figure 1. Microglial Contact Reduces Neuronal Excitability
Schematic representation of communication between neurons and microglial processes. Highly active neurons release ATP through hemichannels, which attract a motile microglial process. The process surrounds the soma of the neuron, correlating with a reduction of neuronal activity. The microglial process then retracts after the neuronal activity is reduced.

do microglial cells also regulate the activity of "lowly active" neurons?

An intriguing possibility might be that astrocytes serve as an intermediary in this regulation of neuronal activity by microglia. Indeed, astrocytes are closely associated with neurons and synapses and are involved in dynamic, bidirectional regulation of neuronal communication (Parpura et al., 2012). Moreover, astrocytes tightly interact with microglial cells through ATP (Schipke et al., 2002). Hence, considering the exciting data of Li and colleagues (2012) and the known functions of astrocytes, it is quite appealing to now include microglia as the new kid on the block among glial cells that set the tone on neuronal excitability and the transfer of information in the brain. Understanding how these intricate interactions between neurons and glia are regulated and influence neuronal functions will help us understand not only how the brain behaves but also why and how such normal and physiological functions become pathological.

REFERENCES

Davalos, D., Grutzendler, J., Yang, G., Kim, J.V., Zuo, Y., Jung, S., Littman, D.R., Dustin, M.L., and Gan, W.B. (2005). Nat. Neurosci. *8*, 752–758.

Henneberger, C., Papouin, T., Oliet, S.H., and Rusakov, D.A. (2010). Nature *463*, 232–236.

Li, Y., Du, X.F., Liu, C.S., Wen, Z.L., and Du, J.L. (2012). Dev. Cell *23*, this issue, 1189–1202.

Nimmerjahn, A., Kirchhoff, F., and Helmchen, F. (2005). Science *308*, 1314–1318.

Panatier, A., Vallée, J., Haber, M., Murai, K.K., Lacaille, J.C., and Robitaille, R. (2011). Cell *146*, 785–798.

Parpura, V., Heneka, M.T., Montana, V., Oliet, S.H., Schousboe, A., Haydon, P.G., Stout, R.F., Jr., Spray, D.C., Reichenbach, A., Pannicke, T., et al. (2012). J. Neurochem. *121*, 4–27.

Perea, G., and Araque, A. (2007). Science *317*, 1083–1086.

Ransohoff, R.M., and Cardona, A.E. (2010). Nature *468*, 253–262.

Schipke, C.G., Boucsein, C., Ohlemeyer, C., Kirchhoff, F., and Kettenmann, H. (2002). FASEB J. *16*, 255–257.

Tremblay, M.È., Stevens, B., Sierra, A., Wake, H., Bessis, A., and Nimmerjahn, A. (2011). J. Neurosci. *31*, 16064–16069.