This Week in The Journal

Radial Glial Endfeet Help Maintain CNS/PNS Boundary

Yan Zhu, Tomoko Matsumoto, Takashi Nagasawa, Fabienne Mackay, and Fujio Murakami

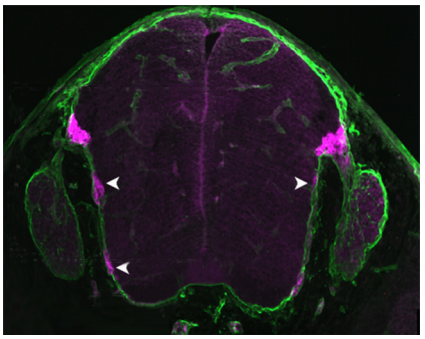
(see pages 9211–9224)

Early in CNS development, radial glia span the neural tube from the lumen (future ventricles) to the pial basement membrane. Although these cells are present throughout the CNS, their functions vary somewhat across regions. In the developing neocortex, radial glia serve as neural progenitors and as scaffolds along which newborn neurons migrate. Whether radial glia generate neurons or guide neuronal migration in the developing spinal cord is unclear, but they have been shown to help define the borders of developing axon tracts and to generate glia (Barry et al., 2014, Int J Biochem Cell Biol 46:76). Work by Zhu et al. now demonstrates an additional role of spinal cord radial glia: helping to maintain the barrier between the CNS and PNS.

Motor and sensory axons pass through the CNS/PNS boundary at the motor axon exit points (MEPs) and dorsal root entry zones (DREZs), respectively. Boundary cap cells derived from the neural crest prevent other cells from exploiting these breaches. Zhu et al. found that knocking out the chemokine Cxcl12 (expressed in the meninges) or its receptors Cxcr4 or Cxcr7 (expressed in radial glia cells) disrupted attachments between radial glial endfeet and the pial surface of the spinal cord. Consequently, gaps appeared between the DREZs and MEPs, allowing boundary cap cells to infiltrate the spinal cord.

The authors went on to show that Cxcl12 modestly increased the adhesion between cultured radial glia and fibronectin or laminin, two components of the extracellular matrix of the pial basement membrane. Cxcl12 also increased levels of the active form of β1 integrin—a subunit of fibronectin and laminin receptors—in cultured cells. Finally, they found that a line of active β1 integrin staining was present along the pial basement membrane in wild-type mice, and that this staining was weaker in Cxcl12-null mice.

Together, these results suggest that by binding to Cxcr4 and Cxcr7 in radial glial cells, Cxcl12 strengthens adhesion between glial endfeet and the pial basement membrane of the spinal cord, and that this adhesion helps to form a barrier that prevents PNS cells, including boundary cap cells, from entering the CNS.



Knocking out Cxcl12 allows boundary cap cells (which express Cxcr4, magenta) to invade the spinal cord (arrowheads). See the article by Zhu et al. for details.

Substance P Exerts Compartment-Specific Effects on Striatal Dopamine Release

Katherine R. Brimblecombe and Stephanie J. Cragg

(see pages 9017–9023)

The striatum helps guide complex motor actions and reward-related learning via the activity of two populations of medium spiny projection neurons (MSNs) that directly inhibit or indirectly activate output nuclei of the basal ganglia. The activity of these MSNs is modulated by dopaminergic projections from the substantia nigra pars compacta (SNc). Specifically, dopamine increases the excitability of direct-pathway MSNs, which express D1-type dopamine receptors, while reducing the excitability of indirect-pathway MSNs, which express D2 receptors.

The effects of dopamine in the striatum can be fine-tuned by other neuromodulators, which may themselves exert different effects on different neuronal populations. Indeed, Brimblecombe and Cragg have discovered that substance P (SP) exerts different effects on dopamine release in two compartments of the striatum: striosomes and the surrounding matrix. These striatal compartments are defined by differential expression of numerous proteins that are involved in regulating neuronal activity. The compartments also have different connection patterns; while striosome MSNs primarily form circuits with limbic-related areas of cortex and thalamus, matrix MSNs are primarily connected to sensorimotor areas. In addition, striosomes house MSNs that project to the SNc, potentially enabling them to regulate the activity of dopaminergic neurons.

Brimblecombe and Cragg found that in striosomes, SP increased the amount of dopamine release evoked by electrical stimulation. In contrast, SP decreased evoked dopamine release at striosome/matrix boundaries, an area populated largely by cholinergic and GABAergic interneurons. SP had no effect on dopamine release in the matrix, however. As a result of these compartment-specific effects, SP changed the relative levels of dopamine release across the striatum. In the absence of SP, evoked dopamine release was lowest in striosomes and highest in the matrix. In the presence of SP, dopamine release levels were similar in striosome and matrix, but lower at boundaries.

What impact these differential effects of SP have on striatal function is difficult to guess. In fact, although the differences in protein expression, connectivity, and neuromodulatory effects strongly suggest that striosome and matrix MSNs have distinct functions, what precisely these functions are remains a mystery. Elucidating these functions will likely be necessary before we can fully understand how the basal ganglia help drive behavioral choices.

This Week in The Journal is written by Teresa Esch, Ph.D.