

This Week in The Journal

Sox11 Inhibits Dendritogenesis

Yoshio Hoshiba, Tomohisa Toda, Haruka Ebisu, Mayu Wakimoto, Shigeru Yanagi, et al.

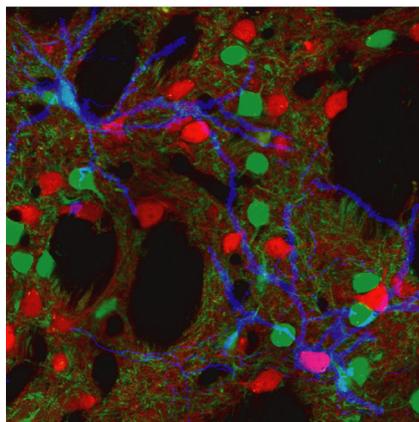
(see pages 5775–5784)

Cortical projection neurons are born near the ventricular surface and migrate radially to form cortical layers. Through most of their journey, the neurons have a bipolar morphology with a single, unbranched leading process that guides them toward the pial surface. Dendrites do not begin to grow until after neurons reach their final position. Indeed, growth of a complex dendritic arbor might be expected to impede migration. Therefore, Hoshiba et al. hypothesized that migrating neurons actively suppress dendritogenesis. They report that this is, in fact, the case, and that the transcription factor Sox11 is responsible for preventing premature dendritic growth.

Sox11 expression was high in the developing cortex of newborn mice, but it declined as the cortical layers were established and dendritic growth began. Terminating radial migration prematurely (by expressing a dominant-negative form of N-cadherin in layer 2/3 neurons) caused a premature reduction in Sox11 expression, supporting the hypothesis that Sox11 expression is tied to migration. When Sox11 was knocked down in newborn layer 2/3 neurons, the number and branching of processes in migrating neurons increased and migration was impaired. Similarly, knocking down Sox11 in layer 2/3 neurons shortly after they arrived in the cortical plate caused the neurons to develop more and longer dendrites. In contrast, overexpressing Sox11 reduced dendritic length and branching.

These results suggest that Sox11 expression facilitates migration of newborn neurons by suppressing process formation and branching. They further suggest that maintenance of Sox11 expression requires active migration. Future studies should identify the signal that maintains Sox11 expression during migration, as well as identifying Sox11 target genes. For example, does Sox11 repress transcription factors that promote dendritic growth?

Answering these questions may provide insight into the mechanisms underlying neurodevelopmental disorders that cause intellectual disability, which often involve abnormal dendritic growth.



Confocal image showing an indirect-pathway MSN (blue, upper left) and a direct-pathway MSN (blue and purple, lower right). See Escande et al. for details.

Dopamine Loss Has Opposite Effects on Direct- and Indirect-Pathway MSNs

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(see pages 5686–5698)

Loss of dopaminergic neurons in the substantia nigra underlies motor impairment in Parkinson's disease (PD), but symptoms do not appear until >50% of dopaminergic neurons have degenerated. This suggests that plasticity in motor control networks compensates for early neuronal loss. The extent to which changes in other dopaminergic neurons, their targets in the striatum, and other striatal inputs contribute to compensatory mechanisms is unclear, however. Therefore, Escande et al. asked how loss of dopaminergic neurons affected the responses of striatal medium spiny neurons (MSNs) to cortical input in a mouse model of PD.

After dopaminergic neurons were killed with 6-hydroxydopamine, unsupervised multivariate clustering analysis was used to group animals based on whether or not

they exhibited motor impairment. The authors then measured the responses of direct- and indirect-pathway MSNs to motor cortical stimulation in control, symptomatic (~60% of 6-hydroxydopamine-treated animals), and asymptomatic mice. Consistent with previous studies, direct-pathway MSNs in control mice were more responsive to cortical stimulation than indirect-pathway MSNs, but the latency of responses was similar in the two MSN subtypes. In dopamine-depleted mice that exhibited motor impairment, the intensity of stimulation required to activate direct-pathway MSNs was much greater than in controls, whereas the intensity required to activate indirect-pathway MSNs was reduced. In addition, indirect-pathway MSNs responded to cortical stimulation with shorter latency than direct-pathway MSNs in symptomatic mice. In contrast, only direct-pathway MSN responsiveness was affected by dopamine depletion in asymptomatic animals. While direct-pathway MSNs in asymptomatic mice were less sensitive than those in control animals, however, they were more sensitive than those in symptomatic mice.

Postmortem examination revealed that impaired mice had lost, on average, ~85% of nigral dopaminergic neurons, whereas asymptomatic mice lost ~42% of dopaminergic neurons. Importantly, the extent of dopaminergic neuron loss was correlated with the change in responsiveness of direct- and indirect-pathway MSNs, as well as with the degree of forelimb dyskinesia.

These results show that loss of dopaminergic input disrupts striatal function before motor symptoms are detected. They also suggest that increased responsiveness of indirect-pathway MSNs to cortical input is an essential contributor to motor impairment after dopamine loss. Finally, the results show that in mice, as in humans, motor impairment does not appear until >50% of dopaminergic neurons have died. Thus, asymptomatic dopamine-depleted mice may be a useful model for investigating the earliest stages of PD.

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