This Week in The Journal

Phosphorylation of Bcl-xL Mediates Cyclin-Dependent Apoptosis

Miguel Veas-Pérez de Tudela, María Delgado-Esteban, Carolina Maestre, Verónica Bobo-Jiménez, Daniel Jiménez-Blasco, et al.

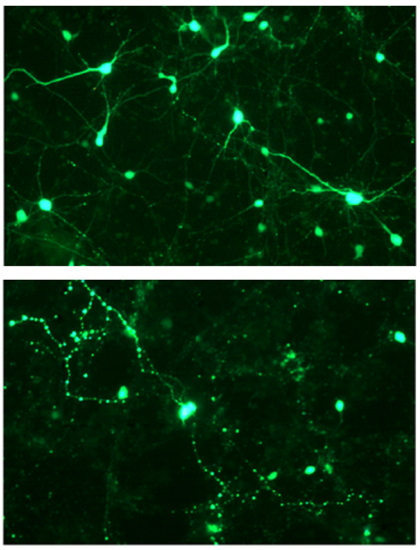
(see pages 9287–9301)

Cyclin B1 participates in mitosis by regulating chromosome condensation and disassembly of the nuclear envelope. In postmitotic neurons, cyclin B1 levels are normally kept low by anaphase-promoting complex/cyclosome (APC/C), which targets cyclin B1 for degradation via ubiquitination. In excitotoxic conditions, however, cyclin-dependent kinase 5 (Cdk5) becomes activated. Cdk5 inactivates APC/C, which allows cyclin B1 to accumulate. This accumulation promotes apoptosis.

Veas-Pérez de Tudela et al. have identified several molecular events linking cyclin B1 accumulation to neuron death. They first showed that glutamate treatment caused Cdk5-dependent accumulation of cyclin B1 in cultured neurons. This led to activation of another cyclin-dependent kinase, Cdk1, and ultimately to activation of mitochondrial caspase-3 and -9, which trigger apoptosis. Knocking down cyclin B1 or inhibiting Cdk1 reduced glutamate-induced superoxide production and the accompanying collapse of the mitochondrial inner membrane potential ($\Delta\psi_m$). Furthermore, overexpressing cyclin B1 in untreated cells increased superoxide production, reduced $\Delta\psi_m$, and ultimately increased caspase-dependent apoptosis.

Subsequent experiments in glutamate-treated neurons or in HEK cells transfected with cyclin B1 suggested that Cdk1 phosphorylates Bcl-xL, an anti-apoptotic mitochondrial protein. Bcl-xL normally increases the efficiency of ATP production by interacting with an ATP synthase, but phosphorylation of Bcl-xL disrupted this interaction, leading to reduced ATP production. The reduction in ATP synthase activity was associated with transient hyperpolarization of $\Delta\psi_m$ and increased superoxide production. This likely led to oxidation of components of complex I of the electron transport chain and subsequent inhibition of this complex. The authors propose that impairment of complex I proton-pumping activity caused the ultimate collapse of $\Delta\psi$m, which has previously been shown to trigger the release of caspase-3 and -9.

Importantly, the decrease in ATP synthase activity, loss of $\Delta\psi_m$, increase in superoxide levels, reduction in complex I activity, and apoptosis were all reduced by inhibiting Cdk1 or by overexpressing a phosphorylation-deficient form of Bcl-xL, supporting the hypothesis that Cdk1-mediated phosphorylation of Bcl-xL is an early step in the pathway linking cyclin B1 elevation to cell death. Thus, these might be good therapeutic targets for neurodegenerative conditions involving cyclin B1 accumulation, including Alzheimer's disease and stroke.



Expressing cyclin B1 in cultured rat cortical neurons (bottom) increased neuronal degeneration compared to control (top). See the article by Veas-Pérez de Tudela et al. for details.

Cholinergic Neurons Are Needed for Extradimensional Set-Shifting

Sho Aoki, Andrew W. Liu, Aya Zucca, Stefano Zucca, and Jeffery R. Wickens

(see pages 9424–9431)

The basal ganglia have essential roles in shaping our interactions with the world. They help us learn and perform complex acts that generate rewards, and they help us to modify strategies—or pursue new ones—if formerly successful strategies become ineffective. The dorsomedial striatum appears to be especially important in behavioral flexibility. Inactivation of this area impairs reversal learning, in which, for example, after learning to travel down one arm of a maze to receive a reward, a rat must switch to traveling down the opposite arm. Similar impairments are produced after muscarinic antagonists are delivered to the dorsomedial striatum, suggesting that cholinergic signaling has an important role in reversal learning (Ragozzino et al., 2002, Brain Res 953:205).

Aoki et al. asked whether cholinergic signaling has a similar role in a different type of behavioral flexibility, called extradimensional set-shifting. Specifically, rats were first required to press a specific lever, left or right, to obtain a food pellet. Subsequently, rats had to press the lever marked by a light stimulus, regardless of its position. Although rats in which striatal cholinergic neurons had been selectively killed learned the new contingency as rapidly as controls, they made different kinds of errors. The type of error depended on the striatal region targeted and whether and how the light stimulus was presented during the first phase. If the light was presented randomly above the rewarded or unrewarded lever during phase 1, then on phase 2, rats lacking cholinergic neurons in the dorsomedial striatum made more perseverative errors than control rats—that is, they were more likely to press the lever that was rewarded in phase 1. In contrast, if no light was present during phase 1, rats lacking cholinergic neurons in the ventral striatum made more perseverative errors than controls.

These results suggest that striatal cholinergic neurons are required when animals must use new environmental cues to find rewards. Furthermore, they suggest that cholinergic neurons in different striatal regions have different roles: those in the dorsomedial striatum are required when a previously irrelevant stimulus becomes relevant, whereas those in the ventral striatum are required when a previously unencountered cue must be heeded.

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