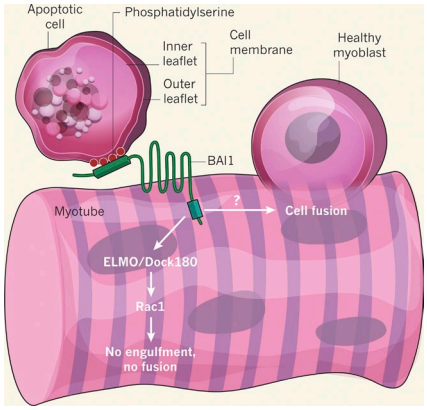
Generally Physiological

Dying cells, dyeing channels, and seasonal changes in neurotransmitter identity

This month's installment of *Generally Physiological* concerns signals from apoptotic cells that promote muscle development, food dyes that selectively block the pannexin 1 (Panx1) ATP channel, and photoperiod-dependent switches in neurotransmitter phenotype.

Dying to get stronger?

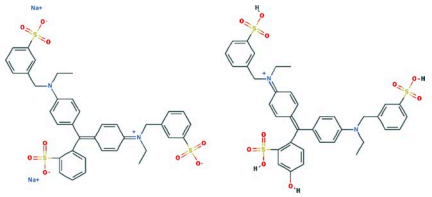
The multinucleated myofibers that make up muscle are generated through the fusion of mononuclear myoblasts. Noting that a signaling module (ELMO-Dock180-Rac1) that promotes engulfment of apoptotic cells by phagocytes has been implicated in myoblast fusion, Hochreiter-Hufford et al. (2013) identified a role in myogenesis for signals from apoptotic cells. During apoptosis, phosphoserine, which typically localizes to the inner leaflet of the plasma membrane, becomes exposed on the cell surface; the exposed phosphoserine acts as a ligand for the receptor BAI1, initiating the ELMO-Dock180-Rac1 pathway in phagocytes to facilitate the clearance of apoptotic cells (see Yu and Baylies, 2013). After determining that BAI1 was also present in developing myofibers and cultured myoblasts—increasing in abundance in the latter during fusion—Hochreiter-Hufford et al. (2013) showed that its overexpression increased both myotube number and the number of nuclei per myotube, effects that depended on signaling through the ELMO-Dock180-Rac1 module. Apoptotic cells were present in developing myofibers as well as in cultures in which myoblasts were undergoing fusion; in vitro analyses indicated that inhibiting apoptosis (or masking phosphoserine) inhibited myoblast fusion, whereas adding apoptotic cells promoted it. Intriguingly, apoptotic myoblasts stimulated myoblast fusion but did not appear to undergo fusion themselves. The muscles of transgenic mice lacking BAI1 were smaller than those of wild-type mice; moreover, their regeneration after injury was impaired. Thus, apoptotic cells appear to signal through the phosphoserine receptor BAI1 to promote myoblast fusion during both muscle development and muscle repair.



Apoptotic cells signal through the phosphoserine receptor BAI1 to promote myoblast fusion. (Reprinted by permission from Macmillan Publishers, Ltd. *Nature*. Yu and Baylies, 496:196–197, copyright 2013.)

Dyeing to inhibit ATP release?

Panx1, which is found in numerous cell and tissue types, forms plasma membrane channels that mediate the release of ATP. Panx1 can interact with the P2X7 purinergic receptor (P2X7R), where it may act to enhance the local concentration of ligand. Both P2X7R and Panx1 have ATP-binding sites, and, intriguingly, various P2X7R agonists and antagonists inhibit Panx1. However, the lack of specific inhibitors for Panx1 has been a barrier in dissecting the physiological contributions of the two receptors. Moreover, given the implication of Panx1 in a range of diseases, the identification of selective inhibitors could prove therapeutically useful. Wang et al. (2013) discovered that the food dye Brilliant Blue FCF (BB FCF; also known as FD&C Blue No. 1) and the related food dye Fast Green FCF (also known as FD&C Green No. 3) act at submicromolar concentrations to inhibit Panx1, without affecting currents through P2X7R. Specifically, whereas up to 100 µM BB FCF failed to inhibit bzATP [3′-O-(4-benzoyl)benzoyl ATP]–induced currents in *Xenopus laevis* oocytes expressing P2X7R, both BB FCF and Fast Green FCF (IC_{50}, 0.27 µM for both dyes) inhibited voltage-activated currents in oocytes expressing Panx1. Moreover, BB FCF inhibited K^+-induced ATP release from oocytes expressing Panx1. The authors also determined that oxidized ATP inhibited P2X7R currents but not those mediated by Panx1. The identification of agents that selectively act on Panx1 or on P2X7R

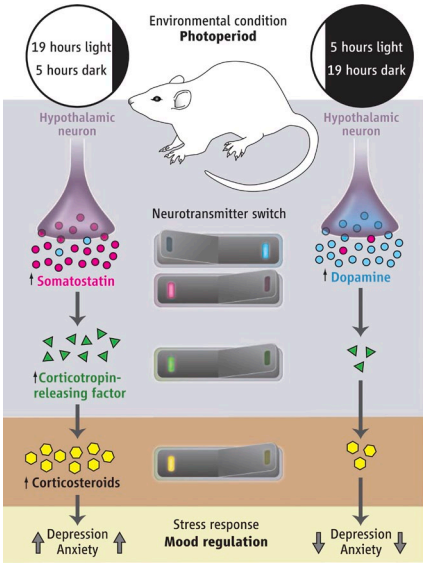


Structures of the Panx1-inhibitory food dyes BB FCF and Fast Green FCF. (From Wang et al., 2013.)

should facilitate the discrimination of the contributions of the two under various physiological and pathophysiological conditions.

A seasonal change in neurotransmitters?

An intriguing study by Dulcis et al. (2013) describes a switch in neurotransmitter phenotype that may mediate the effects of changes in photoperiod on mammalian behaviors. The variations in photoperiod that occur seasonally at high latitudes can elicit physiological and behavioral changes in various organisms and influence mood in humans. Dulcis et al. (2013) found that the number of dopaminergic neurons in hypothalamic nuclei receiving retinal input by way of the suprachiasmatic nucleus decreased in rats maintained for a week on long-day cycles (19 hours of light; 5 hours of darkness), whereas the number of somatostatin neurons increased. Conversely, in rats maintained on short-day cycles (5 hours of light; 19 hours of darkness), the number of dopaminergic neurons increased, whereas the number of somatostatin neurons decreased. These changes did not depend on neurogenesis or apoptosis; rather, they resulted from a switch in neurotransmitter expression and were accompanied by homeostatic changes in D2 dopamine receptor expression on postsynaptic corticotrophin-releasing factor (CRF) neurons. Long-day cycles (leading to decreased D2 receptor abundance) were associated with increased CRF in the cerebrospinal fluid, increased plasma corticosterone, and an increase in stress behaviors (rat models of anxiety and depression) in these nocturnal animals. Focal ablation of dopaminergic neurons (or exposure to dopamine receptor antagonists) also elicited stress behaviors; remarkably, the behavioral effects of focal ablation were partially rescued by subsequent exposure to short-day cycles. Thus, neurons in the adult brain appear to switch transmitter phenotype in response to changes in photoperiod, providing a possible mechanism linking photoperiod to mood and behavior (see Birren and Marder, 2013).



Photoperiod-dependent switches in neurotransmitter identity and stress behaviors. (From S.J. Birren and E. Marder. 2013. *Science.* 340:436–437. Reprinted with permission from AAAS.)

Elizabeth M. Adler
Executive Editor, *JGP*
eadler@rockefeller.edu

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