This Week in The Journal

Chemotherapy Agents Target Kinase Needed for Axon Maintenance

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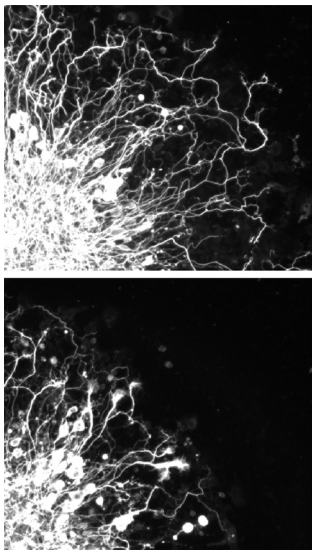
(see pages 6835–6847)

Most cancer drugs have significant toxic side effects. One such effect is chemotherapy-induced peripheral neuropathy, which results in numbness, burning, tingling sensations, and/or pain. Although the mechanisms through which chemotherapy agents induce neuropathy are not fully understood, drugs that target microtubule stability or disrupt the cell cycle cause distal-to-proximal degeneration of sensory axons. Work by Tuttle et al. suggests that another class of cancer drugs, multikinase inhibitors, also causes degeneration of distal sensory axons, in this case by inhibiting activation of the receptor tyrosine kinase c-Kit.

Three multikinase inhibitors that cause peripheral neuropathy in humans caused distal degeneration of sensory axons innervating the tail skin in zebrafish larvae. Of the shared targets of these three inhibitors, only two have paralogs expressed in the affected axons. Knockdown of only one of these—kitb, a paralog of c-Kit—led to degeneration of tail sensory axons. Degeneration of *kitb*-deficient axons was comparable to that induced by the chemotherapy drugs, and the drugs did not induce additional degeneration of *kitb*-deficient axons. In contrast, mosaic overexpression of kitlgb, a kitb ligand normally expressed in the tail skin, increased local axon density. Kitlgb overexpression also led to local increases in activation of Src-family tyrosine kinases (SFKs), which mediate downstream effects of kitb. Furthermore, a selective inhibitor of SFKs caused degeneration of tail sensory axons, whereas inhibitors of other c-Kit targets had no effect. Finally, mutant *kitb* that could not bind SFKs failed to protect *kitb*-deficient axons from degeneration.

Notably, c-Kit is expressed in some nociceptor axons of mammalian dorsal root ganglia (DRGs), and one of its ligands is expressed in the skin. This ligand is sufficient to maintain the growth of mouse DRG axons in culture. But multikinase inhibitors led to degeneration of these axons in explants.

These results suggest that c-Kit ligands present in the skin activate c-Kit receptors in sensory axons. This leads to activation of SFKs that are required for maintaining distal axons. Consequently, chemotherapy agents that inhibit c-Kit cause degeneration of sensory axon terminals, which may explain why these agents cause neuropathy. Developing topical agents that preserve c-Kit-induced signaling in sensory axons might therefore lead to treatments to reduce neuropathy in cancer patients.



Axons grow from mouse dorsal root ganglion explants cultured with a c-Kit ligand (top), but the axons retract when cultures are treated with a multikinase inhibitor used for chemotherapy (bottom). See Tuttle et al. for details.

Several Glial Subtypes in Drosophila Regulate Sleep Patterns

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(see pages 6848–6860)

Molecular clocks are present in cells throughout the body, helping to mediate circadian changes in behavior and physiology. But a set of neurons in the brain form a master pacemaker that coordinates the activity of these peripheral clocks. Although glia are not considered part of the master clock, they influence clock function. In *Drosophila*, for example, small ventral lateral neurons (sLNvs) play a central role in the control of daily activity and rest cycles, but circadian changes in their axonal arborization, which underlies their regulatory function, are influenced by molecular clock proteins in glia. Damulewicz et al. disabled molecular clocks in different subpopulations of glia in adult flies to elucidate their roles in circadian regulation.

Four glial types were examined: astrocyte-like glia, which remove glutamate from synapses; chiasm glia, which envelop large axon tracts; epithelial glia, which undergo circadian changes in morphology that mirror changes in sLNvs; and subperineurial glia, which help form the hemolymph–brain barrier. Overexpressing a dominant-negative form of the clock protein CYCLE in any of these glia subtypes increased the length of daytime sleep bouts and the total amount of sleep without eliminating circadian variation in activity level. In most glia subtypes, disrupting CYCLE function also altered circadian changes in the length of sLNv arbors; the pattern of changes differed depending on which glia were affected, however. sLNv arbors continued to grow longer during the day and retract at night when clock function was disrupted in chiasm glia, but the amplitude of these changes was reduced. In contrast, disrupting the clock in either astrocyte-like glia or chiasm glia eliminated daily changes in sLNv arbors; whereas the arbors remained long throughout the night when CYCLE function was blocked in astrocyte-like glia, the arbors remained short throughout the day when CYCLE function was blocked in chiasm glia.

These results suggest that molecular clocks in several classes of glia regulate sleep patterns and sLNv arborization in *Drosophila*, but they are not required for maintaining circadian rhythms overall. Future work should elucidate the molecular pathways through which different glia affect sLNv arborization and determine whether effects on sleep are secondary to effects on sLNvs.

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