In This Issue

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Good housekeeping maintains a healthy liver

Snider et al. report that differential expression of two key metabolic enzymes may explain why some people are more susceptible to liver damage.

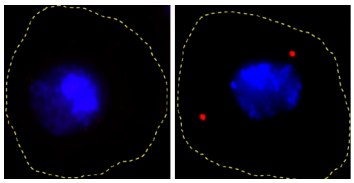
Some forms of liver disease, particularly steatohepatitis, are marked by the formation of misfolded protein aggregates called Mallory-Denk bodies (MDBs). Not all patients display these aggregates, however, and some research suggests that MDBs are more common in patients of Hispanic origin. Different strains of mice also show different susceptibilities to MDB formation when their livers are damaged by the drug 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC), which induces oxidative stress. Snider et al. analyzed the proteomes of livers from two different mouse strains to investigate the cause of their different sensitivities to DDC.

Many metabolic and oxidative stress–related enzymes were differentially expressed in the livers of C57BL (MDB-susceptible) and C3H (MBD-resistant) mice, resulting in higher levels of reactive oxygen species (ROS) in C57BL hepatocytes after DDC treatment. Prominent among these enzymes were two general "housekeeping" proteins: the glycolytic and redox-sensing enzyme glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and the energy-generating protein nucleoside-diphosphate kinase (NDPK), both of which showed reduced expression in C57BL livers and were downregulated further by DDC.

Depleting GAPDH or NDPK by RNAi elevated ROS levels similarly to DDC treatment, whereas overexpressing GAPDH prevented DDC from inducing ROS production in C57BL hepatocytes. Snider et al. think that low GAPDH and NDPK expression causes C57BL livers to be metabolically and oxidatively stressed even under basal conditions and therefore more sensitive to additional stresses like DDC. The researchers also found that GAPDH is aggregated in cirrhotic patient livers, suggesting that similar mechanisms may contribute to liver disease severity in humans.

Snider, N.T., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201102142.

Twins activate! Form of a new centriole!



Cells lacking Twins (left) have fewer centrioles (red) than control cells (right).

Brownlee et al. describe how a phosphatase's regulatory subunit promotes centriole duplication and how a viral oncoprotein may mimic this activity to induce tumorigenesis.

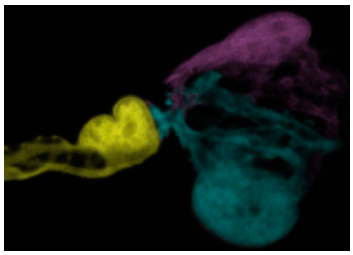
The kinase Plk4 initiates the duplication of centrioles—the barrel-shaped structures that form centrosomes—once per cell cycle. Because centriole overduplication can lead to multipolar spindles, which may cause genomic instability and tumorigenesis, Plk4's activity is limited to mitosis; during the rest of the cell cycle, the kinase triggers its own degradation by phosphorylating itself to create a binding site for the E3 ubiquitin ligase SCF^{Slimb}. Brownlee et al. found that Protein Phosphatase 2A (PP2A) counteracts this autophosphorylation during mitosis to stabilize Plk4 and induce centriole duplication.

Plk4 levels didn't peak in mitosis if PP2A was inhibited, and *Drosophila* cells lacking the PP2A catalytic subunit or its regulatory partner Twins had fewer centrioles. Normal centriole numbers were restored if Plk4 was stabilized by the simultaneous depletion of SCF^{Slimb}, however. Twins overexpression, on the other hand, stabilized Plk4 throughout the cell cycle, leading to centriole amplification.

The oncogenic SV40 virus small t-antigen (ST) also promotes centriole amplification, even though it is thought to inhibit PP2A by binding to the phosphatase and displacing its regulatory subunits. Brownlee et al. found that ST boosted Plk4 levels and restored centriole duplication to cells lacking Twins, suggesting that ST actually mimics Twins' function rather than inhibiting PP2A activity at centrioles. ST, and perhaps other viral oncoproteins, may therefore induce tumorigenesis by keeping Plk4 elevated throughout the cell cycle.

Brownlee, C.W., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201107086.

Schwann cells cover their territory



Sequential photobleaching of Schwann cells expressing GFP allows three cells (colored yellow, cyan, and magenta) to be delineated at an adult neuromuscular junction.

Brill et al. reveal that Schwann cells (SCs) keep nerve terminals fully covered by competing for space at neuromuscular junctions.

SCs wrap around nerve axons to help propagate action potentials, but they also cluster around axon terminals to maintain synapses and support neurotransmission. Terminal SCs are packed so tightly at nerve endings that it's hard to distinguish individual cells, so Brill et al. established techniques to label single SCs in vivo in order to investigate their organization and dynamics at young and adult synapses.

During development, SCs at immature synapses were highly dynamic, extending and retracting processes that intermingled with protrusions from neighboring cells. Later, however, mature SCs became much more static, occupying their own territories and showing no overlap with their neighbors.

This segregated pattern appears to be maintained by continuous spatial competition between the cells. When Brill et al. laser ablated a single SC at an adult neuromuscular junction, its neighbors rapidly swooped in to fill the vacated space, suggesting that contacts between SCs usually stop them from wandering into each other's territory. Contacts with the axon itself also help to position adult SCs, as they intermingled dynamically following axon fragmentation but resumed their segregated arrangement after the nerve re-grew.

Brill et al. also noticed that invading SCs rapidly gobbled up the debris left behind by ablated cells or fragmented axons. Author Thomas Misgeld and his team now want to investigate whether this phagocytic capacity allows SCs to assist in synaptic remodeling.

Brill, M.S., et al. 2011. *J. Cell Biol.* http://dx.doi.org/10.1083/jcb.201108005.