Good housekeeping maintains a healthy liver

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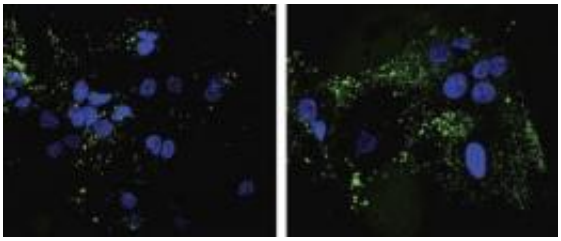

A new study in the *Journal of Cell Biology* suggests that differential expression of GAPDH and NDPK, two key metabolic enzymes, may explain why some people are more susceptible to liver damage.Compared to control cells (left), liver cells lacking GAPDH (right) show increased levels of reactive oxygen species (green) after treatment with the liver-damaging drug DDC. Credit: Image courtesy of Snider, N.T., et al. 2011. J. Cell Biol. doi:10.1083/jcb.201102142

Differences in the levels of two key metabolic enzymes may explain why some people are more susceptible to liver damage, according to a study in the October 17 issue of the *Journal of Cell Biology*.

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 DDC, which induces oxidative stress. A team led by researchers from the University of Michigan 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 expressed at differing levels in the livers of C57BL (MDB-susceptible) and C3H (MDB-resistant) mice, resulting in higher levels of reactive oxygen species in C57BL liver cells after DDC treatment. Prominent among these enzymes were two general "housekeeping" proteins: the metabolic enzyme GAPDH and the energy-generating protein NDPK, both of which showed reduced expression in C57BL livers and were decreased further by DDC treatment.

Depleting GAPDH or NDPK by RNAi elevated reactive oxygen species levels similarly to DDC treatment, whereas overexpressing GAPDH prevented DDC from inducing reactive oxygen species production in C57BL liver cells. The authors think that low GAPDH and NDPK expression causes C57BL livers to be metabolically and oxidatively stressed even under normal conditions and therefore more sensitive to additional stresses like DDC treatment. The researchers also found that GAPDH is localized in protein aggregates in cirrhotic patient livers, suggesting that similar mechanisms may contribute to liver disease severity in humans.

More information: Snider, N.T., et al. 2011. *J. Cell Biol.* doi:10.1083/jcb.201102142

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