

HEPATOCELLULAR CARCINOMA

Working it out—exercise reduces HCC but not steatosis in mice

New research published in the *Journal of Hepatology* has found that in a mouse model of NASH, exercise decreases the size and incidence of hepatocellular carcinoma (HCC) without improving steatosis.

HCC is known to occur on a background of chronic liver disease, and exercise is known to be an effective treatment for patients with NAFLD. “Based on this evidence we got interested in the effects of physical activity on the risk of HCC in NASH,” explains corresponding author Jean-François Dufour.



Hepatocyte-specific PTEN-deficient mice, which develop NASH and HCC spontaneously, were assigned to an exercise or sedentary group for 32 weeks. In the exercise group, mice ran on a treadmill for 1 h per day, 5 days a week. Both groups were sacrificed 72 h after the exercise group's final run.

In the sedentary group, 100% of mice had liver tumours compared with 71% in the exercise group. A greater number of sedentary mice also developed larger tumours (>15 mm³) than exercised mice. “Interestingly this effect was not related to an amelioration of steatohepatitis,” remarks Dufour.

To investigate the signalling pathways regulated just after exercise, mice were sacrificed 15 min after a single episode of running. Analysis of the liver indicated increased activity of AMPK, a regulator of energy homeostasis. Increased Raptor inhibition—a target of AMPK and part of the mTORC1 complex that promotes cellular proliferation—was also found. The authors speculate that exercise

increases AMPK activity, which reduces HCC growth. In support of this theory, histological assessment of tumour tissue showed reduced levels of Ki67, a marker of proliferation. Subsequent RNA sequencing of liver tissue identified six pathways (predominantly involved in fatty acid metabolism) that were substantially changed by exercise. The effects on metabolism seen 15 min after exercise did not result in an improvement in steatosis in the longer experiment (32 weeks).

“Whether this result holds true in models of HCC arising with another underlying liver disease and whether a deeper understanding of the molecular mechanisms at play can reveal interesting therapeutic targets, will be important to investigate,” concludes Dufour.

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Original article Piguet, A.-C. *et al.* Regular exercise decreases liver tumor development in hepatocyte-specific PTEN-deficient mice independently of steatosis. *J. Hepatol.* doi:10.1016/j.jhep.2015.01.017