Lack of mitochondrial topoisomerase I (TOP1mt) impairs liver regeneration

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Résumé en anglais	The liver has an exceptional replicative capacity following partial hepatectomy or chemical injuries. Cellular proliferation requires increased production of energy and essential metabolites, which critically depend on the mitochondria. To determine whether Top1mt, the vertebrate mitochondrial topoisomerase, is involved in this process, we studied liver regeneration after carbon tetrachloride (CCl4) administration. TOP1mt knockout (KO) mice showed a marked reduction in regeneration and hepatocyte proliferation. The hepatic mitochondrial DNA (mtDNA) failed to increase during recovery from CCl4 exposure. Reduced glutathione was also depleted, indicating increased reactive oxygen species (ROS). Steady-state levels of ATP, O2 consumption, mtDNA, and mitochondrial mass were also reduced in primary hepatocytes from CCl4-treated KO mice. To further test whether Top1mt acted by enabling mtDNA regeneration, we tested TOP1mt KO fibroblasts and human colon carcinoma HCT116 cells and measured mtDNA after 3-d treatment with ethidium bromide. Both types of TOP1mt knockout cells showed defective mtDNA regeneration following mtDNA depletion. Our study demonstrates that Top1mt is required for normal mtDNA homeostasis and for linking mtDNA expansion with hepatocyte proliferation.

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