Diploid hepatocytes drive physiological liver renewal in adult humans

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Abstract

Physiological liver cell replacement is central to maintaining the organ's high metabolic activity, although its characteristics are difficult to study in humans. Using retrospective radiocarbon (14C) birth dating of cells, we report that human hepatocytes show continuous and lifelong turnover, allowing the liver to remain a young organ (average age <3 years). Hepatocyte renewal is highly dependent on the ploidy level. Diploid hepatocytes show more than 7-fold higher annual birth rates than polyploid hepatocytes. These observations support the view that physiological liver cell renewal in humans is mainly dependent on diploid hepatocytes, whereas polyploid cells are compromised in their ability to divide. Moreover, cellular transitions between diploid and polyploid hepatocytes are limited under homeostatic conditions. With these findings, we present an integrated model of homeostatic liver cell generation in humans that provides fundamental insights into liver cell turnover dynamics.