Hepatocyte differentiation requires anisotropic expansion of bile canaliculi

Info

PUBLIZIERT AM
2024-11-15

JOURNAL
Development

LINK
https://doi.org/10.1242/dev.202777

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Abstract

During liver development, bipotential progenitor cells called hepatoblasts differentiate into hepatocytes or cholangiocytes. Hepatocyte differentiation is uniquely associated with multi-axial polarity, enabling the anisotropic expansion of apical lumina between adjacent cells and formation of a three-dimensional network of bile canaliculi. Cholangiocytes, the cells forming the bile ducts, exhibit the vectorial polarity characteristic of epithelial cells. Whether cell polarization feeds back on the gene regulatory pathways governing hepatoblast differentiation is unknown. Here, we used primary mouse hepatoblasts to investigate the contribution of anisotropic apical expansion to hepatocyte differentiation. Silencing of the small GTPase Rab35 caused isotropic lumen expansion and formation of multicellular cysts with the vectorial polarity of cholangiocytes. Gene expression profiling revealed that these cells express reduced levels of hepatocyte markers and upregulate genes associated with cholangiocyte identity. Timecourse RNA sequencing demonstrated that loss of lumen anisotropy precedes these transcriptional changes. Independent alterations in apical lumen morphology induced either by modulation of the subapical actomyosin cortex or by increased intraluminal pressure caused similar transcriptional changes. These findings suggest that cell polarity and lumen morphogenesis feed back to hepatoblast-to-hepatocyte differentiation.