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Id2a is required for hepatic outgrowth during liver development in zebrafish

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Abstract

During development, inhibitor of DNA binding (Id) proteins, a subclass of the helix-loop-helix family of proteins, regulate cellular proliferation, differentiation, and apoptosis in various organs. However, a functional role of Id2a in liver development has not yet been reported. Here, using zebrafish as a model organism, we provide *in vivo* evidence that Id2a regulates hepatoblast proliferation and cell death during liver development. Initially, in the liver, *id2a* is expressed in hepatoblasts and after their differentiation, *id2a* expression is restricted to biliary epithelial cells. *id2a* knockdown in zebrafish embryos had no effect on hepatoblast specification or hepatocyte differentiation. However, liver size was greatly reduced in *id2a* morpholino-injected embryos, indicative of a hepatic outgrowth defect attributable to the significant decrease in proliferating hepatoblasts concomitant with the significant increase in hepatoblast cell death. Altogether, these data support the role of Id2a as an important regulator of hepatic outgrowth *via* modulation of hepatoblast proliferation and survival during liver development in zebrafish.

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Keywords: Inhibitor of DNA binding; Differentiation; Biliary epithelial cell; Hepatoblast; Liver specification; Helix-loop-helix

1. Introduction

Liver organogenesis is a multifaceted process involving hepatoblast specification from the ventral foregut endoderm, budding and outgrowth of the liver bud, and hepatoblast differentiation into either hepatocytes or biliary epithelial cells (BECs) (Zaret, 2002;

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Lemaigre, 2003). In both mice (Jung et al., 1999; Rossi et al., 2001) and zebrafish (Shin et al., 2007; Chung et al., 2008), inductive signals of Fibroblast Growth Factors (FGFs) and Bone Morphogenetic Proteins (BMPs) are essential for hepatoblast specification. In conjunction with the BMP and FGF signaling pathways, several homeobox transcription factors, including HHEX and PROX1, also regulate the initial stages of liver organogenesis (Si-Tayeb et al., 2010). HHEX regulates hepatoblast proliferation and delamination from the foregut endoderm as *Hhex*$^{-/-}$ mice lack a liver bud and the hepatoblasts fail to migrate into the surrounding septum transversum mesenchyme (Bort et al., 2004). PROX1 also regulates hepatoblast delamination from the liver diverticulum as hepatoblasts fail to migrate in *Prox1*$^{-/-}$ mice (Sosa-Pineda et al., 2000). Hepatocyte metabolic gene expression is altered in favor of biliary gene expression when *Prox1* is ablated in post-delaminated hepatoblasts (Seth et al., 2014). *hhex* (Wallace et al., 2001) and *prox1a* also regulate liver development in zebrafish. *prox1a*, specifically, marks the initiation of hepatoblast specification in zebrafish (Ober et al., 2006). Besides HHEX and PROX1, zebrafish and mammals share additional transcription factors critical for liver organogenesis, such as GATA6 and hepatic nuclear factors (HNFs) (Bossard and Zaret, 1998; Matthews et al., 2004; Holtzinger and Evans, 2005; Lokmane et al., 2008). However, a comprehensive understanding of the molecular mechanisms underlying transcriptional regulation during liver development still needs to be defined.

One family of transcriptional regulators essential in developmental processes, including cell lineage commitment, proliferation and differentiation, is the helix-loop-helix (HLH) family of transcription factors (Massari and Murre, 2000; Jones, 2004). The HLH domain, essential for dimerization, is important in the formation of homo- or hetero-dimers. While some HLH proteins are ubiquitously expressed (*e.g.*, E proteins), other HLH proteins are tissue-specific (*e.g.*, PTF1, HES1). HES1, in particular, downstream of Notch signaling, is essential for digestive system development, especially in extrahepatic bile duct development (Sumazaki et al., 2004). In *Hes1*$^{-/-}$ mice, no tubular structures form in the ductal plate during intrahepatic bile duct development (Kodama et al., 2004). In addition, the bHLH factor, heart and neural crest derivatives expressed 2 (Hand2), is expressed in tissues that surround the liver primordium, such as the lateral plate mesoderm in zebrafish, which later contributes to the hepatic stellate cells (Yin et al., 2012). Moreover, bHLH-PAS (Per-ARNT-Sim) factors, such as the hypoxia inducible factors (HIFs), participate in hepatic disease, regeneration, fibrosis, and hepatocellular carcinoma (Nath and Szabo, 2012). Hif2α (renamed as Epas1b) binds hypoxia response elements (HREs) and regulates hepatic outgrowth in zebrafish (Lin et al., 2014). The activity of bHLH factors can be regulated by the inhibitor of DNA binding (ID) family of proteins.

ID proteins lack the basic DNA binding domain and regulate HLH factors *via* heterodimerization and subsequent creation of nonfunctional, dominant negative complexes that lack DNA-binding capability (Norton, 2000). By heterodimerizing and sequestering ubiquitously expressed HLH factors, such as E-proteins (E47, E2-2, HEB, E12), or tissue-restricted HLH factors, ID proteins can thereby regulate cell proliferation, differentiation and apoptosis in a cell-context dependent manner (Sikder et al., 2003). In the pancreas, for instance, by binding and sequestering NeuroD, a bHLH factor implicated in pancreatic beta cell survival and differentiation, ID2 regulates pancreatic progenitor expansion (Hua et al., 2006). Non-bHLH factors can also bind and regulate ID protein

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