Seminars in Cell & Developmental Biology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Seminars in Cell & Developmental Biology

journal homepage: www.elsevier.com/locate/semcdb

Molecular mechanisms of Sox transcription factors during the development of liver, bile duct, and pancreas

Chunyue Yin

Division of Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA

ARTICLE INFO

Article history:
Received 1 July 2016
Received in revised form 13 August 2016
Accepted 18 August 2016
Available online xxx

Keywords:
Sox17
Sox4
Sox9
Differentiation
Homeostasis
Regeneration

ABSTRACT

The liver and pancreas are the prime digestive and metabolic organs in the body. After emerging from the neighboring domains of the foregut endoderm, they turn on distinct differentiation and morphogenesis programs that are regulated by hierarchies of transcription factors. Members of SOX family of transcription factors are expressed in the liver and pancreas throughout development and act upstream of other organ-specific transcription factors. They play key roles in maintaining stem cells and progenitors. They are also master regulators of cell fate determination and tissue morphogenesis. In this review, we summarize the current understanding of SOX transcription factors in mediating liver and pancreas development. We discuss their contribution to adult organ function, homeostasis and injury responses. We also speculate how the knowledge of SOX transcription factors can be applied to improve therapies for liver diseases and diabetes.

Contents

Abbreviations: AAV, adeno-associated virus; Arx, aristaless-related homeobox; BA, biliary atresia; BAC, bacterial artificial chromosome; BDL, bile duct ligation; CD, campomelic dysplasia; CDE, choline-deficient ethionine-supplemented diet; Cdx2, caudal type homeobox 2; DDC, 3,5-diethoxycarbonyl-1,4-dihydrocollidine; ENU, *N*-ethyl-*N*-nitrosourea; Fgf, fibroblast growth factor; Foxa3, forkhead box A3; Hes1, hairy and enhancer of split 1; HHEX, hematopoietically expressed homeobox; Hif1α, hypoxia-inducible factor 1 alpha; Hnf6, hepatocyte nuclear factor 6; HMG, high mobility-group; HPC, hepatic progenitor cell; HPD, hepatopancreatic duct; HybHP, hybrid periportal hepatocyte; IRES, internal ribosome entry site; MAFA, v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog a; MCDE, methionine choline-deficient, ethionine-supplemented diet; Mdm2, mouse double minute 2 homolog; NeuroD, neuronal differentiation 1; Ngn3, neurogenin 3; Nkx6.1, Nk6 homeobox protein 1; Pdx1, pancreatic and duodenal homeobox 1; Pkd2, polycystin 2; PP, pancreatic polypeptide; Ptf1a, pancreas transcription factor 1 subunit alpha; Rbpjκ, recombination signal binding protein for immunoglobulin kappa J region; Sox, sex-determining region of Y chromosome-related high mobility-group box; TGFβ, transforming growth factor beta; TβRII, transforming growth factor β receptor II.

E-mail address: Chunyue.yin@cchmc.org

http://dx.doi.org/10.1016/j.semcdb.2016.08.015
1084-9521/

1. Introduction

Development of the liver and pancreas has been researched extensively in the past decade, owing to the drastic increase in the incidence of chronic liver diseases and diabetes and the urgent need for treatment other than organ transplant. Characterization of the molecular mechanisms underlying liver and pancreas development leads to the discovery of networks of transcription factors, including members of the sex-determining region on Y box (SOX) family of transcription factors. There are currently 30 SOX transcription factors in mammals, characterized by the possession of an evolutionarily conserved HMG DNA-binding motif [1]. They are further divided into 9 subgroups. Members of the same subgroup have similar structures and overlapping functions, whereas members from different subgroups have little in common outside of the HMG motif. Depending on the binding partners they recruit, SOX transcription factors can act both as transcription activators and repressors by directly binding to the promoter/enhancer region of their downstream targets. Because of this versatility, the same SOX factor may regulate pluripotency as well as cell fate decision during development. In this review, we focus on the recent insights into the function of SOX transcription factors in specification and maintenance of liver and pancreas progenitors, cell-type differentiation, and tissue morphogenesis. We also review the molecular regulation of SOX factor expression and the interactions between SOX factors and their partners in different steps of liver and pancreas development. In addition, we present the emerging investigation into the contribution of SOX factors to liver and pancreas homeostasis and regeneration postnatally.

2. SOX transcription factors in hepatobiliary development, homeostasis, and injury

The liver is the largest internal organ and possesses crucial function in detoxification, digestion, metabolism, and immunity. The basic architectural unit of the liver is the liver lobule [2]. Within the hexagonal-shaped liver lobule, the central vein is located in the center, and a portal triad composed of a portal vein, hepatic artery, and bile duct occupies each of the six corners. In between the central vein and portal triad are cords of hepatocytes that constitute ~80% of the liver mass. Extending along the hepatocyte cords are the sinusoidal capillaries. Mesenchymal cells, including Kupffer cells and hepatic stellate cells, also reside in the sinusoidal space. The liver is derived from the foregut endoderm. At mouse embryonic day 8.5 (E8.5), the ventral domain of the foregut endoderm adopts the hepatic fate upon receiving inductive signals from the neighboring cardiac mesoderm and septum transversum. The liver progenitor cells called hepatoblasts form a diverticulum at E9. They then change into a pseudostratified morphology and invade the surrounding mesenchyme to give rise to the liver bud at E10. Some hepatoblasts near the portal vein differentiate into cholangiocytes to form bile ducts and the rest hepatoblasts form hepatocytes. We will review the roles of SOX17, SOX9, and SOX4 in liver development. Hepatic expression and function of the other SOX factors remain largely unknown.

2.1. SOX17 in segregation of ventral foregut endodermal organs

Sox17 of SOXF family is expressed in the endoderm from the onset of gastrulation and serves as an important intrinsic regulator of endoderm formation across vertebrate species [3–6]. *Sox17*-/- mutant mice show severe deficit in gut endoderm [6]. During later endoderm development, *Sox17* mediates segregation of the liver, biliary system, and ventral pancreas (Fig. 1A) [7,8]. At the beginning of hepatopancreatic specification, *Sox17* is co-expressed with hematopoietically expressed homeobox *Hhex* and pancreas/duodenum homeobox protein 1/*Pdx1* in the ventral foregut endoderm [8]. The first segregation occurs at E8.5 when the presumptive liver primordium downregulates *Sox17* but continues expressing *Hhex*. The co-expression domain of *Sox17* and *Pdx1* in the posterior ventral foregut segregates at E9.5 so that the *Sox17*+ domain forms the extrahepatobiliary system, while the *Pdx1*+ domain develops into the ventral pancreas. Both global and ventral foregut-specific knockout of *Sox17* causes a complete loss of gallbladder and cystic duct, confirming its role in specification of the extrahepatobiliary system [7,8]. Depletion of *Sox17* in the ventral foregut from E8.5 onwards results in an expansion of *Pdx1* expression throughout the ventral foregut. *Pdx1*+ cells are aberrantly localized in the liver bud and ectopic pancreatic tissue is present in the common bile duct. Conversely, prolonged *Sox17* expression in the *Pdx1*+ domain suppresses pancreas development and results in formation of ectopic ductal tissue in the stomach and duodenum [7]. Ectopic expression of *Sox17* in the *Pdx1*+ domain does not alter *Pdx1* expression but reduces expression of pancreatic transcription factor *Nkx2.2*. This result suggests that SOX17 acts upstream of NKX2.2 to define pancreatic fate. Meanwhile, SOX17 does not directly suppress PDX1 expression during segregation of the biliary and ventral pancreas lineage. A negative feedback loop between SOX17 and hairy enhancer of split-1 (HES1), a transcriptional effector of Notch signaling, has been proposed to regulate segregation of the SOX17/PDX1 lineages [7]. SOX17 promotes high *Hes1* expression in the *Sox17*+*Pdx1*+ progenitors. HES1 in turn restricts *Sox17*+ cells to the presumptive biliary domain to facilitate segregation of the *Sox17*+ biliary lineage and *Pdx1*+ ventral pancreas lineage. The proposed interactions between SOX17 and HES1/HHEX/PDX1 as well as the repressive effect of SOX17 on NKX2.2 are largely based on how these factors changes expression in Sox17 gain- and loss-of-function embryos. The direct targets and binding partners of SOX17 in these processes have not been identified.

Although SOX17 is not required for liver specification, it is expressed in part of the liver bud [9,10]. In mouse, SOX17 cooperates with another SOXF family member SOX18 to mediate neovascularization of the liver [9]. In zebrafish, Sox17 is thought to label a progenitor population that is responsible for the resumption of liver formation in *wnt2bb* mutant in which the initial liver formation is blocked due to impaired Wnt signaling [10].

In line with its role in extrahepatobiliary specification, dysregulation of SOX17 has been linked to congenital biliary atresia (BA), a severe progressive cholangiopathy of infancy due to defective biliary morphology and function. *Sox17* heterozygous mice in C57BL/6 background develop BA-like phenotype as the gallbladder epithelium becomes detached from the luminal wall [11]. Treating cholangiocyte spheroids with a plant toxin biliatresone induces BA-like syndrome in newborn lambs [12]. The expression of *Sox17* is significantly decreased in the biliatresone-treated spheroids and knocking down *Sox17* in the spheroids mimics the effect of biliatresone treatment [13]. It will be interesting to examine whether SOX17 is associated with BA pathogenesis in patients.

2.2. Sox9 in biliary development

SOX9 of SOXE family is one of the most studied SOX factors as haploinsufficiency of *SOX9* in human is associated with Campomelic dysplasia (CD), a disorder characterized by severe skeletal malformation and sex reversals [14,15]. During mouse liver development, *Sox9* is first expressed in the endodermal cells lining the lumen of the liver diverticulum at E10.5 [16]. Its expression is lost as the hepatoblasts invade the septum transversum, but re-emerges in the hepatoblasts near the portal vein at E11.5. Responding to signals from the portal mesenchyme, these *Sox9*+ hepatoblasts

Please cite this article in press as: C. Yin, Molecular mechanisms of Sox transcription factors during the development of liver, bile duct, and pancreas, Semin Cell Dev Biol (2016), http://dx.doi.org/10.1016/j.semcdb.2016.08.015