【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Agricultural sciences)

Title of Project : Morphogenesis, regeneration and congenital disease in gallbladder and bile duct system in mammals

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Research Area : Agricultural sciences
Keyword : Developmental Biology, Pathological condition

【Purpose and Background of the Research】

In mice and humans, the biliary duct system, consisting of gallbladder, cystic duct, intra- and extra-hepatic bile duct and common bile duct, is responsible for transporting bile from the liver to the duodenum. Congenital biliary diseases can lead to the accumulation of bile in the liver, preventing the excretion of detoxification products, which ultimately results in liver injury. It was shown that, in mouse embryogenesis, a cell-autonomous *Sox17* activity is required for the specification/differentiation of gallbladder/bile duct progenitors during ventral foregut morphogenesis. *Sox17* expression is continuously maintained in a certain population of the bile duct progenitor throughout fetal and perinatal periods. However, there remains unclear when, where and how these SOX17-positive progenitor cells contribute to the development and maintenance of the biliary duct system during late organogenic stages and to the congenital biliary disorder in mammals.

【Research Methods】

In this research project, we analyzed the following four aspects of SOX17 function in the morphogenesis, maturation and regeneration of the mouse biliary duct system by using the *Sox17*-mutant embryos and chimeric embryos of *Sox17*-null ES cells in combination with two novel culture systems of the gallbladder primordium and whole-mount anterior trunk including foregut and heart primordia: 1) Dynamics of *Sox17*-null, heterozygotous and wildtype gallbladder progenitor cells during normal development; 2) Pathogenic mechanisms of the embryonic hepatitis in *Sox17* heterozygotous livers, 3) Identification of SOX17-target genes in the gallbladder progenitor cells; and 4) Potential contribution of SOX17-positive progenitor cells into the liver primodium during regeneration of the fetal hepatocytes damaged by TRECK (Toxin Receptor Cell-Kockout) method.

【Expected Research Achievements and Scientific Significance】

This study aims to explore biological significance of SOX17-positive gallbladder progenitor cells in epithelial maturation, maintenance and regeneration of the biliary duct system at the mid- and late-organogenic stages of mammalian embryos. The underlying mechanisms for the dynamics of gallbladder progenitor cells during morphogenesis, maintenance and regeneration will be also clarified at cellular and molecular levels, which will provide cellular and molecular basis of congenital bile-duct dysgenesis and biliary atresia. Moreover, these findings will contribute to develop new insights for prevention and cure of congenital biliary diseases and perinatal hepatitis in newborn infants.

【Publications Relevant to the Project】

・Saund RS et al., Gut endoderm is involved in transfer of left right asymmetry from the node to the lateral plate mesoderm in the mouse embryo. Development, 139(13):2426-2435, 2012.
・ Uemura M et al., Expression and function of mouse Sox17 gene in the specification of gallbladder/bile-duct progenitors during early foregut morphogenesis. Biochem Biophys Res Commun. 391(1):357-363, 2010.
・ Hara K et al., Evidence for crucial role of hindgut expansion in directing proper migration of primordial germ cells in mouse early embryogenesis. Dev Biol. 330(2):427-439, 2009.
・ Matsui T et al., Redundant roles of Sox17 and Sox18 in postnatal angiogenesis in mice. J Cell Sci. 119(17):3513-3526, 2006.
・ Kanai-Azuma M et al., Depletion of definitive gut endoderm in Sox17-null mutant mice. Development. 129(10):2367-2379, 2002.

【Term of Project】 FY2012-2016
【Budget Allocation】 157,200 Thousand Yen
【Homepage Address】
http://www.vm.a.u-tokyo.ac.jp/kaibo/index.html