Hepatol Int
DOI 10.1007/s12072-007-9023-4

Stage-specific regulation of adhesion molecule expression segregates epithelial stem/progenitor cells in fetal and adult human livers

Mari Inada · Daniel Benten · Kang Cheng · Brigid Joseph · Ekaterine Berishvili · Sunil Badve · Lennart Logdberg · Mariana Dabeva · Sanjeev Gupta

Received: 21 May 2007 / Accepted: 23 August 2007

Abstract
Purpose Regulated expression of cell adhesion molecules could be critical in the proliferation, sequestration, and maintenance of stem/progenitor cells. Therefore, we determined fetal and adult stage-specific roles of cell adhesion in liver cell compartments.
Methods We performed immunostaining for the adhesion molecules, E-cadherin and Ep-CAM, associated proteins, β-catenin and α-actinin, hepatobiliary markers, albumin, α-fetoprotein, and cytokeratin-19, and the proliferation marker, Ki-67. Expression of albumin was verified by in situ mRNA hybridization.
Results In the fetal liver, hepatoblasts showed extensive proliferation with wide expression of E-cadherin, β-catenin, and α-actinin, although Ep-CAM was expressed in these cells less intensely and focally in the cell membrane to indicate weak cell adhesion. Hepatoblasts in ductal plate and bile ducts showed less proliferation and Ep-CAM was intensely expressed in these cells throughout the cell membrane, indicating strong adhesion. In some ductal plate cells, β-catenin was additionally in the cytoplasm and nucleus, suggesting active cell signaling by adhesion molecules. In adult livers, cells were no longer proliferating and E-cadherin, β-catenin, and α-actinin were expressed in hepatocytes throughout, whereas Ep-CAM was expressed in only bile duct cells. Some cells in ductal structures of the adult liver with Ep-CAM coexpressed albumin and cytokeratin-19, indicating persistence of fetal-like stem/progenitor cells.
Conclusions Regulated expression of Ep-CAM supported proliferation in fetal hepatoblasts through weak adhesion and helped in biliary morphogenesis by promoting stronger adhesion in hepatoblasts during this process. Restriction of Ep-CAM expression to bile ducts in the adult liver presumably facilitated sequestration of stem/progenitor cells. This stage-specific and cell compartment-related regulation of adhesion molecules should be relevant for defining how liver stem/progenitor cells enter, exit, and remain in hepatic niches during both health and disease.

Keywords Adhesion molecules · Cell proliferation · Stem cells

M. Inada · D. Benten · K. Cheng · B. Joseph · E. Berishvili · M. Dabeva · S. Gupta (✉)
Departments of Medicine and Pathology, Marion Bessin Liver Research Center, Albert Einstein College of Medicine, Ullmann 625, 1300 Morris Park Avenue, Bronx, NY 10461, USA
e-mail: sanjvgupta@pol.net

M. Inada
Department of Medicine and Clinical Oncology, Graduate School of Medicine, Chiba University, Chiba, Japan

S. Badve
Department of Pathology,
Indiana University School of Medicine, Indianapolis, IN, USA

L. Logdberg
Department of Pathology and Laboratory Medicine,
Emory University School of Medicine, Atlanta, GA, USA

Introduction

Liver development requires regulated controls of cell growth and cell differentiation, through complex interplays between intrinsic cell- and extrinsic membrane-bound and soluble signals [1], and signaling from other cells, for example, embryonic endothelial cells [2]. Tissue homeostasis requires that epithelial cells adhere variably to extracellular matrix components and stroma during cell proliferation, migration, and function [3]. During these processes, cell adhesion molecules, such as cadherins, selectins, integrins, and