REVIEW

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The Role of Mesothelial Cells in Liver Development, Injury, and Regeneration

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Mesothelial cells (MCs) cover the surface of visceral organs and the parietal walls of cavities, and they synthesize lubricating fluids to create a slippery surface that facilitates movement between organs without friction. Recent studies have indicated that MCs play active roles in liver development, fibrosis, and regeneration. During liver development, the mesoderm produces MCs that form a single epithelial layer of the mesothelium. MCs exhibit an intermediate phenotype between epithelial cells and mesenchymal cells. Lineage tracing studies have indicated that during liver development, MCs act as mesenchymal progenitor cells that produce hepatic stellate cells, fibroblasts around blood vessels, and smooth muscle cells. Upon liver injury, MCs migrate inward from the liver surface and produce hepatic stellate cells or myofibroblast depending on the etiology, suggesting that MCs are the source of myofibroblasts in capsular fibrosis. Similar to the activation of hepatic stellate cells, transforming growth factor β induces the conversion of MCs into myofibroblasts. Further elucidation of the biological and molecular changes involved in MC activation and fibrogenesis will contribute to the development of novel approaches for the prevention and therapy of liver fibrosis. **(Gut Liver 2016;10:166-176)**

Key Words: Glisson's capsule; Hepatic stellate cells; Liver fibrosis; Mesothelial-mesenchymal transition; Myofibroblasts

INTRODUCTION

Hepatocytes occupy approximately 80% of the total liver volume and play essential roles in metabolism. In mice, the liver consists of median, right, left, and caudate lobes. In each lobe, the liver parenchyma is covered by a serous membrane (serosa) that comprises a single layer of mesothelial cells (MCs). MCs are easily recognized in liver sections under the microscope, based on their location on the liver surface and their flat morphology, but the presence of MCs is often ignored. Accordingly, little is known about their roles in the liver. Recent studies have suggested that MCs are not only a simple barrier of the liver surface but that they also actively contribute to liver development and injury. In this article, we first introduce basic knowledge of MC biology, and then we review their characteristics and functions in liver development, fibrosis, and regeneration.

GENERAL FEATURES OF THE MESOTHELIUM

The name of MCs comes from their presence in the epithelial lining of mesodermic cavities.[1,2] As this name implies, MCs are mesodermal in origin and lie on the organ surfaces as single epithelial sheets. MCs are separated from underlying fibroblasts by the basal lamina. The mesothelium covers the surface of the visceral organs, including the heart, respiratory tract (lung), digestive tract (liver, stomach, and intestine), omentum, and ovaries.[3] It also covers the parietal wall of the pleura, pericardium, peritoneum, and tunica vaginalis. MCs are flat epithelial cells that form epithelial sheets with tight junctions, adherence junctions, gap junctions, and desmosomes.[4] MCs exhibit a squamous epithelial cell shape in normal organs, and they express both epithelial cell and mesenchymal cell markers. MCs secrete a lubricating fluid to create a slippery surface that facilitates movement between organs without friction. MCs synthesize decorin and biglycan, and they are a major source of proteoglycans in the peritoneal fluid.[5] MCs express cell adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1), and cytokines, such as SDF-1/CXCL12, MCP-1/CCL2, and IL-8, and they facilitate inflammatory reactions via the recruitment of monocytes.[6,7] The mesothelium acts as a semipermeable barrier for water and solutes, and

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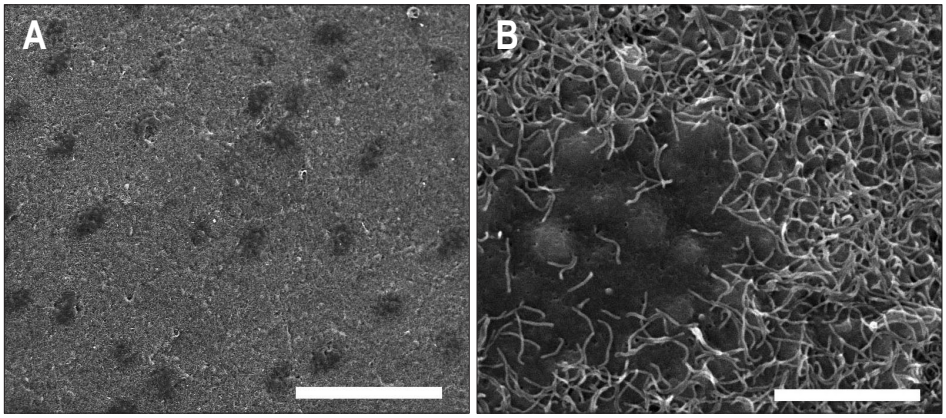

Fig. 1. Ultrastructure of the liver surface analyzed by scanning electron microscopy. Mesothelial cells on the surface of the normal adult mouse liver have microvilli protruding into the peritoneal cavity. The black regions represent areas having few microvilli above the nuclei. Scale bars, 50 μm in (A) and 5 μm in (B).

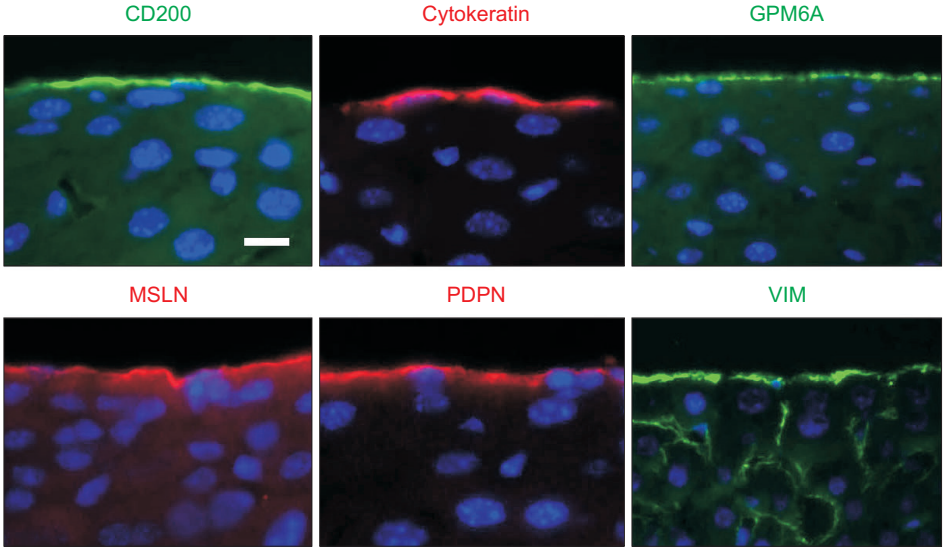

Fig. 2. Expression of markers in liver mesothelial cells (MCs). Immunohistochemistry shows the expression of CD200, cytokeratin, glycoprotein M6A (GPM6A), mesothelin (MSLN), podoplanin (PDPN), and vimentin (VIM) in MCs covering adult mouse livers. Scale bar, 10 μm.

this ability has been exploited for peritoneal dialysis in patients with kidney failure.[8]

CHARACTERISTICS OF LIVER MCs

MCs form a single mesothelial cell layer that lines the liver surface and exhibit squamous epithelial cell morphology.[9,10] MCs in the adult mouse liver have microvilli protruding into the peritoneal cavity (Fig. 1). Microvilli are scarce from the membrane immediately above the nuclei of the MCs, although the reason for this scarcity is unclear.[9,11] Liver MCs express ICAM-1 and VCAM-1 on the microvilli, mediating the binding of monocytes onto MCs due to stimulation by lipopolysaccharide.[11] MCs express cytokeratin 8 and 19, tight junction proteins and gap junction proteins.[10,12,13] In the mouse liver, the expression of E-cadherin is not evident in MCs.[10] Liver MCs express mesenchymal cell markers, such as vimentin (VIM) (Fig. 2). In addition to these markers, MCs express CD200, glycoprotein M6A (GPM6A), mesothelin (MSLN), and podoplanin (PDPN) (Fig. 2).[10]

In the mouse liver, the parenchyma is covered by a single layer of MCs and underlying capsular fibroblasts, also called

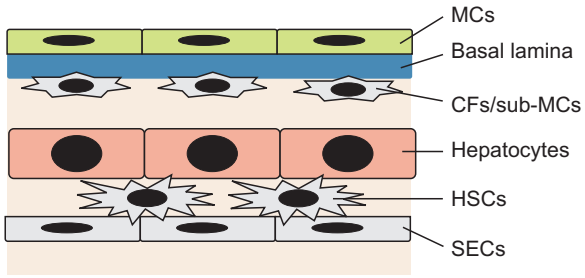

Fig. 3. Structure of the mesothelium in mouse liver tissue. Mesothelial cells (MCs) line up on the liver surface and form a single epithelial cell layer. The basal lamina separates the MCs from the underlying capsular fibroblasts (CFs)/sub-mesothelial cells (sub-MCs). Mouse livers show a single stratum of CFs beneath the MCs. Hepatic stellate cells (HSCs) reside in the space of Disse between hepatocytes and sinusoidal endothelial cells (SECs).

sub-mesothelial cells (sub-MCs) (Fig. 3).[9,14] Capsular fibroblasts synthesize collagen fibers and do not express MC markers.[10,15] Hepatic stellate cells (HSCs) reside in the space of Disse between the hepatocytes and the sinusoidal endothelial cells, and HSCs store vitamin A lipids as retinyl esters (Fig. 3).[16,17] Differing from

HSCs, capsular fibroblasts beneath the MCs do not store vitamin A lipids in their cytoplasm.[14] However, little is known about their characteristics and functions in the liver due to a lack of markers.

MC DEVELOPMENT

The development of the mesothelium has been studied mainly in chick embryos. During gastrulation, the mesoderm is formed between the ectoderm and endoderm. The mesoderm becomes the paraxial mesoderm, intermediate mesoderm, and lateral plate mesoderm.[18] The paraxial mesoderm forms the somite and gives rise to skeletal muscle, cartilage, and the connective tissue of the skin. The intermediate mesoderm gives rise to the urogenital organs, including the kidneys. The lateral plate mesoderm gives rise to blood vessels and mesenchymal cells in the heart, digestive tract, body wall, and limbs. The mesothelium is derived from the lateral plate mesoderm.[18] As the coelomic cavity develops in the lateral plate mesoderm, the mesoderm forms the splanchnic mesoderm and somatic mesoderm. The splanchnic mesoderm develops with the endoderm, and together they form the gut tube. During the gut organogenesis, mesodermal cells, exposing the coelomic cavity, become visceral MCs that cover the surface of the internal organs, including the lungs, liver, and intestine.[18,19] The somatic mesoderm underlying the ectoderm forms the wall of the cavity and gives rise to parietal MCs, which cover the surfaces of the body cavities. Thus, visceral and parietal MCs are separated during the formation of the coelomic cavity in the early developmental stage. In mouse embryogenesis, the nascent mesoderm, expressing mesoderm posterior 1 (MESP1), which is a basic helix-loop-helix transcription factor, contributes to visceral MCs in the liver.[20,21] In contrast, MESP1+ mesoderm does not contribute to parietal MCs on the body wall of the peritoneal cavity, indicating distinct origins of the visceral and parietal MCs in mice.[15] In chick embryos, MCs in the gut derive from resident mesenchymal progenitor cells.[22] MCs seem to have organ-specific functions in each organ.

DEVELOPMENT OF THE SEPTUM TRANSVERSUM MESENCHYME

Liver epithelial cells originate from the definitive endoderm developed in the foregut (Fig. 4). A transplantation study in chick embryos showed that the foregut endoderm differentiates into liver in the presence of the cardiac mesoderm.[23] In mouse embryos, the cardiac mesoderm secretes fibroblast growth factors and induces hepatoblasts from the foregut endoderm.[24] In addition, bone morphogenetic proteins from the septum transversum mesenchyme (STM) are required for the transformation of the endoderm into hepatoblasts.[25] Hepatoblasts are bipotent liver progenitor cells, and they give rise to both hepatocytes and cholangiocytes.[26,27] During liver development, hepatoblasts invade the STM and form a hepatic cord.[28]

The STM surrounding the foregut endoderm is heterogeneous, containing at least mesenchymal cells and endothelial cells.[29] Although the STM is required for liver development, this transient mesenchymal cell population also contributes to heart development and diaphragm formation. Mesenchymal cells budding from the surface of the STM into the pericardial cavity are called proepicardial cells.[30,31] They traverse the pericardial cavity, attach to the heart surface, and form a single layer of MCs on the heart surface, called the epicardium. Epicardial cells undergo epithelial-mesenchymal transition (EMT), migrate inward from the heart surface, and give rise to mesenchymal cells of the coronary vessels in chick embryos.[32,33] In mouse embryos, proepicardial cells express T-box18 (TBX18) and Wilms tumor 1 homolog (WT1). Cell lineage tracing of TBX18+ or WT1+ proepicardial cells revealed their contributions to fibroblasts and

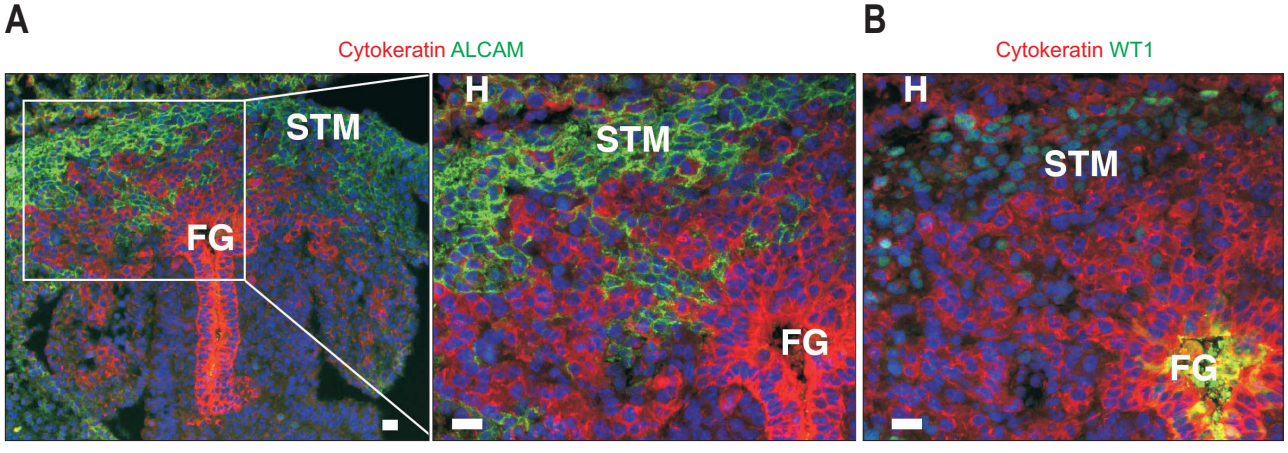

Fig. 4. Mouse liver development at embryonic day 10. Foregut endoderm (FG) differentiates into hepatoblasts that are positive for immunohistochemical staining of cytokeratin (red). Cytokeratin+ hepatoblasts invade the surrounding septum transversum mesenchyme (STM) and form liver buds. The STM expresses mesothelial cell markers, such as activated leukocyte cell adhesion molecule (A, green) and Wilms tumor 1 homolog (WT1) (B). WT1+ mesenchymal cells also differentiate into epicardial cells of the developing heart (H). Scale bar, 20 μm.

smooth muscle cells in the developing heart.[34,35] In addition, lineage tracing of Semaphorin3D (SEMA3D)+ and Scleraxis (SCX)+ proepicardial cells showed their contributions to coronary vascular endothelial cells,[36] suggesting heterogeneity of the STM.

CONTRIBUTION OF THE STM TO LIVER MESENCHYME

Although the STM is known to be important for heart and diaphragm development, little is known about its cell lineage and function in liver development. A morphological study showed that hepatoblasts invade the surrounding STM and form a hepatic cord in mouse embryos (Fig. 4).[28] During this process, mesenchymal cells seem to be trapped between growing hepatoblasts and become HSCs. Conditional cell-lineage tracing in mice revealed that WT1+ cells in the STM give rise to MCs on the liver surface and HSCs in the liver during liver development.[29] GATA binding protein 4 (GATA4) is broadly expressed in both STM and endoderm at the onset of liver development.[37] Rojas *et al*.[38] identified an enhancer of GATA4 which is specifically active in the lateral plate mesoderm and STM around E7.75-9.5 embryos but not in HSCs in the developing liver from E11.5. A lineage tracing study using the STM-specific GATA4 enhancer-Cre mouse showed that the STM contributes to 64% of HSCs during liver development.[39] The results of these studies indicate that the STM is the origin of HSCs during mouse liver development.

The STM expresses forkhead box F1 (FOXF1), GATA4, LIM homeobox protein 2 (LHX2), heart and neural crest derivatives expressed transcript 1 (HAND1), H2.0-like homeobox (HLX), mab-21-like 2 (MAB21L2), TBX18, zinc finger protein multitype 2 (ZFPM2/FOG2), and WT1.[29,37,40-46] Because the STM is the source of epicardium in the heart, of the diaphragm, and of MCs in the liver, deletion of the MAB21L2, TBX18, and ZFPM2 gene resulted in abnormal development of the heart, diaphragm, and liver.[44-46] GATA4-null mouse embryos showed heart defects due to underdevelopment of the STM.[37] Conditional deletion of GATA4 in the STM caused reduced liver size, precocious activation of HSCs, and abnormal deposition of ECM in embryonic livers,[39] indicating that GATA4 regulates the quiescent phenotype of embryonic HSCs. Loss of deletion of β-catenin in MCs and HSCs expressing TWIST2 also caused abnormal activation of HSCs in embryonic livers.[47] WT1 gene deletion resulted in abnormal development of the mesothelium, including of the liver, and impairment of hepatocyte proliferation.[48-50] WT1 could regulate the differentiation of MCs into mesenchymal cells via retinoic acid signaling in developing livers.[49,51] HLX-null embryos impaired hematopoiesis and resulted in liver hypoplasia.[52] MCs in the embryonic liver express pleiotrophin (PTN) and midkine (MDK).[48,53] PTN and MDK are secreted heparin-binding proteins, and they induce the proliferation of hepatoblasts in liver development.[48]

MCs ACT AS MESENCHYMAL PROGENITOR CELLS DURING LIVER DEVELOPMENT

Although the STM emerges as an aggregate of mesenchymal cells surrounding the foregut endoderm, it also expresses MC markers, such as activated leukocyte cell adhesion molecule (ALCAM/CD166) and WT1, on embryonic days (E) 9-10 in mouse embryos (Fig. 4).[29] As the liver bud invades the STM, the surrounding mesenchyme becomes thinner, and flat MCs appear on the liver surface around E11.5. From E12.5, the MCs start to express cytokeratin, CD200, GPM6A, and PDPN, similar to MCs in adult livers.[29] MCs also express podocalyxin-like (PODXL) and MSLN.[48] The expression of ALCAM and WT1 was observed, not only in MCs but also in sub-MCs beneath the MCs in the embryonic liver around E11-14.[20] MCs and sub-MCs are separated by the basal lamina, which is composed of type IV collagen. Different from MCs, sub-MCs cells also express HSC markers, such as nerve growth factor receptor (NGFR/P75NTR) and platelet-derived growth factor receptor α (PDGFRA). HSCs and fibroblasts around the blood vessels express NGFR and PDGFRA but not MC markers, including ALCAM, PDPN, and WT1. Sub-MCs seem to be intermediate cells between MCs and HSCs in embryonic livers.[54]

A morphological study showed possible migration of MCs from the liver surface and differentiation into HSCs in mouse liver development.[49] Conditional lineage tracing of WT1+ MCs/sub-MCs showed that they migrate inward from the liver surface and give rise to HSCs, portal fibroblasts, and smooth

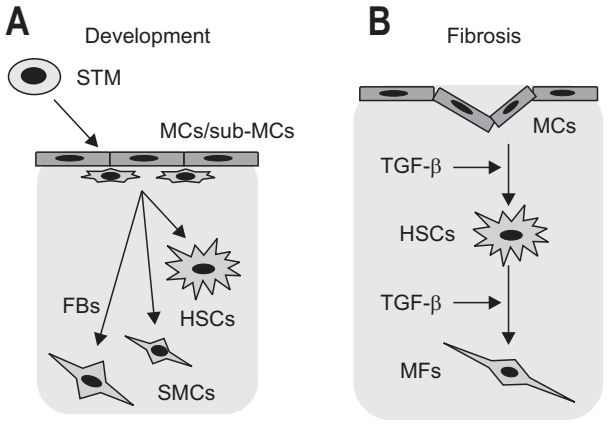

Fig. 5. Differentiation of mesothelial cells (MCs) in liver development and fibrosis. (A) During embryogenesis, mesoderm posterior 1 (MESP1)+ mesoderm gives rise to septum transversum mesenchyme (STM) and MCs. The MCs and underlying sub-MCs express Wilms tumor 1 (WT1). Cell-lineage tracing of WT1+ cells demonstrates their migration from the liver surface and differentiation into hepatic stellate cells (HSCs), fibroblasts (FBs) and smooth muscle cells (SMCs) around the blood vessels in mouse liver development. (B) Upon liver injury caused by CCl_4 injection or bile duct ligation, MCs differentiate into myofibroblasts (MFs) or HSCs in adult mouse livers. Transforming growth factor β (TGF-β) provokes the mesothelial-mesenchymal transition.

muscle cells during mouse liver development (Fig. 5A).[29] Lineage tracing of MSLN+ MCs also showed contributions of MCs to liver mesenchymal cells in embryos.[55] These studies failed to detect the multidifferentiation of MCs into hepatoblasts, sinusoidal endothelial cells, and Kupffer cells. Thus, an HSC lineage from WT1+ MCs is distinct from that of other liver cell types in liver development. Possible migration of WT1+ sub-MCs was also documented in human liver development.[56] The lines of evidence have indicated that MCs act as progenitor cells for liver mesenchymal cells during liver development.

Differentiation of MCs into HSCs has also been reported in chick and zebrafish livers. In chick embryos, after labeling MCs using a vital dye, these cells were found in the liver as HSCs or endothelial cells.[57] In zebrafish, heart and neural crest derivatives expressed transcript 2 (HAND2)+ mesenchymal cells on the liver surface, presumably MCs, give rise to HSCs in liver development.[58] These studies indicated that the migration and differentiation of MCs into HSCs are common processes during liver development in different species.

In addition to the developing liver and heart, differentiation of MCs into mesenchymal cells has been reported in the developing heart, lungs, and intestine.[55,59] During lung development in mice, MCs migrate inward and give rise to smooth muscle cells and mesenchymal cells.[60-62] Similar contributions have been reported in developing gut.[22,63,64] In addition, WT1+ MCs were shown to differentiate into visceral fat in mice.[65] These studies suggested that MCs are the source of mesenchymal cells in organogenesis.

MESODERMAL ORIGIN OF MCs AND HSCs

In adult livers, HSCs reside in the space of Disse and store vitamin A lipids as retinyl esters.[16] Upon liver injury, HSCs are activated, and they differentiate into myofibroblasts expressing α-smooth muscle actin (ACTA2).[17] In addition to HSCs, there are portal fibroblasts around the bile duct, and they have been suggested to be another source of myofibroblasts in biliary fibrosis.[66-68] MESP1 is a basic helix-loop-helix transcription factor expressed in the nascent mesoderm during gastrulation.[69] MESP1+ mesoderm contributes to the primary and secondary heart fields and to other mesodermal cells during embryogenesis. Cell lineage tracing in MESP1-Cre and ROSA26 reporter mice showed that MESP1+ mesoderm gives rise to the STM before liver development.[29] During liver development, MESP1+ cells contribute to MCs, HSCs, and portal fibroblasts around the vein.[29] These cells differentiated into ACTA2+ myofibroblasts in fibrosis induced by CCl_4 or bile duct ligation.[21]

LIVER FIBROSIS AND MYOFIBROBLASTS

Chronic liver injury caused by alcohol intake, drugs, hepatitis virus infection, and obesity results in fibrosis, and finally cirrhosis.[70-72] Upon liver injury, quiescent HSCs are activated, synthesize proinflammatory cytokines and extracellular matrices, and facilitate the regeneration of hepatocytes in injured livers. However, prolonged damage to the liver results in massive accumulation of collagen in the liver, leading to fibrosis and cirrhosis. HSCs have a fibroblastic morphology, and they express mesenchymal cell markers, such as desmin, Vim, and type I collagen. In addition, they express neural cell markers, such as glial fibrillary acidic protein, nestin, and NGFR. Although the neural crest was believed to be the origin of HSCs, based on their expression of neural markers, a cell lineage tracing study refuted this possibility.[73] In addition, the presence of common progenitor cells for HSCs and hepatocytes in the embryonic liver has been proposed.[74,75] However, as described above, the majority of HSCs have been shown to originate in mice from MESP1+ mesoderm.[20,21]

Myofibroblasts seem to be heterogeneous, and they might derive from different sources during liver fibrosis.[76-79] Although bone marrow cells have been shown to differentiate into HSCs or myofibroblasts, their contribution seems to be negligible in liver fibrosis.[80-83] EMT of hepatocytes or cholangiocytes into myofibroblasts was proposed in liver fibrosis, but cell-lineage tracing studies have refuted this possibility in mice.[84-92]

In severely injured livers, oval cells, which are facultative stem cells, emerge in the portal area. Although oval cells are believed to be important for liver regeneration, their origin and roles have been controversial.[93-95] HSCs were suggested to be the origin of oval cells in mice.[96-98] However, lineage tracing of HSCs using lecithin-retinol acyltransferase (LRAT)-Cre mice did not find evidence of such conversion in different mouse injury models.[99] Similarly, HSCs, portal fibroblasts, and MCs derived from MESP1+ mesenchymal cells did not contribute to hepatocytes, cholangiocytes, and oval cells, respectively, in mouse liver injury.[21] These lineage tracing studies refuted the possibility of the conversion of HSCs into epithelial cells in liver injury.

CONVERSION OF MCs INTO MYOFIBROBLASTS IN LIVER FIBROSIS

In liver fibrosis, collagen deposition is observed around the blood vessels and along the sinusoid, depending on the etiology. Conditional lineage tracing of WT1+ MCs revealed that MCs migrated from the liver surface and gave rise to ACTA2+ myofibroblasts in CCl_4-induced liver fibrosis.[10] MC-derived myofibroblasts were detectable at up to 150 μm in depth from the liver surface (Fig. 5B). Similar migration and differentiation of MCs were also observed in mouse livers after bile duct ligation (Fig. 5B).[10] Different from the CCl_4 model, biliary fibrosis induces differentiation of MCs into HSCs, suggesting that MCs differentiate into myofibroblasts or HSCs in injured livers, depending on etiology.

CONTRIBUTION OF MCs TO FIBROSIS IN THE VISCERAL AND PARIETAL ORGANS

Fibrosis is a scarring process in organs. Similar to the liver, fibrosis develops in different organs and myofibroblasts play pivotal roles in collagen deposition.[100] Recent studies show the similar contribution of MCs to myofibroblasts in the peritoneum and lung. Patients who undergo peritoneal dialysis for kidney failure often develop peritoneal fibrosis.[101-103] Prolonged exposure of a dialysis solution to the peritoneal cavity causes injury to MCs and induces conversion into myofibroblasts. Effluent of the dialysis solution from the peritoneal cavity contained MCs, showing a fibroblastic phenotype.[104] Peritoneal fibrosis has been reproduced in mice by injection of dialysis solution or chemicals. Different insults to the peritoneal cavity cause injury to MCs on the body wall, as well as on the liver. In an experimental mouse model of peritoneal fibrosis, WT1+ MCs gave rise to myofibroblasts in both the body wall and liver.[15] The contribution of MCs to myofibroblasts was approximately 16%, and fibroblasts beneath the MCs might be another source.[105] In the lungs, MCs also differentiate into myofibroblasts in idiopathic pulmonary fibrosis.[106] These studies suggest that MCs are among the sources of myofibroblasts in the fibrogenesis of different organs.

MCs exhibit different phenotypes in different organs. Visceral MCs express autotaxin, and they have greater migration capacity than parietal MCs.[107] Upon injury, peritoneal MCs on the body wall differentiate into myofibroblasts, and the MC layer disappears in mice. In contrast, liver MCs give rise to myofibroblasts that migrate beneath the MC layer, whereas the MC layer remains on the surface. It is unclear why visceral and parietal MCs behave differently upon injury. Recent studies have shown that visceral and parietal MCs are inherently different. In embryos, lung MCs are derived from the lung bud but not from other organs.[22] Cell lineage tracing of MESP1+ mesoderm showed its contribution to MCs in the liver but not in the body wall.[15]

MECHANISMS OF CONVERSION OF MCs INTO MESENCHYMAL CELLS

MCs are isolated from the effluent of the peritoneal cavity or by the digestion of organs. In culture, primary MCs grow and form epithelial colonies of MCs.[108,109] Recent studies have identified specific surface markers for liver MCs, such as GPM6A or PODXL, and these markers have allowed for the purification of MCs by fluorescence-activated cell sorting (FACS) or magnetic-activated cell sorting (MACS).[10,48] Primary liver MCs grew and formed epithelial colonies (Fig. 6A). However, MCs lost their epithelial phenotype over several passages and became fibroblastic cells spontaneously.[10]

Transforming growth factor β (TGF-β) is a pleiotrophic factor known to be a strong inducer of EMT.[110] In culture, TGF-β treatment induced morphological changes of MCs into myofibroblasts (Fig. 6B).[10] According to these changes, MCs increased the expression of ACTA2 and type I collagen α1 chain (COL1A1) while decreasing GPM6A. Conversion of MCs into myofibroblasts was blocked by the inhibition of TGF-β receptor or SMAD3, suggesting that a canonical TGF-β/SMAD3 pathway is involved in this process. Epithelial cells undergo EMT and acquire a mesenchymal cell phenotype. During this process, TGF-β is known to induce Snail transcription repressors and to suppress E-cadherin expression. However, liver MCs do not express E-cadherin, and the expression of Snail is low.[10] Because MCs are mesodermal in origin and have an intermediate phenotype between epithelial cells and mesenchymal cells, we call the change of MCs into fibroblastic cells mesothelial-mesenchymal transition (MMT).[10] The cellular mechanisms of MMT might not be identical to what we know about EMT in epithelial cells. Although the details of the downstream pathways of TGF-β signaling have not yet been clarified, suppression of TGF-β signaling with a soluble form of TGF-β type II receptor resulted in decreased MMT in mouse liver fibrosis.[10] Furthermore, conditional deletion of TGF-β type II receptor also reduced their conversion into fibrosis.[15,111] Thus, TGF-β signaling is responsible for the conversion of MCs into myofibroblasts both *in vitro* and

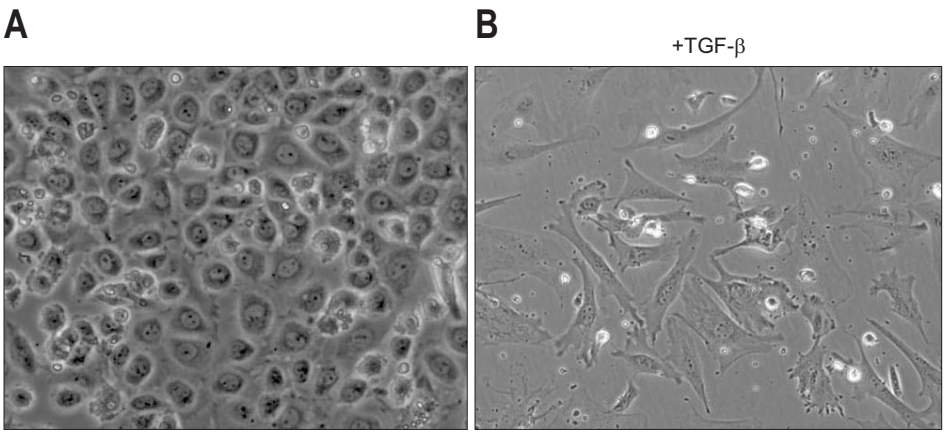

Fig. 6. Primary culture of liver mesothelial cells (MCs). (A) MCs isolated from adult mouse livers form epithelial colonies in culture. (B) Transforming growth factor β (TGF-β) treatment induces the mesothelial-mesenchymal transition.

in vivo.

SECRETORY FUNCTION OF MCs IN PARTIAL HEPATECTOMY AND RESECTION

The liver has remarkable regenerative potential.[112] After 70% partial hepatectomy, hepatocytes start DNA synthesis, and the liver mass returns to the original size by the proliferation and hypertrophy of hepatocytes.[113] Lineage tracing of WT1+ MCs showed no migration of MCs into the regenerating liver after 70% partial hepatectomy.[10] In the regenerating liver, MCs secrete PTN and MDK and support the proliferation of hepatocytes.[114] PTN- or MDK-knockout mice showed decreased proliferation of hepatocytes in the regenerating liver.[115] It remains to be clarified how MCs sense regeneration stimuli by partial hepatectomy and how they coordinate proliferation with growing hepatocytes.

MCs secrete a lubricating fluid and have antiadhesive properties. After resection of liver lobes, the resected liver surface often adheres to the other liver lobes or organs, requiring reoperation to remove adhesions between organs. Suzuki *et al*.[116] developed an adhesion model of liver surgery. After electrocauterization of rat liver lobes, the cauterized lobe formed adhesions with the intact liver lobes. Interestingly, the necrotic area of the cauterized liver lobe rapidly induced the denudation of MCs from the opposite intact lobe, as well as adhesion with the deposition of fibrin. The finding of molecules inducing denudation of MCs will be important to designing anti-adhesion drugs. An MC sheet created using fetal livers prevented adhesion between the liver and body wall after surgery.[114] Thus, MCs might be useful for the prevention of organ adhesion and for supporting regeneration of the liver after surgery.

MESOTHELIOMA

MCs are the source of malignant mesothelioma. Mesothelioma is rare, but exposure to asbestos has increased the risk of mesothelioma in the lung worldwide. Mesothelioma in the liver is extremely rare in humans, but it is experimentally inducible in rats by intraperitoneal injection of asbestos.[117,118] Ovarian carcinoma cells attached to MCs in the peritoneal cavity and induced fibroblastic conversion of MCs.[119] These MC-derived cancer-associated fibroblasts might provide a niche for the growth of ovarian carcinoma. Ovarian cancer cells induced a mesenchymal phenotype in MCs via TGF-β.[120] Noting is known whether liver MCs also participate in cancer metastasis.

FUTURE DIRECTIONS

Although MCs were once considered a simple barrier of the organs, recent studies have indicated that MCs dynamically change their phenotype during liver development, injury, and regeneration. Further studies are necessary to understand how MCs coordinate and regulate liver development and growth with other liver cell types in embryogenesis. During liver fibrosis, MCs contribute to the generation of myofibroblasts near the liver surface. Although TGF-β has been shown to induce MMT, it is unclear how MCs sense hepatocyte injury. Elucidation of biological and molecular changes involved in MC activation and fibrogenesis will contribute to the development of novel approaches for prevention and therapy of liver fibrosis. It will also be interesting to examine whether myofibroblasts from different cell sources play different roles in fibrogenesis.[121] Further studies are necessary to understand how the semi-permeable barrier function of liver MCs is changed in liver fibrosis and how it is involved in ascites formation in cirrhosis.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article are reported.

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