Supplementary material

Liver cell-targeted delivery of therapeutic molecules

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Liver cells and their physiologic roles

Hepatocytes

Hepatocytes account for 70–80% of all liver cells and are involved in the metabolism of lipids, proteins, and carbohydrates; detoxification; synthesis of proteins and lipids; immune/inflammatory responses; and the secretion of lipoproteins, growth factors, and cytokines. Hepatocyte injury is directly/indirectly involved in many liver diseases. Hepatocytes also activate other cell types (e.g. Kupffer cells) and trigger immune/inflammatory responses (Ishibashi et al., 2009; Malhi et al., 2010). These cells are also the primary infection target of hepatotropic viruses (e.g. hepatitis B virus and hepatitis C virus) (Herzer et al., 2007; Nakamoto & Kaneko, 2003). Therefore, hepatocytes are the most important target for treating liver diseases and for the development of hepatocyte-targeted delivery systems.

Kupffer cells

Kupffer cells are the first macrophages to be exposed to gut-derived foreign and toxic materials such as viruses, bacteria, protozoa, immune complexes, and endotoxins. Therefore, Kupffer cells are involved in host defense, immune/inflammatory responses, and detoxification of foreign and toxic materials. Foreign and toxic materials are taken up by phagocytosis and receptor-mediated endocytosis, often via a scavenger receptor and a Fc receptor, and are eliminated by detoxification or degradation in lysosomes (Jacobs et al., 2010; Løvdaal et al., 2000; Naito et al., 2004; Smedsrød et al., 1994).

Generally, Kupffer cells endocytose large particles ($>1\ \mu\text{m}$ in diameter) (Dan & Wake, 1985; Jacobs et al., 2010; Naito et al., 2004; Shiratori et al., 1993; Smedsrød et al., 1994). Kupffer cells are important regulators of liver diseases, including non-alcoholic liver disease (Baffy, 2009; Koek et al., 2011), alcoholic liver disease (Miller et al., 2011; Nanji, 2002), hepatitis (Nanji, 2002; Polakos et al., 2006; Sciot et al., 1986), and hepatocellular carcinoma (HCC) (Bayón et al., 1996). Cytokines [e.g. interleukin-6 (IL-6) and IL-10] secreted from Kupffer cells regulate the immune/inflammatory responses, and modulate the differentiation and proliferation of other liver cells (Emmanuilidis et al., 2001; Gregory et al., 1998; Knolle et al., 1995, 1997; Kolios et al., 2006).

Contrary to their physiologic roles in host defense and detoxification, Kupffer cells can also worsen liver injury. For example, following hepatocyte injury, Kupffer cells induce death receptor-mediated apoptosis of hepatocytes by expressing ligands [e.g. tumor necrosis factor (TNF)] for the death receptor. Activation of the TNF/death receptor signaling pathways increases the risk of hepatic fibrosis (Malhi et al., 2010; Schwabe & Brenner, 2006; Tomita et al., 2006). Moreover, Kupffer cell-derived transforming growth factor- β (TGF- β), a cytokine that is also secreted by stellate and liver sinusoidal endothelial cells (LSECs), stimulates stellate cells and the production of myofibroblasts, and ultimately promotes the development of hepatic fibrosis (Gressner, 1996; Kolios et al., 2006). Although Kupffer cells are involved in the pathophysiology of hepatic fibrosis and HCC, Kupffer cell-targeted therapy may be useful for treating immune and inflammatory liver diseases (Dong et al., 2009; Mochizuki et al., 2013; Wheeler et al., 2001).

LSECs

Liver sinusoidal endothelial cells account for the largest volume of non-parenchymal cells (Blouin et al., 1977), even though they are smaller (8–10 μm) than hepatocytes (20–25 μm) and Kupffer cells (10–12 μm) (Do et al., 1999). Morphologic studies have suggested that LSECs have open fenestrations without tight junctions in their cytoplasm, and lack a basal lamina (Ishibashi et al., 2009; Smedsrød et al., 1994; Wisse et al., 1996). LSECs provide a physical barrier and are involved in host defense and immune/inflammatory responses, and exert scavenger activity (Blouin et al., 1977;

Jacobs et al., 2010; Shiratori et al., 1993). Several cytokines (e.g. IL-6 and TGF- β) released by LSECs regulate the immune/inflammatory responses (Knolle et al., 1997; Smedsrød et al., 1994). LSECs take up soluble macromolecules and small particles ($<0.23\ \mu\text{m}$) by pinocytosis and receptor-mediated endocytosis (Blouin et al., 1977; Jacobs et al., 2010; Shiratori et al., 1993; Smedsrød et al., 1994) via the scavenger receptor (Jansen et al., 2009; Simon-Santamaria et al., 2010), hyaluronan receptor (Harris et al., 2008; Weigel & Weigel, 2003; Zhou et al., 2000), Fc receptor (Fridman, 1991; Løvdal et al., 2000), and mannose receptor (Magnússon & Berg, 1993). Dan & Wake (1985) reported that LSECs are unable to endocytose latex particles $\geq 0.33\ \mu\text{m}$ in diameter.

The primary LSEC-related disease is hepatic veno-occlusive disease, also known as sinusoidal obstruction syndrome (DeLeve et al., 2002; Wang et al., 2000). Because LSECs are a major endothelial source of Factor VIII, they have become an important target for treating hemophilia A, which is caused by a deficiency of plasma clotting Factor VIII (Hollestelle et al., 2001; Yadav et al., 2012). In fact, when hyaluronan-encapsulated *Sleeping Beauty* transposon vectors containing the canine B domain-deleted FVIII gene were injected into hemophilia A mice, the vectors accumulated in LSECs and improved the phenotype of these mice (Kren et al., 2009).

Stellate cells

Stellate cells are also known as fat-storing cells, Ito cells, sinusoidal pericytes, lipocytes, parasinusoidal cells, and perisinusoidal cells. They are located within the liver lobule and contain metabolites or lipid droplets (e.g. vitamin A metabolites/retinoids) (Blomhoff & Wake, 1991; Blouin et al., 1977; Friedman, 2008). The physiologic functions of stellate cells include vitamin A and lipid metabolism, detoxification, immune/inflammatory responses, and the secretion of lipoproteins (e.g. ApoE), growth factors (e.g. epithelial growth factor), and cytokines (e.g. IL-6) (Blomhoff & Wake, 1991; Blouin et al., 1977; Friedman, 2008).

Stellate cells play critical roles in liver fibrosis, particularly in its advanced stage of liver cirrhosis. Stellate cells are quiescent in the normal liver, but persisting liver injury activates stellate cells, which triggers liver fibrosis. The activated stellate cells produce fibrosis-inducing factors (e.g. type I collagen), while enzymes that can degrade

fibrosis-inducing factors (e.g. collagenase I) are downregulated, resulting in the accumulation of fibrosis-inducing factors (Blomhoff & Wake, 1991; Guyot et al., 2006; Friedman, 2008). Myofibroblasts derived from activated stellate cells and/or portal fibroblasts are abundant in fibrotic lesions and promote the accumulation of fibrosis-inducing factors in the fibrotic scar (Blomhoff & Wake, 1991; Guyot et al., 2006; Friedman, 2008). Although activation of stellate cells is associated with the loss of lipid droplets, it was recently reported that this loss does not enhance liver fibrosis but actually decreases carcinogenesis (Kluwe et al., 2011; Shirakami et al., 2012). Stellate cells also activate or support the progression of alcoholic liver disease, particularly liver fibrosis and cirrhosis (Suh & Jeong, 2011), and HCC (Olaso et al., 2003). Taken together, these data indicate that stellate cells represent a useful target for treating liver fibrosis and cirrhosis.

Intrahepatic lymphocytes

Intrahepatic lymphocytes include T cells, natural killer cells, and B cells, with T cells being the most common and B cells being the least common. All three cell types are key components of host defense, together with Kupffer cells, because of their roles in immune/inflammatory responses. In the normal liver, intrahepatic lymphocytes are mainly localized to the portal tracts, where they are involved in portal tract infiltration of antigenic materials (Lalor et al., 2002; Racanelli & Rehermann, 2006). Intrahepatic lymphocyte-derived cytokines regulate the immune/inflammatory responses and stimulate the secretion of cytokines from other cells, especially hepatocytes and LSECs (Lalor et al., 2002; Racanelli & Rehermann, 2006). LSEC-derived cytokines can also promote the recruitment and homing of intrahepatic lymphocytes to the portal tracts or to sites of inflammation (Heydtmann et al., 2005; Shields et al., 1999).

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Table S1. Characteristics of liver cells, and the diseases associated with each cell type.

Liver cell type		Cell volume	Functions	Related diseases
Parenchymal cells	Hepatocytes	70–80% of all liver cells	Lipid, protein, and carbohydrate metabolism	Hepatitis
			Detoxification	Alcoholic liver disease
			Synthesis of proteins and lipids	Non-alcoholic liver disease
			Immune/inflammatory response	Hepatocellular carcinoma
			Secretion of lipoproteins, growth factors, and cytokines	Autoimmune diseases
Non-parenchymal cells	Kupffer cells	~20% of non-parenchymal cells	Host defense	Hepatitis
			Immune/inflammatory response	Alcoholic liver disease
			Detoxification	Non-alcoholic liver disease
			Secretion of cytokines, growth factors, and proteolytic enzymes	Hepatocellular carcinoma
				Hepatic veno-occlusive disease
	Sinusoidal endothelial cells	~50% of non-parenchymal cells	Barrier and defense functions	
			Scavenger function	
			Immune/inflammatory responses	
	Stellate cells	~10% of non-parenchymal cells	Secretion of cytokines	
			Vitamin A and lipid metabolism	Liver fibrosis and cirrhosis
			Detoxification	Alcoholic liver disease
	Intrahepatic lymphocytes	~25% of non-parenchymal cells	Immune/inflammatory responses	Non-alcoholic liver disease
			Secretion of lipoproteins, growth factors, and cytokines	Hepatocellular carcinoma
			Host defense	Hepatitis
			Immune/inflammatory responses	Alcoholic liver disease
			Secretion of cytokines	Non-alcoholic liver disease
				Hepatocellular carcinoma

Table S2. Cellular distribution and functions of liver receptors.

Receptor	Localization	Function	References
Asialoglycoprotein receptor	Hepatocytes, sperm, Leydig, stromal, and Sertoli cells	1. Uptake of carbohydrates (e.g. galactose), cytokines, and lymphocytes 2. Viral entry 3. Overexpression during liver cirrhosis	Burgess et al., 1992; Eisenberg et al., 1991; Rigopoulou et al., 2012; Stockert, 1995; Sun et al., 2013
Complement receptor	Leukocytes (e.g. monocytes, macrophages, and neutrophils), endothelial cells, and epithelial cells	1. Immune cell activation (or immune responses) 2. Uptake of immune complexes (e.g. IgG antibodies) 3. Abnormal expression in autoimmune and inflammatory diseases	Leslie, 2001; Ricklin et al., 2010
Fc receptor	Leukocytes (e.g. monocytes, macrophages, and neutrophils), endothelial cells, and epithelial cells	1. Immune cell activation (or immune responses) 2. Uptake of immune complexes (e.g. IgG antibodies) 3. Abnormal expression in autoimmune and inflammatory diseases	Nimmerjahn & Ravetch, 2006; Ravetch & Bolland, 2001; Mihai & Nimmerjahn, 2013
Hyaluronan receptor	Most epithelial cells, macrophages, lymphocytes, and endothelial cells	1. Hyaluronan-dependent cell adhesion 2. Lymphocyte homing to gut-associated lymphoid tissue (e.g. Peyer's patches) 3. Tumor cell migration 4. Uptake and degradation of hyaluronan	Alho & Underhill, 1989; Necas et al., 2008; Underhill, 1992
LDL receptor	Most epithelial cells including hepatocytes	1. Uptake of lipoprotein and cholesterol 2. LDL receptor gene disruption in patients with familial hypercholesterolemia	Herz, 2001; Jeon & Blacklow, 2005; Pathak et al., 1990
Mannose receptor	Most epithelial, endothelial, and immune cells (e.g. macrophages and dendritic cells)	1. Uptake of carbohydrates (e.g. mannose and glucose) and ligands of microbial and endogenous origin 2. Abnormal expression in tumor and inflammatory diseases	East & Isacke, 2002; Linehan, 2005; Martinez-Pomares, 2012

Scavenger receptor	Epithelial cells, endothelial cells, and macrophages	1. Uptake of glycoproteins, lipoproteins, and ligands of microbial and endogenous origin 2. Immune cell activation (or immune response) 3. Host defense and homeostasis	Canton et al., 2013; Greaves & Gordon, 2009; Plüddemann et al., 2007
M6P/IGF-II receptor	Epithelial, endothelial, and stellate cells	1. Uptake, activation, and degradation of M6P-bearing ligands and growth factors 2. Regulation of cell growth and motility 3. Participation in tumor progression and neurodegenerative diseases	DI-Shewy & Luttrell, 2009; Ghosh et al., 2003; Hawkes & Kar, 2004; Heinz-Erian et al., 1991
Platelet-derived growth factor receptor- β	Epithelial, endothelial, stellate, and mesenchymal cells	1. Regulation of cell proliferation, differentiation, and growth 2. Participation in tumor, vascular disease, and fibroses	Andrae et al., 2008; Demoulin & Montano-Almendras, 2012

Ig, immunoglobulin; LDL, low-density lipoprotein; M6P, mannose-6-phosphate; IGF, insulin-like growth factor

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