LIVER TRANSPLANTATION 17:633-640, 2011

REVIEW

What Is the Role of the Receptor for Advanced Glycation End Products–Ligand Axis in Liver Injury?

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Multiligand receptor for advanced glycation end products (RAGE) is expressed in a wide variety of tissues, including the liver. Interactions with its ligands lead to cellular activation and thus prolonged inflammation and apoptosis. RAGE also exists in a soluble, truncated isoform called soluble RAGE, which has the same ligand-binding specificity as membrane-RAGE; acting as decoy, it can contribute to the removal/neutralization of circulating ligands and the resultant reduction of signaling pathway activation. Experimental and clinical studies have highlighted the idea that the RAGE-ligand axis is involved in the development of liver fibrosis, inflammation, and regeneration after a massive injury and in the setting of liver transplantation. The involvement of the RAGE-ligand axis in vascular disease, diabetes, cancer, and neurodegeneration is well established, but it still needs to be clarified in the setting of liver diseases. We present a review of the recent literature on this receptor in surgical and clinical settings involving the liver, and we highlight the open issues and possible directions of future research. ***Liver Transpl 17:633-640, 2011.*** © **2011 AASLD.**

Received February 3, 2011; accepted March 16, 2011.

Receptor for advanced glycation end products (RAGE) is a multiligand-binding member of the immunoglobulin superfamily of cell surface molecules.[1] The full-length receptor consists of an extracellular region formed from 1 V-type immunoglobulin domain needed for ligand binding and 2 C-type immunoglobulin domains; these domains are followed by a single, short transmembrane domain and a short cytoplasmic domain that is essential for RAGE-mediated signal transduction.[1,2]

Its name is derived from the first known ligands, the advanced glycation end products (AGEs), which are a complex and heterogeneous group of tissue-bound and circulating glycoxidated proteins; among them, the carboxymethyl lysine (CML) adducts are the most abundant.[3] Beyond AGEs, which are occasional ligands, RAGE binds certain members of the S100/calgranulin proinflammatory cytokine family, the non-histone nuclear factor high-mobility group box 1 (HMGB1) protein, β-amyloid peptide, β-sheet fibrils, and other ligands.[4-7] Among these ligands, the HMGB1 protein, which is present in the nuclei of almost all eukaryotic cells and can be released during necrosis or in response to hypoxia, plays a critical role in the mechanisms leading to liver injury. Thus, the HMGB1-RAGE interaction may be crucial in liver inflammatory/injury processes.

Abbreviations: AGE, advanced glycation end product; CML, carboxymethyl lysine; esRAGE, endogenous secretory receptor for advanced glycation end products; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HMGB1, high-mobility group box 1; HSC, hepatic stellate cell; I/R, ischemia/reperfusion; LEC, liver sinusoidal endothelial cell; LT, liver transplantation; MMP, matrix metalloproteinase; MSR-A, macrophage scavenger receptor class A; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; RAGE, receptor for advanced glycation end products; sRAGE, soluble receptor for advanced glycation end products; TNF-α, tumor necrosis factor α.

This work was supported by a grant from the European Foundation for the Study of Diabetes.

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DOI 10.1002/lt.22306
View this article online at wileyonlinelibrary.com.
LIVER TRANSPLANTATION.DOI 10.1002/lt. *Published on behalf of the American Association for the Study of Liver Diseases*

RAGE is typically expressed at low levels under normal physiological conditions in most tissues and organs except for the lungs, in which it exhibits high basal levels of expression. High levels of RAGE expression occur in other tissues only under pathological conditions.[8-11] RAGE-ligand interactions lead to intracellular oxidative stress signals and subsequently up-regulate the expression of proinflammatory genes, including its own receptor.[12-15] A typical feature of RAGE is tissue colocalization with its ligands.[6] Because of its expression in various cell types and its multiligand nature, RAGE has been implicated in many conditions, such as atherosclerosis, diabetes, aging, inflammation, neurodegeneration, amyloidosis, and tumors,[16] but its role in liver injury remains controversial.[11,12,17,18]

In addition to the full-length receptor, several truncated isoforms of RAGE have been described; some are circulating soluble isoforms containing only the extracellular portion of the full-length receptor.[19] Soluble receptor for advanced glycation end products (sRAGE) comprises a heterogeneous population that includes an endogenous secretory isoform generated via alternative splicing [endogenous secretory receptor for advanced glycation end products (esRAGE)] and a form generated through proteolytic cleavage of the full-length cell surface receptor by the action of membrane-associated matrix metalloproteinases (MMPs) such as a disintegrin and metallopeptidase 10 and MMP9.[20,21] Circulating sRAGE is detectable in human serum and is able to bind ligands, and by competing with membrane-bound RAGE for ligand binding, it can have cytoprotective effects.[22,23] Higher circulating levels of sRAGE are associated with reduced risks of coronary artery disease, hypertension, metabolic syndrome, and other chronic diseases.[24-27]

Many observations have been made about the potential role of the RAGE pathway in liver diseases and about the protective role of sRAGE in hepatocellular injury, although they have not been unequivocal.[17,28-35] In vitro and experimental studies have shown that through the activation of intracellular signals and the resulting production of cytokines, the RAGE-ligand axis may be involved in the processes of liver inflammation and regeneration and, consequently, in those mechanisms involved in liver resection and transplantation.[28-31,36]

In this review, we provide an overview of the current literature on the role of the RAGE-ligand axis, focus on the available evidence, and outline potential directions for further research.

HEPATIC CELLS, RAGE EXPRESSION, AND AGE CATABOLISM

RAGE Expression in Hepatic Cells

The liver has a pivotal role in several metabolic processes, including carbohydrate and lipid metabolism, bile production, red blood cell degradation, plasma protein synthesis, hormone production, and detoxification of harmful substances (eg, alcohol, drugs, and also AGEs).[37,38] The liver is unique in its ability to undergo compensatory hyperplasia after cell loss: key tissues that have been lost are restored within a few weeks through a complex network of cells and mediators.[39] In Fig. 1, we illustrate the types and sites of the different cells that constitute the liver. The parenchymal cells (ie, the hepatocytes) perform the majority of the functions, including bile production, whereas the nonparenchymal cells, which are represented by 3 cell types—liver sinusoidal endothelial cells (LECs), Kupffer cells, and hepatic stellate cells (HSCs)—play different roles. LECs form the walls of sinusoids and perform filtration via small fenestrations; they thus regulate the diffusion of different substances between blood and the surfaces of hepatocytes.[40] Kupffer cells are intrasinusoidally located tissue macrophages that modulate the liver immune function and secrete potent mediators of the early inflammatory response, such as reactive oxygen species, tumor necrosis factor α (TNF-α), and other cytokines[40] (Fig. 1). HSCs, located in the perisinusoidal space, store vitamin A, control the turnover of the extracellular matrix, and regulate the contractility of sinusoids modulating sinusoidal blood flow[40] (Fig. 1).

There is conflicting evidence regarding the expression and localization of RAGE in the different cell types of the liver within and across different species (Table 1). The first evidence of this receptor in liver tissue was reported in 1993 when RAGE was found in bovine hepatocytes but was not detectable in Kupffer cells or LECs.[8] More recently, Butscheid et al.[17] reported marked levels of RAGE in the hepatocytes and bile ducts of healthy human livers and weak staining for RAGE in Kupffer cells.

Conversely, a 2001 study found that RAGE was exclusively expressed by HSCs isolated from rat livers,[12] whereas no transcripts were observed in hepatocytes, Kupffer cells, or LECs isolated from rat and mouse livers.[12,38] Another study using human HSC lines showed the expression of RAGE at both transcript and protein levels.[14] These results were confirmed in rat and human HSC lines expressing significant levels of RAGE, whereas no RAGE expression was found in rat hepatocytes.[18] The discrepancies described by different research groups may be due to different experimental settings and methodologies, including the use of antibodies with different specificities. However, according to current data, there seems to be a cell-specific pattern for RAGE expression, with poor or no expression in Kupffer cells and LECs in nearly all species analyzed so far and with marked expression in HSCs and hepatocytes (Table 1 and Fig. 1).

Is RAGE Involved in the Clearance of AGEs?

RAGE is associated with many inflammation-related pathological states,[16,41] but there is no evidence that it plays a catabolic function. On the other hand, in the liver, this function is carried out by other AGE receptors that act mainly as scavenger receptors for AGE detoxification and catabolism.[17,38,42] This was shown in an in vivo study of rats, which demonstrated

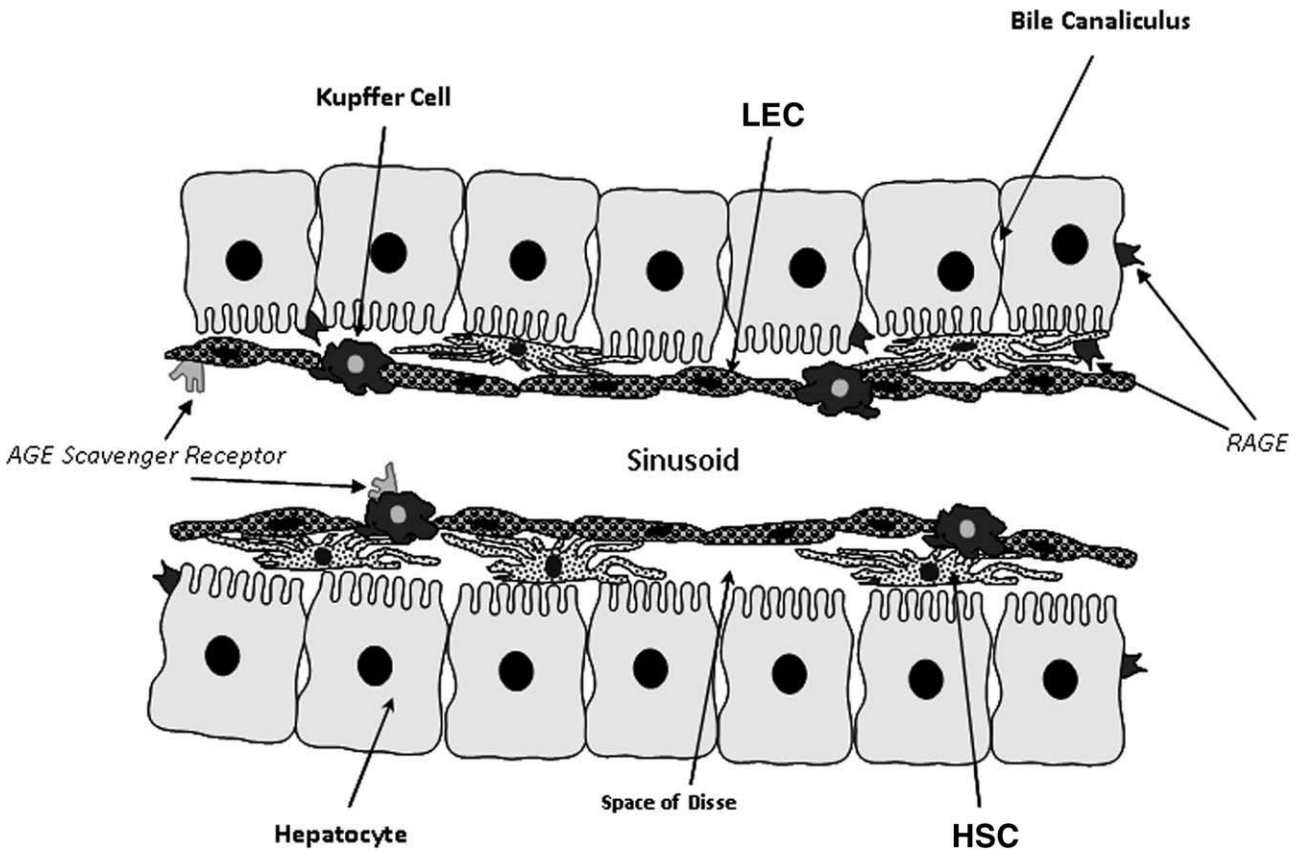

Figure 1. Localization of the AGE scavenger receptor and RAGE in the liver. The liver is composed of different cell types, such as hepatocytes and nonparenchymal cells. The latter are represented by 3 cell types: LECs, Kupffer cells, and HSCs. LECs form the walls of sinusoids in which Kupffer cells are also located. HSCs are in the space of Disse. Bile canaliculi originate from grooves on the lateral aspects of hepatocytes. AGE scavenger receptors are present in LECs and Kupffer cells, whereas RAGE is located in hepatocytes and HSCs.

TABLE 1. Patterns of Liver RAGE Expression Across Different Species

Cell Type	Species	Expression (Authors)
Hepatocytes	Bovine	Yes (Brett et al.,[8] 1993)
	Mouse	No (Matsumoto et al.,[38] 2000)
	Rat	No (Fehrenbach et al.,[12] 2001, and Lohwasser et al.,[18] 2009)
	Human	Yes (Butscheid et al.,[17] 2007)
HSCs	Rat	Yes (Fehrenbach et al.,[12] 2001, and Lohwasser et al.,[18] 2009)
	Human	Yes (Iwamoto et al.,[14] 2008, and Lohwasser et al.,[18] 2009)
Kupffer cells	Bovine	No (Brett et al.,[8] 1993)
	Mouse	No (Matsumoto et al.,[38] 2000)
	Rat	No (Brett et al.,[8] 1993, and Fehrenbach et al.,[12] 2001)
	Human	No (Butscheid et al.,[17] 2007)
LECs	Bovine	No (Brett et al.,[8] 1993)
	Mouse	No (Matsumoto et al.,[38] 2000)
	Rat	No (Brett et al.,[8] 1993, and Fehrenbach et al.,[12] 2001)
Epithelial cells of bile ducts	Human	Yes (Butscheid et al.,[17] 2007)
	Rat	Yes (Lohwasser et al.,[18] 2009)

that the liver removed from circulation more than 90% of intravenously injected AGEs via endocytosis mediated by scavenger receptors in LECs (60%) and in Kupffer cells (25%), whereas the contribution of hepatocytes was low (10%-15%).[43] These results were later confirmed in cultured LECs incubated with AGEs whose intracellular uptake was mediated by scavenger receptors.[43] Furthermore, experiments

using peritoneal macrophages and LECs derived from macrophage scavenger receptor class A (MSR-A)–knockout mice showed that in peritoneal macrophages, AGEs were endocytosed almost exclusively through MSR-A, whereas in LECs, the uptake of AGEs took place through a pathway distinct from MSR-A.[38,44]

Another study using biopsy specimens from patients with various degrees of hepatic dysfunction revealed that, regardless of the diagnosis, CML and galectin 3 (another AGE scavenger receptor) were highly expressed in Kupffer cells, but RAGE was not.[17]

Therefore, AGE catabolism does not seem to be mediated by RAGE for 3 reasons: first, the expression of RAGE in hepatic cells involved in AGE endocytosis (mainly LECs and Kupffer cells) is null or weak; second, RAGE is functionally similar to a cell signaling receptor rather than a scavenger receptor; and third, scavenger receptors (ie, galectin 3 and MSR-A) for AGEs also exist in the liver[17,38] (Fig. 1).

Because the liver is the major site of AGE catabolism, whatever scavenger receptors may be involved in the endocytosis of AGEs, a result of impaired hepatic function is an increase in the levels of circulating AGEs, which can exert their detrimental effects on the whole organism.

RAGE AND LIVER INJURY: A LESSON FROM PRECLINICAL STUDIES

The first study on the role of RAGE in hepatic injury was carried out with a mouse model of total hepatic ischemia/reperfusion (I/R); the blockade of RAGE through the administration of sRAGE, which functioned as a ligand competitor, provided protection against hepatocellular necrosis, attenuated liver I/R injury, and enhanced the expression of the proregenerative cytokine TNF-α.[29] Recently, using the same model, researchers showed that early growth response 1, an inducible transcription factor activated by stress stimuli, was up-regulated in liver remnants after hepatic I/R injury, and it was suppressed by the administration of sRAGE and in RAGE-knockout mice.[45] Moreover, the RAGE ligand HMGB1, which was probably released either from necrotic cells or after induced hypoxia, was up-regulated after I/R in the liver remnants.[45,46]

The activation of RAGE may contribute to proinflammatory and tissue-destructive processes in hepatic I/R, and the blockade of RAGE may limit harmful inflammatory mechanisms and thereby facilitate repair in the injured liver; thus, it is a potential target in clinical transplantation.

Using uncoupling protein-2–knockout mice and a galactosamine/lipopolysaccharide-induced liver injury model, Kuhla et al.[47] recently showed that oxidative stress associated with mitochondrial dysfunction led to increased hepatic levels of AGEs and RAGE and pronounced tissue injury, which could be reduced by a functional RAGE blockade.

In a mouse model of liver resection, RAGE was up-regulated in liver remnants after massive hepatectomy versus partial hepatectomy, especially in monocyte-derived dendritic cells. Blocking RAGE with pharmacological antagonists or using transgenic mice with a signaling-deficient RAGE mutation expressed in cells of a monocyte lineage significantly increased survival after massive liver resection and, in liver remnants, increased the proliferation of hepatocytes and reduced their apoptosis. Liver remnants retrieved from RAGE-blocked mice displayed enhanced expression of TNF-α and interleukin-6 (both cytokines promote inflammation and regeneration) and the anti-inflammatory interleukin-10; this suggests that RAGE mediates stress responses in liver resection and initiates events that critically curtail the limits of regeneration.[30] Therefore, the blockade of RAGE may be a novel strategy for promoting regeneration in massively injured livers. The active involvement of RAGE in the liver was also shown in an acetaminophen-induced hepatotoxicity mouse model: treatment with sRAGE increased survival, attenuated the extent of the liver injury, decreased necrosis, and enhanced the expression of TNF-α and interleukin-6.[31] Although physiologically high levels of RAGE expression in the lungs appear to have a protective role in preventing pulmonary fibrosis, RAGE seems be involved in the mechanisms leading to renal and liver fibrosis.[18,48,49] A number of studies have shown that RAGE expression is up-regulated during the transdifferentiation and subsequent migration of HSCs to myofibroblasts.[12,15,50] It has also been shown that the release of HMGB1[51] (but not AGEs or CML[18]) can directly activate HSCs and stimulate fibrogenesis through (1) cell proliferation, (2) the expression of alpha-smooth muscle actin, transforming growth factor β1, and the collagen type Iα2 gene, and (3) the suppression of MMP2 activity (Fig. 2). In addition, in rats in which liver fibrosis was induced by bile duct ligation or a thioacetamide treatment, both the RAGE transcript and the alpha-smooth muscle actin transcript were up-regulated.[18]

In another rat model in which different stages of hepatic fibrosis were induced with carbon tetrachloride, RAGE gene silencing suppressed nuclear factor kappa B transcriptional activity, HSC activation, and the accumulation of extracellular matrix proteins in the fibrotic liver and thus improved the ultrastructure of liver cells.[49] Altogether, these observations suggest that RAGE may be involved in the initial processes of liver fibrosis and that RAGE blockade or RAGE gene silencing may be a therapeutic modality for preventing fibrosis in liver grafts.

RAGE-LIGAND AXIS AND LIVER DISEASES: CLINICAL ASSOCIATION STUDIES

The liver, a multifunctional organ specializing in detoxification and metabolism, is susceptible to many diseases, including nonalcoholic fatty liver disease (NAFLD), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). NAFLD is difficult to be distinguished

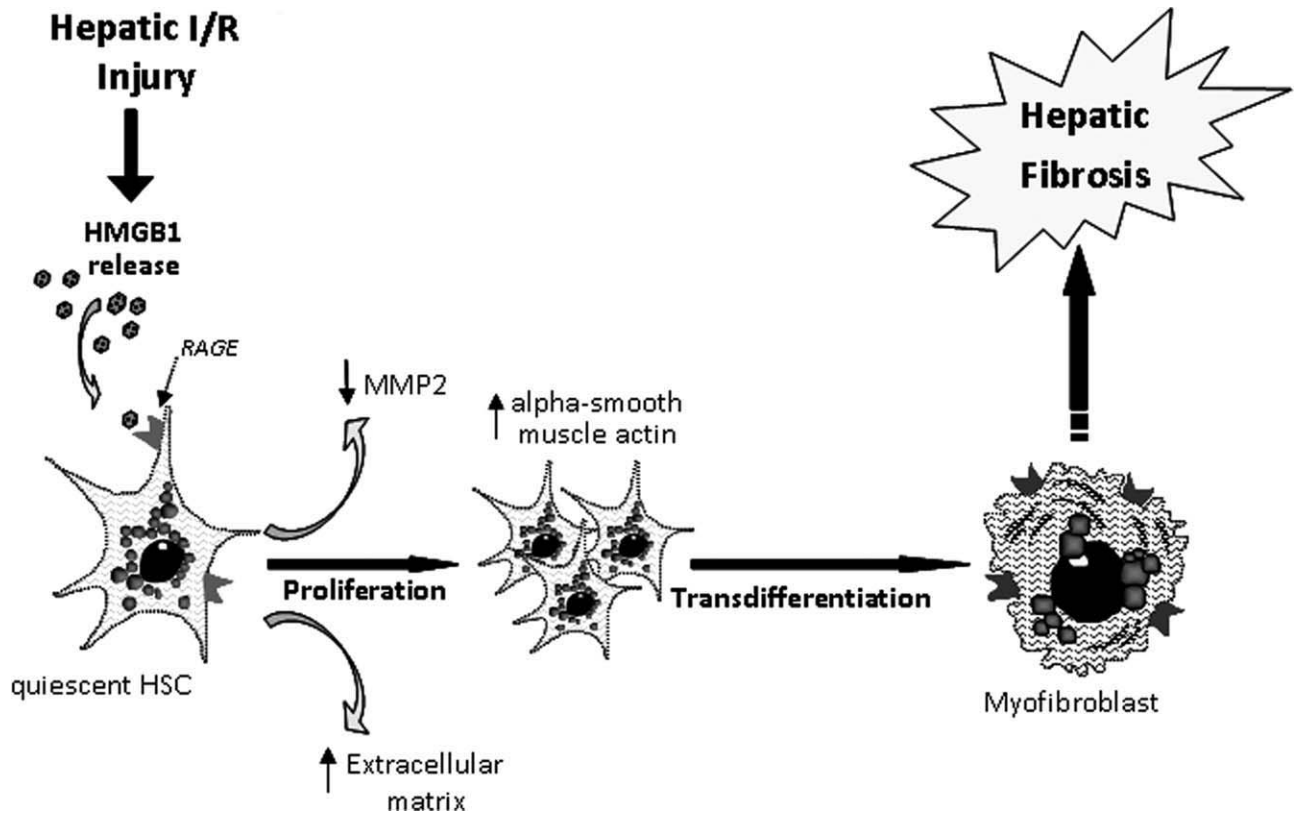

Figure 2. Role of RAGE in hepatic fibrosis. HMGB1, a protein present in the nucleus, can be released by necrotic cells or in response to hepatic hypoxia. Therefore, the HMGB1-RAGE interaction can directly activate HSCs and drive them toward fibrogenesis through the stimulation of cell proliferation, the expression of alpha-smooth muscle actin, and the suppression of MMP2 activity.

histologically from alcoholic liver disease, and its etiology remains partly unknown; however, the fundamental pathophysiological mechanism appears to involve insulin resistance and oxidative stress related to metabolic syndrome.[52] Several clinical studies have investigated the involvement of ligands (AGEs, CML, and HMGB1) and RAGE (its tissue-bound and soluble form) in different liver diseases, such as nonalcoholic steatohepatitis (NASH), liver cirrhosis, and HCC. Butscheid et al.[33] did not find any differences in the CML levels of patients with hepatitis C virus (with or without steatosis), NAFLD, or NASH. Conversely, in patients with liver cirrhosis, high levels of circulating CML were related positively to the severity of the disease and negatively to residual liver function.[28] Furthermore, serum CML levels were significantly higher in patients with chronic liver disease versus healthy controls and were associated with less liver function capacity.[53] Although these results are controversial, they suggest that a moderate impairment of hepatic function does not affect circulating CML levels, which increase in patients with severe cirrhosis as a result of reduced AGE catabolism; CML does not cause the disease. A recent study found that serum levels of HMGB1 were significantly higher in patients with chronic hepatitis B virus (HBV) versus controls and higher in chronic HBV patients with moderate fibrosis versus those with severe fibrosis; this suggests that fibrotic progression in chronic HBV patients may be prevented by the inhibition of HMGB1.[54]

The levels of circulating sRAGE—the cell membrane RAGE competitor for ligand binding—were found to be significantly lower in patients with NASH but not in patients with simple steatosis in comparison with controls.[35] Recently, esRAGE and sRAGE levels were found to be significantly lower in obese prepubertal children with liver steatosis versus control children and were independently related to liver steatosis; this suggests that the ligand-RAGE pathway plays an independent role in the development of liver injury even in this age group.[55] Cheng et al.,[11] using a tissue microarray technique, studied the expression profile of esRAGE in human organs and highlighted the distribution of esRAGE as dotlike granules in the supranuclear regions facing the luminal surfaces of the bile ducts. The fact that esRAGE expression decreases in the hepatocytes of patients with obstructive jaundice suggests that esRAGE may contribute to the secretion of bile.[11]

A number of studies have compared different expression patterns of RAGE, sRAGE, and ligands in

liver specimens of subjects with various degrees of liver impairment. Patients with NASH had detectable tissue AGEs in hepatocytes, but subjects with simple steatosis did not.[32] Biopsy specimens from subjects with different diagnoses (healthy controls and patients with steatohepatitis, virus-related hepatitis, cholestasis, or cirrhosis) were immunostained, and CML and RAGE were detected in the hepatocytes of all patients independently of the diagnosis.[17]

Liver tissues from normal subjects and subjects with hepatitis or HCC showed the coexpression of RAGE and HMGB1 transcripts in all subjects. However, although the HMGB1 transcripts were comparable, the RAGE levels were different: they were lower in the normal subjects versus the subjects with hepatitis and were highest in the subjects with HCC.[34] These data suggest that RAGE expression is involved in HCC because this receptor probably up-regulates the transcription of its own gene through a positive feedback loop with its ligands, which in turn are produced in large quantities in patients with HCC (ie, HMGB1 may be released from necrotic cells, and AGEs may be generated because of impaired hepatic glycemic control).

INVOLVEMENT OF THE RAGE-LIGAND AXIS IN LIVER TRANSPLANTATION (LT)

LT is the treatment option for end-stage liver diseases.[56] Over the last decade, data about the involvement of the RAGE-ligand axis in inflammation and regeneration after solid organ transplantation have emerged from clinical studies of lung transplantation,[57-59] kidney transplantation,[57-59] heart transplantation,[60] and LT.[28,36,61] Interestingly, elevated plasma CML levels in patients with liver cirrhosis decreased by 50% 3 months after LT; this finding confirms that the liver acts as a clearing organ for AGEs through AGE scavenger receptors.[28] More importantly, during LT, circulating levels of the proinflammatory RAGE ligand HMGB1 were undetectable before graft reperfusion and increased after reperfusion, and their level was correlated to graft steatosis.[36] These data suggest that HMGB1 originates from the graft and may be a marker of hepatocellular injury.

New-onset diabetes is frequent after LT and is associated with impaired long-term graft function and reduced patient survival.[62] Patients affected by diabetes or metabolic syndrome show increases in the formation and accumulation of AGEs and other RAGE ligands as well as low levels of sRAGE; this supports their involvement in the pathogenesis of vascular diseases.[19] In studies of diabetes-associated cardiovascular and renal diseases, the up-regulation of RAGE has been linked to enhanced levels of AGEs[63] and has been associated with epithelial-myofibroblast transdifferentiation[64] and the induction of fibrogenesis.[65] According to these observations, it is possible that the RAGE-ligand axis contributes to cardiac complications in patients undergoing LT, and its dysfunction might affect short- and long-term patient survival.

CONCLUSION

The RAGE-ligand axis is involved in several inflammation-based chronic diseases and could be the missing link between environment-induced inflammation and liver disease. We have reviewed the experimental and clinical evidence supporting the hypothesis that ligand-RAGE interactions can alter liver function through several mechanisms (ie, the decreased release of proregenerative cytokines, the increased production of extracellular matrix proteins, and the fibrotic transdifferentiation of HSCs and their subsequent migration). There is also evidence supporting the idea that the RAGE-ligand axis is involved in the regeneration of the graft and its survival after LT. Therefore, this axis is a potential molecular target for the control of liver injury in the setting of transplantation.

The balance of the levels of RAGE ligands, cell surface RAGE, and sRAGE/esRAGE may represent a complex, dynamic system. In liver pathology, the expression of RAGE and its ligands (AGEs, CML, and HMGB1) increases, whereas the expression of sRAGE decreases. A negative feedback has been shown for sRAGE when RAGE interacts with its ligands; therefore, the relationship between the up-regulation of membrane-bound RAGE/RAGE ligands and protective sRAGE levels has pathophysiological and therapeutic implications. The precise mechanisms responsible for the fine balance between cell surface RAGE and its secreted/cleaved circulating form are currently unknown, and the elucidation of the molecular mechanisms underlying their regulation is an important research objective.

ACKNOWLEDGMENT

The authors thanks Alison Frank for her assistance with English.

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