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REVIEW

Role of matrix metalloproteinases in cholestasis and hepatic ischemia/reperfusion injury: A review

Giuseppina Palladini, Andrea Ferrigno, Plinio Richelmi, Stefano Perlini, Mariapia Vairetti

Giuseppina Palladini, Andrea Ferrigno, Plinio Richelmi, Stefano Perlini, Mariapia Vairetti, Department of Internal Medicine and Therapeutics, University of Pavia, 27100 Pavia, Italy

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Correspondence to: Mariapia Vairetti, PhD, Department of Internal Medicine and Therapeutics, University of Pavia, Via Ferrata 9A, 27100 Pavia, Italy. mariapia.vairetti@unipv.it
Telephone: +39-382-986398
Fax: +39-382-986347

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Abstract

Matrix metalloproteinases (MMPs) are a family of proteases using zinc-dependent catalysis to break down extracellular matrix (ECM) components, allowing cell movement and tissue reorganization. Like many other proteases, MMPs are produced as zymogens, an inactive form, which are activated after their release from cells. Hepatic ischemia/reperfusion (I/R) is associated with MMP activation and release, with profound effects on tissue integrity: their inappropriate, prolonged or excessive expression has harmful consequences for the liver. Kupffer cells and hepatic stellate cells can secrete MMPs though sinusoidal endothelial cells are a further source of MMPs. After liver transplantation, biliary complications are mainly attributable to cholangiocytes, which, compared with hepatocytes, are particularly susceptible to injury and ultimately a major cause of increased graft dysfunction and patient morbidity. This paper focuses on liver I/R injury and cholestasis and reviews factors and mechanisms involved in MMP activation together with synthetic compounds used in their regulation. In this respect, recent data have demonstrated that the role of MMPs during I/R may go beyond the mere destruction of the ECM and may be much more complex than previously thought. We thus discuss the role of MMPs as an important factor in cholestasis associated with I/R injury.

Key words: Matrix metalloproteinases; Liver; Ischemia/reperfusion; Cholestasis

Core tip: Induction of matrix metalloproteinases (MMPs) modulates the progression of liver damage such as ischemia/reperfusion (I/R) injury and acute allograft rejection. The high incidence of biliary complications, after liver transplantation, is due to a cascade of events leading to biliary lesions to which cholangiocytes are particularly susceptible. This paper, while focusing on liver I/R and cholestasis, reviews factors and

mechanisms implicated in MMP activation/regulation together with the role of MMPs in biliary complications following I/R injury. Recent data support the view that MMPs play a dual role, both good and bad, in liver I/R depending on the length of time after damage.

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MATRIX METALLOPROTEINASES AND LIVER

Liver fibrosis arises from chronic damage to the liver associated with the over-accumulation of extracellular matrix (ECM) proteins, a characteristic of most types of chronic hepatic diseases[1] including: cholestatic liver diseases; primary biliary cirrhosis and secondary biliary cirrhosis; hepatotoxic diseases such as hepatitis B virus (HBV), hepatitis C virus (HCV), alcoholic liver disease (ALD), and non-alcoholic steatohepatitis (NASH)[2].

Advanced liver fibrosis disrupts the liver's normal architecture; hepatocytes are replaced with abundant ECM causing hepatocellular dysfunction and portal hypertension. Hepatic stellate cells (HSCs) are a major fibrogenic cell type in the liver[3]. Following liver injury, HSCs undergo an activation process and change their phenotype from quiescent retinoid storing HSCs to collagen-producing and contractile myofibroblast-like cells[4]. Activated HSCs migrate and accumulate at the sites of tissue repair, secreting large amounts of ECM and regulating ECM degradation.

While the classic liver injury paradigm asserts that HSCs produce, remodel and turn over abnormal ECMs of fibrosis via MMPs, a recent paper by Calabro *et al*[5] has shown that MMPs are also secreted by other intrahepatic cell populations including hepatocytes.

Major changes in both quantity and composition of ECMs[6] and excessive ECM remodeling arises from a balance between increased synthesis and decreased degradation[7]. One class of zinc and calcium-dependent endopeptidases - matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) - plays a major role in the ECM remodeling[8]. Analysis of human and experimental animal fibrotic liver demonstrates an increase in a number of MMPs with a wide activity spectrum. Like many other proteases, MMPs are produced by activation of zymogens, which are released from cells[9-11]. Several different kinds of MMP have been identified (Table 1). Most of them can act on different collagen types, fibronectin, laminin, elastin, proteoglycans, and surface molecules such as growth factors or selectins.

MMP activity is regulated at three levels: gene transcription; posttranslational activation of zymogens, and interactions of secreted MMPs with specific inhibitors TIMP[12]. However, specific MMP inhibitors do not simply block protease activity but, on the contrary, the role of TIMPs is to modulate MMP functioning. Different protease activation occurs as a response to liver injury[13]. Usually, while injured cells release proteases, healthy cells release TIMPs; put another way, inhibitors are secreted by the cells surrounding these producing proteases[14-17]. Thus, high level of TIMPs occur simultaneously to an increase in proteases; in other words, both proteases and inhibitors could be produced by the same cell type at the same time[13]. TIMP concentrations and MMP/TIMP ratios are critical in this respect: a high MMP/TIMP ratio activate MMPs, while a low MMP/TIMP ratio lead to the opposite effect[18].

The uncontrolled ECM remodeling plays a central role in pathological changes leading to fibrosis[1,7]. A change in quality and quantity of matrix proteins occurs during fibrogenesis, resulting in excessive accumulation of fibrous tissue and an increase in ECM density[19] (Figure 1).

Several animal models of liver fibrosis have been developed, each of these with its strengths and weaknesses[20]. Bile duct ligation (BDL) has been used as an experimental model for chronic liver injury because of its closeness to hepatocyte damage, hepatic stem cell activation and the liver fibrosis found in human cholestatic liver disease[21].

The present study reviews and discusses the published articles searched on PubMed, MEDLINE, Google Scholar, and Google databases using specific keywords to identify articles related to MMPs in cholestasis and I/R injury. These keywords were "liver" and "MMPs," "cholestasis" and "ischemia/reperfusion". The search included letters to the editor, case reports, review articles, original articles, and meeting presentations published in the English-language literature from January 2000 to February 2015.

MMPs AND LIVER I/R

During liver resection, transplantation and trauma a prolonged oxygen deficiency is observed; the following oxygen restoration always induces reperfusion injury. In particular, the sequence of events that occurs during I/R injury is represented by an early increase in oxidative stress, liver sinusoidal endothelial cell damage, Kupffer cell activation and further release of reactive oxygen species, all of which in turn leads to marked tissue damage and liver remodeling[22]. MMPs are enzymes primarily involved in connective tissue remodeling; their inappropriate, prolonged or excessive expression has harmful consequences[23]. I/R is associated with gene expression, activation and release of MMPs, which have profound effects

Table 1 Classification and characteristics of the main matrix metalloproteinases

MMP (class and number)	Name	Extracellular Matrix substrate
Collagenases		
MMP-1	Collagenase 1	Collagen Ⅰ, Ⅱ, Ⅲ, Ⅶ, Ⅷ and Ⅹ, gelatin, proteoglycans, tenascin, entactin
MMP-8	Collagenase 2	Collagen Ⅰ, Ⅱ, Ⅲ, Ⅴ, Ⅷ and Ⅹ, gelatin, aggrecan
MMP-13	Collagenase 3	Collagen Ⅰ, Ⅱ, Ⅲ, Ⅳ, Ⅸ and Ⅹ, fibronectin, gelatin, tenascin, aggrecan, osteonectin
Gelatinases		
MMP-2	Gelatinase A	Collagen Ⅰ, Ⅳ, Ⅴ, Ⅶ, Ⅸ and Ⅹ, gelatin, proteoglycans, elastin, fibronectin, laminin, aggrecan, versican, osteonectin
MMP-9	Gelatinase B	Collagen Ⅳ, Ⅴ, Ⅶ, Ⅹ and ⅩⅣ, gelatin, proteoglycans, elastin, aggrecan, versican, osteonectin
Stromelysins		
MMP-3	Stromelysins 1	Collagen Ⅲ, Ⅳ, Ⅴ, and Ⅸ, gelatin, proteoglycans, tenascin, fibronectin, laminin, aggrecan, versican, osteonectin
MMP-10	Stromelysins 2	Collagen Ⅲ, Ⅳ and Ⅴ, gelatin, proteoglycans, aggrecan, elastin, casein
MMP-11	Stromelysins 3	Collagen Ⅳ, fibronectin, laminin, gelatin, transferrin
Membrane type		
MMP-14	MT1-MMP	Collagen Ⅰ, Ⅱ and Ⅲ, fibronectin, vitronectin, tenascin, laminin, proteoglycans, aggrecan, elastin, casein, entactin
MMP-15	MT2-MMP	Fibronectin, tenascin, laminin
MMP-16	MT3-MMP	Collagen Ⅲ, fibronectin, casein, gelatin
MMP-17	MT4-MMP	ND
MMP-24	MT5-MMP	Activator of proMMP-2
MMP-25	MT6-MMP	Collagen Ⅳ, fibronectin, gelatin, fibrinogen
Others		
MMP-7		Collagen Ⅳ and Ⅹ, gelatin, proteoglycans, tenascin, fibronectin, laminin, aggrecan, osteonectin, entactin, casein, tranferrin, integrin b4
MMP-12		Collagen Ⅳ, gelatin, proteoglycans, fibronectin, laminin, entactin, casein, vibronectin, elastin
MMP-19	ND	Aggrecan, cartilage oligomeric matrix protein (COMP)
MMP-20	Enamelysin	Amelogenin
MMP-23A	MMP-21	ND
MMP-23B	MMP-22	ND
MMP-26	Matrilysin 2	Collagen Ⅳ, fibronectin, casein, fibrinogen
MMP-27	ND	ND
MMP-28	Epilysin	Casein

ND: Not Determined; MMP: Matrix metalloproteinase.

on tissue integrity[22,24] (Figure 2). A main role seems to be played by MMP-2 (gelatinase A; EC 3.4.24.24) and MMP-9 (gelatinase B; EC 3.4.24.35). These two gelatinases are the two main components of the space of Disse[25] and they are critically involved in the degradation of collagen Ⅳ and fibronectin[26]. Hence, increased activity of these MMPs may cause liver injury, with alterations of the sinusoidal cells and remodeling of the stromal structure. Already in 1997, Upadhya *et al*[27] demonstrated that MMP content, following release of MMP-2 and MMP-9 during cold preservation using rat and human liver perfusates, was dependent on the length of cold storage. Other data have since confirmed and extended the role of MMPs in hepatocyte cell death after prolonged cold storage and subsequent reperfusion[28]: the protective effects obtained using MMP inhibitors led the authors to suggest their addition to the liver preservation solution[28] (Table 2).

I/R injury is also typical of other pathological conditions in which the ischemic phase takes place under normothermic conditions. In particular, increased liver MMP-9 expression has been reported after normothermic I/R injury[29]. Moreover, serum MMP-9 has been found to be associated with the progression of liver damage in I/R injury[30], acute allograft rejection[31] and chronic viral hepatitis[32]. Some reports have suggested that specific MMP inhibitors decrease liver injury after normothermic ischemia associated with a concomitant reduction in inflammatory cytokine release[24,33] (Table 2). Other evidence has suggested that targeting MMP-9, using an anti-MMP neutralizing monoclonal antibody, leads to protection against damage after warm liver I/R; this approach appears to be more effective than using MMP inhibitors[23] (Table 2). Furthermore, experimental data suggest that MMP inhibition might be a promising approach in the context of pharmacological strategies designed to limit post-ischemic hepatic damage both in whole liver transplantation and in acute "small-for-size" liver graft injury[34].

That MMPs are secreted by Kupffer cells and hepatic stellate cells (HSCs) is a well-established fact[35]. MMP-9 are predominantly expressed in Kupffer cells, MMP-2 in HSC while MMP-3 and MMP-10 in hepatic stellate cells as well. Membrane type-1 MMP is found in significant amount in all liver cells.

However, another source of MMPs in the rat liver are sinusoidal the endothelial cells (SECs)[36]. In particular, the ability of HSCs to produce significant amounts of matrix degrading enzymes and their inhibitors has been demonstrated by Knittel *et al*[37]. In addition,

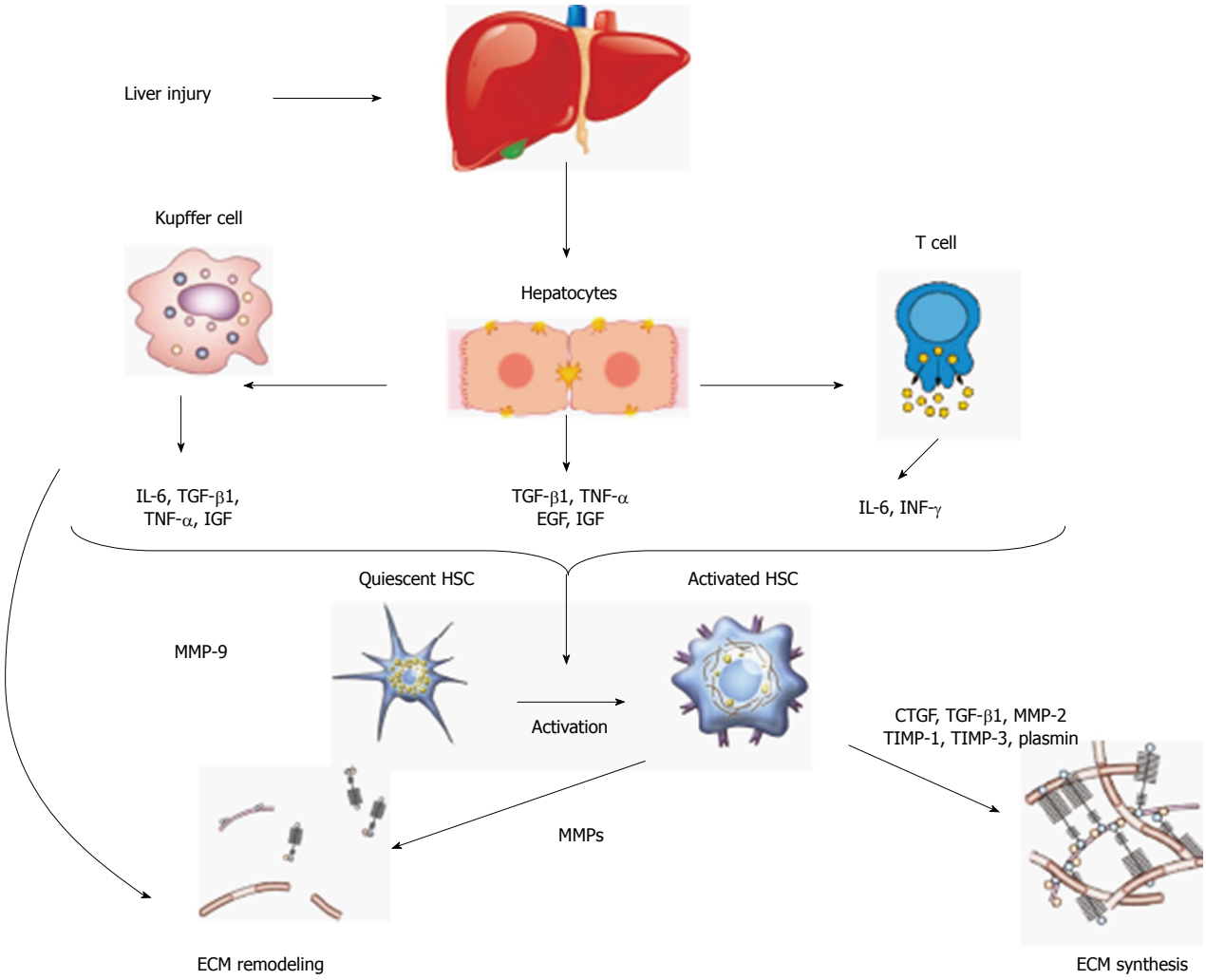

Figure 1 Mechanisms of hepatic fibrogenesis. IL-6: Interleukin-6; INF-γ: Interferon-γ; TGF-β1: Transforming growth factor-β1; EGF: Epidermal growth factor; IGF: Insulin-like growth factor; TNF-α: Tumor necrosis factor-α; HSC: Hepatic stellate cell; CTGF: Connective tissue growth factor; TIMP-1: Tissue inhibitor of metalloproteinase Type1; TIMP-3: Tissue inhibitor of metalloproteinase Type3; MMPs: Matrix metalloproteinases; ECM: Extracellular matrix.

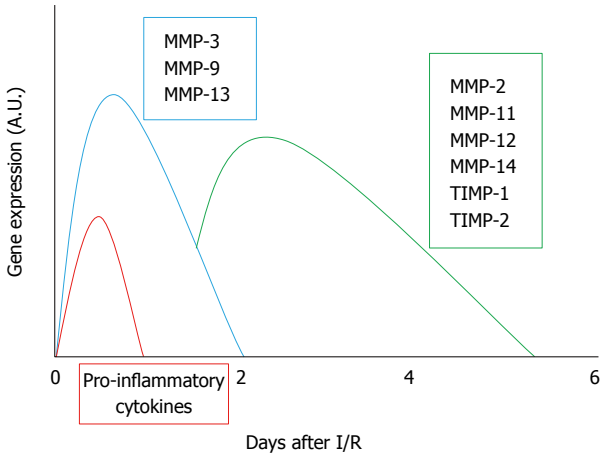

Figure 2 Time-course of matrix metalloproteinase expression following ischemia/reperfusion injury. In response to injury, pro-inflammatory cytokines, which promptly increase, induce expression of matrix metalloproteinases (MMPs) expression by hepatic cells including hepatic stellate cells (HSCs). The MMPs secreted by HSCs degrade the normal extracellular matrix (ECM) in the space of Disse.

hepatic MMPs, released from isolated rat SECs after preservation in cold Euro-Collins and UW solutions, increase as the length of time associated with cold preservation increases[27]. Hamada *et al*[23] have shown that MMP-9 expressed by leukocytes is also a key factor in cell transmigration and activation leading to liver injury. MMP-2 and MMP-9 are expressed not just in nonparenchymal liver cells but also in different subsets of leukocytes (T cells, neutrophils, monocytes, macrophages)[26].

Interestingly, recent data have demonstrated that the role of MMPs during I/R might be more complex than the mere destruction of the ECM or leucocyte recruitment to hepatic parenchyma[38]: the results have demonstrated that, although liver injury decreases in MMP-9-/- mice at 24 h after reperfusion, liver recovery after 72 h of reperfusion was significantly delayed in MMP-9-/- mice when compared with WT mice[38,39]. Thus, MMP-9 seems to play a dual role in liver I/R injury that varies with reperfusion times.

Table 2 Synthetic compounds involved in matrix metalloproteinase regulation

Compounds	Mechanism involved	MMPs involved	I/R model	Ref.
Bortezomib	Downregulation of pro-inflammatory (IL-1β, TNF-α and IFN-γ) and pro-fibrotic (VEGF, TGF-β, HGF, bFGF) factors	MMP-2 MMP-9	Steatotic orthotopic liver transplant	Tiriveedhi *et al*[45], *Transpl Immunol* 2014
KMUP-1 (NO-donor)	Protects from apoptosis-associated free radical generation and pro-inflammation	MMP-9	Hypoxic HepG2 cells	Kuo *et al*[90], *Int J Imm Pharm* 2013
CS-1 peptide	Blocks fibronectin α4β1 and decreases the release of pro-inflammatory mediators	MMP-9 MT-1-MMP/ MMP-14	Cold ischemia	Duarte *et al*[91], *Am J Transpl* 2012
CTT peptide	Reduction in TNF-α, IL-1, IL-2 and IFN-γ	MMP-9	Acute small-for-size liver graft	Ma *et al*[34], *Am J Transpl* 2010
Cyclic RGD peptide	Depresses inflammatory mediators (IFN-γ)	MMP-9	Steatotic Cold ischemia	Fondevila *et al*[92], *Am J Transpl* 2009
ONO-1714	iNOS inhibitor	MMP-9	Warm ischemia	Hamada *et al*[46], *Am J Pathol* 2009
RXP409	Inhibitory effects on MMP activity	MMPs	Cold ischemia	Defamie *et al*[28], *Hepatology* 2008
Anti-MMP-9	Decrease in expression of TNF-α, IL-2 and IFN-γ	MMP-9	Warm ischemia	Hamada *et al*[23], *Hepatology* 2008
CS-1 peptide	Blocks FN α4β1 integrin and its FN ligand	MMP-9	Steatotic orthotopic liver transplant	Moore *et al*[29], *Am J Pathol* 2007
ONO-4817	Reduction in TNF-α, IL-1β	MMP-2 and MMP-9	Warm ischemia	Shirahane *et al*[33], *Surgery* 2006
NAC	Reduction in free radicals	MMP-9	Warm ischemia	Chen *et al*[93], *Transpl Proc* 2005
BB3103	Prostaglandin PGE(1) protection	MMP-2	Cold ischemia	Yang *et al*[94], *Microvasc Res* 2002
RXPO3	Protects from necrosis/apoptosis	MMP-3-9-11-13	Warm ischemia	Cursio *et al*[24], *FASEB J* 2002

MMP: Matrix metalloproteinase; CS-1: Connecting segment-1; FN: Fibronectin; TNF-α: Tumor necrosis factor; TGF-β: Transforming growth factor β; IFN: Interferon; iNOS: Inducible nitric oxide synthase; IL: Interleukin.

PRO-INFLAMMATION MEDIATORS AND MMPs IN I/R

MMP expression and activity in liver I/R injury are topics under continuous development as are the factors involved in their activation. The mechanisms of I/R-induced liver injury include sequestration of inflammatory cells in the liver which causes oxygen radicals, nitric oxide (NO) and TNF-α to rise sharply[40]. In particular, research into the activation of Kupffer cells in I/R injury, which induces the production of proinflammatory cytokines including TNF-α and interleukin-1β (IL-1β), has led to an elucidation of the regulatory activity of cytokines on MMP expression and further suggested distinct roles for TNF-α and TGF-β1[41,42]; the early matrix degradation following liver damage may be enhanced by TNF-α, whereas the reduced matrix degradation observed during chronic tissue injury may be due to the TIMP-mediated action of TGF-β1 (Table 3). We recently demonstrated that the release of TNF-α, which occurs during the early stage of reperfusion after partial hepatic I/R injury, is related to an increase of MMP activity both in the ischemic region and in the non-ischemic lobe[43]. Furthermore, the increase in serum TNF-α after hepatic I/R is also correlated with MMP activation in the lung, a distant organ[44].

Other evidence has also shown that MMP expression by HSCs is regulated in a cytokine-specific pattern. Since TNF-α causes a marked stimulation of MMPs, it may well be that TNF-α and HSC are involved in initial matrix breakdown after liver injury. This initial matrix breakdown may be essential for early tissue repair reactions triggered by tissue inflammation when acute hepatic damage occurs[42]. Moreover, other data suggest that inflammatory cytokines such as TNF-α have a role in ECM degradation after liver I/R injury and that hepatic TNF-α expression runs parallel to MMP induction[26].

Recently, using an orthotropic liver transplant model in Zucker-obese rats, the administration of the proteosomal inhibitor, bortezomib, was shown to inhibit MMP activation and reduce serum proinflammatory cytokines including TNF-α and IL-1β[45] (Table 2).

Significantly, some experiments have also been performed to test the role of inducible nitric oxide synthase (iNOS) expression on the modulation of MMP-9 activity in hepatic I/R injury. Using both mice lacking the gene encoding for iNOS and mice treated with a selective iNOS inhibitor, the authors concluded that MMP-9 activity was induced by iNOS-derived NO and that this also led to detachment of hepatocytes from the ECM and cell death, in addition to increasing leukocyte migration through ECM barriers[46] (Table 3).

Fibronectin (FN) is involved in leukocyte adhesion, migration and activation. Amersi *et al*[47] reported

Table 3 Endogenous factors associated with matrix metalloproteinase modulation

Factors	MMPs Involved	I/R Model	Ref.
FN-α-β1	MMP-9 MT1-MMP/MMP-14	Cold ischemia	Duarte *et al*[91], *Am J Transpl* 2012 Coito[48], *Curr Opin Organ Transplant* 2011 Moore *et al*[29], *Am J Pathol* 2007 Fondevilla *et al*[95], *Transplant Proc* 2005 Amersi *et al*[47], *Am J Pathol* 2003
Tenascin-C	MMP-9	Warm ischemia	Kuriyama *et al*[96], *Hepatology* 2011
iNOS	MMP-9	Warm ischemia	Hamada *et al*[46], *Am J Pathol* 2009
TNF-α	MMP-2 and MMP-9	Warm ischemia	Feng *et al*[39], *J Surg Res* 2013 Palladini *et al*[43], *Toxicol and Pathol* 2012 Khandoga *et al*[26], *J Leukoc Biol* 2006 Chen *et al*[93], *Transplant Proc* 2005
IL-1β	MMP-2 and MMP-9	Warm ischemia	Shirahane *et al*[33], *Surgery* 2006
IL-6	MMP-9	Warm ischemia	Hamada *et al*[46], *Am J Pathol* 2009
IFNα-2a	MMP-2 and MMP-9	Cholestasis	Bueno *et al*[54], *J Hepatol* 2000
CD62	MMP-2 and MMP-9	Warm ischemia	Khandoga *et al*[26], *J Leukoc Biol* 2006
Plasmin	MMP-9	Cholestasis	Martínez-Rizo *et al*[97], *Liver Int* 2010
TGF-β	MMP-9	Warm ischemia	Feng *et al*[39], *J Surg Res* 2013
	MMP-13	Cholestasis	Aldaba-Muruato *et al*[98], *Can J Physiol Pharmacol* 2012
IL-10	MMP-2 and MMP-9	Warm ischemia	Feng *et al*[99], *Int Immunopharmacol* 2012

MMP: Matrix metalloproteinase; TNF-α: Tumor necrosis factor; iNOS: Inducible nitric oxide synthase; IL: Interleukin; IFNα-2a: Interferon α- 2a; TGF-β: Transforming growth factor β; FN: Fibronectin.

that blocking the interaction between FN and the integrin α4β1, the integrin receptors expressed on leukocytes, led to improved liver function in steatotic liver transplantation. Based on this evidence, they demonstrated that this is linked to a reduction in MMP-9 expression/activation on leukocytes of steatotic liver grafts[29]. MMP-9 expression during hepatic I/R was shown to be associated with massive leucocyte infiltration, extensive FN deposition and proinflammatory release, thus emerging as an important mediator of leukocyte traffic in liver I/R injury[48] (Table 3).

All this shows that numerous and rather complex mechanisms affect MMP modulation: for a list of endogenous compounds involved in MMP regulation see Table 3.

CHOLESTASIS AND MMPs

Biliary obstruction leads to a cholestatic inflammatory and fibrogenic process. Current evidence indicates that MMPs are of central importance for cholestatis-induced fibrosis but only limited evidence is currently available on their precise cellular origin and regulation within the damaged liver. Some authors have shown that marked alterations in the expression of MMPs and their inhibitors take place within the first week after BDL[49,50]. Specifically, they found that the proteolytic activities of MMP-2 and MMP-9 increased 2 d after BDL, peaked at day 10, and remained high throughout the study period[49]. The increase in gelatinase activities was accompanied by an increase in TIMP mRNA transcripts while no corresponding increase in TIMP protein activity was detected. This appears to arise from the formation of TIMP/MMP complexes. These findings suggest that complex changes in the local MMP/TIMP balance may underlie the pathological mechanisms of BDL fibrosis.

More recent publications support the view that analysis of the MMP activation not just 1-2 wk after BDL but even a few days after occlusion has a crucial role to play[51]. Ferrigno *et al*[50] have reported a marked alteration in gelatinase activity after BDL showing that this increase takes place in the first few days after BDL mainly in the right lobe. They also observed an increase in MMP-2 and MMP-9 that occurs significantly in the right lobe, more than in the median lobe and left lobe.

Although liver fibrosis has long been considered irreversible, recent studies suggest potential reversibility of liver fibrosis once the pathological trigger is removed[52]. Studies in patients with chronic hepatitis successfully treated with antivirals suggest recover even in cirrhotic patients[53]. In experimental models, reversibility of liver fibrosis depends on the degree of pre-established fibrosis. In an experimental model of cholestasis-induced fibrosis, MMP activity was upregulated in bile duct ligated rats treated with IFNα-2a. Bile duct ligation, itself, promoted MMP activity in both liver tissue and NPCs (non parenchymal cells) isolated from the same tissue[54].

In an elegant study, Popov *et al*[55] have shown that macrophages upregulate MMPs and become fibrolytic effector cells on apoptotic cholangiocyte engulfment *in vitro*, suggesting that phagocytosis-associated MMP induction in macrophages contributes significantly to biliary fibrosis reversal. A relevant finding of this study is the description of the subset of MMPs differentially regulated at the peak of matrix remodeling and degradation. In their study, the study

of expression patterns during biliary fibrosis reversal *in vivo* suggested that MMPs, with the exception of MMP-2, that have a profibrogenic role[56], and MMP-13, that could be involved in removal of the fibrotic matrix.

PRO-INFLAMMATION MEDIATORS AND MMPs IN CHOLESTASIS

During cholestasis a marked increase in liver and serum bile acid levels occurs, leading to acute liver toxicity, bile duct cells proliferation, and fibrosis progressing to cirrhosis[57-59]. However, the molecular mechanisms of liver injury induced by obstructive cholestasis remain unclear. Previous research has suggested a predominant hypothesis: inflammatory cell-mediated liver necrosis, and not bile acid-induced apoptosis, may be directly involved in cholestatic liver damage[60]. However, a recent study[61] indicates that bile acid composition between humans and rodents is different and that mechanisms of cholestasis in humans are different from rodent models.

In humans, during obstructive cholestasis, bile leaking back into the parenchyma can cause direct bile acid-induced necrosis, which, through release of damage-associated molecular patterns can initiate an inflammatory response.

Neutrophil accumulation has been directly implicated in the pathogenesis of early cholestatic liver injury[62,63]. After obstruction of the bile duct, an intense increase in biliary ductal pressure is produced[64] and this is quickly followed by ECM changes[65].

The accumulation of toxic bile acids induces hepatocyte injury, in part by activating death receptors[66]. This event triggers a secondary phase in which infiltration of inflammatory cells, activation of Kupffer cells and transformation of stellate cells to activated myofibroblasts occur, along with a MMPs-induced remodeling of the ECM. This structural hepatic changes further promotes liver injury and enhances hepatocyte apoptosis[67].

An increase in myeloperoxidase activity[68] and the formation of intracellular chlorotyrosine adduct in hepatocytes[62,63] are associated with neutrophil accumulation after bile duct ligation. The neutrophil-derived hypochlorous acid can induce liver injury by intracellular oxidative stress[69], prevented by inhibition of NADPH oxidase that protects against neutrophil cytotoxicity[70,71]. Furthermore, Nox1 and Nox2, hepatic NADPH oxidases respectively located in hepatic stellate cells and Kupffer cells, participate to BDL-induced fibrosis[72,73], though their role to the early liver injury has not yet been defined. Yang *et al*[74] suggest that the neutrophil-mediated liver injury is induced by MMP-induced cleavage of osteopontin (OPN), acting as an early pro-inflammatory signal after BDL in mice. In the cleavage of OPN into its pro-inflammatory form, MMP-3 and MMP-7 have a prominent role[75]. Yang *et al*[74] also reported that BDL induces MMP-3 early in the liver and, in addition, MMP-2, -3 and -9 activities increase in bile. Thus, probably, MMP-3 and other MMPs released into bile, activate OPN as potent chemoattractant for neutrophils. It is well known that MMPs are also involved in the modulation of cytokine and chemokine activity. MMPs can both generate chemotactic gradients by activating chemokines and cytokines, and inactivate these pro-inflammatory mediators[76]. The obstruction of the bile duct, induces an increase in biliary duct pressure, injuring the biliary epithelial cells. OPN and MMPs are released into bile and MMPs activates OPN, producing the factors attracting neutrophils. The high pressure in the biliary system occurring in BDL, provokes ruptures in the Canals of Hering. This process results in infiltration of bile into the parenchyma[77] and is facilitated by the expression on hepatocytes of intercellular adhesion molecule-1 (ICAM-1), induced by bile acids (BAs) into the parenchyma.

BILIARY COMPLICATION DURING ISCHEMIA/REPERFUSION INJURY

The development of biliary complications after liver transplantation is a major clinical problem, due to its relatively high frequency, complications, morbidity and even mortality. The formation of strictures in the liver bile ducts is accompanied by tissue remodeling in which MMP-2 and MMP-9 are considered to play a key role in connective tissue remodeling processes in the liver. The mechanisms by which ischemia/reperfusion (I/R) lead to liver injury are complex and multifactorial; these events also involve profound changes in MMP expression[24]. Based on the above considerations, further evaluation of a possible link between MMP-2 and 9 gene polymorphisms and non-anastomotic biliary strictures after liver transplantation might help explain MMP involvement[78]. Ten Hove *et al*[78] have shown that MMP-2 polymorphism is significantly associated with biliary strictures: genetically determined reduced MMP-2 tissue remodeling contributes to the development of biliary complications.

Reperfusion of liver grafts after cold preservation is associated with diminished bile production both in clinical liver transplantation and experimental models. Indeed, biliary complications represent a major surgical problem with an incidence of up to 30% after liver transplantation[79-81]. Cholangiocytes play a substantial role in the damage caused by preservation in hypothermic conditions: compared to hepatocytes and Kupffer cells, they are particularly susceptible to injury, and, in particular, to injury induced by cold hypoxia[82]. Hence, biliary strictures that occur after transplantation often require endoscopic, radiological and surgical procedures[83-85] designed to avoid graft dysfunction and/or re-transplantation.

Post-transplant biliary complications are usually classified into two types: (1) anastomotic strictures and (2) non-anastomotic strictures. Anastomotic

strictures of the biliary tree are located where bile duct anastomosis occurred and are generally well treated by stent placement[86]. Their incidence is between 5% and 10%[82]. Non-anastomotic strictures may be either extrahepatic (Type Ⅰ) or intrahepatic (Type Ⅱ). Arising from hepatic artery thrombosis, stenosis or ischemic cholangiopathy, they account for 10%-25% of stricture complications after liver transplantation[82]. In addition, ischemic cholangiopathy seems to be associated with prolonged periods of cold ischemic storage, delayed arterization of the graft or transplant from a donor after cardiac death (DCD) indicating that I/R injuries play a key pathogenetic role[82].

Clinical evaluation of biliary complications after liver transplantation has shown that a storage time of over 10-12 h leads to biliary strictures and other complications in more than 25% of liver transplant recipients[87]: a retrospective review of liver transplant patients demonstrated that liver grafts procured from DCDs showed a higher re-transplantation rate due to ischemic tract biliary lesions combined with severe intrahepatic cholestasis[88]. A meta-analysis and meta-regression of outcomes including biliary complications in donation after cardiac death liver transplantation published in 2014 confirmed and extended the finding that an increase in biliary complications, graft loss and mortality occurs with DCD liver transplantation[89]. Nevertheless the use of these organs needs to be balanced against the risk of recipients dying while on the waiting list[89].

CONCLUSION

Data from humans and experimental models supports the view that MMPs play a crucial role as modulators of tissue development, remodeling and repair in response to infection, disease of injury. Currently, it has been evaluating whether MMPs merely have a structural role in matrix remodeling, or they also have a role in regulating access to signaling molecules. One of the most important findings in MMP biology has been the realization that extracellular proteolysis is not only a mechanism that destroys structure or information. Instead, various studies have demonstrated that MMPs can release growth factors from the ECM and cell surfaces, activating latent proteins and generating new bioactive molecules through proteolysis.

Reperfusion damage is dependent on the degree of injury in previous phases and involves complex mechanisms and mediators that are not as yet completely understood.

Changes in extracellular MMP activities already occur in the early phases of reperfusion and are coupled with morphological changes to hepatic tissue, the biliary tree included. Significantly, as recent data have clarified, the multifactorial mechanisms of MMP modulation are associated to a possible dual role for MMPs during I/R injury; hence, only a detailed time-course evaluation of events occurring during reperfusion will provide specific indications for appropriate pharmacological treatments.

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