Review


# Matrix metalloproteinase functions in hepatic injury and fibrosis

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## Abstract

Liver fibrosis is the most common final outcome for chronic liver diseases. The complex pathogenesis includes hepatic parenchymal damage as a result of a persistent noxe, activation and recruitment of immune cells, activation of hepatic stellate cells, and the synthesis of fibrotic extracellular matrix (ECM) components leading to scar formation. Clinical studies and animal models demonstrated that fibrosis can be reversible. In this regard matrix metalloproteinases (MMPs) have been focused as therapeutic targets due to their ability to modulate tissue turnover during fibrogenesis as well as regeneration and, of special interest, due to their influence on cellular behavior like proliferation, gene expression, and apoptosis that, in turn, impact fibrosis and regeneration. The current review aims to summarize and update the knowledge about expression pattern and the central roles of MMPs in hepatic fibrosis.



## Introduction

ECM is a complex meshwork composed of fibrous proteins and proteoglycans that provides physical scaffold and structural support for liver parenchyma and non-parenchyma cells to form the functional architecture of the organ. In addition, ECM modulates crucial cellular functions like cell attachment, migration, differentiation, proliferation, repair, and survival in order to direct the morphological organization and physiological function of the liver [1]. The ECM is mainly composed of collagens, elastins, fibronectins, and laminins as well as proteoglycans that fill the majority of the extracellular interstitial space within the tissue in the form of a hydrated gel [2]. Collagens are the most abundant structural proteins within the ECM and constitute up to 30% of total protein mass of animals [3]. The composition and organization of different types of collagens in the ECM functions to limit the elasticity of the tissue and contributes to the unique physical properties of organs [3]. In healthy liver collagen types I, III, and V are predominant interstitial components of the ECM whereas collagen type IV and Laminin are an essential constituent of basement membranes [4]. Notably, hepatocytes and endothelial cells lack a basement membrane, but are separated by the ECM of Disse's space containing predominantly fibronectin, type I collagen, and spotty deposits of type IV collagen, allowing metabolic exchanges between the blood flow and the hepatocytes [4]. The dysregulation of ECM homeostasis is often associated with degenerative diseases [5]. In healthy liver the maintenance of the dynamic structure and composition of the ECM is sustained by a precisely regulated, moderate turn-over directed by a family of zinc-dependent endopeptidases, the MMPs [1,6].

Collagenolytic activity mediated by MMPs has been first described in the context of amphibian tissue metamorphosis in 1962 [7]. Up to now, 25 structurally and specificity related mammalian MMPs were identified and associated with the degradation of most proteins of the ECM [8]. The potential of proteolytic processing of the extracellular microenvironment and intercellular signaling enable MMPs to modulate cell behavior in order to play a crucial role in a variety of physiological and pathological processes of the liver [9–11]. Moreover, MMPs

regulate cell behavior directly through finely tuned and tightly controlled proteolytic processing of a large variety of signaling molecules that can also have beneficial effects in hepatic disease resolution [12]. These key functions have to be tightly controlled in order to maintain normal tissue homeostasis. In 1971 it was shown for the first time that MMPs are secreted in a latent form as zymogens that require activation [13]. The next level of control was found in 1975 with the discovery of the first of at least four endogenous metalloproteinase inhibitors, the tissue inhibitors of metalloproteinases (TIMPs) [14]. Nevertheless, TIMP-1 has been found to be upregulated, but not essential in hepatic fibrogenesis in mice [15]. MMP gene as well as protein expression, activity, and secretion is orchestrated by inflammatory and fibrogenic cytokines like tumor necrosis factor (TNF)-α, Interferon α, Interleukin (IL)-1α, IL-6, IL-8, platelet derived growth factor (PDGF)-D, and transforming growth factor (TGF)-β1 [16–20] which was reviewed recently [21,22]. The hepatic regulation of MMP activity includes epigenetic regulation, transcriptional regulation, MMP-targeting miRNAs, translational modifiers, posttranslational modifications, factors that influence their secretion, their cell surface localization, specific activators, substrate specificity, and their own degradation and clearance [23–29]. The overlapping specificities and functions of MMPs could serve as redundant safeguard mechanisms against any losses of regulatory control which highlight another complex level of regulation [26]. On the other hand, also counter-regulatory roles e.g. between MMP-12 and ECM-degrading enzymes like MMP-2, MMP-9, and MMP-13 were described on protein and activity level in Th2 cytokine-driven fibrosis [30]. Furthermore, MMPs can activate each other and inflammation can initiate tissue destruction by activating MMP cascades [31]. The understanding of the interplay between these processes will result in a more rational approach toward reducing or entirely alleviating morbid effects of MMPs in liver disease while maintaining their necessary and beneficial functions [12,26]. In healthy liver MMPs and TIMPs seem to have important roles in the preservation of liver homeostasis, illustrated by moderate ECM turnover, potential involvement of MMP-2 and MMP-9 in the preservation of vascular homeostasis and vascular rearrangement, and MMPs-1-3 have been shown to modulate the basal activity of cytokines and chemokines proteolytically [32,33]. A broad range of MMPs, among which MMP-2 was predominantly expressed in the septum transversum and MMP-14 in the hepatoblasts is involved in the onset of liver development, which was demonstrated on mRNA-, protein-, and activity-level [34]. Transcriptional and protein expression analyses revealed that MMP-23 promotes liver development and hepatocyte proliferation through the TNF pathway [35].

## Matrix metalloproteases in acute liver injury

Hepatic functions like metabolism and storage of nutrients the clearance of toxins and pathogens, and the regulation of immune responses are frequently accompanied by insults which can cause cell death and hepatic dysfunction [36]. In order to manage these injuries the liver has a unique and extraordinary capacity for regeneration that is attributed to the replicative capabilities of mature hepatocytes and cholangiocytes as well as progenitor cells in the case of chronic liver injury [37–39]. Apoptosis and necrosis are the most widely recognized forms of hepatocyte cell death caused by toxic xenobiotic metabolites, hepatotrophic viruses, dysregulated lipid metabolism in the metabolic syndrome, toxic bile acids in hepatobiliary diseases, and other less common disease states [40]. Injured or destroyed hepatocytes or cholangiocytes can release reactive oxygen or nitrogen species (ROS and NOS), cytokines, chemokines, growth factors, hormones, and apoptotic bodies which are able to activate hepatic stellate cells (HSC) for transdifferentiation into myofibroblasts, the major matrix producing cell type in liver fibrosis [41]. Activated hepatic stellate cells proliferate, become contractile, and secrete fibrosis specific ECM components like type I and type III collagens abundantly [42]. Additionally, they secrete TIMPs, profibrogenic-, proinflammatory-, and proangiogenic cytokines like TGF-β, IL-6, and VEGF [8]. Factors released from activated HSC and injured parenchymal cells stimulate and recruit T-cells and macrophages but also liver sinusoidal endothelial cells (LSEC) that de-differentiate toward a capillarized phenotype which is associated with the loss of endothelial fenestration [43,44]. Thus, a self-perpetuating cycle between injured hepatocytes, collagen producing activated HSC, activated leukocytes, and capillarized LSEC stimulate each other, further contributing to liver fibrosis if the injurious trigger is not removed [41,43]. In activated HSCs especially the expression of TIMP-1 is upregulated leading to the inhibition of MMP activity and subsequent accumulation of fibrillary collagens in the extracellular space. Depending on the type of liver injury, the normal composition of ECM in the space of Disse, the Glisson's capsule, around portal tracts, and around the central veins is replaced by up to tenfold amounts of type I and type III collagens during fibrogenesis [45]. Thus, it is reasonable to speculate that a proteolytic degradation of the normal ECM may occur at the onset of liver fibrogenesis [46]. Many MMPs are absent or marginally expressed in healthy, adult liver, but expressed immediately after hepatic injury (e.g. MMP-3 mRNA [47]) where they probably mediate ECM breakdown and the control of cellular functions. The MMP-mediated breakdown of