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Extracellular matrix degradation in liver fibrosis: Biochemistry and regulation☆,☆☆

John P. Iredale *, Alexandra Thompson, Neil C. Henderson **

MRC Centre for Inflammation Research, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, UK

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ABSTRACT

Fibrosis is a highly conserved wound healing response and represents the final common pathway of virtually all chronic inflammatory injuries. Over the past 3 decades detailed analysis of hepatic extracellular matrix synthesis and degradation using approaches incorporating human disease, experimental animal models and cell culture have highlighted the extraordinarily dynamic nature of tissue repair and remodelling in this solid organ. Furthermore emerging studies of fibrosis in other organs demonstrate that basic common mechanisms exist, suggesting that bidirectionality of the fibrotic process may not solely be the preserve of the liver. In this review we will examine the cellular and molecular mechanisms that govern extracellular matrix degradation and fibrosis resolution, and highlight how manipulation of these processes may result in the development of effective anti-fibrotic therapies. This article is part of a Special Issue entitled: Fibrosis: Translation of basic research to human disease.

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1. Background

Chronic inflammation invariably gives rise to tissue fibrosis, which can be considered a dysregulated fibroproliferative response ultimately impacting on tissue architecture and function. Fibrosis results from the interplay of a number of different cell types including macrophages, myofibroblasts and epithelial cells and results in the accumulation of fibrillar collagens (predominantly collagens I and III) as a result of both changes in matrix synthesis and in the pattern of extracellular matrix (ECM) degradation. It has been estimated that inflammation and fibrosis contribute to 45% of deaths in the western hemisphere [1].

Hepatic fibrosis, the common final pathway of virtually every chronic inflammatory liver injury, represents a particularly well investigated model of the generic inflammation–fibrosis–progression/resolution pathological continuum [2]. Research interest in liver fibrosis continues to grow particularly because the burden of chronic liver disease is increasing; cirrhosis, the end-stage of fibrotic liver disease, is currently the fifth commonest cause of mortality in the UK [3]. Liver fibrosis can be considered a paradigm for the generic aspects of this pathological process and as such it is at the vanguard of studies of ECM and ECM turnover in experimental pathology [2]. Indeed, hepatic fibrosis in both progression and resolution has arguably been studied in greater detail than any other organ model system. This is in part because of the tractability of animal models of liver fibrosis where induction of sterile inflammatory injury is relatively straightforward, consistent and can be studied in a predictable and practical timeframe. But there has also been an increase in our detailed knowledge of both the natural history of human liver disease and the response of the fibrotic human liver to well characterised therapeutic interventions (particularly interferon in the treatment of chronic hepatitis B and C) which has established a powerful model illuminating critical aspects of matrix synthesis and degradation across relevant species [2,4–9]. For these reasons this review will focus primarily on the pathogenesis of liver fibrosis, but with reference to other organ systems where appropriate.

2. Introduction of key concepts

At a cellular level the perisinusoidal hepatic stellate cell (HSC) has been extensively studied as a key effector of fibrogenesis [10–12]. In acute and chronic injury this vitamin A storing cell sheds its retinoid and lipid droplets and transforms to an "activated" myofibroblast-like phenotype. Activation of this cell to an extracellular matrix-secreting myofibroblast phenotype is associated with fibrillar collagen production and fibrotic matrix deposition in vivo. Activated HSCs also express tissue inhibitors of metalloproteinases (TIMPs) [13–15] as well as chemotactic and vasoactive factors. The major secreted TIMP, TIMP-1 inhibits the endogenous matrix degrading activities of a wide range of matrix metalloproteinases (MMPs) favouring scar deposition. Furthermore, using a host of different model systems has allowed us to gain a deeper understanding of the complexity of liver inflammation and repair. In particular the dynamic interplay between the epithelial, inflammatory, myofibroblast and extracellular matrix components of tissue repair are becoming increasingly well defined [16]. Other key emerging

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* Corresponding author. Tel.: +44 131 242 6686; fax: +44 131 242 6682.

** Corresponding author. Tel.: +44 131 242 6653; fax: +44 131 242 6682.

E-mail addresses: John.Iredale@ed.ac.uk, jiredale@staffmail.ed.ac.uk (J.P. Iredale), Neil.Henderson@ed.ac.uk (N.C. Henderson).

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concepts include the idea that inflammatory cell phenotypes demonstrate plasticity and that specific inflammatory cell types may contribute to matrix degradation not only in the development but also in the spontaneous resolution of liver fibrosis [17], and the observation that liver myofibroblasts may arise from a number of different cell lineages [2]. Perhaps most promising and of direct relevance to this review is the growing body of in vivo and in vitro evidence that suggests that liver fibrosis is a bidirectional process [2]. These data challenge the traditional dogma that fibrosis is at best irreversible and importantly are supported by robust clinical observations in humans. Understanding fibrosis resolution has the potential to highlight the essential attributes of an antifibrotic, or more accurately a pro-resolution therapy applicable to the liver and potentially other organs.

3. Matrix components of the liver in health and disease

The extracellular matrix within the normal liver is composed of a series of classes of macromolecules which include collagens (types I, III, IV, V and VI), the non- collagenous glycoproteins which encompass laminin and fibronectin amongst others and proteoglycans [18,19]. In the normal liver sinusoid, there is a non-electron dense basement membrane matrix which comprises laminin and type IV collagen. During the development of fibrosis this matrix becomes progressively replaced by one rich in interstitial collagens particularly collagens I and III [19–21]. Initially, and by virtue of changes in cell-matrix interactions, this accumulation of fibrillar ECM is associated with capillarization of the sinusoids; a loss of the sinusoidal endothelial fenestrae and physical change in the hepatocytes which lose their microvilli [19–21]. Ultimately the accumulation of collagens increases until vascular structures are linked and the architecture of the liver is disrupted significantly. Furthermore, areas of hepatocyte regeneration form spheres which further distort the structure and angiogenesis may occur in dense areas of scarring [19,22].

Studies have demonstrated a 4- to 7-fold increase in the content of collagen and glycosaminoglycans in the cirrhotic liver compared with normal liver. There is a disproportionate increase in the fibrillar collagen, collagen type I, and there are also increases in laminin and proteoglycans [19], with cross-linking of matrix also documented [22]. End-stage cirrhosis is associated with swathes of dense extracellular matrix rich in elastin in addition to the fibrillar collagens described above. Indeed, elastin is used as a pathological benchmark for chronicity of fibrotic change. The accumulation of matrix is associated with an impairment of hepatic function and predisposition to the development of hepatocellular cancer, although the mechanisms governing neoplastic change in the fibrotic liver are still incompletely understood [23]. This profound architectural disruption of liver anatomy results in the well-known complications of liver cirrhosis, particularly the development of portal hypertension, which is a major cause of death in patients with cirrhosis.

This review is necessarily brief, and therefore we will focus on the changes that occur to the cellular and extracellular matrix components in progressive fibrosis, fibrosis resolution and irreversible end-stage cirrhosis, with particular emphasis on collagens I and III and elastin as critical determinants of disease outcome.

4. Sources of extracellular matrix within the liver

With respect to the fibrillar collagens and elastin, the major source of these matrix components is the hepatic myofibroblast. In turn, this cell type has typically been described as representing an activated phenotype of the hepatic stellate cell [24–26]. Hepatic stellate cells are mesenchymal cells which lie in the space of Disse between the specialised hepatic sinusoidal endothelium and the palisades of hepatocytes. Rich in vitamin A in health, which is stored in the form of retinol esters within cytoplasmic droplets, these cells lie in close proximity to the normal basement membrane matrix consisting of type IV collagen, laminin and heparin sulphate proteoglycans. During liver injury stellate cells proliferate, become activated to a myofibroblast-like phenotype expressing alpha smooth muscle actin, and secrete fibrillar collagens, elastin and matrix proteins [24–27]. Recent interest has focused on the specific origins of these cells. Whilst there is evidence that portal myofibroblasts, circulating fibrocytes and mesenchymal stem cells in addition to peritoneal mesoepithelial cells may all give rise to a myofibroblast population [28–33], the relative contribution of each lineage is currently moot. Indeed, the relative contributions of individual cell lineages likely depend on the site and duration of injury and current evidence still supports hepatic stellate cells as being the predominant source of liver myofibroblasts. Of note, recent interest in epithelial–mesenchymal transition (EMT) as a major process deriving myofibroblasts from hepatocytes appears to have been misplaced [34–36]. Certainly, in genetically modified animal models in which robust lineage tracing can be undertaken no clear cut evidence of EMT has been demonstrated in in vivo models of hepatic fibrogenesis, or recently in models of renal fibrosis. We have recently demonstrated in unpublished data that the PDGFRβ gene (platelet derived growth factor receptor beta) can be used to effectively drive both marker proteins and gene deletion strategies identifying a commonality between hepatic stellate cells and pericytes seen elsewhere in the body, including the kidney, lung and heart. The mechanisms underpinning stellate cell activation have been studied in enormous detail using genetically modified mice in addition to tissue culture models and these studies have recently been reviewed extensively by Friedman [37]. A detailed discussion is beyond the scope of this article, but critical activating stimuli include TGFβ1 to promote a fibrogenic collagen-secreting phenotype and PDGF stimulation which promotes a proliferative phenotype [38,39]. Additionally stellate cells appear exquisitely sensitive to the extracellular components that they are in direct contact with, demonstrating profound changes in their behaviour in response to the physical environment provided by the matrix [40].

5. Extracellular matrix degradation during liver fibrosis

Even during progressive liver fibrosis there is evidence of a potential for matrix degradation. Matrix may be degraded by a number of enzymatic families, but foremost are the matrix degrading metalloproteinases (MMPs). These are a family of zinc and calcium dependent endopeptidases which are produced by connective tissue cells and inflammatory cells and have a range of activity against the major constituents of ECM including fibrillar and non-fibrillar collagens and elastin [41]. Individual MMPs are more or less promiscuous with respect to their direct substrate specificity with certain enzymes demonstrating a wide range of substrate specificity. Expression of MMPs has been demonstrated in a spectrum of liver cells which includes hepatocytes, hepatic stellate cells, kupffer cells and neutrophils and recruited hepatic macrophages [41]. Interestingly, for both HSC and macrophages the repertoire of MMPs expressed by the cells appears to alter with specific changes in phenotype that accompany fibrogenesis in vivo.

MMPs can be grouped according to enzymatic substrate; collagenases are central to the process of remodelling fibrotic tissue because they cleave the native helix of fibrillar collagens rendering the product (a gelatin) susceptible to degradation by other MMPs. Neutrophil collagenase, MMP-8, is expressed by both neutrophils and macrophages (both populations are well represented in the inflammatory stages of liver injury) [42]. Interstitial collagenase or MMP-1 has been described, particularly in inflammatory cells in human liver [15], and its counterpart in rodents MMP-13 has been shown to be expressed by stellate cells and macrophages [14,43]. Whereas in stellate cells MMP-13 is a feature of early activation and the fully activated fibrogenic stellate cell phenotype downregulates MMP-13, expression in macrophages appears to be relatively constant regardless of the stage or stimulus for activation in models of liver injury. It is always considered axiomatic that

interstitial collagenases only possess activity against fibrillar collagen, but there are reports that gelatinase A (MMP-2) may demonstrate a similar function [44,45]. The stromelysins have a promiscuous substrate profile and activity against collagens, laminin and fibronectin [44,45]. In the context of liver fibrosis, stromelysins are expressed by inflammatory cells [46] but in HSC (just as MMP-13 is down regulated) the expression of stromelysin (MMP-3) appears to have a distinct regulation as it rises and then falls during activation [47]. Thus stromelysin expression is a transient feature of the HSC activation process. This has led to the hypothesis that stromelysin expression may be responsible for basement membrane degradation in early fibrogenesis. The gelatinases have a relatively wide range of substrate specificity. Gelatinase A (MMP-2) has activity against gelatins, collagens IV, V, VI, and VII, X and XI and some elastase activity and has been reported to have some collagenase activity. Gelatinase B (MMP-9) shares a similar substrate profile but there is no reported collagenase activity. Both may act as sheddases and regulate cytokine and soluble signal activation and deactivation. Gelatinase B (MMP-9) has been shown to be expressed by kupffer cells and inflammatory macrophages [48] and gelatinase A (MMP-2) has been documented to be expressed by activated stellate cells [49,50]. Functionally this enzyme has been linked with the pro-proliferative phenotype of activated stellate cells also [51]. Metalloelastase (MMP-12) is an MMP with potent elastin degrading activity. We have recently described its expression by hepatic macrophages and shown the degradation of elastin in models of hepatic fibrosis is dependent on this enzyme using gene knockout mice [27] (Fig. 1).

Exuberant matrix synthesis by myofibroblasts unquestionably contributes to the development of fibrosis. However, evidence for the progression of fibrosis resulting in part from a change in the pattern of matrix degradation is now compelling. Moreover, there is increasing evidence for a wide range of MMPs with a broad combined substrate specificity being present in the fibrotic liver [14,15]. The range is such that one might anticipate matrix turnover during fibrogenesis of not only the fibrillar collagens but elastins, gelatins and non-collagenous matrix components also. For example, MMP-12 knockout mice accumulate elastin more rapidly than their wild-type counterparts in progressive murine fibrosis models [27], establishing that MMP-12 mediated elastin degradation is occurring even in progressive fibrogenesis.

Evidence suggesting that there are changes in the pattern of ECM degradation as well as synthesis in progressive fibrosis was first postulated in the 1970s [52,53]. In these studies collagenase activity was detectable in rat fibrotic liver and decreased with duration of fibrotic injury (in this case CCl_4 administration). Whilst these studies have been criticised because the precise assay conditions used may have resulted in gelatinase rather than collagenase activity being measured, current evidence suggests that the detected activity may indeed have reflected overall liver collagenase activity and in any case can be considered a barometer for changes in overall matrix remodelling mediated by metalloproteinases. Similar results were obtained in studies of primate alcohol mediated injury [54,55]. More compelling evidence for the potential of matrix degradation in hepatic fibrosis comes from models of spontaneous recovery of liver fibrosis. We and others have used carbon tetrachloride induced liver injury with a period of fibrosis induction followed by spontaneous recovery and bile duct ligation followed by bilio-jejunal anastomosis in the rat and mouse to characterise and contrast the cell lineage and secreted products active in progressive fibrosis with those present in spontaneously resolving fibrosis (see below and Fig. 1) [56,57].

The extracellular activity of each MMP is regulated in a series of stages as one might expect for such a powerful and potentially destructive family of proteases. All are regulated to a greater or lesser extent at the level of the gene, the result of stimulation by a range of cell signals which include growth factors and cytokines such as TNFα, PDGF, EGF, BFGF and IL-1 [41]. Critically, pro-fibrogenic cytokines such as TGFβ1 may differentially affect MMP expression by downregulating interstitial collagenase expression whilst upregulating expression of gelatinase A, TIMP-1 and collagen-I [41]. MMP activity is further regulated through the cleavage of the pro-piece from the inactive zymogen. Finally active MMPs are susceptible to inhibition by the key extracellular inhibitors, the tissue inhibitors of metalloproteinases (TIMPs), a family of soluble proteins which bind nonconvalently to active MMPs to inhibit enzymatic activity [41].

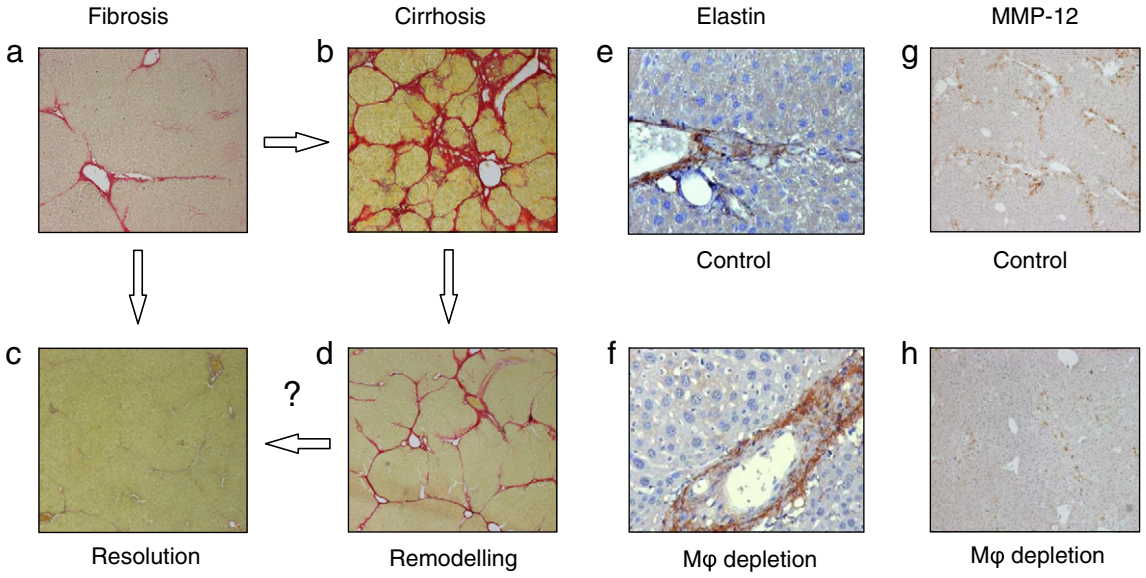

Fig. 1. The development of fibrosis within the liver is a dynamic process. This figure illustrates the approaches in which animal models can be used to dissect fibrosis and fibrosis resolution. Damage to the normal liver (in this case using carbon tetrachloride in a rat model) is associated with the development of fibrotic septae (a) as described in the text. If damage is protracted or iterative it leads to cirrhosis (b) in which the liver architecture is disrupted, there is nodular hepatic regeneration and linking of the vascular structures by dense fibrotic septae. Following cessation of injury significant remodelling occurs from even well established fibrosis (c). Some remodelling is possible with cessation of injury in the context of cirrhosis (d). It is not entirely clear whether it is possible for cirrhosis to remodel completely with a return to absolute histological normality. Following liver injury there is an accumulation of elastin in the hepatic scars (e) and with selective macrophage depletion the accumulation of elastin is enhanced (f). Having defined a role for macrophages in fibrosis remodelling, this data can be linked with expression of specific matrix degrading metalloproteinases. Panel (g) illustrates a fibrotic liver stained for metalloelastase (MMP-12). MMP-12 is abundantly expressed by macrophages associated with the scar. Macrophage depletion (h) is associated with a diminution in MMP-12 expressing cells within the liver, identifying these cells as a critical source of matrix degrading metalloproteinases during fibrosis and fibrosis resolution.

6. TIMP and changes in the pattern of matrix degradation during fibrogenesis

Members of the TIMP family function as important inhibitors of the extracellular activity of MMPs by stabilising the proenzyme and most importantly by inhibition of the active species. TIMP-1 and TIMP-2 are both expressed by activated stellate cells; indeed the expression of TIMP-1 is closely linked to activation and parallels the development of other markers of HSC activation such as alpha smooth muscle actin and collagen-I expression. This close correlation of TIMP-1 with activated stellate cells, and indeed activated HSC numbers [14], means that serum levels of TIMP-1 correlate relatively closely with fibrosis activity and serum levels of TIMP-1 are now a component of non-invasive serum markers of fibrosis [15,58–60]. TIMP-2 is also expressed by stellate cells in the fibrogenic phenotype, but is induced to a lesser extent as it is also expressed in the quiescent phenotype observed in the normal liver. TIMP-1 and - 2 share common structural features. There is a 40% amino acid sequence homology and both have a 3-looped structure linked by a series of six disulphide bonds [41]. Both TIMP-1 and -2 are secreted into the extracellular milieu (in contrast a further member of the family, TIMP-3, appears to be closely associated with extracellular matrix). Although non-covalent, the binding of TIMPs to active MMPs appears to be effectively irreversible, or at least irreversible in functional terms, under physiological conditions. Separation of MMP from TIMP though results in both retaining activity. Both TIMP-1 and TIMP-2 have a wide spectrum of MMP inhibitory activity and if present would be anticipated to be highly effective in altering the extent and pattern of matrix degradation in any fibrogenic process [41]. TIMPs are also regulated by cytokines and growth factors. Interestingly, TGFβ1 which as noted above downregulates collagenase activity, will upregulate TIMP-1 and gelatinase A thus reinforcing a highly fibrogenic pericellular milieu [41].

As noted above, TIMP-1 expression is strongly linked to HSC activation, although myofibroblasts derived from other sources also express this metalloproteinase inhibitor and there is probably some expression by kupffer cells and macrophages [14]. The expression of TIMP-1 has been extensively characterised in cell culture models of stellate cell activation wherein low or undetectable levels of TIMP-1 mRNA characterise quiescent cells and these rise significantly upon activation. The presence of active TIMP-1 secreted by myofibroblast-like stellate cells can be demonstrated in the extracellular media and it has been shown, by analysis of gelatinase A activity before and after chromatography (to separate TIMP-gelatinase complexes), that TIMP-1 in this model exerts an approximately 20-fold inhibitory activity on concurrently secreted gelatinase A [61]. Descriptive studies in rodent models, utilising carbon tetrachloride, thioacetamide or bile duct ligation to induce fibrosis all demonstrate HSC derived TIMP-1 rising with activation of stellate cells and development of fibrosis, and the expression and secretion of TIMP-1 remaining at high levels during progressive fibrosis [14]. In contrast expression of interstitial collagenase in humans (MMP-1) and rodents (MMP-13) fibrosis models remains relatively unaltered compared with uninjured control liver [14,15]. Taken together these data suggest that the balance between TIMP and MMPs in fibrosis may, through fine changes in the relative levels of each mediator, alter the rate and pattern of matrix degradation. Moreover they provide a mechanism through which matrix degradation can be tightly regulated in a fibrogenic milieu. Finally, the data suggest that even in progressive fibrosis MMPs are present within the liver of both rodent models and human pathological samples, but are inhibited by the concurrent expression of TIMP-1 by activated myofibroblast/HSCs.

These observations led us and others to posit the hypothesis that the development and progression of fibrosis results not only from exuberant matrix synthesis but changes in the pattern of matrix degradation. More compelling evidence for this hypothesis is provided by studies of spontaneous resolution of liver fibrosis. In both rats and mice, carbon tetrachloride can be used in a regular dosing regime to induce dense fibrosis of the liver (4–8 weeks of exposure) and cirrhosis (12–16 weeks of exposure) [22,56,57]. If exposure to carbon tetrachloride is abruptly halted after 8 weeks of treatment, over the succeeding 28 days there is progressive remodelling of the fibrotic septa and the loss of myofibroblasts through apoptosis and return of architecture to normality or near normality (Fig. 1). Additionally hepatic function appears to be maintained/restored. Detailed studies of this process indicate that there is a progressive decrease in hepatic levels of TIMP-1 (and TIMP-2) which parallel closely the reduction in myofibroblast numbers mediated by apoptosis [56,57]. As this occurs, although the expression of collagenase (MMP-13), gelatinase-A and B (MMP-2 and 9) and elastase (MMP-12) does not change dramatically, there is a net increase in hepatic MMP activity which coincides with the remodelling of the fibrotic matrix [56]. Exhaustive mechanistic evidence for a change in the pattern of matrix degradation during both progressive fibrosis and spontaneous resolution came from elegant work undertaken by Yoshigi and colleagues who created a TIMP-1 over expressing mouse [62,63]. In the presence of excess TIMP-1 fibrosis progresses more rapidly than that seen in a wild-type mouse during carbon tetrachloride mediated injury (suggesting that as outlined above modest matrix turnover and remodelling does occur during fibrogenesis and is regulated by the TIMP-MMP balance) but importantly TIMP-1 over-expressing animals fail to show evidence of matrix remodelling during spontaneous resolution of fibrosis. Interestingly the persistent fibrosis was associated with a persistence of activated myofibroblast-like hepatic stellate cells (HSC) within the hepatic scar [63]. The link between the persistence of activated myofibroblasts and the persistence of scar has been further highlighted by studies of the rr collagen mouse which expresses mutated collagen-I not susceptible to the initial collagenase cleavage necessary for interstitial collagen degradation [64]. During spontaneous resolution of fibrosis in these animals there is persistence of the scar and an associated persistence of activated myofibroblasts also suggesting that a failure of matrix degradation is sufficient to support persistence of activated hepatic stellate cells [64], likely mediated by critical integrin-matrix interactions (see article by Henderson and Sheppard). Other mechanistic approaches to regulating the TIMP-MMP balance have all demonstrated results compatible with the Yoshigi data and supporting the hypothesis that changes in the pattern of matrix degradation contribute significantly to the development of fibrosis. These include adenovirus mediated over expression of MMP-8 (neutrophil collagenase) in rodent models which was associated with a decreased fibrosis during experimental liver injury [42] and the deployment of a neutralising TIMP-1 specific antibody which decreased the collagen content in CCl_4 induced fibrosis [65]. An ingenious approach to exploiting the biochemistry of the TIMP-MMP relationship was employed by Roeb and colleagues who engineered a non-functional form of MMP-9 that would nevertheless actively bind TIMPs and sequester MMP inhibitory activity [66,67]. This represents a particularly sophisticated approach in that by reducing the TIMP activity globally in an organ in vivo the totality and range of the ECM degrading potential present in any tissue can be unleashed – theoretically in advanced scarring non-collagen matrix components such as elastin may be significantly represented, whereas a collagenase-only based approach might prove less effective. This TIMP scavenging approach was used effectively in CCl_4 induced fibrosis resulting in the decrease in collagen levels in treated animals and enhanced HSC/myofibroblast apoptosis.

7. ECM degradation and evidence from human disease

The most compelling evidence that spontaneous resolution of fibrosis is possible in humans comes from the large scale trials of antiviral treatments for hepatitis B and C (although evidence that human liver fibrosis is at least partially reversible following the withdrawal of chronic hepatic insults is extant for a range of other disorders reviewed in [5–9,68,69]). These large scale trials in which biopsies were undertaken

provided clear evidence for fibrosis remodelling with resolution of fibrosis and at least a partial return to normal hepatic architecture. Intriguingly, these and other pathological studies have also highlighted the possibility that there may be discernible matrix remodelling and architectural restitution even in cases of advanced cirrhosis, although it seems unlikely that all such advanced pathologies are entirely reversible and this area remains controversial [7,9,68,69]. A detailed and exhaustive summary of current therapeutic targets and active antifibrotic trials is presented in [70].

8. Reversibility and advanced cirrhosis

Cirrhosis represents not only advanced fibrosis, but an extensive scarring characterised by architectural disruption, aberrant and nodular hepatocyte regeneration, and vascular changes with angiogenesis, particularly in dense fibrotic septae, and the presence of old and relatively pauci-cellular areas of fibrosis. Using rats, we have demonstrated that an advanced cirrhotic lesion satisfying the pathological description above will undergo some remodelling during spontaneous resolution but that this is incomplete, leaving an attenuated macronodular cirrhosis [22]. The pattern of limited change seen mirrors closely that observed by Wanless and colleagues in their detailed study of human explants which suggests that matrix degradation in advanced fibrosis favours the loss of the most recently formed sub septae and that the extensive elderly septae linking vascular structures are relatively inert and resistant to degradation [69]. Using this model we were able to identify septal features which resisted matrix degradation compared to their remodelled counterparts. These included angiogenesis and the development of new vessels within the septum, evidence of cross-linking mediated by tissue transglutaminase, the presence of elastin and a relatively pauci-cellular scar containing comparatively few myofibroblasts or inflammatory cells [22]. Interestingly, the elastin rich scars might be expected to be more cross linked partly by virtue of the substrate available for lysyl oxidase and tissue transglutaminase mediated cross-linking and in part because they represented the oldest scars present in the organs. Our understanding of the irreversible components of fibrosis is still significantly limited. A key study by Popov and colleagues using the tissue transglutaminase knockout suggested that tissue transglutaminase mediated cross linking alone was insufficient to render fibrosis irreversible [71]. Interestingly, the expression of lysyl oxidase itself may have pro-inflammatory effects in addition to enhancing matrix stability and enzymatic resistance [72]. Furthermore, any matrix cross-linking may stiffen the matrix and result in the concealment of epitopes important for integrin-mediated hepatocellular regeneration and stabilisation of the physical properties of the matrix which in turn may promote a persistent activated state of the hepatic myofibroblast.

Because of the potential importance of elastin to the content and stability of the hepatic scar, this has recently been the subject of investigation. Studies using carbon tetrachloride and thioacetamide-induced fibrosis models have demonstrated that a metalloelastase (MMP-12) derived from macrophages represents a key elastase associated with turnover in progressive fibrosis [27]. Moreover, in the absence of MMP-12 there is not only a prominence of elastin during fibrogenesis but interestingly other collagenous matrix proteins (as defined by Sirius red staining) also [27].

9. Functional contribution of individual cell lineages to fibrosis resolution

Whilst gene array and molecular studies can be used to document expression of MMPs by a wide range of liver cells, it is only possible to define functional contributions by using genetically modified mice permitting tracking or deletion of specific cell lineages or proteins. One of the key defining features of spontaneous resolution of liver fibrosis is apoptosis of myofibroblast-like hepatic stellate cells [5], although there are recent studies which have demonstrated evidence for some phenotypic reversion to quiescence in these cells also [73–75] (Fig. 2). Either process though would be expected to be associated with a diminution in hepatic TIMP levels. Indeed, in detailed recovery models this has been quite clearly documented. Crucially, it is difficult to postulate

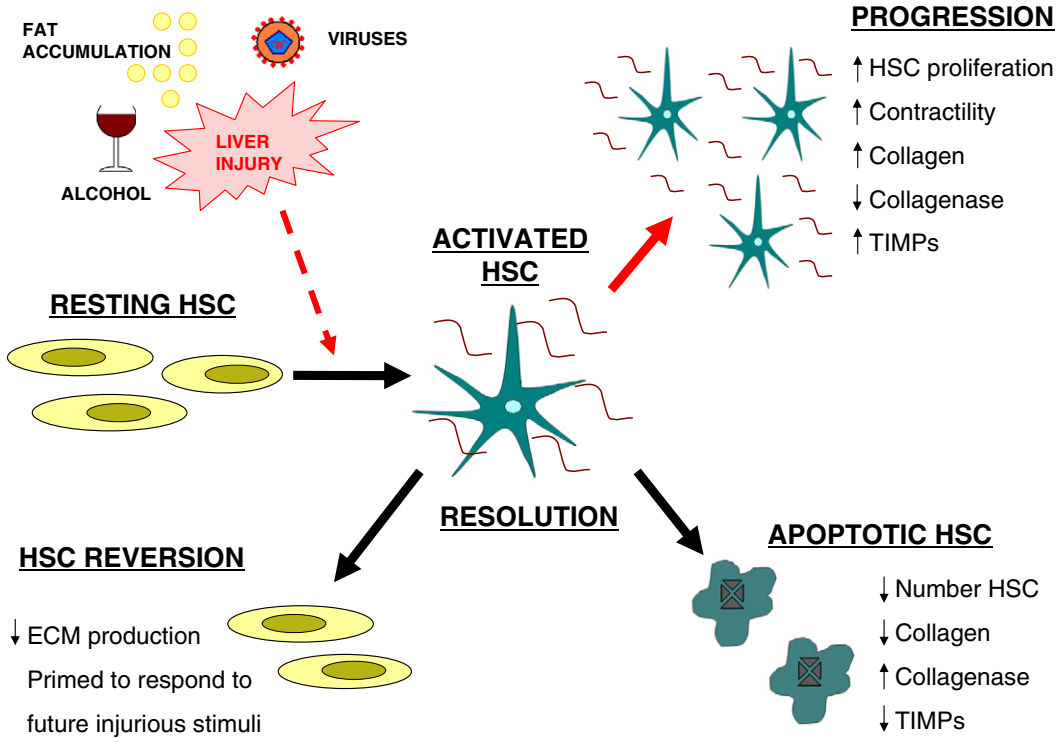

Fig. 2. Summary of the processes mediating progression or recovery from liver fibrosis. Liver injury results in activation of quiescent HSC to activated HSC (liver myofibroblasts) with secretion of extracellular matrix proteins, including fibrillar collagens. Iterative liver injury results in progression and amplification of this process eventually leading to cirrhosis and end-stage liver disease. During resolution of liver fibrosis HSC can undergo programmed cell death (apoptosis) or reversion to a deactivated state with a reduction in ECM production.

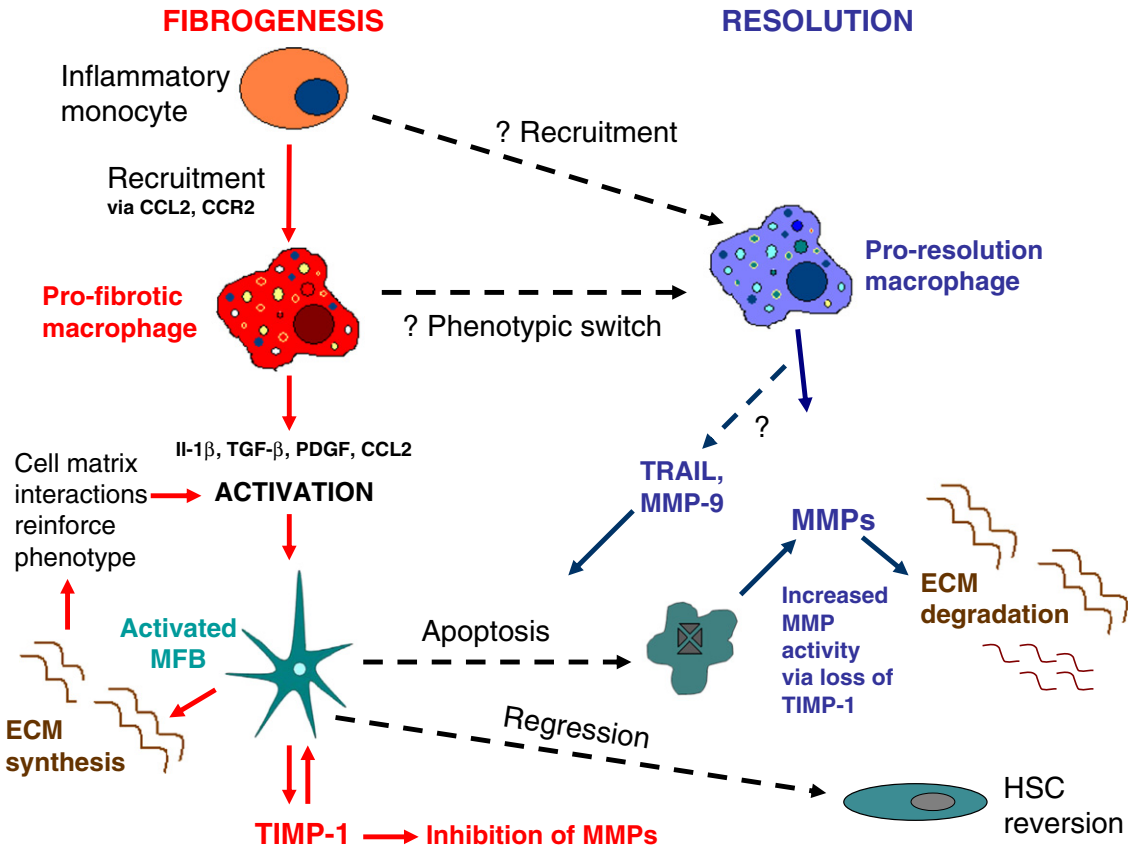

Fig. 3. Macrophages as key mediators of liver fibrogenesis and fibrosis resolution. During fibrosis evolution inflammatory monocytes are recruited to the injured liver via CCL2 (chemokine (C-C motif) ligand 2) and CCR2 (chemokine (C-C motif) receptor 2), forming the pro-fibrotic macrophage population. Il-1β, TGFβ, PDGF and CCL2 expression by pro-fibrotic macrophages promotes activation of liver myofibroblasts. Activated myofibroblasts secrete extracellular matrix (ECM) and TIMP-1 (a potent inhibitor of MMP activity). Both ECM and TIMP-1 interactions promote persistence of the activated myofibroblast phenotype. As fibrosis resolves, it is likely that a change in macrophage phenotype occurs, either secondary to a phenotypic switch of pro-fibrotic macrophages or a separate recruitment of monocytes. Pro-resolution macrophages express mediators that promote myofibroblast apoptosis, leading to reduced ECM production, loss of TIMP-1 expression and enhanced MMP activity. Pro-resolution macrophages can also directly promote ECM degradation via expression of MMPs.

logically that a cell population declining through apoptosis is the major source of the metalloproteinases critical for matrix degradation. Although detailed studies of MMP expression during phenotypic reversion may identify expression of critical MMPs, studies in which activated HSC/myofibroblasts have been deleted through induced apoptosis have demonstrated enhanced fibrosis remodelling suggesting that HSC are not necessary for resolution [57]. These observations have led to a focus on macrophages [17,27,43], and latterly dendritic cells [76] as potential sources of MMPs critical to fibrosis resolution.

Using a CCl_4-induced spontaneous resolution model, we have shown that whilst CD11b+ macrophages are critical to fibrosis development, their deletion at the onset of spontaneous resolution is associated with a failure of fibrosis remodelling. Moreover, we have gone on to show that macrophage derived MMP-13 (collagenase) is essential for remodelling the critical matrix substrates collagen-I and III, and that macrophages are a major source of liver metalloelastase, MMP-12 [17,27,43]. Recently we have shown that the adoptive transfer of macrophages is sufficient to enhance resolution of fibrosis even in continuing progressive injury both by direct effect and potentially through recruitment of other inflammatory cells producing MMPs such as neutrophils [77]. Intriguingly, parallel studies manipulating dendritic cells (described in detail by Aloman) demonstrate an important role for CD11c+ cells potentially mediated via gelatinase B (MMP-9) [76].

There is accumulating evidence that a specific Ly6c intermediate and low phenotypic macrophage present in the liver during the resolution of fibrosis represents not only the most numerous macrophage at any time in the whole experimental fibrosis/fibrosis resolution continuum, but that these cells are also the major source of MMPs crucial to resolution. In turn specific MMPs, and particularly MMP-12, appear to be upregulated in these $Ly6c^{int/lo}$ macrophages as a response to ingestion of apoptotic hepatocyte debris. Most intriguingly, this ingestion of apoptotic debris appears to also result in macrophage expression of the mitogen TWEAK [77] and key Wnt signalling molecules which promote, respectively, proliferation and hepatocellular differentiation of the bipotential hepatic progenitor cell, which is a major contributor to the hepatocyte repopulation that occurs during fibrosis remodelling and resolution [78]. A diagram summarizing the key role of macrophages in hepatic fibrogenesis and fibrosis resolution is shown in Fig. 3.

10. Evidence of bidirectional fibrosis in other key human models

For reasons of clarity, this review has been largely limited to rodent and human models of liver fibrosis. Nevertheless, there is increasing evidence of similar patterns of matrix remodelling occurring in other organ systems. Experimental renal fibrosis models in rodents demonstrate reversibility [79–81]. In particular, recent evidence from studies of human kidney fibrosis suggests that significant ECM remodelling is possible [82,83] and evidence from the heart has shown beneficial effects of angiotensin receptor inhibitors and angiotensin receptor blockers in promoting the remodelling of fibrosis in the cardiac scar, enhancing myocardial contractility and function [84].

11. Conclusions

The detailed studies of hepatic matrix synthesis and degradation that have occurred over the last 30 years have identified a model that

is dynamic with respect to ECM synthesis, modification, turnover and degradation. By the effective analysis of complimentary approaches encompassing cell culture, human disease and experimental animal models we have arrived at an appreciation of the highly dynamic nature of liver wound healing and fibrosis. It is anticipated that the development of effective and targeted antifibrotic therapy is now a real possibility. Studies in other human organ systems suggest a commonality of mechanism and importantly early evidence that in both the heart and kidney, fibrosis is bidirectional and the capacity for matrix remodelling and architectural restoration is at least partly preserved even in chronic injury. Two key areas of the ECM and its degradation which remain incompletely investigated include defining those features of the irreversible components of the fibrotic response which may then need a specialised approach and ensuring organ specificity of any clinical approach based on matrix degradation, to limit potentially significant off target effects.

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