

Is Cirrhosis of the Liver Reversible?

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ABSTRACT

Extensive and persistent hepatic fibrosis has for a long time been considered irreversible. Accumulating evidence suggests that liver fibrosis is reversible and that recovery from cirrhosis may be possible. The application of molecular techniques to models of reversible fibrosis are helping to establish the events and processes that are critical to recovery. The problem consists in identifying and eliminating its cause. Although fibrosis in the liver has little functional significance by itself, its severity derives from associated vascular changes. Disappearance of fibrosis can be accompanied by remodeling of vascular changes. However, depending on its duration, the fibrosis may be irreversible.

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Liver fibrosis and cirrhosis are generally the end result of majority of chronic liver insults. The development of fibrosis, and particularly cirrhosis, are associated with a significant morbidity and mortality. There is considerable research going on to develop antifibrotic strategies that are applicable to liver fibrosis. Such an approach is attractive because it is aimed at the final common pathological pathway of chronic liver disease, regardless of the etiology. Recent developments in understanding of the process of hepatic fibrogenesis confirm that the process is a dynamic one and suggest that a capacity for recovery from any degree of fibrosis including those associated with cirrhosis is possible. Moreover, with the advent of effective antiviral therapies, biopsy documented examples of improvement in fibrosis and in some examples resolution, including that of cirrhotic change, are being described.

Origin of fibrosis and cirrhosis

The causes of hepatic fibrosis and cirrhosis are multiple and include congenital, metabolic, inflammatory, and toxic liver diseases. In all circumstances, the composition of the hepatic scar is similar.

Development of liver fibrosis entails major alterations in both the quantity and quality of hepatic ECM and there is overwhelming evidence that activated hepatic stellate cells (HSC, Ito, fat storing cell,

or lipocyte) are the major producers of the fibrotic neomatrix.¹ The components of hepatic extracellular matrix (ECM) include several families of structural and supporting molecules: collagens, noncollagen glycoproteins, matrix-bound growth factors, glycosaminoglycans, proteoglycans, and matricellular proteins. In the normal liver, collagens (types I, III, V, and XI) are largely confined to the capsule, the area around the large vessels, and the portal triad, with only scattered fibrils containing types I and III in the subendothelial space. Cirrhotic liver contains approximately six times more ECM overall than normal liver, and in the space of "Disse, collagen" types III and V and fibronectin accumulate in early injury. In chronic injury, there is increasing deposition of collagen types I and IV, undulin, elastin, and laminin. Hyaluronan, normally a minor component of the space of Disse, is increased more than eightfold and dermatan and chondroitin sulphate and heparan sulphate proteoglycans also increase. Although collagen types I, III, and IV are all increased, type I increases most and its ratio to types III and IV therefore increases.^{2,3} With progressive injury ECM spurs link the vascular structures, ultimately resulting in the architecturally abnormal nodules and vascular changes that characterise cirrhosis.

Early, subendothelial matrix accumulation leading to "capillarization" of the subendothelial space of Disse is a key event, and may be more important than overall increase in the matrix content. Normally, this space contains the components of a basement membrane. Replacement of the normally low-density matrix of basement membrane by high-density interstitial matrix

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directly influences the hepatocyte function and activates HSCs. The latter may explain the synthetic and metabolic dysfunction and the impaired transport of solutes from the sinusoid to hepatocytes in advanced fibrosis and cirrhosis. ECM can directly influence the function of surrounding cells through interaction with cell surface receptors, including integrins and nonintegrin matrix receptors. ECM can also indirectly affect cell function via release of soluble cytokines, which in turn are controlled by local metalloproteinases.^{3,4}

Stellate cell "activation" is a key event in liver injury, and refers to the transition from a quiescent vitamin A-rich cell to a highly fibrogenic cell. Cells with features of both quiescent and activated states are often called "transitional cells." Proliferation of stellate cells occurs in regions of greatest injury, and is typically preceded by an influx of inflammatory cells and associated with subsequent ECM accumulation.

Activation consists of 2 major phases: (1) initiation (also called a preinflammatory stage) and (2) perpetuation (Fig. 1). Initiation refers to early paracrine-mediated changes in gene expression and phenotype that render the cells responsive to other cytokines and stimuli. Perpetuation then results from the effects of these stimuli on maintaining the activated phenotype and generating fibrosis.

The earliest changes in the stellate cells are likely to result from paracrine stimulation by all neighbouring cell types, including sinusoidal endothelium, Kupffer cells, hepatocytes, platelets, and leukocytes. Endothelial cells are also likely to participate in activation, both by production of cellular fibronectin and via conversion of

transforming growth factor (TGF)-beta from the latent to active, profibrogenic form.⁵

Perpetuation of the stellate cell activation involves several discrete changes in cell behaviour.

- Proliferation. PDGF is the most potent stellate cell mitogen identified.
- Chemotaxis. Stellate cells can migrate towards cytokine chemoattractants. Chemotaxis of stellate cells explains in part why stellate cells align within inflammatory septa in vivo.
- Fibrogenesis. Increased matrix production is the most direct way that stellate cell activation generates hepatic fibrosis. The most potent stimulus to collagen I production is TGF-beta, which is derived from both paracrine and autocrine sources. Lipid peroxidation products are emerging as important stimuli to ECM production; their effects may be amplified by loss of antioxidant capacity of stellate cells as they activate.⁶
- Contractility. Contractility of stellate cells may be a major determinant of early and late increases in portal resistance during liver fibrosis. Activated stellate cells impede portal blood flow by both constricting individual sinusoids and contracting the cirrhotic liver, because the collagenous bands typical of end-stage cirrhosis contain large numbers of activated stellate cells. The major contractile stimulus towards stellate cells is endothelin-1.⁷ Locally produced vasodilator substances may counteract the constrictive effects of endothelin-1. NO, which is also produced by stellate cells, is a well-characterized endogenous antagonist to endothelin.
- Matrix degradation. Quantitative and qualitative

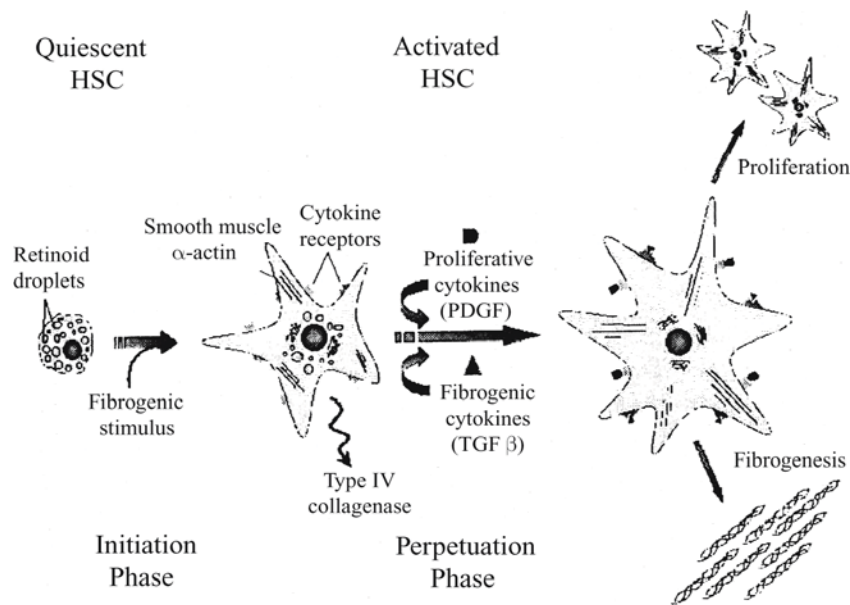


Fig. 1. Stellate cell activation

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changes in matrix protease activity play an important role in ECM remodeling accompanying fibrosing liver injury. Stellate cells express virtually all of the key components required for pathologic matrix degradation and therefore play a key role not only in matrix production, but also in matrix degradation. An enlarging family of matrix-metalloproteinases has been identified that are calcium-dependent enzymes which specifically degrade collagens and noncollagenous substrates⁸

- WBC chemoattractant and cytokine release. Increased production and/or activity of cytokines may be critical for both autocrine and paracrine perpetuation of stellate cell activation. Stellate cells can amplify the inflammatory response by inducing infiltration of mono- and polymorphonuclear leukocytes.

REVERSIBILITY OF FIBROSIS

The phrase “reversal ” is often used to imply a complete restoration of normal architecture. Skepticism surrounds this concept. A more palatable working definition would be to refer instead to “regression” of fibrosis or cirrhosis, indicating that the fibrosis content is less than earlier, without quantifying the extent of regression or suggesting that the histology has returned completely to normal. A concept of equal clinical importance is the potential to achieve “stasis” of fibrosis, or lack of progression in the face of continued liver injury. Such an outcome—in response to treatment of the underlying disease or to effective anti-fibrotic therapy—would be a great therapeutic advance in patients who are asymptomatic with well-preserved liver function, as it might ensure that such individuals eventually die of other causes “with” liver fibrosis rather than dying “of ” cirrhosis.⁹

The notion that fibrosis can be degraded and be eliminated is old one. At the moment of the childbirth clear degradation of the matrix of the uterus occurs, allowing its softening. During embryogenesis and morphogenesis, there are many examples of degradation and reabsorption of the fibrous tissue. The rheumatologists have known since long that, fibrosis can diminish or disappear in the joints. This process is also known in the periodontal illnesses. In the process of angiogenesis, as well as in the infiltrative growth of the neoplasms and their metastases, the occurrence of degradation of the extracellular matrix is recognized since long.¹⁰ But, for long, the impression prevailed that the removal of the fibrotic tissue happened only in these limited processes, in small amounts. But when fibrosis resulted in an illness and involved a substantial part of an organ, it was irreversible. This belief started to be shaken by some research done in last decades of the last century. The studies on hepatic fibrosis associated

with schistosomiasis had decisive participation. Schistosomiasis was the first human illness where it was demonstrated that extensive hepatic fibrosis could regress, leading to morphological and functional improvement.

The reversibility of hepatic fibrosis in schistosomiasis.

Clinical aspects: In 1966, Katz and Brener¹¹ observed spontaneous regression of splenomegaly in a few patients with hepatosplenic form of schistosomiasis. Later,¹² a new drug (Hycanthon), was found to improved the clinical picture in some patients with hepatosplenic form of schistosomiasis. The well controlled clinical works that followed consolidated the notion of the reversion or reduction of hepatic fibrosis in human beings.^{13,14,15} When the treatment is done in young individuals with the hepatosplenic form of schistosomiasis , the reversibility of the clinical picture can be noticed as early as six months.¹⁶ The studies carried through surgical biopsies on patients done at the time of splenectomies, demonstrated the presence of unequivocal signals of degradation of periportal fibrosis.¹⁷ Disappearance of the esophageal varices also occurred, suggesting that the elimination of fibrosis can lead to remodelling of the vascular injuries.

Experimental aspects: It has been shown that granulomas, the reactional hepatitis and fibrosis disappeared from the liver of the treated murine hepatosplenic schistosomiasis.^{18,19} But, then studies appeared demonstrating that such data were valid for recent schistosomiasis (8-10 weeks after the cercaria exposure), and fibrosis of the delayed infections (16- 20 weeks) were irreversible.²⁰ These data indicated that recent disease is reversible and the delayed one is irreversible. Studies demonstrated that such difference was due to the presence of different types of collagens (collagen type III, predominant in the recent fibrosis, was more easily degraded than type I, that predominated in dense and old fibrotic regions).²¹

The model of capillaria hepatica induce septal fibrosis: Rats infected with the Capillaria nematodes develop septal hepatic fibrosis 20-30 days after infection.²² Rats infected with the helminth Capillaria hepatica regularly develop septal fibrosis of the liver. Fibrosis starts when the focal parasitic lesions begin to show signs of resorption, thus suggesting an immunologically mediated pathogenesis of this fibrosis.²³ During its life cycle the larvae of the capillaria hepatica, become worms in the interior of the liver of the host and there they deposit its eggs, and die some time later. In the rats all the worms are already dead by the end of the first month of the infection. Septal fibrosis starts a little before and it increases in the following month. But, from then on fibrosis starts to regress. However, it does not disappear completely. The eggs deposited in the focal fibrotic lesions start to lose

viability at about 4th month after-infection and become imperceptible from 6th month. Therefore, all the parasitic stimulations are absent from 6th month after-inoculation. Then why septal fibrosis persists remains to be elucidated.

Antifibrotic therapy for chronic liver disease is an emerging reality. The paradigm of stellate cell activation provides an important framework for defining sites/targets of antifibrotic therapy. These strategies include: (A) curing the primary disease to prevent injury; (B) reducing inflammation or the host response in order to avoid stimulating stellate cell activation; (C) directly downregulating stellate cell activation; (D) neutralizing proliferative, fibrogenic, contractile, and/or proinflammatory responses of stellate cells; (E) stimulating apoptosis of stellate cells; and (F) increasing the degradation of scar matrix, either by stimulating cells that produce matrix proteases, downregulating their inhibitors, or by direct administration of matrix proteases. An array of studies in animal models have defined dozens of potential antifibrotics worthy of clinical trials.²⁴

The balance of all the factors involved in fibrosis development is dynamic. It has fibrogenic and fibrolytic forces. When, the stimulators of fibrogenesis surpass those of fibrolysis, fibrotic tissue accumulates. But, when the causes that had provoked these alterations are eliminated, the inverse process occurs, and the excess fibrotic tissue is removed. Complete recovery from liver fibrosis would involve remodeling and breakdown of ECM components, with degradation of the predominant component, collagen I, being particularly important for recovery of normal liver histology. At present, the identities of the enzyme(s) that degrade the fibrillar collagens (collagens I and III) in the liver are unclear. The matrix metalloproteinases (MMP), a family of zinc dependent endoproteinases, have the capability to degrade these various ECM components and are expressed particularly by HSCs and Kupffer cells.²⁵ Studies in animal models and human liver fibrosis indicate that interstitial collagenolytic activity decreases in liver extracts in advanced fibrosis, which would promote net collagen deposition.^{26,27} Collagenase inhibition may arise from increased expression in fibrotic liver of endogenous MMP inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). Activated HSC may be an important source of these TIMPs in injured liver.^{28,29,30} The resulting increase in TIMP : MMP ratio in liver may promote fibrosis by protecting deposited ECM from degradation by MMPs. However, other MMP inhibitory mechanisms might contribute to fibrosis. MMPs are released as inactive pro-enzymes, and an important regulatory step involves cleavage of the inhibitory N-terminal peptide to confer enzymatic activity. The means of proenzyme activation varies between different

MMPs, but the protease plasmin is required for efficient activation of proMMP-1.³¹ Activated HSC may however inhibit plasmin synthesis in fibrotic liver through synthesis of plasminogen activator inhibitor-1 (PAI-1).³² In summary, activated HSC might produce a fibrogenic environment within the liver through a combination of ECM overproduction, diminished MMP activation and inhibition of active MMPs by TIMPs. The removal or inactivation of activated HSC from the liver is therefore likely to be a key process before recovery from fibrosis can occur.

A key question which needs to be tackled is: does liver fibrosis reach a point where it becomes irreversible, and if so what are the qualitative and quantitative differences in the liver structure compared with recoverable fibrosis. Several factors might dictate whether liver fibrosis can recover. Firstly, recovery requires degradation of the existing fibrotic matrix, but this matrix may be modified to resist degradation as fibrosis progresses. Newly secreted collagen fibrils can be cross-linked by both tissue transglutaminase and lysyl oxidase pathways; the activity of both pathways is increased during liver fibrogenesis.³³ Such cross-linking during maturation of collagen might reduce its susceptibility to collagenase.³⁴ Mature ECM is also relatively rich in elastin; to date there are very limited data on the turnover of this important matrix protein in fibrosis. Secondly, recovery is unlikely if collagenolytic enzymes remain inactive following cessation of liver injury. The full range of enzymes having interstitial collagenase activities in liver still require identification. Collagenase activity becomes deficient during evolution of liver fibrosis in animal models and in humans, and this may be caused by TIMP overexpression. Continued inhibition of ECM degradation by TIMPs may block the ability to recover from fibrosis, even after removal of the injury. As activated hepatic stellate cells are an important source of both ECM and TIMPs, recovery from fibrosis might require either removal of the activated HSC population, as shown in rat models, or possibly the phenotypical reversal of stellate cell activation, a process yet to be observed *in vivo*. In non-recovering liver fibrosis activated HSC might persist as a result of a "memory" effect, possibly mediated by collagenous and non-collagenous components of the deposited fibrotic neomatrix, which either promote HSC activation or protect them from apoptotic stimuli.^{35,36} Studies of gene therapy using protease delivery, in experimental models of fibrosis, have established proof-of-principle that even dense scar can be resorbed.³⁷

THE REVERSIBILITY OF CIRRHOSIS

Clinical aspects: If one accepts that "regression" simply indicates a bona fide decrease in matrix content

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without necessarily returning the histology to normal, then there is little doubt of the capacity of the healing liver to resorb scar. In clinical circumstances where an effective treatment for the underlying insult is available, remodeling of the scar tissue can occur and a return towards architectural normality has been documented even in advanced fibrosis and cirrhosis. This has been most clearly documented in autoimmune disease, but is paralleled by observations of hemochromatotic patients after venesection and patients with hepatitis B and C after successful interferon therapy.^{38,39,40} Moreover, fibrosis reversal associated with antiviral therapy can also lead to meaningful improvement in liver function.⁴¹ Whether such improvement will also ameliorate portal hypertension, decrease the incidence of hepatocellular carcinoma or improve survival is uncertain.

When the possibility of reversibility of hepatic cirrhosis is argued, it must be very clear what it is being argued. Cirrhosis must not be confused with fibrosis, the later is only one of the components of cirrhosis and it is reversible, at least partially, when its cause is eliminated. Cirrhosis is a generalized process of regeneration to form nodular parenchyma, followed by complex vascular alterations, that includes intrahepatic arterio-venous connections, porto-systemic shunting (collateral circulation) and sinusoidal capillarization.⁴² It is important to define cirrhosis with precision. The clinical concept is of a chronic illness of the liver, of varied etiology, that attends a course with manifestations of hepatic insufficiency and portal hypertension. The anatomical concept foresees the presence of fibrosis, followed by the transformation of parenchyma to regenerative nodules. The problem is that the two pictures, anatomical and the clinical can be dissociated. It is possible that individuals presenting with portal hypertension and hepatic insufficiency of variable degrees may not have the anatomical picture of the cirrhosis. The reciprocal one can also be true and this has given to place myths and dogmas on the reversibility of cirrhosis.⁴³ It has been observed in the recent years that, when an individual has a clinical picture of cirrhosis [due to chronic alcoholism, hemochromatosis, chronic hepatitis B or C, etc] and its cause is removed or attenuated, it can have the disappearance of the symptoms and signs of cirrhosis.^{44,45} This means that the cirrhosis is clinically reversible. But, whether the anatomical picture improves or not, is a different aspect. Recently, Wanless *et al*⁴⁶ examined 52 livers removed at transplantation having cirrhosis or incomplete septal cirrhosis and these were graded for histologic parameters that suggest progression or regression of fibrosis. They listed a series of histopathologic findings, what they had called the hepatic repair complex. The complex includes delicate perforated septa, isolated thick collagen fibers, delicate periportal fibrous spikes, portal tract remnants,

hepatic vein remnants with prolapsed hepatocytes, hepatocytes within portal tracts or splitting septa, minute regenerative nodules, and aberrant parenchymal veins. Regression parameters were found in all livers and were prominent in the majority. Livers with micronodular cirrhosis, macronodular cirrhosis, and incomplete septal cirrhosis demonstrate a histologic continuum. A continuum of regressive changes was also seen within individual livers. Many examples of incomplete septal cirrhosis could be the product of regressed cirrhosis. The difficulties in clarifying the problem of the reversibility of the hepatic cirrhosis with human material, have stimulated the studies with experimental models.

Experimental aspects : The results on the reversibility of the experimental cirrhosis have been contradictory, possibly related with the period to the evolution of the cirrhosis when the stimulus is discontinued. Quinn and Hingginson had suggested that everything in the experimental cirrhosis is reversible, except the regenerative nodules⁴⁷ Iredale JP *et al* examined spontaneous recovery from liver fibrosis in carbon tetrachloride treated rats. Rats treated for four weeks with intraperitoneal carbon tetrachloride developed established liver fibrosis with extensive intervascular bridging with collagen fibres. Carbon tetrachloride dosing was then stopped and livers were examined at various times up to four weeks of recovery. After this time, histological analysis showed a noticeable dissolution of the collagenous fibrotic matrix and a return of liver structure to virtual normality. There was prominent apoptosis of activated HSC during recovery, particularly in the first three days concomitant with the largest drop in hepatic TIMP and procollagen I mRNA. Apoptosis therefore effectively removed the activated HSC, which were overproducing ECM and TIMPs. Therefore, during progressive fibrotic liver injury both HSC mitosis and apoptosis increase that is, turnover of these cells is increased, although proliferation predominates such that there is net increase in HSC numbers. During recovery, apoptosis becomes the overriding process with resulting net HSC loss from the liver.⁴⁵ There are relatively few studies of how apoptosis of HSC is controlled in the liver. Recently possibility has been raised that ECM degradation may result in HSC apoptosis rather than HSC apoptosis facilitating ECM degradation.⁴⁸ Recently, Di Vinicius *et al* had approached the problem of the reversibility of the cirrhosis in the rat. The objective was to verify if the findings observed in human material and listed as hepatic repair complex are found in CC1₄ treated cirrhotic mice.⁴⁹ An investigation for the presence of these morphologic features was performed at monthly intervals in rats with CC1₄-induced cirrhosis over a period of 9 months following discontinuation of treatment, using sequential liver biopsies. Within the

first 4 months, features of the "hepatic repair complex" were identified, together with the enlargement of the hepatic nodules and thinning of the fibrous septa. Subsequent to the 4 months, the histological picture, composed of large and inconspicuous nodules and delimited by thin and frequently incomplete fibrous septa "incomplete septal cirrhosis", appeared to be stabilized. These fibrous septa, when injected with India ink from the portal trunk, presented blood vessels that were seen to drain directly into the sinusoids. These findings suggested that when the cause of cirrhosis is removed, the liver may adapt itself to a new and permanent structure, probably compatible with normal or near-normal function, which may render hepatic cirrhosis clinically, although not morphologically, reversible.

In summary, there is unequivocal evidence of regression of fibrosis, cirrhosis may also be reversible at least clinically and possibly morphologically also. The molecular determinants of fibrosis regression in animals and humans need to be more comprehensively defined. The mechanisms and sources regulating matrix protease activity and cross-linking in the fibrotic milieu need further characterization. These findings will help customize the antifibrotic strategies by linking them with the extent of fibrosis accumulation or cross-linking.

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