CHAPTER 10

Matrix Metalloproteinases, Tissue Inhibitors of Metalloproteinase and Matrix Turnover and the Fate of Hepatic Stellate Cells

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Abstract

Liver injury is associated with activation of hepatic stellate cells (HSC) to a myofibroblast-like phenotype. In cirrhotic liver injury, activated HSCs are the major sources of fibrillar collagens, an excess of which characterise fibrotic matrix. HSCs also have the capacity to remodel this matrix as they express matrix metalloproteinases (MMPs) and their specific inhibitors, the tissue inhibitors of metalloproteinases (TIMPs). Recovery from acute and chronic injury is characterized by apoptosis of the TIMP expressing HSCs thereby relieving the inhibition of matrix degradation. HSC apoptosis is regulated in progressive injury and counterbalances cell proliferation. Apoptosis probably also represents a default pathway for the HSCs resulting from the withdrawal of survival signals after cessation of injury. The survival of activated HSCs in liver injury is dependent on soluble growth factors and cytokines, and on components of the fibrotic matrix itself. Additionally, stimulation of death domain receptors expressed on HSCs can precipitate their apoptosis.

Introduction

In many respects, liver fibrosis can be considered to be a model for solid organ wound healing. There is increasing evidence in models derived from other organs and the skin that demonstrate common features in the processes of inflammation, repair and resolution. Specifically the response to tissue damage is associated with activation of myofibroblasts, the secretion of fibrillar collagens to effectively mediate repair and, with withdrawal of the injurious stimulus, resolution. Resolution is characterized by degradation and remodelling of the fibrillar collagens with the restitution of normal architecture. In association with this there is reepithelialisation as well as loss of the myofibroblasts through apoptosis. In liver injury, the wound healing myofibroblasts are derived in major part from activated hepatic stellate cells, although there may also be contributions from peri-portal myofibroblasts.

With the advent of effective treatments for chronic liver disease, most importantly the development of interferon and other anti-virals for the treatment of chronic viral hepatitis, there is increasing evidence that liver fibrosis is, at least in part, reversible. Models of liver fibrosis in

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animals have provided key experimental data which identify the events determining resolution.7 Prominent amongst these is loss of the activated hepatic stellate cells through apoptosis. This has the effect of removing the major source of fibrillar collagen. Increasing evidence indicates that stellate cell apoptosis is determined by an imbalance in the presence of survival factors and pro-apoptotic stimuli. Amongst these, there is evidence for a role for soluble factors providing survival stimuli and critical changes to the matrix providing survival signals.2,8 In addition, soluble pro-apoptotic factors have been demonstrated to impact on stellate cells which express a variety of receptors for ligands of the TNF receptor super family.8–10

A Brief Review of the Role of Activated Stellate Cells/Myofibroblasts in Hepatic Fibrosis

Liver fibrosis can be considered as a paradigm for wound healing elsewhere in the body. In response to injury, virtually regardless of the insult, the hepatic stellate cell, which is normally a noncycling, quiescent vitamin A storing cell lying in the space of Disse, becomes activated to a myofibroblast-like state (the so called 'activated stellate cell).11–13 When activated these cells express a variety of cytoskeletal markers, including α smooth muscle actin.13,14 In addition, the cells enter the growth cycle with the result that the number of activated stellate cells present within the space of Disse and ultimately, in more extensive areas of bridging fibrosis, increases. Stellate cell activation is mediated via the impact of soluble factors secreted by facets of the inflammatory response in addition to products released by damaged hepatocytes and critical changes to the sub-cellular matrix. Once activated, the stellate cells exhibit a number of autocrine and paracrine functions, several of which perpetuate the activation state.15 These include expression of transforming growth factor β-1.15 Stellate cell expression of type 1 collagen is significantly upregulated whilst concurrently its degradation is inhibited by expression of TIMPs 1 and 2. However stellate cells also express MMPs, including those with collagenase activity demonstrating the latent capability that the liver has for matrix degradation. Therefore changes in phenotype and cell behaviour leading to the laying down of matrix proteins in which a fibrillar matrix critically predominates depend on the balance between these factors.

Previously considered irreversible, there are extensive (albeit anecdotal or numerically small clinical trials) which have documented an improvement in overall liver fibrosis as a result of the effective treatment of underlying liver disorders. These examples include venesection in haemochromatosis and effective immunosuppression in autoimmune chronic active hepatitis.16 With the advent of effective anti-viral treatments, however, the first evidence based on large scale studies is available and is providing compelling evidence for at least partial reversibility of fibrotic change in successfully treated patients in whom viral eradication occurs.6,16 It is important to note, however, that evidence for a reversal of cirrhotic change is as yet incomplete. Indeed compelling histological evidence for reversal of cirrhosis has yet to be demonstrated. Moreover, animal models of advanced cirrhosis do not demonstrate the complete resolution observed in models of fibrosis.17,18 In each of these examples, resolution may take months or years but the improvement in overall histology and the net loss of fibrotic tissue must, by definition, be associated with a net loss of activated hepatic stellate cells. An alternative view is that there may be a change in activation status of the hepatic stellate cells. However, in none of these examples is there evidence of increased numbers of quiescent hepatic stellate cells present in the recovered liver. Furthermore, there is good evidence for resolution of injury being associated with the loss of hepatic stellate cells in the acute setting. Following paracetamol (acetaminophen) injury, in areas of necrosis and inflammation, stellate cells become activated and α smooth muscle actin positive. Successful resolution following conservative treatment was associated with a return to normal histological appearance with a loss of these actin expressing cells. Therefore, this study provides direct evidence that resolution of injury is associated with a reduction in the number of α smooth muscle positive myofibroblast cells.1