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Medicine in focus

Hepatic fibrosis and cirrhosis: The (myo)fibroblastic cell subpopulations involved

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Abstract

Fibrosis, defined as the excessive deposition of extracellular matrix in an organ, is the main complication of chronic liver damage. Its endpoint is cirrhosis, which is responsible for significant morbidity and mortality. The accumulation of extracellular matrix observed in fibrosis and cirrhosis is due to the activation of fibroblasts, which acquire a myofibroblastic phenotype. Myofibroblasts are absent from normal liver. They are produced by the activation of precursor cells, such as hepatic stellate cells and portal fibroblasts. These fibrogenic cells are distributed differently in the hepatic lobule: the hepatic stellate cells resemble pericytes and are located along the sinusoids, in the Disse space between the endothelium and the hepatocytes, whereas the portal fibroblasts are embedded in the portal tract connective tissue around portal structures (vessels and biliary structures). Differences have been reported between these two fibrogenic cell populations, in the mechanisms leading to myofibroblastic differentiation, activation and "deactivation", but confirmation is required. Second-layer cells surrounding centrolobular veins, fibroblasts present in the Glisson capsule surrounding the liver, and vascular smooth muscle cells may also express a myofibroblastic phenotype and may be involved in fibrogenesis. It is now widely accepted that the various types of lesion (e.g., lesions caused by alcohol abuse and viral hepatitis) leading to liver fibrosis involve specific fibrogenic cell subpopulations. The biological and biochemical characterisation of these cells is thus essential if we are to understand the mechanisms underlying the progressive development of excessive scarring in the liver. These cells also differ in proliferative and apoptotic capacity, at least in vitro. All this information is required for the development of treatments specifically and efficiently targeting the cells responsible for the development of fibrosis/cirrhosis.

Keywords: Fibroblast; Myofibroblast; Extracellular matrix; Liver fibrosis; Cirrhosis; Remodelling

1. Introduction

The processes of liver repair and of fibrogenesis resemble a wound healing process. When injury and the associated acute inflammation response result in moderate cell necrosis and extracellular matrix damage, tissue repair normally takes place. In this process, dead cells are replaced by normal tissue, with regeneration of specialised cells by proliferation of the surviving ones, formation of a granulation tissue, and tissue remodelling

Abbreviations: CCl_4, carbon tetrachloride; CRBP-1, cellular retinol-binding protein-1; MMP, matrix metalloproteinase; TGF-β1, transforming growth factor-β1; TIMP-1, tissue inhibitor of metalloproteinase-1

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with scar formation. The specific regenerative capacities of the liver generally allow it to reconstitute itself entirely following acute, moderate lesions. However, chronic injuries to the liver do not always heal as effectively and fibrosis is the main complication of the many known chronic liver diseases. Various types of chronic injury, due to alcohol abuse, viral hepatitis (especially Hepatitis B and C), drugs, metabolic diseases (mainly due to overload of iron or copper), autoimmune destruction of hepatocytes or bile duct epithelium, and congenital abnormalities may lead to liver fibrosis (for review, see Bataller & Brenner, 2005).

The liver parenchyma is divided into functional units called lobules. The lobules are polygonal, generally hexagonal, and each is 1–2 mm in diameter and composed of a labyrinth of interconnected hepatocyte plates separated by endothelium-lined sinusoids. Each lobule is crossed by a central structure, the centrolobular vein. The hepatocyte plates radiate out from the centrolobular vein to the perimeter of the lobule; the portal triads (portal vein, hepatic artery, and bile ductule), and the surrounding connective tissue are typically found at the angles of the polygon (Fig. 1a and b).

Liver fibrosis is defined as the abnormal accumulation of extracellular matrix in the liver. Its endpoint is cirrhosis, which is responsible for a significant morbidity and mortality. Cirrhosis is an advanced stage of fibrosis, characterised by the formation of regenerative nodules of liver parenchyma separated by fibrotic septa. Three major mechanisms are involved in the generation of cirrhosis: cell death, aberrant extracellular matrix deposition (fibrosis), and vascular reorganisation. Fibrous septa connecting the portal tracts and hepatic veins form, leading to portovenous and arteriovenous shunting, and effective bypassing of the parenchymal nodules. This results in vascular thrombosis of the medium-sized and large portal veins and of the hepatic veins and the progression of parenchymal extinction to full-blown cirrhosis. Parenchymal extinction is the loss of continuous hepatocyte layers due to fibrosis of the parenchymal stroma (Wanless, 2002). In most cases, significant lesions are observed only after months or years of injury. However, they may appear more rapidly in congenital liver diseases, such as biliary atresia. Liver fibrosis is reversible, whereas cirrhosis is generally irreversible (Benyon & Iredale, 2000; Bioulac-Sage et al., 2000). Prevention of the progression of fibrosis to cirrhosis is therefore a major clinical goal. Unfortunately, current treatments of the underlying diseases responsible for liver damage are only partly successful in preventing this progression. The poor prognosis of cirrhosis is aggravated by the frequent occurrence of hepatocellular carcinoma, which may also develop, albeit much more rarely, in normal or only slightly fibrous livers.

The accumulation of extracellular matrix observed in fibrosis and cirrhosis is due to the activation of fibroblasts, which acquire a myofibroblastic phenotype. Myofibroblasts are absent from normal liver. They are produced by the activation of precursor cells, such as hepatic stellate cells (for review, see Lotersztajn, Julien, Teixeira-Clerc, Grenard, & Mallat, 2005). It has been suggested that liver fibrogenic cells are heterogeneous, as the portal fibroblasts present in portal tracts may also play a major role in liver fibrogenesis (Dranoff et al., 2002; Kinnman et al., 2003; Knittel et al., 1999b; Tang, Tanaka, Marumo, & Sato, 1994; Tuchweber, Desmoulière, Bochaton-Piallat, Rubbia-Brandt, & Gabbiani, 1996). In this review, we will identify the various fibrogenic cell subpopulations involved in liver fibrogenesis, and discuss the mechanisms underlying myofibroblastic differentiation and extracellular matrix deposition in various liver disease. Finally, we will evaluate the possibility of tissue remodelling, which may render fibrosis and cirrhosis reversible in some cases.

2. Definition of the myofibroblast

Inflammation occurs in response to tissue damage, with the formation of a provisional matrix favouring cell migration and proliferation in the lesion. Granulation tissue, facilitating the replacement of the injured tissue, then develops. This tissue displays fibroblast proliferation, angiogenesis, and extracellular matrix deposition. During tissue repair and granulation tissue formation, fibroblasts acquire the smooth muscle features characteristic of myofibroblasts (for review, see Serini & Gabbiani, 1999; Tomasek, Gabbiani, Hinz, Chaponnier, & Brown, 2002), the main cell type in granulation tissue. Myofibroblasts therefore appear to be a morphological and functional intermediate between fibroblasts and the smooth muscle cells. Myofibroblasts contain cytoplasmic bundles of microfilaments or stress fibres, which play a role in contraction, via mechanisms similar but not identical to those in smooth muscle cells. Myofibroblasts are surrounded by an irregular basal membrane, and are connected to each other by gap junctions and to the extracellular matrix by focal contacts called fibronexi—transmembrane complexes containing intracellular microfilaments in continuity with extracellular fibronectin fibrils (Eyden, 1993). Myofibroblasts are the main cellular type involved in extracellular matrix deposition during tissue repair, but they are also responsible for synthesising enzymes involved in matrix degradation, tissue remodelling, and scar formation.