The Origin of Myofibroblasts in Liver Fibrosis

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Abstract

Aim: To do a systematic review on origin of myofibroblasts in liver fibrosis.

Objective: To do a systematic review on origin of myofibroblasts in liver fibrosis by review of articles.

Background: Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases. Studies of fibrogenesis in the liver demonstrate that the primary source of the extracellular matrix in fibrosis is the myofibroblast. Hepatic myofibroblasts are not present in the normal liver but transdifferentiate from heterogeneous cell populations in response to a variety of fibrogenic stimuli. There are at least three potential sources of myofibroblasts in the liver:
1. Resident mesenchymal cells (consisting of the quiescent hepatic stellate cell and portal fibroblasts).
2. Hepatocytes, cholangiocytes and endothelial cells.
3. The bone-marrow derived cells.

Reason: Advanced liver fibrosis results in cirrhosis, liver failure and portal hypertension and often requires liver transplantation. It is considered that the hepatic cells and portal fibroblasts have fibrogenic potential which serves as a major origin of hepatic myofibroblasts. Therefore, identifying the origin of these myofibroblasts will provide insight into the pathology of liver fibrosis and perhaps into new therapeutic targets.

Key words: Myofibroblast, Liver, Fibrosis, Hepatic, Fibroblasts

INTRODUCTION TO LIVER FIBROSIS:
Liver fibrosis represents a major worldwide health care burden. It represents a significant health problem worldwide of which no acceptable therapy exists and not just that, liver fibrosis is a major cause of morbidity and mortality worldwide due to chronic viral hepatitis and more recently from fatty liver disease associated with obesity. Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases. Advanced fibrosis results in cirrhosis and is characterized by an accumulation of extracellular matrix (ECM) rich in fibrillar collagens (predominantly collagen I and collagen III). It results in liver failure and portal hypertension and is associated with an increased risk of liver cancer. Progressive liver fibrosis is the main cause of organ failure in chronic liver diseases of any etiology. The accumulation of ECM proteins distorts the hepatic architecture by forming a fibrous scar and the subsequent development of nodules of regenerating hepatocytes defines cirrhosis. Myofibroblasts are the cells which form the extracellular matrix (mainly Type-1 collagen fibres), which is responsible for the fibrous scar in liver fibrosis. Advanced liver fibrosis results in cirrhosis, liver failure and portal hypertension and often requires liver transplantation. It is considered that hepatic stellate cells and portal fibroblasts have fibrogenic potential and are the major origin of hepatic myofibroblasts. Therefore, identifying the origin of these myofibroblasts will provide insight into the pathology of liver fibrosis and perhaps into new therapeutic measures.

The main causes of liver fibrosis in industrialized countries include chronic HCV infection, alcohol abuse and nonalcoholic steatohepatitis (NASH).
Myofibroblasts
In that spirit, this review will focus on the concept that has recently emerged, which emphasizes the dynamic nature of liver fibrosis: the paradigm that liver myofibroblasts might arise from multiple cell lineages.8 Myofibroblasts are a unique group of smooth-muscle-like fibroblasts that have a similar appearance and function regardless of their tissue of residence or in other words they are alpha smooth muscle actin positive cells. Through the secretion of extracellular matrix proteins (including fibrillar collagen) and proteases, they play an important role in liver fibrosis and organogenesis, oncogenesis, inflammation repair in most organs and tissues. That produce extracellular matrix proteins. Myofibroblasts are the cells that are prominent in liver fibrosis.10,11 They are characterized immuno-phenotypically by a spindle or stellate shape, pale eosinophilic cytoplasm, expression of abundant pericellular matrix and fibrotic genes (vimentin, α-smooth muscle actin (α-SMA), non-muscle myosin, fibronectin and collagen Type I).10,11 Ultrastructurally, myofibroblasts are defined by prominent rough endoplasmic reticulum, a golgi apparatus producing collagen, peripheral myofilaments, fibronexus (no lamina) and gap junctions.11 In liver fibrosis, the myofibroblasts are imbedded in the fibrous scar. In both experimental and clinical liver fibrosis, there is a close correlation between the regression of liver fibrosis and the disappearance of these myofibroblasts. There is general fact that these myofibroblasts ultimately serve as the source of excessive extracellular matrix proteins in liver fibrosis. Therefore, identifying the origin of these myofibroblasts will provide information about the pathology of liver fibrosis and perhaps even about new therapeutic targets.

Origin of Myofibroblasts
The origin of myofibroblasts in liver fibrosis is still being debated, although morphologic evidence to date has suggested that these cells are derived from lipocytes (fat-storing cells, Ito cells).12 There are at least three potential sources of myofibroblasts in the liver:
1. Resident mesenchymal cells (consisting of the quiescent hepatic stellate cell and portal fibroblasts).
2. Hepatocytes, cholangiocytes and endothelial cells.
3. The bone-marrow derived cells.

1. Resident mesenchymal cells (the quiescent hepatic stellate cell and the tissue fibroblasts)
The resident mesenchymal cells, which mainly consists of the quiescent hepatic stellate cell and the tissue fibroblasts, can become myofibroblasts. These cells are characterized by cell markers like CD45−, CD34−, desmin+, glial fibrillar associated protein (GFAP)+ and thy-1+.13 Fibroblasts are primarily located in the portal tract in the normal liver. Recent studies14 had demonstrated that thy-1 is a potential marker of activated myofibroblasts in the injured liver. Many studies have demonstrated an overlap in experimental fibrosis between thy-1 and alpha smooth muscle actin, indicating that same myofibroblasts are derived from fibroblasts in liver fibrosis. Studies from other researchers have proposed that TE-7 (Human Thymic Fibroblasts Antibody), an antibody against elastin, specifically identifies fibroblasts in the liver.15,16 Generally in a normal liver, HSCs reside in the space of Disse and they are the major storage sites of vitamin A. Following chronic injury, HSCs activate or transdifferentiate into myofibroblast-like cells, acquiring contractile, pro-inflammatory and fibrogenic properties.17,18 Activated HSCs migrate and accumulate at the sites of tissue repair, secreting large amounts of ECM and regulating ECM degradation. Myofibroblasts derived from small portal vessels proliferate around biliary tracts in cholestasis-induced liver fibrosis to initiate collagen deposition19,13 HSCs and portal myofibroblasts differ in specific cell markers and response to apoptotic stimuli.20 Several markers have been proposed to be specific for hepatic stellate cells, whether in the quiescent or activated state. These include the florescence of Vitamin A in the lipid droplets, GFAP, p75 NGF receptor, and synaptophysin.21-23 Using these markers one should be able to distinguish between myofibroblasts that originate from fibroblasts or from hepatic stellate cells in experimental liver fibrosis.

2. Bone-marrow derived cells (fibrocytes and circulating mesenchymal cells)
Bone-marrow derived cells, consisting of fibrocytes and circulating mesenchymal cells, can also be recruited to the injured liver to become myofibroblasts. These cells are CD45+ (fibrocytes), CD45+/− (circulating mesenchymal cells), collagen type I+, CD11d+ and MHC class II+. Culture of CD34+CD38− hematopoietic stem cells with various growth factors has been shown to generate HSCs and myofibroblasts of bone marrow origin that infiltrate human livers undergoing tissue remodelling.24,25 These data suggest that cells originating in bone marrow can be a source of fibrogenic cells in the injured liver.

Figure 2: Origin of Myofibroblasts and cell markers12.
3. **Hepatocytes, Cholangiocytes, and Endothelial cells**

Recent studies have also proposed hepatocytes, cholangiocytes, and endothelial cells can become myofibroblast through epithelial or endothelial mesenchymal transition (EMT). These cells include CD45-, albumin+ (i.e. hepatocytes), CD45-, CK19+ (i.e. cholangiocytes) or Tie2+ (endothelial cells).\(^\text{13}\)

**CONCLUSION:**
From several published studies it can be concluded that in experimental models of liver fibrosis, most fibrogentic cells (myofibroblasts) are endogenous to the liver. It appears that the activated hepatic stellate cells and fibroblasts are the major endogenous fibrogenic cells that gives origin to myofibroblasts and result in liver fibrosis.

**REFERENCES:**