Review

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Adipocytokines and hepatic fibrosis

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Obesity and metabolic syndrome pose significant risk for the progression of many types of chronic illness, including liver disease. Hormones released from adipocytes, adipocytokines, associated with obesity and metabolic syndrome, have been shown to control hepatic inflammation and fibrosis. Hepatic fibrosis is the final common pathway that can result in cirrhosis, and can ultimately require liver transplantation. Initially, two key adipocytokines, leptin and adiponectin, appeared to control many fundamental aspects of the cell and molecular biology related to hepatic fibrosis and its resolution. Leptin appears to act as a profibrogenic molecule, while adiponectin has strong-antifibrotic properties. In this review, we emphasize pertinent data associated with these and other recently discovered adipocytokines that may drive or halt the fibrogenic response in the liver.

Focusing on fibrosis fat: a connection derived from endocrine function and hepatic dysfunction

Liver fibrosis (see Glossary) occurs as a consequence of acute or chronic liver injury. While hepatic fibrosis is reversible, deposition of dense extracellular matrix (ECM) is progressive in many chronic liver diseases. The consequence of progressive ECM deposition leads to histological cirrhosis, in which swirls of collagen and other ECM proteins surround functioning hepatocytes. Although functionally liver has extensive functional reserve(s), when normal hepatocyte function is significantly impaired (usually less than 20%), clinical cirrhosis, or end-stage liver disease (ESLD), can ensue, leading to portal hypertension and other clinical complications [1]. Cirrhosis places patients at considerable risk for the development of hepatocellular carcinoma (HCC) [2]. Although both palliative and supportive treatments are widely available, the definitive treatment of ESLD and many cases of HCC remains limited to liver transplantation (LT).

The primary cell associated with liver fibrosis is the hepatic stellate cell (HSC). In the early years of fibrosis research, conventional thought was that these cells originated from embryologic mesoderm [3]. Today, there is some degree of controversy concerning not only the origin of these cells, but also whether they are the result of epithelial-mesenchymal transition (EMT) [4], and whether there are subsets of these cells [5–7]. There are three broad components to the life cycle of the activated HSC: quiescence, activation, and perpetuation (Figure 1A).

In quiescence, the HSC is a storage depot for retinyl esters, has a low mitotic index, and lacks key proteins associated with cytoskeletal contraction. During the process of 'activation', a loosely defined term, the HSC becomes a myofibroblast-like cell. Characteristics of activated HSCs include a marked increase in mitotic rate, the loss of retinyl ester stores, and a spindle-like appearance under light microscopy [8]. The change in microscopic appearance is a consequence of a marked increase in both transcriptional and translational activation of cytoskeletal proteins, such as alpha smooth muscle actin (αSMA), and intermediate filaments (e.g., desmin) [9].

Fibrosis can be a perpetual pathophysiological condition, because activated HSCs present cell surface receptors for key cytokines, including platelet-derived growth factor (PDGF) and transforming growth factor β1 (TGFβ1) [10]. By both autocrine and paracrine stimulation, the activated HSC continues to proliferate and becomes characteristically resistant to apoptosis. These derangements best define the perpetuation phase. Activated HSCs can partially reverse phenotype, termed 'reversion' [11].

Glossary

Autocrine: the cell can not only secrete the agonist, but also has receptors for it and, thus, is responsive to the cytokines that it synthesizes.
Hepatic stellate cell (HSC): the principle cell that, following activation, is responsible for laying down ECM in the Space of Disse in the liver. The primary molecule is fibrillar collagen, or type I collagen. The activated HSC is also called a myofibroblast because its cytoskeleton has contractile (myo-) properties. A key marker of activation is detection of αSMA. In cirrhosis, these contractile properties are important for the development of portal hypertension.
Liver fibrosis: the excessive accumulation of extracellular matrix proteins, including type I collagen, that occurs as a result of chronic liver injury. Activated HSCs, portal fibroblasts, and myofibroblasts have been identified as major collagen-producing cells in the injured liver. These cells are activated by fibrogenic cytokines. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension, and often requires LT.
Myofibroblast: a term used to describe either the activated stellate cell, or cells found in the portal areas of the liver. Portal fibroblasts have similar functions but may be more involved in biliary tract diseases; they also do not express desmin but do express αSMA.
Nonalcoholic fatty liver disease (NAFLD): a spectrum of diseases that is characterized by the storage of free fatty acids, or triglyceride in hepatocytes. This is consistent with 'bland steatosis', meaning that fat storage does not induce inflammation or death.
Nonalcoholic steatohepatitis (NASH): a disease that is defined by progressive inflammation and injury to hepatocytes, as well as pericellular fibrosis, or 'chicken wiring'this seems to be a significant risk factor for developing cirrhosis and is associated in humans with higher cardiovascular risk.
Paracrine: the idea that, in liver Kupffer cells, resident macrophages in the liver secrete cytokines that affect nearby activated myofibroblasts to set off biochemical and cellular responses, in this case in myofibroblasts.

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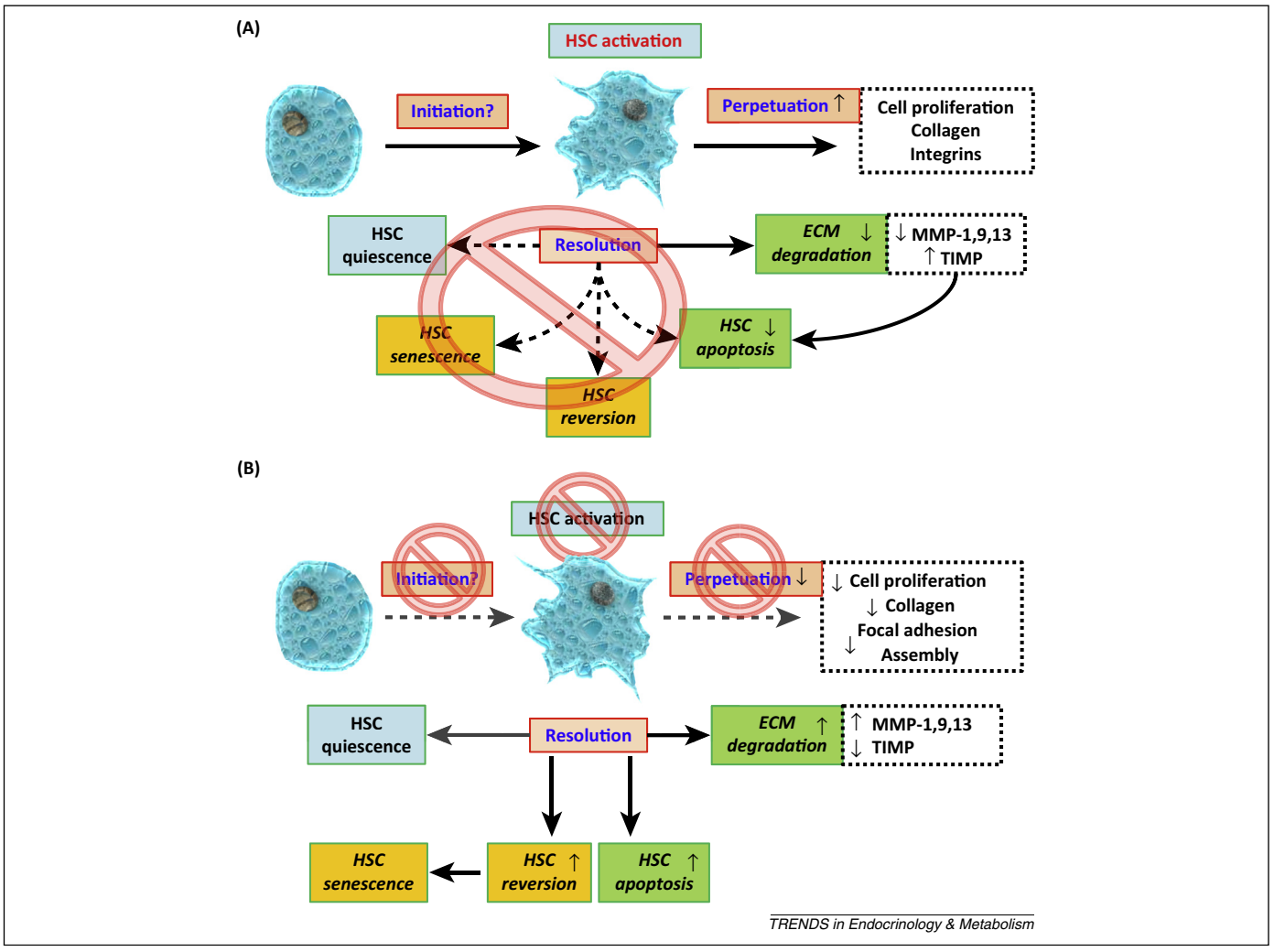

Figure 1. Role of leptin and adiponectin in liver fibrosis. **(A)** Leptin acts as a profibrotic adipocytokine in liver fibrosis. The profibrotic role of leptin is mediated via central effector cells of the liver, the hepatic stellate cells (HSCs). All the stages of liver fibrosis (initiation, perpetuation and resolution) are impacted by leptin. It modulates initiation of liver fibrosis by priming quiescent HSCs and transforming them to activated HSCs. In the later stage known as perpetuation, leptin maintains the activated HSC phenotype and increases HSC proliferation, impedes tumor necrosis factor alpha apoptosis-inducing ligand (TRAIL)-induced HSC apoptosis, and creates a molecular environment favorable for the net production of extracellular matrix (ECM). Leptin has also been attributed to inhibit the final stage of liver fibrosis (resolution). Leptin is known to inhibit the expression of matrix metalloproteinase 1 (MMP-1) and increases the expression and activity of tissue inhibitor of metalloproteinase I (TIMP-1), thereby inhibiting ECM degradation. Finally, leptin prohibits HSC phenotypic reversal or death. **(B)** Adiponectin is an antifibrogenic adipocytokine in liver fibrosis. Adiponectin can block leptin activity by inducing suppressors of cytokine signaling 3 (SOCS3); however, adiponectin has several properties that disengage the HSC and the fibrosis process, independent of other molecules. Adiponectin can induce HSC apoptosis and results in the loss of alpha smooth muscle (αSMA) proteins in HSCs. Still unknown is whether adiponectin pushes HSCs to partial reversion, or inactivation, or to senescence via a p53 mechanism. This mechanism has been reported to be critical to the resolution and inhibition of hepatic fibrosis from the HSC. Adiponectin also inhibits HSC proliferation and suppresses alpha collagen biosynthesis. Importantly, adiponectin inhibits the transcription and activity of TIMP-1. Conversely adiponectin increases transcription of MMP mRNA as well as increases, *in vitro*, the ability of MMP-1 to degrade fibrillar collagen in matrix. Adiponectin inhibits focal adhesion kinase (FAK) activity and disrupts formation of mature focal adhesions (FA).

Activated HSCs may undergo senescence, and others may fully revert back to a retinyl ester storage depot. Taken together, these fundamental changes in HSC biology, along with sensitization to apoptosis and the increased destruction of ECM by matrix metalloproteinases (MMPs), are collectively termed 'resolution' of fibrosis [12] (Figure 1).

Contributions to research in liver fibrosis research are in part due to the discovery of adipocytokines. Derived from white adipose tissue (WAT), adipocytokines, or adipokines, are secreted molecules with diverse biological functions. WAT has far-reaching effects in liver as well as in the immune and central nervous systems. Over the nearly two decades since leptin was first discovered [13], liver investigators have concluded that adipokines have a dynamic role in modulating control of ECM in liver [14,15]. Initially, these observations had little to do with nonalcoholic fatty liver disease (NAFLD). Rather, the discovery that leptin, and adiponectin in particular, were critical to fibrosis development and resolution, respectively, was observed in models designed to study liver fibrosis.

In this review, we provide insights into the primary adipocytokines [leptin, adiponectin, and plasminogen activator I (PAI-1)] that have established, well-defined roles in the pathophysiology of fibrosis and NAFLD-related pathology [16]. We also briefly review newly discovered adipocytokines. Table 1 provides a succinct review of major adipokines with their currently held respective contributions to hepatic fibrosis, while Table 2 provides take-home points related to established adipocytokines associated with liver fibrosis. In the broad field of digestive diseases,