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Cells in focus

Hepatic stellate cell: A star cell in the liver

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ABSTRACT

Hepatic stellate cells represent a highly versatile cytotype that plays a significant role in liver development and differentiation, regeneration, xenobiotic response, immunoregulation, control of hepatic blood flow and inflammatory reactions. Because of the wide panel of molecular intermediates they may produce and secrete, particularly after their sustained activation in a disease state, hepatic stellate cells are definitely involved in the pathogenesis of various liver pathologies, besides the well know key role in fibrosis and extracellular matrix remodelling. In particular, they can actively contribute to the progression of hepatitis and steatohepatitis of different aetiology, and of liver carcinogenesis.

Cell facts

- The most characteristic feature of resting hepatic stellate cells is vitamin A storage.
- Following activation by various stimuli, hepatic stellate cells acquire a myofibroblast-like phenotype.
- Hepatic stellate cells are key-players in the pathogenesis of liver fibrosis, inducing collagen deposition and abnormal extracellular matrix remodeling.

1. Introduction

Hepatic stellate cells (HSC) appear to possess a vital trait in evolutionary terms, since detectable even in primitive vertebrates. Stellate cells approximately account for 5–8% of total cells in normal liver. They are located in the perisinusoidal space of Disse, in between the fenestrated endothelium of sinusoids and the hepatocytes, with a higher frequency in the periportal area than centrilobularly. Under physiological conditions, HSC show a moderately developed rough endoplasmic reticulum, a small Golgi complex, and long cytoplasmic processes that wrap around sinusoids in the space of Disse. These processes exhibit numerous micro-projections that serve as sensors for transmission of chemotactic signals. In addition, stellate cells are in direct contact with nerve endings, confirming their neuro-humoral interactions (Giampieri et al., 1991; Wake, 1995).

These cells have been first described by Kupffer in 1876 and termed “sternzellen”. Only in 1996, after 120 years of various histological characterization under many different names, such as perisinusoidal cells, parasinusoidal cells, hepatic pericytes, lipocytes, fat storing cells, Ito cells, investigators agreed to call them “hepatic stellate cells”.

The main morphological feature of HSC in normal liver is the presence of cytoplasmic droplets containing vitamin A as retinyl palmitate. The number of droplets varies with the location of stellate cells in the hepatic lobule and the abundance of vitamin A stores. In response to liver injury, HSC loose vitamin A droplets and undergo significant morphological and functional changes, a complex process defined as “activation”, leading to the acquisition of a myofibroblast-like cell phenotype and to excessive production of collagen, mainly of type I.

2. Cell origin, plasticity and activation

The embryological origin of HSC is still debated. Recent experiments support their origin from either endoderm or septum trasversum. In support of an endodermic origin is the finding of a transient expression of the same cytokeratins of hepatoblasts (Suskind and Muench, 2004). In support of a mesodermal origin, common to smooth muscle cells (SMC), is the fact that undifferentiated fetal HSC express α-smooth muscle actin (SMA), an early marker of SMC differentiation but do not store yet vitamin A (Gerts, 2004).

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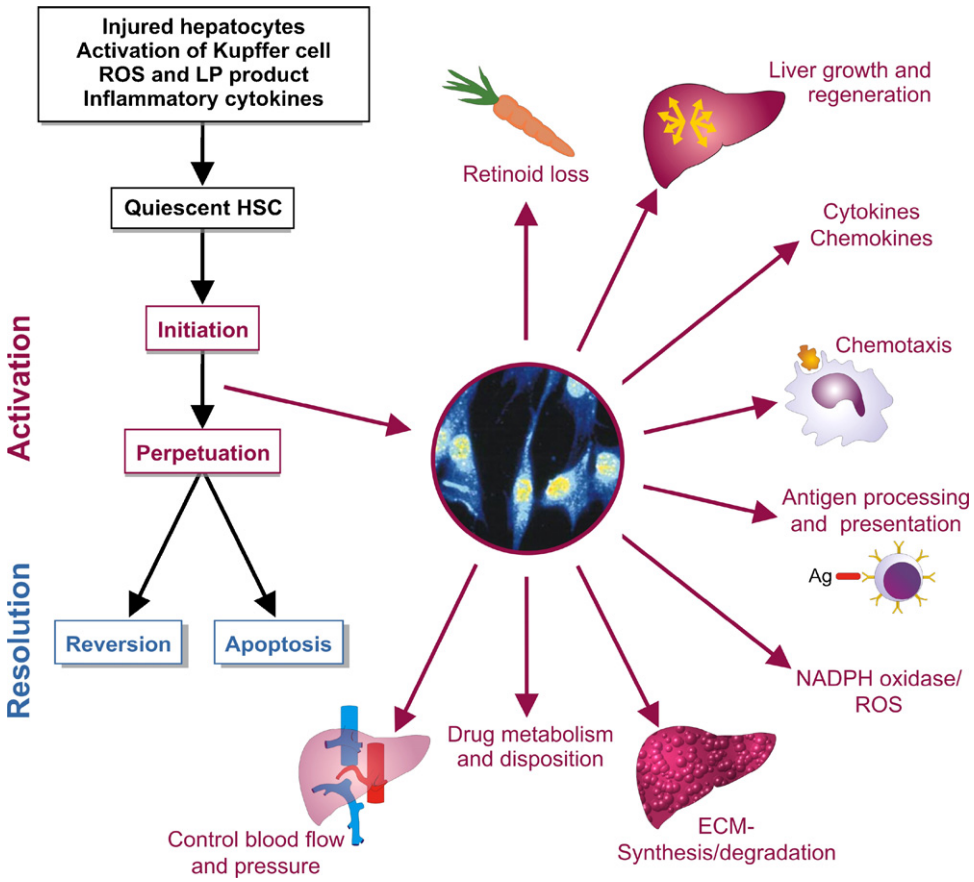

Fig. 1. Pathways of HCS activation and functions. A laser confocal microscopy picture of human hepatic stellate cells is shown. In response to injury, quiescent hepatic stellate cells undergo activation and become proliferative, contractile, and fibrogenic cells acquiring a myofibroblast-like phenotype. Factors released by activated hepatic stellate cells and by the surrounding environment may lead to either perpetuation or resolution of the process, the latter one achieved through reversion to a quiescent phenotype or apoptotic death. The great variety of biochemical effects exerted by activated hepatic stellate cells are depicted. ROS: reactive oxygen species; Ag: antigen; ECM: extracellular matrix.

Stellate cells can be found within the progenitor cell niche in normal and regenerating liver, near the intrahepatic bile ductules. Moreover, the demonstrated expression of the stem cell marker CD133 by a subset of HSC led to propose these cells as progenitors not only of liver myofibroblasts but also of hepatocytes and bile duct epithelial cells (Kordes et al., 2007).

Analysis of cytoskeletal and cell surface markers has demonstrated a certain degree of heterogeneity and plasticity of HSC in adult liver, depending on actual location in the hepatic lobule, animal species, type of tissue considered, either normal or injured. For instance, desmin, an intermediate filament typical of contractile cells is present in rodent, but not in human HSC (Kiassov et al., 1995). Further, a significant fraction of resting stellate cells is detectable which lacks vitamin A droplets.

Activation of quiescent HSC and subsequent differentiation into myofibroblast-like cells is very reliably indicated by the expression of α-smooth muscle actin, an actin isoform which is absent in the other resident liver cells in either normal or injured liver, with the exception of smooth muscle cells surrounding large vessels (Rubbia-Brandt et al., 1997). Differentiated HSC also express several other marker genes that are in common with smooth muscle cells, like smooth muscle myosin heavy chain, calponin and myocardin (Wirz et al., 2008). But, activated HSC still differ from myofibroblasts and smooth muscle cells, both *in vitro* and *in vivo*, for their vitamin content, contractile activity, and relative responsiveness to cytokines, particularly to transforming growth factor-β1 (TGF-β1) (Ramadori and Saile, 2002). Further, the gene expression pattern of HCS keeps evolving, during the cell life, with eventual acquisition of a more inflammatory but less fibrogenic phenotype.

Many of the available data on activation of this peculiar cytotype were first obtained using stellate cells isolated from either human of rat liver then cultivated on plastic dishes. Unfortunately, the plastic substrate was per se leading to a number of cellular changes all taken as expression of cell activation. Importantly, HSC primary culture on a gel matrix as well as human and rat stellate cell lines have nowadays provided a more reliable *in vitro* model where to mimic and understand as much as possible the actual dynamic properties that this kind of cell shows *in vivo*.

3. Functions

As schematically depicted in Fig. 1, increased steady-state levels of reactive oxygen species (ROS) and lipid peroxidation products or other molecules stemming from neighbouring cells, like activated Kupffer cells and sinusoidal endothelial cells or injured hepatocytes may initiate quiescent HSC to a functionally active state, first of all characterized by cell proliferation and increased responsiveness to a variety of paracrine stimuli through the up-regulation of specific plasmamembrane receptors. Functional state may then develop (perpetuation) being sustained by cell–cell and cell-extracellular matrix interactions with the expression of different activities, whose the most eminent and studied one is certainly the enhancement of fibrogenesis. As supported by *in vitro* evidence, active HSC could revert to a quiescent state once the applied stimuli have subsided, but this event has still to be confirmed *in vivo*.