Review

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Sinusoidal communication in liver fibrosis and regeneration

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Summary

Cellular crosstalk is a process through which a message is transmitted within an individual cell (intracellular crosstalk) or between different cells (intercellular crosstalk). Intercellular crosstalk within the liver microenvironment is critical for the maintenance of normal hepatic functions and for cells survival. Hepatic cells are closely connected to each other, work in synergy, and produce molecules that modulate their differentiation and activity. This review summarises the current knowledge regarding paracrine communication networks in parenchymal and non-parenchymal cells in liver fibrosis due to chronic injury, and regeneration after partial hepatectomy.

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Review

Key point

Liver cells, mainly LSEC, KC, HSC and Hepatocytes readily interact each other, thus conforming a highly efficient signalling network that maintains sinusoidal homeostasis.

Introduction: Liver sinusoidal cells and cellular crosstalk

The hepatic sinusoid represents a well-organized vascular matrix that provides the structural and biochemical environment in which non-parenchymal liver cells live and communicate. The space of Disse separates sinusoidal cells from parenchymal cells and contains extracellular matrix (ECM) components. Thus, the liver microenvironment can be described as a multidirectional interaction complex (cell-matrix-cell) organized to manage the delivery of molecular signals, where every piece has a crucial role. It is due to this particular structure that hepatic cells, composed mainly of hepatocytes, liver sinusoidal endothelial cells (LSEC), hepatic stellate cells (HSC), and Kupffer cells (KC), precisely "talk" to each other.

The word crosstalk was firstly used in electronics and technology communication to explain any phenomena by which a signal transmitted on one circuit creates an undesired effect in another circuit. In biomedical science we do not view this phenomenon as undesired but consider it a mechanism cells have to transmit "instructions" both in physiological and pathophysiological situations. In the latter scenario instructions are considered as transmitted errors, and are therefore an event or multi-events that could be considered as biological targets.

LSEC, the hepatic cell population that interfaces blood components and forms the barrier of sinusoids, are pivotal regulators of the liver microcirculation and have a key role in sinusoidal crosstalk. Their peculiarities (small cells with non-diaphragmed fenestrae and without a basement membrane) make them a vital link in the complex network of hepatic cellular interactions both in health and disease. Fenestrae, arranged in sieve plates, contribute to LSEC permeability and functions [1], facilitating oxygenation of hepatocytes and enhancing hepatocytes exposure to macromolecules from the portal circulation. They are capable of contracting or dilating, can change in size, porosity (number of fenestrae per μm^2), and frequency, acting like a filter for the transit of substances. Modifications in fenestrae properties, a process known as pseudo-capillarization, are associated with aging and hypoxia [2,3], while capillarization (complete loss of fenestrae) [4] seems to precede the development of most chronic liver diseases [5,6]. Note that the crude term "capillarization" in this specific context means that the unique and highly specialized phenotype of LSEC is lost and cells become ordinary non-specialized endothelial cells, or endothelial cells of an ordinary capillary.

LSEC are the main source of the endothelium-derived nitric oxide (NO), an important modulator of vascular tone, where it is produced by the endothelial nitric oxide synthase (eNOS).

Moreover, LSEC express singular sets of adhesion molecules that correlate with the micro-environmental characteristics of the sinusoidal wall [7]. These adhesion molecules include ICAM-1 (Intercellular Adhesion Molecule 1), VCAM-1 (vascular cell adhesion molecule 1), and selectins, are regulated by inflammatory cytokines, and influence cell-to-cell interactions [8]. Interestingly, LSEC phenotype is maintained, at least in part, by paracrine secretion of vascular endothelial growth factor (VEGF) by hepatocytes and HSC [9].

HSC, localized in the space of Disse, are the main collagen-synthesizers of the liver [10], and contribute to its architecture and functions by interacting with neighbouring cells [11]. They provide retinoid storage and homeostasis, ECM metabolism, and sinusoidal lumen diameter [12]. A single stellate cell can wrap up to 4 sinusoids and regulate sinusoidal blood flow by contraction. Injuries to the hepatic microvasculature activate the trans-differentiation of HSC conferring them a proliferative and fibrogenic myofibroblast-like phenotype. HSC activities mainly depend on their interactions with ECM components, endothelial cells and hepatocytes [11,13].

KC are hepatic macrophages that have an essential role in the liver immune system [14] and inflammation [15]. They are attached to the sinusoidal endothelial layer, where they uniquely capture signals from the blood and contribute to hepatic blood flow regulation [16]. They are mainly the source rather than the target of soluble mediators [14], eliciting a physiological response to all other liver cells.

Hepatocytes represent the most abundant cell type within the liver and, although they are the major functional hepatic cells, their interactions with sinusoidal cells are totally necessary for their multiple activities. While consequences of endothelial capillarization and HSC phenotype dysregulation on liver function are well characterised, the exact process of hepatocyte dysfunction in chronic liver disease is not completely known. Indeed, the liver can function normally with less than half of its hepatocytes, although they have the unique ability for continuous turnover and replenishment [17].

As a consequence of parenchymal and non-parenchymal interactions, cells grow, proliferate, migrate and differentiate, preserving their normal cellular phenotype. In this interactive network, healthy or injured cells become the positive or negative regulators of the closest neighbouring cells (via juxtacrine signalling and receptor-ligand complexes or through indirect contact), or of the hypothetically most distant cells (via a variety of soluble paracrine and endocrine factors, such as cytokines, growth factors, second messengers and hormones) (Table 1). In this regard, ECM is considered a depository for growth factors, cytokines and other proteins that can be released when required to be used by proximal cells, contributing to cellular programming [18,19]. Understanding the intercellular crosstalk within the sinusoids is critical for a better knowledge of the progression, aggravation, and resolution of liver disease, and modifications in the coordinated interactions may lead to disease development/improvement.

Sinusoidal crosstalk in fibrosis, cirrhosis and portal hypertension

Fibrosis is characterised by intra-hepatic accumulation of ECM, mainly in the perisinusoidal space of Disse and portal tracts [20]. The formation of abnormal nodules with consequent distortion of the liver architecture, inflammation, vascular occlusion, and intra-hepatic angiogenesis aggravate the fibrotic state leading to the development of cirrhosis [21]. Alterations in the normal crosstalk cause progressive microvascular dysfunction in the cirrhotic liver, increase in hepatic vascular resistance and development of the main complication of cirrhosis, portal hypertension [22]. All sinusoidal cells take part in this process: they communicate and acquire a vasoconstrictor phenotype that is further exacerbated in response to biomechanical, pathogenic and inflammatory stimuli [23,24]. However, our understanding of the mechanisms underlying the changes in phenotype of sinusoidal cells and the divergent cellular communication during cirrhosis progression is far from complete. Unfortunately, the only treatment for end-stage cirrhosis is transplantation [25], and the need to develop anti-fibrotic compounds is a must.

Liver fibrosis is initiated by crosstalk from LSEC and Hepatocytes

The fibrogenic reaction is initiated by two major intercellular crosstalk pathways that are ultimately connected. In the presence of hepatic injury, LSEC become rapidly dysregulated and start de-differentiation towards a capillarized phenotype. This is accompanied by the production and release of soluble factors that rapidly travel to neighbouring cells affecting their phenotype [26]. As an example, it has been demonstrated that LSEC-derived fibronectin affects HSC phenotype, promoting their activation [27]. In parallel, exogenous hepatic injury significantly modifies hepatocytes transcriptional programs promoting their proliferation and death. Hepatocyte apoptosis results in the formation of apoptotic bodies that once captured by the non-parenchymal cells (HSC and KC) contribute to their activation [17,28,29]. In turn, HSC begin

Abbreviations: ECM, extracellular matrix; LSEC, liver sinusoidal endothelial cells; HSC, hepatic stellate cells; KC, Kupffer cells; eNOS, endothelial nitric oxide synthase; VEGF, vascular endothelial growth factor; α-SMA, alpha-smooth muscle actin; KLF2, kruppel-like factor 2; PMF, portal myofibroblast; BM SPC, bone marrow-derived endothelial sinusoidal progenitor cells.

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