Disse (Space of Disse)

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Space of Disse: a thin perisinusoidal area between the endothelial cells and hepatocytes filled with blood plasma, nutrients and oxygen, but also debris from our organism, that have acquired great importance in liver disease

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1. Introduction

The space of Disse is home for the hepatic stellate cells (HSCs), the major fibrogenic players in the liver. Quiescent HSCs (qHSCs) store vitamin A, and upon activation they lose their retinol reservoir and become activated. Activated HSCs (aHSCs) are responsible for secretion of extracellular matrix (ECM) into the space of Disse. This early event in hepatic injury is accompanied by loss of the pores—known as fenestrations—of the endothelial cells, triggering loss of balance between the blood flow and the hepatocyte, and underlies the link between fibrosis and organ dysfunction. If the imbalance persists, the expansion of the fibrotic scar followed by the vascularized septae leads to cirrhosis and/or end-stage hepatocellular carcinoma (HCC).

2. Involvement of the Space of Disse in Liver Disease

Liver fibrosis is a common outcome generated as result of chronic liver injury including viral hepatitis infection, alcohol abuse, metabolic disorders, metabolic-associated fatty liver disease/metabolic-associated steatohepatitis (MAFLD)/MASH and other rare diseases including autoimmune hepatitis (AIH)[1]. The self-protective behavior of the body allows fighting pathogenic factors that can limit damage, regressing early-stage fibrosis when its origin is eliminated. However, advanced fibrosis can progress into more severe stages, like cirrhosis, with irreversible damage to the liver and end-stage HCC[1][2][3]. Due to the relevance in the number of deaths associated to cirrhosis worldwide, affecting between 1% and 2% of global population with more than 1 million deaths per year[4][5], many studies focused on understanding the molecular mechanisms that drive HCC, but also establishing efficient diagnostic and therapeutic strategies. Animal models have been used combined with diets, chemical compounds, surgical approaches or viral infections to mimic the stages in an injured liver, although efforts to relate those stages with the human pathologies are still far from complete. Several reports classified the different in vivo models based on the compound used for the treatment[1][6][7].

2.1. Hepatotoxicity

2.1.1. Drug-Induced Liver Injury (DILI)

DILI remains the most common cause of acute liver failure in the Western world, associated with drug abuse and herbal medicines or other xenobiotics that lead to liver failure.

After uptake by hepatocytes, drugs are metabolized by phase I and phase II enzymatic reactions. After phase I reactions, the metabolites have minor modifications but still can have very different pharmacological actions[8]. Phase II metabolism involves the conjugation of a drug or metabolite with endogenous molecules such as glucuronic acid, sulfate or glutathione resulting in a more polar product that usually does not have pharmacological activity. Drugs and metabolites efflux from hepatocytes into the bile or back into the sinusoidal blood for subsequent renal excretion, which is mediated mainly by ATP-binding cassette (ABC) transporters such as multidrug resistance protein 1 (MDR1), also called P-glycoprotein, which is encoded by ABCB1, and anion exchange mechanisms[8]. The mechanism of action of DILI is a complex interplay between different organelles: mitochondrial dysfunction and endoplasmic reticulum (ER) stress associated with immune cell-derived inflammation. Mitochondrial oxidative stress and membrane permeability transition (MPT) combined with inhibition of the mitochondrial electron transport lead to cell death and release of DAMPs to the milieu. Furthermore, the metabolization of drugs increases reactive oxygen species (ROS) production that causes dysregulation of Ca^{+2} and activation of the unfolded protein response (UPR). If the programmed mechanisms in the cell

cannot alleviate ER stress, the cell is programmed for apoptosis. Cell death and DAMPs induce infiltration of immune cells, expression of pro-inflammatory cytokines, activation of HSCs via TGF-β, and deposition of ECM in the space of Disse.

2.1.2. Alcoholic Liver Disease (ALD)

Alcohol consumption is a worldwide cause of chronic liver disease and results in approximately 3 million deaths each year (5.3% of all deaths) with most of them associated with ALD[9]. ALD starts with hepatic steatohepatitis that can progress into fibrosis and later cirrhosis. Perivenular fibrosis that extends outward along the sinusoids and accumulation of ECAM is primarily observed in the space of Disse. Because this pericellular or perisinusoidal fibrosis extends outward, it shows a classic chicken-wire fence pattern, sometimes all the way to the portal tract. Chronic ethanol consumption upregulates cytochrome P450 2E1 (CYP2E1); thus, ROS are generated triggering a proinflammatory response and activation of HSCs. However, alcohol also disrupts the microbiota in the gut, leading to an increase in the bacterial products to the portal circulation and activation of KCs by the TLR4 and expression of inflammatory mediators like TGF-β, that also activates HSCs via SMAD pathway[10]. These mechanisms lead to hepatocytes apoptosis, inflammation and ECM deposition by HSCs.

2.1.3. NAFLD/MAFLD and NASH/MASH

Obesity is a strong risk factor for the development of metabolic syndrome (MS) and is associated with insulin resistance (IR) and type 2 diabetes (T2D) as well as non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), recently re-termed as metabolic-associated fatty liver disease (MAFLD)/metabolic-associated steatohepatitis (MASH)[11]. Dietary lipids are stored in hepatocytes leading to loss of function of the hepatocytes and protein unfolding thus activating the ER stress pathways. As a result, hepatocytes are unable to function properly and undergo cell death. The release of intracellular content to the milieu, DAMPs, recruits immune cells to the space of Disse and expression of pro-inflammatory cytokines. TGF-β activates HSCs via SMAD2/SMAD3/SMAD4 inducing the deposition of ECM[12]. Importantly, in adult steatohepatitis-related fibrosis, ECM is deposited primarily in the zone three perisinusoidal space of Disse, and then spreads to surround hepatocytes and thicken the space of Disse; forming characteristic “chicken-wire” fibrosis (see ALD section). Eventually, the pericentral fibrosis forms septa to isolate regenerating nodules[13][14].

2.1.4. Portal Hypertension

During the development of chronic liver disease, hepatic cell types suffer intense modifications in their phenotype that ultimately lead to liver microvascular dysfunction, increased intrahepatic vascular resistance (IHVR) and portal hypertension. It appears to have two major mechanisms for IHVR progression: a profound alteration in liver architecture (structural component) and a pathological increase in the hepatic vascular tone (dynamic component) [6]. The structural component greatly contributes to fibrogenesis (exaggerated ECM deposition), disorganized regenerative nodules (non-neoplastic nodules with surrounding fibrosis), vascular occlusion and sinusoidal capillarization (de-fenestration of the LSECs). For the dynamic component, contractile elements influencing the hepatic vascular bed include sinusoidal and extra-sinusoidal cells, such as HSCs and vascular smooth muscle cells, which compress sinusoids, regenerative nodules and venous shunts in response to vasoactive molecules[6]. Furthermore, LSECs and KCs, actively contribute to the dynamic component of IHVR by promoting the production of vasoconstrictors and having reduced capacity to produce or respond to vasodilators. These changes profoundly affect the hepatic vascular tone of the fibrotic liver. However, there is an extrahepatic contributor as well, the splanchnic vascular bed[15]. Several reports showed that elevation in splanchnic blood flow and reduced splanchnic arteriolar resistance lead to chronic elevations in portal pressure and hyperdynamic systemic circulation with high cardiac index and low systemic arterial resistance[6][16][17][18][19][20][21].

2.1.5. Chronic Cholestatic Liver Diseases

Chronic cholestatic liver diseases including primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are associated with active hepatic fibrosis, and ultimately cirrhosis. The progressive structural damage of the intrahepatic biliary three leads to cholestasis, which has been traditionally considered an important pro-fibrogenic factor[22]. In experimental models of cholestasis, fibrogenic markers like TIMP-1, α-SMA, collagen 1 and TGF-β, and accumulation of B-cells and T-cells in the portal tracts generate ROS and liver damage[23].

2.2. Liver Regeneration

The liver is the only visceral organ that possesses the capacity to regenerate after surgical removal or chemical injury. Regeneration is a complex process that relies on the proliferation of hepatocytes and non-parenchymal cells after loss of liver mass, although hepatic progenitor cells (HPCs) appeared to have an important function in regeneration too. HPCs differentiate into bile duct cells and hepatocytes after a severe liver injury. However, the origin and function of HPCs after

liver injury is not well-established and their ability to participate in liver regeneration is far from clear[24]. Traditionally, regeneration is an orchestrated mechanism that combines three phases: the priming phase, where HPCs activate more than 100 genes in response to cytokines like TNFα and IL-6, the proliferation phase, where HPCs respond to growth factors (TGF-α) moving to mitosis and termination phase, with inhibition of proliferation of HPCs controlled by TGF-β and activin. Several pathways are involved in the activation and proliferation of HPCs like Wnt pathway, Notch pathway, NFκB pathway and PI3K/AKT pathway among others (reviewed in[25]). Vascularization is very important for liver regeneration, and HSCs seem to be a major role for this phenomenon. Proliferation of HSCs and their interaction with LSECs allow neovascularization during regeneration [26].

ECM degradation is another step crucial for regeneration; while Col I and III do not change their expression, Col IV, fibronectin and laminin increases their expression after partial hepatectomy (PHx). Several models showed that deficient and uncontrolled HSCs activation impairs liver regeneration. Therefore, a precise HSCs response may be an important factor to guarantee a satisfactory regeneration [26].

However, the conditions after PHx are not the same as in an injured liver. Inflammation, activated immune cells, hepatocyte death and fibrosis are some of the characteristics after chronic liver disease. It seems that liver fibrosis progression is related with liver regeneration failure and subsequently, hepatocyte proliferation impairment. Several mechanisms (cytokine production[27] or deficiency EGFR pathway[28]) tried to explain this lack of proliferation in a NAFLD/MAFLD model, but hepatocytes had abnormal oxidative stress that was rescued when mice were treated with antioxidants[29].

2.3. Progression from Fibrosis to Cirrhosis

Chronic liver disease is associated, usually, with injury and death of hepatocytes among other cell types, and activation of an immune response leading to inflammation, also called hepatitis. While this stage is reversible, progression to further stages like cirrhosis is not. In the last decade, a lot of effort has been made in order to develop novel anti-fibrotic strategies to minimize the progression of liver fibrosis and accelerate fibrosis resolution. All the strategies are based on the inactivation or death of HSCs, the main source of ECM deposition. TRAIL-mediated and TNFα-mediated apoptosis of HSCs, expression of MMP by restorative Ly6C^{low} monocytes and interferon (IFN)γ by NK cells or ER stress are some directions that seem to improve fibrosis resolution[1][30][31]. Nevertheless, cells stay in a stage that predisposes them to reactivate into myofibroblast, after a local stimulus, developing a more severe stage of fibrosis[32]; thus, full recovery cannot be achieved and more studies have to be developed to address this issue.

A fibrotic liver may progress to cirrhosis, irreversible stage that is characterized for hardening of the liver, where normal tissue is replaced by scar tissue and nodule formation of the liver. The normal flow of blood through the liver is impaired, leading to an increase in death of hepatocytes and finally, a loss of function of the liver. Vascularized fibrotic septa links portal tracts with central veins surrounding by hepatocytes islands, increasing intra-hepatic resistance (portal hypertension) and the development of HCC[33]. Although the mechanism of action is different for every disease, the impairment of resolving fibrosis and the excessive production of ROS and pro-inflammatory cytokines lead to an overactivation of HSCs that finally triggers higher ECM deposition[33].

2.4. Hepatocellular Carcinoma (HCC)

HCC is the fourth most common cause of cancer-related death worldwide and the chance of potentially curative treatment and surveillance is based on early detection; however, incidence and cancer-specific mortality still continue to increase in many countries. Early-stage HCC can be treated curatively by local ablation, surgical resection or liver transplantation although the majority of HCC patients still present at an advanced stage in many parts of the world [34].

Development of HCC is a multifaceted process that involves continued inflammatory damage, hepatocyte death and lack of regeneration, associated with ECM deposition. HCC has an enormous molecular heterogeneity due to the accumulation of somatic genomic alterations in passenger and driver genes in addition to epigenetic modifications. Risk factor like tobacco, diabetes or infection with HIV are associated with development of HCC; although the promotion to healthy life habits may reduce the risk of progression to HCC, it is increased when cirrhosis is established[35].

2.5. Hemochromatosis

Hemochromatosis is a clinical condition associated with an abnormal deposition of iron causing several organ dysfunctions. Although iron absorption in the body is quite controlled, the excess of iron accumulation inside the cells disrupts their function, leading to an organ failure. Hereditary hemochromatosis is the most common autosomal recessive disorder in whites and is associated with mutations of: hemochromatosis (HFE) gene, hepcidin, the hormone associated

with iron absorption in the cells, transferrin transporter-2 or ferroportin. However, there is another second type of hemochromatosis that appears to be related with iron deposition in damaged tissue or due to the presence of excessive iron in the body because of continuous transfusions or iron administration in disease like anemia or thalassemia. Basically, the excess of iron deposition inside the cells is controlled by hepcidin that binds up and induces degradation of ferroportin transporter. Thus, hepcidin concentrations are inversely correlated with iron absorption. Co-regulators of hepcidin synthase are related with SMAD4, a member TGF-β superfamily. TGF-β activates HSCs leading to ECM deposition and fibrosis, and, finally, liver failure[36][37].

2.6. Other Diseases Related with the Space of Disse

Hepatic sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease (VOD), is an obliterative venulitis of the terminal hepatic venules, which in its more severe forms imparts a high risk of mortality. This pathogenic event leads to the destruction of the LSECs, with sloughing and downstream obstruction of terminal hepatic venules. Glutathione and NO depletion, increased expression of MMPs and vascular endothelial growth factor (VEGF) and expression of clotting factor are some features that contribute to SOS. Hematopoietic stem cells transplantation has become the most important and frequent cause of SOS[38].

Several mice models, with diets and drug treatments, studied the progression of SOS in the liver. The sinusoid is eventually obstructed and aggregation of LSECs, red blood cells and adherent monocytes. KCs are replaced by phagocytic infiltrated monocytes which accumulate in the injured centrilobular area. Increased expression of MMP-9 into the space of Disse leads to a breakdown of ECM and further loss of LSECs fenestrae. Absorption of oxygen and nutrients from hepatocytes is impaired and leads to cell death. Thus, inflammation activates HSCs that start the deposition of ECM, hardening the liver and impeding its function[39].

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