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Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
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Baishideng Publishing Group Inc
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Pleasanton, CA 94588, USA
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Fax: +1-925-2238243
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REVIEW

Embrionary way to create a fatty liver in portal hypertension

Maria-Angeles Aller, Natalia Arias, Isabel Peral, Sara García-Higarza, Jorge-Luis Arias, Jaime Arias

Maria-Angeles Aller, Isabel Peral, Jaime Arias, Department of Surgery, School of Medicine, Complutense University of Madrid, 28040 Madrid, Spain

Natalia Arias, UCL Division of Medicine, Institute for Liver and Digestive Health, London NW3 2PF, United Kingdom

Sara García-Higarza, Jorge-Luis Arias, Laboratory of Neuroscience, Department of Psychology, University of Oviedo, 33003 Asturias, Spain

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Correspondence to: Maria-Angeles Aller, MD, PhD, Department of Surgery, School of Medicine, Complutense University of Madrid, Plaza de Ramón y Cajal s.n., 28040 Madrid, Spain. maaller@med.ucm.es
Telephone: +34-91-3941388
Fax: +34-91-3947115

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Abstract

Portal hypertension in the rat by triple partial portal vein ligation produces an array of splanchnic and systemic disorders, including hepatic steatosis. In the current review these alterations are considered components of a systemic inflammatory response that would develop through three overlapping phenotypes: The neurogenic, the immune and the endocrine. These three inflammatory phenotypes could resemble the functions expressed during embryonic development of mammals. In turn, the inflammatory phenotypes would be represented in the embryo by two functional axes, that is, a coelomic-amniotic axis and a trophoblastic yolk-sac or vitelline axis. In this sense, the inflammatory response developed after triple partial portal vein ligation in the rat would integrate both functional embryonic axes on the liver interstitial space of Disse. If so, this fact would favor the successive development of steatosis, steatohepatitis and fibrosis. Firstly, these recapitulated embryonic functions would produce the evolution of liver steatosis. In this way, this fat liver could represent a yolk-sac-like in portal hypertensive rats. After that, the systemic recapitulation of these embryonic functions in experimental prehepatic portal hypertension would consequently induce a gastrulation-like response in which a hepatic wound healing reaction or fibrosis occur. In conclusion, studying the mechanisms involved in embryonic development could provide key results for a better understanding of the nonalcoholic fatty liver disease etiopathogeny.

Key words: Inflammation; Non-alcoholic fatty liver disease; Hepatic steatosis; Extraembryonic functions; Fibrosis; Portal hypertension

Core tip: The current hypothesis proposes that the re-expression of two embryonic systemic functional axes in the rat after partial portal vein ligation produces a non-alcoholic fatty liver disease. These axes, a coelomicamniotic axis and a trophoblastic yolk-sac or vitelline axis, would then integrate in the interstitial liver space of Disse. If so, these recapitulated embryonic functions would produce firstly, the evolution of liver steatosis. In this way, this fat liver could represent a yolk-saclike in portal hypertensive rats. After that, these embryonic functions would induce a gastrulation-like response in which liver fibrosis occcur. For that reason, studying the mechanisms involved in embryonic development could provide key results for a better understanding of the non-alcoholic fatty liver disease pathophysiology.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a pathological condition derived from a wide spectrum of liver damage[1-3]. NAFLD covers from nonalcoholic fatty liver (NAFL) to nonalcoholic steatohepatitis (NASH). While NAFL is characterized by hepatic steatosis without hepatocellular injury such as ballooning of the hepatocytes, NASH condition shows hepatic steatosis, inflammatory state accompanied with hepatocyte injury and ballooning, with or without fibrosis[4]. Although NAFLD is strongly associate with obesity, diabetes mellitus and dyslipidemia, its pathogenesis remains poorly understood and therapeutic options are limited[3,4].

The concept that this range of related hepatic disorders is an evolutive inflammatory condition could simplify the integration of the different etiopathogenic mechanisms involved in each one of its evolutive phases. Even, NAFLD has been already considered like the hepatic manifestation of a systemic auto-inflammatory disorder[5]. The earliest inflammatory phase of NAFLD consists in hepatic steatosis, which is characterized by the deposition of triglycerides inside of hepatocytes[3]. This early evolutive period of the disease is usually clinically silent, which is why its clinical diagnosis is delayed and why it is difficult to identify the risk contribution of the splanchnic and systemic etiopathogenic factors[2].

Using experimental liver steatosis models can be very useful to prevent this gap in etiopathogenic knowledge during the early phase of this disease[6,7]. Therefore, the partial portal vein ligation of the rat can be considered one of the experimental surgical models of hepatic steatosis[8]. We have shown an increase in tryglicerides, diacylglicerol and cholesterol in the liver of these animals, together with a microvesicular hepatocytic fatty infiltration. Moreover, the presence of megamitochondria at short (1 mo) and long-term (1 year)[8-10] has been found. Liver steatosis was described in rats with portal hypertension by Izzet *et al*[11] in 2005, a pathological association suggested in humans 35 years ago[12]. Moreover, the liver parenchyma in portal hypertensive rats, due to the hepatocytic fatty infiltration, is progressively converted into fat[8,10] (Figure 1).

Portal hypertension is a type of vascular pathology due to the pressure of mechanical energy on splanchnic venous circulation[13]. In mammals there are five cellular pathways able to translate mechanical forces into biologic programs, such as integrin-matrix interactions, cytoskeletal strain responses, stretch ion channels, cell traction forces and G-protein-coupled receptors[14,15]. Therefore, mechanical energy may act after TPVL in the rat on the vascular splanchnic endothelium as a stressor stimulus triggered by mechanotransduction[16].

Tissue injury caused by this process can produce a systemic inflammatory response in the body. This response is developed by three successive and overlapping phenotypes: The neurogenic, the immune and the endocrine[17,18]. Similar overlapping could also be expressed in the body through the action of the intrinsic endogenous mechanical energy on the splanchnic venous system after the partial PVL[19]. Therefore during its evolution, prehepatic portal hypertension would induce a low-grade inflammatory response which could be developed during the above mentioned phenotypes, the neurogenic, the immune and the endocrine[19] (Table 1).

THE NEUROGENIC INFLAMMATORY PHENOTYPE

The systemic inflammatory response in prehepatic portal hypertension could begin with an immediate neuromuscular response including the splanchnic and systemic vascular smooth muscle with vasoconstriction and vasodilation producing an ischemia-reperfusion phenomenon. This pathologic vasomotor response induces local and systemic hemodynamic impairments, *i.e.*, hyperdynamic splanchnic and systemic circulation[20]. Within systemic and splanchnic alterations, hyperdynamic circulation is pointed out in relation to prehepatic portal hypertension[21]. Regarding this, the hyperdynamic or progressive vasodilator syndromes could be triggered by splanchnic and systemic vasodilation. Moreover, multiorgan failure in chronic liver disease could be attributable to this syndrome[21,22]. Once developed, the hyperdynamic syndrome induces tissue hypoxia, stress (oxidative and nitrosative) accompanied by mild edema, and inflammation in tissues and organs causing their dysfunction[19]. Multiple studies

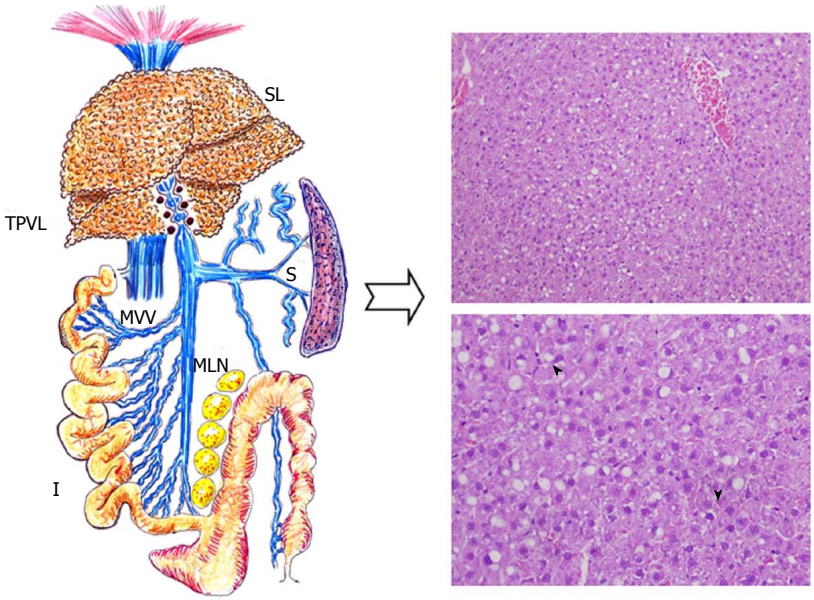

Figure 1 Liver histopathological changes of a rat after three months with triple partial portal vein ligation. Hepatic steatotic areas are mainly distributed in zone 1 of the liver acinus, but tipically hepatocyte ballooning is more apparent near zone 3. Both macrovesicular and microvesicular steatosis are evident as well as scattered necroinflammatory foci (arrowheads) (H and E stain, × 200). I: Intestine; MVV: Mesenteric venous vasculopathy; S: Spleen; SL: Steatotic liver; TPVL: Triple partial portal vein ligation.

Table 1 Similarities between the inflammatory changes developed after triple partial portal vein ligation in the rat and the extra-embryonic functions in mammals

Inflammatory phenotype		Extra-embryonic and embryonic functions
Neurogenic	Portal ischemia	Coelomic-amniotic functions
	Hepatic arterial reperfusion	Neurogenic potential
	Neuroendocrine response	Interstitial edema
	Hyperdynamic circulation	Bacteriostasis
	Mild edema of space of Disse	Anti-inflammation
Immune	Kupffer cell and hepatic stellate cell activation	Trophoblastic-yolk sac functions
	Leukocyte infiltration	Digestive (phagocytic) functions
	Acute phase response	Acute phase proteins
	Angiogenesis	Angiogenic switch
	Hepatic steatosis	Lipid and protein nutrients (vitellum)
Endocrine	Sinusoidal remodeling	Gastrulation-like functions
	Capillarization of hepatic sinusoids	Epithelial-mesenchymal transition
	Perisinusoidal fibrosis	Intra-embryonic mesenchyma
	Steatohepatitis	

have shown that the central nervous system plays a key role in the pathophysiology of the hyperdynamic circulation[23,24]. In particular c-Fos is detected in the brain stem and hypothalamic nuclei of rats following portal vein ligation[23]. Then, hyperdynamic circulation leads to decreased mean arterial pressure thus stimulating the sympathetic nervous system and the multiple neuro-endocrine axes, including the renin-angiotensin-aldosterone system. This results in sodium retention and volume expansion[20,25,26]. Sodium retention seems to be critical for inflammatory response. Under inflammatory circumstances, endothelium tends to increase permeability in tissues and organs affected. This strategy will allow a selective diffusion of circulating substances from the blood into the interstitial space[27].

Stress of the neuro-endocrine system by portal hypertension could be induce by three mechanisms: The hypothalamic-pituitary-adrenal axis, the sympathetic-adrenal medullary and the sympathetic nervous system[28] (Figure 2). Moreover, the localization of the early inflammatory response could also favor the posterior storage of substances derived from the acute phase response[29]. Therefore, in the liver of the rats with prehepatic portal hypertension, the space of Disse could represent the anatomically definable compartment where the early inflammatory response is expressed (Figure 2).

The main and immediate effect on the liver vascular flow after the partial portal vein ligation is greatly reduced portal blood flow, which normally represents the 70% of its blood supply[30]. Nevertheless, initial portal ischemia is followed by arterial reperfusion. It has been described that decreased portal venous flow is able to induce an increase in hepatic arterial blood flow or "hepatic arterial buffer response"[31]. In turn, this vascular compensatory mechanism arterializes the liver and produces a capillarization of hepatic sinusoids[30]. This phenomenon is defined by fenestrae loss and the formation of a continuous basement membrane[32]. Although the mechanism of defenestration induced in the arterialized liver is not well known, it has been demonstrated that liver sinusoidal endothelial cell phenotype in capillarized

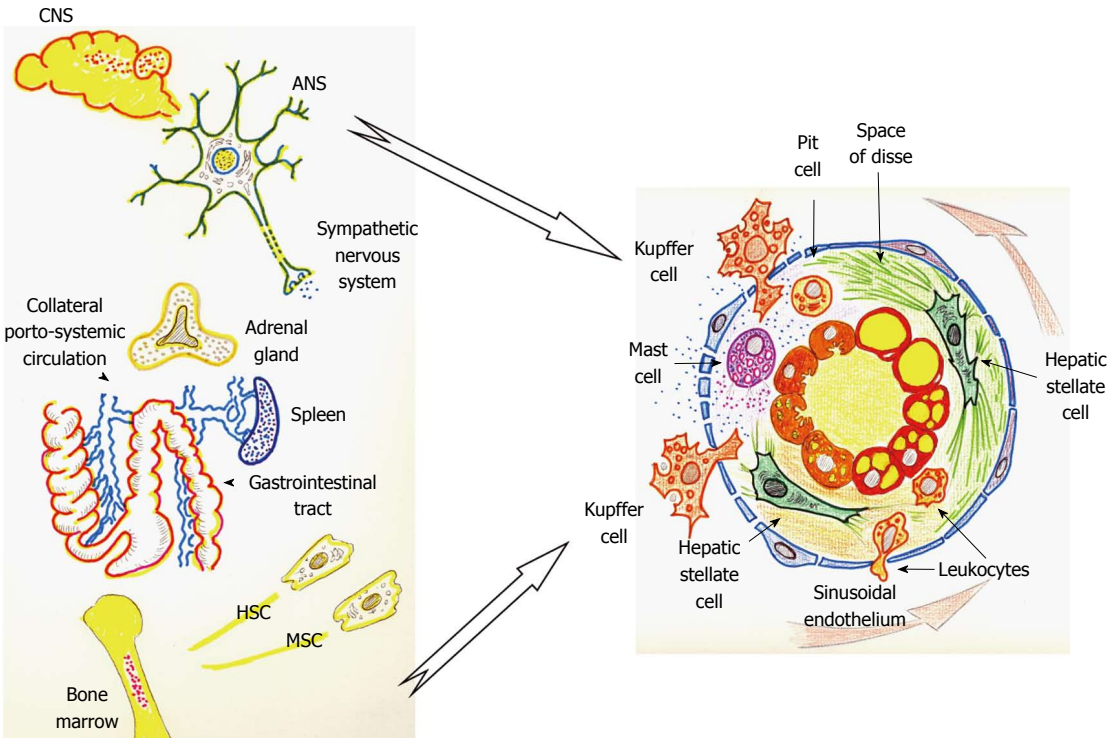

Figure 2 Inflammatory phenotypes, neurogenic and immune in prehepatic portal hypertensive rat. ANS: Autonomic nervous system; CNS: Central nervous system; HSC: Hematological stem cell; MSC: Mesenchymal stem cell.

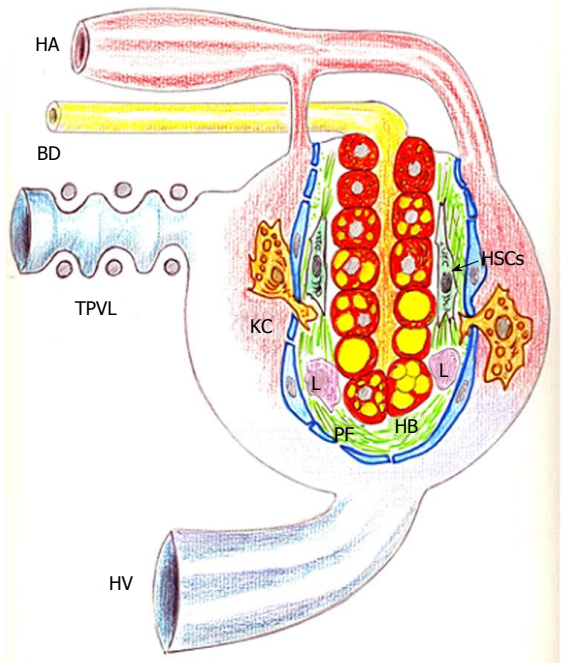

Figure 3 Schematic representation of the liver parenchyma after partial portal vein in the rat. The deposit of lipids within the hepatocytes and the liver arterialization, associated with defenestration of the sinusoidal endothelium, and the perisinuosidal fibrosis stand out. BD: Bile duct; HA: Hepatic artery; HV: Hepatic vein; HB: Hepatocyte ballooning; HSCs: Hepatic stellate cells; KC: Kupffer cell; L: Leukocyte; PF: Perisinuosidal fibrosis; TPVL: Triple partial portal vein ligation.

liver promotes Kupffer cell[30] and hepatic stellate cell[33] activation (Figure 3). Moreover, it has been suggested that intrasinusoidal crawling behavior could represent a form of immune surveillance. So, this mechanism could explain the reduction in CD8 T cell surveillance by infected or transformed hepatocytes. Furthermore, intrasinusoidal crawling behavior could participate in the hepatocarcinoma's development and progression[34]. This liver ischemia-reperfusion phenotype with progressing interstitial edema in the space of Disse could activate lymphatic circulation[35]. As a consequence, increased hepatic lymph flow and the transmigration of free cells, such as dendritic cells and lymphocytes, have been shown[34]. In addition, the edematous space of Disse may also serve as a stem cell niche for substances derived from the neuro-endocrine response to portal hypertensive stress, for mediators of the acute phase response and cytokines, and for activated hepatic stellate cells and lymphocytes[35-37] (Figure 4).

THE IMMUNE INFLAMMATORY PHENOTYPE

The immune inflammatory phenotype by the splanchnic system after ischemia/reperfusion, and therefore suffer oxidative and nitrosative stress, is coupled with the activation of intracellular signaling pathways including the nuclear factor-κB (NF-κB) pathway, and the inflammasome[38]. Reactive oxygen species are central in the regulation of NF-κB, although their role is not completely understood on account of the contrasted outcome reported: Activation *vs* inhibition. Most likely,

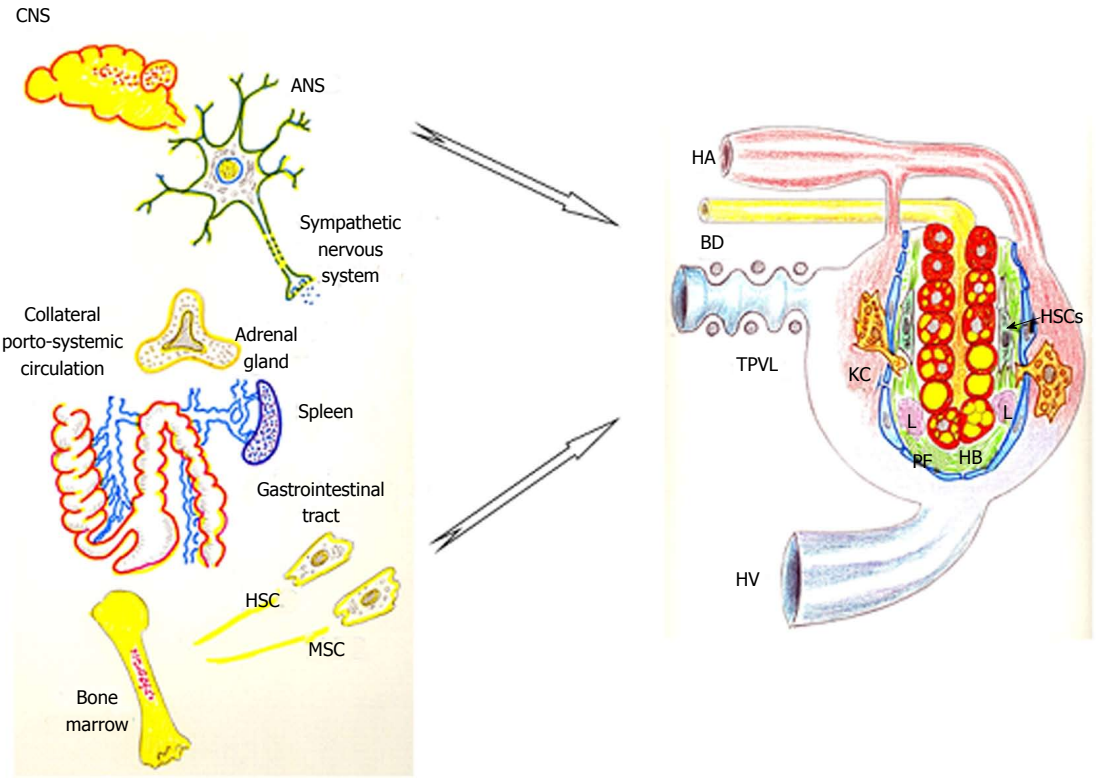

Figure 4 The preferential expression of the neurogenic and immune inflammatory phenotypes into the space of Disse induces hepatic steatosis, steatohepatitis and fibrosis in portal hypertensive rats by triple partial portal vein ligation. ANS: Autonomic nervous system; BD: Bile duct; CNS: Central nervous system; HA: Hepatic artery; HB: Hepatocyte ballooning; HSC: Hematological stem cell; HSCs: Hepatic stellate cell; HV: Hepatic vein; KC: Kupffer cell; L: Leukocyte; MSC: Mesenchymal stem cell; PF: Perisinuosidal fibrosis; TPVL: Triple partial portal vein ligation.

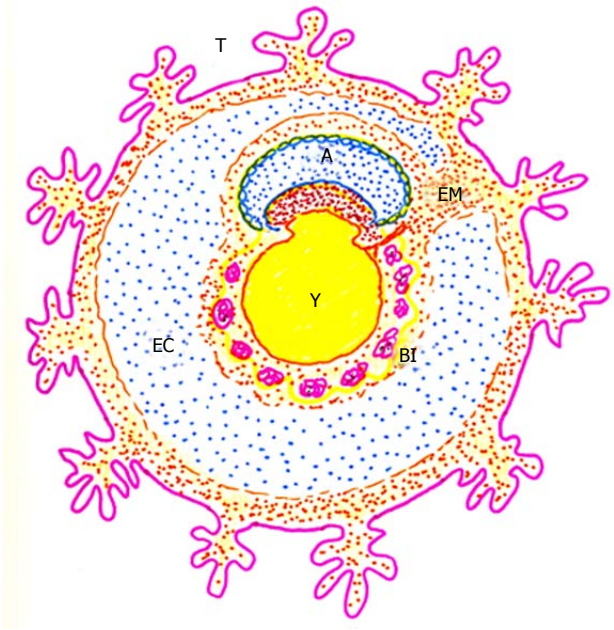

Figure 5 Schematic representation of early embryo development. The extra-embryonic mesoderm and the exocoelomic cavity connect the trophoblast with the amnion and the yolk sac. A: Amnion; BI: Blood islands; EC: Exocoelomic cavity; EM: Extra-embryonic mesoderm; T: Trophoblast; Y: Yolk sac.

reactive oxygen species could promote NF-κB responses in the early stages of the inflammatory response instead of inhibiting these responses at later stages. Reactive oxygen and nitrogen species could also favor the induction of tissue repair or remodeling[38-40].

During this phase the oxygen is creating enzymatic stress[19]. Along this acute phase the compensatory mechanisms include production of proteins which bind proteolytic enzymes, inhibitors of leukocyte and lysosomal proteolytic enzymes[41,42]. Likewise, anti-enzymatic stress could be promoted by the natural inhibitors of matrix metalloproteinases[19]. The immune phenotype could be coupled with bacterial intestinal translocation to mesenteric lymph nodes, increased mast cells in the splanchnic area, an acute phase response, dyslipidemia and hepatic steatosis[43]. We have shown that splanchnic and systemic inflammatory changes develop in TPVL-rats, including portal hypertensive enteropathy[43,44], mesenteric adenitis[45,46], portal hypertensive encephalopathy[47], liver steatosis[8-10], aortic atherosclerosis-like disease[48-50] and metabolic syndrome[51].

Hepatic steatosis and visceral adipose tissue are metabolic risk factors in accumulation of visceral fat. Due to their anatomical position, the venous blood from there is drained directly into the liver through the portal vein[52]. We speculate that the induction of intraabdominal fat deposits around the portal venous system could represent ontogenic reminiscences, associated with yolk sac, or phylogenetic reminiscences, related to vitellogenesis[53,54] (Figure 5). Regarding the ontogenic origin, the liver, and in particular the omentum, could

be mimicking the yolk sac, in which pathological lipid deposition takes place. Under this scenario, the liver and the omentum would be regressing to evolutive phases with suitable metabolic conditions, supported by the expression of inflammatory markers such as tumor necrosis factor (TNF)-α, IL-6, C reactive protein and leptin[19,29]. In terms of phylogenetic approach, the body would be adopting the molecular mechanisms related to the vitellogenesis[53,54], in which oviparous species provide a glycolipoprotein yolk storage called vitelline to the egg as food-source for the embryo[54]. Lipoprotein transport through the circulatory system by eukaryotes has been an important function for the existence[53]. Thus, the evolutionary perfection of energy accumulation in fat has provided organisms an advantage in adapting to environmental and developmental changes[54].

The increased uptake of free fatty acids derived from the hydrolysis of adipose-tissue triglycerides results in hepatic steatosis. Moreover, the contribution of dietary chylomicrons, hepatic biogenesis and insulin resistance increased the uptake[3,4,55]. Hepatic steatosis is a key concept in the two-hit NAFLD hypothesis, which postulates that hepatic steatosis sensitizes fatty liver to secondary hits, such as oxidative and nitrosative stress or inflammatory cytokines[56]. In addition, cholesterol sensitizes fatty livers to secondary hits, particularly when trafficking to mitochondria as it has been recently recognized[57,58]. In portal hypertensive rats by TPVL the distinction between simple steatosis and steatohepatitis (NASH) includes hepatocyte ballooning, leukocyte infiltration (lobular inflammation) and perisinusoidal (zone 3) fibrosis[9] (Figures 3 and 4). In long-term portal hypertensive rats, the plasmatic increase of low density lipoprotein and lipopolysaccharide binding protein as well as high-density lipoprotein reduction has been associated with NASH[8-10]. These findings could suggest a NASH role in developing cardiovascular disease by two ways: Systemic release of inflammatory mediators and/or the production of insulin resistance and atherogenic dyslipidemia[49,50]. In this line, recent evidence supports a relationship between NAFLD and cardiovascular disease[50,55]. Particularly in TPVL-rats NASH, this association could be considered a risk factor for a wound-like inflammatory aortic response[49], with increased expression of NF-κB, TNF-α, IL-1β and IL-6 in the aortic wall[48,49].

THE ENDOCRINE INFLAMMATORY PHENOTYPE

During the expression of the endocrine inflammatory phenotype in TPVL-rats there is a splanchnic remodeling by angiogenesis, which implies growth of new vessels from pre-existing ones[59], and fibrosis. Moreover, an abnormal splanchnic and systemic angioarchitecture, such as portosystemic collaterals have been observed in chronic liver diseases[60-62]. This vascular alteration found in the gastrointestinal tract under portal hypertension conditions is called "hypertensive portal intestinal vasculopathy"[63,64]. However, not only vascular alterations have been described, even histological changes have been found[64]. So, angiogenesis is key role in portal hypertension and represents a potential therapeutic target[65]. Splanchnic hyperemia which is followed by increased splanchnic vascularization, together with portal-systemic collateral circulation in experimental portal hypertension have angiogenic origins partly driven by the vascular endothelial growth factor (VEGF)[65,66]. Mast cells are able to release VEGF among others[67], being involved in promoting hypertensive portal vasculopathy and portal systemic collateral circulation[43].

Fibrosis is a scarring response that seems to be reversible in rats with long-term TPVL. Hepatic stellate cells (HSCs) play a central role in liver fibrosis and homeostasis[68]. In particular, perisinusoidal/pericellular fibrosis is typically found in NASH. Excess deposits of the extracellular matrix are primarily found in the spaces of Disse surrounding sinusoids or groups of hepatocytes. This leads to "capillarization of sinusoids" or "chickenwire pattern", respectively[69] (Figures 3 and 4). HSCs express both mesenchymal markers and neuronal or glial markers[70]. The activation of HSCs is needed to develop hepatic fibrogenesis[68,69]. HSCs activate resident immune cells such as Kupffer and Pitt cells which trigger hepatic inflammation[71], as well as mono- and polymorphonuclear leukocytes infiltration[70].

In addition, HSCs, once in their myofibroblastic phenotype, respond to vasoactive substances by contracting being important in the pathogenesis of portal hypertension[72]. They also respond to sinusoidal morphogenesis since direct hepatic stellate cell-endothelial cell contact inhibits endothelial cell capillary/sinusoidal formation[73]. Dynamic interplay between HSCs and endothelial cells could be important for understanding how the sinusoidal remodeling process is regulated in NAFLD in portal hypertensive rats[73] (Figure 3).

RECAPITULATED EXTRA-EMBRYONIC FUNCTIONS RELATED TO NAFLD

The inflammatory response associated with NAFLD in portal hypertensive rats could be an ontogenic process based on the re-expression of two speculative extra-embryonic axes (exocoelomic-amniotic and trophoblastic-yolk sac) in the space of Disse. If so, the NAFLD concept which vary from steatosis and NASH to advanced fibrosis and cirrhosis[58] could be representing a normal embryonic development (Table 1).

The hypothetical recapitulation of these initial embryonic phases during the evolution of NAFLD would be accompanied by functions similar to the extra-embryonic membranes that surround the embryo. The extra-embryonic coelom or exocoelomic cavity surrounds the blastocyst, which is composed of two structures, the amnion and the primary yolk sac (Figure 5). Coelomic

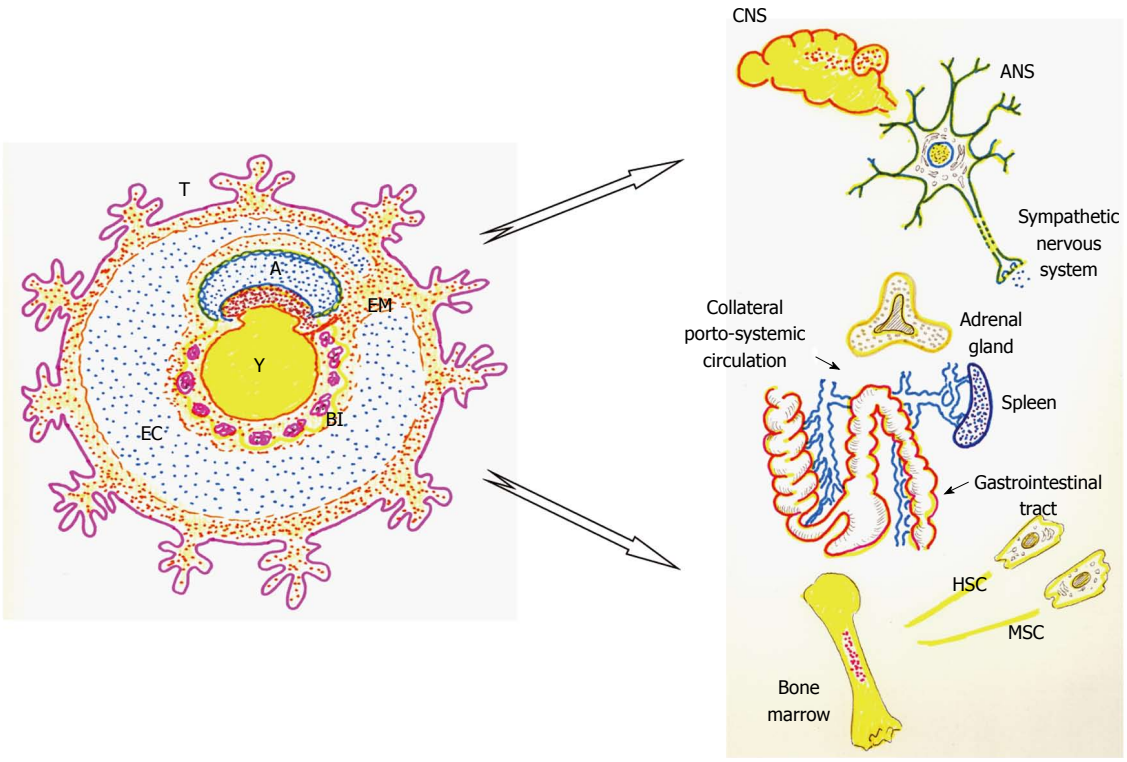

Figure 6 The coelomic-amniotic functions could be hypothetically recapitulated by the systemic neurogenic phenotype activation, while the trophoblastic-yolk sac functions could be carried out by the systemic immune inflammatory phenotype activation. A: Amnion; ANS: Autonomic nervous system; BI: Blood islands; CNS: Central nervous system; EC: Exocoelomic cavity; EM: Extra-embryonic mesoderm; HSC: Hematological stem cell; MSC: Mesenchymal stem cell; T: Trophoblast; Y: Yolk sac.

fluid results from an ultrafiltrate of maternal serum with the addition of specific placental and secondary yolk sac byproducts[74]. Accordingly, the embryonic phenotype could be adopted by the inflamed liver interstitium, which will induce fluid accumulation with low pH and oxygen environment as coelomic fluid[74,75]. This interstitial edema seems to occur secondary to hepatic ischemia-reperfusion. Moreover, the edema shows proinflammatory characteristics due to the high content in proteins such as albumin, electrolytes, metals, amino acids, antioxidants, cytokines and cholesterol-derived hormones[75,76]. So the edema will be leading liver trophism.

Biological and anatomical data of the exocoelomic cavity stand it out as a nutritional pathway before placental circulation is established[76]. The strong neural potential of the amnion, an embryonic functional axis, has been previously stated[77]. Moreover, from the amnion is secreted the "amnio-derived cellular cytokine solution" which highlighting a connection between mesenchymal and epithelial cells during embryo development[78]. Furthermore, the amniotic fluid could be understand as an extension of the extracellular space of the fetal tissues[79]. Finally, pluripotent stem cells within the amniotic fluid could also be a new source for stem cell research[80,81]. Because of these characteristics, the amnio-like phenotype could favor nutrition by diffusion, transport, excretion, and bacteriostatic and antiinflammatory protection[78,79] (Figure 5).

The development of hematopoiesis and angiogenesis[81] occurs in the mesenchymal layer which builds the wall of the secondary yolk sac in mammals[74]. This sac appears from the sixth week of gestation and is covered by superficial small vessels[82]. Others layers of the secondary yolk sac include, mesothelial and endodermal layers which are active in endocytosis/digestion and absorptive functions[81,82], and the endodermal layer which produces acute phase proteins, such as transferrine, α1-antitrypsin, and α-fetoprotein (produced by both the adult and fetal liver)[74,83] (Figure 5). So, the yolk sac provides lipids, carbohydrates, proteins and vascular integrity to the embryos[84] and could be involved in lipid metabolism gene regulation[85], immune cells recruitment and angiogenic switch[86]. Phagocytosis has been associated to trophoblast differentiation as well[87].

THE RECAPITULATED SYSTEMIC EXTRA-EMBRYONIC FUNCTION AND THE INTERSTITIAL INFLAMMATORY SPACE OF DISSE IN NAFLD

NAFLD systemic inflammatory pathophysiology shares mechanisms with the pluripotential extra-embryonic pathways. It is hypothesized that during NAFLD evolu-

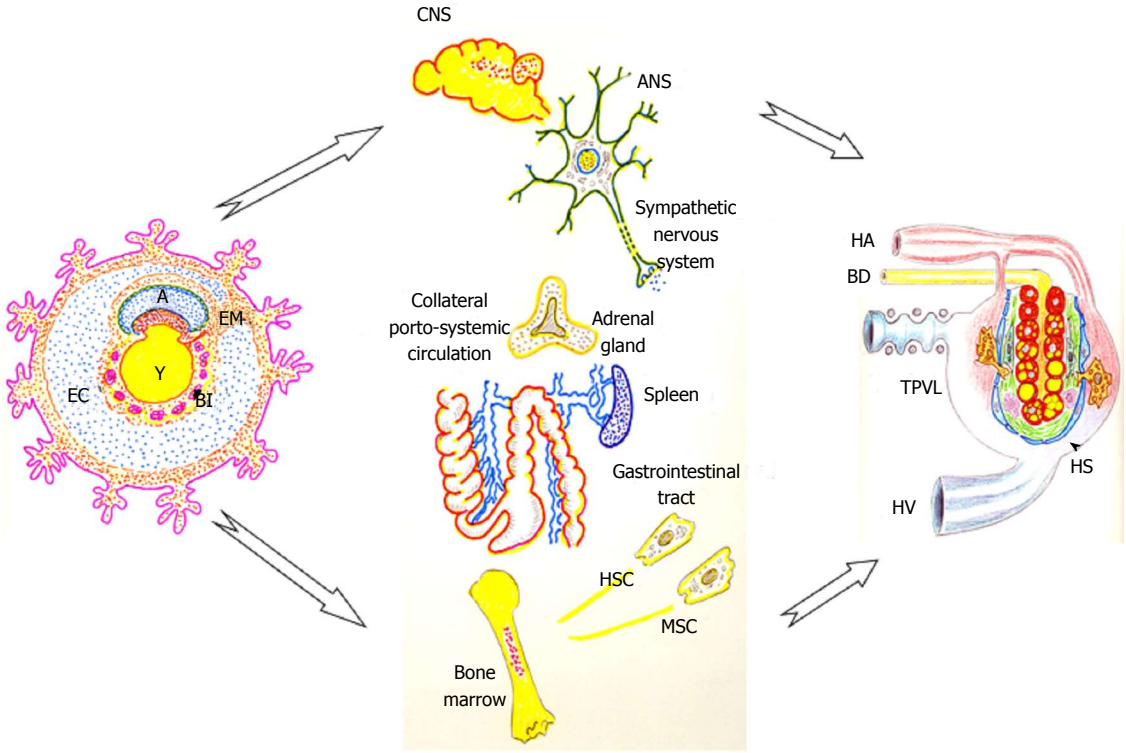

Figure 7 The recapitulated systemic extra-embryonic functions, that is, the coelomic-amniotic and the trophoblastic-yolk sac (or vitellum), are located into the space of Disse. This fact results in the development of hepatic steatosis and steatohepatitis in prehepatic portal hypertensive rats. A: Amnion; ANS: Autonomic nervous system; BD: Bile duct; BI: Blood islands; CNS: Central nervous system; EM: Extraembryonic mesoderm; HA: Hepatic artery; HS: Steatotic liver; HSC: Hematological stem cell; HV: Hepatic vein; MSC: Mesenchymal stem cell; TPVL: Triple partial portal vein ligation; Y: Yolk sac.

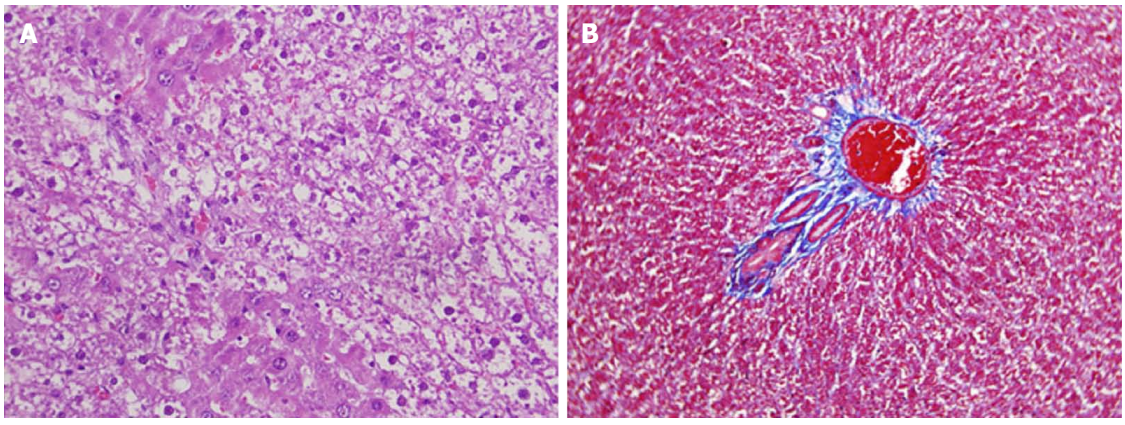

Figure 8 Histological appearance of non-alcoholic steatohepatitis in portal hypertensive rats at three months of postoperative evolution. It's shown the hepatocyte ballooning (A) with lobular inflammation and perisinuosidal fibrosis (B) (H and E stain, × 200).

tion, the coelomic-amniotic and trophoblastic-yolk sac functions are integrated into the interstitial space of Disse, thereby activating embryonic programs in the acinus. In this line, coelomic-amniotic functions would be embodied by the systemic neurogenic inflammatory phenotype, while the trophoblastic-yolk sac functions could be represented by the immune inflammatory phenotype[88] (Figure 6). Furthermore, the polarization of neurogenic and immune-related phenotypes in the interstitial space of Disse would condition the evolution of NAFLD, including a wound-healing response producing fibrosis in the rat[88,89] (Figure 4 and Table 1).

Essentially, the recapitulation of the extra-embryonic functions when focused on the space of Disse[88] would produce a gastrulation-like process which is a recapitulation of the intra-embryonic mesenchyme formation process[89]. Therefore, mesoderm-derived cells, particularly fibrocytes and hepatic stellate cells have shown a main role in liver restore (Figure 5) after TPVL. The involution or dedifferentiation of the liver in portal hypertensive rats could be exemplifying a prenatal specialization[88] which involves or angiogenic regenerative or fibrotic/scarring repairing processes[89].

The systemic complications of the prehepatic portal

hypertensive syndrome in rats could be connected to similar metabolic functions of the extra-embryonic coelomic-amniotic and trophoblastic-yolk sac axes[88]. For example, hydroelectrolytic decompensation and its effects, including hyperdynamic circulation, multiple neuroendocrine axis activation, edema due to sodium and water accumulation, increase interstitial hepato-intestinal lymph flow and stimulation of the sympathetic nervous system, might be associated to the upregulation of a systemic coelomic-amniotic axis after TPVL in the rat (Figure 7). In this line, an upregulation of a systemic trophoblastic-yolk sac or vitellogenic-like axis could be represented through the immune phenotype activation of NF-κB and inflammasome, acute phase response, splanchnic infiltration by mast cells, bacterial intestinal translocation which implies hepatic dyslipidaemia and the excessive splanchnic angiogenic response. The convergence of these systemic extraembryonic axes in the interstitial space of Disse could favor a gastrulation-like response in which NAFLD develops (Figure 7).

Recently, it has been established that human NAFLD is commonly associated with hypertension, type 2 diabetes, obesity, dyslipidemia, metabolic syndrome and cardiovascular abnormalities leading to death[90-92]. The array of alterations associated with the evolution of NAFLD make up a syndrome of great pathophysiological complexity. Studying this syndrome would help the experimental model of liver steatosis in the rat after TPVL. Also, the results obtained from studying multiple splanchnic and systemic alterations produced in the surgical experimental model of NAFLD suggest that the systemic inflammatory response could condition the evolution of hepatic steatosis. Thus, when the animals are isolated in individual cages after TPVL, accelerating the development of the liver histopathological changes typical of steatosis is possible (Figure 8). This early appearance of liver steatosis in TPVL-rats could be attributed to stress induced by isolation when rats are separated from other rats, and to their limited space for movement when kept in individual holders. If the stress related to isolation and movement limitation favors liver steatosis development, studying the influence of systemic neuroendocrine alterations associated with stress in NAFLD development in rats with TPVL would be an attractive goal for the future.

Finally, if our hypothesis presented in the current review of the NAFLD model secondary to TPVL in the rat represents the focus of two systemic functional axes that recapitulate extra-embryonic functions in the interstitial space of Disse, then modulating the evolution of experimental liver steatosis is possible by modifying the re-expression of these functions. For that reason, studying the mechanisms involved in embryonic development could provide key results for a better understanding of the NAFLD etiopathogeny.

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