Chapter

The Wound-Healing Portal Hypertensive Response

Maria Angeles Aller, Javier Blanco-Rivero, Ana Arias and Jaime Arias

Abstract

Portal hypertensive inflammation is associated with chronic liver diseases. The three successive and overlapping systemic inflammatory phenotypes, i.e., neurogenic, immune, and endocrine, which characterize the wound-healing response, are expressed by the portal venous system upon liver injury. The diverse functions of hepatic stellate cells in homeostasis and inflammation indicate the versatile nature of these mesenchymal-derived cells, which could adopt numerous phenotypes according to the interstitial microenvironmental characteristics. Consequently, these inflammatory phenotypes could represent the reexpression of two extra-embryonic functional axis, i.e., coelomic-amniotic and trophoblastic-vitelline, whose coupling in the portal system would induce a gastrulation-related phenotype. Therefore, hepatic stellate cells and liver-specific mesenchymal cells could recapitulate and couple these abovementioned extra-embryonic phenotypes during portal hypertension. These hepatic cellular population, thanks to their potential ability to integrate and reexpress functions showing analogies to extra-embryonic functions, display characteristics of stem/progenitor cells. In this way, during the development of portal hypertension, hepatic stellate cells not only could reexpress extra-embryonic functions, but also could adapt themselves in order to induce a gastrulation-related process in the space of Disse. Hence, by understanding the ontogenic interactions between hepatic stellate cells and the host inflammatory response in portal hypertension, it is possible to design effective therapeutic and prophylactic strategies to avoid or reverse wound-like hypertensive response.

Keywords: liver fibrosis, extra-embryonic functions, inflammation, wound-healing, portal hypertension

1. Introduction

Portal hypertension is a frequent complication of chronic liver disease [1]. At the same time, cirrhosis represents the final stage of chronic liver disease due to any cause [2]. Cirrhosis can be defined as an advanced stage of fibrosis involving the formation of the regenerative nodule of the parenchyma surrounded and separated by fibrotic septa, a scenario also characterized by significant changes in hepatic angioarchitecture [3–5].

The cause-effect relationship existing between inflammation and fibrotic processes is so narrow that the term “inflammatory fibrosis” [6] appropriately describes multiple fibrotic diseases, including local conditions, such as wound healing [7] and liver cirrhosis [5]. Therefore, the chronic activation of the wound-healing response represents the driving force for progressive fibrosis, eventually leading to liver cirrhosis and hepatic failure [5].

2. The wound-healing response

Knowledge relating to wounding repair and healing comprises a significant fraction of the science of surgery and its specialties [8]. Wound healing is an obligatory sequence of events starting with inflammation due to a variety of stimuli [9]. In lower vertebrate tissues, regeneration can restore injured organs and even severe limbs or other body segments [10]. However, in higher vertebrates, tissue repair consists of a fibroproliferative response that usually results in a fibrotic scar [10, 11]. Regenerating vertebrates, such as zebrafish and salamanders, offer a unique example where wounds are not only resolved without the formation of a fibrotic scar, but also the wound tissue executes tissue patterning equivalent to the original process of embryonic development to restore lost tissue [11, 12].

Scarring is a frequent consequence of full-thickness mammalian wound healing [10, 13]. However, the mid-gestation fetus is capable of regenerative healing with wound healing indistinguishable from surrounding skin [14, 15]. Current therapies to minimize scarring in postnatal wound have attempted to recapitulate singular aspects of the fetal regenerative phenotype and have met with varying degrees of clinical success [14].

Cutaneous wound repair is an integration of dynamic interactive processes involving soluble mediators, formed blood elements, extracellular matrix, and parenchymal cells [10]. These processes follow a specific time sequence which is classically grouped into three interrelated phases: inflammation, proliferation with tissue formation, and tissue remodeling [16, 17]. In brief, coagulation and inflammatory cells are crucial to the initial inflammatory phase. Neutrophils and macrophages enter the fibrin-rich zone. In addition to phagocyte pathogens and tissue debris, these cells secrete a multitude of chemokines, cytokines, and growth factors. Granulation tissue—composed of macrophages, fibroblasts, and endothelial cells—is the hallmark of the proliferative phase. Reepithelization is essential for the reestablishment of tissue integrity [18]. During the remodeling phase, formation of granulation tissue ceases through apoptosis of the responsible cells. With maturation of the wound, the type III collagen deposited during the proliferative phase is slowly degraded and replaced with stronger type I collagen. Furthermore, the wound undergoes a contractile response and reduces the surface area of the scar [19].

3. The systemic wound-healing phenotypes

From a general point-of-view, the wound-healing response could be considered as a systemic inflammatory response in the body, which appears to develop through the expression of three successive and overlapping phenotypes, the neurogenic, immune, and endocrine [20]. The above-mentioned phenotypes, which characterize the evolution of the systemic inflammatory response to the injury, are focused and integrated within the interstitial space of the injured tissue or organ [7, 21, 22].

3.1 The neurogenic inflammatory phenotype

The systemic inflammatory response begins with an immediate pathological neuromuscular response that includes sensitive impairments like stress sensation, pain, analgesia, and motor alterations. In particular, these motor alterations are harmful to the skeletal muscle (fight-to-flight and withdrawal reflexes), myocardium (tachycardia), and vascular smooth muscle (vasoconstriction and vasodilation), which induces systemic and local hemodynamic impairments, including blood flow redistribution and ischemia-reperfusion [21, 22]. A common and basic pathogenic mechanism of this complex neuromuscular response would be sudden hydroelectrolytic alterations [20–22]. Consequently, there is increasing evidence that the systemic inflammatory response is actually associated with abnormal ion transport [23].

The ischemia-reperfusion phenomenon, which causes oxidative and nitrosative stress, could be responsible for exudation and the progression of interstitial edema in the injured tissues or organs [21]. While edema is being produced, the lymphatic circulation is activated [20, 22]. Since the inflammatory *interstitium* is initially hypoxic and shows metabolic anaerobic acidosis, mainly due to the accumulation of acid by-products including lactate, the hypoxic and acid environment could represent an ideal stem cell niche [24].

In the early evolutionary period of the neurogenic stress response, the hypothalamic-pituitary-adrenocortical, sympathetic-adrenal-medullary, and renin-angiotensin-aldosterone axes, with the secretion of catecholamines, glucocorticoids, and mineralocorticoids in the circulation, are activated [25, 26]. Chromaffin vesicles in adrenal medullary chromaffin cells also store granins, which can function as prohormones giving rise to bioactive peptides, some with potent antimicrobial activity [27]. Consequently, these substances are selectively accumulated in the interstitial space of the tissues suffering from ischemia-reperfusion because endothelial permeability is increased, especially in the post-capillary venules [7, 20–22] (**Table 1** and **Figure 1**).

3.2 The immune inflammatory phenotype

The immune inflammatory phenotype corresponds to the intermediate phase of systemic wound-healing response to injury. In this phase, the tissue or organ which has previously suffered ischemia-reperfusion is infiltrated by inflammatory cells and even by bacteria [22]. This infiltration occurs in an edematous oxygen-poor environment [7, 21].

Today, the inflammatory bone marrow-related response is considered both a key and complementary arm of the stress response [7, 22]. The inflammatory activation of the bone marrow stem cell niche indicates the stimulation of the hematopoietic stem cells (HSCs) and the mesenchymal stem cells (MSCs), which are both multipotent stem cells [28, 29]. HSCs are the progenitors of all blood and immune cells that infiltrate all the tissues and organs that have been previously primed by oxidative and nitrosative stress [22]. Inflammatory signaling molecules, including chemokines, interferons, tumor necrosis factor-alpha, and toll-like receptors appear to stimulate HSC proliferation in the short term [30]. In turn, interferon gamma mediates HSC stimulation in response to chronic inflammation [31].

This immune phenotype could be characterized by enzymatic stress related to intracellular digestion, i.e., autophagy [32], phagocytosis, and antigen presentation [21, 22]; and extracellular digestion, i.e., fermentation [20], all of which favor tissue tropism [7, 20]. In addition, macrophages and dendritic cells also take advantage of the lymphatic circulation activation. Macrophages migrate within the lymphatic circulation until reaching the lymph nodes where they activate lymphocytes [7, 33].

The cells that infiltrate the *interstitium* in the inflamed tissues and organs, thanks to the open microcirculatory system, acquire metabolic characteristics that transform them into tissues with great functional autonomy. Thus, leukocytes express adrenoceptors, catecholamines [34, 35], serotonin [36], pro-opiomelanocortin (POMC)

The neurogenic phenotype

Neuromuscular response

- Sensitive
  - Stress sensation, pain analgesia
- Motor
  - Skeletal muscle
  - Myocardium
  - Vascular smooth muscle
- Ischemia-reperfusion
- Oxidative and nitrosative stress
- Interstitial edema and storage of catecholamines, glucocorticoids, mineralocorticoid and granins
- Impairment of lymphatic pumping
- Increased lymphatic drainage

The immune phenotype

Inflammatory bone marrow-related response

- Hematopoietic stem cells
  - Leukocytes
- Mesenchymal stem cells
  - Resolution of the immune response
  - Enhance the regenerative potential of the tissues

Acute-phase reaction

- Positive acute-phase proteins
- Alteration in lipid metabolism

The endocrine phenotype

Proliferative inflammatory mesenchyma

- Granulation tissue
  - Angiogenesis
  - Fibrosis
- Reepithelization

Table 1.
The systemic wound-healing inflammatory phenotypes.

peptides [37], and cholinergic activity [38]. Perhaps, these are the reasons why the stress response axis can be retrieved by the immunocytes participating in the inflamed *interstitium* of tissues and organs, where the corticotrophin-releasing hormone (CRH), adrenocorticotrophin (ACTH)-like and biogenic amines are present [37].

MSCs are usually derived from bone marrow, but can also be isolated from adipose and other tissues [29]. MSCs act through complex interactions with the endogenous cells and tissues, and they may function in the multiple mechanisms of tissues [39]. MSCs in the wound bed contribute to the generation of a high-quality well-vascularized granulation tissue; they enhance reepithelialization of the wound and attenuate the formation of fibrotic scar tissue [39, 40]. Bone marrow-derived MSCs secrete molecules that inhibit the effector function of immune cells and are implicated in the resolution of inflammation [41, 42].

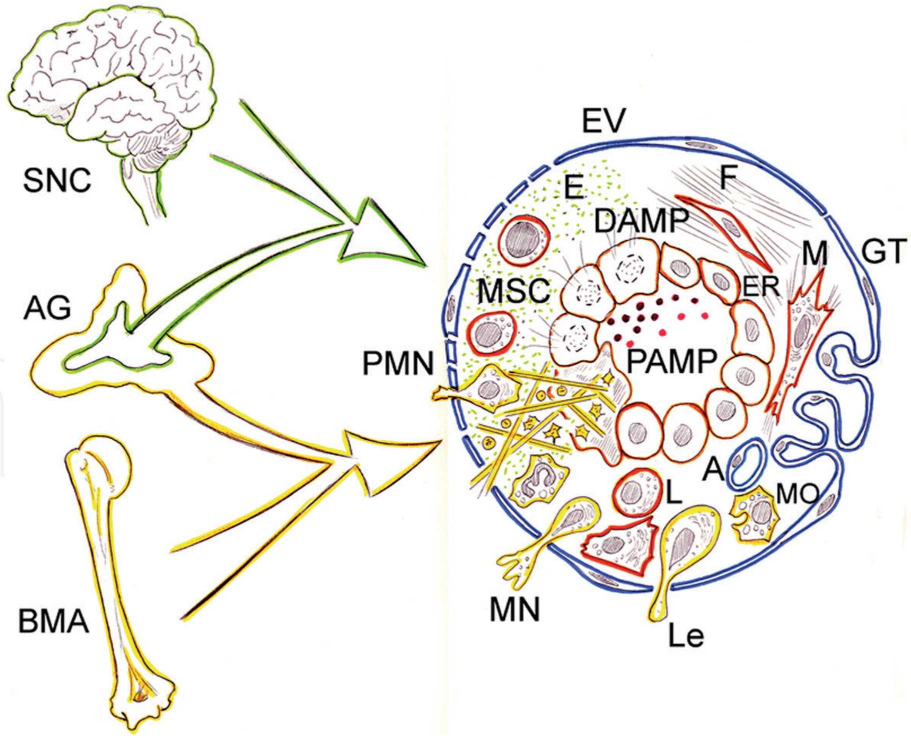

Figure 1.
The systemic wound-healing phenotypes. N: the neurogenic phenotype with sensitive and motor functions including ischemia-reperfusion and edema. A niche is created that can host stem cell-like cells. This interstitial niche accumulates molecules from the neuroendocrine stress response of the organism. I: the immune phenotype is associated with acute-phase response and an inflammatory bone marrow-related response, i.e., hematopoietic stem cells and mesenchymal stem cells. E: the endocrine phenotype. Formation of a new tissue that could execute a regenerative role or a reparative role through fibrosis. A: angiogenesis; AG: adrenal gland; BMA: bone marrow; CNS: central nervous system; DAMP: damage-associated molecular pattern; E: edema; ER: epithelial regeneration; EV: post-capillary vascular endothelium; F: fibrosis; GT: granulation tissue; L: lymphocyte; Le: leukocyte; Mo: macrophages; M: myofibroblast; MN: monocyte; MSC: mesenchymal stem cell; PAMP: pathogen-associated molecular pattern; PMN: polymorphonuclear neutrophil leukocyte; SC: stem cells.

During the expression of the immune phenotype, the acute-phase reaction becomes more prominent and exhibits diverse pathophysiological changes, including pyrexia, leukocytosis, and dramatic changes in the plasmatic concentrations of acute-phase proteins [43, 44]. Acute-phase proteins are circulating biomarkers of inflammation and are defined as either positive or negative, depending on whether they increase or decrease during the inflammatory response [43]. Positive acute-phase proteins are synthesized by hepatocytes in response to IL-6 as part of the innate immune response [45]. Positive acute-phase proteins include proteins of the coagulation-fibrinolysis system (fibrinogen, prothrombin, factor VIII, Von-Willebrand factor, complement factors plasminogen), protease inhibitors (alpha-1-antitrypsin, alpha-1-antichymotrypsin), transport proteins (ceruloplasmin, hemopexin, haptoglobin), and lipid transport proteins (serum amyloid A and serum amyloid P) [43, 44]. However, C-reactive protein is the main human acute-phase protein and one of the more sensitive markers of inflammation [44, 46].

Negative acute-phase proteins including albumin invade the *interstitium* of the injured tissues or organs through its plasmatic storage [21]. In turn, a pivotal function of the positive acute-phase proteins increases the availability of cellular free cholesterol. In particular, it has been suggested that acute-phase serum amyloid A is part of a systemic response to injury to recycle and reuse cholesterol from destroyed and damaged cells [47]. In this case, the recycling of cholesterol during serious injury could play an important role in survival [47]. In fact, the predominance of the lipid metabolism with accumulation of cholesterol in the inflamed tissue could be attributed to its role as a precursor molecule of many hormones, including aldosterone, corticoids, progesterone, androgens, and estrogens [48] and even vitamin D [49] (**Table 1** and **Figure 1**).

3.3 The endocrine inflammatory phenotype

It could be proposed that the expression of this inflammatory phenotype represents a metamorphosis through the creation of a pseudo-tissue made by a provisional parenchyma, with stem-like cells, and leukocytes, associated with a provisional stroma, i.e., coagulation and complement systems-related, which is finally transformed into a definitive tissue [50]. There is scattered evidence supporting the hypothesis that mononuclear phagocytes interact with cells with progenitor or "bona fide" stem cell properties, and that this interplay may contribute to repair and remodeling [51]. Even, it has been hypothesized that the immune system could create overriding signals that push the mesenchyme toward scarring rather than regeneration [52].

It has been proposed that the focus of the systemic phenotypes, neurogenic and immune, on the interstitial space of the injured tissue could be completed in two steps [7]. First, the upregulated neurogenic phenotype, characterized by systemic cardiovascular, hemodynamic, and hydroelectrolytic alterations, could favor the development of an interstitial niche with appropriate biochemical properties for the recruitment of cells with stem cell properties [7, 53]. In turn, the upregulated immune phenotype could mediate the inflammatory bone marrow response with an acute-phase reaction and a lipid metabolic switch linked to steroid synthesis [7]. Finally, the progressive polarization and integration of the functions that characterize both systemic inflammatory functions phenotypes, i.e., neurogenic and immune, in the injured tissue would condition the evolution of the tissue repair [7, 54].

The new tissue, a proliferative inflammatory mesenchyma, could execute a regenerative role or by default, repair through fibrosis [54, 55]. If so, several days after injury, a subset of wound fibroblasts can differentiate into myofibroblasts, which is responsible for repopulating the wounded area in parallel to angiogenesis, thus forming the granulation tissue [21]. Macrophages, fibroblasts, and blood vessels move into the wound space as a unit, suggesting an interdependence of these cells during the tissue repair [10, 51].

However, the dominating cell in this phase is the fibroblast, which fulfills different functions, such as the production of collagen and extracellular matrix substances, i.e., fibronectin, glycosaminoglycans, and proteoglycans [13]. Fibrosis is generally preceded by robust angiogenesis and vascular regression suggesting that the vascular apoptotic burden may be important to the fibrotic outcome [56, 57]. Recruited bone marrow mesenchymal cells could also transdifferentiate into epithelial cells [58] (**Figure 1**).

Therefore, the wound-healing response could be viewed as a successive and overlapping of systemic phenotypes, i.e., neurogenic and immune, which are coupled in the wounded area in order of reconstructing the injured tissue by regeneration or, by default, repairing it by fibrosis.

4. Inflammatory phenotypes and recapitulated ontogeny

Inflammation could recapitulate ontogeny by reexpressing two hypothetical extra-embryonic axes, i.e., exocoelomic-amniotic and trophoblastic-yolk sac in the interstitial space of the injured tissue [7, 22, 54]. If so, the inflammatory response could represent the postnatal debut of ancestral biochemical mechanisms that were used for normal embryonic development [22].

After fertilization, the first stage of embryogenesis is the zygote, which undergoes cleavage by mitosis. When the morula stage is reached, the embryo establishes polarity. The cells bind tightly to each other, forming a compact sphere or blastocyst, with two cell layers. The outermost layer becomes the trophoblast, giving rise to the placenta. The inner cells become the inner cell mass, giving rise to the embryo and the remaining structures, including the exocoelomic cavity, the amnion, yolk sac, and allantois [59]. The extra-embryonic coelom or exocoelomic cavity surrounds the blastocyst, which is composed of two structures, the amnion and the primary yolk sac. At the end of the fourth week of gestation, the developing exocoelomic cavity splits the extra-embryonic mesoderm into two layers, the somatic mesoderm, lining the trophoblast, and the splanchnic mesoderm, covering the secondary yolk sac and the embryo [60] (**Figure 2**).

The hypothetical recapitulation of these initial phases of the embryonic development during the early inflammatory response would imply the expression of functions similar to the extra-embryonic exocoelomic-amniotic and trophoblastic-yolk sac structures [22]. Accordingly, the exocoelomic-amniotic phenotype could be adopted by the inflamed *interstitium* that subsequently induces the accumulation of fluid with similar characteristics to coelomic and amniotic fluids in an environment with low pH and oxygen [60–62]. In essence, interstitial edema with high levels of proteins, in particular albumin, as well as electrolytes, metals, amino acids, antioxidants, cytokines, growth factors, and cholesterol-derived hormones would be produced in the inflammatory exudate [60–65]. In addition, the amnion is an embryonic functional axis with strong neural potential [66]. Amnion-derived multipotent progenitor cells secrete a unique combination of cytokines and growth factors, called the *amnion-derived cellular cytokine solution*, which establishes a connection between mesenchymal and epithelial cells during embryo development [67]. Furthermore, pluripotent stem cells within the amniotic fluid could be a new source for stem cell research [68] (**Figure 2**).

In turn, during trophoblast differentiation, trophoblast cells exhibit intense phagocytic activation leading to events as diverse as engulfment and destruction of extracellular material and the production of inflammatory mediators that may modulate both the immune response [69] and trophoblast invasiveness [70]. The wall of the secondary yolk sac in mammals is formed by an external mesothelial layer facing the exocoelomic cavity, a vascular mesenchyme and an endodermal layer facing the yolk sac cavity [60]. The formation of blood islands in the mesenchymal layer promotes the development of hematopoiesis and angiogenesis. Hemangioblasts found in these blood islands could generate blood cells through intermediate progenitors called hemogenic endothelial cells [71]. From the sixth week of gestation, the secondary yolk sac appears as a cystic structure covered by numerous superficial small vessels [60]. The mesothelial and endodermal layers have absorptive functions and are active in endocytosis/digestion [72]. In addition, the endodermal layer in the source of several proteins including acute-phase proteins, such as prealbumin, albumin, transferrin, and α_1-antitrypsin [73], as well as α-fetoprotein, which is produced by both the adult and fetal liver [60, 71]. A major function of the yolk sac is carbohydrate, protein, and lipid accumulation for embryo nutrition (*vitellum*) [74]. The yolk sac, therefore, provides lipids and lipid-soluble nutrients to embryos during the early phases of development [74].

It could be considered that the trophoblastic-yolk sac-related phenotype could favor the regulation of lipid metabolism genes [75], the hematopoietic-cell derived control with recruitment of immune cells and the induction of an angiogenic switch [71] to enable new tissue immunological tolerance during the inflammatory response [22]. In addition, through the synthesis and release of acute-phase

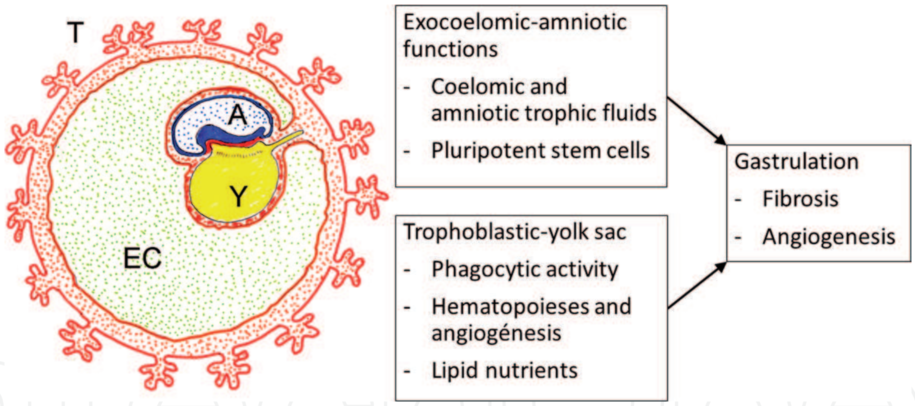

Figure 2.
The recapitulated extra-embryonic functions in the portal hypertensive inflammatory response. Inflammation could recapitulate ontogeny by reexpressing two hypothetical extra-embryonic axes: the exocoelomic-amniotic axis and the trophoblastic-yolk sac axis in the interstitial space of the injured tissue. The interstitial integration of both pathological axes into the injured tissues and organs could finally induce a gastrulation-like process, which contributes to develop a new tissue by regeneration and/or by scarring. A: amnion; EC: exocoelomic cavity; T: trophoblast; Y: yolk sac.

proteins, this extra-embryonic phenotype could reduce oxidative, nitrosative, and enzymatic stress, activate the complement-coagulation system, regulate the lipid metabolism [74], and favor phagocytosis [69, 70, 72], a specific form of endocytosis primarily associated with nutrition in unicellular organisms and with innate and adaptive immunity in mammals [69] (**Figure 2**).

The molecular and cellular contribution made by the above-mentioned extra-embryonic membranes, i.e., coelomic-amniotic and trophoblast-yolk sac to the intra-embryonic mesoderm, could be essential for embryo development and organogenesis [76]. Moreover, these primitive extra-embryonic structures can be internalized by the embryo at the early developmental stages [76]. Consequently, the hypothesized reexpression of the functions made by these extra-embryonic membranes during the postnatal life, when an inflammatory process is produced, could be a key process needed to repair the injured organism [7, 22, 54].

Both the coelomic-amniotic and trophoblast-yolk sac phenotypes reexpressed during the inflammatory response would therefore contribute to the formation of new tissue by regeneration and/or by scarring. Therefore, these two extra-embryonic phenotypes could act on the injured *interstitium* in a similar fashion as they act during embryonic development, using similar mechanisms [7, 22].

The hypothesized comparison between the coelomic-amniotic and trophoblastic-yolk sac phenotypes with the neurogenic and immune inflammatory phenotypes, respectively, would explain that the interstitial integration of both pathological axes in the injured tissues and organs could finally induce a gastrulation-like process [54] (**Figure 3**). It could be accepted that the above-mentioned extra-embryonic phenotypes are internalized during gastrulation to create the intra-embryonic mesoderm [76]. Gastrulation is the first major shape change of the developing embryo. In this development phase, the three embryogenic germ layers, i.e., ectoderm, mesoderm, and endoderm, are delineated [37]. Afterward, mesenchymal-epithelial transitions occur to create a secondary epithelium as part of somitogenesis. Then commitment and diversification of cells forming mesoendodermal structures are produced [77, 78]. The concept that fibroblasts are simple residual embryonic mesenchymal cells explains the incorrect and often interchangeable substitution of the term *fibroblast* for *mesenchymal cell* [78]. The vast arrangement of the mesenchyma, in the extra- and intra-embryonic structures, suggests an important role of the mesenchyma in orchestrating embryo development. In addition, mesenchymal stem cells are a versatile group of cells derived from mesodermal progenitors and can be found in several fetal and adult tissues [28–39].

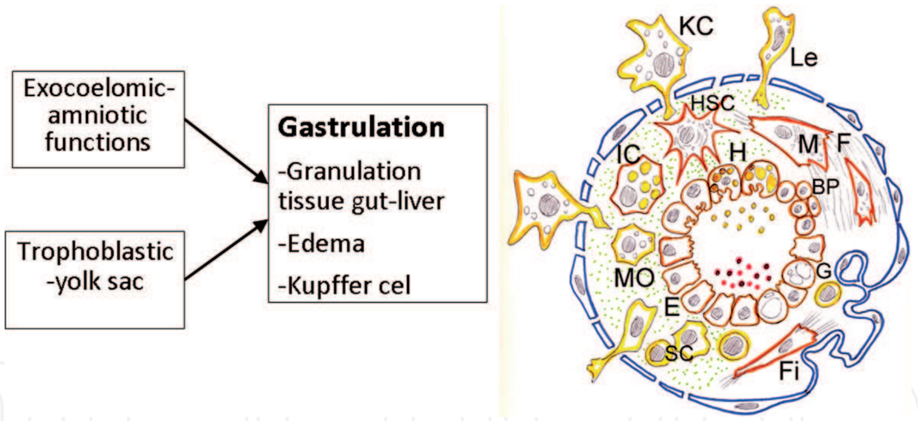

Figure 3.
The reexpression of the two hypothetical extra-embryonic axes. The exocoelomic-amniotic axis and the trophoblastic-yolk sac axis in the interstitial splanchnic space; i.e., the gut-liver axis. The interstitial activation of these two extra-embryonic axes induce a gastrulation-like process, which causes portal fibrosis and steatosis in the liver while in the gastrointestinal tract an excessive angiogenic response is produced. BP: biliary proliferation; E: enterocyte; F: fibrosis; Fi: fibroblasts; G: goblet cell; KC: Kupffer cell; H: hepatocyte; HSC: hepatic stellate cell; IC: Ito cell; Le: leukocyte; Mo: macrophages; MF: myofibroblasts; SC: stem cells.

5. The portal hypertensive inflammatory response: an ontogenic recapitulation

The portal venous system includes all veins that carry blood from the abdominal part of the alimentary tract, spleen, pancreas, and gallbladder to the liver [79]. The fetal architecture of the afferent portal venous circulation of the liver is acquired between the fourth and sixth week. At the end of this process, the portal venous system is formed from several distinct segments of the previous extra-embryonic vitelline veins. The efferent venous vessels of the liver also derive from the extra-embryonic vitelline veins [80].

The right and left paired vitelline veins transport blood from the yolk sac to the heart [80]. Hence, this type of circulation will be maintained and represented by the portal venous system; although, in this case, the blood transport is from the abdominal part of the alimentary tract, including the microbiome, spleen, pancreas, and gallbladder to the heart, but after passing through the liver [79]. Therefore, the portal venous system allows for the spatial distribution of different splanchnic functions and their coordinated integration that also is essential for the physiological functioning of the organism.

The existence of hyperpressure in the portal venous system induces the impairment of the splanchnic functions that, in addition are aggravated by the associated progression of the liver disease [81]. It could be hypothesized that chronic hemodynamic, vascular, and metabolic changes in portal hypertension could have an inflammatory origin, most probably subsequent to splanchnic inflammation [81–83]. Since, it has been proposed that the inflammatory response could recapitulate ontogeny by reexpressing the two hypothetical extra-embryonic axes, i.e., coelomic-amniotic and trophoblastic-yolk sac, in the interstitial space of the injured tissue [7, 22, 54], the splanchnic alterations related to portal hypertension could be also attributed to a recapitulation of the embryonic functions of the tissues and organs whose venous drainage is made for the portal system.

In this case, the splanchnic changes related to portal hypertension would represent the ontogenic recapitulation of the coelomic-amniotic-related (neurogenic inflammatory phenotype) and trophoblastic-yolk sac-related (immune inflammatory phenotype) functions. These functions would induce a gastrulation-like process (endocrine inflammatory phenotype), which would remodel it, since they are coupled into the *interstitium* of the splanchnic organs and tissues.

6. The reexpresion of the coelomic-amniotic-related phenotype in portal hypertension

Portal hypertension could evolve with the reexpression of the coelomic-amniotic phenotype, which begins with a pathological neuromuscular response that includes sensitive impairment, like unconscious stress sensation with autonomic dysfunction, and motor alterations including liver vasoconstriction (ischemia) and gut vasodilation (reperfusion) [1, 83]. It is noteworthy that although the mesenteric and the hepatic vascular beds share alterations in the same vasoactive pathways, they are not working in parallel [1]. Unlike the vasoconstriction in the intrahepatic vasculature, the alimentary tract vasculature undergoes a progressive vasodilation. In turn, the splanchnic vasodilation produces systemic hypotension, vascular underfilling, stimulation of endogenous vasoactive systems, including the renin-angiotensin-aldosterone system with save of Na^+ and water, plasma volume expansion, and increased cardiac index (hyperkinetic syndrome) [2, 79].

It is accepted that the hyperkinetic syndrome plays a key role in the pathogenesis of renal dysfunction and ascites in chronic liver disease [83]. Therefore, a basic pathogenic mechanism of this complex neurovascular response would be chronic hydroelectrolytic alterations [81].

The central nervous system has an initial and important influence in the evolution of portal hypertension. Chronic liver disease and portal hypertension can stimulate the hypothalamic-pituitary-adrenal axis and produce chronic secondary autonomic dysfunction [84] associated with a decreased response to vasoconstrictors, which may be caused by an increased concentration of vasodilators, including vasodilating peptides [85]. Chronic secondary autonomic dysfunction produces orthostatic hypotension, fatigue, gastrointestinal mobility disorders, with delayed gastric emptying, and prolonged transit times [84]. In addition, the central nervous system can influence immune function by stimulating the hypothalamic-pituitary-adrenal axis. It can also activate specific pathways within the sympathetic nervous system, which mainly damps down the immune phenotype triggered by the inflammatory splanchnic response [86].

The later evolution of the portal hypertensive syndrome is possibly determined by increased endothelial permeability in the gut-liver axis, which is secondary to a complex neurovascular response, that it also produces interstitial edema [81]. The increased hydrostatic pressure should preferentially drive fluid into the lymphatics, thus increasing mesenteric lymph flow [87, 88] and resulting in dilation of cistern chili [89]. It is accepted that when the high-output state of the mesenteric lymph circulation is overwhelmed, excess lymph is collected in the peritoneal cavity leading to ascites [87] and in 0.5–1% of cirrhotic patients even chylous ascites [90]. It has been proposed that decompensation related to severe hepatic insufficiency would induce an acute-on-chronic inflammatory response [81]. In this case, the splanchnic *interstitium*, the mesentery lymph, and the peritoneal mesothelium seem to create an inflammatory axis that produces ascites [91, 92].

Ascitic fluid formation is a not well-known pathogenic mechanism. However, ascitic fluid is a bioactive medium containing electrolytes, with high levels of sodium and proteins including albumin and enzymes, as well as cells including leukocytes [93]. Some of these characteristics make it similar to another bioactive medium, the amniotic fluid [94, 95]. Amniotic fluid, the protecting liquid contained in the amnion cavity, is an essential component for fetal development and maturation during pregnancy [95–97]. The hypothetical comparison of amniotic and ascitic fluid characteristics would make it worthwhile to reapproach the role of peritoneal mesothelial cells in the etiopathogeny of ascites in the portal hypertensive syndrome [81]. The functional comparison of amniotic and ascitic fluids would imply that in the decompensated portal hypertensive syndrome, the abdominal mesothelium acquires properties of the amniotic membrane or amnion. This hypothesis would imply several suggestions. For example, the intestine and, by extension, the liver, could not benefit from the supposed trophic properties of the ascitic fluid, given that peritoneal cavity-gastrointestinal tract pathway does not exist [91, 92]. In this way, the ascitic fluid could have therapeutic actions if it is administered by the enteral route in the cirrhotic patients [91, 92].

The interstitial edema in the gut-liver axis could be considered as the space where the battle of inflammation develops. In particular, during the intestinal inflammatory response secondary to portal hypertension the interstitial space increases in size as a consequence of successive infiltration suffered by plasmatic molecules, blood cells, and bacteria. The impairment of the lymph pumping and lymphangiectasia also collaborate in producing splanchnic edema [98, 99]. There is increased intestinal epithelial permeability associated with the endothelial post-capillary permeability in patients with chronic liver disease [100]. Findings of increased endotoxin and bacterial DNA in blood in patients with cirrhosis support the relevance of the increased intestinal epithelial permeability observed in these patients with portal hypertension [99, 100].

Liver and biliary tract diseases are common extra-intestinal manifestations for inflammatory bowel diseases, including gut microbiota alterations [101–105]. This is why the etiopathogenic participation of the intestinal inflammatory response cannot be excluded from the pathology produced in the hepatic parenchyma in the cases of portal hypertension. In particular, this pathophysiological mechanism occurs when portal hypertension leads to increased permeability of the sinusoidal endothelium that, in turn, causes edema in the interstitial space of Disse [106]. It is evident that the space of Disse has a connection to the interstitial space of the portal tract or space of Mall [98]. Therefore, it is likely that fluid filtered out of the inflamed sinusoids into the space of Disse flows through the channel traversing the limiting plate to reach the interstitial space of the portal tracts [98]. Interestingly enough, it was found that superphysiological or pathological levels of interstitial flow could induce fibroblast motility as well as drive myofibroblast differentiation and matrix alignment [106]. Hence, fibroblasts appear to be highly sensitive to interstitial flow and heightened flow could drive myofibroblast differentiation and extracellular matrix remodeling that recapitulates certain pathological features of cirrhosis [107]. Besides, in cases of endotoxemia, this increased interstitial flow would collaborate in the production of edema in the space of Disse. In addition, endotoxemia favors the intrahepatic lymph stasis, which may be caused by a reduction in the pumping activity of the extra-hepatic and the intrahepatic large lymph vessels [108]. In turn, the edematous interstitial space of Disse could show analogies to typical stem cell niches to retain mesenchymal stem cells or stem-like cells as well as to influence their cellular fate [109]. In this sense, the edematous space of Disse could serve as a niche of the hepatic stellate cells because of their mesodermal origin [109].

7. The reexpression of the trophoblastic-yolk sac-related phenotype in portal hypertension

An array of functions made up by the secondary yolk sac seems to be expressed by the organism when it suffers portal hypertension. In rats with prehepatic portal hypertension, the reexpression of this extra-embryonic phenotype by the splanchnic tissues and organs is coupled with the upregulation of the immune cells [2, 110, 111], as well as with the development of dyslipidemia and hepatic steatosis [112, 113].

Prehepatic portal hypertension is one factor determining bacterial intestinal translocation to mesenteric lymph nodes [111, 114]. In addition, the increased presence of mast cells in the hypertrophied mesenteric lymph nodes [115] would not only collaborate in the production of mesenteric adenitis [111], but also would constitute a source of inflammatory mediators located between the intestine and systemic blood circulation [116]. The mesenteric lymph nodes are key structures involved in the gut-associated lymphoid tissue (GALT) [117]. GALT constitutes the largest lymphoid organ of the body, and its activation in portal hypertensive enteropathy results in the release of several inflammatory mediators. These mediators would be transported by the intestinal lymph nodes to the pulmonary circulation inducing an inflammatory phenotype and later to the systemic circulation [91, 118, 119].

In response to bacterial translocation, gut epithelial cells release chemokines that induce the recruitment of dendritic cells to the mucosae [100, 114]. Once activated, mature intestinal dendritic cells can induce and prime mucosal and mesenteric lymph nodes, B and T cells [100, 114]. After maturation, these B and T cells are released into the blood stream and, due to surface expression of the specific homing markers, home back to reside within the lamina propria [114]. In addition, aberrant intestinal T lymphocytes homing to the liver may contribute to trigger immune hepatic damage [100]. Moreover, data from the literature indicate a relationship between the gut microbiota and the intestinal stem cells. Thus, lipopolysaccharide-sensitive cell types can be seen within bone marrow-derived cells which are involved in the development of inflammation in the adipose tissue of obese and type 2-diabetic mice [120]. Intestinal epithelial cells not only produce and release mediators affecting immune cells, but they also respond to factors produced by the subjacent immune cells [121]. In addition to the damage of intestinal epithelial cells, intestinal epithelial barrier dysfunction can result from loss of junctional complex integrity with increased paracellular permeability [100].

Nowadays, there have been various reports suggesting the role of gut flora and bacterial translocation in the pathogenesis of portal hypertension and chronic liver disease [101, 102, 122]. Translocated bacterial products could activate Kupffer cells through pattern recognition receptors such as toll-like receptors (TLRs) and NOD-like receptors (NLRs). Recent studies suggested that TLR4 signaling can be activated not only by pathogen-associated molecular patterns (PAMPs), but also by some endogenous ligands or damage-associated molecular patterns (DAMPs), which are released from damaged cells [123, 124]. In turn, activated Kupffer cells significantly increase their release of oxidative and nitrosative stress species and proinflammatory cytokines, including chemokines [101].

Chemokine expression by Kupffer cells, hepatic stellate cells, and sinusoidal endothelial cells drive the migration of immune cells populations [125]. In particular, CXCL12 (SDF-1α), which binds to the CXCR4 receptor, regulates several pathological responses. CXCL12 is crucial in early embryogenesis, hematopoiesis, and angiogenesis, as well as maintenance of the bone marrow stem cell niche [125]. In addition, the liver with its dual arterial and venous blood supply has a low oxygen tension, which has worsened during portal hypertension leading to hypoxic environment that could stimulate CXCL12 production with recruitment of immune cells [125].

Hepatic macrophages hold a central position in the pathogenesis of chronic liver injury. Resident hepatic macrophages or self-renewing embryo-derived local macrophages, i.e., Kupffer cells, appear essential for initiating inflammatory response while infiltrating bone marrow-derived macrophages originated from circulating monocytes are linked to chronic inflammation and fibrogénesis [126]. However, after local differentiation into resident macrophages they could restore liver integrity and then are termed restorative macrophages [126].

In the yolk sac, the blood islands are generated by mesodermal cell aggregates that differentiate into both hematopoietic and endothelial cells [127]. The simultaneous appearance of these two lineages suggests the existence of a common ancestral precursor for endothelial and hematopoietic cells: the hemangioblast [128]. In addition, the embryo could generate their definitive hematopoiesis from a hemogenic endothelium derived from a transient mesenchymal population [126, 127]. This close physiological ontogenic association between hematopoiesis and angiogenesis could persist during the pathophysiological response that produces portal hypertension. In this case, during the evolution of portal hypertensive pathology, the gut-liver axis could recapitulate the functions derived from the mesenchymal-angiogenic-hematopoietic axis that form the blood islands in the yolk sac [125, 127].

It has been suggested that mast cells could mediate the pathogenic relationship between portal hypertension and the angiogenic hyperactivity that occurs in experimental portal hypertension, particularly in the alimentary tract [110, 115]. The formation of new blood vessels is a key mechanism in the pathogenesis of portal hypertension [129]. Although the precise mechanisms by which the angiogenesis-associated response in portal hypertension is modulated remain to be defined, several mediators produced by mast cells are involved in angiogenesis [110]. This is the reason why it has been proposed that the angiogenic hyperactivity occurring in portal hypertension could mainly be mediated by mast cells [110, 115]. In addition, the exceeding angiogenesis through the neoformed collateral circulation allows portal blood flow to directly reach the systemic circulation [79]. However, the morphological vascular alterations stand out in the chronic portal hypertensive enteropathy [130]. The exacerbated angiogenesis produced in the intestinal wall during the evolution of portal hypertension is similar to the process of vasculogenesis that occurs in the extra-embryonic membranes [131]. More explicitly, the endothelial cells of the blood islands expand to cover the entire yolk sac creating a vascular network known as the capillary plexus [131], the precursor of the vitelline veins which, in turn, are the embryonic origin of the portal system [80].

From an ontogenic point of view, vitellogenesis plays a vital role in providing lipids and lipid-soluble nutrients to embryos [132]. The ability to transport fat in the form of lipoproteins through the circulatory system by eukaryotes is one of the most significant functions right from the beginning of existence [133]. Thus, the evolutionary advancement of storing energy in the form of fat has provided organisms with enormous advantages for adapting to environmental and developmental changes [134].

We have previously shown that prehepatic portal hypertension in the rat induces liver steatosis and causes changes in lipid and carbohydrate metabolisms similar to those produced in chronic inflammatory conditions described in metabolic syndrome in humans [112, 113, 135]. It has been suggested that in experimental prehepatic portal hypertension, the liver could constitute a kind of yolk sac in which the animal carries out a pathological deposit of lipids [81, 92]. Prehepatic portal hypertension in the rat, both in short- (1 month) and in the long-term (1 year), produces hepatic accumulation of triglycerides and cholesterol [112, 113]. Nonetheless, the mechanisms by which portal hypertension could induce liver steatosis are not finally understood [135] (**Figure 4**).

Inflammation, and the concomitant acute-phase response, induces marked changes in the lipoprotein profile [136]. Thus, in the prehepatic portal hypertensive rat, liver steatosis is associated with the plasmatic increase of low density lipoprotein (LDL) and lipopolysaccharide binding protein (LBP) as well as a reduction of high-density lipoproteins (HDL) [135]. In turn, hepatic steatosis might play a key role in the pathogenesis of cardiovascular disease through the systemic release of several inflammatory mediators and/or through the production of insulin resistance and atherogenic dyslipidemia [137, 138].

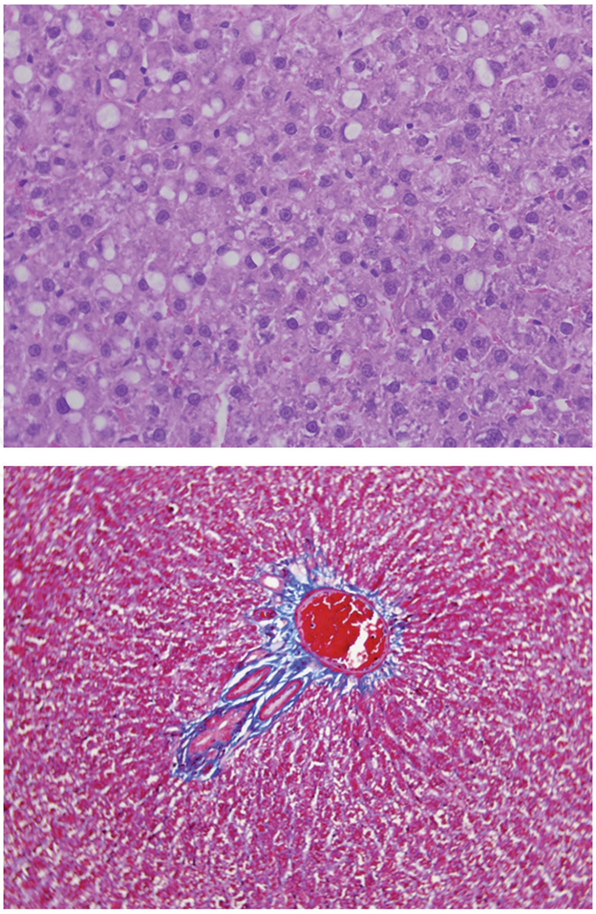

Figure 4.
Histopathological images of rat liver with long-term portal hypertension (3 months). The liver presents diffuse steatosis (superior) and portal fibrosis (inferior) as the result of splanchnic and systemic inflammatory responses. This inflammatory process could be proposed as the representation of the recapitulated extra-embryonic functions in the splanchnic area when portal hypertension is developed.

Gut microbiota could alter nutrient absorption, energy homeostasis, and intestinal permeability, with a translocation of bacteria-derived products to the liver. It could also cause hepatocellular inflammation and nonalcoholic fatty liver disease (NAFLD) [105, 139]. Western diet seems to cause dysbiosis, i.e., vitellogenic microbiome, which affects host gastrointestinal metabolism and contributes to higher incidences of metabolic syndrome, including NAFLD [139, 140]. Genetics might also modulate the spectrum of liver disease and its progression [141]. In turn, when portal hypertension coexists, the factors previously mentioned would represent an associated risk factor for the development of NAFLD and metabolic syndrome.

In portal hypertension, cholesterol synthesis could play a key role during the hypothesized reexpression of the vitellogenic phenotype. The liver plays a central role in cholesterol metabolism. Hepatocytes not only express a number of different lipoprotein receptors that enable them to take up cholesterol, but also synthesized cholesterol *de novo* within the liver [142, 143]. In addition, to these input pathways, the liver secretes cholesterol by two routes, the first, within triglyceride-rich very low density lipoprotein (VLDL) to supplying peripheral cells with fatty acids, fat soluble vitamins, and cholesterol. And, secondly, the liver releases cholesterol into bile, either directly as free cholesterol or after conversion into bile acids [142].

Cholesterol is used locally to synthesize glucocorticoids and mineralocorticoids, which could regulate microcirculatory functions and immune cell activation [144]. Perhaps, the ability of local corticosteroid synthesis is upregulated in the inflamed tissue due to the metabolic and functional needs of the neoformed tissue including angiogenesis in portal hypertension [7, 22]. Moreover, the pro-inflammatory and anti-inflammatory functions of androgens and estrogens and progesterone, respectively, suggest that endogenous sex steroids may influence immune functions [145–147] and, therefore, the evolution of the portal inflammatory response. In particular, estrogen has been shown to be effective in animal models of portal hypertension with cirrhosis by suppressing hepatic fibrosis and relaxing the hepatic sinusoid, and could reverse the severity of hyperdynamic circulation and the vascular hyporeactivity of the mesenteric arteries in portal hypertensive rats without cirrhosis [148].

Hence, it could be proposed that within the splanchnic impairments related to portal hypertension, the stimulation of the angiogenic-hematopoietic axis, the cellular and bacterial interstitial infiltration of the tissues and organs and the acute-phase-response, including dyslipidemia and hepatic steatosis (vitellogenic phenotype), seem to recall the functions characteristic of the secondary yolk sac during embryo development.

In this sense, the microvesicles, released from practically all cells including mesenchymal stem cells [149], would collaborate in inducing the recapitulation of extra-embryonic functions during the evolution of portal hypertension. Microvesicles contain lipids, proteins, RNA, and micro-RNAs and could act as vectors of information that regulate the function of target cells [150]. Microvesicles from inflammatory cells are suspected to be involved in various diseases. In particular, microvesicles probably enhance portal hypertension by contributing to splanchnic vasomotor alterations and angiogenesis [151].

8. Coupling extra-embryonic phenotypes to induce a gastrulation-like liver phenotype

In the current review, we propose that during the evolution of portal hypertension different extra-embryonic functions, such as the coelomic-amniotic and the trophoblastic-yolk sac or vitelline function, would be successively recapitulated. If so, the inflammatory conditions that characterize portal hypertension could actually represent the reexpression of extra-embryonic mechanisms that have been already used during the early phases of embryonic development. In this way, the pathophysiological mechanisms involved in the above-mentioned inflammatory response could represent the recapitulation of the extra-embryonic functions, which collaborate together to make an embryo-like tissue from gastrulation [7, 54] (**Figure 3**).

The liver stands out among other organs since its persistent injury usually results in the chronic activation of inflammation and the wound-healing response [7, 152]. Development of the liver during early embryogenesis may share similarities with pathophysiological processes seen in adulthood, such as acute liver injury and liver regeneration, but also in liver fibrosis [152–154]. The increasing knowledge of the extra-hepatic involvement typical of this fibrotic liver disease, however, suggests that this wound healing process is associated with a complex systemic pathogenesis [155]. Portal hypertension is the major hemodynamic complication of a variety of diseases that obstruct portal blood flow, including liver cirrhosis [79]. Portal hypertension in the cirrhotic patient could be associated with hyperkinetic syndrome, increased total blood volume by sodium and water retention [155], endothelial dysfunction [81, 83, 156] in the splanchnic and systemic circulation [81, 83, 119], esophageal varices, ascites, encephalopathy, and hepatorenal syndrome [157].

The severe systemic complications of the portal hypertension syndrome accompanying the wound-healing liver reaction could be based on some metabolic similarities that can be established with the extra-embryonic coelomic-amniotic and trophoblastic-yolk sac functions playing the leading role during embryonic development [7]. Thus, the confluence of these two extra-embryonic axes in the injured liver could favor a gastrulation-like response in which fibrogenesis could predominate [7, 22, 54]. Therefore, the wound-healing liver reaction that characterizes the cirrhotic process could have properties comparable to an embryo and, in particular, with its initial evolutive phase, namely gastrulation [22]. If so, the gastrulation-related process with neoformation of a reparative tissue could be based on the recapitulation of the developmental process of the intra-embryonic mesenchyme [158].

The interstitial space of Disse could be schematically represented like an area fundamentally surrounded by a sinusoidal endothelium. Inside this endothelium, an inflammatory response is developed, which is made up by the hepatic stellate cell. In turn, the liver interstitial inflammation would be activated by means of the reexpression of extra-embryonic functions by the host organism, which provides molecules and cells selectively to the inflamed interstitial space through the sinusoidal endothelium [22] (**Figures 3** and **5**).

Hepatic stellate cells are liver-specific mesenchymal cells located in the space of Disse between the sinusoidal endothelial cells and hepatic epithelial cells [159]. Hepatic stellate cells also known as Ito cells, fat-storing cells, vitamin A-storing cells, or lipocytes, store excess vitamin A as retinyl esters in lipid droplets within their cytoplasm [159, 160]. In pathological conditions, hepatic stellate cells upon activation lose the vitamin A-containing lipid droplets and produce large amounts of collagen [160]. Therefore, modulation of vitamin A-containing lipid droplets has been suggested to have a therapeutic impact on the development of liver fibrosis [160] (**Table 2**). Hepatic stellate cells are known to express both mesenchymal and neural lineage markers [161, 162]. Moreover, during

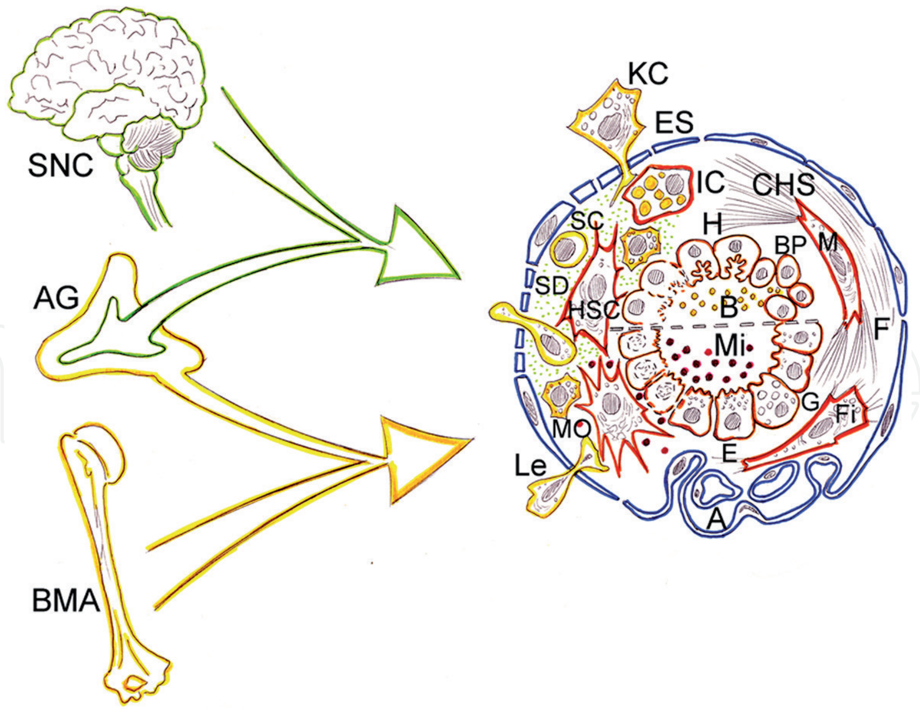

Figure 5.
Schematic representation of the systemic inflammatory response in portal hypertension in order to produce a systemic wound-healing phenotype. By means of two inflammatory phenotypes expression; i.e., neurogenic (CNS and AG) and immune (BMA), into the interstitial injured splanchnic area, an endocrine phenotype could be induced, that ultimately would causes a wound-like response. Thus, fibrosis and angiogenesis will be produced in the splanchnic area. A: angiogenesis; AG: adrenal gland; B: bile; BMA: bone marrow; BP: biliary proliferation; CHS: cholestasis; CNS: central nervous system; E: enterocyte; ES: endothelial sinusoid; G: goblet cell; HSC: hepatic stellate cell; IC: Ito cell; KC: Kupffer cell; Le: leukocyte; Mo: macrophages; M: myofibroblast; Mi: microbiome; SC: stem cells; SD: space of Disse.

The coelomic-amniotic phenotype

- Hyperkinetic syndrome
- Stimulation of the hypothalamo-pituitary-adrenal axis and the sympathetic nervous system
- Interstitial splanchnic edema
- Increased mesenteric lymph circulation
- Ascitic fluid

The trophoblastic-yolk sac (vitelline) phenotype

- Acute-phase response
- Dyslipidemia
- Local metabolism of cholesterol (steroid hormones)
- Hepatic steatosis
- Recapitulated mesenchymal-angiogenic-hematopoietic axis
- Portal hypertensive enteropathy
- Dysbiosis and intestinal bacterial translocation
- Splanchnic microvesicles

The gastrulation-like phenotype

- Hepatic stellate cell activation
- Fat-storing cells
- Myofibroblast
- Hepatic fibrosis

Table 2.
Portal hypertensive inflammatory phenotypes.

liver injury, stellate cells activate into alpha smooth muscle actin-expressing contractile myofibroblasts, which increase vascular resistance thereby promoting portal hypertension [163, 164]. Mesodermal mesenchymal cells including hepatic stellate cells are the major source of myofibroblasts [164]. In this sense, activated-hepatic stellate cells also strengthen the immune response through the production of a wide array of cytokines and chemokines [4]. Finally, hepatic stellate cells are able to adopt a fibrogenic phenotype and participate in extracellular matrix remodeling [163] (**Figure 4**).

Kupffer cells activate hepatic stellate cells via paracrine mechanisms, likely involving the profibrotic and mitogenic cytokines TGF-β and PDGF [165, 166]. Early deposition of an extracellular matrix in the subendothelial space of Disse causes *capillarization* of the sinusoid, diminished liver function, and contributes to the perpetuation of hepatic stellate cell activation [159, 160, 167]. Liver fibrogenesis is not only sustained by a heterogenic population of profibrogenic hepatic myofibroblasts [3, 4], but also includes mesothelial-related capsular fibrosis [167]. Mesothelial cells have a phenotype intermediate between epithelial cells and mesenchymal cells and these both type of cells could then undergo myofibroblastic transdifferentiation. Upon liver injury, it has been demonstrated that mesothelial cells participate in capsular fibrosis of the liver surface via differentiation to hepatic stellate cells and myofibroblasts [167]. In portal hypertension, the formation of a fibrotic scar tissue in the liver is associated with the development of an excessive gastrointestinal angiogenic response [110]. Therefore, the two principal components for creating granulation tissue, i.e., fibroplasia and angiogenesis, are distributed along the portal axis. In essence, the portal venous system continues playing a key role as a spatial delivery of functions in pathological situations.

9. Conclusion

The diverse functions of hepatic stellate cells in homeostasis and inflammation indicate the versatile nature of these mesenchymal-derived cells, which could adopt numerous phenotypes according to the interstitial microenvironmental characteristics [163]. Therefore, these hepatic cellular population, thanks to their potential ability to integrate and reexpress functions showing analogies to extra-embryonic functions, display characteristics of stem/progenitor cells [109]. In this way, during the development of portal hypertension, hepatic stellate cells not only could reexpress extra-embryonic functions but also could adapt themselves in order to induce a gastrulation-related process in the space of Disse. Therefore, by understanding the ontogenic interactions between hepatic stellate cells and the host inflammatory response in portal hypertension, it is possible to design effective therapeutic and prophylactic strategies to avoid or reverse wound-like hypertensive response.

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Author details

Maria Angeles Aller[1], Javier Blanco-Rivero[2,3,4], Ana Arias[5] and Jaime Arias[1]*

1 Department of Surgery, School of Medicine, Complutense University of Madrid, Madrid, Spain

2 Department of Physiology, School of Medicine, Autonomous University of Madrid, Madrid, Spain

3 Instituto de Investigación Biomédica La Paz (IdIPAZ), Madrid, España

4 Centro de Investigación Biomédica en Red (Ciber) de Enfermedades Cardiovasculares, Madrid, España

5 Department of Internal Medicine, Puerta de Hierro Hospital, School of Medicine, Autonoma University of Madrid, Madrid, Spain

*Address all correspondence to: jarias@med.ucm.es

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