Portal Hypertension as Immune Mediate Disease

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Context: Portal Hypertension (PH) is a progressive complication due to chronic liver disease. In addition to pathophysiologic changes in the micro-circulation, in PH are established fibrous tissue (peripoortal fibrous septal) and regenerative hyperplastic nodules (from micro- to macro-nodules) promoting hepatic architectural distortion.

Evidence Acquisition: A literature search of electronic databases was undertaken for the major studies published from 1981 to today. The databases searched were: PubMed, EMBASE, Orphanet, Midline and Cochrane Library. We used the keywords: "portal hypertension, children, immune system, endocrine system, liver fibrosis".

Results: It is believed that PH results from three "phenotype": ischemia-reperfusion, involving nervous system (NS); edema and oxidative damage, involving immune system; inflammation and angiogenesis, involving endocrine system. However, its exact cause still underdiagnosed and unknown.

Conclusions: PH is a dynamic and potentially reversible process. Researchers have tried to demonstrate mechanisms underlying PH and its related complications. This review focuses on the current knowledge regarding the pathogenesis, and immune, endocrine-metabolic factors of disease. The strong positive association between immune system and development of PH could be efficient to identify non-invasive markers of disease, to modify prognosis of PH, and to development and application of specific and individual anti-inflammatory therapy.

Keywords: Portal Hypertension; Children; Immune System; Endocrine System; Liver Fibrosis

1. Context

Portal hypertension (PH) occurs when portal pressure gradient or the pressure difference between the portal and inferior cava vein strongly increases. In the best of our knowledge, exact epidemiological data of PH are still unknown. However, its incidence is very similar to PH-related complication (ascites, hepatorenal syndrome, life threatening gastroesophageal bleeding, portosystemic encephalopathy, hepatopulmonary syndrome, hyperkinetic syndrome and sepsis). In fact, PH is diagnosed when its clinical manifestations appear (1). In healthy subjects, the portal venous pressure ranges from 7 to 10 mmHg and the hepatic venous pressure gradient changes from 1 to 4 mmHg. PH is clinically significant when portal vein pressures or portal vein to hepatic vein greater than 5 mmHg and 10 mm Hg gradient respectively (2). In adults, pressure gradients above 10 mmHg cause esophageal varices formation whether greater than 12 mmHg lead to ascites and variceal bleeding (3). On other hand, several children can present misunderstood presinusoidal PH.

Therefore the diagnosis of PH often can be made by the indirect clinical signs as well as esophageal varices and/or splenomegaly. PH is a progressive complication due to chronic liver disease in which are established fibrous tissue (periportal fibrous septal) and regenerative hyperplastic nodules (from micro- to macro-nodules) promoting hepatic architectural distortion (4). Persistent hepatic structural alterations induce vasoconstriction which can dramatically increase local resistance to blood flow range from 20% to 30% (5). In addition to pathophysiologic changes in the micro-circulation of the liver, it has been also describe abnormalities of sinusoidal endothelial cells (SEC) (obstruction of endothelial fenestrae, accumulation of collagen within the space of Disse, development of a sinusoidal basement membrane) producing lower amounts of nitric oxide (NO) (6). This latter further favour an increase in vascular resistance. Adaptation to these consequences causes development of porto systemic collaterals, splanchic arteriolar vasodilatation
Table 1. Etiology of Portal Hypertension in Children

<table>
<thead>
<tr>
<th>Types of Portal Hypertension</th>
<th>Etiology</th>
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<tbody>
<tr>
<td>Pre-hepatic</td>
<td>Arteriovenous fistula</td>
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<tr>
<td></td>
<td>Splenomegaly</td>
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<td></td>
<td>Congenital stenosis of the portal vein</td>
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<td></td>
<td>Portal vein thrombosis</td>
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<tr>
<td>Intra-hepatic</td>
<td>Autoimmune hepatitis</td>
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<td></td>
<td>Hepatitis B and C</td>
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<tr>
<td></td>
<td>Idiopathic portal hypertension</td>
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<tr>
<td></td>
<td>Gaucher’s disease</td>
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<td></td>
<td>Schistosomiasis</td>
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<tr>
<td></td>
<td>Veno-occlusive disease</td>
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<tr>
<td></td>
<td>Alfa 1 anti-trypsin deficiency</td>
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<td></td>
<td>Wilson’s disease</td>
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<tr>
<td></td>
<td>Steato-hepatitis</td>
</tr>
<tr>
<td></td>
<td>Glycosen storage disease type IV</td>
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<tr>
<td></td>
<td>Toxins</td>
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<tr>
<td></td>
<td>Biliary atresia</td>
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<tr>
<td></td>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td></td>
<td>Primary biliary cirrhosis</td>
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<tr>
<td></td>
<td>Caroll’s disease</td>
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<tr>
<td></td>
<td>Congenital hepatic fibrosis</td>
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<tr>
<td></td>
<td>Cystic fibrosis</td>
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<tr>
<td></td>
<td>Peliosishepatis</td>
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<td></td>
<td>Familial cholestasis</td>
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<tr>
<td></td>
<td>Choledochal cyst</td>
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<tr>
<td>Post-hepatic</td>
<td>Inferior vena cava obstruction</td>
</tr>
<tr>
<td></td>
<td>Budd-Chiari syndrome</td>
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<td></td>
<td>Congestive heart failure</td>
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</table>

and splenomegaly (5). PH also persists for increased cardiac output (result from elevated venous return and decreased afterload). In conclusion, both, increased intra- and extra-hepatic resistance, lead to development and perpetuation of PH. However, these hemodynamic events have not been confirmed in pediatric patients. Therefore, in this population underlying mechanisms are still unclear (Table 1) (1, 3).

2. Evidence Acquisition

A literature search of electronic databases was undertaken for the major studies published from 1981 to today. The databases searched were: PubMed, EMBASE, Orphanet, Midline and Cochrane Library. We used the keywords: "portal hypertension, children, immune system, endocrine system, and liver fibrosis”.

3. Results

3.1. Portal Hypertension and Nervous-Immune-Endocrine Systems: A Possible Interaction

Today, the pathogenetic mechanism of PH has not been fully understood. It is believed that PH results from three “phenotype”: ischemia-reperfusion, involving nervous system (NS); edema and oxidative damage, involving immune system; inflammation and angiogenesis, involving endocrine system (6). A large number of studies were conducted on role of NS in PH. Both in humans and animals, the mesenteric vascular system has sympathetic innervation, mediated by post-synaptic α1-adrenoreceptors (7). PH patients show a neural dysregulation. The signals of PH are detected via afferent nerves and transmitted to nucleus of the solitary tract, paraventricular nucleus and supraoptic nucleus. Efferent nerves originate from these nuclei. Blockade of any part of the reflex arc arrests development of vasodilation and hyperdynamic circulation in PH. Furthermore, PH is characterized by downregulation of mRNA and proteins involved in adrenergic transmission in the superior mesenteric artery (SMA) and sympathetic nerve atrophy/regression in the mesenteric arterial vasculature. Therefore, this mechanism might contribute to aggravating splanchnic vasodilation associated with PH (8). Otherwise, Bockx et al. demonstrated that vagus nerve stimulation improves portal hypertension. Vagus nerve also acts on liver. Its efferent neurotransmitters are acetylcholine and vasoactive intestinal peptide are vasodilators. Therefore it improves portal hypertension (9). Moreover, taking into consideration the biological activity of immune system, it seems likely that a significant role in the development of pathological changes in the liver is played by immunological imbalance. PH often appears with other autoimmune diseases such as systemic lupus erythematosus, systemic sclerosis, Raynaud’s phenomenon, celiac disease, and chronic thyroiditis (10). Several hypothesis have been given to explain these associations. Moreover, in patients affected by PH it was detected the presence of anticardiolipin antibody and anti-RNP antibody (11). Probably, immunoglobulins (Ig) an interference with prostacyclinsynthesis and favours obliteration of small vessels portal and hepatic veins (12). It has been also proposed that the altered clearance of the circulating immune complexes by hepatic kupffer cells (KC) may further favour abnormal deposition and trombosis. This leads to focal ischemia, therefore remaining well-perfused areas induce neo-angiogenesis (capillarisation of the sinusoids), increase shunt formation and subversion of liver parenchyma (13). On other hand, in patients with primary hypogammaglobulinemia was also demonstrated severe histological features, especially rare liver disorders such as nodular regenerative hyperplasia (14). PH is strongly correlated to liver injury and fibrosis, and, pathogenically, to several inflamma-
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Table 2. Distribution of Intra-Hepatic T Lymphocytes

<table>
<thead>
<tr>
<th>T-Cell-Phenotype</th>
<th>Liver</th>
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<tbody>
<tr>
<td>CD4</td>
<td>22</td>
</tr>
<tr>
<td>CD8</td>
<td>72</td>
</tr>
<tr>
<td>CD4^+</td>
<td>5</td>
</tr>
<tr>
<td>CD8^+</td>
<td>5</td>
</tr>
<tr>
<td>CD4^+</td>
<td>14</td>
</tr>
<tr>
<td>CD8^+</td>
<td>5</td>
</tr>
<tr>
<td>CD8a^+R^+</td>
<td>15.4</td>
</tr>
<tr>
<td>CD56</td>
<td>32</td>
</tr>
</tbody>
</table>

^a Data are presented as %.

Ziol et al. demonstrated a high percentage of CD8^+/CD3^+/CD57^+ cytotoxic T cells in liver sinusoids. Therefore, they hypothesized that lymphocyte could participate in the pathogenesis of nodular regenerative hyperplasia (NRH). T cells promote NRH by several ways: they are strongly expressing granzyme B, responsible for endothelial injury; they are recruited to the liver and located in atrophic areas; they also are able to achieve antigen (intra- and/or extra-hepatic) recognition and cytotoxicity in a non-major histocompatibility complex (MHC) (30). Moreover, Guo and co-workers reported that T lymphocyte subsets (CD4^+CD25^+CD127 low/-Treg) and Foxp3 ratio was strongly increased in subjects affected by hypersplenism and PH (31). In addition, reduced antigen-presenting ability of non-T cells might further promote immunological dysregulation. Merino et al. reported that these inflammatory alterations could be also drive by chemotactic cytokines (fractalkine or CX3CL1 and stromal cell-derived factor alpha or SDF1-a) and their respective receptors (CX3CR1 and CXCR4). Chemokines are differentially expressed during chronic liver diseases (32).

Therefore, in the absence of an adequate immune defense, gut bacteria and/or bacterial-derived antigens, also known pathogen-associated molecular patterns (PAMPs), can more easily reach portal venous system, promoting fibrosis and PH, recruitment of inflammatory extra-hepatic and hepatic cells, and acting as “cytokine-releasing” organ (32). IL-10 is a pleiotropic and anti-inflammatory cytokine. Gut flora of patients with PH can produce, through T and B lymphocytes, monocytes/macrophages, mast-cells, endotoxin, glucocorticoids, reactive oxygen intermediates, and pro-inflammatory cytokines (such as TNF-a and IL-1), IL-10. Bacteria colonizing the gut are also capable of inducing production, it plays an important role as a chemotactic factor, activating eosinophiles, basophiles, and neutrophiles, and T lymphocytes and drawing them to the place where a toxic agent is working. IL-8 does not seem to play a role in the hyperdynamic circulation. All these phenomena are also known as “leaky gut syndrome”, it is characterized by increased gut permeability, bacterial overgrowth, and changes in the composition of exogenous molecules and environment splenic promotes and enhances lymphocyte response (24).
TLR 2, 4
β
tLR 2-4
γ
The role of endothelin (ET)-1, ET-3, promoting increased intrathelial resistances. Cytokines, epinephrine, vasopressin, and angiotensin-II induce the synthesis of ET-1 and ET-3. These are acting through a specific receptor, named A and B, on smooth muscle cells, HSCs, endothelial and sinusoidal endothelial cells. Activation of ET-A receptor induces vasoconstriction while activation of ET-B leads to vasodilation. Serum ET-1 levels are positively correlated with degree of PH (40, 41). Vascular remodeling processes are also resulting from "hyperdynamic circulation" and/ or "forward flow" theory (42). This has been observed in all forms of PH. It is due to the presence of both increased splanchic blood flow and higher portal vascular resistance (43). Several are involved molecules. NO, arterial vasodilator factor acting through guanylyl cyclase, is produced by endothelial nitric oxide synthases (eNOS), in the splanchnic arterial circulation; by neuronal NOS (nNOS), in the nervous system; by mitochondrial nitric oxide synthase (mNOS); and by inducible NOS (iNOS), in several cell types such as vascular smooth muscle cells and macrophages. NO exerts a paradoxical role. Altered inflammatory response in patients with PH, promotes the production of NO, enhancing cyclic guanosine 3'5'-monophosphate (cGMP) related- hyperdynamic circulatory syndrome. On other hand, NO deficiency leads to elevated vascular resistances (23, 44). eNOS related-NO can be reduced by endogenous circulating amino acid asymmetric dimethylarginine (ADMA). ADMA, synthesized by proteolysis of citrulline and dimethylamine, is associated with multiorgan failure, especially liver damage (45).

In addition to heme oxygenase, guanylyl cyclase also induces the release of carbon monoxide (CO), endogenous regulator that further contributes, in the early stage of PH to maintain arterial vasodilation and systemic hyperdynamic circulation. In fact, CO is required for maintaining hepatic microvascular blood flow. CO also acts as a potent anti-inflammatory molecule that reduces synthesis of the pro-inflammatory cytokines (such as TNF-α, IL-1β, and MCP-1, MIP-1β) limits the infection (34). Disease fibrogenic processes are further induced by lipopolysaccharide (LPS) bacterial ligand of Toll-like receptor (TLR) and increased serum leptin levels, especially in patients affected by hepatitis C virus (Table 3) (35, 36).

TLRs, a family of transmembrane-protein receptors, recognize bacteria, fungi, and virus and play a critical role in the induction of innate immune responses through inflammatory cytokine including IFN. Especially, TLR4 over-expression confers hypersensitivity to LPS and higher release of vasoconstrictor molecules after endotoxin-induced KC activation. Previous studies also showed that the TLR4/ liver endothelial cells pathway, by effector protein MyD88, also regulates liver TGF-β-mediated fibrosis, and angiogenesis (37). On other hand, the splenic expression of TLR4 might be a further cause of PH due to hypersplenism. Probably, bacterial overgrowth enhances expression of TLR4 on splenic macrophage that destroy red blood cells. TLR2 genetic variants favours altered intestinal permeability and elevated risk of bacterial translocation (38).

PH also results from an increase local resistance to blood flow. The intact endothelium has a crucial role in vascular tone, as main source of vasoconstrictor and vasodilator molecules (25). In PH, the massive release of vasoconstrictors, derived from arachidonic acid, such as thromboxane (TX)-A2 or cysteinyl leukotrienes (Cys-LTs), leukotrienes C4, D4, E4, and decreased synthesis of vasodilators further promote a vascular hyper-tone (39). In addition, it has been also demonstrated vasoconstrictor role of endothelin (ET)-1, ET-3, promoting increased intrathelial resistances. Cytokines, epinephrine, vasopressin, and angiotensin-II induce the synthesis of ET-1 and ET-3. These are acting through a specific receptor, named A and B, on smooth muscle cells, HSCs, endothelial and sinusoidal endothelial cells. Activation of ET-A receptor induces vasoconstriction while activation of ET-B leads to vasodilation. Serum ET-1/e levels are positively correlated with degree of PH (40, 41). Vascular remodeling processes are also resulting from "hyperdynamic circulation" and/ or "forward flow" theory (42). This has been observed in all forms of PH. It is due to the presence of both increased splanchic blood flow and higher portal vascular resistance (43). Several are involved molecules. NO, arterial vasodilator factor acting through guanylyl cyclase, is produced by endothelial nitric oxide synthases (eNOS), in the splanchnic arterial circulation; by neuronal NOS (nNOS), in the nervous system; by mitochondrial nitric oxide synthase (mNOS); and by inducible NOS (iNOS), in several cell types such as vascular smooth muscle cells and macrophages. NO exerts a paradoxical role. Altered inflammatory response in patients with PH, promotes the production of NO, enhancing cyclic guanosine 3'5'-monophosphate (cGMP) related- hyperdynamic circulatory syndrome. On other hand, NO deficiency leads to elevated vascular resistances (23, 44). eNOS related-NO can be reduced by endogenous circulating amino acid asymmetric dimethylarginine (ADMA). ADMA, synthesized by proteolysis of citrulline and dimethylamine, is associated with multiorgan failure, especially liver damage (45).

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and enhance and maintain the transformation of quiescent hepatic stellate cells (HSCs) towards so-called myofibroblast-like cells, eliciting fibrosis through synthesis of extracellular matrix, increased vascular distortion and resistance, thereby promoting portal hypertension (15). The conversion involves the loss of vitamin A and lipid store, expression of contractile and migratory properties favored by alpha-smooth muscle actin (a-SMA), increased half-life cellular mediated by transcription factor nuclear factor-kB (NF-kB), and transcriptional repressor activation such as Rev-erb-alpha (51). This has recently been discovered, its role is not still clear. Probably, it promotes both pro- or anti-fibrogenic response and a contractile phenotype of HSCs (52).

HSCs contraction can be also mediated by CXCL12 in CXCR4-specific manner, through a calcium-independent pathway (53). In addition to CXCL12-CXCR4 pathway, Rhokinase activation also enhances cell contraction, intrahepatic resistance and consequently portal pressure (54). Sinusoidal endothelial cells (SEC) are directly and/or indirectly partecipate to liver fibrosis and angiogenesis. This phenomenon is also called “endothelial-mesenchymal transition”. Precisely, HSC and SEC release growth factors that influence the critical role of one and the other. The link between angiogenesis and fibrosis is hypoxia. It promotes the release of several angiogenic growth factors vascular such as endothelial growth factor (VEGF); platelet-derived growth factor (PDGF); hypoxia inducible factor 1 alpha (HIF-1a), an oxygen sensitive transcription factor; and angiopeotin-1, inducing capillarization and collagen deposits in perisinusoidal space (55). VEGF contributes to elevated overall blood flow in spleen. VEGF exerts its action trough a VEGF-eNOS-phosphatidylinositol-3-kinase (PI3K-Akt) pathway. Precisely, VEGF stimulates eNOS and PI3K-Akt which in turns increasing release of NO. Therefore, this axis is involved in the maintenance of hyperdynamic circulation in portal hypertension (56). Furthermore, VEGF, activating proliferation of endothelial tubule and cells, promotes formation of new portal-systemic collateral vessels (57). Otherwise, PDGF pathway modulates maturation of new vessels. Angiopoetin-1, a member of the Ang family, acts by binding to Tie2, a tyrosine kinase receptor expressed on liver vessels. It is involved in survival and recruitment endothelial cells. It is also been reported increased angiopoetin-1 levels in patients with PH (58). Cytokines that alsoorchestrate fibrosis are IFN-a; TNF-a; TGF-ß, activated by av86 integrin, contributes to apoptotic activation through Bcl-2 and caspase family of protein (59); PDGF (57); angiotensin II; cannabinoid receptor CB1/CB2 signaling (60); and HMG-CoA-reductase, it can enhance eNOS expression, vasodilatation and formation of portal-systemic collaterals (61-63).

The RAS (renin-angiotensin system) is recognized as an important regulator of portal pressure. Liver damage induces activaton of RAS, angiotensin-converting enzyme and their specific receptors which promote inflamma-

tion, synthesis of collagene and PH. In fact, angiotensin II, by binding angiotensin type I receptors, promotes pro-

fibrogenic effect mediated by TGF-ß1. Apelin also binds angiotensin-like- receptor 1. Several studies were conducted on critical role of apelin. It is endogenous ligand; it is expressed on nervous, cardiac, gastrointestinal, and hepatic cells. Precisely, it is over-expressed in HSCs where it promotes collateral circulation. Chen and co-workers proposed apelin as a new possible prognostic factor in PH patients (64). KC-derived TGF-ß seems to partecipate to transformation of HSC, promoting release of proteoglycans and collagen, and induce mRNA expression of metalloproteinasises (MMPs) (65). Fibrogenic factors also include reactive oxygen species, antiapoptotic pro-
teins, and tissue inhibitors of matrix metalloproteinasises (TIMPs). These latter inhibit MMPs, proteolytic enzymes containing metal ions, that degrade all types of ECM, such as collagen (I, IV, V, VII, X, XI), fibronectin, hyalurono-
nan, undulin, elastin, and proteoglycans, which are then released into the circulation. Therefore, it has been hy-
pothesized that all small fragments of degraded extracel-

lular matrix can be used as markers reflect the severity of disease (66). MMPs activation is probably mediated by heparin- and chitin-binding glycoprotein (YKL-40). YKL-

40, expressed on the surface of spleen, acts as growth and migration factor in muscle and connective tissue, This further confirms that portal hypertension and sple-

nomegaly influence each other (67). Cannabinoids are a group of molecules binding CB1 and CB2 receptors on nervous, liver and gut cells, and adipocytes. In normal liver their expression is absent or low. During chronic progressive liver diseases, their serum levels are increas-
ing and promoting fibrosis in early stage. Otherwise, can-
nabinoids contribute to splanchic vasodilatation and PH in end-stage liver disease (68).

Moreover, genetic factors have been recognized as play-
ing an important role in the development of PH. Single-
nucleotide polymorphisms (SNPs) that influence hepatic architectural distorction are: TNF-a, IL-10, TGF-ß, CCR5, angiotensinogen, and peroxisome proliferator-activated receptor a (PPARa). It, transcription factor activated by ligands, influences genes related to PH pathway such as oxidative stress, vascular tone, and fibrogenesis (69). However, othermechanisms promoting PH are still un-
clear. PH seems to be also endocrine- metabolic-immu-
nological changes. Hormone molecules also appear to in-
fluence fibrosis. Recently, it has been demonstrated that elevated serum levels of insulin, leptin, and adiponectin. Insuline resistance (IR) is strongly associated with the progression of chronic liver disease. Although molecular pathways explaining the relationship between insulin resis-
tance and PH are largely unknown, it has been hypothe-
sized that IR can result from two ways: reduced insulin degradation due to liver failure, and development of in-
tra- and extra-hepatic collateral circulation, contributing to decreased insulin clearance (70, 71). IR can cause sinu-
soidal endothelial dysfunction, decrease in NO produc-
tion, and increment of peripheral vascular resistance. Leptin, through specific receptors (ObR) in HSCs, might upregulate several signaling pathways involved in angiogenic and fibrotic mechanisms. In fact, leptin induce synthesis of collagen; release of VEGF, angiopoietin-1 and HIF-α; monocyte chemoattractant protein 1 (MCP-1) and NF-κB expression (72-75). However, in humans the critical role of leptin is still unclear. Delgado et al. demonstrated that blockade of leptin-NO pathway is significantly associated with reduction of PH (76). Adiponectin may influence liver fibrosis. In fact, inducing IL-10 release by KCs, also inhibits TNF-α synthesis. In addition, elevated serum adiponectin levels inhibit HSCs proliferation, favouring cellular apoptosis and inducing HSCs quiescence. Otherwise, in the late stage of PH, it was noted normal or reduced serum adiponectin levels. A less hepatic extraction is the most common cause of this phenomenon. In addition to serum insulin levels, adiponectin significantly predict the presence of PH related-complications such as esophageal varice and bleeding risk (77). Recently, it was discovered helpful effects of the peptide hormone relaxin. It induces, by binding with specific receptor (RXFP1) expressed on HSCs, reduction of contractile filament expression, PH and collagen deposition. It has been demonstrated that relaxin is associated with increased expression of the fibrillar collagen-degrading enzyme MMP3, decreased expression of TIMP2, and impaired TGFβ signalling. However, this function has only been demonstrated in pathologically distinct PHT models. In fact, in early cirrhosis relaxin seems to promote portal blood flow. Moreover, relaxin reverses insulin resistance. It increases vascular reactivity and angiogenesis which in turns favours an increase in peripheral glucose utilization and in muscle glucose uptake (78).

4. Conclusions

PH is a dynamic and potentially reversible process. Researchers have tried to demonstrate mechanisms underlying PH and its related-complications. Several studies showed that PH continuously varies according to degree and duration of injury, angiogenesis, and areas of fibrosis. The influence of the immune system on the development of PH has recently been the object of attention. However, the connection between PH, altered immune response, and development of changes in the liver has not been fully explained. Here, we want highlight the critical role of immunological disregulation underlining all stages of the disease. The strong positive association between immune system and development of PH could be efficient to identify patients with increased hepatic vein pressure gradient and to modify prognosis of PH, especially unrecognized form of liver disease. Furthermore, non-invasive markers could emerge as an alternative to the staging of severity disease by means of invasive procedures. Longitudinal studies have already shown their utility as predictors of complications from portal hypertension and mortality. It would be very attractive for daily clinical practice. Moreover, a better knowledge of the immunological pathogenic mechanisms might be useful to development and application of specific and individual anti-inflammatory therapy. Further investigations are also required to understand the relationship of these processes.

Authors’ Contributions

All authors contribute equally in this study.

References

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