6

The Role of the Acute-Phase Proteins in the Development and Progression of Liver Diseases

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1. Introduction

The liver is a unique organ that is rich in cellular effectors for diverse systems, including the innate immune system, which plays a central role in hepatocellular injury (Gabay & Kushner, 1999). The innate immune system is based on broadly specific antigen recognition and does not rely on the more specialized antigen recognition pathways of the adaptive immune system. Although the innate immune response has broad specificity and is complex, acute-phase proteins (APPs) have been identified as biomarkers of the innate response (Table 1).

APPs are mostly synthesized in the liver. Their concentrations in plasma increase (positive APPs) or decrease (negative APPs) by at least 25% during inflammatory disorders. Most changes in APP concentration are due to infection, trauma, surgery, burns, tissue infarction, immunologically mediated or crystal-induced inflammation, and advanced cancer. Exercise, heatstroke, childbirth, or even psychological stress and some psychiatric disorders may also affect concentrations of these proteins. Cytokines are the chief stimulators and regulators of the production of these proteins. Interleukin (IL)-6 is the principal stimulator of APPs but other proinflammatory cytokines such as IL-1β, tumor necrosis factor alpha (TNF-α), interferon gamma (INF-γ), and transforming growth factor beta (TGF-β), and chemokines such as IL-8 are also involved.

In the liver, the Janus kinase signal transducer and activator of transcription (STAT) pathway has been implicated in the action of cytokines. STAT 1 and STAT 2, which are activated by INF-α/β, are involved in antiviral defense and the former is involved in liver inflammation and injury. STAT 3 has been implicated in the acute-phase response as well as in hepatoprotective effects and liver regeneration. This pathway is mostly activated by IL-6. STAT 4 and STAT 6 are associated with the ischemia/reperfusion cycle as promoters of and protectors against injury, respectively, and STAT 5 plays an important role in the regulation of hepatic genes and growth factors. Several studies have confirmed that IL-6 and IL-22 (a related cytokine) are responsible for important liver functions such as liver regeneration, glucose and lipid metabolism, and induction of antiapoptotic proteins (Gao, 2005).

ACUTE PHASE PROTEINS	
POSITIVE	**NEGATIVE**
Complement system	Albumin
C3, C4, C9, Factor B, C1 INH, C4b-binding protein, Mannose binding lectin	Transferrin
Coagulation and fibrinolytic system	Transthyretin
Fibrinogen, Plasminogen, Tissue plasminogen activator, Urokinase, Protein S, Vitronectin, Plasminogen activator inhibitor-1	A2-HS glycoprotein
Antiproteases	Alpha-fetoprotein
α1-Protease inhibitor, α1-Antichymotrypsin, Pancreatic secretory trypsin inhibitor, Inter- α -trypsin inhibitors	Thyroxin-binding globulin
Transport proteins	Insulin-like growth factor-1
Ceruloplasmin, Haptoglobin, Hemopexin	Factor XII
Inflammation responders	Antithrombin
Phospholipase A2, Lipopolysaccharide-binding protein, IL-1R antagonist, Granulocyte colony-stimulating factor	Retinol-binding protein
Others	**α**1-Acid glycoprotein
C-reactive protein, Serum amyloid A and P, Fibronectin, Ferritin, Angiotensinogen, α2-Macroglobulin	

Table 1. Descriptive table of some of the positive and negative acute-phase proteins.

Many clinical applications are based on these proteins. The most widely used indicators of the APP response are erythrocyte sedimentation rate (ESR) and plasma C-reactive protein (CRP) concentration. The latter is considered more reliable because ESR changes slowly, whereas CRP concentration changes rapidly.

2. Acute-phase proteins and the liver

The synthesis of these proteins takes place, as mentioned before, in the liver, which is an organ with multiple implications for the metabolism of many compounds in the organism. It is logical to believe that any impairment in the functioning of this organ would affect the concentrations of and, therefore, the function of these proteins. In this chapter, the pathophysiology of these changes and the clinical repercussions thereof are discussed.

To begin this chapter, it is important to review information on one of the APPs that has been most associated with the liver. It is well known that albumin is the most abundant protein in the body and albumin concentration is often used to assess liver function as well as the nutritional state of the patient because a decrease in the level of this protein is often associated with liver dysfunction. As such, it is an important component in several scales of dysfunction and prognosis. Albumin level is a component of the Child–Turcotte–Pugh scale, the Model of End-stage Liver Disease scale (specifically designed for the liver), and global scales such as the Sepsis-related Organ Failure scale and the Acute Physiology and Chronic Health Evaluation scale. Some authors (Chan, 2010) have detected albumin mRNA in the blood, indicating that cell death could occur in liver impairment, which would release this element to the blood. Unlike albumin, the albumin mRNA level increases at an early stage of liver impairment.

Research is needed to confirm this finding, but analysis of levels of circulating nucleic acids may be an interesting option for opportune detection of liver damage. Furthermore, in acute liver failure, the reduction in the production of albumin and α1-acid-glycoprotein alters the protein-bound fraction of many drugs, resulting in higher levels of the free and active forms of drugs and their associated effects. Nevertheless, albumin is not entirely specific for liver function impairment or injury; therefore, several other biomarkers have been investigated. These will be discussed in relation to the various liver pathologies.

2.1 Alcoholic liver disease

Although liver disease may have many etiologies, alcohol is still the most frequent cause of liver deterioration, whether acute or chronic. The hepatotoxic threshold at which alcoholic liver disease (ALD) develops is 40 g of ethanol per day (about four drinks) for men and 20 g of ethanol per day (about two drinks) for women and it has been estimated that 7.4% of the adult population of the USA and 20–30% of the adult population of Europe consume high quantities of alcohol. It is alarming that, in these locations and in many developing countries, the increase in alcohol consumption has been continuous and is predicted to continue during the next decade. Figure 1 shows worldwide mortality due to alcoholic liver disease.

	Country	Description	Amount
1.	Hungary	496.89 deaths per 1 million people	
2.	Denmark	132.26 deaths per 1 million people	
3.	Finland	130.78 deaths per 1 million people	
4.	Mexico	129.39 deaths per 1 million people	
5.	Germany	126.91 deaths per 1 million people	
6.	Estonia	120.00 deaths per 1 million people	
7.	Lithuania	108.37 deaths per 1 million people	
8.	Bahamas, The	96.76 deaths per 1 million people	
9.	Czech Republic	86.86 deaths per 1 million people	
10.	Croatia	82.72 deaths per 1 million people	
11.	Chile	81.33 deaths per 1 million people	
12.	Luxembourg	77.80 deaths per 1 million people	
13.	Romania	50.59 deaths per 1 million people	
14.	Puerto Rico	46.17 deaths per 1 million people	
15.	Austria	40.49 deaths per 1 million people	
16.	Korea, South	37.67 deaths per 1 million people	
17.	Costa Rica	36.14 deaths per 1 million people	
18.	Brazil	34.86 deaths per 1 million people	
19.	Canada	33.96 deaths per 1 million people	
20.	Norway	32.57 deaths per 1 million people	
21.	Australia	32.24 deaths per 1 million people	
22.	Netherlands	30.39 deaths per 1 million people	
23.	Malta	30.23 deaths per 1 million people	
24.	Nicaragua	28.73 deaths per 1 million people	

Fig. 1. Annual mortality from alcoholic liver disease. The countries with the highest mortality rates are shown.

Nevertheless, alcohol consumption is considered by many people to be normal and customary; this and the fact that patients usually do not seek medical assistance until the damage is well established (it is usually asymptomatic in the early stages) suggests that the prevalence of ALD is underestimated.

Several studies have proven that activation of Kupffer cells increases TNF-α secretion, and therefore the immune response. Su and colleagues (Su et al., 1998) found in rat models that lipopolysaccharide, an endotoxin usually present in Gram-negative bacteria, is responsible for the activation of Kupffer cells. Lipopolysaccharide binding protein (LBP) opsonizes cells and presents the endotoxin to CD14, a membrane-bound glycoprotein that activates macrophages. Alcohol is one of the stimuli necessary to increase the level of LBP-1 and, therefore, mediates liver damage. Until recently, IL-17 was thought to play an important role in alcohol-induced liver damage by activating T-helper cells, which maintain and increase inflammatory damage.

Another APP that has been associated with alcohol is alpha-fetoprotein (AFP). Although AFP has been considered a biomarker for hepatocellular carcinoma (see later in this chapter), this can be misleading because AFP is also present in ALD.

2.2 Liver steatosis

Nonalcoholic fatty liver disease (NAFLD) is the most common metabolic cause of liver dysfunction worldwide. It is believed that 10–24% of the general population has NAFLD, most cases of which are asymptomatic. It is a form of chronic liver disease that encompasses a wide spectrum of conditions that range from deposits of lipids (liver steatosis) to liver damage caused by proinflammatory compounds (nonalcoholic steatohepatitis, NASH). The natural history of this pathology has been thoroughly studied and it has been reported that NAFLD represents the first step in a progression to NASH (10–20% of cases develop NASH), liver cirrhosis (3–5% of cases develop liver cirrhosis), and hepatocellular carcinoma (Figure 2).

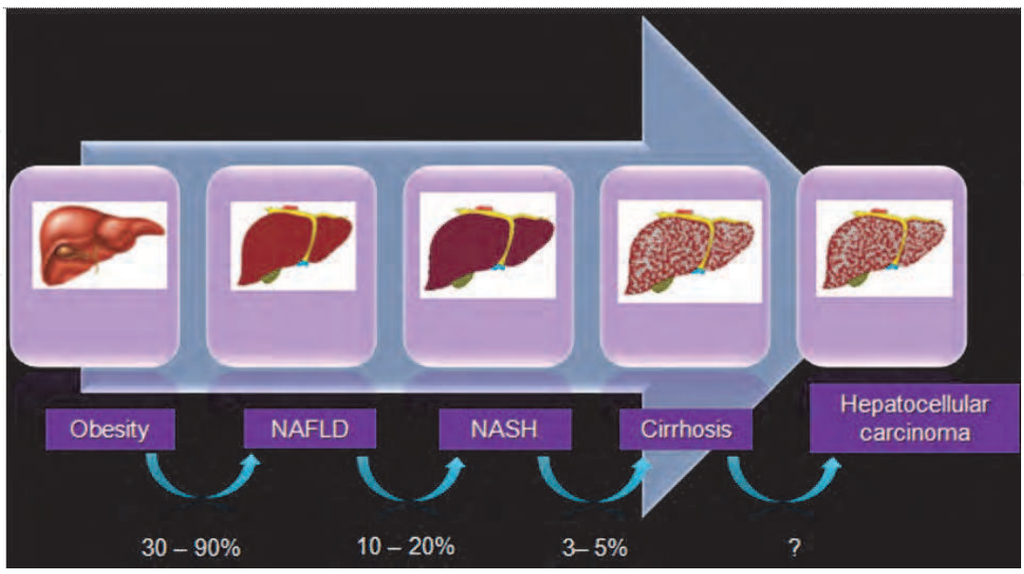

Fig. 2. Natural history of metabolic liver disease. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

Under normal conditions, the liver is often exposed to endo- and exotoxins, which initiate the innate immune response. TNF-α target genes are normally expressed at minimal levels, preventing damage to the organ. Furthermore, it has been demonstrated that TNF-α is responsible for promoting liver regeneration. NAFLD and NASH are characterized by an increase in free fatty acid levels and NASH is also accompanied by an increase in lipid peroxidation and high concentrations of TNF-α, which cause mitochondrial dysfunction. Mitochondrial impairment renders the cell susceptible to TNF-α-induced cytotoxic damage.
Obesity has been considered a major risk factor for the development of NAFLD because it produces a proinflammatory state that gradually injures the liver. Nevertheless, authors such as Crespo and colleagues found that TNF-α levels are significantly higher in patients with NASH than in obese patients without NAFLD, suggesting that the former patients have increased susceptibility to TNF-α-mediated injury, rather than there being a cause–effect relationship between the cytokine and NASH.
Although several biomarkers of hepatic fibrosis have been identified (as is discussed later in this chapter), there are no reliable markers for NAFLD or NASH. Alanine aminotransferase is considered a marker for liver injury, but obesity may reduce the level of alanine aminotransferase, rendering it misleading in patients with NASH. Another issue is that identification of alcoholic and nonalcoholic liver damage is difficult. Gamma-glutamyl transpeptidase (GGT) levels are commonly used for this purpose but, in cases of NASH, they have also led to uncertain conclusions. Another report (Ohtsuka, 2005) suggested that carbohydrate-deficient transferrin could be a marker for differentiating between NAFLD and NASH. Nevertheless, Yoneda and colleagues (Yoneda et al., 2008) found that, although CRP and amyloid A levels are often used to assess inflammatory injury to the liver in clinical practice, these APPs are members of the short pentrexin family, the levels of which are only elevated as a systemic response to inflammation, whereas the long pentrexin, PTX3, is rapidly induced in damaged tissue in a tissue-specific manner. Thus, they concluded that PTX3 could be a more important biomarker for NASH than for non-NASH cases of liver damage.

2.3 Viral hepatitis

Infection with the hepatitis C virus (HCV) is a leading cause of chronic liver disease. According to the World Health Organization, over 3% of the world's population (about 180 million people) is infected and about 130 million are at risk of developing cirrhosis. The majority of those infected with HCV (60–80%) develop chronic hepatitis, which is associated with progressive fibrosis. Of chronic hepatitis patients, 3–9% develop cirrhosis within 20 years. El-Serag and colleagues (El-Serag et al., 2003) found that HCV-infected patients are more frequently coinfected with viral or bacterial entities than are patients with other liver diseases. Few studies have been performed to explain this finding, but Wegert and colleagues (Wegert, 2009) found that CRP, SAA, haptoglobin, and fibrinogen levels are diminished secondary to an impairment caused by an HCV core protein that inhibits activation of transcription factors for protein production and disrupts TNF-α and IL-6 signaling, affecting the whole immune response, at least in mice. Complement activity has also been suggested as an inducer of fibrosis and, therefore, of progression to cirrhosis in HCV-infected patients. It was reported that C5 is associated with this progression (Hillebrandt, 2005), but subsequent studies have failed to demonstrate this relationship; thus, it is unclear if this component is relevant to the induction of fibrosis in humans (Halangk, 2008). Despite this, the involvement of complement in the progression of fibrosis is still a topic of research. Interestingly, HCV-infected patients also have significantly lower

cholesterol levels than normal subjects. This may be associated with APP level, which, as mentioned before, is reduced, as in the proinflammatory and proatherogenic states.
On the other hand, even though vaccination has considerably diminished the number of cases of HBV infection, the prevalence of this disease is high. About 350 million people worldwide are infected and are at risk of progression to a worse state (Te, 2002). Some authors have found that the response to the vaccine is closely related to complement activity. C4, a crucial protein for the classical complement pathway, links innate immunity with adaptive immunity by targeting the antigen to follicular dendritic cells and B cells through the specific receptors, CD21 and CD35. It has been shown that patients who do not show the expected response to the vaccine have human leukocyte antigen class-II alleles, which impair C4 activity. Vaccines should be linked to complement fragments to avoid this problem.
Both HCV and HBV infections are considered chronic. This characteristic enables a proinflammatory state to exist, which will eventually affect the synthesis of APP in the liver. Although other hepatotropic infections may also produce an acute state, it is usually self-limited and therefore the levels of APP do not change markedly.

2.4 Liver cirrhosis

Fibrosis is a type of tissue repair that is characterized by the replacement of normal parenchyma with connective tissue (collagen) and is mainly secondary to chronic inflammation. Fibroblasts and myofibroblasts are partly responsible for this process, and it is important to note that the principal stimulus for these cells is IL-6, which is initially secreted by macrophages and subsequently secreted by B cells at the site of the lesion. When inflammation is chronic, the stimulus is persistent; thus, abundant amounts of collagen are synthesized, resulting in abnormal accumulation of connective tissue. The gold standard for the diagnosis of cirrhosis is still the liver biopsy. Several scoring systems have been developed to stage cirrhosis. The Metavir scoring scale is most commonly used to indicate the grade of inflammation and scarring on the liver and was first developed for HCV-infected patients. The Knodell score is a histological staging system that assesses the extent of inflammation: a score of 0–10 is allocated to periportal or bridging necrosis and a score of 0–4 is allocated to intralobular degeneration and portal inflammation. The various grades used in these two scoring systems are shown in tables 2 and 3.

Grade	Description
0	No scarring
1	Minimal scarring
2	Scarring has occurred and extends to blood vessels
3	Bridging fibrosis
4	Advanced scarring, cirrhosis

Table 2. The METAVIR scoring system for cirrhosis.

Score	Description
0	No inflammation
1–4	Minimal inflammation
5–8	Mild inflammation
9–12	Moderate inflammation
13–18	Marked inflammation

Table 3. The Knodell scoring system for cirrhosis.

Although the gold standard for the diagnosis of cirrhosis is the liver biopsy, the invasive nature of this procedure makes it difficult to perform with every patient. Although noninvasive methods such as the FibroScan and FibroTest are available, they may result in false-negative results in obese patients or patients with ascites. Although CRP and serum amyloid A (SAA) levels are biomarkers for liver injury and inflammation, it has been demonstrated that they are not correlated with fibrosis. Fortunately, there are other biomarkers that have been validated in several studies. Alpha-2 macroglobulin (A2M) is a protein that inactivates proteinases and inhibits fibrinolysis by reducing plasmin and kallikrein expression; thus, it inhibits the catabolism of matrix proteins, facilitating the development of fibrosis. The FibroTest involves this biomarker (Franciscus, 2010). The level of apolipoprotein A1 (ApoA1), a structural component of high-density lipoprotein cholesterol, is also correlated with the advanced stages of fibrosis (F3–F4). Other authors (Ho et al., 2010) described a novel biomarker: vitamin D binding protein (VDBP). Although A2M expression is upregulated in fibrotic livers, both ApoA1 and VDBP are negative APPs and are downregulated in fibrotic livers.

As mentioned in the introduction, there are several signaling pathways that control diverse functions. In the case of fibrosis, the STAT 3 family has the greatest impact. Activation and high activity of this signaling pathway have been implicated in the genesis of cirrhosis as well as in its evolution to HCC. Under normal circumstances, insulin-like growth factor-1 (IGF-1) maintains the activity of the STAT 5 signaling pathway; nevertheless, when liver damage occurs, growth hormone is released, with consequent lowering of IGF-1 level (therefore, it is known as a negative APP), which stops the activation of the STAT 5 pathway and the phosphorylation of STAT 3. TGF-β is a closely related cytokine because it is also secreted when liver damage occurs and it activates the STAT 3 pathway as well as the expansion of T-helper cells, which increases fibrosis.

It has also been reported (Parsian et al., 2010) that expression of other components such as hyaluronic acid, alpha glycosaminoglycan distributed in extracellular spaces and synthesized by hepatic stellate cells in the liver, and laminin, a basal membrane glycoprotein synthesized in hepatocytes, also increase in the early stages of fibrosis in chronic liver diseases. These serum parameters have been compared with APP-based indices such as A1-apolipoprotein level and prothrombin time, and it was found that hyaluronic acid is the most strongly correlated with liver fibrosis.

2.5 Hepatocellular carcinoma and other liver tumors

As mentioned in the discussion of cirrhosis, downregulation of the STAT 5 signaling pathway and activation of the STAT 3 pathway increase fibrosis. Practically all chronic liver diseases result in fibrosis and, if not controlled, in malignant transformation of hepatocytes, and HCC (figure 3).

HCC accounts for 5.6% of all human cancers, more so among men than women (7.5% and 3.5%, respectively), and its prevalence increases with age. It has a 5-year survival rate of 6.5% and is considered responsible for 660,000 deaths per year worldwide. Viral hepatitis, alcohol, oral contraceptives, and aflatoxins are the most important risk factors for its development and its prevalence is expected to increase in the future.

HCV and HBV infection are the main causes of HCC; they are responsible for 80% of HCC cases (96% in HBV endemic regions). It has been established that 10–40% of all chronic HBV patients will develop this entity. The progression to liver cancer is monitored using serum levels of alpha-fetoprotein (AFP), an oncofetal glycoprotein that serves as an APP for several

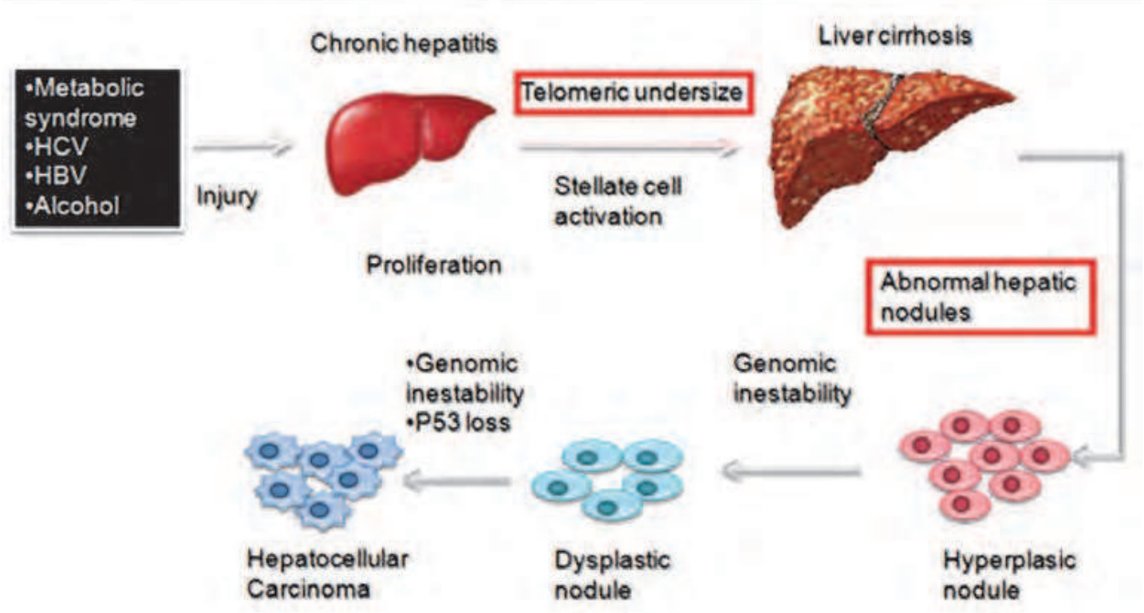

Fig. 3. Evolution and risk factors for the development of hepatocellular carcinoma.

liver diseases; nevertheless, it is not cancer specific. Comunale and colleagues (Comunale et al., 2010) identified more than 100 glycoproteins that are elevated in cirrhotic and HCC patients and that may serve as markers of the early development of HCC, and they suggested that alpha-1-antitrypsin was the most promising.

CRP and SAA levels are correlated with tumor activity (Jong, 2001), i.e., with increasing tumor load, necrotic tumors, and tissue destruction. Levels of these proteins are even increased by gastric and colorectal metastases. It has also been suggested that APPs provide an ideal environment for tumor recurrence or growth (Harimoto et al., 2009). It is also accepted that CRP-positivity in HCC patients often indicates a poor prognosis and portal vein invasion.

As mentioned earlier in the chapter, hypoalbuminemia was considered a marker of liver impairment. For a long time, it was thought that tumor activity was responsible for the decrease in albumin level; however, recent studies (Al-Shaiba et al., 2004) have demonstrated that the reduction in serum albumin level is related to the inflammatory response rather than to nutritional depletion caused by the tumor.

2.6 Autoimmune hepatitis

Autoimmunity is also an important cause of liver disease. It encompasses a broad spectrum of diseases, including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), and autoimmune cholangitis. The most common are AIH and PBC. Clinical, biochemical, histopathological, and cholangiographic criteria are used for differential diagnosis (Table 4).

AIH is characterized by severe liver damage with a modest or low elevation of alkaline phosphatase level (Oo, 2010). It is classed into three types according to the autoantibodies expressed: type 1, smooth muscle antibodies (SMA) or anti-nuclear antibodies (ANA) are present; type 2, anti-liver kidney microsomal antibodies (LKM) are present; and type 3, soluble liver antibodies (SLA) or liver/pancreas antigens are present. All of these antibodies induce proinflammatory cells that mostly activate T-helper cells, which cause liver damage.

Parameter	AIH	PBC	PSC	AIC
Female:male	4:1	9:1	1:2	9:1
Liver test elevation	ALT, AST	AP, GGT	AP, GGT	AP, GGT
Ig elevation	IgG	IgM	IgG, IgM	IgM
Autoantibodies	ANA, ASMA, LKM, SLA, p-ANCA	AMA, AMA-M2	p-ANCA	ANA, ASMA
HLA association	A3, B8, DR3, DR4	DR8	DR52	B8, DR3, DR4
Histology	Lymphocyte interface hepatitis	Florid bile duct lesion	Fibrosing bile duct lesion	Florid bile duct lesion

Table 4. Comparative table for the differential diagnosis of autoimmune liver diseases. AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; AIC, autoimmune cholangitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; Ig, immunoglobin; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibodies; LKM, anti-liver kidney microsomal; SLA, anti-soluble liver antigen; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; AMA, anti-mitochondrial antibodies; UDCA, ursodeoxycholic acid.

In PBC (Poupon, 2010), inflammation is associated with similar rates of apoptosis and proliferation of biliary cells. Cytolytic T cells are attracted to autoantibody-marked cells by cytokines and chemokines, which also induce the killing of cells via TNF-α, CD-40, and Fas receptors. It is under this pressure that cholangiocytes proliferate to compensate for cell death. It has been suggested that the cholinergic pathway, the IGF-1 system, and estrogens (through alpha receptors) are possible mediators of this process.

Takahashi and colleagues (Takahasi et al., 2010) found that ALT and transferrin levels are correlated in autoimmune diseases and in other collagen-related diseases. CRP and AP levels are also correlated, at least in vasculitis syndrome. The explanation for these results is that, because the immunological response is increased in all these diseases, APPs are induced. IL-17 is a new cytokine that has been suggested to play an important role in the pathogenesis of AIH, as it is a strong neutrophil recruiter and, importantly, is also associated with the pathogenesis of ALD.

Furthermore, several authors have described "overlap syndromes". These entities are characterized by clinical or biochemical features common to two or more autoimmune diseases affecting the liver. In overlap syndromes, the magnitude of the immunological response in the early stage is elevated in that APP levels are altered to a greater extent. Comorbidities are not considered overlap syndromes. Kessel and colleagues (Kessel et al., 2007) reported that HCV-infected patients have a high titer of CRP antibodies, which is correlated with the level of rheumatoid factor, cryoglobulinemia, and the severity of liver disease, suggesting that it facilitates autoimmune liver disorders. This is important because it has been shown that 65% of patients infected with HCV have low titers of ANA, SMA, and anti-thyroid antibodies, and 7% have anti-LKM-1 antibodies. Some authors suggest that, if titers of these antibodies are >1:320, and/or hypergammaglobulinemia, and other risk factors (female gender, young age, and other autoimmune disorders) are present, it should be considered as a co-morbidity between HCV and AIH (Beuers, 2005).

3. Clinical repercussions

Clinically, insulin resistance (IR) and cardiovascular disease (CVD) have been suggested to arise from a common basis, i.e., chronic inflammation. As mentioned before, chronic liver diseases are important sources of a proinflammatory state and, therefore, several studies have tried to link liver impairment with the development of IR, type 2 diabetes mellitus (T2DM), and CVD. It is important to comment on this situation because several reports have suggested that the prevalence of chronic liver diseases will increase in the next few years and have shown that chronic liver diseases are currently among the leading causes of mortality in all parts of the world.

3.1 Liver-related insulin resistance (IR)

One of the manifestations of liver impairment is IR. IR is defined as an increased need for insulin in the peripheral tissues (muscle and adipose tissue) to achieve normal cellular glucose uptake and to reduce glucose output from the liver. The incidence of T2DM is increasing worldwide. IR is considered the pathophysiological basis of T2DM and is responsible for micro- and macrovascular complications associated with this condition. Some studies have associated IR with other deleterious effects on the biliary tract and liver such as the induction of gallstones and NAFLD, considered the most common chronic liver disease in Western countries and the liver manifestation of metabolic syndrome (MS), a pathology proven to be intrinsically related to IR. Some studies have even found that IR tends to favor the progression of NAFLD to NASH, cirrhosis, and HCC.

To comprehend the entire pathophysiology of IR, it is important to understand the normal physiology of insulin signaling. The main signaling pathway begins with the binding of insulin to its receptor, which activates insulin receptor substrates (ISR-1 or ISR-2), which activate phosphatidylinositol-3 kinase (PI3K). The subsequent cascade results in the production of protein kinase Cξ or λ, which promotes translocation of the glucose transporter, GLUT 4, and activation of Akt, facilitating glucose uptake, gluconeogenesis, and protein synthesis through the production of GSK-3, FOXO-1, and mTOR, respectively. The last-mentioned mediator also exerts negative feedback on insulin signaling by phosphorylating IRS-1 (Méndez et al., 2005) (figure 4).

Two main pathways are involved in liver-related IR. One path is through the production of free fatty acids, an increased level of which inhibits insulin-induced suppression of endogenous glucose production, and the other is through stimulation of gluconeogenesis, associated with activation of protein kinase Cδ.

Nevertheless, there are other factors associated with IR, such as a mutation of 2,6 fructose bisphosphonatase that causes an alteration in the fructose 2,6-bisphosphonate, which causes three results: a lower efficiency of suppression of hepatic glucose production (increased gluconeogenesis); a disruption of glucose flux, and a decrease in insulin-induced Akt phosphorylation in the liver. Furthermore, phosphorylation of ISR-2 in the cascade of activation of insulin also has an important impact on glycogen synthesis. It has been demonstrated that ISR-2 phosphorylation inhibits glycogen synthetase-3-kinase, which, in normal situations, induces glycogen synthesis and increases the use of plasma glucose. In pathological cases, synthesis is interrupted and glucose is not taken up by cells, promoting the progression of IR.

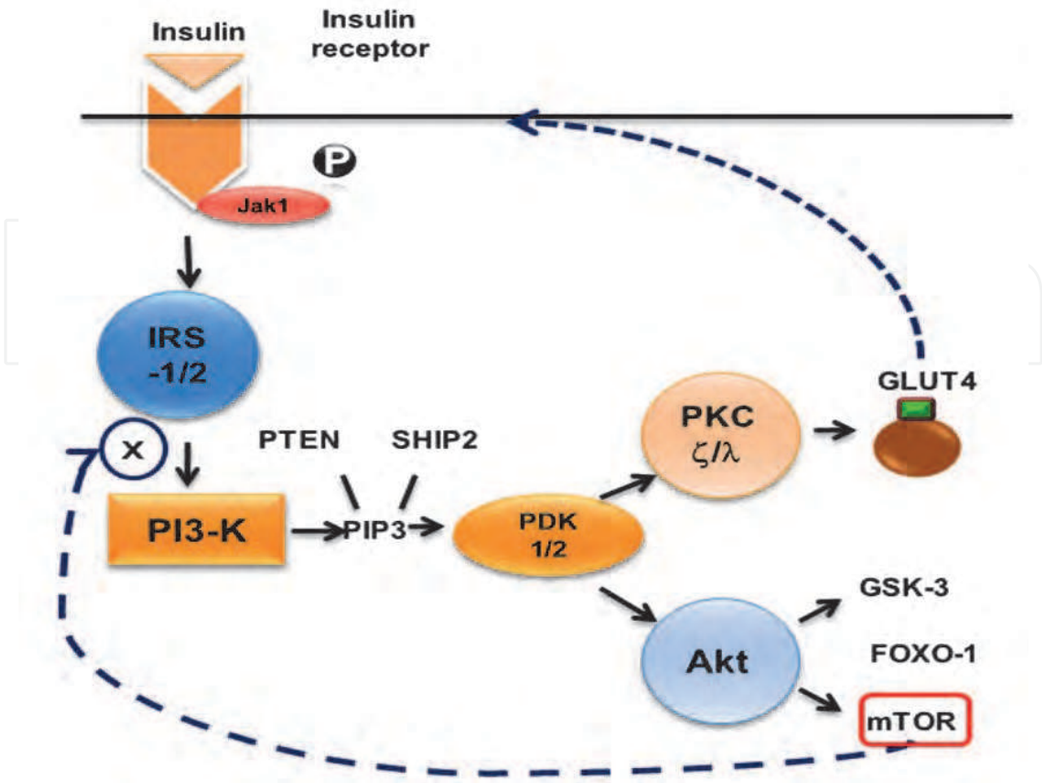

Fig. 4. Mechanisms involved in insulin signaling. Under normal circumstances, insulin binds to its receptor, which activates IRS 1/2, which then initiates a cascade of reactions that activate PKC, inducing the synthesis and migration of GLUT4 to the cell membrane, and Akt, which promotes glucose uptake, gluconeogenesis, and protein synthesis. mTOR also exerts negative feedback on the activation of IRS. IRS, insulin receptor substrate; PI3K, phosphatidylinositol-3 kinase; PKC, protein kinase C.

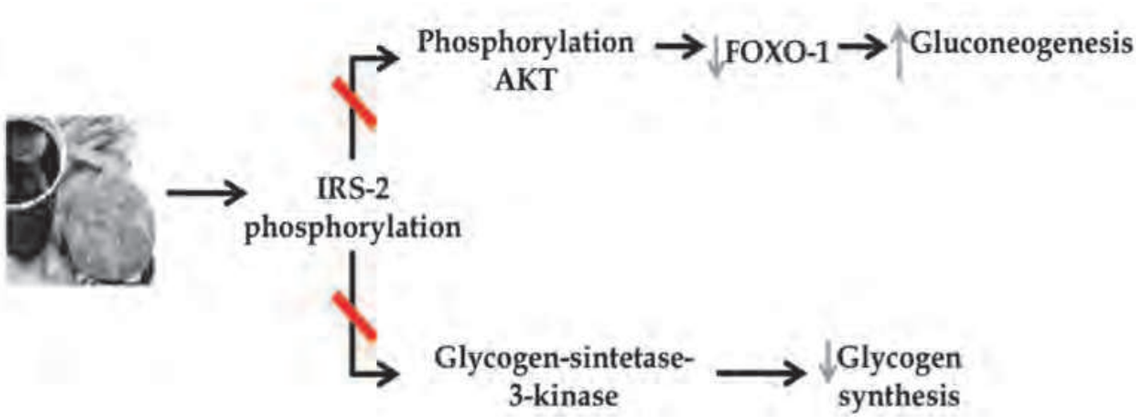

Fig. 5. Liver-related insulin resistance. FFA, free fatty acids; IRS, insulin receptor substrate.

As mentioned before, TNF-α concentrations are elevated in liver diseases and, through the activation of inhibitory κB, which enables activation of nuclear factor-κB, cause

upregulation of IL-6. IL-6 induces the suppressor of cytokine signaling (SOCS), which induces IR through a specific inhibitor of IRS-2 (SOCS-1) or by competition for the docking sites of SOCS-3 (Méndez et al., 2005).

Festa and colleagues (Festa et al., 2002) reported that APPs are not only impaired in cases of T2DM but proposed that they serve as early biomarkers of T2DM. CRP and fibrinogen were related to IR, but several studies have related them to adipose tissue secretion, and therefore to body mass index. Nevertheless, they also found that PAI-1 was independently related to the development of T2DM when compared with BMI and other risk factors, even IR, suggesting that this APP is suitable for early screening of people who are predisposed to T2DM.

Recent studies have also confirmed a close relationship between IR and liver diseases such as chronic hepatitis caused by HBV and HCV, hemochromatosis, cirrhosis, and HCC. Some authors have even reported so-called "hepatogenous diabetes", which is recognized by the World Health Organization as an independent entity that refers to the development of the T2DM due to cirrhosis.

It is important to note that the incidence of viral hepatitis has increased worldwide, especially the types that produce a chronic state. In regards to these, some studies have reported that HCV infection induces degradation of IRS-1 through activation of the mTOR pathway (genotype 1) or SOCS-7 and PPAR-γ (genotype 3). In either eventuality, the result is IR. It is also important to mention that these two genotypes have been related to IR in HCV infection.

Several studies have been performed to analyze the relationships of IR and T2DM with liver disease. Although the prevalence of liver diseases varies between countries, it has been noted that liver cirrhosis and viral hepatitis C infection have the strongest relationship with T2DM; nevertheless, other liver diseases have also been correlated with T2DM. Table 5 shows the prevalence of these diseases.

3.2 Relationship between cardiovascular risk and liver impairment

Metabolic syndrome is the pandemic of the new millennium and is considered a major risk factor for CVD. NAFLD is now considered a liver manifestation of this syndrome. As mentioned before, IR is the pathophysiological basis of metabolic syndrome and is therefore closely linked to both CVD and liver diseases.

As also mentioned above, CRP is considered the most important APP correlated with IR and CVD; nevertheless, there are some studies that have shown that CRP has anti-inflammatory properties and is involved in the reduction of the development of atherosclerosis in mouse models with hypercholesterolemia. This is most probably due to CRP-mediated upregulation of the IL-1 receptor antagonist and upregulation of serum leptin-interacting protein activity.

NASH, as also mentioned before, characteristically elevates CRP, PAI-1, and fibrinogen activities (more so than NAFLD), which are also correlated with CVD and could be considered markers for this entity because these APPs have been demonstrated to be related to cardiovascular events independently of other risk factors such as age, visceral adiposity, and metabolic abnormalities. As such, patients with viral hepatitis also have a markedly greater carotid artery intimae medial thickness. Figure 6 shows the physiopathology of this interaction.

Study	Country	Prevalence of T2DM (%)
Hepatitis B virus		
Arao M et al., 2003	Japan	11.9
Knobler H et al., 2000	USA	12
Kobashi R et al., 2010	Mexico	16.7
Hepatitis C virus		
Moucari R et al., 2008	USA	33
Mangia A et al., 1998	Italy	23
Lecube A et al., 2004	Spain	
Arao M et al., 2003	Japan	20
Singal AK et al., 2008	Saudi Arabia	22
Fraser GM et al., 1996	Israel	39
Kobashi R et al., 2010	Mexico	22.7
Nonalcoholic fatty liver disease		
Dixon JB et al., 2001	USA	20–45
Gaiani S et al., 2009	Italy	80
Bellentani S et al., 2007		30–50
Targher G et al., 2007		
Mendez N et al., 2007	Mexico	15.9–45
DeLusong MAA et al., 2008	Philippines	60
Kobashi R et al., 2010	Mexico	17.6
Nonalcoholic steatohepatitis		
Nugent C et al., 2007	USA	25–45
Harrison SA et al., 2006		
Prashanth M et al., 2009	India	25
Amarapurkar DN et al., 2008		27
Kobashi R et al., 2010	Mexico	25
Cirrhosis		
Tolman KG et al., 2007	USA	25–30
Hickman IJ et al., 2007		
Zeinn NN et al., 2000		34
Arao M et al., 2003	Japan	30.8
Costa-Braganca et al., 2010	Brazil	64.5
Kobashi R et al., 2010	Mexico	34.4
Hepatocellular carcinoma		
Davila JA et al., 2010	USA	9.7
Donadon V et al., 2008	Italy	31.2
Lagiou P et al., 2000	Greece	18
Kobashi R et al., 2010	Mexico	35.7
Hemochromatosis		
Sampson MJ et al., 2000	USA	0.4
Conte D et al., 1998		1.34
Adams PC et al., 1991		50–85 (hereditary)
Kobashi R et al., 2010	Mexico	0.77 (general)
Autoimmune hepatitis		
Jalihal A et al., 2009	Brunei	21
Choudohuri G et al., 2003	India	39.5
Kobashi R et al., 2010	Mexico	25

Table 5. Prevalence of type 2 diabetes mellitus (T2DM) and liver diseases reported from several studies worldwide (from Kobashi et al., 2010).

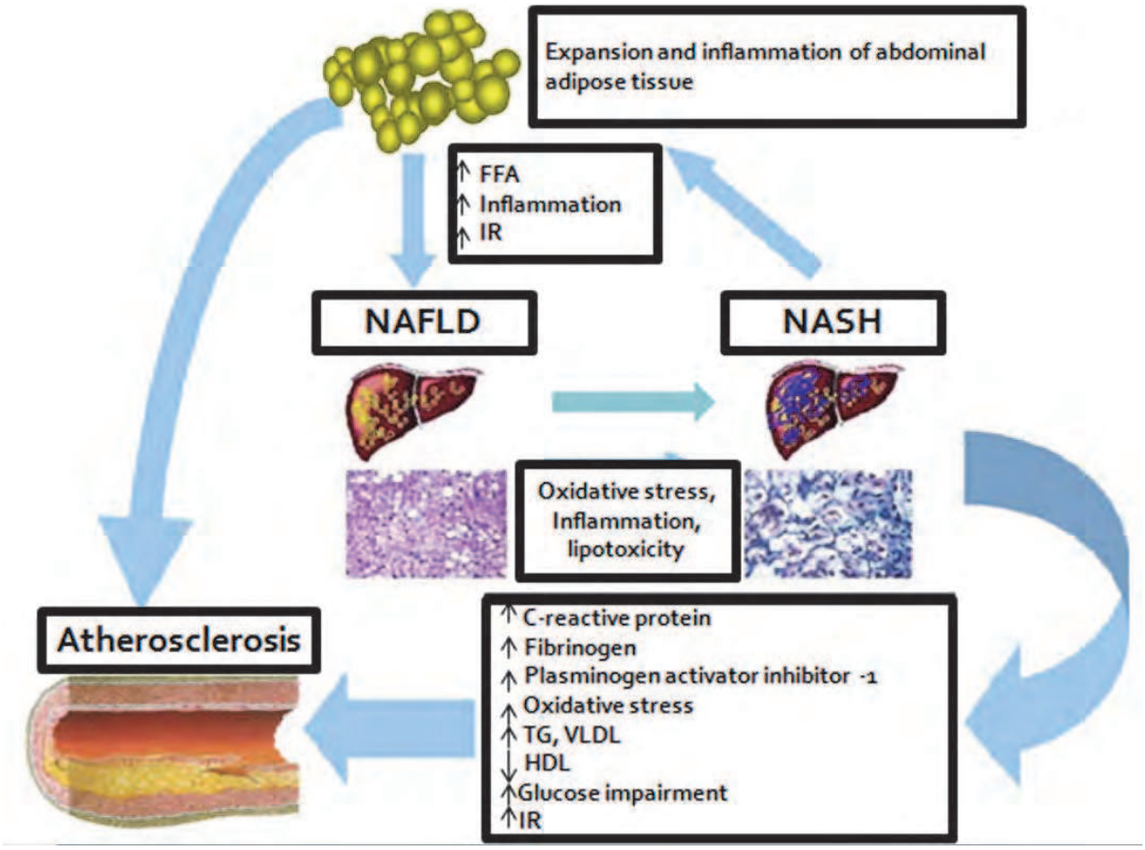

Fig. 6. Relationship between liver steatosis and cardiovascular events (atherosclerosis). Several APPs are elevated in NASH, which may directly injure the endothelium, but adipose tissue alone may also produce the same alteration. FFA, free fatty acids; IR, insulin resistance; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; TG, triglyceride; VLDL, very low density lipoprotein; HDL, high density lipoprotein.

It is important to mention that several risk factors for the development of CVD are also important risk factors for diabetes and some liver diseases. The transport of cholesterol is intrinsically related to these pathologies. Recently, studies have focused on the ATP binding cassette, A-1 (ABCA-1), an ATP-binding membrane transporter that plays an important role in cholesterol efflux from tissues and interacts directly with apolipoprotein A1, which is a structural component of high density lipoprotein cholesterol (HDL-c) and therefore plays a crucial role in lipid transportation. Because ABCA-1 and Apo-A1 have been demonstrated to be reduced in some liver diseases, it is comprehensible that liver impairment could be reflected in decreased HDL-c levels through this mechanism (Figure 7). HDL-c plays a protective role in cardiovascular events because it transports cholesterol from peripheral tissues to the liver where lipid is metabolized. The metabolism and transport of cholesterol demonstrates the close relationship between liver diseases and cardiovascular events.

Several studies have also pointed out that adiponectin, an adipocyte-derived enzyme, plays a protective role in the pathogenesis of liver impairment (induction of NAFLD) and therefore, in the increase in cardiovascular risk. Acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS) are important rate-limiting enzymes for fatty acid synthesis. The

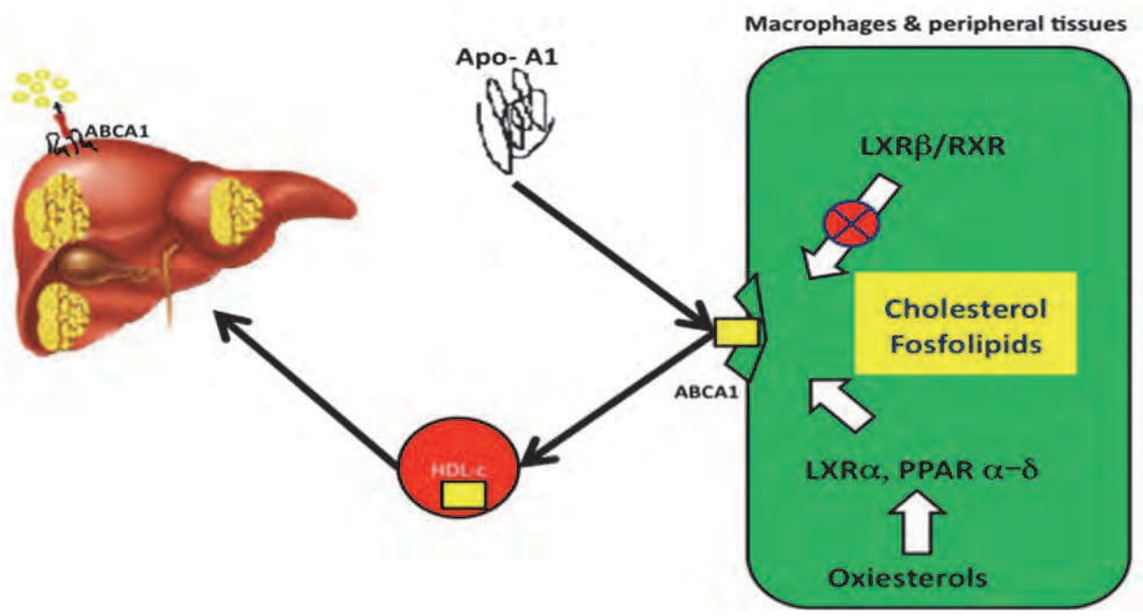

Fig. 7. Cholesterol reverse transport metabolism. Oxysterols (ligands for LXR receptors) and activators of PPARα−δ induce the production of ABC-A1, which transports molecules of cholesterol from inside the cell to the outer cell membrane. Once presented, the structural molecule, ApoA1, of HDL-c attaches to the molecules of cholesterol and they are transported to the liver where they can be metabolized and excreted from the organism. In the absence of HDL-c stimulation (i.e., in liver diseases), the LXR-β receptor and RXR are activated and inhibit ABC-A1, maintaining cholesterol accumulation within tissues. LXR, liver X receptor; RXR, retinoid X receptor.

activity of these enzymes and that of carnitine palmitoyl transferase I (CPT-I), which mediates fatty acid entry to the mitochondrion, where the fatty acids are degraded, are regulated by adiponectin. This enzyme promotes CPT-I expression and inhibits ACC and FAS expression, reducing serum and hepatic lipid concentrations and, thus, the activity of TNF-α. Uribe and colleagues (Uribe et al., 2008) have shown that adiponectin expression is reduced in metabolic liver diseases and in obesity.

4. Conclusions

Although albumin level is generally correlated with liver disease, it is not specific for the various liver diseases. Consequently, several studies have been conducted to identify biomarkers specific for each liver disease. Table 6 lists APPs associated with various liver diseases.

It is important to mention that although chemical analysis has improved over the years, the clinical status of the patient is the most important and reliable factor in the approach of the patient. APPs measurement gives the clinician, the proper guidance and orientation of the problems, that usually are subclinical, but they are not the gold standard for any liver disease; therefore, they all need a confirmation with some other studies.

Liver disease	Positive APP	Negative APP
Alcoholic disease	AFP, LBP-1	
NAFLD	ALT	
NASH	GGT, CRP, SAA, PTX3	
Viral hepatitis		CRP, SAA, Fibrinogen, Complement activity (C4, C5)
Cirrhosis	A2MG	ApoA1, VDBP, HA, IGF-1
HCC	AFP, A1AT, CRP, SAA	
Autoimmune	CRP, ALT, AP	

Table 6. APP, acute-phase protein; AFP, alpha-fetoprotein; LBP-1, lipopolysaccharide binding protein 1; NAFLD, nonalcoholic fatty liver disease; ALT, alanine aminotransferase; NASH, nonalcoholic steatohepatitis; GGT, gamma-glutamyl transpeptidase; CRP, c-reactive protein; SAA, serum amyloid A; PTX3, pentrexin 3; A2MG, alpha-2 macroglobulin; ApoA1, apolipoprotein A1; VDBP, vitamin D binding protein; HA, hyaluronic acid; IGF-1, insulin-like growth factor-1; HCC, hepatocellular carcinoma; A1AT, alpha-1 antitrypsin; AP, alkaline phosphatase.

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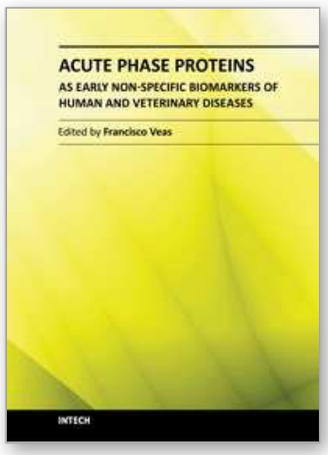

Acute Phase Proteins as Early Non-Specific Biomarkers of Human and Veterinary Diseases

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The two volumes of Acute Phase Proteins book consist of chapters that give a large panel of fundamental and applied knowledge on one of the major elements of the inflammatory process during the acute phase response, i.e., the acute phase proteins expression and functions that regulate homeostasis. We have organized this book in two volumes - the first volume, mainly containing chapters on structure, biology and functions of APP, the second volume discussing different uses of APP as diagnostic tools in human and veterinary medicine.

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