Liver-Lung Interactions in Critical Illness

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Introduction

Though acknowledged to have a central role in host defense homeostasis as well as immunological, biochemical, and metabolic regulation, the liver has not been recognized as pivotal to outcome in the acute respiratory distress syndrome (ARDS) for several reasons. Patients with liver disease have often been excluded from study, and hepatic dysfunction has often been nonspecifically defined by "liver function tests" [1]. The liver is not as accessible for study as the lung and other organs, and acute liver dysfunction is not as immediately evident as is acute lung injury [2, 3]. We have proposed an expanded conception of sepsis- and trauma-related ARDS as the central pulmonary manifestation of a generalized disorder of immunoregulation; the pathogenesis and resolution of lung injury are linked to more fundamental derangements in systemic host defense [2–8]. This reorientation implies that understanding the pathways by which changes in hepatic performance affect pulmonary function in ARDS may have therapeutic utility. Here we examine the thesis that hepatic performance modulated predisposition and resolution of lung injury in ARDS by affecting four interrelated elements of host defense: (a) control of systemic endotoxemia, bacteremia, and vasoactive byproducts of sepsis and trauma, (b) regulation of the production and export of endogenous inflammatory mediators by mononuclear phagocytes (Kupffer cells), (c) metabolic inactivation and detoxification of these mediators, and (d) synthesis of acute-phase proteins essential in intermediary metabolism and control of the inflammatory response. As a corollary, we assess clinical and experimental evidence suggesting that alterations in hepatic performance augment lung inflammation and mortality owing to a cytokine:eicosanoid axis of inflammation within the intravascular compartment and lower respiratory tract.

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Control of Systemic Endotoxemia, Bacteremia, and Vasoactive By-Products of Sepsis and Trauma

Determinants of Kupffer Cell Uptake and the Gut-Liver-Lung Axis of Cardiopulmonary Homeostasis

Anatomic, physiological, and cellular factors unique to the liver support its regulation of circulating concentrations of microbial products, tissue debris, bioactive particulates, and products of intravascular coagulation [9–13]. Several lines of evidence strongly support the thesis that derangement of one or more elements in this hierarchy initiates and amplifies extrahepatic organ dysfunction associated with sepsis or trauma [7, 8, 14–20]. Even so, the pathogenetic significance of these intrahepatic changes relative to multiple organ dysfunction syndromes and ARDS must be interpreted against the backdrop of hierarchic interactions within a gut-liver-lung axis [7, 21–28].

Hepatic mononuclear phagocytic uptake and detoxification of endotoxin is the major mechanism limiting the magnitude and duration of systemic endotoxemia [9, 14–16, 29–31]. Several key determinants regulate such hepatic clearance mediated by Kupffer cells lining the extensive sinusoidal network, which constitute nearly 80%–90% of the body's reticuloendothelial cell mass. These include:

- The magnitude and kinetics of endotoxin/microbial entry into systemic and portal circuits
  - Systemic vs. peritoneal sepsis
  - Gut-liver interactions: gut mucosal barrier function (altered digestive tract microflora, ischemia-reperfusion injury)
- Liver blood flow
  - Fractional distribution of cardiac output to splanchnic circuit
  - Flow partitioning between portal venous flow and hepatic arterial flow
  - Back pressure to hepatic outflow
  - Intrahepatic distribution of sinusoidal perfusion
  - Transhepatic sinusoidal transit time
- Preexisting liver disease
- Plasma opsonins
  - Nonspecific (fibronectin)
  - Specific (complement peptides, immunoglobulins)
- Receptor-mediated clearance by Kupffer cells
  - CD14 receptor uptake mediated by lipopolysaccharide binding protein (bactericidal permeability-increasing protein-lipopolysaccharide binding protein stoichiometry
  - Fc and complement receptor function
- Non-receptor-mediated endotoxin uptake
- Hepatocytic function and biliary elimination

Besides uptake of endotoxin, microbial pathogens, and sepsis- and trauma-related particulates, Kupffer cell clearance of altered platelets and products of intravascular coagulation protects the lungs and other extrahepatic organs [10, 32–35]. Kupffer cell mediated clearance is subserved by vascular and microcirculatory factors. The splanchnic circulation contains 20%–25% of the systemic blood volume and receives 25% of the cardiac output [36], all of which is gated through the anastomosing hepatic sinusoidal capillaries before returning to the systemic venous circuit. The prolonged transit time and physical contact of blood elements with Kupffer cells optimizes clearance. Delivery of phlogistic substances to the Kupffer cell population varies with two variables: (a) total liver blood flow (Q_L), and (b) Q_L partitioning between portal venous flow (Qpv) comprising up to 75% of Q_L and hepatic arterial flow (Qha) [12]. Although sinusoidal cells receive a mixed arterioportal nutritive supply, differences exist in the pressure-flow and autoregulatory behavior of these circuits [37, 38]. These may have pathogenetic implications under changing conditions of intestinal O_2 delivery [39, 40]. In contrast to the hepatic artery, pressure-flow autoregulation is minimal in the portal circuit [12, 38], such that decreases in Qpv are not offset by corresponding elevations in portal pressure. As Qpv constitutes a large fraction of total Q_L, the hepatic O_2 supply is critically dependent on upstream hemodynamic events [41]. An important feature of hepatic vascular physiology from the standpoint of liver phagocytic clearance and O_2 delivery-uptake is flow reciprocity [37, 42, 43]. By this process reductions in the flow of one circuit are partially compensated by increases in perfusion through the other by changes sensed in osmolarity, pH, gas tensions, or endogenous vasodilators such as adenosine [43]. Although this process increases O_2 delivery during falls in Qpv, compensatory increments by Qha may be inadequate to restore phagocytic clearance of gut-derived substances. The in-series arrangement of mesenteric and portal circuits can thus be viewed as the substrate for occult hemodynamic interactions between the gut and liver [41, 44]. These derive primarily from the sensitivity of the splanchnic circulation to increases in α-adrenoceptor tone during circulatory stress including hypovolemic shock, during which mesenteric inflow is limited by arteriolar vasoconstriction [38, 41]. Sustained sympathoadrenal activation due to inadequate resuscitation or α-agonists in high doses result in protracted splanchnic flow diversion that may compromise the gut mucosal barrier [21, 45, 46]. Whether these otherwise homeostatic effects can be mitigated by dopaminergic receptor stimulation is unclear [47]. In a porcine model of hemorrhagic shock low-dose dopamine ($5\ \mu g\ kg^{-1}\ min^{-1}$) given prior to volume resuscitation improved hepatic as well as subcutaneous and transcutaneous O_2 tensions for the same cardiac output [48].

Nonbacteremic oxidant stress of the gut during mesenteric ischemia-reperfusion activates a complex inflammatory network consisting of activated neutrophils (PMNs), cytokines, and their second messengers. Elements of this network include tumor necrosis factor-α (TNF-α), interleukin (IL) 1, 6, and 8, complement peptides, platelet-activating factor (PAF), and eicosanoid

products of the cyclo-oxygenase and lipoxygenase pathways [49, 50]. These may damage the liver owing to its strategic location downstream from the splanchnic reservoir of gram-negative bacteria and their products. Several reports links changes in gut mucosal barrier function owing to reduced O_2 delivery with increases in portal venous endotoxemia and bacteremia [21, 46, 51–53]. Nelson et al. demonstrated that the critical level of gut O_2 delivery needed to maintain enterocyte integrity during endotoxemia was higher than in other organs of the body [54]. Despite reports that shock and organ damage during endotoxemia are mediated chiefly by host-derived proinflammatory mediators such as cytokines, eicosanoids, complement peptides, and reactive intermediates of oxygen and nitrogen [55–64] (see below), lipopolysaccharide (LPS) itself is synergistic with LPS-induced mediators [65].

Hepatic clearance mechanisms for endotoxin or pathogens may be overwhelmed by preexisting liver disease [66, 67], systemic and splanchnic hemodynamic derangements [25, 26, 45, 46], opsonic factor depletion [13], or other changes in the gut microflora [21, 25] (see above). Singly or in combination these may result in "spillover" of microbial products past the liver to secondarily impair lung function [7, 10, 68]. Evidence in support includes the following considerations: (a) patients with end-stage liver disease awaiting liver transplantation are predisposed to ARDS which once initiated, is irreversible despite ventilatory support [8, 69]; (b) established ARDS during acute liver allograft rejection resolves within hours of hepatic retransplantation [70]; (c) pulmonary deposition of *Escherichia coli* is augmented during experimental biliary cirrhosis compared with predominant hepatic uptake in noncirrhotic controls [16]; (d) Decamp et al. reported that hepatic uptake of intraportal colloidal particles and *Pseudomonas* spp. in an ovine model was efficient compared with *E. coli* LPS, a significant fraction of which escaped hepatic clearance to result in lung inflammation [71]; and (e) Matuschak et al. found evidence of enhanced lung uptake of *E. coli* LPS and neutrophilic alveolitis following endotoxemia during steady-state reductions in Q_L in porta-caval shunted rats, compared with those animals having normal Q_L [72].

Data are sparse concerning portal endotoxemia and hepatic vascular responses in terms of real-time changes in endotoxin clearance and functional measures of organ performance. Halvorsen et al. [73] recently showed that portal endotoxemia in a porcine model (LPS infusion of 1 g/h) increased hepatic arterial resistance by nearly 350% and portal venous resistance by 160% in conjunction with incomplete hepatic LPS uptake. Moreover, hepatic endotoxin spillover increased pulmonary vascular resistance. Compared with other regional circulations, most vasoconstriction to portal endotoxemia in this study was limited to the liver and the lungs.

The concept of a multiorgan axis of inflammation coupled by gram-negative bacteremia and/or portal endotoxemia has antecedents. Fine et al. postulated that endogenous endotoxemia of enteric origin accounts for the irreversibility of hemorrhagic shock [74] while Nolan et al. showed that ^{51}Cr-labeled endotoxin is transported across the gut wall [75]. A large database supports this mechanism as a cause of lung injury [76]. Our perspective of

these interactions has become more comprehensive in regard to systemic inflammation because of two factors: (a) clarification of the mediators of injury, and (b) recognition that Kupffer cell phagocytic function is one among several important hepatic defense mechanisms.

Q_L During Sepsis and Trauma: Effects of Positive-Pressure Ventilation

Assessment of Q_L during critical illness has been an elusive goal. Elements of flow-dependent hepatic performance can vary independently, making analysis problematic [77–79]. In contrast to measurements of Q_L in healthy subjects by clearance of indocyanine green (ICG) or galactose [80, 81], and by Doppler sonography [82], only limited clinical studies have determined the impact of sepsis and trauma on Q_L [83]. Assessing the dual hepatic vascular input is difficult and usually entails hepatic vein catheterization. The dependence of clearance on hepatocytic function can be also altered independently of sinusoidal perfusion by critical illness or preexisting liver disease ("sick hepatocyte hypothesis") [84]. Dahn et al. found that hepatic ICG extraction decreased by 64% in patients with sepsis, but that Q_L calculated using bolus clearance methods was significantly increased compared with controls [85]. By contrast, parallel increases in the portal fraction of Q_L determined by ICG clearance and Doppler laser flowmetry have been reported early in experimental peritonitis in rats [86]. Q_L and functional responses to nonbacteremic shock or trauma after resuscitation to systemic hemodynamic endpoints such as cardiac output or arterial pressure may nonetheless be accompanied by sustained Q_L reductions and functional impairment [87, 88]. This may reflect no-reflow phenomena secondary to sinusoidal cell swelling, neutrophilic influx, and oxidant-mediated endothelial damage typifying hepatic ischemia-reperfusion injury [89, 90].

Positive-pressure ventilation is used to support impaired lung function but can adversely modulate extrapulmonary organ function [91–97]. The effects of positive-pressure ventilation on Q_L and flow-dependent performance have not been fully defined because of the complexity of forces generated during its application. Phasic inspiratory increases in intrathoracic pressure (ITP) cause parallel increases in the effective hepatic back pressure, whether defined as right atrial pressure (Pra) or hepatic venous pressure (Phv). These could affect hepatic clearance processes by several mechanisms: (a) altering the partitioning of Q_L between Qpv and Qha; (b) increasing the heterogeneity of sinusoidal perfusion owing to generation of intrahepatic closing pressures from hepatic compression by the descending diaphragm; and (c) reducing sinusoidal cell:blood contact time owing to retrograde pressure wave propagation of the inspiratory Pra pulse [93]. Reductions in Qpv by electromagnetic flowmetry during phasic increases in ITP over a respiratory frequency (f) spectrum from 0.4 to 2.5 Hz modulate the outflow pressure in a postsinusoidal flow-limiting segment in which compression of the liver by the

diaphragm increases resistance to Qpv in f-dependent manner [93]. However, the pharmacokinetics of ICG showed no f-dependent effects, suggesting that substances with similar hepatic extraction vary with inflow over this f spectrum. No studies have evaluated these issues with respect to Kupffer cell phagocytic function. During positive end-expiratory pressure (PEEP) a variety of changes in Q_L and hepatic performance have been reported. These include reductions in Qpv [94, 95] and decreases in sulfobromophthalein sodium excretion [91]. After accounting for PEEP-related changes in cardiac output we found that phasic respiratory swings in hepatic outflow over single positive-pressure respiratory cycles were not influenced by adding 10 cm H_2O PEEP to intermittent positive pressure ventilation [98]. Moreover, reductions in Q_L during PEEP in two acute canine models were prevented by intravascular volume loading to pre-PEEP cardiac output, and hepatic performance was not impaired as assessed by ICG extraction and clearance. By increasing Q_L gut feeding may also augment Q_L and O_2 delivery despite the otherwise flow-limited state associated with PEEP independently of cardiac output [99]. Important questions remain unanswered concerning the effects of PEEP on the liver. These include whether hemodynamic forces affect mononuclear phagocytic function, and the role of dopaminergic agents including dopexamine on flow-dependent clearance.

Hepatic Production and Export of Inflammatory Mediators

The role of the liver in host defense affecting predisposition to ARDS extends beyond the filtering function of mononuclear phagocytic elements. Hepatic regulation of the production and export of early-acting cytokine mediators after bacteremic and nonbacteremic stimuli is complex, involving interdependent microbial, hemodynamic, and host factors [7, 100, 101]. We focus here on hepatic cytokine production as a second major element of host defense relevant to ARDS, recognizing that other noncytokine mediators such as the recently described "injurin" [102] synergize to cause lung injury. In addition to pathogen-specific characteristics and kinetics of Kupffer cell uptake, several hierarchic mechanisms govern cytokine production: (a) receptor-mediated induction of transcriptional elements regulating cytokine gene expression such as nuclear factor (NF) κB by endotoxin, lipoteichoic acid, or other microbial products [103, 104]; (b) control of cytokine mRNA stability by the untranslated 3' consensus octomer [105]; (c) translational efficiency of mRNA; (d) membrane shedding of soluble receptors that by ligand-specific binding preempt cytokine binding to cell targets [106]; and (e) natural antagonists such as the IL-1 receptor antagonist synthesized in the liver among other sites [107]. LPS-induced cytokine expression by the liver is modulated by a network involving coinduced anti-inflammatory cytokines such as IL-4, IL-6, IL-10, and transforming growth factor-β (TGF-β), eicosanoid species including E-series prostaglandins, PAF, and reactive oxygen species (ROS) [1, 2, 19, 55–64, 108–110].

Hepatic Cytokine Secretory Capacity

What is the capacity of the liver to produce and export inflammatory cytokines into the systemic circulation following gram-negative microbial challenge? The data of Fong et al. [20] show that the liver is a major source of circulating TNF-α early after *E. coli* endotoxemia in humans, as the peak hepatic cytokine efflux was approximately 7 μg. Production of bioactive and antigenic TNF-α during perfusion of rat liver is likewise substantial after intraportal viable *E. coli* [100]. As with TNF-α, IL-6 gene expression increased after gram-negative bacteremia compared with saline controls in that study. Although peak circulating bioactive TNF-α 180 min after an equivalent inoculum of exotoxin C-producing *Staphylcoccus aureus* was similar, TNF-α and IL-6 mRNA levels were significantly less [100]. Despite this there were no pathogen-specific differences in microbial clearance or O_2 uptake. The large secretory output of TNF-α, IL-1, and IL-6 by the liver following LPS challenge has been confirmed [111].

Cytokine Biology in Liver Disease

Hepatic functional impairment modulates cytokine biology in several ways relevant to acute lung injury. Circulating cytokine levels and spontaneous or LPS-induced secretion of TNF-α, IL-1, and IL-6 from mononuclear phagocytes in vitro are increased in patients with liver disease [112–114]. The increases are disease stage-dependent but unrelated to the type or chronicity of liver disease, having been observed in acute viral or alcoholic hepatitis [112, 114], fulminant hepatic failure [115], and cirrhosis [113, 116]. The highest increases in circulating TNF-α, IL-1β, IL-6, γ-interferon, and C-reactive protein (CRP) occur in patient with cirrhosis compared with noncirrhotic hepatic involvement in chronic liver diseases [116]. Liver diseases associated with viral infection may cause ongoing stimulation of hepatic macrophages [117]. Endotoxemia associated with liver disease [66, 67] may also stimulate cytokine production in the absence of viral-induced organ injury. Further, there may be impaired Kupffer cell or hepatocytic clearance of circulating mediators secreted in otherwise normal amounts. These processes may account for the impact of preexisting cirrhosis on circulating cytokine levels and mortality in patients with septic shock. Thus, patients with liver disease had higher serum levels of IL-6 and were at enhanced risk for lethal multiple organ failure compared with noncirrhotic septic patients [118].

Hepatic Cytokine Production in Fungal Sepsis

Infection with *Candida albicans* has increased 20-fold over the past decade [119], with hepatic candidiasis common in ICU patients after trauma, burns, or immunosuppression [120, 121]. Regulation of hepatic cytokine production

during candidemia differs compared with gram-negative or gram-positive bacteremia [100, 122]. In contrast to bacteria, intraportal candidemia with human pathogenic strains of viable yeast-phase *C. albicans* elicited the weakest stimulatory responses in perfused rat liver with respect to TNF-α or IL-6 gene expression and TNF-α protein production [100]. These differences between bacterial and fungal infections are likely due to the molecular mimicry of yeast-phase *Candida* spp. adhesion molecules with the mammalian integrin superfamily and other molecules [123], as similar findings have been observed in Kupffer cell cultures [124] in vivo, the magnitude of hepatic and systemic TNF-α production and TNF-α-dependent immunophysiological responses are differentially regulated in conscious rats after lethal *Candida* spp. *vs. E. coli* infection [122]. In neither immunocompetent nor immunosuppressed neutropenic models [125] was TNF-α found to be a pivotal mediator of the acute *Candida* septic shock syndrome with disseminated candidiasis.

Cytokine Kinetics During Nonbacteremic vs. Bacteremic Oxidative Stress of the Liver

Reductions in the hepatic O_2 supply are common during shock caused by hemorrhage, trauma, or gram-negative bacteremia [2, 39, 40, 54, 85, 126–128]. Decreases in intracellular ATP, conversion of hepatic xanthine dehydrogenase to xanthine oxidase [129], and mitochondrial activation [130] generate ROS which modulate the release, binding, and cytotoxicity of cytokines including TNF-α [131]. One mechanism for ROS-related cytokine induction during oxidative hepatic stress is their role as messengers in activating NF-κB which rapidly upregulates cytokine gene expression [103]. Ultimately, changes in cardiovascular function which cause even transient nonbacteremic ischemia-reperfusion and/or hypoxia-reoxygenation of the liver are linked to immunological alterations, manifested by activation of cytokine-dependent inflammatory responses. Colletti et al. demonstrated that 90 min of no-flow hepatic lobar ischemia-reperfusion resulted in focal liver injury in rats [132]. Reperfusion was associated with localized hepatic injury, increased circulating TNF-α, augmented lung microvascular permeability, and enhanced pulmonary leukosequestration, all of which were prevented by pretreatment with anti-TNF-α antiserum. This may explain the enhanced PMN influx into the lungs after hepatic ischemia-reperfusion shown in a similar model by Jaeschke et al. [133], a process linked to cytokine-dependent upregulation of the Mac-1 (CD11b/CD18) PMN adhesion protein [134]. Such upregulation may also explain the increased PMN aggregation in the liver and lungs after soft tissue injury [135]. Ayala and coworkers reported that murine hemorrhagic shock had differential effects on Kupffer cells, with increased TNF, IL-1 and IL-6 release contrasting with reductions in antigen presentation mediated by cyclo-oxygenase metabolites [136]. We recently showed that even brief (e.g., 30 min) periods of global, nonbacteremic hypoxic stress of the intact perfused liver releases TNF-α without increasing

TNF-α mRNA accumulation [137]. This presumably resulted from cleavage at the Kupffer cell surface of the 26-kDa membrane-bound TNF-α isoform [122, 138].

Acquired hepatic dysfunction is a frequent complication of sepsis and trauma [1, 7, 77–79] though the mechanisms are unclear. One postulate is that microbial products and/or the paracrine action of cytokines stimulate formation of ROS which initiate parenchymal injury. Bautista et al. showed that endotoxemia produced increased superoxide anion generation in perfused rat liver [139], while Hewett et al. defined interactions between TNF-α and PMNs in endotoxin-induced liver injury [140]. Most likely sequential Kupffer cell stimulation by microbial products and secondary oxidant stress during ischemia/reperfusion or hypoxia/reoxygenation occur in this setting. However, their sequence dependent effects have not been characterized. In contrast to increases in TNF-α protein during nonbacteremic hypoxia/reoxygenation [137], equivalent hypoxic stress beginning after intraportal *E. coli* bacteremia downregulates TNF-α at a posttranscriptional level, independent of cyclo-oxygenase products or xanthine oxidase-derived ROS.

Metabolic Inactivation of Inflammatory Mediators: Kupffer Cell–Hepatocyte Interactions

Inactivation and detoxification of inflammatory mediators by hepatobiliary elimination is a third critical element of systemic and pulmonary host defense. Circulating and tissue-based concentrations of several classes of mediators implicated in ARDS and multiple organ failure reflect a balance between synthesis and metabolism. Insight into ARDS therefore requires analysis of intrapulmonary cytokine networks as well as hepatic metabolic pathways [141]. TNF-α and eicosanoids, particularly the leukotrienes (LTs), have been studied the most in this regard [61, 72, 110]. However, they are not the only endogenous substances so affected. This variant of the spillover paradigm has been proposed to play a role in chronic, non-ARDS pulmonary expressions of abnormal liver-lung interactions. These include liver disease-induced pulmonary hypertension and the hepatopulmonary syndrome, the triad of liver disease, lung vascular dilations, and abnormal arterial oxygenation [7, 141, 142]. Thus, failure of the damaged liver to inactivate as yet unidentified endogenous compounds can induce acute endothelial injury and inflammation typifying ARDS, chronic pulmonary vasoconstriction, or pulmonary vasodilation in the hepatopulmonary syndrome.

Mechanisms for impaired hepatocytic clearance include changes in the characteristics of Q_L (see above), acute or chronic hepatocytic damage, or a combination of these factors. Accordingly, experimental approaches have targeted one or another of these mechanisms. In most respects the hemodynamic derangements which affect Kupffer cell phagocytic uptake likewise alter hepatobiliary elimination of vasoactive cytokines and eicosanoid lipoxygenation products. A TNF-α:LT axis of inflammation is unmasked by im-

paired hepatocytic performance. Several lines of evidence suggest that this axis functionally prefers the liver and lungs in ways relevant to ARDS: (a) both TNF-α and LTs undergo extensive hepatic metabolism [144–146]; (b) both are present in increased concentrations in the lower respiratory tract of patients with ARDS or at enhanced risk for ARDS [147, 148]; (c) systemic generation of LTs is enhanced during ARDS [149]; (d) even without sepsis renal excretion of LTs is increased in patients with cirrhosis [150]; (e) TNF-α stimulates production of LTs in vivo [151]; and (f) impairment of hepatocytic performance by the hepatotoxin d-galactosamine increases mortality and lung injury during endotoxemia [152, 153], gram-negative bacteremia, or gram-positive bacteremia, processes mediated by TNF-α but reversible by lipoxygenase inhibition [154, 155].

Changes in flow-dependent performance likewise alters the metabolism of these mediators. Diversion of Qpv after a portacaval shunt selectively decreases Q_L by up to 75% and models reductions in Q_L occurring after sepsis and trauma. In conscious rats with a portacaval shunt we tested the hypothesis that reductions in Q_L amplify shock, lung inflammation, and mortality during endotoxemia by impairing the clearance of endogenously synthesized TNF-α [72]. For equivalent serum endotoxin in shunted and sham-operated animals, mortality, peak circulating TNF-α, neutrophilic alveolitis, and LTB_4 in bronchoalveolar lavage fluid were all increased. Hepatic, cardiac, and cecal microvascular permeability were also greater. Consonant with the evolving understanding that *reciprocal* rather than *unidirectional* interactions occur among mediator classes during endotoxemia, downregulation of LPS-induced TNF-α expression was observed after posttreatment with the lipoxygenase blocker diethylcarbamazine or the 5-lipoxygenase activating protein inhibitor MK-886. This suggested LPS-related production of LTs stimulate TNF-α gene expression, and that such selective reductions in Q_L early during endotoxemia functionally linked the liver and the lungs via a cross-modulating TNF-α:LT axis of inflammation. These findings agree with data obtained during acute liver injury induced by D-galactosamine [154].

Modulation of Inflammatory Responses by Hepatic Acute-Phase Protein Synthesis

The host response to inflammation or tissue injury mediated by the acute-phase response centered in the liver is characterized by a highly coordinated set of immunophysiological reactions ultimately involving the lungs and other organs [156, 157]. That this is a fourth mechanism of systemic and pulmonary defense is supported by two lines of investigation which clarify aspects of the acute-phase response relevant to liver-lung interactions. The first relates to cytokine-mediated responses to acute illness resulting in a reprioritization of the synthesis of acute-phase proteins by the liver [157, 158]. These include α_2-macroglobulin, CRP, serum amyloid A, fibrinogen, and the proteinase inhibitors α_1-antitrypsin and α_1-antichymotrypsin, among others, whose con-

centrations increase rapidly to exceed those of otherwise phenotypically dominant proteins such as albumin and transferrin [159]. Second, TNF-α, IL-1α, IL-1β, IL-6, and γ-interferon are major regulators of acute-phase gene expression based on the discovery of cell surface receptors, *cis*-acting regulatory elements, and *trans*-acting nuclear proteins that mediate the effects of acute-phase reactants on target genes [157, 160, 161]. The metabolic effects of certain acute-phase reactants support interorgan substrate fluxes while the anti-inflammatory effects of others dampen excessive inflammatory responses. Teleologically these processes might be viewed as facilitating recovery by compensating for impairments in the other three mechanism of host defense.

The acute-phase response orchestrated by the liver alters the interorgan exchange of substrates for protein synthesis and energy production [158, 159], which is balanced by production of nitric oxide which can impair hepatocytic functions [162–164]. The hyperdynamic cardiovascular response to critical illness is paralleled by elevations in VO_2 requirements from increased energy expenditure. This is accompanied by changes in cytokine and counter-regulatory hormone (e.g., epinephrine, cortisol, glucagon) profiles typifying the stress response [165, 167]. The latter process generates alanine from muscle which is a precursor for hepatic gluconeogenesis. At the same time hepatic uptake of circulating amino acids increases which constitute an important oxidative fuel source [168], reflected by ureagensis. Finally, enhanced hepatic pyruvate decarboxylation increases acetyl-coenzyme A entering the Krebs cycle as citrate and drive ATP production [169]. The ATP so produced stabilized hepatic gluconeogenesis, ultimately liberating glucose for host defense functions including white cell energy metabolism. To summarize: (a) Kupffer cell-hepatocyte paracrine interactions after stress balance the stimulatory actions of LPS, TNF-α, IL-1, and especially IL-6 against the inhibitory effects of nitric oxide and other reactive nitrogen intermediates on hepatic protein synthesis; and (b) the metabolic changes initiated by these elements and counterregulatory hormones alters the metabolic milieu directly and by reprioritization of de novo hepatic protein synthesis to acute-phase reactants. These complex interactions have been reviewed [165, 166]. Recent data also support the premise that acute-phase reactants such as α_2-macroglobulin and CRP possess cytoprotective functions.

α-Macroglobulins are glycoproteins (718000 kDa) with proteinase-binding activity, α_2-macroglobulin is secreted by the liver which is abundant in normal human plasma ($\sim$2 mg/ml) [170]. Two functions of α_2-macroglobulin are important in cytoprotection: (a) antiproteinase activity and (b) cytokine binding, transport, and/or neutralization [171]. Tissue-damaging proteinases such as collagenase, cathepsin G, and trypsin released by phagocytic cells can be internalized by α_2-macroglobulin via a "molecular trap" mechanism [170]. Clearance of these complexes from the circulation occurs by cellular uptake via α-$_2$-macroglobulin receptors on hepatocytes and macrophages [170, 171]. The pathways by which α_2-macroglobulin exerts regulatory influences on cytokine biology in vivo include the following (from [171]):

- Uptake by low-density lipoprotein receptor-related protein/α_2-macroglobulin receptors
  - Clearance, endocytosis, and lysosomal degradation
  - Delivery of cytokine activity to cells that coexpress low-density lipoprotein receptor-related protein/α_2-macroglobulin receptors
- Antiproteinase activity of α_2-macroglobulin
  - Altered proteolytic activation of latent cytokines
  - Reduced proteolytic degradation of active cytokines
- Proteinase activity (of α_2-macroglobulin-proteinase complexes)
  - Proteolysis of small cytokines in presence of macromolecular antiproteinases
- Cytokine-binding activity
  - Receptor competition
  - Cytokine reservoir or concentration
  - Inactivation

Multiple pro-and anti-inflammatory cytokines are bound by α_2-macroglobulin, including TNF-α, IL-1β, IL-6 TGFβ-1, TGFβ-2, nerve growth factor, and platelet-derived growth factor [172, 173]. Of relevance to determination of the role of specific circulating cytokines in shock and trauma is the transport function of cytokines by α_2-macroglobulin (see above). This carrier process may shield bound but biologically active cytokines from detection systems despite fluxes in interorgan transport and deposition.

CRP is one of a group of structurally related proteins called pentraxins circulating in the blood as molecules composed of five noncovalently associated subunits [157]. Tillett and Francis observed that acute pneumococcal infection was associated with appearance of CRP [174] whose concentration decreases after resolution of acute illness. CRP has multiple activities relevant to pathogenetic events in ARDS and multiple organ failure. CRP levels are elevated in patients with ARDS and these elevations correspond with inhibition of PMN chemotaxis in vitro [175]. Elevated serum CRP concentrations were associated with decreased pulmonary leukosequestration and vascular permeability in a rabbit C5a-induced alveolitis model [176]. Similar inhibition of C5a des arg-induced neutrophil alveolitis was recently confirmed in transgenic mice expressing CRP [177]. The mechanisms(s) by which such inhibition of PMN chemotaxis occurs is incompletely understood. Physical interactions with PMN adhesion molecules, alteration of the PMN cytoskeleton increasing cell stiffness, or changes in the availability/binding of Ca^{2+} to PMNs are being investigated. CRP has other actions relevant to host defense. These include phosphorylcholine-mediated binding to damaged cell membranes [178] and activation of the classical pathway of the complement system with resultant opsonization of particulates and micro-organisms [179].

Conclusion

Here we have outlined a conceptual paradigm concerning the role of the liver in host defense during critical illness. The principal utility of this schema is that it facilitates integration of recent experimental and clinical data from diverse lines of investigation. From this discussion, it is clear that changes in the characteristics of the splanchnic circulation can have significant, but clinically occult consequences on immunoregulatory aspects of hepatic performance. Further mechanistic analyses of this gut–liver axis will be central to an understanding of pivotal organ system interactions in the critically ill.

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