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Brief Reviews

The Journal of Immunology

The Acute-on-Chronic Liver Failure Syndrome, or When the Innate Immune System Goes Astray

Joan Clària,*,† Vicente Arroyo,‡ and Richard Moreau§

The acute-on-chronic liver failure (ACLF) syndrome is characterized by acute decompensation of cirrhosis, organ failure, and high 28-d mortality. ACLF displays key features of systemic inflammation and its poor outcome is closely associated with exacerbated systemic inflammatory responses. In this review, we describe the prevailing characteristics of systemic inflammation in patients with decompensated cirrhosis and ACLF, with special emphasis on the principal features of the cytokine storm the mechanisms underlying this intense systemic inflammatory response (i.e., presence of circulating pathogen- and damage-associated molecular patterns), and their implication in tissue and organ damage in this condition. ***The Journal of Immunology*****, 2016, 197: 3755–3761.**

Acute-on-chronic liver failure (ACLF) is defined as the acute deterioration of pre-existing chronic liver disease, usually related to a precipitating event and associated with increased mortality because of multisystem organ failure (1). ACLF typically progresses in patients with cirrhosis undergoing acute decompensation with ascites, jaundice, variceal hemorrhage, encephalopathy, and bacterial infections. The epidemiology, diagnostic criteria, characteristics, clinical course, and prognosis of ACLF have recently been detailed in the CANONIC study, a large multicenter European prospective observational investigation in 1383 patients consecutively admitted to 29 European university hospitals for the treatment of acute decompensation of cirrhosis (2). According to the CANONIC study, ∼31% of patients admitted to the hospital for acute decompensation of cirrhosis have ACLF at admission (20%) or it develops during hospitalization (11%). ACLF encompasses multiorgan failure (liver, kidney, brain, coagulation, circulation, and/or lung) and high short-term mortality rate (3). Mortality rate depends on the number of failing organs as defined by the CLIF-C OFs (a simplified version of the CLIF-SOFA score) (4). ACLF grade 1, defined as single-kidney failure (grade 1a) or single nonkidney organ failure with serum creatinine concentration of 1.5–1.9 mg/dl and/or hepatic encephalopathy grade 1–2 (grade 1b), is the most prevalent form of ACLF (15.8% of patients admitted to the hospital with acute decompensation) and has a 28-d mortality rate of 23% (Table I). Patients with ACLF grade 2 (two failing organs; prevalence rate, 10.9%) have an intermediate prognosis (28-d mortality rate of 31%). Finally, patients with three or more organ failures (ACLF grade 3), the less frequent form of ACLF (4.4%), show extremely high mortality rates reaching 75% at 28 d.

Although the CANONIC study was not primarily intended to address the mechanisms underlying ACLF, it provided seminal discoveries indicating that ACLF occurs in the setting of an exacerbated systemic inflammatory response. In particular, the CANONIC study revealed that the WBC count and the serum levels of C-reactive protein (CRP), two well-established nonspecific markers of systemic inflammation, were remarkably elevated in patients with ACLF as compared with patients without ACLF (2). In addition, in patients with ACLF, the WBC count and CRP levels increased in parallel with the severity of the syndrome, as estimated by the number of organ failures. Finally, ACLF was frequently associated with precipitating events that promote systemic inflammation such as bacterial infections or acute alcoholic hepatitis. All of these observations have led the investigators of the CANONIC study to recently propose the systemic inflammation hypothesis to explain the pathogenesis of ACLF in decompensated cirrhotic patients (5). According to this hypothesis, acute decompensation in patients with pre-existing cirrhosis would occur in the setting of an exacerbated systemic inflammatory response. The systemic inflammation hypothesis has been widely accepted and has opened new avenues for the study of ACLF pathophysiology. Unfortunately, information on this subject is still scarce, and the full characterization of systemic inflammation in patients with decompensated cirrhosis is a work in progress. This review describes most of the

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Abbreviations used in this article: ACLF, acute-on-chronic liver failure; CRP, C-reactive protein; DAMP, damage-associated molecular pattern; ILC, innate lymphoid cell; NLR, nucleotide-binding oligomerization domain–like receptor; PAMP, pathogen-associated molecular pattern; PMN, polymorphonuclear neutrophil; PRR, pattern-recognition receptor; SNP, single nucleotide polymorphism.

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Table I. ACLF grading system

	Grades of ACLF
No ACLF	No organ failure
	One organ failure (liver failure, coagulation, circulatory or respiratory failure) with creatinine <1.5 mg/dl and no hepatic encephalopathy
	Single cerebral failure and creatinine <1.5 mg/dl
ACLF grade 1a	Single-kidney failure without mild or moderate hepatic encephalopathy
ACLF grade 1b	Single-organ failure with serum creatinine ranging from 1.5 to 1.9 mg/dl and/or mild-to-moderate hepatic encephalopathy
ACLF grade 2	Presence of two organ failures
ACLF grade 3	Presence of three or more organ failures

Data from Moreau et al., Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 144: 1426–1437, Elsevier, 2013 (2).

characteristics and mechanisms of systemic inflammation reported to date in patients with acutely decompensated cirrhosis and ACLF.

Innate immune system and excessive inflammatory response in decompensated cirrhosis

Several studies have attempted to properly address the distinctive profile of the innate immune system in patients with decompensated cirrhosis. The innate immune system, which protects the body against potentially disease-causing microorganisms (pathogens) and other foreign or damaging molecules, is composed of different cell types including polymorphonuclear leukocytes (polymorphonuclear neutrophils [PMNs]), mononuclear phagocytes (monocytes, macrophages, and dendritic cells), NK and NKT cells, innate lymphoid cells, eosinophils, basophils, and mast cells (6). PMNs and monocytes are phagocytic cells that are characterized by their ability to ingest invading bacteria and other microorganisms, foreign molecules, and dying cell corpses. Monocytes also have the ability to stop circulating in the blood and enter the tissues to become macrophages, a process that is associated with a remodeling of the expression of >800 different genes (7). Macrophages exert similar and overlapping functions to circulating monocytes, although typically, tissue macrophages polarize into distinct subsets, expressing mainly M1 (potent proinflammatory and antimicrobial activities) or M2 (anti-inflammatory and tissue-reparative activities) phenotypes (8). Dendritic cells and monocytes also participate in the activation of the adaptive immune system through a process known as Ag presentation, which further enhances the body's response to the pathogen or injury by displaying proteins derived from ingested pathogens and other molecules on their surface (9). Peripheral blood eosinophils and basophils and tissue-resident mast cells have been classically associated with a role in the pathogenesis of allergic disorders, although they are also required for the defense against parasitic infections (10). Finally, NK, NKT, and innate lymphoid cells share common features of the adaptive immune system and have some capability to differentiate into memory cells (11). A lower number and decreased function of peripheral NK cells has been reported in patients with hepatitis B virus–related ACLF (12). Given that ACLF shares some similarities with sepsis and because dysfunctional PMNs and monocytes are the major contributors to excessive inflammation leading to tissue damage and multiple organ failure in this condition, this review focuses on the role of these two peripheral blood immune cell types in the pathogenesis of ACLF.

PMN and monocyte immune responses are orchestrated by soluble inflammatory factors, in particular by cytokines. Cytokines are the primary determinants of the innate immune response, and the term cytokine storm was originally coined to describe the excessive release of proinflammatory cytokines in graft-versus-host diseases (13). The term earned recognition in bacterial sepsis along with other examples of tissue injury (e.g., trauma, burns), pathologies that all have in common an excessively activated innate immune system along with systemic inflammation (13). Cytokines are low m.w. proteins produced and released by immune cells in response to damage and stress stimuli (14). The production of cytokines by immune cells is one of the initial steps of the inflammatory cascade. Once released, cytokines interact with specific receptors in their target cells (mainly neutrophils and monocytes/macrophages), where they induce multiple responses in both autocrine and paracrine fashion (i.e., interacting with the same cell or with neighboring cells). Many cytokines act synergistically either by binding to the same cell-surface receptor or by exerting multiple overlapping effects (14). Moreover, cytokines tend to have pleiotropic functions that may alter different cell functions such as proliferation, migration, adhesion, and apoptosis, although they are best known by their immunomodulating actions. A general agreement exists that cytokines are the major determinants of systemic inflammation because they not only favor a proinflammatory environment but also amplify the inflammatory process in a positive feedback loop (14).

A comprehensive study analyzing 29 different cytokines and chemokines in plasma samples from 522 patients with decompensated cirrhosis with and without ACLF and 40 healthy subjects has recently provided conclusive evidence of the role of these inflammatory mediators in the pathogenesis of ACLF (15). Specifically, as compared with healthy subjects, patients with cirrhosis showed markedly increased levels of cytokines, a feature that was more evident in patients presenting with ACLF. In these patients, cytokine levels were comparable with those described in patients with sepsis (16). Moreover, compared with patients without ACLF, those with ACLF had a predominance of proinflammatory cytokines (i.e., TNF-α and IL-6) and chemokines (IL-8 and MCP-1) (Table II). Among the proinflammatory cytokines, IL-6 and IL-8 showed a clear relationship with the clinical course of ACLF, in such a way that lower levels were associated with improvement, whereas high levels were associated with worsening of ACLF. IL-6 levels were particularly higher in patients with bacterial infection–associated ACLF, whereas IL-8 was a discriminate marker of active alcoholism as the ACLF precipitating

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event. Furthermore, IL-6 and IL-8 levels followed a parallel trend with the severity of ACLF and were strongly associated with 28- and 90-d mortality. It is important to mention that IL-6 is one of the most important mediators of the hepatic acute-phase response and that both IL-6 and TNF-α are known to potently stimulate the hepatic synthesis of acute-phase proteins such as CRP (17). Therefore, high IL-6 and TNF-α concentrations probably contribute to increased CRP levels in patients with ACLF, despite these patients having liver dysfunction or failure. In contrast, IL-8, which predicts organ function decline in patients with decompensated cirrhosis and ACLF, is a chemokine that bears principal responsibility for recruitment of PMNs to the site of inflammation (18). This view is consistent with earlier studies showing increased circulating levels of IL-8 and its receptors in patients with severe alcoholic hepatitis along with the observation that IL-8 protein expression in the liver is an independent predictor of short-term mortality (19, 20). Of interest, IL-8 is produced by a wide variety of cells including monocytes, T lymphocytes, PMNs, vascular endothelial cells, epithelial cells, and hepatocytes, among others, and its presence in the circulation leads to a variable degree of tissue damage in critically ill patients undergoing organ damage (18).

Increased circulating levels of proinflammatory cytokines in ACLF are consistent with previous investigations describing enhanced production of these mediators by circulating immune cells in cirrhotic patients (reviewed in Ref. 21). Along those lines, ex vivo studies in freshly isolated monocytes or PBMCs have demonstrated that the production of proinflammatory cytokines and chemokines in response to LPS is higher in immune cells from patients with cirrhosis than in those from healthy subjects (22, 23). Moreover, plasma proinflammatory cytokine levels have been reported to be higher during the first hours of bacterial infection in patients with cirrhosis than in those without, confirming the existence of an excessive innate immune response to bacterial pathogens in this disease (22–24). The mechanisms responsible for this exaggerated response in cirrhosis are poorly understood but could involve several TLR4-mediated negative feedback mechanisms (i.e., activation of the PI3K/AKT pathway and induction of IRAK-M) known to dampen the proinflammatory response to LPS (24).

In addition to proinflammatory cytokines, patients with decompensated cirrhosis and ACLF also present an exacerbated production of anti-inflammatory cytokines such as IL-10 and IL-1ra (Table II) (15). This finding suggests: 1) the engagement of a full-blown inflammatory response in ACLF; 2) the presence of a mixed inflammatory–anti-inflammatory systemic cytokine response in these patients; and 3) that the compensatory anti-inflammatory response cannot effectively compensate or counteract the massive production of proinflammatory cytokines in this condition. Notably, it has been previously reported that a subset of $CD14^+$ monocytes from patients with ACLF exhibit overexpression of the tyrosine protein kinase MER (encoded by *MERTK*), which results in inappropriate inflammatory responses to ex vivo LPS stimulation (25), suggesting that excessive systemic inflammatory response may lead to a form of compensatory immune suppression. Along these lines, ex vivo TNF-α production by monocytes has also been reported to be remarkably decreased in patients with decompensated cirrhosis and ACLF (26), a finding that confirms previous studies indicating that these patients present a reduced cellular immune function or sepsis-like immune paralysis (27, 28).

Patients with decompensated cirrhosis and ACLF also have increased levels of G-CSF (15), which is a key regulatory cytokine that targets committed progenitors to promote differentiation and activation of neutrophils (29). Interestingly, increased plasma levels of G-CSF have been shown to drive the process called emergency hematopoiesis which develops in the context of systemic inflammation (30, 31). Therefore, high levels of this cytokine detected in patients with ACLF may contribute to high WBC count, a hallmark of ACLF. In contrast, changes in cytokines signaling for the shaping of the adaptive immune system (i.e., IFN-γ, IFN-α2, and IL-17a) were mild or not statistically different in patients with ACLF (Table II) (15), suggesting that the progression to ACLF in decompensated cirrhosis is mainly due to the activation of the innate immune system.

Finally, the involvement of the IL-1 cytokine family in systemic inflammation associated with ACLF deserves some comment. The IL-1 family forms a gene cluster located on chromosome 2q and contains within a 430-kb region three related genes (*IL1A*, *IL1B*, and *IL1RN*) that encode for three of the most important cytokines of the inflammatory process, namely IL-1α, IL-1β, and IL-1ra, respectively (32, 33). Among these, IL-1β, which is produced via a unique signaling pathway termed the inflammasome, is the most relevant. The inflammasome, of which different types have been identified, is a cytosolic macromolecular multiprotein complex composed of members of the nucleotide-binding oligomerization domain–like receptor (NLR) family together with the protease

Table II. Plasma cytokine levels in healthy subjects and in patients with decompensated cirrhosis with and without ACLF

	Healthy Controls (n = 40)	No ACLF (n = 285)	ACLF (n = 237)	p Value[a]
TNF-α, pg/ml	9 (7–12)	20 (14–27)	29 (17–41)	<0.001
IL-6, pg/ml	0.3 (0.3–0.3)	21 (11–41)	39 (17–115)	<0.001
IL-8, pg/ml	1.6 (0.6–3.3)	37 (20–76)	84 (41–169)	<0.001
MCP-1, pg/ml	37 (21–41)	318 (228–436)	410 (288–713)	<0.001
IL-10, pg/ml	1.1 (0.4–1.1)	3.4 (1.1–9.2)	8.1 (2.1–29.9)	<0.001
IL-1ra, pg/ml	7 (3–9)	10 (5–22)	23 (9–63)	<0.001
IFN-γ, pg/ml	0.8 (0.8–4.9)	6 (2–18)	7 (3–24)	0.044
IFN-α2, pg/ml	3 (3–3)	22 (8–56)	27 (11–63)	0.113
IL-17a, pg/ml	0.7 (0.7–2.7)	3.7 (1.6–10.3)	4.5 (1.6–15.6)	0.128

Data are median (interquartile range).
Modified from Clària et al. (15).
[a]The p value is between ACLF and no ACLF.

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caspase-1 and usually the protein adaptor ASC (apoptosis-associated speck-like protein containing CARD) (34). In particular, the activation of the NLRP3 inflammasome promotes the proteolytic processing by caspase-1 of the immature forms of IL-1β and IL-18 (34). In addition to the secretion of these two proinflammatory cytokines, inflammasomes are also responsible for the induction of inflammatory caspase-mediated, gasdermin-elicited pyroptosis (35). This is a programmed cell death of the infected cells that is distinct from classical apoptosis because dying cells release all the intracellular contents firing up the inflammatory response (34). In contrast, IL-1α is found constitutively inside cells under normal conditions and its release serves as an alarm signal for initiating inflammation in response to tissue injury (36). Of interest, unlike IL-1β, IL-1α is very resistant to degradation in inflammatory fluids, a feature that may explain why IL-1α is more frequently detected in human plasma (37). In this regard, compared with IL-1α, IL-1β was detectable in only 16% of patients with decompensated cirrhosis, whose levels ranged from 0.8 to 82.6 pg/ml (J. Clària and J. Alcaraz-Quiles, unpublished observations). In any event, cytokines of the IL-1 family are within the "eye of the cytokine storm" and trigger acute-phase signaling, trafficking of immune cells to the site of primary infection, epithelial cell activation, and secondary cytokine production (33–37). In a recent study, we have identified two single nucleotide polymorphisms (SNPs) within the IL-1 gene cluster that protected patients with decompensated cirrhosis from excessive systemic inflammation, and therefore reduced the susceptibility of these patients to development of ACLF (38). Specifically, we identified an SNP in the promoter of the gene coding for IL-1β, which was associated with a lower risk for development of ACLF. This SNP had functional significance, and carriers of this SNP presented reduced circulating levels of IL-1β accompanied by an attenuated degree of systemic inflammation as estimated by lower levels of IL-1α, IL-6, G-CSF, and GM-CSF and reduced CRP and WBC count. In addition to the IL-1β SNP, we identified another SNP in the promoter of the IL-1ra gene, a cytokine that inhibits inflammation by antagonizing the binding of IL-1 to its receptor. This finding opens new avenues for exploring anti-inflammatory therapies based on recombinant human IL-1ra, which has been shown to be effective in critically ill pediatric patients and in patients with sepsis and organ dysfunction and/or a predicted risk of mortality of ≥24% (39, 40).

Mechanisms underlying systemic inflammation in ACLF

The mechanisms underlying this intense systemic inflammatory response in ACLF are not precisely delineated, but recent studies suggest that it could be evoked by the presence of pathogen-associated molecular patterns (PAMPs) in the systemic circulation of cirrhotic patients. PAMPs are common pathogen-derived molecules mostly produced by bacteria and other pathogens that promote systemic inflammation by activating innate immune cells such as monocytes and PMNs (41). PAMPs are unique conserved molecular structures that are recognized by the host via dedicated receptors called pattern-recognition receptors (PRRs), including, among others, TLRs, NLRs, and retinoic acid–inducible gene I (a member of the retinoic acid–inducible gene I–like receptor family) (41). These receptors are cell surface or intracellular receptors for molecular signatures characteristic of bacteria, viruses, and parasites, including features of their nucleic acids, proteins, and lipid and carbohydrate components. PAMPs are basic and common features of these microorganisms that cannot readily be modified by genetic mutation. The engagement of PRRs results in the stimulation of signaling cascades that activate transcription factors such as NF-κB or AP-1 (42), which, in turn, induce a battery of genes encoding for molecules involved in inflammation (i.e., IL-6 and TNF-α). A prime example of this is LPS, a PAMP present in the cell wall of Gram-negative bacteria, which engages the PRR, TLR4, activating multiple downstream signaling pathways that result in the synthesis of cytokines, and IFNs (42).

Considering that ~30% of patients with ACLF have infections caused by bacteria, viable bacteria can translocate from the intestinal lumen to extraintestinal organs and cause overt infections such as spontaneous bacterial peritonitis, which is the most common (2, 43). Bacteria most likely use the transcellular route (transcytosis) through epithelial cells. Intestinal inflammation in cirrhosis may impair the intestinal and gut barriers, and therefore contribute to the translocation of viable bacteria. Also, the intestinal immune surveillance response might not be adequate to clear translocated bacteria in the lamina propria, which is restored with antibiotic treatment (43). In addition, changes in the intestinal microbiota composition might initiate intestinal inflammation, because nonabsorbable antibiotics reduce intestinal inflammation and gut barrier dysfunction in preclinical animal models (44). Moreover, in contrast with other pathologies, the presence of circulating PAMPs in decompensated cirrhosis may also occur independently of bacterial infections. In this case, circulating PAMPs are the result of the translocation of bacterial products from the intestinal lumen to the systemic circulation. This is a frequent feature in patients with decompensated cirrhosis caused by increased intestinal production related to intestinal bacterial overgrowth, increased permeability of the intestinal mucosa, and impaired function of the intestinal innate immune system (43, 44). This phenomenon would explain why some decompensated cirrhotic patients experience development of ACLF without having an active bacterial infection.

Apart from activating immune cells in the circulation, PAMPs directly stimulate immune responses by binding to PRRs in solid organs and tissues. This is very relevant and biologically significant for the liver, which directly receives blood from the intestine and therefore is constantly exposed to PAMPs derived from harmless commensal bacteria in the gut lumen (45). Indeed, the liver plays an important physiological role in LPS detoxification and, in particular, hepatocytes are involved in the clearance of this PAMP of intestinal derivation (46). Importantly, translocation of bacterial products from the intestinal lumen is increased in cirrhosis, and LPS challenge in cirrhotic animals, which are sensitized to this PAMP, results in increased production of TNF-α and the development of TNF-α–induced hepatocyte apoptosis and necrosis (47). In patients, evidence of LPS-induced hepatic injury has been reported in cirrhosis, autoimmune hepatitis, and primary biliary cirrhosis (48). This is also relevant to patients with severe alcoholic hepatitis, who represent 20% of the cases of ACLF (2). Excessive alcohol consumption also alters the gut microbiome and increases intestinal permeability (44, 49), favoring the translocation of bacteria expressing PAMPs which reach the liver where they are recognized by TLRs

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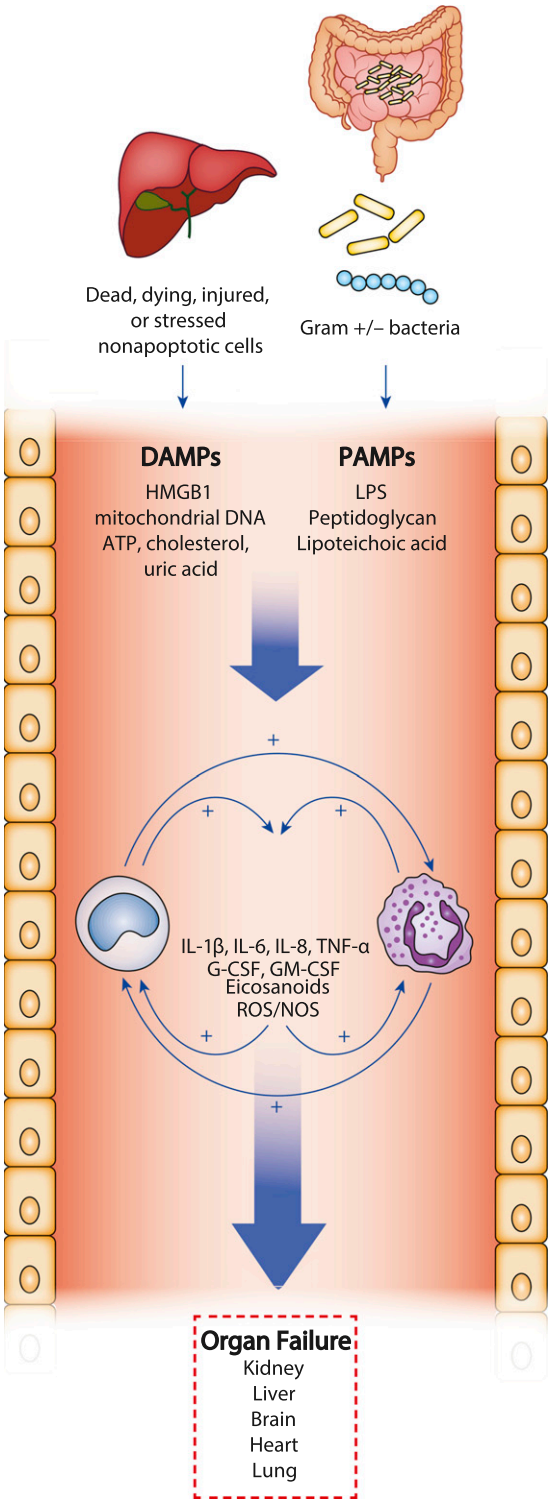

FIGURE 1. Schematic diagram summarizing the role of systemic inflammation in the progression of organ failure in patients with acutely decompensated cirrhosis. In this condition, systemic inflammation is likely due to the presence in the systemic circulation of PAMP molecules released by Gram-positive/-negative bacteria or DAMP molecules from dead, dying, injured, or stressed nonapoptotic liver cells. These molecules interact with specific receptors present in cells of the innate immune system, especially monocytes and neutrophils, resulting in the bulk release of inflammatory (IL-1β, IL-6, IL-8, and TNF-α) and hematopoietic (GM-CSF and G-CSF) cytokines, accompanied by the production of eicosanoids (small lipid mediators with inflammatory properties) and reactive oxygen (ROS) and NO species (NOS). The concerted action of these inflammatory mediators may cause organ failure through mechanisms related to organ hypoperfusion, tissue ischemia, tissue cell dysfunction/necrosis, and hypercoagulopathy. Reprinted in adapted form with permission from Arroyo and Bernardi (68).

expressed in resident macrophages (i.e., Kupffer cells). This recognition stimulates the production of CXCL chemokines (e.g., IL-8), which are potent chemotactic factors that attract and induce PMN infiltration in the liver, a hallmark of alcoholic hepatitis (20). In addition to this, a recent study has provided evidence that markers of macrophage activation, such as CD163 and mannose receptor released from the liver into the circulation after shedding as soluble biomarkers, closely correlate with severity and mortality in ACLF patients (50), further supporting the existence of a tight connection between liver and systemic inflammation in this condition.

It has become increasingly clear in recent years that systemic inflammation can occur in patients with decompensated cirrhosis and ACLF in the absence of bacterial infections. Under these conditions, systemic inflammation can be the result of the release of damage-associated molecular patterns (DAMPs) from the injured liver. Inflammation caused by DAMPs in the absence of any overt infection is called sterile inflammation, and these endogenous inducers of inflammation play a major role linking local tissue damage to systemic inflammation in the absence of an active infection (41). DAMPs are released by dead, dying, or injured cells and originate from several cellular compartments, especially from the nucleus (high mobility group box 1 [HMGB1] and histones), mitochondria (fragments of mitochondrial DNA and formyl peptides), and the cytosol (ATP, members of the S100 calcium-binding protein family [S100A8, S100A9, and S100A12], cholesterol, and urate crystals) (51). These endogenous inducers initiate a sterile inflammatory response by binding to specific PRRs. For example, ATP is recognized by purinergic receptors present at the surface of macrophages, resulting in an increased potassium ion efflux and activating the NLRP3 inflammasome (42, 52, 53). In contrast, HMGB1 can induce cytokine production and promote chemotaxis by engaging by itself or by forming heterocomplexes with other molecules, numerous receptors including the so-called advanced glycation endproduct-specific receptor, TLR2, TLR4, TLR9, syndecan-3, CD24–Siglec-10, CXCR4, and certain integrins (51). Necrotic cells may also release IL-1α and IL-33, which triggers inflammation though their respective MyD88-coupled cognate receptors. Products of the extracellular matrix break down during tissue damage, which is common in the cirrhotic liver, may also link tissue injury with systemic inflammation in ACLF (52, 53). This is the case with hyaluronate, which is broken down into low m.w. fragments in injured tissues, activating TLR4 and promoting an inflammatory response (52, 53). It is important to note that DAMPs such as HMGB1 and IL-33 can be actively secreted, and not just released by necrotic cells, thus notifying the immune system of tissue injury or impending danger (51). For example, PAMPs such as LPS can trigger the active secretion of HMGB1 by human primary PBMCs and primary macrophages from LPS-sensitive mice (54).

Mechanisms underlying organ failure in ACLF

The systemic inflammation hypothesis proposed by the CANONIC investigators also postulates systemic inflammation as the driver of organ failure in decompensated cirrhosis (5). According to this hypothesis, organ failure in these patients is not only due to impairment in systemic circulatory function and organ perfusion but also to the direct deleterious effects of

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the overactivated innate immune system on the microcirculation and tissue cell homeostasis (5). Exacerbated systemic inflammation in patients with severe sepsis leads to organ failure by a direct effect of the inflammatory mediators on microvascular function, tissue cell function, and cell death mechanisms (55–57). Indeed, patients with sepsis almost invariably show excessive systemic production of proinflammatory cytokines and chemokines (cytokine storm), which causes collateral tissue damage, a process known as immunopathology (52). For example, effectors of the immune response such as PMNs, monocytes, activated Th1 and Th17 cells, and cytotoxic T cells are known to be associated with a high risk for immunopathology (58). There are also some examples of DAMP-induced excessive inflammatory response causing major tissue damage. For example, mice deficient for *Ripk1* develop Ripk3-Mlkl–mediated necroptosis resulting in systemic inflammation, multiorgan injury, and death within 3 d of birth (30).

Based on the observation that the severity of systemic inflammation in ACLF is similar to that of patients with sepsis, the structural and functional characteristics of organ failure associated with sepsis can help us to understand the sequence of events leading to ACLF in cirrhosis. For example, TNF-α–induced activation of the NF-κB–inducible NO synthase pathway has been reported to account for impaired left ventricular contractility and cardiac dysfunction in cirrhosis (59). Similarly, systemic inflammation could also be implicated in the pathogenesis of pulmonary dysfunction characterized by increased NO release in pulmonary circulation in parallel with overactivation of chemokines and macrophage accumulation in lung microvasculature (60). Experimentally, liver failure in the context of cirrhosis is the result of hepatocyte death caused by TNF-α–induced apoptosis and/or endothelin-elicited necrosis (61). Hepatocyte death is seen in cirrhotic livers as the consequence of the lack of translation of NF-κB–dependent survival mRNAs into proteins, but not in healthy hepatocytes, which are protected by the induction of NF-κB–dependent prosurvival proteins (62). The presence of endoplasmic reticulum stress in cirrhotic hepatocytes also contributes to the impairment in the translation of antiapoptotic mRNAs into prosurvival proteins (63). In the kidney, organ failure is histopathologically characterized by intense capillary leukocyte infiltration, microthrombosis, cell apoptosis, and signs of mitochondrial injury (reduced mitochondrial mass, disruption of cristae, and extensive mitochondrial swelling) (64, 65). Regarding coagulation failure, it is plausible that inflammation triggers the release of local procoagulant factors (including tissue factor and membrane microparticles) from the endothelial cells, inducing microthrombosis in the microcirculation (66). In summary, systemic inflammation may cause organ failure in patients with decompensated cirrhosis through mechanisms not only related to arterial vasodilation and impairment in left ventricular function, organ hypoperfusion, and tissue ischemia, but also through mechanisms leading to cell dysfunction. This cell dysfunction leading to organ failure can be promoted by cytokines through mechanisms involving mitochondrial damage, impaired oxygen consumption and ATP synthesis, intense cellular bioenergetic failure, and cell/cycle arrest. Damaged mitochondria and cell injury are in turn major sources of endogenous inducers of inflammation (i.e., DAMPs) that further promote local inflammation, thus leading to a vicious cycle linking cell injury to organ failure (56, 67).

Conclusions

This brief review summarizes and discusses our current understanding of the salient features of systemic inflammation in patients with decompensated cirrhosis and ACLF. It describes the most important hallmarks of systemic inflammation in this disease and highlights the role of the innate immune system and the exacerbated production of cytokines as drivers for the development of organ failure in acutely decompensated cirrhosis. The immunopathological mechanisms underlying systemic inflammation in this condition include pathogen-derived PAMPs, as well as DAMPs derived from dead, dying, injured, or stressed nonapoptotic liver cells that trigger inflammation by interacting with specific PRRs (i.e., TLRs and NLRs) present in immune cells. A schematic diagram of the mechanisms and characteristics involved in these processes is given in Fig. 1. Future studies are needed for the identification of these inducers of the inflammatory response in the context of ACLF.

Disclosures

The authors have no financial conflicts of interest.

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