Acute-on-Chronic Liver Failure

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Acute-on-chronic liver failure (ACLF) is a complex syndrome that develops in patients with cirrhosis and is characterized by acute decompensation, organ failure(s) and high short-term mortality. ACLF frequently occurs in close temporal relationship to a precipitating event, such as acute alcoholic, drug-induced or viral hepatitis or bacterial infection and, in cases without precipitating events, probably related to intestinal translocation of bacterial products. Dysbalanced immune function is central to its pathogenesis and outcome with an initial excessive systemic inflammatory response that drives organ failure and mortality. This hyperinflammatory state ultimately impairs the host defensive mechanisms of immune cells, rendering ACLF patients immunocompromised and more vulnerable to secondary infections, and therefore to higher organ dysfunction and mortality. (Draft for you)

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1. Acute-on-Chronic Liver Failure (ACLF)

ACLF is a severe syndrome evolving in patients with acutely decompensated (AD) liver cirrhosis. ACLF is characterized by the manifestation of organ dysfunctions and failures across the six major organ systems (liver, kidney, brain, coagulation, circulation, and respiration) resulting in high short-term mortality (28-day mortality of 32%)[1][2][3]. The liver and the kidney are the most commonly affected organ systems followed by coagulation, brain, circulation and respiration. ACLF is classified in three grades of severity (ACLF-1, -2 and -3) according to the number of organ failures and may exhibit a variable course during hospitalization as it can follow a steady course or resolve, improve or worsen within a few days. The CANONIC study, a prospective observational investigation in 1343 patients hospitalized for acute decompensation of cirrhosis, provided the first evidence-based definition of ACLF which includes the presence of organ failure(s) and a 28-day mortality risk of 15% or higher[1]. In Western countries, ACLF is particularly prevalent among young patients with alcoholic cirrhosis and in 60% of the cases develops in close association with potential precipitating events, mainly bacterial infections or active alcoholism. In Asian countries, ACLF is more commonly diagnosed in patients with hepatitis B-related cirrhosis who exhibit lower prevalence of extrahepatic organ failures.

2. Systemic Inflammation and Immunopathology Are Major Drivers of ACLF

Recent advances in our understanding of the pathophysiological basis of ACLF indicate that a systemic hyperinflammatory state is the main driver of widespread tissue and organ injury in patients with AD cirrhosis developing ACLF[4][5]. This hyperinflammatory state is produced by the massive release of inflammatory mediators

such as cytokines, chemokines, growth factors and bioactive lipid mediators (see below) that lead to immune-mediated tissue damage, a process that is also known as immunopathology. For example, in the microvasculature of vital organs, proinflammatory cytokines damage the endothelium glycocalyx and trigger neutrophil and monocyte adhesion to endothelial cells and their transmigration into tissues[6]. Activated immune cells, in turn, release mediators such as proteases, oxidative molecules, cytotoxic cytokines, prostaglandins (PGs) and leukotrienes (LTs) (see below), which further intensify tissue damage.

At present little is known about the identity of the triggers (either of infectious or noninfectious origin) leading to immune cell activation and immunopathology in patients with AD cirrhosis evolving to ACLF. Bacterial infections are present in 33% of cases of ACLF and therefore pathogen-associated molecular patterns (PAMPs) released by infecting bacteria are likely contributing[7]. In addition, circulating PAMPs can be the result of the translocation of bacterial products from the intestinal lumen to the systemic circulation. In fact, bacterial overgrowth, increased permeability of the intestinal mucosa, and impaired function of the intestinal innate immune system are common in AD patients developing ACLF[8][9]. PAMPs are unique conserved molecular structures that are recognized by the host via dedicated receptors called pattern-recognition receptors (PRRs), including among others Toll-like receptors (TLRs) present at the cell surface or in the endosomal compartment and NOD-like receptors (NLRs), present in the cytosol of the cells[10]. These receptors recognize nucleic acids and protein, lipid and carbohydrate components characteristic of bacteria and viruses. The engagement of PRRs results in the stimulation of signaling cascades that activate transcription factors such as nuclear factor (NF)-kB or activator protein 1[11], which in turn induce the expression of a battery of genes encoding for molecules involved in inflammation (i.e., interleukin 6 (*IL6*) and tumor necrosis factor α (*TNF*). Lipopolysaccharide (LPS) from the cell wall of Gram-negative bacteria, which engages TLR4-mediated activation of multiple downstream signaling pathways that result in the synthesis of cytokines and interferons, is a prime example of PAMPs[11].

Systemic inflammation can occur in patients with AD cirrhosis and ACLF in the absence of bacterial infections and/or bacterial translocation as the result of the release of damage-associated molecular patterns (DAMPs) from injured organs and tissues. 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 (mitochondrial DNA and formyl peptides) and the cytosol (adenosine triphosphate (ATP))[10]. Apart from necrosis, other immunogenic forms of cell-death such as necroptosis and pyroptosis are common in advanced liver disease and contribute to the enhanced release of DAMPs in this condition[12]. Similar to PAMPs, DAMPs initiate an immune response by binding to specific PRRs. In certain cases, inflammatory cytokines such as IL-1α and IL-33 can act as DAMPs and trigger inflammation through binding to their respective MyD88-coupled cognate receptors.

The intensity of systemic inflammation and the response of the immune system to PAMPs and DAMPs may depend on host genetic factors. For example, single-nucleotide variants might modulate the release of inflammatory molecules by innate immune cells or might induce changes in the expression of PRRs, such as TLRs. Consistent with this, genetic variants in genes coding for receptors of the innate immune system such as nucleotide-binding oligomerization domain 2 (NOD2) or ligands as mannan-binding lectin (MBL) and MBL-associated serine proteases (MASP) 2 have been shown to associate with increased short-term mortality in AD

and ACLF patients[13]. Moreover, single nucleotide polymorphisms within the IL-1 gene cluster have been reported to protect patients with AD cirrhosis from uncontrolled systemic inflammation and to reduce the predisposition of these patients to develop ACLF[14].

3. Immunosuppression Is a Common Feature in ACLF

The hyperinflammatory response in patients with ACLF frequently occurs in parallel with the presence of dysfunctional innate immune system at the humoral, physical and cell-mediated level [8][15][16]. Due to hepatocellular insufficiency, cirrhotic patients commonly display reduced humoral anti-defense capacities as a result of decreased production of acute phase proteins, hypoalbuminemia and defective complement system[17][18][19]. Additionally, the physical barrier in cirrhosis is impaired, and even more so in ACLF, with gut leakage and dysfunction of the vasculature and sinusoidal endothelium being the most prominent features.

Taking all these components of the innate immune system into account, the overall immune status in patients with ACLF ranges in the spectrum from immunosuppressive/immunoregulatory/tolerogenic to exuberantly hyperinflammatory, and these extremes are not mutually exclusive. Rather the contrary, these two conditions frequently coexist in the same patient, as a constant and persistent hyperinflammatory milieu characterized by increased circulating proinflammatory and anti-inflammatory mediators (e.g., galectin-3, IL-6, TNFα, IL-10)[4][20] and lipid mediators such as PGE_2 can cause the downplaying of innate immune defensive responses and the expansion of regulatory immune cells leading to immunosuppression[21][22], probably in an attempt to keep the proinflammatory response at bay. The predominance of one or the other depends on temporal and spatial aspects: immune cells in the circulation may behave differently (inflammatory phenotype with production of cytokines) than their counterparts in the liver for example (more tolerogenic phenotype), and the immunodeficient phenotype tends to assume greater importance with increasing disease severity[23].

Bernsmeier et al. proposed a model which harmonizes these two extremes: Circulating inflammatory mediators, released by immune cells in an excessive manner in cirrhosis in response to PAMPs and DAMPs induce the formation of immunoregulatory monocytes/macrophages[20]. Thereupon, these cells migrate across endothelia facilitated by endothelial dysfunction into inflamed tissues. In ACLF, tissue macrophages tend to display functionally endotoxin tolerant/immunoregulatory features. Due to their enhanced migratory potential, these cells reverse migrate into the circulation, where they further expand into other tissues and lymph nodes, contributing to the immunosuppressive phenotype in ACLF[20]. The clinical consequence is increased susceptibility to bacterial infections as major precipitating event of organ failure(s), which is the discriminant feature of ACLF[1].

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