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What's new in acute liver failure?

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Acute liver failure (ALF) is characterised by a mortality rate over 40 % despite of established treatment modalities such as *N*-acetylcysteine (NAC) and liver transplantation. In order to develop targeted therapeutic strategies, insight into the pathophysiological mechanisms is needed. Here we summarise the current pathophysiologic knowledge integrated in its clinical context and highlight recent advances and their possible future therapeutic implications.

ALF is a multisystem disorder, comprising acute-onset icterus, elevated transaminases, coagulopathy and encephalopathy in patients without pre-existing hepatopathy. The evolution of extrahepatic disease involves marked activation of systemic inflammatory response (SIRS) and multiple organ dysfunction following massive hepatocellular death [1]. Secondary infection is a frequent complication and accounts for its high mortality [2].

Pathophysiology of ALF has been mostly studied in models of acetaminophen toxicity. The precipitating event of the ALF syndrome is the overwhelming death of hepatocytes exceeding the regenerative capacity of the liver.

Subsequently hepatocyte death triggers activation of the innate immune response leading to pro-inflammatory cytokine production (e.g. TNF-α, IL-6), leucocyte recruitment and propagation of liver injury. The process is initiated through damage associated molecular patterns (DAMPS, e.g. HMGB-1, DNA) released by dying cells that interact with toll-like receptors on resident macrophages (Kupffer cells) [3]. The number of hepatic macrophages expands within hours of injury through recruitment of circulatory monocytes and proliferation of resident Kupffer cells. In this "initiation" phase, macrophages polarise towards a "pro-inflammatory" phenotype necessary for "propagation" of the local inflammation. Upon heretofore unidentified mediators, macrophages undergo a functional "switch" and polarise towards an "anti-inflammatory" phenotype thereby initiating the "resolution" phase of acute liver injury [4].

As a result of massive "spill-over" of cytokines to the circulation the described inflammatory response is not restricted to the liver causing SIRS in the initiation/propagation phase and compensatory anti-inflammatory response (CARS) thereafter. CARS consists in predominance of anti-inflammatory circulatory monocytes. Persistent CARS responses are linked to recurrent infections complicating ALF, conferring a poor prognosis [5]. SIRS and CARS further affect other organ systems e.g. circulating inflammatory mediators crossing the blood–brain barrier and induce encephalopathy/cerebral oedema through microglial activation.

Certain important details have recently been added to the pathophysiologic model described (Fig. 1) and might be translatable into clinical practice.

The identification of circulating histones as DAMPs gave valuable insight into the initiation of tissue inflammation in ALF. In a murine model of ALF, plasma levels of circulating histones were increased. Systemic administration of exogenous histones aggravated liver inflammation histologically and biochemically, and increased circulatory TNF-α levels. Removal of circulating histones reduced inflammation and prolonged survival in mice [6].

An unsolved question is which inflammatory mediators induce the "macrophage/monocyte switch" locally necessary for resolution of tissue inflammation but simultaneously result in infectious complications? Recent work of our group identified secretory leukocyte protease inhibitor (SLPI) as such a micro-environmental mediator of anti-inflammatory response in acetaminophen-induced ALF [7]. SLPI is an enzyme (protease inhibitor) with known immune-modulatory properties. SLPI was expressed in macrophages and biliary epithelial cells in areas of hepatic necrosis in patients with ALF. Concomitantly hepatic tissue and plasma levels of SLPI were increased in ALF compared to healthy controls. In vitro, recombinant SLPI induced an anti-inflammatory phenotype in previously healthy monocytes, similar to the phenotype of monocytes from patients with ALF ($CD163^{high}$; impaired TNF-α/IL-6 production in response to lipopolysaccharide through inhibition of NF-κB). Blocking SLPI partially reversed the anti-inflammatory polarisation of monocytes in vitro [7].

As micro-environmental mediators trafficking from the liver to the circulation exacerbate pro-inflammatory (e.g. histones) and anti-inflammatory response (e.g. SLPI), targeting these proteins by monoclonal antibodies might be worth studying.

Given the variety of mediators involved, targeted therapy might not alleviate immuno-paresis sufficiently. Plasma exchange has been discussed in the context of ALF since the 1970s. The rationale is to clear accumulating albumin-bound and high molecular weight mediators from the plasma. Recent publications [8] provide encouragement to reinitiate controlled trials evaluating the role of plasma exchange in ALF.

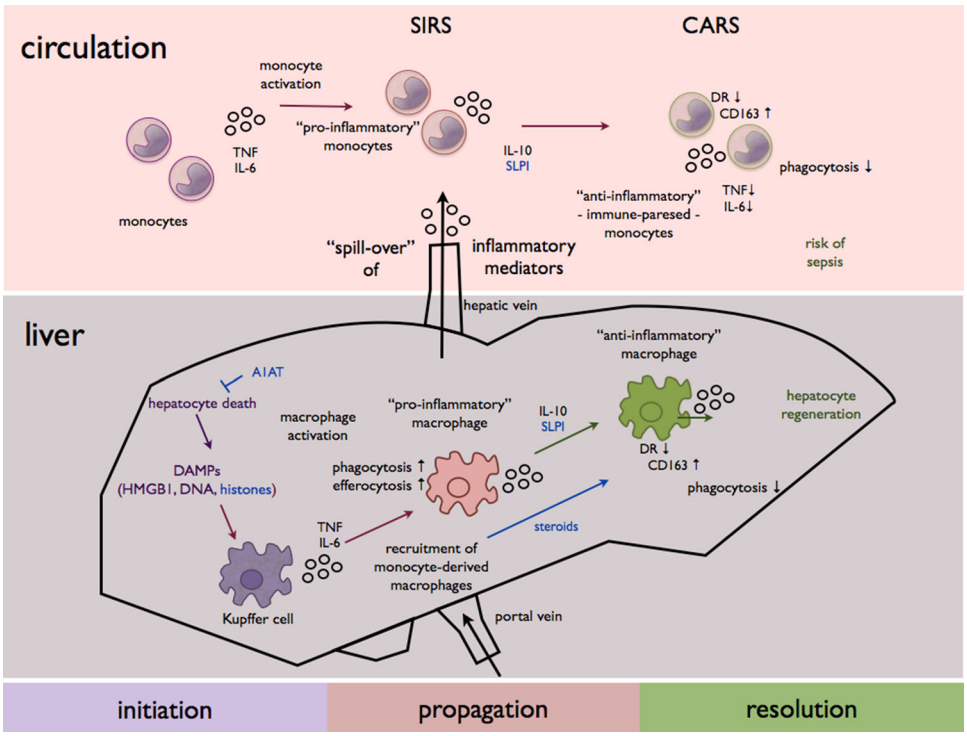

Fig. 1 Pathophysiology of acute liver failure (ALF)—a systemic inflammatory disorder. Reciprocal interaction of the immune responses between the liver tissue and the systemic circulation throughout different phases of ALF (initiation–propagation–resolution). Initiation phase: Kupffer cells become activated following hepatocyte death through DAMPs and initiate a pro-inflammatory response. Propagation phase: Hepatic macrophages expand through recruitment of monocytes and local proliferation of Kupffer cells, and differentiate towards a pro-inflammatory phenotype promoting tissue destruction. Resolution phase: Macrophages undergo a functional "switch" towards an anti-inflammatory phenotype favouring resolution and regenerative responses. "Spill over" of various inflammatory mediators during all phases of disease induces pro-inflammatory orientation of circulating monocytes during the initiation/propagation phase and anti-inflammatory orientation during resolution. Immuno-paresis during resolution predisposes to infectious complications. New aspects detailing the pathophysiologic mechanisms are highlighted in *blue*

α1-Antitrypsin (A1AT), another protease inhibitor with immune-modulatory properties, was recently found to be protective in mouse models of ALF. Systemic administration of A1AT reduced hepatic apoptosis through inhibition of caspase-3 and -8, decreased circulatory TNF-α levels, and prolonged survival in different mouse models including acetaminophen toxicity [9]. The possible benefit of A1AT treatment to reduce hepatic apoptosis in patients with ALF needs to be tested.

Although NAC is the standard of care for the treatment of acetaminophen-induced and non-acetaminophen-induced ALF, prolonged administration might have deleterious consequences. In experimental models, administration of NAC 72 h following acetaminophen significantly aggravated liver injury and delayed regeneration involving inhibition of NF-κB in a mouse model of acetaminophen-induced ALF [10]. In clinical practice the timing and duration of NAC administration should be considered more carefully, and further evaluated in clinical studies.

Various studies attempted to use corticosteroids to offset the severity of acute liver injury. Although steroid treatment did not reduce mortality in patients with septic shock, the Corticus study pointed out a significantly faster improvement in organ dysfunction (assessed by SOFA score), driven by improvement in cardiovascular organ dysfunction and in liver failure [11]. A recent retrospective analysis of ALF patients did not show an overall survival benefit; but transplant-free survival was marginally higher in the steroid-treated group. As overall numbers of treated patients were low, and steroids were introduced before the onset of ALF in half of the cohort, this remains an area of ongoing controversy [12]. Generally, critically ill patients were found to accumulate steroids as a result of reduced clearance by cortisol-metabolising enzymes. Moreover hypercortisolaemia was dissociated from its regulation by ACTH, suggesting a different regulatory mechanism, possibly involving inflammatory cytokines or catecholamines [13]. These studies excluded patients with ALF, but may have relevant implications for this subgroup of critically ill patients.

Steroids are known for their pivotal influence on monocyte/macrophage differentiation, inducing anti-inflammatory genes involved in chemotaxis, phagocytosis and antioxidative stress and suppressing pro-inflammatory genes involved in apoptosis, adhesion and T cell chemotaxis. Therefore, steroid administration might be beneficial during the initiation/propagation phases of liver injury. A clinical pilot study using an experimental access through the hepatic artery previously supported this concept [14].

Will biomarkers help to schedule appropriate therapy in the future?

Elevations in plasma microRNA-122, HMGB1 and keratin-18 have recently been shown to identify patients with acute liver injury early after acetaminophen ingestion, even if ALT and INR are normal [15]. These markers might facilitate early diagnosis of ALF.

Two markers of macrophage activation, plasma neopterin and soluble CD163, were elevated in patients admitted for ALF [16]. Highest levels were found in non-survivors or patients requiring transplantation, indicative for their possible prognostic value. In acetaminophen-induced ALF they were positively correlated with disease severity (APACHE II; SOFA).

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