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# Modulation of monocyte/macrophage function: A therapeutic strategy in the treatment of acute liver failure

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## Summary

Acute liver failure (ALF) is a condition with a high mortality and morbidity for which new treatments are desperately required. We contend that although the initial event in ALF is liver cell death, the clinical syndrome of ALF and its complications including multi-organ dysfunction and sepsis, are largely generated by the immune response to liver injury.

Hepatic macrophages fulfil a diversity of roles in ALF, from pro-inflammatory to pro-resolution. Their inherent plasticity means the same macrophages may have a variety of functions depending on the local tissue environment at different stages of disease. A better understanding of the mechanisms that regulate macrophage plasticity during ALF will be an essential step towards realising the potential of immune-modulating therapies that re-orientate macrophages to promote the desirable functions of attenuating liver injury and promoting liver repair/regenerative responses.

The key dynamics: temporal (early *vs.* late phase), regional (hepatic *vs.* systemic), and activation (pro-inflammatory *vs.* pro-resolution) are discussed and the potential for novel ALF therapies that modulate monocyte/macrophage function are described.



## Acute liver failure as a model of dysregulated immune-cell driven inflammation

Acute liver failure (ALF) is a clinical syndrome consisting of jaundice, encephalopathy, and coagulopathy due to overwhelming hepatocyte death. Currently, specific treatments for ALF include the use of N-acetylcysteine, liver transplantation (OLT), and best supportive care. Although OLT has markedly improved the survival in ALF, it commits patients to life-long immunosuppression and utilises the precious resource of a transplantable organ [1].

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Immune dysregulation is central to the pathogenesis of ALF, in which massive leucocyte infiltration of the injured liver is contrasted by a depletion and dysfunction of immune cells in the circulation [2]. From a clinical perspective, it is widely accepted that the mortality in ALF is a consequence of profound activation of systemic inflammatory responses (SIRS) and its attendant complications of recurrent sepsis and extra-hepatic organ dysfunction [3,4].

In this review, we show that ALF is an innate immune-driven disorder, in which monocytes/macrophages are key determinants of the initiation, propagation, and resolution phases of acute liver injury. Uncontrolled immune activation leads to the clinical consequences of recurrent sepsis and organ failure encountered in this devastating condition (Fig. 1).

**Key Points**

- Macrophages are central to the pathogenesis of ALF, driving the initiation, propagation, and resolution of liver injury
- Macrophage plasticity provides an exciting platform to base therapies aimed at functional re-orientation, thereby promoting the resolution of inflammation
- Mechanistic biomarkers will have an important role in signposting the phases of immune activation in ALF, thus guiding the timing of intervention
- The relationship between beneficial local (hepatic) and deleterious systemic (circulatory) effects of key mediators is likely to be a challenge in developing immunotherapeutic strategies

## Immunopathology of acute liver failure

### *Local immunopathology of acute liver failure: The role of tissue macrophages*

Macrophages are tissue resident members of the mononuclear phagocytic system that play a central role in the innate immune response to infection and sterile inflammation and are additionally able to recruit adaptive immune cells.

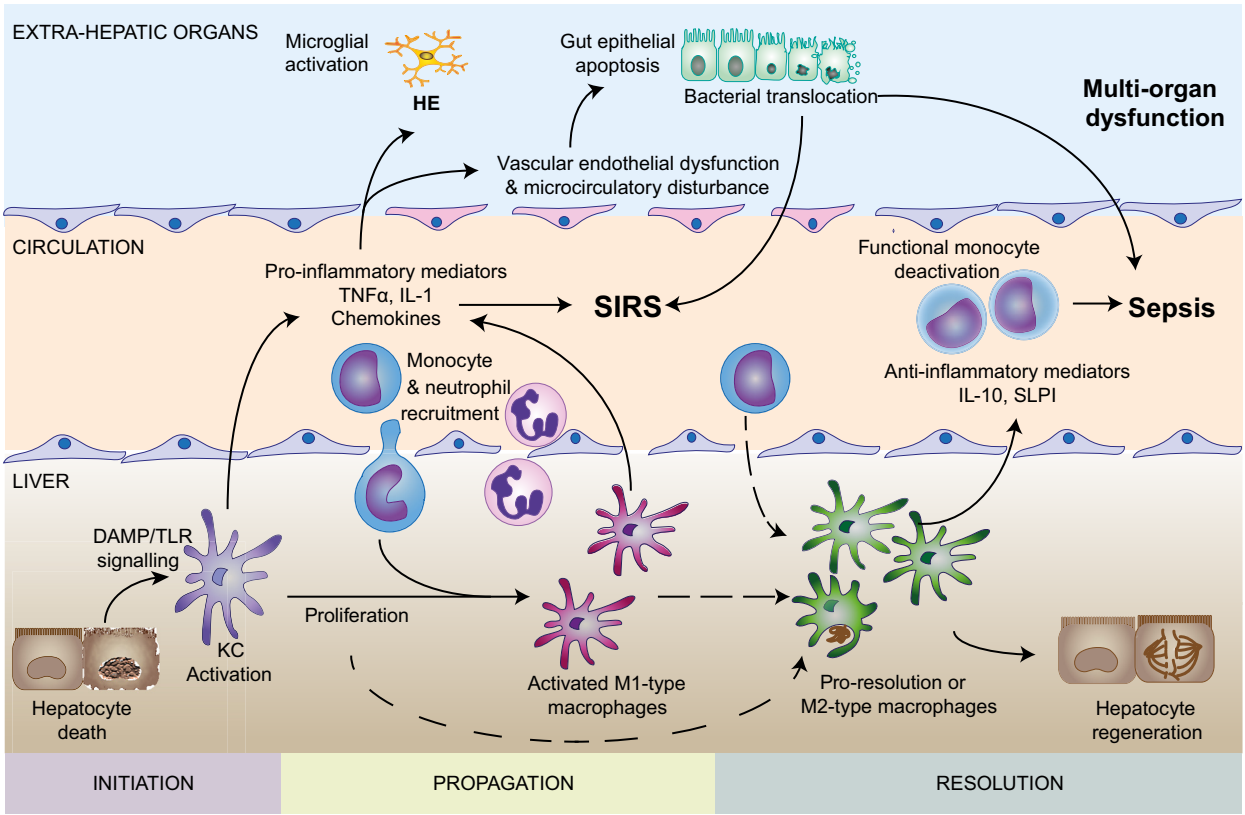


**Fig. 1. A simplified model of monocyte and macrophage function in acute liver failure.** KCs detect hepatocyte death through DAMP/TLR signalling and initiate a pro-inflammatory response. Bone-marrow derived monocytes traffic to the liver to contribute to an expanded macrophage population which are initially pro-inflammatory. During the propagation phase, immune activation is self-perpetuating with recruitment of effectors driving further cytokine and chemokine production. The release of cytokines and vasoactive mediators into the systemic circulation provokes SIRS. Macrophage-derived mediators contribute to vascular endothelial dysfunction and microcirculatory disturbances that result in extra-hepatic organ dysfunction. Later, the presence of pro-resolution macrophages aids tissue recovery. The spill over of anti-inflammatory mediators from the liver into the circulation contributes to functional monocyte deactivation and an increased susceptibility to sepsis.



In the adult liver, macrophages may originate from either a haematopoiesis-independent, self-renewing population derived from embryonic yolk sac cells (Kupffer cells) or from the recruitment of bone marrow derived circulating monocytes [5].

*Macrophage plasticity: the importance of the microenvironment*

Macrophages have pleiotropic actions and diverse roles in inflammation. Their protoxicant responses, such as the production of cytokines and reactive oxygen species, are aimed at microbial elimination and tissue destruction. Equally, they possess anti-inflammatory properties that resolve acute inflammation and trigger tissue remodelling and repair [6]. The functional characteristics of macrophages have been broadly categorised as either 'M1', pro-inflammatory, or 'M2', anti-inflammatory, phenotypes in a classification analogous to $T_H1$ and $T_H2$ responses. In recent years however, this definition has evolved with the recognition that the dichotomous phenotypes really represent extremes, between which numerous macrophage activation states exist [7]. Furthermore it is understood that macrophages exhibit considerable plasticity during inflammation, being able to reversibly transition through distinct activation states in response to microenvironmental mediators [8].

The microenvironmental milieu is a critical determinant of macrophage function during tissue inflammation. In early inflammation the presence of TLR ligands such as HMGB1, DNA, and pro-inflammatory cytokines drive macrophage polarisation towards a classical 'M1-like' activation state through the activation of NF-κB and STAT1 signalling pathways. This leads to the propagation and perpetuation of inflammation as it induces further pro-inflammatory cytokine secretion and MHCII expression. At the later stages of inflammation, macrophages undergo a functional "switch" towards an anti-inflammatory or pro-resolution "M2-like" phenotype; with an increasing number of microenvironmental mediators responsible for this functional switch being identified [9] (Fig. 2).

*Hepatic macrophages in acute liver failure*

In ALF, resident Kupffer cells are important in the initial transduction and amplification of the 'alarm' signal following an injurious event. Hepatocyte death leads to the release of DAMPS, which initiate the activation of innate immune and tissue destructive responses through production of NF-κB dependent pro-inflammatory mediators (e.g., TNFα, IL-1β, IL-6) and reactive nitrogen and oxygen species [10].

Within 12 h of injury in experimental models of ALF, there is a massive expansion in the number of hepatic macrophages. These may be derived from proliferation of resident Kupffer cell population and/or recruitment from the circulating pool of monocytes. Evidence from human and experimental models of acetaminophen toxicity (APAP) suggests that the CCR2-dependent influx