Acute Liver Failure

Mechanisms of Disease and Multisystemic Involvement

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KEYWORDS

• Acute liver failure • Disease mechanisms • Pathophysiology • Inflammation

KEY POINTS

- Acute liver failure is a systemic syndrome that effects many downstream organ systems.
- The syndrome of acute liver failure is initiated and propagated through systemic inflammation.
- Severe liver injury leads to decreased hepatic synthetic capacity and breakdown of metabolism.
- The combined effects of liver failure and systemic inflammation lead to the clinical picture of the acute liver failure syndrome.

INTRODUCTION

The syndrome of acute liver failure (ALF) includes not only severe liver injury and resultant hepatic dysfunction, but also widespread secondary organ dysfunction, regardless of the etiology of the initial liver insult. Beyond simply a liver problem, ALF has been known for decades to have severe consequences affecting most of the major organ systems in the body. Less clear is how severe hepatic injury leads to complex, multisystemic ramifications. As the mechanisms of the underlying pathophysiology are decoded, more understanding into this devastating syndrome is accomplished providing hope for more meaningful clinical interventions in the future.

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LIVER

ALF is a race initiated by a severe liver insult leading to competition between hepatocyte cell death and regeneration. In ALF, hepatocyte death typically proceeds along 2 well-conserved pathways: apoptosis and necrosis, depending on the etiology of ALF. As apoptosis in its pure form induces cellular shrinkage and subsequent implosion while maintaining the cellular membrane, this form of cell death tends to be silent, inducing minimal inflammation. This is opposed to necrosis, in which adenosine triphosphate (ATP) depletion triggers cell swelling and eventual rupture, inducing a significant inflammatory response.[1] Cell death is mediated by a multitude of interrelated factors and signals, including caspases, oxidative stress and antioxidants, transcription factors, cytokines, chemokines, and kinases.[2]

After hepatocyte injury leads to ATP depletion, cellular swelling results in the development of membrane bleb formation in the necrotic pathway. This is followed by mitochondrial depolarization, lysosomal breakdown, and rapid ion changes inducing more extreme volume shifting, cell swelling, and further bleb formation, culminating in cell membrane rupture.[3] Membrane rupture leads to irreconcilable destabilization of the cell and ultimately cell death. Theoretically, hepatocytes can be resurrected up until fatal membrane rupture, and this is evidenced in certain injuries, such as ischemia/reperfusion injury.[4] Cellular rupture spills intracellular contents, instigating secondary inflammation.

Hepatocyte death via the apoptotic pathway in ALF follows a cascade of several steps reliant more on paired binding interactions. Apoptosis has both an extrinsic (type 1, external to the cell) and intrinsic (type 2, internal to the cell) pathway. The intrinsic pathway starts with oxidative stress, such as DNA damage or p53 activation.[4] The extrinsic pathway begins with binding of ligands (tumor necrosis factor [TNF]-α, FasL) to their transmembrane proteins (TNF-R1, Fas), which then cleave procaspase 8 to its active form. With adequate activation, caspase 8 activates caspase 3 leading to apoptosis, and can even affect mitochondrial expression of proapoptotic signals, thus influencing the intrinsic pathway as well. More recently, there are descriptions of overlap between the apoptotic and necrotic pathways, appropriately labeled necroapoptosis.

If the liver injury is severe enough, and the rate of cell death rapid enough to outpace the regenerative capabilities of the liver, a critical mass of hepatocyte loss will develop, leading to ALF. In this setting, hepatic insufficiency develops, leading to synthetic dysfunction and breakdown of intrahepatic metabolism, which tremendously impacts downstream organ systems and processes. The necrotic burden of hepatocyte death subsequently leads to a wave of systemic inflammation that is compounded by decreased hepatic ability to clear circulating cytokines. Taken together, these consequences of severe liver injury lead to the syndrome of ALF, which has multiorgan ramifications and carries a grave prognosis (**Fig. 1**).

IMMUNE SYSTEM

The immune system plays a large role in the syndrome of ALF, both in its propagation and its consequences. The similar phenotype of the systemic inflammatory response syndrome (SIRS) and ALF belies a similar underlying pathogenesis centered around inflammatory response and immune activation. Those patients with ALF who do develop SIRS, whether secondary to infection or not, more often progress to encephalopathy and have worse prognosis, highlighting the role of the immune system and its importance in ALF.[5]