Mechanisms of Acute Liver Failure

25

Christian Trautwein and Alexander Koch

Key Points

- Acute liver failure (ALF) is characterized by the sudden onset of liver failure in a patient without evidence of chronic liver disease.
- Mainly four different mechanisms are mainly responsible for ALF: (1) infectious (mostly viral), (2) drugs/toxins/chemicals, (3) cardiovascular, and (4) metabolic.
- Suicidal acetaminophen ingestion is the most frequent cause of drug-induced liver failure.
- Three factors determine the prognosis of liver failure: (1) the metabolic consequences resulting from liver failure, (2) the release of mediators and toxic metabolites, and (3) the capacity of the remaining hepatocytes to restore liver mass.
- Cerebral edema, infections, and renal failure are important clinical complications limiting the survival of the patients.
- Ammonia levels can be used for risk stratification in patients with ALF and subsequent hepatic encephalopathy.
- Intravenous administration of *N*-acetylcysteine improves transplant-free survival in patients with early stage non-acetaminophen-related ALF.
- Mild hypothermia might improve the outcome of patients with ALF by reduction of intracranial pressure and improvement of disturbed autoregulation in cerebral blood flow.
- Cytokines are involved in the pathogenesis of ALF as well as in controlling the balance between survival and proliferation of hepatocytes.
- The mode of liver cell death which is predominantly induced in ALF (apoptosis or necrosis) is determined by the underlying etiology, the duration of the disease, and the extent of liver injury.
- Future characterization of the molecular cell death mechanisms might establish potential diagnostic and therapeutic targets in ALF.
- Cytokeratin (CK)-18 and the CK-18 modified MELD appear to be novel promising tools for ALF patients to predict the prognosis in the clinical routine.

C. Trautwein, M.D. (✉) • A. Koch, M.D.
Department of Gastroenterology, Hepatology and Intensive Care Medicine, University Hospital Aachen,
Pauwelsstrasse 30, 52072 Aachen, Germany
e-mail: ctrautwein@ukaachen.de

Introduction

Acute liver failure (ALF) is characterized by the sudden onset of liver failure in a patient without evidence of chronic liver disease. This definition is important, as it differentiates patients with ALF from patients who suffer from liver failure owing to end-stage chronic liver disease [1].

Clinically, patients present with severe liver failure (icterus and coagulation failure, as reflected by an international normalized ration (INR) $\geq$1.5) and hepatic encephalopathy. The time between the first symptoms and the manifestation of hepatic encephalopathy has been shown to affect prognosis of these patients. Therefore several groups have included in their definition the time frame between the onset of symptoms and start of encephalopathy. The definition of the US ALF study group uses the term ALF as an umbrella and differentiates between three subgroups: hyperacute, acute, and subacute. The time between first symptoms and encephalopathy in hyperacute ALF is 7 days, in acute ALF it is 8–28 days, and in subacute ALF it is 5–26 weeks [2–4] (Fig. 25.1). More generally, ALF can be defined as a severe liver injury, clinically characterized by coagulopathy and hepatic encephalopathy within 26 weeks of symptom onset in previously healthy subjects [5]. Owing to loss of hepatic function, ALF results in hepatic encephalopathy, coagulopathy, and multiorgan failure within a short period of time.

However, the mortality rate is high and ALF accounts for 6–8 % of liver transplantations in the United States and in Europe [4]. Data of the US ALF study group are depicted in Fig. 25.2; spontaneous survival occurs in approximately

M.E. Gershwin et al. (eds.), *Liver Immunology: Principles and Practice*,
DOI 10.1007/978-3-319-02096-9_25, © Springer Science+Business Media New York 2014

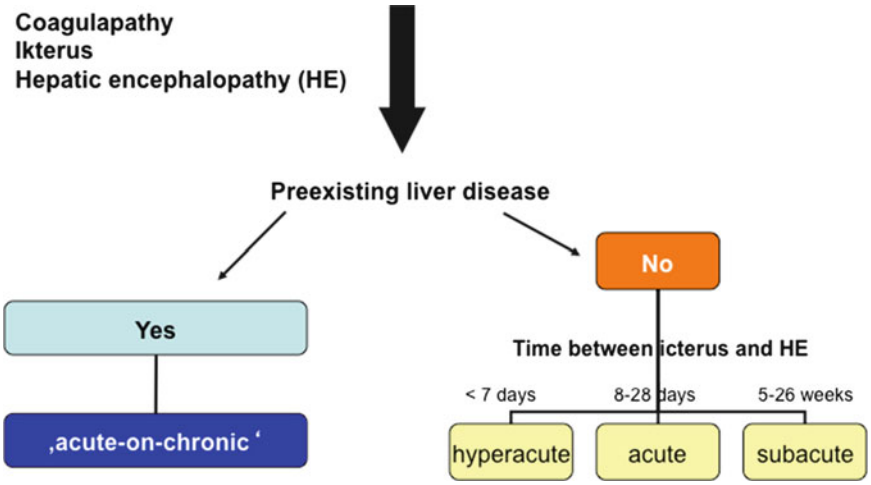

Fig. 25.1 Definition of ALF. ALF is defined as a severe liver injury, clinically characterized by coagulopathy and hepatic encephalopathy within 26 weeks of symptom onset in previously healthy subjects

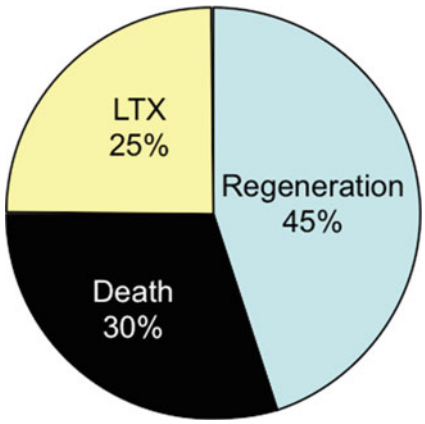

Fig. 25.2 Natural history of ALF. Liver regeneration with spontaneous survival occurs in approximately 45 %, liver transplantation in 25 %, and death without transplantation in 30 % of adults with ALF (Data from the United States); LTX, liver transplantation [4]

45 %, liver transplantation in 25 %, and death without transplantation in 30 % of adults with ALF [4].

Mechanisms of Disease

Different causes may result in ALF. In principal four different classes can be differentiated: (a) infectious (mostly viral), (b) drugs/toxins/chemicals, (c) cardiovascular, and (d) metabolic [6] (Table 25.1).

There are obvious differences in the mechanisms that initially trigger liver failure. However, at the time of clinical presentation, in most cases a common final stage has been reached in ALF patients. At this stage, three main factors seem important in determining prognosis: (1) the metabolic consequences resulting from the loss of liver cell mass, (2) the release of mediators and toxic metabolites from liver tissue,

Table 25.1 Causes of acute liver failure

Infectious (viral)
Hepatitis A
Hepatitis B
Hepatitis C
Hepatitis D
Hepatitis E
Hepatitis non-A/non-B
Rare causes of infectious etiology
Herpes simplex virus types 1 and 2
Human herpes virus type 6
Varicella virus
Cytomegalovirus
Epstein–Barr virus
Parvovirus B19
Togavirus
Paramyxovirus
Parainfluenza virus
Drugs/toxins/chemicals
Acetaminophen
Amanita phalloides
Halothane
Isoniazid
Sodium valproate
Tetracycline
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Pirprofen
Ketoconazole
Cardiovascular
Budd–Chiari syndrome
Hypotension (circulatory shock)
Heart failure (e.g., right ventricular)
Hyperthermia
Malignant tumors
Veno-occlusive disease
Portal vein thrombosis
Sepsis

(continued)

Table 25.1 (continued)

Metabolic
Wilson's disease
Reye's syndrome
Acute fatty liver of pregnancy (AFLP)
HELLP syndrome (hemolysis elevated liver enzymes, low platelet count)
Galactosemia
Hereditary fructose intolerance
Hereditary tyrosinemia

Table 25.2 Specific therapeutic options in ALF

Cause of ALF	Treatment	Dosage
Acetaminophen	*N*-acetylcysteine	600 mg/kg/day total dose
Amanita poisoning	Silibinin	20–50 mg/kg/day
Acute hepatitis B	Lamivudine	100–300 mg/day
	Entecavir	0.5–1 mg/day
	Tenofovir	245 mg/day
HELLP/AFLP	Termination of pregnancy	
Autoimmune hepatitis	Prednisolone	1–2 mg/kg/day
Budd–Chiari syndrome	TIPSS/surgical shunt	
Herpes simplex hepatitis	Aciclovir	3×10 mg/kg/day

Source: Modified from ref. [10]

and (3) the capacity of the remaining vital hepatocytes to restore liver mass [3, 7].

Therefore in terms of the mechanisms that are important during ALF, two different phases of ALF can be differentiated: the mechanisms that initially trigger liver failure and those that eventually determine outcome. Etiology of ALF and coma grade on admission are two prominent factors influencing prognosis. ALF due to acetaminophen toxicity, hepatitis A, ischemia, and pregnancy are associated with at least 60 % short-term transplant-free survival, whereas drug-induced liver injury, hepatitis B, autoimmune hepatitis, and indeterminate causes are associated with a spontaneous recovery rate of only 30 % [8]. Patients presenting with early grades of hepatic encephalopathy in ALF (independent of etiology) have usually a more favorable outcome than those with established stupor or coma [9]. Liver transplantation, intensive care medicine, and specific therapeutic options [10] (Table 25.2) can improve prognosis.

Etiology

Infectious Causes

Viruses in particular are an essential cause of ALF and, depending on the geographical region, can comprise between 30 and 70 % of all forms of ALF [3, 6, 7]. In the developing world, infections with hepatitis A, B, and E viruses are accounting for most cases of ALF. For Europe, most recent data from the ELTR database reveal that liver transplantation for ALF due to hepatitis A virus (HAV) and hepatitis B virus (HBV) decreased significantly in the last 5 years (from 1 % to 0.5 % and from 17.9 % to 13.2 %, respectively) [11].

Hepatitis A Virus

Due to effective use of vaccination, infections with the HAV have declined over the last decade and they accounted for 3 % of ALF cases in the United States [12]. The proportion of patients with ALF is higher in older than in younger patients. This is of relevance, as over the last decades in Western countries, HAV infection has occurred more frequently in older patients, and thus the risk of ALF increases in this population [13, 14]. Moreover, patients with underlying chronic liver disease, especially chronic hepatitis C, have an increased risk of ALF [15].

The pathogenesis of HAV-related ALF is not completely understood. Current studies indicate that a combination of a direct cytopathic effect of the virus and immune-mediated mechanisms results in liver destruction.

Hepatitis B Virus

The risk of ALF of all patients who are hospitalized because of an acute HBV infection is around 1 % [16]. Fulminant HBV is the most predominant viral cause of ALF in Western countries [8, 17] and accounts for 7–10 % of ALF in Europe and for 7 % in the United States [4, 11]. Due to the implementation of routine vaccination, the incidence of fulminant HBV has been decreased. In fulminant HBV infection, antiviral therapy with lamivudine, entecavir, or tenofovir has been proven efficient and safe, with significant reduction of HBsAg concentrations [18, 19] (Table 25.2). Reactivation of HBV or infection with highly replicative HBV harboring precore and core-promoter gene mutations become a more important cause of ALF [20, 21]. Virus reactivation is associated with a much higher risk of ALF than novel acute HBV infection, and antiviral prophylaxis should be administered to HBsAg-positive patients who are about to receive immunosuppressive therapy [22].

In general, the virus itself is not cytopathic, but the immune response directed against the virus is essential [23]. Frequently at the time of hospitalization, the viral load is already decreasing while transaminases are still rising. This may reflect the possibility that different factors contribute to the elimination of the virus. Data indicate that cytokines—namely interferon (IFN)—are operating through a noncytopathic mechanism to eliminate the HBV genome in hepatocytes, whereas at a later stage, T cells infiltrate the liver and destroy hepatocytes [24]. Therefore activation of HBV-specific T cells is essential to determine the degree of hepatic injury during ALF.

In the case of HBV/hepatitis D virus (HDV) coinfection, the risk of ALF is increased [25]. The exact mechanisms that lead to more pronounced liver failure are not defined.

Hepatitis C Virus

The risk of ALF through hepatitis C virus (HCV) is very low [3]. In Japan in particular cases of HCV-related ALF have been documented [26]. As there are only a few reports in the literature, the pathogenesis of HCV-related ALF is incompletely understood. However, there is evidence that elimination of HCV-specific T cells is associated with chronic HCV infection [27]. This indicates the HCV-specific immune response is involved during acute infection and thus is most likely also the determining factor during ALF.

Hepatitis E Virus

ALF owing to hepatitis E virus (HEV) infection is seldom seen in Western countries. However, hepatitis E has a predilection for older men in whom it causes substantial morbidity and mortality. Based on a poor prognosis in combination with preexisting liver disease, patients with unexplained hepatitis should be tested for HEV [1]. Epidemic outbreaks are known in developing countries including patients with ALF. In India and Pakistan, China, and southeast Asia, HEV infection is the most predominant cause of ALF [1]. Pregnant women, especially in the third trimester, have been regarded to be at high risk for ALF (up to 20 %) [28].

However, recent data indicate that pregnancy does not affect outcome of ALF resulting from HBE infection [29]. The mechanisms operating in patients with HBE infection-induced ALF have not yet been sufficiently studied. Therefore, there is no clear hypothesis in the literature, and it is only speculative to draw parallels with HAV.

Rare Cases of Viral Hepatitis

In rare cases, different systemic virus infections can present as ALF owing to a predominant manifestation in the liver. These are the herpes simplex virus types 1 and 2 (Table 25.2), human herpes virus type 6, cytomegalovirus, varicella virus, Epstein–Barr virus, and parvovirus B19. A few cases of ALF related to an infection with the toga-, paramyxo-, and parainfluenza virus have also been described.

Drugs/Toxins/Chemicals

Drug toxicity is the predominant cause of ALF in Western countries. Several drugs, chemicals, and toxins can lead to ALF (Table 25.1), by either direct toxicity or idiosyncratic drug reaction. The most frequent examples are discussed in this review.

Acetaminophen

Acetaminophen (paracetamol, Tylenol) is the most common cause of ALF. In adults, only higher doses (in general more than 10–12 g) are dangerous, and in most of the cases, acetaminophen was taken in a suicide attempt. Patients who consume alcohol chronically may be more susceptible for acetaminophen toxicity as cytochrome P450 has been induced in their liver [30]. Measurement of serum acetaminophen-protein adducts can reliably identify acetaminophen toxicity in cases of ALF in which no clinical or historic data are given that would reveal the cause [31]. At present, these analyses are only available in specialized laboratories.

The pathogenesis of acetaminophen injury is related to the formation of toxic metabolites through the cytochrome P450 enzymes, especially cytochrome P450 2E1 [32, 33]. These toxic metabolites are normally conjugated and inactivated through glutathione. However, when glutathione stores are depleted, these toxic metabolites accumulate and result in hepatocyte injury. Necrosis has been shown to be the more prominent form of cell death in acetaminophen toxicity [34]; however, in vitro data and animal data suggest that also apoptosis contributes to acetaminophen-induced ALF [35–37].

N-acetylcysteine (NAC), the standard antidote for acetaminophen overdose, exerts its therapeutic effects by restoration of depleted hepatic glutathione stores [38] (Table 25.2). Moreover, intravenous NAC improves transplant-free survival in patients with early stage non-acetaminophen-related ALF. However, patients with advanced coma grades do not benefit from NAC and typically require emergency liver transplantation [39].

Mushroom (*Amanita*) Poisoning

Mushroom poisoning, mainly through the species *Amanita phalloides*, frequently leads to ALF, especially in the fall. The clinical spectrum of *Amanita* poisoning varies from acute gastroenteritis to development of ALF. Amanatoxin and phalloidin are the two distinct toxins produced by mushrooms. Whereas phalloidin is not absorbed in the gastrointestinal tract, the dose-dependent systemic and hepatotoxic effect of amanatoxin is mediated through inhibition of mRNA synthesis [6, 40–42]. Although there a no controlled trials proving its efficiency, silibinin is used in Europe because of cytoprotective effects against amanatoxin and has been reported to be more effective than penicillin G in *Amanita* poisoning (silibinin is not available as a licensed drug in the United States) [43, 44] (Table 25.2). Despite advances in intensive care

therapy, the morality rate in patients who develop ALF after *Amanita* ingestion is high [43].

Halothane

Halothane is the prototype of an idiosyncratic drug reaction that (less frequently) can also be found after anesthesia with other members of the same family. In general, halothane-related ALF is only found after the second exposure to the drug. Halothane hepatitis is a paradigm for immune-mediated adverse drug reactions. The mechanism appears to be related to development of sensitization to both autoantigens (including CYP2D6) and halothane-altered liver cell determinants [45]. For the pathogenesis of the disease, specific antibodies are involved in hepatic injury. These antibodies can only be determined in specialized laboratories.

Cardiovascular Disorders

Cardiovascular diseases can lead to ALF either by ischemia or by impaired blood flow leaving the liver. Examples for ischemic events are severe hypotension or heart failure. Stasis of blood flow in the liver may occur owing to malignant tumors, veno-occlusive disease, or Budd–Chiari syndrome.

Budd–Chiari Syndrome

Classically, Budd–Chiari syndrome is characterized by a symptomatic occlusion of the hepatic veins and is more frequently found in females [46]. Depending on the progression of the disease, Budd–Chiari syndrome may result in ALF when sudden closening of at least two main liver veins occurs. Typically, acute Budd–Chiari syndrome presents with ascites, abdominal pain, jaundice, and hepatomegaly [47]. Budd–Chiari syndrome is frequently associated with primary myeloproliferative disorders, a factor V Leiden mutation, anticardiolipin antibodies, and protein C and S deficiencies that increase the risk of thrombotic complications [48]. In general, the course of disease in Budd–Chiari syndrome leads to liver transplantation. Transjugular portosystemic stent shunt (TIPSS) or percutaneous transjugular direct porto-caval shunt, in patients with inaccessible hepatic veins, seems to be a therapeutic option to decrease the portal pressure gradient, improve synthetic functions, reduce transaminase levels, and control ascites [49, 50] (Table 25.2).

Metabolic Disorders

Different metabolic disorders may present as ALF, for example, Reye's syndrome which is more common in children; its frequency has declined over the last decades. Also, during pregnancy acute fatty liver of pregnancy (AFLP) or the HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome may develop. Patients with HELLP syndrome typically presents with LDH, ALT, and bilirubin elevation. Immediate termination of pregnancy and delivery usually reverses hepatopathy, but patients are at increased risk for complications in future pregnancies [51] (Table 25.2).

Wilson's Disease

Wilson's disease is an autosomal recessive genetic disorder of copper metabolism and a rare cause of ALF. The Wilson gene is a copper-transporting P-type ATPase involved in copper transport across cell membranes, with over 200 known mutations, although its precise location and function is not known [52, 53]. In general, patients with ALF owing to Wilson's disease present with only moderately elevated aminotransferases, low alkaline, but very high bilirubin. Hemolytic anemia induced by copper ions leaking from necrotic hepatocytes into the circulation and causing lysis of erythrocytes is another typical clinical feature of Wilson's disease [54]. The patients frequently already have liver cirrhosis and are therefore not in accordance with the "real" definition of ALF. However, many of the patients were healthy before onset of the disease and therefore are treated like patients with ALF [55].

There is evidence that elevated copper levels are directly toxic for the cell and involve CD95-mediated apoptosis [56]. The current hypothesis postulates that excess copper generates free radicals that deplete cellular stores of glutathione and oxidize lipids, enzymes, and cytoskeletal proteins.

Mechanisms of Organ Failure

As a consequence of ALF, multiorgan failure (MOV) develops rapidly (Fig. 25.3). Different factors contribute to MOV. Frequent problems that occur during this process are cerebral edema and encephalopathy, an impairment of the immune response with an increased rate of infections, coagulation disorders, and cardio-vascular and kidney failure; pulmonary and metabolic complications also develop.

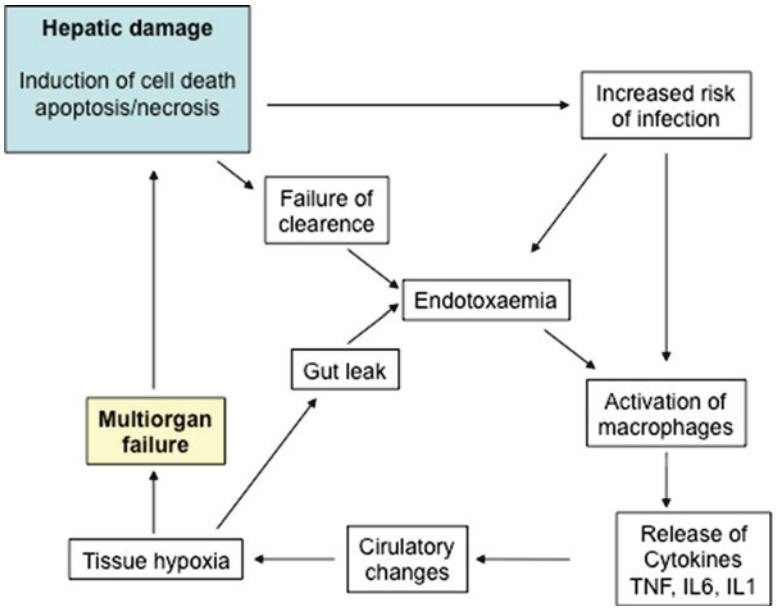

Fig. 25.3 Mechanisms that contribute to multiorgan failure during acute liver failure

Table 25.3 Stages of acute hepatic encephalopathy

Stage	Mental state
I, Prodrome	Mild confusion, slurred speech, slowness of mentation, disordered sleep rhythm, euphoria/depression
II, Impending coma	Accentuation of stage I, drowsy but speaking, inappropriate, behavior, incontinence
III, Stupor	Sleeps most of the time but rousable, incoherent or no speech, marked confusion
IV, Coma	Patient may (stage IVA) or may not (stage IVB) respond to painful stimuli

Source: Modified from ref. [74]

Encephalopathy and Cerebral Edema

Hepatic encephalopathy is essential for the diagnosis of ALF and is subdivided into four different grades, I–IV (Table 25.3). In 75–80 % of the patients in stage IV, cerebral edema develops independent of the cause of ALF.

The precise pathophysiological mechanisms that lead to hepatic encephalopathy are incompletely understood. However, laboratory studies indicate that the cause is an ammonia-induced deficit in neurotransmitter synthesis rather than a primary deficit in cerebral energy metabolism [57]. Most likely the astrocytes and the pre- and postsynaptic neurons contribute to the clinical picture of hepatic encephalopathy (Fig. 25.4). Astrocytic swelling during ALF determines the degree of cerebral edema and thus the degree of cerebral dysfunction [58].

In the literature, several factors are discussed that contribute to hepatic encephalopathy, but ammonia (with a consequent dysregulation of the glutamate neurotransmitter system) seems especially relevant for the development of hepatic encephalopathy and cerebral edema. Ammonia is primarily metabolized from glutamine in the small bowel and is converted to urea in healthy liver, but in ALF concentrations rise and ammonia is alternatively metabolized back to glutamine.

Arterial ammonia levels at presentation have been demonstrated to be predictive of outcome in patients with ALF. Patients with encephalopathy grade III and IV showed significantly higher serum ammonia levels than patients with lower grade encephalopathy. Possibly, patients with advanced cerebral dysfunction can be determined by a serum ammonia cutoff value of 124 µmol/L or more. Ammonia levels can be used for risk stratification [59].

Ammonia has direct effects on cerebral function by direct and indirect mechanisms (Table 25.4). There is clear evidence that arterial ammonia concentrations directly correlate with cerebral edema and thus herniation [60]. Experimental evidence also demonstrates that physiological ammonia concentrations alone result in astrocyte swelling. Additionally, higher glutamine concentrations are a consequence during this process, and they accelerate cerebral edema [61, 62].

Higher ammonia concentrations have a direct effect on the glutamate neurotransmitter system. Glutamate is the major excitatory neurotransmitter in the mammalian brain (Fig. 25.4). After release at the presynaptic neuron, glutamate binds to glutamate receptors on the postsynaptic neuron (NMDA) or on both the postsynaptic neuron and astrocytes (AMPA/KA). Additionally, glutamate transporter on astrocytes (GLT-1 and GLAST) and neurons (EAAC1) limit the expression of glutamate in the neuronal cleft. After uptake of glutamate in astrocytes via GLT-1, it is transformed into glutamine. Ammonia downregulates GLT-1

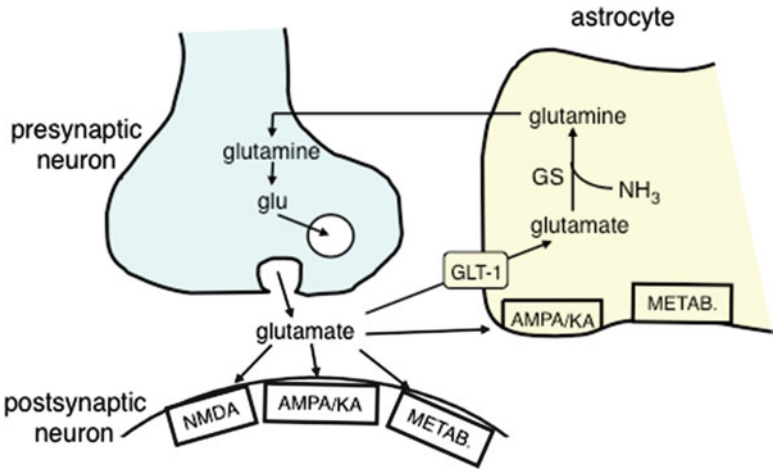

Fig. 25.4 The role of glutamate/glutamine in the brain. Shown are the localizations of the glutamate transporter (GLT-1) and glutamate receptor subtypes (NMDA, AMPA/KA, METAB) on astrocytes and neurons involved in glutamatergic neurotransmission are shown. *Glu* glutamate (Modified from ref. [62])

Table 25.4 Effects of ammonia on brain function

Electrophysiological effects of the ammonium ion
Effects on the inhibitory postsynaptic potential
Effects on glutamatergic neurotransmission
Effects on brain energy metabolism
Inhibition of α-ketoglutarate dehydrogenase
Effects on astrocyte function
Decreased expression of the glutamate transporter GLT-1
Increased expression of "peripheral-type" benzodiazepine receptors
Alzheimer type II astrocytosis
Effects on the glutamate neurotransmitter system
Direct postsynaptic effects
Impaired neuron-astrocytic trafficking of glutamate
Inhibition of glutamate uptake
Altered glutamate receptors
Effects mediated by formation of glutamine in brain
Cytotoxic brain edema
Increased uptake of aromatic amino acids
Other effects
Stimulation of L-arginine uptake and neuronal nitric oxide synthase (nNOS) expression

Source: Data from ref. [62]

expression on astrocytes, and this results in higher and prolonged extracellular glutamate concentrations in patients with ALF. Additionally, there is evidence that the glutamate receptors are differentially expressed during ALF and thus dysregulation of the glutamate system is one of the important determinants for hepatic encephalopathy during ALF [61, 62].

Other neurotransmitters that participate in hepatic encephalopathy are GABA, serotonin, and the opioid system. Systemic circulation of proinflammatory mediators during ALF might also contribute to hepatic encephalopathy, as they might modulate cerebral permeability to neurotoxins, initiate inflammatory responses, and impair cerebral blood flow [63].

A few uncontrolled studies [64–66] show a protective effect of mild hypothermia in ALF and cerebral edema. Hypothermia (32–35 °C) can be safely and easily applied. The risk of complications (arrhythmias, myocardial ischemia, infections, coagulopathy) increases with the degree and duration of hypothermia, mainly with body temperatures below 32 °C. Hypothermia reduces intracranial pressure and reestablishes disturbed autoregulation of cerebral blood flow. Some studies suggest that hypothermia can reduce the extent of liver injury in ALF [67]; in contrast, hypothermia might also lead to impaired liver regeneration. Further research and controlled clinical studies are required to clarify the significance of hypothermia in ALF.

Cardiovascular Dysfunction

Patients with ALF are characterized by hypotension and tachycardia. The basis for this observation is vasodilatation in the periphery that results in relative hypovolemia, hypotension, and high output failure. Factors that contribute to this dysregulation are capillary leakage, low osmotic pressure, and systemic inflammatory response syndrome (SIRS).

Some patients with ALF may suffer from hypertension. This problem may arise especially in patients with hepatic encephalopathy grade IV and typically occurs when cerebral edema is evolving.

Infection

Infection and thus sepsis is a major problem in patients with ALF. Patients with a long stay in the ICU have a very high risk in particular and this may actually be the ultimate reason for death [68]. Studies from the King's Collage Hospital group clearly indicated that monitoring by daily cultures (sputum, urine, blood) identifies bacteria in up to 90 % and fungal infections in around 30 % of the patients [69, 70]. Frequently the classical signs (fever, leukocytosis, biochemical

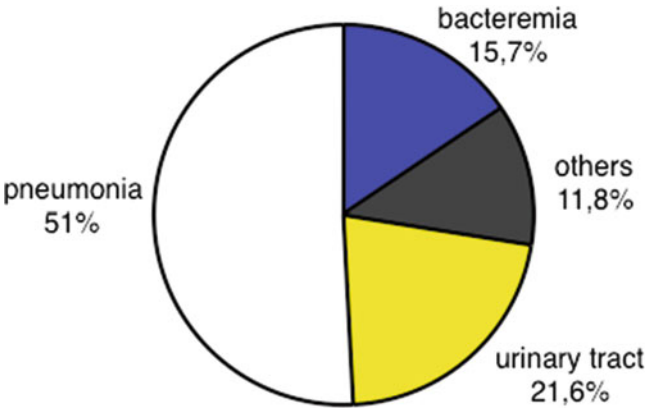

Fig. 25.5 Sites of infections during acute liver failure (From ref. [69])

parameters like c-reactive protein and procalcitonin) in patients with ALF are not directly correlated with infection or are absent. The sites of the body with the most common infections are the lung, the urinary tract, and the blood (Fig. 25.5). If antibiotic or antifungal treatment is necessary in these patients, the potential of further liver injury caused by antibiotic drugs should be considered.

Besides the increased risk of patients being managed in ICU, additional factors contribute to the higher risk of infections in patients with ALF, namely, defects in the immunological defense mechanisms (complement, Kupffer cell function, polymorphonuclear cell function, cell-mediated immune response). The liver is the main source of complement (e.g., C3 and C5) production. As a consequence of lower complement levels, activity of polymorphonuclear leukocytes and complement-mediated opsonization is reduced. Therefore phagocytosis and killing of polymorphonuclear cells is inhibited in patients with ALF. Through the portal circulation, bacterial toxins are regularly brought to the liver tissue that is cleared by the resident Kupffer cells of the liver. In ALF there is a correlation between hepatic damage and Kupffer cell dysfunction. Additionally, Kupffer cells are a major source of cytokines, and their dysregulation also contributes to the impaired immune response. Defective lymphocyte function has been attributed to impaired interleukin-2 (IL-2) production in these patients. Thus the defect in immune response can be explained on different levels of the immune system [6, 69].

Pulmonary Complications

Pulmonary complications are frequent [71]. Different mechanisms contribute to this observation. Up to 50 % of the patients have infections, especially after intubation and subsequent mechanical ventilation (Fig. 25.3) [72]. The possible consequent capillary leakage can result in an ARDS-like syndrome that is further augmented by the often required infusion of albumin, fresh frozen plasma (FFP), and coagulation factors.

Besides these local mechanisms, systemic causes, as a result of liver failure, also lead to intrapulmonary vasodilatation and pulmonary, which further increase the risk of hypoxic complications [73].

Renal Failure

Renal failure with oliguria and anuria is found in 40–50 % of patients with ALF [44, 45]. In acetaminophen and *Amanita* poisoning, a direct toxic effect additionally contributes to kidney failure. Therefore, in these patients the rate of kidney failure is increased up to 70 %.

The association of liver failure and kidney failure is functional and known as hepatorenal syndrome. The syndrome is characterized by a contraction of the vessels with a distinctively reduced renal perfusion. At this stage the kidney impairment is completely reversible. In the further course of the disease, at a more advanced stage, hepatorenal syndrome may progress to tubulus necrosis, which is not reversible [74].

Additional severe complications in patients with hepatorenal syndrome such as long periods of hypotension or sepsis have a fatal effect on kidney function and significantly reduce the prognosis of patients with fulminant hepatic failure [75].

As SIRS has been recently identified as an independent predictor of renal dysfunction in patients with non-acetaminophen-induced ALF, SIRS has been suggested to be functionally linked to the development of renal dysfunction in patients with non-acetaminophen-induced ALF, but not in patients with acetaminophen-induced ALF [76].

Metabolic Complications

The liver is essential for several metabolic functions. Two particular problems are frequent in patients with ALF: hypoglycemia and acid–base disturbances.

Different mechanisms lead to hypoglycemia during ALF. The damaged liver loses its capacity to mobilize glycogen stores and to perform gluconeogenesis. Additionally, the liver is the major site of insulin metabolism, and the consequently reduced disintegration of insulin results in elevated insulin serum levels. All three mechanisms contribute to hypoglycemia, and this may also aggravate mental status. In terms of treatment, it might be important to differentiate between hypoglycemia and hepatic encephalopathy as possible causes for disturbed mental status at certain stages.

Both acidosis and alkalosis might be present. Metabolic alkalosis is most frequent, as urea synthesis in the liver is impaired, which results in the accumulation of the two precursor substrates bicarbonate and ammonium. Alkalosis is associated with hypokalemia, which is further aggravated by high sodium reabsorption in patients with ALF.

Acidosis is found in up to 30 % of patients with acetaminophen-dependent ALF. In patients with a different etiology, acidosis is evident in only 5 %, in which lactate acidosis is present because of tissue hypoxia owing to a disturbed microcirculation and the inability of the injured liver tissue to metabolize lactate.

Coagulation Disorders

Because of the central role of the liver in coagulation and thrombolysis, severe coagulation disorders are a major problem in ALF. As a result of reduced coagulation factors and a deficit of inhibitors of fibrinolysis, the hemostasis situation in ALF is complex [77, 78].

Factors I, II, V, VII, IX, and X are synthesized in the liver. Therefore prothrombin time is a useful parameter—besides the measurement of single factors—to assess the lack of production of coagulation factors. An additional factor that may contribute to the decrease in blood coagulation factors is disseminated intravasal coagulation (DIC), which may be associated with sepsis during ALF.

Antithrombin-III (AT-III) is also synthesized in the liver and is thus reduced. The decrease in AT-III concentration further contributes to coagulation problems.

The number of blood platelets is frequently decreased, and additionally the function and morphology of blood platelets are impaired. Together, these changes result in adhesion abnormalities, leading to decreased aggregation and increased adhesion. Without clinical signs of bleeding, the application of FFP, single coagulation factors, or platelets is not indicated.

Pathophysiological Aspects of Acute Liver Failure

ALF occurs when the extent of hepatocyte death exceeds the regenerative capacity of the liver. Mainly two different mechanisms of liver cell death can be differentiated: (a) direct cellular damage and activation of cell signalling cascade pathways, resulting in disturbance of intracellular homeostasis, and (b) innate and adaptive immune responses leading to immune-mediated liver injury.

Similar to sepsis, patients with ALF commonly display immune paralysis with characteristic features of systemic inflammation and cellular immune depression contributing to severe extrahepatic complications, such as multiple organ failure [68, 79]. In this context cytokines exert crucial pathophysiological functions in ALF, comprising hepatocellular death, extrahepatic complications, and hepatocellular regeneration.

Dysregulation of the Cytokine Network in Acute Liver Failure

In the last years it has become obvious that there is a dysregulation of cytokine expression during ALF in humans. For example, it has been shown that mediators of the acute-phase response—IL-6 and tumor necrosis factor (TNF)—are strongly elevated in the liver and serum of ALF patients. The meaning of this observation becomes more evident through the development of animal models whereby the role of each of the molecules can be more clearly defined. As there is evidence that several cytokines might be involved in the pathogenesis of ALF, all the different aspects cannot be covered in this review. We focus here on two cytokines, TNF and IL-6.

IL-6/gp130-Dependent Signals

IL-6 interacts on the cell surface with the IL-6 receptor (gp80). This complex associates with two gp130 molecules, which results in the activation of Janus kinases and in turn in phosphorylation of tyrosines at the intracellular part of gp130. After phosphorylation of tyrosines, the RAS/MAP kinase pathways and transcription factors Stat1 and Stat3 become activated (Fig. 25.4) [80]. In hepatocytes, IL-6 is one of the main inducers of the acute-phase response, and in recent years it has become evident that IL-6 also contributes to the regulation of additional pathophysiological conditions in the liver [81, 82].

One of the simplest models to study the loss of liver tissue is removal of two-thirds of the liver by surgical resection. This model has been applied mainly in rodents (e.g., rat and mouse), and after 1–2 weeks, liver tissue has been restored by hepatocyte proliferation. In recent years it has become obvious that IL-6 and TNF are involved in the restoration of liver mass [83], as it has been observed that liver regeneration was impaired in IL-6 and TNF receptor 1 (TNF-R1) knockout mice after two-thirds hepatectomy. The defect in regeneration in both knockout strains could be restored through IL-6 stimulation [84, 85]. The model of how IL-6 and TNF may work in concert during liver regeneration after partial hepatectomy is shown in Fig. 25.5.

In humans suffering from ALF, IL-6 serum levels are highly elevated, and in the liver infiltrating cells express tremendous (tenfold higher compared with controls) amounts

of IL-6 [81, 82, 86]. In animal models of ALF, IL-6 serum levels are also greatly increased [87], and treatment with a hyper-IL-6 designer molecule reduces liver cell damage in several animal models [88, 89]. Therefore, not only during liver regeneration after partial hepatectomy, but also during ALF it is obvious that IL-6 plays a protective role for hepatocytes; cDNA arrays further demonstrate that IL-6 activates antiapoptotic pathways, e.g., Bcl-xl in hepatocytes [90, 91]. Our group generated a hepatocyte-specific knockout mouse for gp130.

Most IL-6 data in animal models show that gp130-dependent pathways in hepatocytes activate protective mechanisms [81, 82], and in humans it is also likely that IL-6 renders hepatocytes more resistant. Therefore, it might be promising to modulate IL-6/gp130-dependent pathways in humans during ALF as a potential therapeutic approach.

TNF-Dependent Pathways

TNF belongs to a family of several known Fas (CD95) and TNF receptor apoptosis-inducing ligands (TRAIL). There is also evidence for an involvement in the pathogenesis of fulminant hepatic failure. At present the role of TNF has been studied in more detail in both human and animal models.

TNF binds to two receptors, TNF-R1 and TNF-R2, on the cell surface. After ligand binding, the intracellular domains of the receptors interact with adapter molecules that activate different pathways (Fig. 25.6). In case of TNF-R1, first the molecule TNF-R-associated death domain (TRADD) and then additional molecules bind that activate the caspase cascade either via Fas-associated death domain (FADD) or via TNF-associated factor-/receptor-interacting protein (TRAF/RIP) jun kinase (JNK) and nuclear factor-kB (NF-kB) [92].

Recently, it has become evident that TNF—besides inducing apoptosis—can also trigger necrosis. Therefore, TNF and its family members seem to be essential mediators of cell death during ALF. In humans it has been shown that TNF serum levels correlate with prognosis in ALF patients [86]. In animal models, blocking experiments using anti-TNF attenuates liver failure, and therefore it is obvious that TNF plays a central role in the pathogenesis of ALF. However, further studies indicated that TNF has no uniform role in the different models. Depending on the model, the TNF-dependent effect might be related to a different cell in the liver or another intracellular pathway. Three models of ALF and the role of TNF will be discussed.

Endotoxin/Galactosamine Model

During LPS/galactosamine (GaIN)-induced liver injury, TNF induces the transcription of several proinflammatory genes, e.g., chemokines, nitric oxide, and adhesion molecules like intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and P-selectin [93–95]. These changes in the liver are essential to trigger the extravasation of neutrophils into the liver parenchyma, which results in cytotoxic liver cell damage. During this scenario a stepwise cascade has been described consisting of three events: (1) sequestration of neutrophils in the liver vasculature, (2) transendothelial migration, and (3) adherence-dependent cytotoxicity against hepatocytes [96].

Therefore, in the LPS/GalN model, TNF obviously triggers an inflammatory mechanism mediated via NF-kB that results in liver cell damage. In this model, not only parenchymal, but also non-parenchymal cells are involved in this process.

Galactosamine/TNF Model

Administration of GaIN and TNF triggers apoptosis of hepatocytes in vivo and in vitro. The essential role of TNF-R1 in this model has been demonstrated by TNF-R1 knockout mice that are resistant against GalN/TNF treatment [97]. GaIN will directly inhibit transcription and thus synthesis of antiapoptotic signals. Therefore, in this model the FADD-dependent pathway leading to apoptosis is the essential step in ultimately inducing liver cell damage. In contrast, the NF-kB and JNK pathway does not seem to be involved in the pathogenesis of liver damage, and also non-parenchymal cells play no role. In this model, simple administration of an adenoviral construct expressing a dominant molecule blocking the FADD pathway is protective [86]. These data indicate that the caspase cascade activated by TNF might be a relevant target during ALF.

Concanavalin A Model

Concanavalin A (ConA) is a leptin with high affinity towards the hepatic sinus [98]. Accumulation of ConA in the hepatic sinus results in the activation of liver natural killer T (NKT) cells, i.e., NK 1.1 $CD4^+$ $CD8^-$ T-cell receptor (TCR)$\alpha\beta^+$ and NK1.1. $CD4^-$ $CD8^-$ TCR $\alpha\beta^+$, which are essential to trigger the early phase of ConA-induced liver injury [99, 100]. Consecutively, CD4-positive and polymorphonuclear cells are attracted to the hepatic sinus and trigger an increase of cytokines like TNF, IL-2, IFN-γ, IL-6, granulocyte macrophage-colony stimulation factor (GM-CSF), and IL-1 [58]. TNF-α and IFN-γ have direct implications for the induction of liver cell injury, as anti-TNF-α and anti-IFN-γ antibodies protect from ConA-induced liver injury [101, 102] and IFN–/– and TNF–/– mice are resistant to ConA-induced liver cell damage.

Until now a stepwise process of liver damage, as shown for the endotoxin/LPS model, could not be defined for the ConA model. Adhesion molecules like ICAM-1 or VCAM-1 seem to play a minor role. Mice pretreated with antibodies against both adhesion molecules or ICAM-1 knockout mice still undergo liver cell injury [103].

Recently, it has been shown that hepatocyte-specific caspase-8 knockout mice are more susceptible to ConA-induced liver injury [104]. These results show that during ConA-induced liver injury, necrosis is the more prevalent form of cell death. Therefore the ConA model is especially helpful to better define this form of hepatocyte injury in vivo.

Apoptosis and Necrosis in Acute Liver Failure

Apoptosis—the programmed form of cell death—is inevitable to maintain the balance of cell proliferation and elimination of injured cells. Caspase proteases are involved in initiation, execution, and regulation of apoptotic pathways. Effector caspases (e.g., caspase-2, caspase-6, caspase-7) cleave various cellular proteins (e.g., cytokeratin-18) [105] and initiator caspases (e.g., caspase-8, caspase-9, caspase-10) exhibit regulatory functions by activation of downstream effector caspases [106]. The major signalling routes for caspase activation are the extrinsic death receptor and the intrinsic mitochondrial pathway [107] (Fig. 25.6).

Death receptors are transmembrane proteins that consist of the following domains: (a) extracellular ligand-interacting domain, (b) transmembrane domain, and (c) intracellular death domain. Typically involved in ALF are death receptors CD95 (Fas), tumor necrosis factor-receptor 1 (TNF-R1), TNF-related apoptosis-inducing ligand receptors 1 and 2 (TRAIL-R), and death receptors 3 and 6. Binding of death ligands such as TRAIL, CD95L, or TNF to their specific receptors leads to the recruitment of the adapter protein FADD and caspase-8 into death-inducing signalling complex (DISC), wherein caspase-8 is activated [108]. In most cells and hepatocytes, respectively, only low amounts of caspase-8 are activated in the DISC, which is not effectual for cell death. In order to exert cell death, the extrinsic receptor pathway has to be amplified by the intrinsic mitochondrial apoptotic pathway through the caspase-8-effected cleavage of Bid (a proapoptotic Bcl-2 family protein). Subsequently, together with the Bcl-2 family members Bak and Bax, the release of proapoptotic mediators from the mitochondria is initiated [109].

ALF, induced by agonistic CD95 antibody, could be abolished by silencing of CD95 or caspase-8 protected mice [110, 111]. On the other side, CD95 and caspase-8 are involved in liver regeneration by inducing differentiation of stellate cells and other non-parenchymal liver cells [112, 113]. TNF-α plays a key role in liver regeneration by activation of NF-kB, which exerts antiapoptotic functions in the liver [114].

Necrosis is mediated by opening of the mitochondrial membrane permeability transition (MPT) pore, leading to disruption of ATP formation and finally resulting in mitochondrial swelling and rupture of the outer mitochondrial membrane. Interestingly, recently it has been shown that TNF

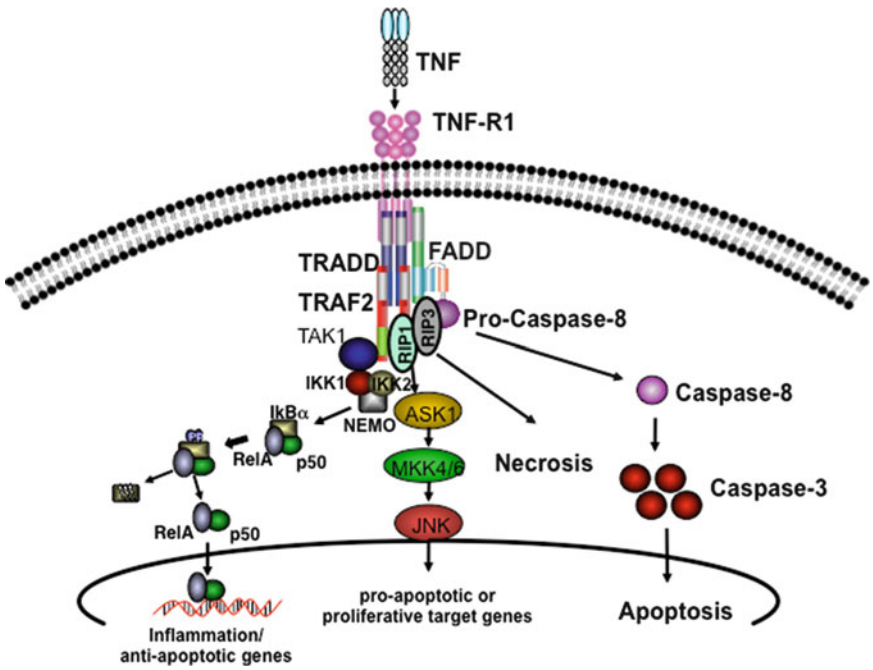

Fig. 25.6 TNF-dependent signalling pathways. The molecules and pathways that are involved in TNF/TNF-R1-dependent signalling are depicted. After TNF/TNF-R1 interaction different adaptor proteins bind to the intracellular part of TNF-R1. As a consequence at least four pathways (NF-kB, jun kinase (JNK), apoptosis and necrosis) can be activated. Recently, it has been demonstrated that downstream from FADD—dependent on the cellular context—programmed apoptosis or necrosis can be initiated

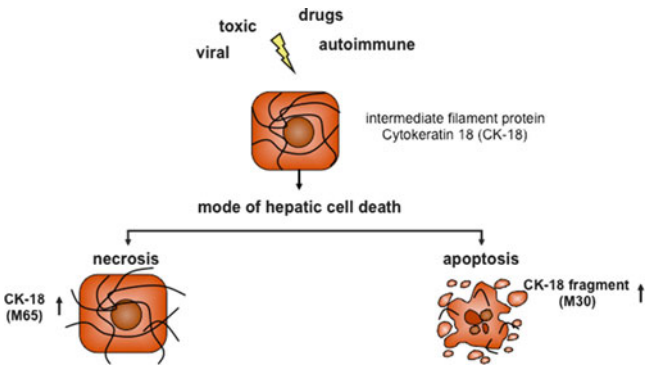

Fig. 25.7 Cytokeratin-18 is associated with the mode of hepatic cell death. In apoptotic cell death (induced by toxin, drugs, viruses, or autoimmune etiology), cytokeratin (CK)-18 is cleaved by caspases into specific fragments, which can be measured in serum by the M30 ELISA. Whereas cleaved CK-18 levels represent apoptosis, uncleaved CK-18 (M65 ELISA) reflects necrosis

can also induce controlled necrosis. Therefore now necrosis is also considered a programmed form of cell death which is initiated by RIP1/RIP3 activation. Additionally, massive ATP depletion, formation of reactive oxygen species (ROS), activation of non-apoptotic proteases, and strongly increased intracellular calcium concentrations—aggravating ATP deficiency by loss of mitochondrial membrane potential— contribute to necrosis. As loss of ATP leads to necrosis and apoptosis is ATP-dependent, the intracellular amount of ATP itself might determine the way of cell death, either by apoptosis or by necrosis [115, 116]. Necrosis is associated with inflammation, as rupture of necrotic cells induces an inflammatory response owing to the release of intracellular components including the M65 form of cytokeratin-18 (CK-18). Whereas apoptotic cells are rapidly cleared by phagocytic cells, thereby preventing release of intracellular contents.

Cytokeratin-18 as a Novel Prognostic Biomarker in ALF

CK-18 is a filament protein, which is cleaved by caspases into specific fragments, which can be measured in serum by the M30 ELISA (Fig. 25.7). CK-18 levels at the time of admission have been demonstrated to be a predictor of mortality in patients with ALF with a prognostic impact that is comparable to the model for end-stage liver disease (MELD). Additionally, a modified MELD score where uncleaved necrotic CK-18 (M65 ELISA) substituted bilirubin predicted significantly better the prognosis of ALF patients compared with the current MELD score [117].

The observation that ALF patients who died or required transplantation displayed increased serum levels of total CK-18, but reduced levels of caspase-cleaved fragments indicate that necrosis and not apoptosis is the more prominent cell death mode in these most critically ill ALF patients [118]. In line with this, patients with acetaminophen-induced liver injury, where necrosis is the predominant cell death mode, showed higher levels of total CK-18 than caspase-cleaved CK-18.

Translation of Experimental Data into Therapeutic Approaches in Humans

The current data in animal models and humans indicate that TNF plays an essential role in the pathogenesis of ALF. However, as demonstrated for the three animal models discussed—depending on the pathogenesis—the intracellular pathways that are activated by TNF could have opposing effects.

The mode of liver cell death in ALF is still controversial. Induction of apoptosis or necrosis of hepatic cells is potentially depending on the etiology and the duration and extent of liver injury. Severe liver damage causes oxidative stress and concomitant depletion of ATP resulting in necrosis. On the other hand, sufficient cellular ATP stores are essential for the execution of apoptosis. Necrosis as a consequence of severe hepatic injury is associated with an unfavorable prognosis.

Potentially, differentiation of necrosis and apoptosis might be novel tools to early identify patients requiring transplantation. The identification of the molecular cell death mechanisms might offer new therapeutic perspectives for ALF. Reduction of cellular death without inhibition of the hepatic regenerative capacity seems to be the main goal for new therapeutic interventions. Whereas extreme liver injury results in necrosis, milder injury leads to apoptosis. Potentially, inhibition of apoptosis by caspase inhibitors can prevent liver cell death but can also possibly change only the cell death mode from apoptosis to necrosis. Considering the therapeutic use of caspase inhibitors to prevent apoptosis, the involvement of caspases in liver regeneration must not be ignored, as this might lead to potential severe adverse effects. Therefore further studies are needed to better understand the molecular mechanisms determining the mode of cell death during ALF.

In mouse models the administration of cyclooxygenase (COX) inhibitors resulted in decreased oxidative stress and a reduction of hepatic necrosis [119]. Therefore, COX inhibitors could be further investigated as potential agents in the prevention of ALF.

Another promising novel target in acetaminophen-induced ALF is cyclophilin A. Cyclophilin A is an intracellular protein that is proinflammatory when released by cells. In an animal model of acetaminophen-induced liver injury, it has been demonstrated that cyclophilin A acts as a damage-associated molecular pattern (DAMP) to mediate acetaminophen toxicity and that experimental inhibition of cyclophilin A ameliorates acetaminophen-induced liver injury [120].

Concluding Remarks and Open Questions

ALF is characterized by sudden onset in patients without evidence of chronic liver disease, by which ALF is differentiated from end-stage chronic liver disease. According to the time between first symptoms and encephalopathy, ALF is divided into three subgroups: hyperacute, acute, and subacute. The prognosis of ALF patients is determined by the metabolic situation resulting from the loss of liver cell mass, the release of mediators and toxic metabolites from injured liver tissue, and the capacity of remaining vital hepatocytes to restore functional liver mass.

Suicidal acetaminophen ingestion is the most frequent cause of drug-induced liver failure worldwide, with approximately 500 deaths a year in the United States. Other important mechanisms are viral hepatitis, cardiovascular, and metabolic disorders.

ALF leads to multiorgan failure, especially to cerebral edema and encephalopathy. Owing to the diminished liver function, higher rates of infections and coagulation disorders are observed. Cerebral edema, infections, and renal failure are important clinical complications limiting survival. For risk stratification in patients with ALF and subsequent hepatic encephalopathy, serum ammonia levels can be used. Advanced cerebral dysfunction is expected at serum ammonia levels of 124 μmol/L or higher.

Cardiovascular dysfunction is characterized by peripheral vasodilatation that results in relative hypovolemia, hypotension, and high output failure. Capillary leakage and high-volume therapy can lead to an ARDS-like syndrome and cause hypoxic complications. Prothrombin time is a useful parameter to assess the extent of remaining liver function.

Intensive care therapy is crucial for patients with ALF to manage multiorgan failure, and mild hypothermia to reduce cerebral edema should be considered. Further research and controlled clinical studies are needed to evaluate the importance of hypothermia.

The mode of liver cell death which is predominantly induced in ALF (apoptosis or necrosis) is potentially determined by the underlying etiology, the duration of the disease, and the extent of liver injury. Severe liver injury leads to oxidative stress and depletion of ATP stores favoring necrosis, whereas sufficient cellular ATP resources are required for the execution of apoptosis. As necrosis is associated with an inferior outcome as compared with apoptotic cell death, the discrimination of the cell death mode in ALF might be a novel prognostic tool for instant identification of patients requiring transplantation. Moreover, the molecular cell death mechanisms in ALF are promising targets for future research aiming at reducing hepatocellular death without inhibiting liver regeneration.

References

1. O'Grady JG. Acute liver failure. Postgrad Med J. 2005;81(953):148–54.
2. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. Lancet. 1993;342(8866):273–5.
3. Williams R. Classification, etiology, and considerations of outcome in acute liver failure. Semin Liver Dis. 1996;16(4):343–8.
4. Lee WM, Squires Jr RH, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: Summary of a workshop. Hepatology. 2008;47(4):1401–15.
5. Larson AM. Diagnosis and management of acute liver failure. Curr Opin Gastroenterol. 2010;26(3):214–21.
6. Sussman NL. Fulminant hepatic failure. In: Zakim D, Boyer TD, editors. A textbook of liver disease. New York: Mc Graw-Hill; 1996. p. 618–50.
7. Losser MR, Payen D. Mechanisms of liver damage. Semin Liver Dis. 1996;16(4):357–67.
8. Lee WM. Acute liver failure. Semin Respir Crit Care Med. 2012;33(1):36–45.
9. Lee WM. Liver: determining prognosis in acute liver failure. Nat Rev Gastroenterol Hepatol. 2012;9(4):192–4.
10. Canbay A, Tacke F, Hadem J, Trautwein C, Gerken G, Manns MP. Acute liver failure: a life-threatening disease. Deutsch Arztebl Int. 2011;108(42):714–20.
11. Germani G, Theocharidou E, Adam R, Karam V, Wendon J, O'Grady J, Burra P, Senzolo M, Mirza D, Castaing D, et al. Liver transplantation for acute liver failure in Europe: outcomes over 20 years from the ELTR database. J Hepatol. 2012;57(2):288–96.
12. Taylor RM, Davern T, Munoz S, Han SH, McGuire B, Larson AM, Hynan L, Lee WM, Fontana RJ. Fulminant hepatitis A virus infection in the United States: Incidence, prognosis, and outcomes. Hepatology. 2006;44(6):1589–97.
13. Fagan EA, Williams R. Fulminant viral hepatitis. Br Med Bull. 1990;46(2):462–80.
14. Masada CT, Shaw Jr BW, Zetterman RK, Kaufman SS, Markin RS. Fulminant hepatic failure with massive necrosis as a result of hepatitis A infection. J Clin Gastroenterol. 1993;17(2):158–62.
15. Vento S, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, Ferraro T, Concia E. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. N Engl J Med. 1998;338(5):286–90.
16. Hoofnagle JH, Carithers Jr RL, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatology. 1995;21(1):240–52.
17. Canbay A, Jochum C, Bechmann LP, Festag S, Gieseler RK, Yuksel Z, Lutkes P, Saner FH, Paul A, Gerken G. Acute liver failure in a metropolitan area in Germany: a retrospective study (2002–2008). Z Gastroenterol. 2009;47(9):807–13.
18. Jochum C, Gieseler RK, Gawlista I, Fiedler A, Manka P, Saner FH, Roggendorf M, Gerken G, Canbay A. Hepatitis B-associated acute liver failure: immediate treatment with entecavir inhibits hepatitis B virus replication and potentially its sequelae. Digestion. 2009;80(4):235–40.
19. Tillmann HL, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, Graziadei I, Encke J, Schmidt H, Vogel W, et al. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. J Viral Hepat. 2006;13(4):256–63.
20. Ozasa A, Tanaka Y, Orito E, Sugiyama M, Kang JH, Hige S, Kuramitsu T, Suzuki K, Tanaka E, Okada S, et al. Influence of genotypes and precore mutations on fulminant or chronic outcome of acute hepatitis B virus infection. Hepatology. 2006;44(2):326–34.

21. Wai CT, Fontana RJ, Polson J, Hussain M, Shakil AO, Han SH, Davern TJ, Lee WM, Lok AS. Clinical outcome and virological characteristics of hepatitis B-related acute liver failure in the United States. J Viral Hepat. 2005;12(2):192–8.
22. Katz LH, Fraser A, Gafter-Gvili A, Leibovici L, Tur-Kaspa R. Lamivudine prevents reactivation of hepatitis B and reduces mortality in immunosuppressed patients: systematic review and meta-analysis. J Viral Hepat. 2008;15(2):89–102.
23. Chisari FV. Rous-Whipple Award Lecture. Viruses, immunity, and cancer: lessons from hepatitis B. Am J Pathol. 2000;156(4): 1117–32.
24. Guidotti LG, Rochford R, Chung J, Shapiro M, Purcell R, Chisari FV. Viral clearance without destruction of infected cells during acute HBV infection. Science. 1999;284(5415):825–9.
25. Mendez L, Reddy KR, Di Prima RA, Jeffers LJ, Schiff ER. Fulminant hepatic failure due to acute hepatitis B and delta co-infection: probable bloodborne transmission associated with a spring-loaded fingerstick device. Am J Gastroenterol. 1991;86(7): 895–7.
26. Yoshiba M, Dehara K, Inoue K, Okamoto H, Mayumi M. Contribution of hepatitis C virus to non-A, non-B fulminant hepatitis in Japan. Hepatology. 1994;19(4):829–35.
27. Gruener NH, Lechner F, Jung MC, Diepolder H, Gerlach T, Lauer G, Walker B, Sullivan J, Phillips R, Pape GR, et al. Sustained dysfunction of antiviral CD8+ T lymphocytes after infection with hepatitis C virus. J Virol. 2001;75(12):5550–8.
28. Hamid SS, Jafri SM, Khan H, Shah H, Abbas Z, Fields H. Fulminant hepatic failure in pregnant women: acute fatty liver or acute viral hepatitis? J Hepatol. 1996;25(1):20–7.
29. Bhatia V, Singhal A, Panda SK, Acharya SK. A 20-year single-center experience with acute liver failure during pregnancy: is the prognosis really worse? Hepatology. 2008;48(5):1577–85.
30. Jalan R, Williams R, Bernuau J. Paracetamol: are therapeutic doses entirely safe? Lancet. 2006;368(9554):2195–6.
31. Davern 2nd TJ, James LP, Hinson JA, Polson J, Larson AM, Fontana RJ, Lalani E, Munoz S, Shakil AO, Lee WM. Measurement of serum acetaminophen-protein adducts in patients with acute liver failure. Gastroenterology. 2006;130(3):687–94.
32. Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. JAMA. 1994;272(23): 1845–50.
33. Makin AJ, Williams R. Acetaminophen-induced hepatotoxicity: predisposing factors and treatments. Adv Intern Med. 1997;42: 453–83.
34. Gujral JS, Knight TR, Farhood A, Bajt ML, Jaeschke H. Mode of cell death after acetaminophen overdose in mice: apoptosis or oncotic necrosis? Toxicol Sci. 2002;67(2):322–8.
35. El-Hassan H, Anwar K, Macanas-Pirard P, Crabtree M, Chow SC, Johnson VL, Lee PC, Hinton RH, Price SC, Kass GE. Involvement of mitochondria in acetaminophen-induced apoptosis and hepatic injury: roles of cytochrome c, Bax, Bid, and caspases. Toxicol Appl Pharmacol. 2003;191(2):118–29.
36. Kon K, Kim JS, Jaeschke H, Lemasters JJ. Mitochondrial permeability transition in acetaminophen-induced necrosis and apoptosis of cultured mouse hepatocytes. Hepatology. 2004;40(5): 1170–9.
37. Ray SD, Mumaw VR, Raje RR, Fariss MW. Protection of acetaminophen-induced hepatocellular apoptosis and necrosis by cholesteryl hemisuccinate pretreatment. J Pharmacol Exp Ther. 1996;279(3):1470–83.
38. Keays R, Harrison PM, Wendon JA, Forbes A, Gove C, Alexander GJ, Williams R. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. BMJ. 1991;303(6809):1026–9.
39. Lee WM, Hynan LS, Rossaro L, Fontana RJ, Stravitz RT, Larson AM, Davern TJ, II, Murray NG, McCashland T, Reisch JS et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology 2009;137(3):856–864, 864 e851.
40. Shakil AO, Mazariegos GV, Kramer DJ. Fulminant hepatic failure. Surg Clin North Am. 1999;79(1):77–108.
41. Badmann A, Keough A, Kaufmann T, Bouillet P, Brunner T, Corazza N. Role of TRAIL and the pro-apoptotic Bcl-2 homolog Bim in acetaminophen-induced liver damage. Cell Death Dis. 2011;2:e171.
42. Kaufmann P. [Mushroom poisonings: syndromic diagnosis and treatment]. Wien Med Wochenschr. 2007;157(19–20):493–502.
43. Broussard CN, Aggarwal A, Lacey SR, Post AB, Gramlich T, Henderson JM, Younossi ZM. Mushroom poisoning–from diarrhea to liver transplantation. Am J Gastroenterol. 2001;96(11): 3195–8.
44. Escudie L, Francoz C, Vinel JP, Moucari R, Cournot M, Paradis V, Sauvanet A, Belghiti J, Valla D, Bernuau J, et al. Amanita phalloides poisoning: reassessment of prognostic factors and indications for emergency liver transplantation. J Hepatol. 2007; 46(3):466–73.
45. Neuberger J. Halothane hepatitis. Eur J Gastroenterol Hepatol. 1998;10(8):631–3.
46. Okuda K, Kage M, Shrestha SM. Proposal of a new nomenclature for Budd-Chiari syndrome: hepatic vein thrombosis versus thrombosis of the inferior vena cava at its hepatic portion. Hepatology. 1998;28(5):1191–8.
47. Faust TW. Budd-Chiari syndrome. Curr Treat Options Gastroenterol. 1999;2(6):491–504.
48. Fox MA, Fox JA, Davies MH. Budd-Chiari syndrome–a review of the diagnosis and management. Acute Med. 2011;10(1):5–9.
49. Khuroo MS, Al-Suhabani H, Al-Sebayel M, Al Ashgar H, Dahab S, Khan MQ, Khalaf HA. Budd-Chiari syndrome: long-term effect on outcome with transjugular intrahepatic portosystemic shunt. J Gastroenterol Hepatol. 2005;20(10):1494–502.
50. Quateen A, Pech M, Berg T, Bergk A, Podrabsky P, Felix R, Ricke J. Percutaneous transjugular direct porto-caval shunt in patients with Budd-Chiari syndrome. Cardiovasc Intervent Radiol. 2006;29(4):565–70.
51. Hay JE. Liver disease in pregnancy. Hepatology. 2008;47(3): 1067–76.
52. Mercer JF. The molecular basis of copper-transport diseases. Trends Mol Med. 2001;7(2):64–9.
53. Thomas GR, Forbes JR, Roberts EA, Walshe JM, Cox DW. The Wilson disease gene: spectrum of mutations and their consequences. Nat Genet. 1995;9(2):210–7.
54. Kiss JE, Berman D, Van Thiel D. Effective removal of copper by plasma exchange in fulminant Wilson's disease. Transfusion. 1998;38(4):327–31.
55. Gow PJ, Smallwood RA, Angus PW, Smith AL, Wall AJ, Sewell RB. Diagnosis of Wilson's disease: an experience over three decades. Gut. 2000;46(3):415–9.
56. Strand S, Hofmann WJ, Grambihler A, Hug H, Volkmann M, Otto G, Wesch H, Mariani SM, Hack V, Stremmel W, et al. Hepatic failure and liver cell damage in acute Wilson's disease involve CD95 (APO-1/Fas) mediated apoptosis. Nat Med. 1998;4(5): 588–93.
57. Felipo V, Butterworth RF. Neurobiology of ammonia. Prog Neurobiol. 2002;67(4):259–79.
58. Bjerring PN, Eefsen M, Hansen BA, Larsen FS. The brain in acute liver failure. A tortuous path from hyperammonemia to cerebral edema. Metab Brain Dis. 2009;24(1):5–14.
59. Bhatia V, Singh R, Acharya SK. Predictive value of arterial ammonia for complications and outcome in acute liver failure. Gut. 2006;55(1):98–104.
60. Clemmesen JO, Larsen FS, Kondrup J, Hansen BA, Ott P. Cerebral herniation in patients with acute liver failure is correlated with arterial ammonia concentration. Hepatology. 1999; 29(3):648–53.

61. Butterworth RF. Hepatic encephalopathy and brain edema in acute hepatic failure: does glutamate play a role? Hepatology. 1997; 25(4):1032–4.
62. Hazell AS, Butterworth RF. Hepatic encephalopathy: An update of pathophysiologic mechanisms. Proc Soc Exp Biol Med. 1999;222(2):99–112.
63. Wright G, Shawcross D, Olde Damink SW, Jalan R. Brain cytokine flux in acute liver failure and its relationship with intracranial hypertension. Metab Brain Dis. 2007;22(3–4):375–88.
64. Jalan R, Olde Damink SW, Deutz NE, Hayes PC, Lee A. Restoration of cerebral blood flow autoregulation and reactivity to carbon dioxide in acute liver failure by moderate hypothermia. Hepatology. 2001;34(1):50–4.
65. Jalan R, Olde Damink SW, Deutz NE, Davies NA, Garden OJ, Madhavan KK, Hayes PC, Lee A. Moderate hypothermia prevents cerebral hyperemia and increase in intracranial pressure in patients undergoing liver transplantation for acute liver failure. Transplantation. 2003;75(12):2034–9.
66. Roberts DR, Manas D. Induced hypothermia in the management of cerebral oedema secondary to fulminant liver failure. Clin Transplant. 1999;13(6):545–7.
67. Fu T, Blei AT, Takamura N, Lin T, Guo D, Li H, O'Gorman MR, Soriano HE. Hypothermia inhibits Fas-mediated apoptosis of primary mouse hepatocytes in culture. Cell Transplant. 2004;13(6):667–76.
68. Rolando N, Wade J, Davalos M, Wendon J, Philpott-Howard J, Williams R. The systemic inflammatory response syndrome in acute liver failure. Hepatology. 2000;32(4 Pt 1):734–9.
69. Rolando N, Philpott-Howard J, Williams R. Bacterial and fungal infection in acute liver failure. Semin Liver Dis. 1996;16(4): 389–402.
70. Wade JJ, Rolando N, Hayllar K, Philpott-Howard J, Casewell MW, Williams R. Bacterial and fungal infections after liver transplantation: an analysis of 284 patients. Hepatology. 1995;21(5):1328–36.
71. Trewby PN, Warren R, Contini S, Crosbie WA, Wilkinson SP, Laws JW, Williams R. Incidence and pathophysiology of pulmonary edema in fulminant hepatic failure. Gastroenterology. 1978;74(5 Pt 1):859–65.
72. Rolando N, Harvey F, Brahm J, Philpott-Howard J, Alexander G, Gimson A, Casewell M, Fagan E, Williams R. Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients. Hepatology. 1990;11(1):49–53.
73. Williams A, Trewby P, Williams R, Reid L. Structural alterations to the pulmonary circulation in fulminant hepatic failure. Thorax. 1979;34(4):447–53.
74. Sussman NL, Lake JR. Treatment of hepatic failure–1996: current concepts and progress toward liver dialysis. Am J Kidney Dis. 1996;27(5):605–21.
75. Wong F, Blendis L. Hepatorenal failure. Clin Liver Dis. 2000; 4(1):169–89.
76. Leithead JA, Ferguson JW, Bates CM, Davidson JS, Lee A, Bathgate AJ, Hayes PC, Simpson KJ. The systemic inflammatory response syndrome is predictive of renal dysfunction in patients with non-paracetamol-induced acute liver failure. Gut. 2009; 58(3):443–9.
77. Izumi S, Langley PG, Wendon J, Ellis AJ, Pernambuco RB, Hughes RD, Williams R. Coagulation factor V levels as a prognostic indicator in fulminant hepatic failure. Hepatology. 1996;23(6):1507–11.
78. Lee WM. Management of acute liver failure. Semin Liver Dis. 1996;16(4):369–78.
79. Wasmuth HE, Kunz D, Yagmur E, Timmer-Stranghoner A, Vidacek D, Siewert E, Bach J, Geier A, Purucker EA, Gressner AM, et al. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. J Hepatol. 2005;42(2): 195–201.
80. Heinrich PC, Behrmann I, Muller-Newen G, Schaper F, Graeve L. Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. Biochem J. 1998;334(Pt 2):297–314.
81. Streetz K, Fregien B, Plumpe J, Korber K, Kubicka S, Sass G, Bischoff SC, Manns MP, Tiegs G, Trautwein C. Dissection of the intracellular pathways in hepatocytes suggests a role for Jun kinase and IFN regulatory factor-1 in Con A-induced liver failure. J Immunol. 2001;167(1):514–23.
82. Streetz KL, Wustefeld T, Klein C, Manns MP, Trautwein C. Mediators of inflammation and acute phase response in the liver. Cell Mol Biol (Noisy-le-grand). 2001;47(4):661–73.
83. Trautwein C, Rakemann T, Niehof M, Rose-John S, Manns MP. Acute-phase response factor, increased binding, and target gene transcription during liver regeneration. Gastroenterology. 1996;110(6):1854–62.
84. Cressman DE, Greenbaum LE, DeAngelis RA, Ciliberto G, Furth EE, Poli V, Taub R. Liver failure and defective hepatocyte regeneration in interleukin-6-deficient mice. Science. 1996;274(5291):1379–83.
85. Yamada Y, Kirillova I, Peschon JJ, Fausto N. Initiation of liver growth by tumor necrosis factor: deficient liver regeneration in mice lacking type I tumor necrosis factor receptor. Proc Natl Acad Sci U S A. 1997;94(4):1441–6.
86. Streetz K, Leifeld L, Grundmann D, Ramakers J, Eckert K, Spengler U, Brenner D, Manns M, Trautwein C. Tumor necrosis factor alpha in the pathogenesis of human and murine fulminant hepatic failure. Gastroenterology. 2000;119(2):446–60.
87. Trautwein C, Rakemann T, Malek NP, Plumpe J, Tiegs G, Manns MP. Concanavalin A-induced liver injury triggers hepatocyte proliferation. J Clin Invest. 1998;101(9):1960–9.
88. Hecht N, Pappo O, Shouval D, Rose-John S, Galun E, Axelrod JH. Hyper-IL-6 gene therapy reverses fulminant hepatic failure. Mol Ther. 2001;3(5 Pt 1):683–7.
89. Galun E, Zeira E, Pappo O, Peters M, Rose-John S. Liver regeneration induced by a designer human IL-6/sIL-6R fusion protein reverses severe hepatocellular injury. FASEB J. 2000;14(13): 1979–87.
90. Kovalovich K, Li W, DeAngelis R, Greenbaum LE, Ciliberto G, Taub R. Interleukin-6 protects against Fas-mediated death by establishing a critical level of anti-apoptotic hepatic proteins FLIP, Bcl-2, and Bcl-xL. J Biol Chem. 2001;276(28):26605–13.
91. Li W, Liang X, Leu JI, Kovalovich K, Ciliberto G, Taub R. Global changes in interleukin-6-dependent gene expression patterns in mouse livers after partial hepatectomy. Hepatology. 2001;33(6):1377–86.
92. Bradham CA, Plumpe J, Manns MP, Brenner DA, Trautwein C. Mechanisms of hepatic toxicity. I. TNF-induced liver injury. Am J Physiol. 1998;275(3 Pt 1):G387–92.
93. Essani NA, Bajt ML, Farhood A, Vonderfecht SL, Jaeschke H. Transcriptional activation of vascular cell adhesion molecule-1 gene in vivo and its role in the pathophysiology of neutrophil-induced liver injury in murine endotoxin shock. J Immunol. 1997;158(12):5941–8.
94. Jaeschke H, Smith CW, Clemens MG, Ganey PE, Roth RA. Mechanisms of inflammatory liver injury: adhesion molecules and cytotoxicity of neutrophils. Toxicol Appl Pharmacol. 1996;139(2): 213–26.
95. Xu H, Gonzalo JA, St Pierre Y, Williams IR, Kupper TS, Cotran RS, Springer TA, Gutierrez-Ramos JC. Leukocytosis and resistance to septic shock in intercellular adhesion molecule 1-deficient mice. J Exp Med. 1994;180(1):95–109.
96. Jaeschke H, Essani NA, Fisher MA, Vonderfecht SL, Farhood A, Smith CW. Release of soluble intercellular adhesion molecule 1 into bile and serum in murine endotoxin shock. Hepatology. 1996;23(3):530–6.
97. Leist M, Gantner F, Jilg S, Wendel A. Activation of the 55 kDa TNF receptor is necessary and sufficient for TNF-induced liver

failure, hepatocyte apoptosis, and nitrite release. J Immunol. 1995;154(3):1307–16.
98. Tiegs G, Hentschel J, Wendel A. A T cell-dependent experimental liver injury in mice inducible by concanavalin A. J Clin Invest. 1992;90(1):196–203.
99. Takeda K, Hayakawa Y, Van Kaer L, Matsuda H, Yagita H, Okumura K. Critical contribution of liver natural killer T cells to a murine model of hepatitis. Proc Natl Acad Sci U S A. 2000;97(10):5498–503.
100. Kaneko Y, Harada M, Kawano T, Yamashita M, Shibata Y, Gejyo F, Nakayama T, Taniguchi M. Augmentation of Valpha14 NKT cell-mediated cytotoxicity by interleukin 4 in an autocrine mechanism resulting in the development of concanavalin A-induced hepatitis. J Exp Med. 2000;191(1):105–14.
101. Gantner F, Leist M, Lohse AW, Germann PG, Tiegs G. Concanavalin A-induced T-cell-mediated hepatic injury in mice: the role of tumor necrosis factor. Hepatology. 1995;21(1):190–8.
102. Kusters S, Gantner F, Kunstle G, Tiegs G. Interferon gamma plays a critical role in T cell-dependent liver injury in mice initiated by concanavalin A. Gastroenterology. 1996;111(2):462–71.
103. Wolf D, Hallmann R, Sass G, Sixt M, Kusters S, Fregien B, Trautwein C, Tiegs G. TNF-alpha-induced expression of adhesion molecules in the liver is under the control of TNFR1–relevance for concanavalin A-induced hepatitis. J Immunol. 2001;166(2):1300–7.
104. Liedtke C, Bangen JM, Freimuth J, Beraza N, Lambertz D, Cubero FJ, Hatting M, Karlmark KR, Streetz KL, Krombach GA, et al. Loss of caspase-8 protects mice against inflammation-related hepatocarcinogenesis but induces non-apoptotic liver injury. Gastroenterology. 2011;141(6):2176–87.
105. Leers MP, Kolgen W, Bjorklund V, Bergman T, Tribbick G, Persson B, Bjorklund P, Ramaekers FC, Bjorklund B, Nap M, et al. Immunocytochemical detection and mapping of a cytokeratin 18 neo-epitope exposed during early apoptosis. J Pathol. 1999;187(5):567–72.
106. Bantel H, Ruck P, Schulze-Osthoff K. In situ monitoring of caspase activation in hepatobiliary diseases. Cell Death Differ. 2000;7(5):504–5.
107. Schulze-Osthoff K, Ferrari D, Los M, Wesselborg S, Peter ME. Apoptosis signaling by death receptors. Eur J Biochem. 1998;254(3):439–59.
108. Bantel H, Schulze-Osthoff K. Mechanisms of cell death in acute liver failure. Front Physiol. 2012;3:79.
109. Schwerk C, Schulze-Osthoff K. Regulation of apoptosis by alternative pre-mRNA splicing. Mol Cell. 2005;19(1):1–13.
110. Song E, Lee SK, Wang J, Ince N, Ouyang N, Min J, Chen J, Shankar P, Lieberman J. RNA interference targeting Fas protects mice from fulminant hepatitis. Nat Med. 2003;9(3):347–51.
111. Zender L, Hutker S, Liedtke C, Tillmann HL, Zender S, Mundt B, Waltemathe M, Gosling T, Flemming P, Malek NP, et al. Caspase 8 small interfering RNA prevents acute liver failure in mice. Proc Natl Acad Sci U S A. 2003;100(13):7797–802.
112. Ben Moshe T, Barash H, Kang TB, Kim JC, Kovalenko A, Gross E, Schuchmann M, Abramovitch R, Galun E, Wallach D. Role of caspase-8 in hepatocyte response to infection and injury in mice. Hepatology. 2007;45(4):1014–24.
113. Canbay A, Higuchi H, Bronk SF, Taniai M, Sebo TJ, Gores GJ. Fas enhances fibrogenesis in the bile duct ligated mouse: a link between apoptosis and fibrosis. Gastroenterology. 2002;123(4):1323–30.
114. Wullaert A, van Loo G, Heyninck K, Beyaert R. Hepatic tumor necrosis factor signaling and nuclear factor-kappaB: effects on liver homeostasis and beyond. Endocr Rev. 2007;28(4):365–86.
115. Ferrari D, Stepczynska A, Los M, Wesselborg S, Schulze-Osthoff K. Differential regulation and ATP requirement for caspase-8 and caspase-3 activation during CD95- and anticancer drug-induced apoptosis. J Exp Med. 1998;188(5):979–84.
116. Hinson JA, Roberts DW, James LP. Mechanisms of acetaminophen-induced liver necrosis. Handb Exp Pharmacol. 2010;(196):369–405.
117. Bechmann LP, Jochum C, Kocabayoglu P, Sowa JP, Kassalik M, Gieseler RK, Saner F, Paul A, Trautwein C, Gerken G, et al. Cytokeratin 18-based modification of the MELD score improves prediction of spontaneous survival after acute liver injury. J Hepatol. 2010;53(4):639–47.
118. Volkmann X, Anstaett M, Hadem J, Stiefel P, Bahr MJ, Lehner F, Manns MP, Schulze-Osthoff K, Bantel H. Caspase activation is associated with spontaneous recovery from acute liver failure. Hepatology. 2008;47(5):1624–33.
119. Liong EC, Xiao J, Lau TY, Nanji AA, Tipoe GL. Cyclooxygenase inhibitors protect D-galactosamine/lipopolysaccharide induced acute hepatic injury in experimental mice model. Food Chem Toxicol. 2012;50(3–4):861–6.
120. Dear JW, Simpson KJ, Nicolai MP, Catterson JH, Street J, Huizinga T, Craig DG, Dhaliwal K, Webb S, Bateman DN, et al. Cyclophilin A is a damage-associated molecular pattern molecule that mediates acetaminophen-induced liver injury. J Immunol. 2011;187(6):3347–52.