Published in final edited form as:
Gastroenterology. 2012 September ; 143(3): e1–e7. doi:10.1053/j.gastro.2012.07.011.

Pathogenesis of Liver Injury in Acute Liver Failure

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Acute liver failure (ALF) represents the most severe damage an organ can sustain and can lead to shock, coagulopathy, altered mentation, cerebral edema, renal failure, infection, and, ultimately, multiorgan failure. The US Acute Liver Failure Study Group (ALFSG; available at: acuteliverfailure.org), convened a meeting on October 17 and 18, 2011, and included clinical, translational and fundamental investigators to discuss the pathogenesis of acute hepatocyte injury, how it occurs, and its downstream effects. The ALFSG has, for the past 14 years, carefully collected detailed clinical information and bio-samples from roughly 2000 patients with ALF at 24 tertiary medical centers across the United States. This meeting sought to summarize our current understanding of the pathogenetic factors that drive acute liver injury. These included consideration of (1) the contribution of innate immunity to liver injury, (2) the role of cytokine release in perpetuating liver injury and causing multiorgan failure, (3) mechanisms of apoptosis in ALF, (4) alterations in signal transduction with a focus on the role of c-Jun N-terminal kinase (JNK), (5) the contribution of infection to the pathogenesis of ALF, (6) the emerging centrality of inflammasome and sterile inflammation in the pathogenesis of ALF, (7) systems biology approaches to integrating and ordering the wide array of seemingly massively perturbed effectors in ALF, (8) host genetics and its contribution to ALF susceptibility, including a consideration of the power of next generation sequencing tools as they relate to ALF, and (9) contribution of liver regeneration to counteraction of ALF. Finally, we considered novel therapeutic strategies for ALF based on these pathogenetic concepts.

Role of Innate Immunity in Liver Injury

This area was covered by presentations that addressed the molecular sensors that trigger the innate immune response and the effector cells of this response. The pathogenesis of ALF includes both direct and immune-mediated liver injury triggered by diverse etiologies.

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Conflicts of interest

No author received any additional compensation related to this meeting summary. Authors were provided airfare and lodging for the meeting as were all invited attendees via the ALFSG U-01 grant: DK-056389.

Innate immune-mediated injury is initiated early and may then be followed later by injury resulting from adaptive immune responses. Innate immune activation is etiology-specific. Pathogen-associated molecular patterns (PAMPs) are more important in ALF caused by hepatotropic viruses, whereas damage-associated molecular patterns (DAMPs), endogenous signals derived from injured cells, are more important in toxic etiologies.[1] Many cell types participate in the innate immune response, including monocytes, macrophages, dendritic cells, leukocytes, natural killer cells (NK) and NKT cells and express receptors that can recognize both PAMPs and DAMPs. Monocytes, macrophages, and leukocytes also constitute the effector cells of innate immunity and regulate the inflammatory response by producing reactive oxygen radicals and pro- and anti-inflammatory cytokines. Dendritic cells present antigen and induce T cells through expression of co-stimulatory molecules and also produce cytokines, whereas NK cells provide interaction with virus-infected cells, T lymphocytes, and dendritic cells. Recognition of viral or other pathogens by a coordinated interaction of the cells of the innate immune system eventually leads to activation of adaptive immunity targeting viral- or drug-specific antigens. Of the various pattern recognition receptors, Toll-like receptors (TLRs), RNA helicase receptors and Nod-like receptors/inflammasomes sense endogenous and exogenous danger signals and induce pro-inflammatory cytokines and type I interferons. The specificity of ligands, pattern recognition receptors, intracellular adaptor molecules, and signal transduction pathways, and the relative concentration of each innate immune cell type determine the pattern of cytokines release locally within the liver, and eventually in the systemic circulation, defining the clinical characteristics and outcome of the ALF syndrome Additional work to define the precise sequence of innate immune-triggered events that lead to fulminant liver injury is necessary.

Cytokines in ALF

This section addressed the contribution of pro-inflammatory cytokines to the development of ALF, as well as to multiorgan failure. The 2 most common causes of death in patients with ALF are cerebral edema and multiorgan system failure, precipitated by the systemic inflammatory response syndrome (SIRS), which is mediated by release of pro-inflammatory cytokines, for example, tumor necrosis factor-α, interleukin (IL)-1β, and IL-6.[2] These SIRS mediators contribute to cerebral edema by decreasing cerebrovascular tone causing cerebral hyperperfusion. Although a compensatory anti-inflammatory response syndrome mediated by anti-inflammatory cytokines (IL-4, IL-10, transforming growth factor-β) exists concomitantly in patients with ALF to dampen the SIRS, persistent compensatory anti-inflammatory response syndrome may not be beneficial, because it can lead to sepsis and late mortality. ALF is, therefore, the clinical syndrome that results from pro- and anti-inflammatory cytokines spilling into the systemic circulation from the liver.

In patients with ALF not owing to acetaminophen (APAP), *N*-acetylcysteine (NAC) was recently shown to improve transplant-free survival if administered to subjects with early-stage hepatic encephalopathy (Table 1). Measurement of cytokines in patients enrolled in the study suggested that IL-17 levels were higher in patients with advanced versus early grade hepatic encephalopathy, whereas IL-6 and IL-10 levels correlated strongly with SIRS features and inversely with mean arterial pressure (unpublished data). Further work is required to define the imbalance of pro- and anti-inflammatory cytokines that results in unchecked organ injury.

Apoptosis in ALF

ALF occurs when hepatocyte death exceeds regeneration. Hepatocyte death in ALF follows 1 of 2 patterns, necrosis or apoptosis, which may coexist. In contrast with necrosis, which involves depletion of adenosine triphosphate leading to cell lysis and secondary

inflammation from lytic byproducts, apoptosis represents the execution of an adenosine triphosphate-dependent death program, leading to orderly resorption of cell nuclei and cytoplasm, minimizing the inflammatory response. This section covered our current understanding of the contribution of apoptosis to certain forms of ALF. Overwhelming apoptosis constitutes a major mode of hepatocyte death in certain forms of ALF, particularly those attributable to viral and toxic etiologies. The sequential activation of a series of cysteine–aspartate proteases known as caspases can be triggered either by activation of death receptors located on cell membranes, or by oxidative stress in mitochondria and the endoplasmic reticulum. The M30 antigen, a marker of apoptotic hepatocyte cell death that represents an exposed keratin 18 epitope after cleavage by caspases, was found to be 10-fold elevated in ALF patients compared with normal or hepatitis C-infected controls.[3] Median M30 levels were significantly higher among patients who underwent liver transplantation or died compared with transplant-free survivors, suggesting that serum M30 levels might be useful to predict outcome in ALF. These data demonstrate a central role for apoptosis in ALF attributable to a wide range of etiologies, and support the conceptual use of caspase or other apoptotic inhibitors in its management (Table 1).

Signal Transduction Pathways in APAP ALF: The Example of JNK

This section considered specific examples of activation of death pathways by known hepatotoxins. In the setting of hepatocyte injury by APAP (in humans or experimental models) or galactosamine (in experimental models), cell stress results in the activation of pro-death and pro-survival pathways. Covalent binding of highly reactive intermediates (such as *N*-acetyl-P-benzoquinone imine in APAP toxicity) to cell proteins and the formation of reactive oxygen species provide the stress that leads to activation of cytokines and death pathways. JNK, one of the stress-activated mitogen-activated protein kinases, represents a pro-death apoptotic pathway. Even in the setting of cell necrosis, apoptotic mechanisms are activated to an extent and the balance struck between pro-survival and pro-death pathways may be responsible for the eventual outcome in this setting. The role of mitochondria in redox management is being clarified. The mitochondrial permeability transition is induced by APAP injury and the related mitochondrial pore determines the outcome of pro- and anti-apoptotic forces. JNK activation in the setting of APAP-induced hepatic injury promotes cell death as evidenced by the protection afforded in models of injury utilizing JNK inhibitors. A newly described protein found on the outer mitochondrial membrane, SH3 domain-binding protein that preferentially associates with Btk (Sab), is important for JNK binding to mitochondria and for the resultant injury that determines next steps in cell death. Silencing of Sab ameliorates injury owing to APAP presumably by inhibiting JNK binding to mitochondria, suggesting that Sab is a key factor in this vicious cycle.[4] These data indicate specific pathways traversed by specific etiologic agents of ALF and suggest rational targets for modulating hepatocyte injury.

Role of Infection in ALF: Septic Inflammation

This section considered the contribution of infection and bacterial products to ALF. The milieu of inflammation and necrosis in ALF is presumed to predispose patients to infection due to complement deficiency, and/or impaired polymorphonuclear or Kupffer cell function. ALF-related infections have varied in the recognized incidence of bacteremia (between 22% and 80%), with fungemia noted in 32%. Gram-positive infections have predominated although this is counter-intuitive, since gastrointestinal tract organisms should be common if the liver's filtering function is abrogated. Although infection and/or markers of the SIRS have been linked to progression of early stage encephalopathy, this has not been shown to worsen outcomes, nor has a clear benefit been realized from prophylactic antibiotic use. A

full understanding of the role of infection in ALF has remained elusive and represents an important area for future work.

Sterile Inflammation: The Inflammasome

In contrast to the septic or "wet" inflammation triggered by systemic responses to bacteria and their products, a growing body of knowledge, summarized here, has defined an inflammatory response triggered by damage mediated by noninfectious sources. Intracellular molecules released during pathological cell death are also responsible for the sterile inflammation that occurs locally and in distant organs driven by DAMPs. The TLR family is responsible for sensing foreign biomaterials and activating intracellular defenses. These same receptors can detect DAMPs and PAMPs (Figure 1). However, activation of inflammatory mechanisms can promote further cell damage rather than repair. Specifically, in APAP injury in mice, there is activation of Kupffer-like macrophages and heat shock protein 70 and high-mobility group box-1 (HMGB-1), 2 recognized DAMPs[5] mediated by TLR-9. The use of biosamples from ALFSG to assess the contribution of DAMPs in human ALF will be an important next step.

Caspase-1 activation is regulated by the assembly of the inflammasome, which consists of 3 components: Nalp3 (NACHT, LRR, and pyrin domain-containing protein 3), ASC (apoptosis-associated speck-like protein containing a caspase activation and recruitment domain [CARD]), and caspase-1. Each component has been tested in inflammasome activation and IL-1β formation during experimental APAP hepatotoxicity.[6] Of course, innate immune cells, including neutrophils, Kupffer cells, and NK/NKT cells, also play variable roles in different cell injury and inflammation settings, and there may be large differences between individuals in their responses. Thus, targeting components of the inflammasome may represent a fruitful therapeutic avenue for management of ALF.

Systems Biology Approaches to Analyzing Inflammation in ALF

How does one integrate the bewildering array of massively perturbed analytes, including cytokines, DAMPs, and apoptosis markers, to generate hypotheses regarding pathogenetic pathways? This section considered the value of applying systems biology to panels of analytes in ALF. The very complexity of the immunoinflammatory response has stymied attempts at therapeutic modulation of acute inflammation, resulting in a dearth of therapeutic options. Mathematical modeling of complex systems has emerged as an approach to understand the interactions among biologic pathways. Principal component analysis is a modeling tool to identify the key drivers of inflammation in both patient cohorts and individual patients. Using ELISA for cytokine concentrations in a cohort of pediatric ALF patients, the raw cytokine data were uninformative; however, certain key inflammatory drivers or bio-signatures (ie, patient-specific "inflammation barcodes") were observed using patient-specific principal component analysis.[7] Certain outcome groups were enriched within clusters of patients defined by principal component analysis. Thus, mathematical simulations of liver inflammation and injury may aid in determining ALF outcomes, and possibly uncovering unappreciated therapeutic pathway targets.

Genomics in ALF

Does the host contribute susceptibility to ALF, this most extreme phenotype of liver injury? This section considered the merits of the hypothesis that unique host susceptibility factors are involved in the pathogenesis of ALF. Variation in susceptibility as well as outcome in ALF may reside in the host genome, transcriptome, or at the level of protein expression. Use of either a candidate gene or a whole genome approach must account for the frequency of the genetic variant in controls, strength of the association, and accuracy/certainty of the

phenotype being studied to ensure that the study is adequately powered. Strengths of phenotyping within ALFSG include the use of standardized diagnostic definitions and detailed data and outcomes reporting. Nonetheless, some ALF diagnoses such as hepatic ischemia, drug-induced liver injury (DILI), and autoimmune hepatitis rely on clinical criteria rather than pure objective and quantitative parameters. In addition, as many as 15% of the ALF cases are of indeterminate etiology. In genetic association studies of ALF susceptibility, one could compare the frequency of a single nucleotide polymorphism in all of the ALF cases with population controls. Alternatively, the ALF cases could be compared with individuals who had a milder form of the same disease but did not progress to ALF. For genetic association studies of ALF outcomes, the spontaneous survivors could be compared with those who died or required a transplant at 3 weeks. In contrast with the candidate gene studies described, pursuit of an unbiased approach to identification of ALF susceptibility single nucleotide polymorphisms could be accomplished through a genome-wide association study (GWAS). The merits of these approaches are considered below.

Candidate Gene Studies

Candidate gene studies have revealed important potential susceptibility loci. For example, keratins 8 and 18 are intermediate filament cytoskeleton proteins that provide important anti-apoptotic function in hepatocytes and specific K8 and K18 variants have been associated with more severe forms of chronic liver disease. A significant association of various K8 and K18 genetic polymorphisms with ALF susceptibility and outcome was noted among Caucasian ALFSG patients, whereas different mutations were associated with ALF susceptibility and outcome among African-American ALFSG patients.[8] Other candidate genes identified through the ALFSG have included UDP glucuronyltransferases, a CD44 variant in APAP overdose patients, and Nuclear factor-erythroid 2-related factor 2 (Nrf2) and JNK polymorphisms in overall ALF susceptibility.

GWAS and Next-Generation Sequencing

The great advantage of GWAS studies is their inherently unbiased approach to identification of pathogenetic disease or susceptibility loci. Currently, GWAS studies are being conducted in other uncommon forms of acute liver injury such as DILI. These studies have provided important mechanistic insights into DILI pathogenesis. Use of GWAS in the ALFSG setting should provide similar novel data. However, the identification of unique susceptibility loci using unbiased approaches requires large numbers of cases and controls to provide adequate statistical power to generate meaningful candidates.

In addition to GWAS, more complete genotyping of the human genome that can identify rarer disease-causing variants with a frequency of only 1 in 1000 to 1 in 10,000 in the general population is now available using “next-generation sequencing.” Currently, the entire exome of all known genes can be genotyped and compared in cases and controls. These techniques should increase further the power of detecting rare causal variants in ALF and DILI settings. Studies of epigenetic regulation involving DNA methylation and transcriptomics may also help to elucidate pathogenetic mechanisms. In particular, methods to quantify circulating messenger RNA from the serum and microRNAs that regulate gene expression post-transcriptionally represent ideal and powerful tools, to take advantage of the large biorepository of prospectively collected biological samples from ALFSG patients.

Liver Regeneration: Mechanisms and Markers

Spontaneous survival (survival without liver transplantation) in ALF has improved over the years, but is still only 40%. If liver regeneration exceeds liver necrosis and apoptosis, then survival should occur, barring irreversible complications such as uncontrolled intracranial

hypertension, severe sepsis, or necrotic pancreatitis. Although the mechanisms of liver regeneration after partial hepatectomy are well-elucidated, those associated with ALF are less well-established. This section considered evidence for the power of exploiting liver regenerative forces to counteract the massive injury and cell death surrounding ALF.

Prognosis and liver regeneration seem related and to be etiology specific. Certain etiologies (APAP or ischemic liver injury) carry a much better prognosis than most other etiologies, and are characterized by short symptom duration and primarily liver necrosis.

Liver regeneration factors and markers are numerous and include the Wnt/β-catenin signaling system, prostaglandin E2 (PGE2), TLRs, tumor necrosis factor-α, IL-6, hepatocyte growth factor, epidermal growth factor, vascular endothelial growth factor, and transforming growth factor-α. However, clinical data are often sparse in ALF. Initial clinical studies focused on alpha-fetoprotein as a marker of liver regeneration. Increasing alpha-fetoprotein levels between hospital days 1 and 3 seemed to indicate a good prognosis.

Early activation of the Wnt/β-catenin signaling system contributes to liver regeneration in animal models and in patients with APAP-induced ALF and this system may serve as a marker of liver regeneration in ALF. Progenitor cells (oval cells) can be activated when hepatocyte necrosis exceeds approximately 50% and can differentiate into hepatocytes or cholangiocytes as needed. One study of CD34-positive peripheral blood stem cell infusions showed improvement in a severe case of DILI-induced ALF preceding stimulation with granulocyte colony–stimulating factor. Recently, an exciting model of growing high-quality human hepatocytes has been developed. Human hepatocytes are engrafted into Fah-null fetal pigs, where they persist and continue to function after birth. These hepatocytes may be excellent candidates for infusions into humans in the future.

PGE2 increases liver size and hepatocyte number in zebrafish. In APAP toxicity, PGE2 injections reduced mortality and prolonged the therapeutic window for the effects of NAC, suggesting a possible therapeutic role for PGE2 in the future for patients with ALF. Collectively, these data suggest that liver regenerative pathways may be manipulated to therapeutic effect in the face of massive hepatocyte injury and death.

Novel Therapeutic Strategies for ALF

Treatment of ALF is chiefly supportive, with liver transplantation ultimately offering a lifesaving option. Etiology-specific interventions include NAC for APAP-related ALF and possibly for other etiologies, nucleoside analogs for hepatitis B-related ALF, delivery of the infant in acute fatty liver of pregnancy, and corticosteroids for autoimmune hepatitis. Much work has been done, and a number of novel promising approaches have emerged from preclinical and early clinical work (Table 1).

Use of recombinant human hepatocyte growth factor, has been observed to reduce mortality, especially in subacute and early liver failure but has not been studied outside of Asia.

HMGB-1 is a nonhistone nuclear protein and a DAMP that serves as a late mediator of lethal systemic inflammation. In rats with D-galactosamine–induced ALF, the use of anti–HMGB-1 resulted in suppression of plasma HMGB-1 and hepatic enzymes, plasma inflammatory cytokines, and an improvement in histologic findings and survival, suggesting HMGB-1 blockade as a potential treatment for ALF. Inhibitors of other inflammasome components may be attractive strategies as well.

Endothelin-1 plays a key role in the pathogenesis of microcirculatory abnormalities by mediating sinusoidal vasoconstriction, lowering perfusion, and promoting leukocyte

adhesion. Endothelin-1 blockade may ameliorate microcirculatory abnormalities in ALF decreasing liver injury.

Other potential interventions for ALF include cardiotrophin-1, possibly through its effects on apoptosis and cell repair. Cardiotrophin-1 has recently received orphan drug status from the US Food and Drug Administration for use in ALF.

Human hepatocarcinoma–intestine–pancrease/pancreatitis-associated protein acts as a free-radical scavenger that targets death effectors and favors liver regeneration. Human hepatocarcinoma–intestine–pancrease/pancreatitis-associated protein is expected to enter early phase clinical trials soon.

Bone marrow-derived stem cells might facilitate hepatic regeneration by supporting resident hepatocyte functions that promote vascular remodeling, macrophage-led matrix, remodeling and immune modulation. Bone marrow-derived stem cells may exert beneficial effects through paracrine mechanisms and by enhancing angiogenesis.

Nrf2 is a transcription factor belonging to the cap-n-collar family of activators and protects cells against oxidative stress by activating the antioxidant defense system. Activation of Nrf2 has recently shown promise in lessening inflammation in diabetic nephropathy.

An important role of growth factors including erythropoietin and darbepoietin in stimulating hepatic regeneration or altering the inflammation/apoptosis balance has been suggested, based on animal studies only.

Summary and Future Steps

Advances continue to be made in the management of ALF, yet major challenges remain. The hope and expectation is that, in time, some of the interventions that have been effective in experimental animal models can be translated to clinical care of a condition that continues to have high rate of morbidity and mortality.

Moving forward, use of available ALFSG resources, including data and biorepositories, should be strongly encouraged to develop or validate hypotheses regarding pathogenesis, particularly as they relate to generation of biomarkers and therapeutic candidates. One of the aims of this meeting was to encourage further collaboration across disciplines and use of the >60,000 available bio-samples in the ALFSG repository. More than 100 requests have been made for data and/or sera or other biosamples from the ALFSG repository. Samples are collected daily of 5–10 mL serum for 7 days, 7 mL plasma, and 10 mL urine on the first day and a DNA sample as well. In addition, detailed information regarding past medical history, medication record, and ongoing clinical information for the initial hospitalization are available as well as follow-up to 24 months. Because the patient with ALF by definition has mental alteration, informed consent is obtained from next of kin. We anticipate wider use of samples in the future to study, among other things, novel biomarkers as predictors of outcome so that resource utilization can be appropriately stratified. Other targets of study should include systems analysis of cytokine studies, correlation with genomic analyses, development of prognostic scores, and basic understanding of the inciting agents for liver injury. Where possible, not only traditional, National Institutes of Health-derived mechanisms of support, but also collaborations with industry and biotech should be leveraged to support trials of novel agents. The ALFSG constitutes a ready-made platform for the conduct of such studies.

Acknowledgments

The authors acknowledge the ongoing support of the staff at NIDDK, including Drs. Patricia Robuck, Ed Doo, and Averell Sherker, as well as Rebekah Rasooly and the staff of the NIDDK Repository. Further thanks go to all the sites that have enrolled patients over the past 14 years, including the investigators, coordinators, staff, and patients who make the study possible.

Funding

Supported by a U01 Cooperative Agreement with NIDDK; DK-58369. Additional support was provided by ARRA grants (U01 DK058369-10S1 and U01 DK058369-10S3) and by the Rollin and Mary Ella King Fund and the Jeanne Roberts Fund at the Southwestern Medical Foundation.

Abbreviations used in this paper

ALF	acute liver failure
ALFSG	US Acute Liver Failure Study Group
APAP	acetaminophen
DAMP	damage-associated molecular pattern
DILI	drug-induced liver injury
GWAS	genome-wide association study
HMGB-1	high-mobility group box-1
IL	interleukin
JNK	c-Jun N-terminal kinase
NAC	N-acetylcysteine
NK	natural killer cells
Nrf2	nuclear factor-erythroid-related factor 2
PAMP	pathogen-associated molecular pattern
PGE2	prostaglandin E2
SIRS	systemic inflammatory response syndrome
TLR	Toll-like receptor

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Appendix

List of Speakers

Udayan Apte, University of Kansas; Jody Balko, University of Texas Southwestern; Ray Chung, Harvard Medical School; Mark Daly, Harvard University; Jamil Faivre, Paul Brousse Hospital France; Robert Fontana, University of Michigan; Wolfram Goessling, Harvard University; Hartmut Jaeschke, University of Kansas; Neil Kaplowitz, University of Southern California; William M. Lee, University of Texas Southwestern; Joseph Lillegard, Mayo Clinic; Wajahat Mehal, Yale University; Bishr Omary, University of Michigan; Biju Parekkadan, Harvard University; Jesus Prieto, University of Navarra, Spain; Jorge Rakela, Mayo Clinic; K. Rajender Reddy, University of Pennsylvania; William Salminen, FDA; Frank Schiødt, Bispebjerg Hospital Denmark; R. Todd Stravitz, Virginia Commonwealth University; Gyongyi Szabo, University of Massachusetts; Yoram Vodovotz, University of Pittsburgh; Paul Watkins, University of North Carolina.

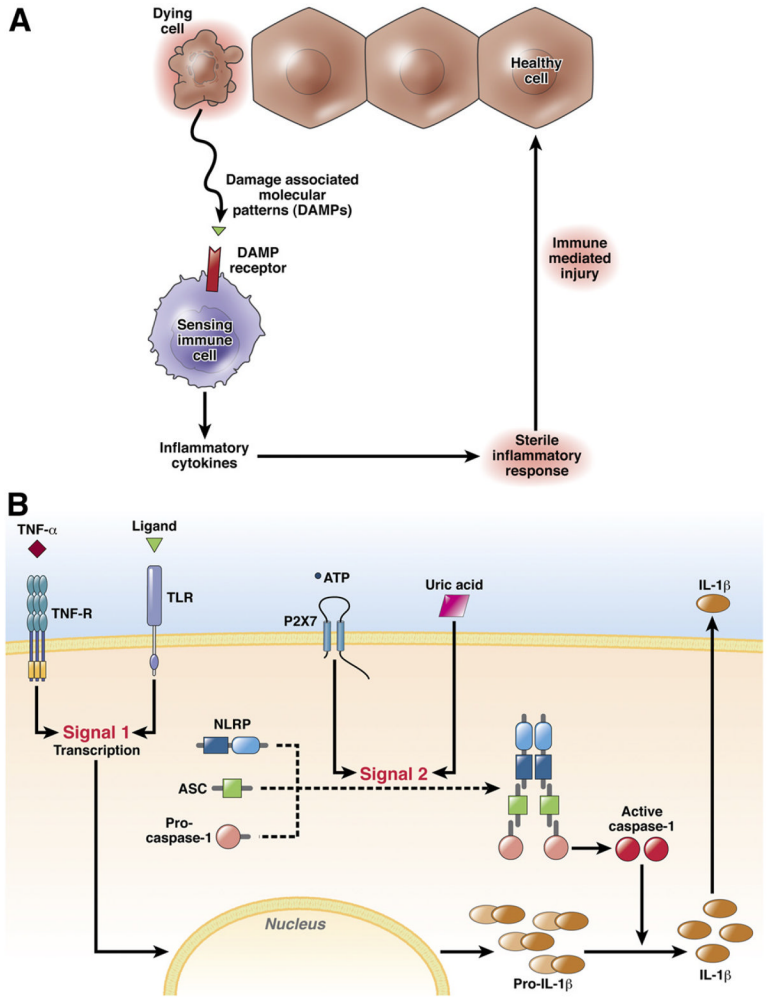

Figure 1.

Overview of sterile inflammation. (*A*) When a cell undergoes an entirely apoptotic mode of death, damage associated molecular patterns (DAMPs) remain sequestered and are not visible to extracellular receptors. With a primary or secondary necrotic cell death DAMPs are released from the dying cell and can engage a variety of receptors on immune cells, resulting in the initiation of a sterile inflammatory response. (*B*) Inflammasome activation typically requires a priming step that can occur through TLRs and an activation step that can be initiated by a wide range of signals such as adenosine triphosphate, uric acid crystals and reactive oxygen species. Modified with permission from Mehal WZ et al.[9]

Table 1

Possible Therapeutic Approaches to Acute Liver Failure

Treatment	Pathway/mechanism	Clinical trial status	References
N-acetylcysteine (non-acetaminophen ALF)	Antioxidant	Completed	Lee et al, Gastroenterology 2009;137:856
Caspase inhibitors	Block apoptosis	Preclinical	Volkmann et al, Hepatology 2008;47:1624
PGE2	Increases hepatocyte number and liver size	Preclinical	Goessling et al, Cell Stem Cell 2011;8:445
Recombinant human hepatocyte growth factor	Enhances regeneration	Many trials, meta-analysis	Cui et al, Contr Clin Trials 2008;29:696
Anti–HMGB-1	Blocks inflammasome (DAMP)	Preclinical	Zhou et al, BMC Gastroenterol 2011;11:21324; Takano et al, Shock 2010;34:573
Endothelin-1 antagonism	Relieves microcirculatory dysfunction	Preclinical	Palmes et al, J Hepatol 2005;42:350
Cardiotrophin-1	Anti-apoptotic, enhances cell repair	Phase 1	Bustos et al, Gastroenterology 2003;125:192
Human hepatocarcinoma–intestine–pancrease/pancreatitis-associated protein	Free radical scavenger, promotes regeneration	Phase 1	Moniaux et al, Hepatology 2011;53:618
Bone marrow-derived stem cells	Facilitates regeneration	Preclinical	Fernandez-Ruiz et al, J Hepatol 2011;55:828
Nrf2 agonists	Induces antioxidant genes	Preclinical Phase 2; (diabetic nephropathy)	Xu et al, Lab Invest 2008;88:1068; Pergola et al, N Engl J Med 2011;365:327
Erythropoietin	Hepatic regenerator	Preclinical	Ben-Ari et al, Transplantation 2011;92:18; Le Minh et al, Am J Pathol 2007;170:1954