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Review

Pathogenesis of Fulminant Hepatic Failure

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SUMMARY

Acute liver failure (ALF) is characterized by severe and sudden liver cell dysfunction leading to coagulopathy and hepatic encephalopathy in previously healthy persons. A critical degree of liver cell death not adequately decompensated by hepatocellular regenerative activity is fundamental to the development of ALF. Interaction between two dominant pathological pathways is illustrated as the triggering event: apoptosis and necrosis. A correlation has been demonstrated between the etiology of ALF and the dominating pathological pathway. Liver cell death signaling pathways modulated by an increasingly recognized number of tyrosine kinases, adapter molecules, transcription factors, proinflammatory and vasoactive cytokines and chemokines through both stimulating and depressant interactions have been demonstrated. What's more Systemic Inflammatory Response Syndrome whether or not precipitated by infection, appears to be implicated in the progression of encephalopathy, reducing the chances of transplantation and conferring a poorer prognosis. Hepatic encephalopathy and brain edema arising from exposure of the brain to circulating neurotoxins also signifies a serious prognosis in ALF.

Key words: Fulminant Hepatic Failure, Apoptosis, Necrosis, Tumour Necrosis Factor, Systemic Inflammatory Response Syndrome, Caspases, Oxidative Stress, Hepatocellular Regeneration, Hepatic Encephalopathy, Brain Edema.

1. INTRODUCTION

Acute liver failure (ALF) is characterized by severe and sudden liver cell dysfunction leading to coagulopathy and hepatic encephalopathy in previously healthy persons with no known underlying liver disease[1]. Mortality rates are estimated up to 40-100%[2] yet each new case is considered a crisis, a severe and potentially fatal event with few guideposts for management or prognosis[3]. Although categorization into hyperacute, acute and subacute liver failure much more accurately reflects the differing clinical pattern and course of these subgroups and correlates also with etiology and survival, the use of the term ALF has proven difficult to substitute.

A critical degree of liver cell death not adequately decompensated by hepatocellular regenerative activity is fundamental to the development of ALF. Interaction between two dominant pathological pathways is illustrated as the triggering event: apoptosis and necrosis[4]. A correlation has been demonstrated between the etiology of ALF and the dominating pathological pathway such as necrosis in the case of severe acetaminophen overdose and apoptosis in the case of ischemia-reperfusion injury, viral hepatitis, alcohol induced liver disease, non alcoholic fatty liver disease[5] and fulminant Wilson's disease[6-10]. Also regardless of the dominating death pathway a variable degree of liver regeneration deregulation is required in order for ALF to develop.

Clinical research in ALF has been directed toward the study of metabolic and biotransformary processes, the deterioration of which may facilitate hepatocellular regenerative activity and multiorgan recovery rates. Evolving knowledge in ALF directed against those liver cell death signaling pathways modulated by an increasingly recognized number of tyrosine kinases, adapter molecules, transcription factors, proinflammatory and vasoactive cytokines and chemokines through both stimulating and depressant interactions is reviewed by this current article. Also molecular mechanisms interfering in liver regeneration processes and neurobiology of ALF involving brain osmolarity disturbances resulting in brain edema and encephalopathy dominating in the research fields are

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reviewed. Etiology of acute liver failure around the world is displayed (Tables 1,2).

We searched the database PubMed using the following key-words: "pathogenesis in fulminant hepatic falure", "acute liver failure". We also included review articles, book chapters, or commonly referenced older publications. We reviewed the reference lists of articles identified by the search strategy and selected those we judged relevant. The search was restricted to papers published in English.

2. DEATH PATHWAYS

2.1 Apoptosis

Apoptosis is manifested by nuclear and cytoplasmic shrinkage without disturbance of cell membrane integrity or liberation of intracellular content. Consequently secondary inflammation is not a feature[4]. Apoptosis can be triggered by extrinsic or intrinsic mechanisms, the former involving activation of death receptors and the latter involving oxidative stress of mitochondria and the endoplasmic reticulum[6,11-14]. The death receptor pathway is predominately initiated by death receptor ligands following their binding to death receptors. These ligands include tumor necrosis factor (TNF)-α, Fas ligand, CD95, transforming growth factor beta (TGF)[15] and tumor necrosis factor-related-apoptosis-inducing ligand (TRAIL). Death receptors' expression in hepatocytes has been attributed to evolutionary pressure to eliminate hepatotropic viruces. The mitochondria pathway is triggered by a variety of intracellular stresses such as DNA damage, growth factor deprivation, metabolic disturbances etc[16]. Apoptosis is induced by the sequential activation of a series of cysteine proteases known as caspases; caspase 8 mediates proapoptotic signal transduction downstream of activated cell surface death receptors whereas caspase 9 mediates signals that follow oxidative mitochondrial damage. Dysregulation of apoptotic pathways contributes to diseases such as hepatocellular carcinoma, viral hepatitis, autoimmune hepatitis, ischaemia-reperfusion injury, iron or copper deposition disorders and toxic liver damage[15]. Recently an important mechanism that underpins the failure of infused hepatocytes to engraft and survive in liver injury has been elucidated, the loss of beta-1-intergrin receptor activity which controls adhesion to collagen[17].

2.2. Necrosis

Necrosis involves depletion of adenosine triphosphate (ATP) with resultant cell swelling and lysis leading to release of cellular content and secondary inflammation[6]. Processes leading to marked oxidative stress favorable liver cell death by necrosis rather than by apoptosis through induction of severe mitochondrial damage and also inhibition of the proapoptotic caspase cascade[18-20]. Nonetheless an insult capable of inducing apoptosis may cause cell death by necrosis, particularly if the degree of mitochondrial damage is sufficient to exhaust ATP stores[4].

There have been many reports about the severity of hepatic necrosis caused by fulminant hepatitis; however, the relationship between proliferated bile ductules and osteopontin (OPN) expression in inflamed areas in each of the clinical forms of fulminant hepatitis has only recently been assessed. Comparison of acute form fulminant hepatitis with the subacute form showed OPN expression in proliferated bile ductules and serum aspartate aminotransferase (ALT) max to be decreased in the subacute form of fulminant hepatitis. OPN expression is an important marker of the degree of liver inflammation, and its regulation mechanism is very important to understanding the pathophysiology of fulminant hepatitis[21].

2.3. Death domains

2..3.1 TNF-α/TNF receptor and Fas receptor/Fas ligand pathways

TNF-α has been involved in the pathogenesis of viral hepatitis, alcoholic hepatitis, ischemia-reperfusion injury and fulminant hepatic failure. Serum levels of TNF-α are significantly increased in fulminant hepatitis[22]. TNF-α exerts a variety of effects that are mediated mainly by TNF-receptor 1(TNF-R1) in apoptotic cell death pathways. The activation of TNF-R1 leads to the activation of multiple apoptotic pathways involving the activation of caspase cascade, the pro-death Bcl-2 family proteins, reactive oxygen species, C-Jun NH2-terminal kinase (JNK), cathepsin B, the transcription factor nuclear factor kappa B (NF-ϰB), acidic sphingomyelinase and neutral sphingomyelinase. These pathways are closely interlinked and mainly act on mitochondria which eventually release the apoptogenic factors resulting in apoptosis.

Three functional domains of intracellular interactions are recognized: the C-terminal death domain, the middle A-SMase (acidic sphingomyelinase) activating domain (ASD) and the N terminal N-SMase (neutral sphingomyelinase) activating domains (NSD). (Figure 1) The death domain can mediate both the pro-apoptosis and anti-apoptosis pathways while the other two sphingomyelinases pathways mainly modulate apoptotic and inflammatory responses[23]. The binding of TNF-α to TNF-R1 leads to the trimerization and recruitment of adaptor proteins, TRADD or FADD, through homophilic interactions be-

Table 1: Etiology of acute liver failure around the world. ACM, acetaminophen; NR, non-reported; ref, reference; N, number of patients; indent, indeterminant; Others included: autoimmune hepatitis, hypo perfusion of the liver, cardiogenic shock, Wilson's disease, pregnancy related hepatic syndromes, indeterminant hepatic failure

Ref	Country	Yrs surv/lance	N	HAV	HBV	HEV	nonA-nonE	Drugs	Indent/ other
Ritt et al. Medicine 1969;48:151-72	USA	1958-1968	31	42%	32%	0		23%	0
Rakela et al. Dig Dis Sci 1991;36:1223-1228	USA	1974-1982	34	0%	18%			18%	44% other 21%
Schiodt et al. Liver Transplant Surgery 1999;5:29-34	USA 13 centers	1994-1996	295	7%	10%		15%	ACM 60(20%) others 12%	15%
Trigo et al. Hepatology 2001;34:657A	Argentina	1996-2001	83	7 (8,4%)	18 (22%)			12 (14,5%)	21(25%)
Khuroo et al J Viral Hepat 2003;10:224-31	India	1989-1996	180	4 (2%)	25 (14%)	79 (44%)	56 (31%)		
Rakela et al. Dig Dis Sci 1991;36:1223-1228	USA	1975-1978	64	2 (3,1%)	34 (53%)	0		17 (26,5%)	34
Shakil et al. Liver Transpl 2000;6:163-169	USA Pittsburgh	1983-1995	177	13 (7,3%)	33 (18%)	0	6 (3,3%)	ACM 12(19%) others 21(12%)	49 (28%)
Poddar U et al Arch Dis Child 2002;87:54-56	India (children)	1997-2000	67	34 (51%)	5 (8%)	17 (25%)	4 (6%)		
Tessier et al, Can J Gastroenterol. 2002;16:672-6	Canada	1991-1999	81	33%		NR	NR	NR 27 %others	27% other 12%
Schiodt et al. Am J Gastroenterol 2003;98:448-53	USA		354	16 (4,5%)	26 (7,3%)				65 (18%)
O'Grady et al. J Viral Hepat 2000;7:9-10	UK	1973-1990	943	19%				ACM 53% others 7%	17%
Ellis et al Crit Care 1998 ;2 : P150	UK Kings-London	1991-1997	999	5%				ACM 70% others 5%	
Ostapowicz et al. Ann Intern Med 2002;137:947-54	USA 17 centers	1998-2001	308	14 (4,5%)	22 (7,1%)			ACM 39%, others 13%	50 (17%)
Acharya et al. Hepatology 1996;23:1448-1455	India	1987-1993	423	7 (1.7%)	117 (28%)	31 (7%)		19(4,5%) anti-turbeculocis	
Bendre SV et al. Indian Pediatr. 2000	India (children)		36	12 (33%)	3 (8%)	4 (11%)			
Papaevangelou Hepatology 1984;4:369-372	Greece	1981-1983	65	1 (1,5%)	48 (74%)	0	16 (24%)	Non-included	0
Hippocration university hospital of Athens (non published)	Greece	1997-2005	34	0	16 (47%)	0	0	5 (15%)	4 (12%)
Ostapowicz G, et al. J Gastroenterol Hepatol 2000;15:480-488	Denmark	1973-1990		2%	31%	NR	NR	19% ACM 17 %others	15% other 16%
Ostapowicz G, et al. J Gastroenterol Hepatol 2000;15:480-488	France	1972-1990		4%	32%	NR	NR	2%ACM 17% others	18% other 34%
Ostapowicz G, et al. JGastroenterol Hepatol 2000;15:480-488	Japan	1992-1999		3%	18%	NR	NR	0%ACM 0% others	71% other 8%
Ostapowicz G, et al. J Gastroenterol Hepatol 2000;15:480-488	UK	1993-1994		2%	2%	NR	NR	73%ACM 2 %others	8% other 12%
Lee WS, et al. J Pediatr Gastroenterol Nutr. 2005;40:575-581	UK (children)	1991-2000	97	53				19	22 metabolic, 3auto-immune
Shin SJ, et al. Korean J Hepatol 2004;10:298-307	Korea	1992-2003	60		30%	10%(including HAV infection)		41,6%	

tween the conserved death domains (DD). FADD further recruits caspase-8 and cause its activation, which is followed by Bid cleavage and Bax-Bac translocation to the mitochondria and/or oligomerization. Meanwhile, tBid also activates mitochondria permeability transition (MPT) which is further enforced by N-SMase, A-SMase and their metabolites ceramide and ganglioside GD3. MPT opening or the activation of Bax-Bac (deletion of both Bax and Bak renders the cell completely resistant to all major mitochondria death stimuli, including DNA damage, growth factor, withdrawal and endoplasmic reticulum stress, and the extrinsic death signals mediated by Bid[24]) results in cytochrome c and Smac-Diablo release and caspase (caspases 3 and 9) activation. In addition, lysosome related cathepsin B mediated via the N-SMase and its adaptor protein FAN and TRAF-2 mediated JNK activation synergistically contribute to mitochondria activation[16]. As a consequence mitochondria can depolarize and MPT can contribute to the release of apoptogenic proteins from the intermembrane space and also generation of reactive oxygen species. Meanwhile one of the unique features of TNF-α/TNF-R1 signaling is the simultaneous activation of the NF-κB pathway which can inhibit the TNF-α induced cell death process. NF-κB dimmers are translocated to the nucleus following TRADD/RIP-TRAF2 interaction, IKK activation and phosphorylation and degradation of I-κBα, thus transcriptionally activating a number of protective molecules to suppress apoptosis via multiple mechanisms[16].

Hepatocytes are normally resistant to the harmful effects of TNF-α. Susceptibility to cell death occurs in the settings of global transcription or translational arrest or selective inhibition of NF-κB orc-Myc[25,26]. TNF gene polymorphism in patients with acute and fulminant hepatitis has been recently assessed. ALF patients with a poor prognosis had higher frequencies of positions -1031C and -863A in the TNF-α promoter region, and higher frequencies of the B2 allele of the TNF-beta gene. These data suggest that the genomic background may be associated with the prognosis of ALF[27]. The overall effect of TNF-α on hepatocytes is influenced not only by the oxidative state of the cell but also by the cytokine milieu generated in response to a toxic insult.

Direct targeting to the TNF-α apoptotic signaling pathways may constitute a future therapeutic potency. Targeting towards the activation of mitochondria using chemi-

Table 2. Etiologies displayed for which a causal relationship with ALF has been elucidated by the literature

Acute viral hepatitis	**Other causes**
HAV	Ischemia-reperfusion injury
HBV	Thermal injury
HDV	Autoimmune hepatitis
HCV	Giant cells hepatitis
HEV	Wilson's disease
Herpes simplex virus	Steatosis (drug-induced, Reye syndrome)
HSV 1-2	Obstructive hepatic veins' disease (Budd-Chiari syndrome)
Varicella zoster virus	Schimdt syndrome
Cytomegalovirus	Metastatic invasion of the liver
Epstein-Barr virus	Hepatic transplantation
HSV-6	Partial hepatectomy
Other viruces	Sickle cell anemia
Parbovirus B-19	Hemochromatosis
Adenovirus	Glycogen storage disorders
Malaria f.	Erythropoietic protoporphyria
Coxsackie B virus	Primary biliary cirrhosis-Autoimmune hepatitis
Acute poisoning	Mirizzi syndrome
Paracetamol	Clove oil
Amanita phalloides	Acute fatty liver of pregnancy
Ecstasy	
Herbs	

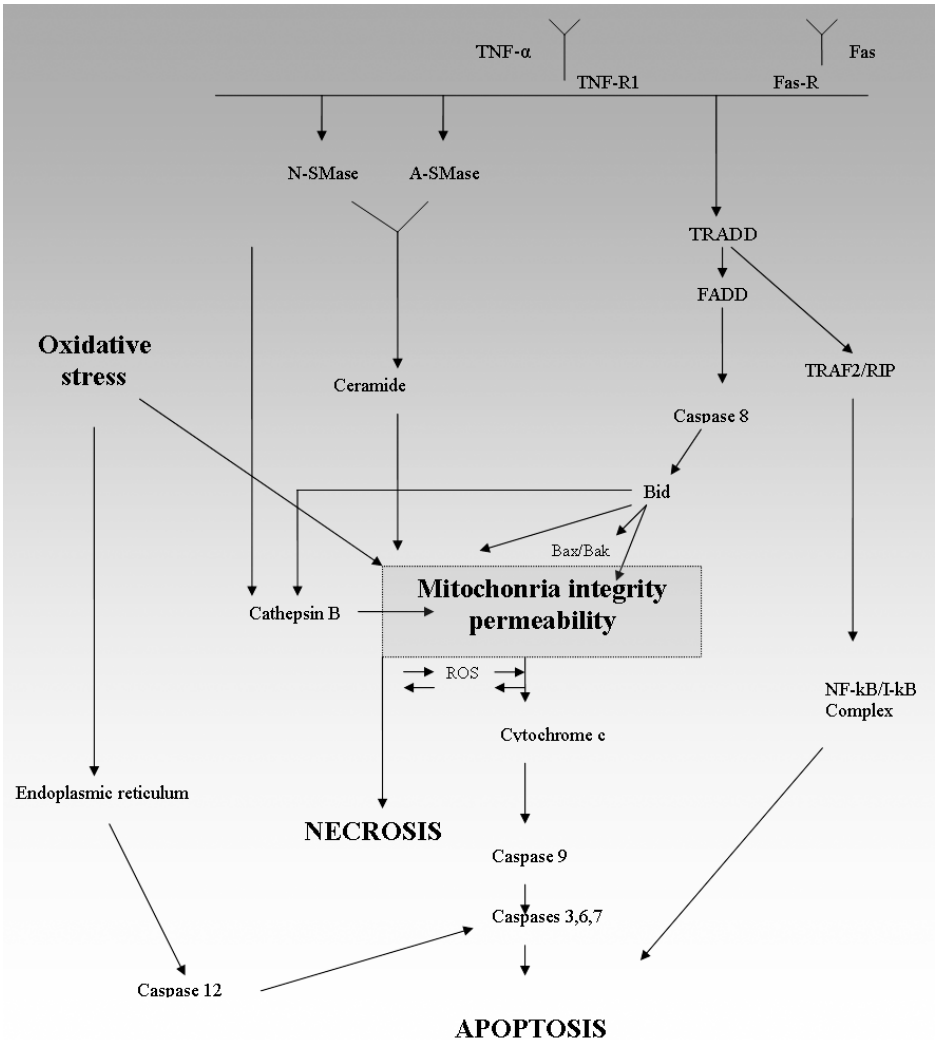

Fig. 1. Pathogenesis elucidated in ALF. Intracellular interacting signaling pathways promoting apoptotic or necrotic hepatocellular death cascade (modified from 16,4).

cals such as cyclosporine A (MPT inhibitor), Sp6001265 (JNK inhibitor) and antioxidants (MnTBAP or Trolox) may alleviate liver damage[16].

Fas receptor-Fas ligand pathway (facilitated by caspases cascade activation including caspases 3 and 8) plays a pivotal role in the pathogenesis of fulminant viral hepatitis B[28] and fulminant Wilson's disease[9]. Hepatocytes are very sensitive to Fas ligand-induced apoptosis (hepatocytes express lower constitutive levels of Bcl-2 and Bcl-x_l[29]). Hyperosmotic cell environment has been correlated with activation of JNK and consequent Fas receptor trafficking thus facilitating apoptotic pathways[30].

2.3.2 Intracellular stress

Although the pathophysiology of ALF has not been fully elucidated, oxidative stress has been in part implicated in its pathogenesis. In response to intracellular stress mitochondrial injury is required to initiate apoptosis[31,32] although in some cases intracellular stress bypass mitochondria to directly activate caspases that can secondarily cause mitochondria injury. Oxidative stress of the endoplasmic reticulum promoted by caspase 12 and disturbed calcium homeostasis can also trigger apoptosis without mitochondria interaction[33,34]. Mitochondrial oxidative stress is promoted by several factors including TNF-α, ceramide, bile acids, the microsomal cytochrome P450 enzyme system, Bid and Bax and ischemia/reperfusion[6]. Oxidative mitochondrial injury modulates apoptotic pathways consequent to opening of the MPT and release of cytochrome c and apoptosis-inducing factors into the cy-

tosol[35]. Protective effects of Bcl2, $BclX_L$ glutathione and NO have been demonstrated[6]. Heme oxygenase-1 (HO-1) is known to be induced not only by its substrate, heme, but also by various oxidative stresses, and thought to play an important role in the protection of the host from oxidative tissue injuries[36].

Accumulating evidence suggest that some degree of oxidative stress is necessary for TNF-α related apoptosis and resultant ALF due to ischemia/reperfusion injury[37]. Oxidative stress may not be directly toxic to the ischemic liver but rather act as a facilitator of TNF-α mediated apoptotic cell death. Yet in case of marked oxidative stress the proapoptotic caspase cascade is inhibited and necrosis is favoured through depletion of mitochondria ATP[6].

2.3.3. NO-iNOS

Protective effects of NO on hepatocytes have been demonstrated including microcirculation improvement (through vasodilatation), antiplatelet effects, neutrophil activation inhibition, toxic free radicals neutralization and apoptosis inhibition (S-nitrosylation of caspases related)[38]. Protective effects of NO on hepatocytes have been described in the setting of endotoxin or thioacetamide induced liver injury, hemorrhagic shock related liver failure and ischemia-reperfusion injury[4]. Conversely the cytotoxic properties of iNOS have been verified in acetaminophen induced ALF[39] attributed to the formation of peroxynitrite after a reaction of excess NO with superoxide in the setting of marked oxidative stress leading to cell necrosis[40] whereas its cytoprotective role has been elucidated in regenerative liver[41].

2.3.4. Cytokines/Chemokines and other interacting molecules

The levels of several cytokines and chemokines are elevated in various liver diseases, especially in fulminant hepatic failure (FHF). Activated macrophages may have a role in the production of these immune modulators. In the clinical setting, intrahepatic expression of IFN-γ, IL-12 and IL10 has recently been assessed in patients with ALF of various etiologies including autoimmune hepatitis, ecstacy-related hepatotoxity, cryptogenic and hepatitis B fulminant hepatitis, and an imbalance between proinflammatory (IFN-γ and IL-12) and anti-inflammatory (IL-10) cytokine mediators has been demonstrated. Increased circulating levels of IL-6, IL-8 TNF-α, soluble TNF-R1 and IL-10 have also been documented[42]. Anti-inflammatory properties of IL-10 and IL-11 have been documented in acetaminophen-induced ALF in mice whereas IL-4 and IL-13 have been implicated in protecting the liver from ischemia-reperfusion injury in experimental models[4]. CD163 is a member of a scavenger receptor family and is expressed mainly on activated macrophages. A soluble form of CD163 (sCD163) is released from activated macrophages. sCD163 levels in patients with FHF were evaluated and their clinical significance was assessed by a recently published series[43].

There have been many reports about the severity of hepatic necrosis caused by fulminant hepatitis; however, the relation between proliferated bile ductules and osteopontin (OPN) expression in inflamed areas in each of the clinical forms of fulminant hepatitis has only recently been assessed. Comparison of acute form fulminant hepatitis with the subacute form and LOHF showed OPN expression in proliferated bile ductules and serum aspartate aminotransferase $(ALT)_{max}$ to be decreased in the subacute form of fulminant hepatitis. OPN expression is an important marker of the degree of liver inflammation, and its regulation mechanism is very important to understanding the pathophysiology of fulminant hepatitis[21].

Antibodies to cardiolipin (aCLA), a phospholipid primarily localized in inner mitochondrial membranes, were transiently elevated ($P<0.01$) when mice were exposed to an industrial surfactant and then infected with influenza B virus, a model ALF. Children with ALF also had elevated levels of aCLA[44].

Serum cytochrome C levels have been correlated with serum mitochondria (m)-GOT, hepatocyte growth factor (HGF), aspartate aminotransferase (AST), lactic dehydrogenase (LDH) and alkaline phosphatase (ALP) whereas they have been also negatively correlated to serum alpha fetoprotein (AFP) and total bilirubin[45].

Finally a dominant role has been elucidated for a Ca(2+) regulated cytosolic cysteine protease that mediates crucial cellular functions, Caplain, in the progression of toxicant-induced liver damage. Evidence suggest that caplain leaking out of necrotic hepatocytes is highly activated in the extracellular milieu and hydrolyzes proteins in the plasma membrane of neighboring cells leading to progression of injury. Experimental intervention with caplain inhibitors substantially mitigates progression of liver injury initiated by toxicans, thereby preventing ALF, and toxicant induced animal death, pointing to a new potential therapeutic strategy against acute toxicities[46].

3. HEPATOCELLULAR REGENERATION

A variable degree of liver regeneration is evident in most cases of ALF with the extent of regenerative activity typically more pronounced in hyperacute than in subacute categories[4]. TNF-α and IL-6 are key initiators

of liver regeneration although TNF-α related cell death rather than regeneration dominates in the presence of oxidative stress[41]. The role of IL-6 in liver regeneration and the activity of the designer IL-6/Sil-6R fusion protein, hyper-IL-6, in particular, suggests that this molecule could significantly enhance liver regeneration in humans[47]. Elevated plasma levels of stimulatory hepatocyte growth factor (HGF) and inhibitory transforming growth factor-β (TGF-β) attributed to release from damaged extracellular matrix have been documented[48-50]. Increased activity of fibrinolytic system inducing activation of those factors has been demonstrated whereas toxins that impair HGF induced DNA synthesis by hepatocytes were also described in plasma of ALF patients[51,52]. Fatty acids[53] and phosphate metabolism[54,55] have also been interrelated with the regeneration process. Activin A, a member of the TGF-beta superfamily, inhibits hepatocyte DNA synthesis and induces apoptosis[50].

Supplementation with free fatty acids, carnitine[56] (the carrier responsible for transport of fatty acids into mitochondria), or ciprofloxacine[57] augment the rate of regeneration in experimental models.

4. SYSTEMIC INFLAMMATORY RESPONSE SYNDROME-MULTIOGRAM FAILURE

The systemic inflammatory response syndrome (SIRS) is the clinical manifestation of inflammation and therefore the end product of the activation of a normally quiescent multicomponent system comprising leukocytes, endothelial cells and mediator networks. In response to a variety of stimuli, neutrophils and monocytes transform into phagocytes with enhanced production of cytokines, enzymes and reactive oxygen intermediates, and are focused at sites of infection by chemotactic mediators and adhension molecules with resolution being affected through the compensatory anti-inflammatory response syndrome. In its most severe form SIRS reflect widespread reduction in cellular oxygen use, adenosine triphosphate depletion, cell injury and death. The varied clinical and laboratory manifestations of SIRS and sepsis in ALF patients are likely to be the result of an excessive cytokine production from cells, such as monocytes and macrophages in response in a number of stimuli, including bacterial lipopolysaccharide[58].

Liver injury induced by various pathogenic factors (such as hepatitis virus, ethanol, drugs and hepatotoxicants, etc.) through their respective special pathogenesis, is referred to as primary liver injury (PLI). Liver injury resulting from endotoxin (lipopolysaccharide, LPS) and the activation of Kupffer cells by LPS, while intestinal endotoxemia (IETM) occurring during the presence and development of hepatitis is named the secondary liver injury (SLI). The latter which has lost their own specificities of primary pathogenic factors is ascribed to IETM. More severe IETM commonly results in excessive inflammatory responses, with serious hepatic necrosis, further severe hepatitis and even induces acute liver failure. If PLI caused by various pathogenic factors through their independent specific mechanisms is regarded as the first hit on liver, then SLI mediated by different chemical mediators from KCs activated by IETM in the course of hepatitis is the second hit on liver. For this reason, the viewpoint of SLI induced by the second hit on liver inflicted by IETM suggests that medical professionals should attach great importance to both PLI and SLI caused by IETM. That is, try to adjust the function of KS(s) and eliminate endotoxemia of the patient[59].

In ALF, the SIRS, whether or not precipitated by infection, appears to be implicated in the progression of encephalopathy, reducing the chances of transplantation and conferring a poorer prognosis[58]. In fact sepsis, a major component of SIRS, exacerbates the already increased energy requirements in ALF (accelerated glycolysis, impairment of glycogen storage, reduced capacity for gluconeogenesis, reduced hepatic synthesis of insulin-like growth factor-1)[60,61] and at the same time sepsis-related oxidative stress has been shown to promote hepatocellular necrosis and inhibit liver cell regeneration[62]. What's more accumulation of toxins such as ammonia and lactate and effects of vasoactive cytokines (IL-6, IL-8) produced in response to the initiating cause of liver injury of complicating sepsis contribute to the development of multiorgan dysfunction in ALF[4].

5. PATHOGENESIS IN MOST COMMON CAUSES OF ALF

5.1 Viral-hepatitis related ALF

Acute viral hepatitis A or B leads, to ALF in less than 1% of affected patients[63,64]. Yet acute hepatitis B has been listed as the etiological agent in 20-30% of ALF cases from Europe, South Africa, and Asia whereas hepatitis A has accounted for 3-8% of cases[65-67]. Review from a series of studies conducted in the USA revealed a gradual decrease in the incidence of viral induced ALF from 32%[68] in the middle sixties to less than 10%[69] in the nineties. Review from a series of studies conducted in different geographical regions (1980-2000) demonstrated a prevalence of HBV-induced ALF ranging from 2% in UK to around 30% in France and Denmark[2]. An apparent exception is the striking geographical variation in the reported prev-

alence of ALF due to hepatitis C virus infection, with a much higher proportion of cases generally attributed to this agent in Japan and Taiwan than in Western countries. Recent work has focused on the possible importance of mutant hepatitis B viral strains, co- and super-infection with known hepatitis viruses and certain newly described agents that may account for otherwise unexplained cases of acute liver failure[70]. The prevalence of occult hepatitis B infection in patients with ALF was reported to be 30% to 50% in 3 studies that involved a total of 31 patients[71-73] but absent in 2 other studies that involved a total of 23 patients[74,75]. More rare viral causes of ALF include hepatitis E, delta virus, cytomegalovirus, herpes simplex virus and Epstein Barr virus infections.

Fas receptor/Fas ligand-induced apoptotic pathways have been elucidated in the pathogenesis of fulminant viral hepatic injury[76]. Cytotoxic T lymphocytes recognize viral antigens expressed on Fas receptor-positive hepatocytes and kill virus infected hepatocytes partially through Fas-induced activation of caspases[77]. Recently the pivotal role of mitochondrial production of reactive oxygen metabolites has been elucidated in this setting of fulminant hepatic failure[78]. Thus a pivotal role for IFN-γ has also been demonstrated in fulminant hepatitis B. Following initial signaling via the Fas receptor/Fas ligand pathway, the cytotoxic T cells secreted IFN-γ resulting in macrophage activation and a delayed-type hypersensitivity response that eventually destroyed the liver[79]. Among patients with ALF secondary to hepatitis B infection an association between mutations in the precore and core promoter region of the HBV and a fulminant course of the diseases has been indicated[80].

5.2. Drug-induced-ALF

Acetaminophen overdose is the most common etiology of ALF in the US estimated to affect 39% of ALF patients[3]. Around the world its prevalence varies greatly; 73% in the United Kingdom whereas in some countries such as Argentina, India and Japan is still not observed[2]. Although comprising only 13% of cases, the idiosyncratic drug reactions demand extreme clinical attention since they are associated with poor outcome. Prominent among these cases are isoniazid, bromfenac and troglitazone. Other agents included isoniazid, trimethoprim/sulfa, phenytoin, disulfiram, propylthiouracil herbs and a variety of drugs administered in the treatment of acquired immunodeficiency syndrome[3]. The incidence of drug-induced hepatotoxicity in the general population has recently been estimated to be around 14/100,000 inhabitants in a Western country. Drugs appear to be responsible for 10-52% of all causes of acute liver failure. The natural prognosis varies among drugs. The spontaneous mortality rate ranges from 32% to 50% for paracetamol intoxication and more than 75% for other drugs[81]. Drug-induced liver injuries often have a somewhat characteristic signature, as regards type of injury (hepatocellular vs cholestatic) and time of onset. With many drugs, intermediary products produced during metabolism are highly reactive and toxic. In these situations, the balance between the rate of production of the metabolite and the effectiveness of the drug may determine whether or not hepatic injury occurs. In acetaminophen induced ALF necrosis is the dominating death pathway enhanced by critical depletion of cellular ATP, especially in the setting of inhibition of caspase activity by marked oxidative stress.

6. MOLECULAR NEUROBIOLOGY-HEPATIC ENCEPHALOPATHY-INTRACRANIAL HYPERTENSION

Hepatic encephalopathy (HE) arising from exposure of the brain to circulating neurotoxins signifies a serious prognosis in ALF. Brain edema and intracranial hypertension are major causes of death in this syndrome. A key role for ammonia in the pathogenesis of both HE and brain edema is now firmly supported by clinical and experimental data. Additional factors, such as infection, products of the necrotic liver, and synergistic toxins, may contribute to an altered mental state. Regarding infection parameters, binding of cytokines to receptors in cerebral endothelial cells with subsequent signal transduction into the brain is a likely scenario[82]. The necrotic liver hypothesis was derived from scattered reports indicating improvement of intracranial pressure in ALF after hepatectomy[83]. In the mid-1970s Zieve and Nicoloff coined the concept of "synergistic toxins" in which a wide array of gut derived substances potentiated ammonia's deleterious effects on the brain[84]. The impact of compounds that cross the blood brain barrier and activate gamma aminobutyric acid (GABA)-ergic pathways as well as the role of serotoninergic abnormalities in the encephalopathy of ALF are aspects requesting further experimental and clinical evaluation[85]. A low plasma osmolarity, high temperature, and both high and low arterial pressure may affect brain water content. A combined derangement of cellular osmolarity coupled with cerebral hyperemia can explain the development of brain edema in ALF[85]. In patients with ALF evidence further supports the existence of a dilated cerebral vasculature and failure of cerebral autoregulation in which there is impaired brain response to systemic pressure fluctuations and changes in pCO_2[86]. More than two decades ago, the role of altered GABA-ergic neurotransmission was proposed following evidence of "increased GABAergic tone" in HE. Pathophysiological mechanisms put forward to explain increased GABAergic

tone in HE include (1) increase in brain GABA content due to increased brain GABA uptake through altered permeability of the blood brain barrier, (2) alteration of the integrity of constituents of the GRC, and (3) increase of endogenous GRC modulators such as benzodiazepines (and more recently neurosteroids) with potent agonist properties at the GRC. Studies performed subsequently excluded alterations of either GABA content or GRC integrity in favour of increased brain concentrations of endogenous agonists. While the role of endogenous benzodiazepines remains controversial, the presence of neurosteroids with GABA agonist properties affords a plausible explanation for increased GABA-ergic tone in HE[87].

Brain edema resulting in increased intracranial pressure and brain herniation is the major cause of mortality in ALF. Neuropathological investigation of brain capillaries from patients who died of ALF revealed marked swelling of astrocytes[88] indicating a dominant feature of CNS dysfunction. Increased brain ammonia may cause cell swelling via the osmotic effects of an increase in astrocytic glutamine concentrations or by inhibition of glutamate removal from brain extracellular space[89]. Compromised brain metabolism in ALF has predominately been attributed to increased brain uptake and metabolism of ammonia and amino acids, increased glycolytic flux, lactate accumulation, and alterations in the expression of gene coding for key astrocytic proteins including the glucose (GLUT-1) and glutamate (GLT-1) transporters, the astrocytic structural protein glial fibrillary acidic protein (GFAP), the "peripheral-type" benzodiazepine receptor (PTBR) and the water channel protein, aquaporin IV[90]. Loss of expression of GLT-1 and EAAT-2 results in increased extracellular brain glutamate and glycine concentrations and a limit on the capacity of glutamine synthetase to remove ammonia in acute liver failure. Experimental acute liver failure also results in post-translational modifications of the serotonin and noradrenaline transporters resulting in increased extracellular concentrations of these monoamines[90]. Magnetic resonance spectroscopic studies reveal increased brain lactate concentrations that are positively correlated with severity of encephalopathy and brain edema in acute liver failure, suggesting a deficit of cellular oxidative capacity and impending brain energy failure[91]. The role of inflammation in the pathogenesis of increased intracranial pressure (ICP) in patients with ALF and its interplay with cerebral blood flow (CBF) and ammonia were assessed in a recent study. An important synergistic role was illustrated for inflammation in the pathogenesis of increased ICP possibly through its effects on CBF[92]. Serum S100 beta levels correlated with the degree of brain edema of FHF. It has the potential to be a new clinical, non-invasive indicator of brain damage due to FHF[93].

Table 3. Pathophysiological cascade of increased intracranial pressure in acute liver failure and the therapeutic modalities (modified from[95]).

ACUTE LIVER FAILURE
1. Ammonia: Lactulose, L-ornithine L aspartate
2. Systemic inflammatory response: Antibiotics
3. Increased brain glutamine, increased vascular mediators: Phenytoin, Mannitol, continuous venovenous hemofiltration
4. Increased cerebral blood flow: Propofol, Hypothermia, Hyperventilation, Thiopentone, N-acetylcysteine
5. Liver transplantation, liver support

Increased intracranial pressure (ICP) in patients with acute liver failure (ALF) remains a major cause of morbidity and mortality. Conventional methods of ammonia reduction such as the use of lactulose do not improve outcome, and metabolic substrates such as L-ornithine L aspartate may offer more promise. Mannitol remains the mainstay of therapy. An important role for cerebral hyperemia in the pathogenesis of increased ICP has led to a re-evaluation of established therapies such as hyperventilation, N-acetylcysteine, thiopental sodium, and propofol. Recent studies have focused on the role of systemic inflammatory response in the pathogenesis of increased ICP and support the use of antibiotics prophylactically. Moderate hypothermia reduces ICP in patients with uncontrolled intracranial hypertension and prevents increases in ICP during orthotopic liver transplantation (OLT)[92]. (Table 3)

7. CONCLUSIONS

Time is of the essence in the management of patients with ALF in that rapid deterioration can be expected in such patients. Novel, fascinating aspects highlighted in the ALF research field include potential interference in apoptotic signaling pathways, in the molecular neuropathology of ALF and accumulation of factors facilitating the regeneration processes. Circulatory disturbances, coagulapathy, renal failure, respiratory distress syndrome, infection and adrenocortical insufficiency are potential therapeutic targets along with the therapeutic intervention aiming at the recognized etiological agent. A critical question has been set by R. Williams[94]; "whether toxin removal alone can interrupt the vicious cycle of liver damage and multiorgan dysfunction or is an additional function, as may be provided by living hepatocytes, required?"

Those therapeutic issues along with liver support systems and liver transplantation remain to be assessed in another review article.

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