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Losing balance : cytokine signaling and cell death in the context of hepatocyte injury and hepatic failure



Abstract

Fulminant hepatic failure (FHF) represents a clinical scenario that is associated with high morbidity and mortality, and very limited treatment options. Therefore, great efforts have been made recently on defining its biological mechanisms. This article gives an overview of the cellular processes that are linked to the loss of hepatocytes as a reaction to various agents that cause hepatic failure, and summarizes recent results from clinical and experimental studies of the role of pro- and antiapoptotic cytokines and their intracellular signaling in this context.

Full text

Introduction

Fulminant hepatic failure (FHF) represents a clinical scenario that is associated with high morbidity and mortality. It is characterized by typical clinical findings: a combination of jaundice, coagulopathy and hepatic encephalopathy.

Depending on the existence of an underlying liver disease, additional definitions are used. If the above mentioned clinical findings are seen in patients that have not suffered from chronic liver disease previously, they are defined as acute hepatic failure (AHF) [1]. In contrast, an acute deterioration of a chronic liver disease is defined as acute-on-chronic liver failure, a clinical situation that the vast majority of patients that are referred to a specialist hepatological center suffer from [2]. Fulminant hepatic failure can have very different causes. On a world-wide basis the Hepatitis B virus remains the leading cause of FHF, followed by non-A non-B hepatitis. Drugs such as paracetamol or halothane, ingestion of *Amanita phalloides*, as well as metabolic disorders, for example Wilson's disease, acute fatty liver of pregnancy, Budd-Chiari-syndrome, sepsis and ischemic hepatitis are other important etiologies of FHF [3].

Despite the advances in management and pharmacological therapy, patients very often deteriorate rapidly and progress to multi-organ failure. Up to now, liver transplantation has remained the only effective treatment option for these patients, but organ availability can be a limiting factor. Artificial liver support as a bridge to organ transplantation and hepatocyte transplantation are promising new approaches, but these therapies are still in an experimental stage and their usefulness remains to be proven. Therefore, in order to develop new and innovative strategies to treat FHF, it is important to gain a better understanding of the events that take place during FHF and to evaluate cytokines and molecular pathways that mediate hepatocyte damage during this process.

Mechanisms of hepatic damage: apoptosis versus necrosis

Hepatic failure takes place when the amount of viable hepatocytes decreases until the organ is not able to fulfil both its metabolic and synthesization functions. There are different concepts regarding how cells are driven towards

cell death. Necrotic cell death is the result of acute metabolic disruption, with ATP depletion, ion dysregulation, mitochondrial and cellular swelling and activation of degradative enzymes. This culminates in rupture of the plasma membrane and loss of intracellular proteins, metabolites and ions [4]. On the other hand, apoptosis, synonymously used for programmed cell death, is an important mode of cell death when specific cells need to be removed during development or normal tissue turnover [5, 6]. It leads to the orderly resorption of target cells without severe impairment of cellular metabolism. Its onset is triggered by specific signaling through the activation of a cascade of cysteine-aspartate proteases called caspases [7].

Excessive apoptosis has been implicated in a number of acute and chronic liver diseases, e.g. viral and autoimmune hepatitis, cholestatic disease, alcoholic or drug/toxin-induced liver injury and transplantation-associated liver damage, including ischemia reperfusion injury and graft rejection [8]. Nevertheless, both in clinical settings and especially in experimental models of liver failure, it has become evident that a clear pathological and mechanistic distinction between apoptosis and necrosis is often very difficult and might not completely represent the reality of the situation. Classical tools to detect apoptosis such as the 'Tunel-Assay' have been shown to be insufficient for clearly distinguishing between apoptosis and necrosis in the liver [9]. Furthermore, pathophysiological mechanisms such as the mitochondrial permeability transition (MPT), are common to both apoptosis and necrosis, and there is evidence that, in experimental models of liver failure, it mainly depends on the cellular abundance of ATP that determines the mode of cell death [10]. Another point that blurs the differentiation between apoptosis and necrosis is that, even though a lack of an inflammatory response is considered as one of the hallmarks of apoptosis, it was shown recently that apoptotic cell death can be equally as effective as oncotic necrosis in inducing hepatic inflammation [11]. Therefore, it should be kept in mind that pure apoptosis or necrosis might just represent extremes in the spectrum of so called "necroapoptotic" responses, and that the more typical response of liver cells to injury might be a mixture of events associated with apoptosis, necrotic cell death and inflammation.

Cell death and cytokines: TNF- α and FasL in hepatocyte injury and acute hepatic failure

Although very different agents can cause hepatocyte injury and FHF, many studies in patients and animal models have strongly suggested that soluble cell death cytokines such as tumor necrosis factor (TNF)- α and Fas ligand (FasL) are involved in the induction of apoptosis and in triggering destruction of the liver, which ultimately leads to hepatic failure. TNF- α and FasL belong to a family of nine ligands (TNF- α , lymphotoxin- α , TNF- β , FasL, OX40L, CD40L, CD27L, CD30L, 4-1BBL and lymphotoxin- β) that activate structurally related receptor proteins known as the TNF receptor superfamily. Currently, twelve different death receptors are known, including TNF receptor 1 (TNF-R1), TNF-R2, TNF-RP, Fas, OX-40, 4-1BB, CD40, CD30, CD27, pox virus PV-T2, PV-A53R gene products, the p75 NGFR, the apoptosis-signaling receptors death receptor 3 (DR3), DR4 and DR5 with their ligand TRAIL, and a nonsignaling decoy receptor TRID/DcR [12].

First described in 1989 [13], the interaction between Fas receptor and FasL has become the best-characterized extracellular system triggering apoptosis [14, 15]. Hepatocytes constitutively express Fas (APO-1/CD95). The fact that FasL is primarily expressed by activated T-cells initially suggested that this signaling pathway would have an important role in immune-mediated liver injury. However, several studies have indicated that this signaling pathway may function in a variety of injuries, including those caused by toxins [16, 17]. Accumulating data have incriminated the Fas/FasL- interaction in the pathogenesis of many liver diseases, including hepatitis and organ rejection [18, 19]. The significance of Fas antigen-mediated apoptosis in fulminant hepatic failure has been suggested by several clinical studies. Among others, Ryo *et al.* found that patients with FHF show Fas ligand expression on liver-infiltrating lymphocytes and peripheral lymphocytes. They also found significantly elevated serum levels of soluble Fas ligand in these patients when compared to healthy controls [20]. Thus, Fas-mediated apoptosis might be one of the triggers for the induction of fulminant hepatic failure. Moreover, in animal experiments, a single-dose injection of an activating anti-Fas-antibody can lead to apoptosis and cell death in parenchymal and non-parenchymal liver cells [21, 22].

TNF- α was originally identified by its capacity to induce hemorrhagic necrosis in mice tumors [23], but severe side effects led to a rejection of its use as a systemic anticancer chemotherapeutic agent [24, 25]. A very prominent effect was the direct, cytotoxic role of TNF- α for human hepatocytes, resulting in increased levels of serum transaminases and bilirubin. Since then, many clinical studies have underlined the crucial role of TNF- α in fulminant hepatic failure and

other liver diseases. TNF- α participates in many forms of hepatic pathology, including ischemia/reperfusion injury, alcoholic and viral hepatitis, and injury through hepatotoxins [26, 27, 28, 29]. Exogenous TNF- α induces fulminant liver failure and hepatocyte apoptosis in combination with other toxins [29]. TNF- α serum levels are clearly elevated in patients with FHF [30]. In another study, it was shown that serum TNF- α levels were significantly higher in patients who died than in patients who survived [31]. Recently, our group analysed in more detail the role of TNF- α in fulminant hepatic failure. We were able to show that serum TNF- α , TNF-R1 and TNF-R2 levels were markedly increased in patients with fulminant hepatic failure and that these changes correlated directly with disease activity. In explanted livers of patients with FHF, infiltrating mononuclear cells expressed high amounts of TNF- α , and hepatocytes overexpressed TNF-R1. Moreover, we found that the number of apoptotic hepatocytes was significantly increased in livers from FHF-patients, and there was a strong correlation with TNF- α expression [32]. Thus, it is very likely that the TNF- α system is involved in the pathogenesis of FHF in humans, and its significance has also been shown in several animal models of hepatic failure, e.g. in the endotoxin/D-galactosamine (GalN) and the concavalin A (ConA) model [33, 34].

FasL- and TNF- α -dependent signaling in hepatocytes: activation of upstream caspases

Fas and TNF- α facilitate programmed cell death in a similar manner. They share many signaling molecules and mechanisms, but there are some important structural and functional differences between the two pathways that have an impact on the different effects caused by the two ligands. Figure 1 gives an overview on molecules involved in these pathways. An important target of both pathways orchestrating cellular death is the aspartate-specific cysteine protease- or caspase-cascade [35]. Several different caspases are constitutively expressed in cells and are found in the cytosol as an inactive form [36]. The most prevalent caspase in the cell is caspase-3. This caspase is ultimately responsible for the majority of the apoptotic effects, although it is supported by 2 others: caspase-6 and caspase-7. Together, these 3 caspases are often referred to as the "executioner caspases" because of their role in coordinating programmed cell death. Since proteolytic cleavage generates the mature caspases, one way in which these enzymes are activated is *via* the action of proteases, including other caspases. "Upstream" caspases, such as

caspase-8 and caspase-9, are referred to as initiator caspases, indicating their role in triggering apoptosis by activating the executioners.

Signaling from death receptors to the activation of the executioner caspases varies between different death receptor ligands, but appears to be cell type-specific. The Fas-FasL interaction is the simplest example of a signaling pathway of death receptor-induced apoptosis. Upon binding of FasL to its receptor, the Fas-associated death domain (FADD) protein is recruited rapidly to the receptor's death domain (DD), a conserved protein-protein interaction motif of about 80 amino acids, *via* DD-DD interaction. This in turn leads to the recruitment of procaspase-8 via the so called "death-effector-domain" (DED) of FADD. Procaspase-8 then becomes activated to caspase-8 *via* the aggregation of 2 or more procaspase-8 molecules by a self-processing mechanism [37]. While the death domain of FADD interacts directly with Fas, another adapter protein is needed for TNF- α dependent caspase-8 activation. After TNF- α binding to TNF-R1, FADD binds TNF-R1 *via* the TNF-R1-associated death domain protein (TRADD), which then leads to procaspase-8 recruitment and activation [38].

Mitochondrial release of cytochrome c is involved in death receptor-mediated apoptosis in hepatocytes

In several studies, involvement of mitochondria in apoptotic processes has been demonstrated [39, 40]. This has also been shown for Fas- and TNF- α -mediated apoptosis. Activated caspase-8 has been shown to cleave a cytosolic protein called p22 Bid to its active form, p15 Bid, which translocates to the mitochondria as an integral membrane protein [41, 42]. This affects the mitochondria in a way that leads to the release of cytochrome c, a 12-kDa protein which normally functions in the mitochondrial electron transport chain. This process is accompanied by the so-called mitochondrial permeability transition (MPT), an abrupt increase in permeability of the inner mitochondrial membrane to solutes with a molecular mass of less than 1500 Da [43]. After cytochrome c release, caspases are activated, and the cell undergoes apoptosis. This occurs through the formation of an "apoptosome", consisting of cytochrome c, apoptotic protease activating factor-1 (Apaf-1) and procaspase-9. The apoptosome then recruits procaspase-3, which is cleaved and activated by the active caspase-9, and then released to mediate apoptosis.

When Scaffidi *et al.* characterized the events that led to activation of "executioner caspases" in Fas-mediated apoptosis, they found that the dependency on mitochondrial cytochrome *c* release varies between different cell types. Thus, they suggested the differentiation between Type 1 cells (such as the B lymphoblastoid cell line SKW6.4) and Type 2 cells (such as the Jurkat cell line). Both cell types are able to induce Fas-dependent release of cytochrome *c* and caspase-3 activation, but only Type 2 cells are dependent on mitochondria during induction of apoptosis. In contrast, Type 1 cells have developed a mechanism to bypass mitochondrial functions, as they can activate caspase 8 directly followed by caspase-3 activation, independent of MPT [44]. Bradham *et al.* first suggested that MPT is essential for TNF- α -induced apoptosis in mouse livers, and that cyclosporin A, an inhibitor of the MPT, blocks FADD-dependent cytochrome *c* release, caspase-3 activation and apoptotic nuclear morphological changes [45]. Furthermore, mice deficient for functional Bid, are protected from Fas-dependent hepatocellular apoptosis *in vivo*, and hepatocytes from these mice that are stimulated with a Fas antibody show only very reduced effector caspase activity [46]. Thus, Fas- and TNF- α -dependent apoptosis appears to be dependent on mitochondrial function in hepatocytes *in vivo* and thus hepatocytes belong to the Type 2 cells.

Activation of alternative substrates in TNF- α - and Fas-signaling

Ligand binding of death receptors does not necessarily lead to caspase-3 activation and cell death, it can also lead to activation of alternative molecules and pathways that might even have a protective role in this context. Studies of signaling through TNF-R1 for example have demonstrated the activation of both the proapoptotic caspase pathway, and the activation of the transcription factor NF- κ B. Interaction with the NF- κ B-pathway is mediated by interaction of both TNF receptors, with the receptor-associated factors 1 and 2 (TRAF1 and TRAF2) [38]. In the case of TNF-R1, the NH₂-terminal region of TRADD binds TRAF2, mediating the interaction between TRAF2 and TNF-R1. The NH₂-terminal ring finger domain of TRAF2 mediates the downstream signals that result in NF- κ B-activation. NF- κ B is normally retained in the cytoplasm through interaction with its inhibitor I κ B, and is activated by a kinase cascade [48] involving the serine/threonine kinase NF- κ B-inducing kinase and TRAF2. TNF- α -mediated NF- κ B activation is dependent on I κ B kinase-b (IKK-b) and is accomplished through I κ B phosphorylation and ubiquitin-dependent degradation of I κ B by the proteasome. The loss of I κ B binding unmask nuclear localisation signals on NF-

kB, resulting in NF- κ B translocation to the nucleus. Importantly, one study showed that NF- κ B activation by TNF- α is only mildly impaired in TRAF2(-/-) mice, suggesting that NF- κ B activation occurs *via* both TRAF2-dependent and independent pathways [49].

In the context of TNF- α mediated apoptosis, NF- κ B appears to provide survival signals whose mechanisms are under current investigation. They are presumed to involve the transcriptional induction of various apoptotic suppressors [50]. This protective role is probably reflected by the fact that, in contrast with Fas-mediated apoptosis, hepatocytes resist TNF- α -mediated apoptosis unless they are also treated with a protein synthesis inhibitor such as cycloheximide or actinomycin D [51]. Moreover, blocking of NF- κ B-activation with an adenovirus expressing a non-degradable form of I κ B α renders hepatocytes sensitive to TNF- α -mediated apoptosis [45]. Thus, simultaneous activation of NF- κ B seems to provide some kind of counterbalance to proapoptotic caspase activation in the context of TNF- α -dependent signaling. The role of NF- κ B in Fas-dependent apoptosis is controversial. Some studies have found that FADD can act as an inducer of NF- κ B, whereas a recent study has shown that FADD can actually suppress NF- κ B [52, 53]. Another study has shown a pro-apoptotic function of NF- κ B in Fas-mediated apoptosis of hepatocytes [54]. Overall, the role of NF- κ B in death receptor-mediated apoptosis has not been sufficiently explained and requires further examination.

TRAF2 also mediates the activation of the JNK pathway. JNK phosphorylates the activation domains of the transcription factors c-jun, ATF-2, and Elk-1. The role of JNK activation in apoptosis signaling is hotly debated. It has been reported that JNK activity is required for the induction of Fas-mediated apoptosis in fibroblasts and leukaemia cells. However, other results demonstrate that JNK activity is not required for TNF- α -mediated apoptosis in 293, HeLa, and MCF7 cells or Fas-mediated apoptosis in Jurkat cells [50, 55]. Interestingly, lymphocytes derived from TRAF2 (-/-) mice were sensitized to TNF- α -mediated apoptosis despite intact activation of NF- κ B, suggesting that JNK activity may play a protective role in this context [49]. Recently, several studies have implicated an interaction between NF- κ B and JNK in modulating TNF- α -dependent apoptosis. It was shown in fibroblast cells that the NF- κ B pathway negatively modulates TNF- α -dependent JNK activation, partly through the NF- κ B-induced X-chromosome-linked inhibitor of apoptosis (XIAP) [56]. Another study demonstrated that the protective mechanism of NF- κ B is mediated in part

by the transcriptional upregulation of *gadd45b/myd118* and consecutive downregulation of JNK signalling, thus assigning JNK a proapoptotic role in TNF- α induced apoptosis [57]. This proapoptotic role was underlined in a hepatocellular cell line, where inhibition of NF- κ B signaling led to prolonged JNK activation in response to TNF- α , whereas inhibition of the JNK substrate c-Jun blocked cell death from NF- κ B inactivation and TNF- α stimulation [58]. However, our group demonstrated recently in hepatoma cells that inhibition of JNK activity by adenoviral vectors expressing dominant negative TAK1, results in an earlier and stronger induction of TNF- α -dependent apoptosis [59]. Taken together, the function of JNK signaling in TNF- α -mediated apoptosis remains controversial and might be influenced by the experimental setting and the cell line used. At this point, more *in vivo* studies in experimental models of liver failure are needed in order to gain an insight into JNK function.

IL-6: a protective cytokine in the context of liver failure ?

IL-6 belongs to a family of cytokines comprising of IL-6, IL-11, leukaemia inhibitory factor (LIF), oncostatin M, ciliary neurotropic factor, novel neurotrophin-1/B cell stimulating factor-3 and cardiotropin 1 [60]. IL-6 binds to hepatocytes by interacting with an 80-kd membrane glycoprotein (gp80) that complexes with a signal transducing molecule named gp130 (Figure 2A). Binding of gp130 leads to dimerization of the intracellular domains of two gp130 molecules, which promotes association with receptor-associated Janus kinases (JAKs; JAK1, JAK2, and TYK). The JAKs become activated, and phosphorylate different tyrosine residues of the gp130 molecule. Depending on the location of the phosphorylated tyrosines, signal transducers and activators of transcription (STAT) proteins (mainly STAT-3) and also the Ras/mitogen-activated protein (MAP) kinase pathway, become activated and mediate the numerous downstream effects mediated by the signaling of IL-6 and related cytokines (Figure 2B) [60].

In the liver, it has been suggested that IL-6 is one of the key regulators of the initial steps of liver regeneration [60]. An important role of IL-6-dependent signaling in the liver is also attributed to the induction of the acute phase response [61, 62]. In terms of apoptosis, many experiments have shown a role for gp130 in promoting antiapoptotic effects in different cell types. Activation of STAT3 in B cells and human myeloma cells causes activation of antiapoptotic genes such as *bcl-2* and *bcl-xl*, and protects these cells from Fas-dependent

apoptosis [63]. Similar results were found in T cells. STAT3-deficient T-cells were severely impaired in IL-6-induced proliferation, which was due to the profound defect in IL-6-mediated prevention of apoptosis. In hepatocytes, IL-6 protects from transforming growth factor- β (TGF- β)-induced apoptosis by blocking TGF- β -induced activation of caspase-3 *via* rapid tyrosine phosphorylation of phosphatidylinositol 3 kinase (PI 3 kinase), which constitutively activates the protein kinase Akt [64].

In humans, there is strong evidence that IL-6 is directly involved in the pathogenesis of different diseases, including multiple myeloma and congestive heart disease [65, 66]. Recently, our group analysed the potential role of IL-6 in the development of acute and chronic liver injury in humans and examined the pathophysiological basis in animal models. We found a direct correlation of IL-6 expression in serum and liver tissue with disease progression in FHF patients. Additionally, we could show abolished acute phase response and an increased susceptibility to LPS-induced liver injury in mice deficient for functional gp130 in hepatocytes [67, Streetz *et al.*, submitted for publication]. Therefore, IL-6 might have a protective function in hepatic failure.

Cytokines and liver failure: imbalance of pro- and antiapoptotic signals

This article summarizes the effect of different cytokines that are involved in the context of hepatocyte cell death in clinical and experimental settings. Although it is very likely that many cytokines and signaling pathways other than those mentioned above are involved in the pathogenesis of hepatic failure, it becomes more and more obvious that hepatic failure might represent the dysregulation of hepatic homeostasis as a result of an imbalance between damaging and protective mechanisms that are very tightly regulated under physiological conditions. This balance is reflected not only at the cytokine level, where proapoptotic cytokines such as Fas and TNF- α appear to be counteracted by protective cytokines such as IL-6, but also at the molecular level, where intracellular TNF- α signaling recruits both the proapoptotic caspase-cascade and NF- κ B as a protective factor.

A possible aim of future experimental therapies could be to shift the disturbed endocrine and cellular environment towards protective signals. Promising experimental approaches have been adopted to both exaggerate protective signals and to diminish damaging signals. In a gene therapy approach, it was

shown in experimental models of liver failure that a dominant negative FADD adenovirus could block apoptosis in mouse livers *in vivo* [32]. Also, pharmacological inhibitors of caspases, such as the caspase-8 inhibitor IETD-CHO and the caspase-3 inhibitor DEVD-CHO, have shown beneficial effects in experimental, *in vivo* models of TNF- α - and Fas-induced liver failure [22, 68]. Finally, the artificial protein hyper-IL-6 was designed by covalently linking IL-6 to soluble gp80 [69]. This artificial molecule causes a 10-fold increase in STAT3-dependent gene transcription (haptoglobin) in hepatocytes *in vitro* and *in vivo*, indicating a promising role for this designer cytokine in influencing pathophysiological conditions [70]. In conclusion, these or similar approaches might be promising candidates for future drug therapies for hepatic failure.

This work is supported by a grant of the Deutsche Forschungsgemeinschaft (DFG Tr. 285/4-1 and SFB 566,B08)

Accepted on 1st August 2002

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Figures

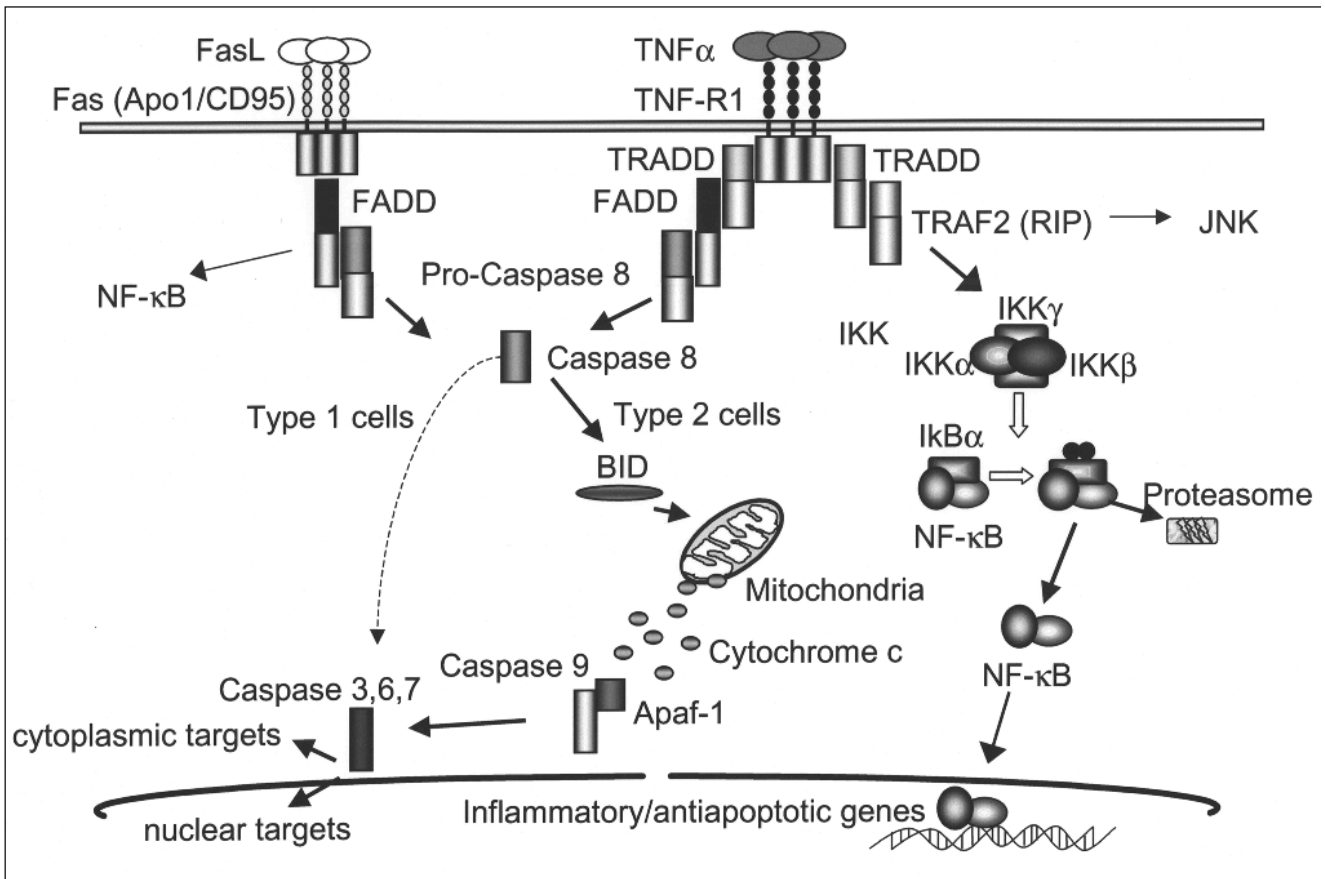


Figure 1 : FasL- and TNF- α -dependent signaling in the liver.

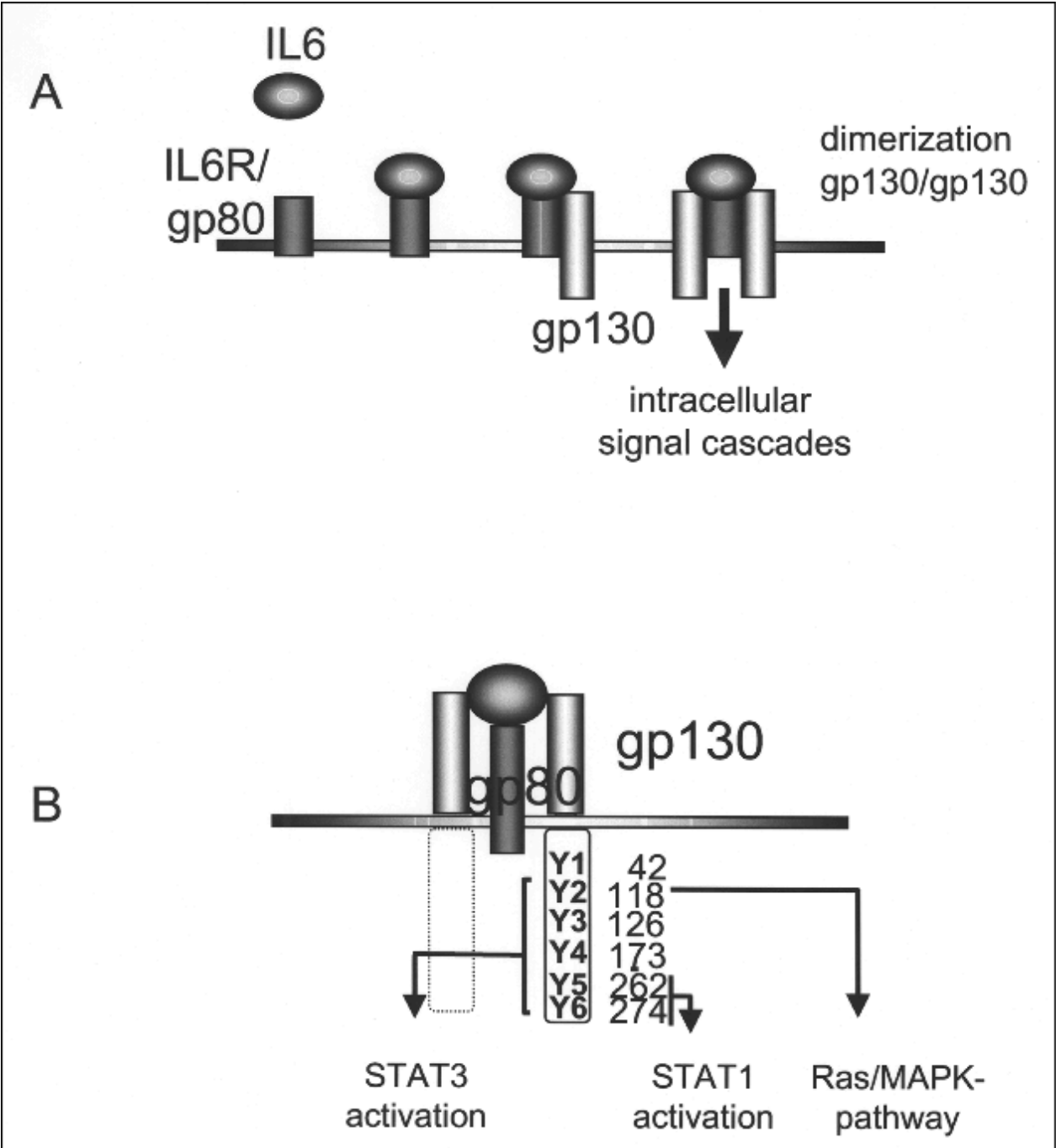


Figure 2 : IL-6-dependent signaling
A: IL-6 binding and receptor dimerization, **B:** Signal transduction through gp130

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