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DIFFERENTIAL CYTOKINE PROFILES IN PATIENTS WITH VIRAL AND NON-VIRAL RELATED LIVER CIRRHOSIS

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Cytokines are pleiotropic peptides that are produced by nearly every nucleated cell in the human body. The liver is one of the most affected tissues. Hepatic inflammation, apoptosis and necrosis of liver cells, cholestasis, fibrosis, and cirrhosis are all mediated by cytokines. Interleukins (IL) like IL17 and IL10, the tumour necrosis factor (TNF) family of cytokines like TNF-α, chemokines like IL-8, and others are representing these cytokines. There is growing evidence that numerous cytokines play a key role in various aspects of liver disorders caused by viruses such as hepatitis C and B viruses, as well as non-viral liver diseases like autoimmune liver disease, Budd-Chiari syndrome, and other non-viral liver diseases. Biological response of cytokines involved in inflammation and cirrhosis may have an impact on the prognosis of certain disorders With respect to acute and chronic liver diseases. The present state of cytokine thoughts and functions in the pathogenesis of liver diseases, with a focus on liver cirrhosis, is discussed in this review.

INTRODUCTION

Cytokines and their role in liver damage
Definition

Cytokines are proteins or peptides that are produced by cells, primarily immune cells, as a result of a stimulus. The main functions of cytokines are to regulate immunological responses and to influence the behavior of various cell types by modulating proliferation, differentiation, and activation[1]. Cytokines are engaged in nearly every function of inflammation and immunological responses, from the stimulation of the innate immune response to the production of cytotoxic T cells and the manufacture of antibodies by the humoral immune system[2]. They also work with the rest of the body to coordinate immune system operations. There are many classes of cytokines as interleukins (ILs), interferons (IFNs), transforming growth factors (TGFs), tumor necrosis factors (TNFs) and colony-stimulating factors (CSFs)[3].

Role of cytokines in immune response activation and immunomodulation

Cytokines are best known for their roles in inflammation, immunological response, tissue repair, and organ failure[4]. The needed immune response is formed by the modulation and balance of T-helper 1 (Th1) and T-helper 2 (Th2) cell types. Th1 and Th2 cells modulate various immune response pathways, which is adapted to human immunity. Th-1-driven cellular immunity is the initial line of defense against viruses and other intracellular pathogens, as well as the elimination of malignant cells. Th2 cells are responsible for the type-2 humoral immune system, allergy responses, and up-regulation of antibody production in the fight against external pathogens, such as parasite eradication[5].

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Overactivation of any pathway can result in disease, and each pathway can suppress the other[6].

Th1 cells secrete a wide range of cytokines, including IL-2, IFN-α and IL-12, Th2 cells, on the other hand, produce IL-5 and IL-4. Other cell types release equivalent levels of IL-10. Previously, it was considered that IL-10 was the primary mechanism by which Th1 cells is down-regulated by Th2 cells[7]. Th1 cytokines behave as pro-inflammatory mediators which affect the pathophysiology of numerous disorders, particularly liver damage. IL-12 and IFN-γ, for example, are well-known pro-inflammatory Th1 cytokines. They, together with TNF-α, IL-6, and IL-1β, play an important role in the human defense against bacterial infections in the liver[8]. Furthermore, a large number of cytokines have anti-inflammatory effects, including IL-1 receptor antagonist (IL-1Ra), IL-22, transforming growth factor-β (TGF-β) and the most important anti-inflammatory cytokine IL-10[9]. When confronted with an infectious agent, the balance of anti-inflammatory/pro-inflammatory cytokines is disrupted. Anti-inflammatory cytokines are down-regulated as a result of pro-inflammatory cytokines being over-regulated. This occurrence indicates the severity for disease[10]. As a result, the immune system regulatory process aims to restore cytokine balance to normal homeostatic levels with no increase or decrease of any of them. Although Th1/Th2 regulation is extremely complicated, its value in the research of various illnesses and autoimmune disorders cannot be overstated. Trying to define all of the mechanisms that control these processes, as well as the use of immunomodulatory compounds, will aid the development of therapies to control Th1/Th2 balance during diseases[11].

Helper T cells have four types of cells which are :Th1, Th17,Th2, and Treg cells based on their biological properties[12].

Tregs are a type of T cell that make up roughly 5-10% of CD4+ T cells in the peripheral circulation[13]. Treg cells mainly express FOXP3, CD4, and CD25. FOXP3 is the transcription factor that is specific to Treg cells. As a result, Treg cells are frequently described as CD4+CD25+FOXP3+ cells.[14]. Treg cells function in the regulation of immunological tolerance in the body to maintain normal immune responses in a normal physiological condition[15]. In a study of hepatic fibrosis caused by the hepatitis C virus, Claassen et al. observed a substantial number of Treg cells in the liver, and a higher number of Treg cells was connected to less severe liver fibrosis, suggesting that Treg cells may act as a fibrosis inhibitor[16]. These cells not only contributed to the cause of liver cirrhosis, but also worked as a positive regulator, avoiding liver fibrosis as the disease advanced. Treg cells' anti-hepatic fibrosis function is most likely linked to IL-10 production[17] . Treg cells release IL-10, a key immunosuppressive agent. It protects liver cells and fights hepatic fibrosis and hepatocellular damage[18]. The anti-liver fibrosis effect of IL-10 may be mediated by one or more of the mechanisms listed below: (1) L-10 inhibits HSC activation by inhibiting or down-regulating TNF, PDGF, and COX-2 synthesis in liver tissues; and (2) TGF1 stimulates HSCs to make collagen fibers, while IL-10 inhibits TGF1I expression, preventing fibrosis. (3) IL-10 reduces the proliferative response in acute liver damage, reducing the development and progression of liver fibrosis[19].

In contrast to Tregs, Th17 cells have important role in inflammatory responses, autoimmune disorders, malignancies, and infectious diseases. By mobilizing, attracting, and activating neutrophils, IL-17 increases inflammation and the advancement of autoimmune diseases[20]. According to Sun et al., an increase in Th17 cells in the liver of individuals with hepatitis B-associated liver cirrhosis supported an increase in HSC activity, which finally led to cirrhosis deterioration[21]. According to a study by Sparna *et al.*, the more severe the liver fibrosis is, the more Th17 cells are detected, suggesting that Th17 cells may have a role in the progression of liver fibrosis[22].

Treg and Th17 are related to progression of liver cirrhosis, and they collaborate on differentiation and development, but they are constrained by one another. The discovery of a relationship between Treg and Th17 cells and liver cirrhosis will aid researchers in better understanding how liver diseases arise[12].

Cytokines' role in liver damage

Cytokines have been linked to the development and progression of chronic liver disease. The liver is essential for cytokine metabolism. All cells in the liver can create cytokines, which stimulate neighboring cells (paracrine effect) or stimulate themselves (autocrine effect), resulting in increased cytokine production and an inflammatory response[23]. Whereas certain cytokines release from the resting cells of the liver, the levels and types of cytokines produced by stimulation by a range of inducers, such as LPS, viruses, chemical agents, malignancies, hepatic ischeemia and alcohol intake, are raised substantially after stimulation[24].

Several cytokines appear to be engaged in developing liver diseases, according to emerging research[25]. Data suggests that, in liver fibrosis transforming growth factor (TGF- β) plays a major role. IL-1β, 6, 8, TNF-α, and IFN-γ, on the other hand, appear to have a role in hepatic inflammatory responses. Neither IFN- nor IL-10 can reverse fibrotic/inflammatory processes, according to the findings. Furthermore, Although the relationship between persistent hepatocellular damage, hepatic inflammation, and cirrhosis has yet to be fully elucidated in chronic liver disease, cytokines may represent the common thread connecting these disparate clinical outcomes[26].

Liver cirrhosis

Definition

Cirrhosis is a widespread process characterized by fibrosis and the production of nodules. Cirrhosis is the end result of the fibrogenesis[27]. Cirrhosis is modification of the liver morphology characterized by the full destruction of its normal structure as a result of the production of nodular patches of hepatic parenchyma surrounded and separated by fibrous septa, both of which implicate the entire organ[28].

Cirrhosis is an irreversible transformation because the changed hepatic architecture does not reverse following complete and protracted cessation of the damaging agent/s' action. Altered functions may remain compensated for variable lengths of time. Still, in due course, they decompensate, and end-stage complications occur, which become fatal. The worst of these complications is the development of hepatocellular carcinoma (HCC), one of the most fatal cancers in humans[29].

Cirrhosis etiologic types and other end-stage CLD

Cirrhosis mostly caused by environmental agents and causes. Cirrhosis was previously thought to be the result of a protein deficit in chronic alcoholics and the impoverished population of poor countries until the mid-1960s. Alcohol is directly hepatotoxic, and protein-calorie malnutrition does not produce cirrhosis, it was discovered soon after. The identification of the hepatitis B virus (HBV) was a huge step forward in the fight against cirrhosis, and chronic HBV infection caused the majority of CLD and HCC in underdeveloped nations and a smaller proportion in industrialized western countries by the mid-1970s[30]. The extensive use of blood transfusions, combined with increased intravenous drug addiction, led to a rapid rise in HCV-related CLD and HCC in the post-World War II period. HBV-related diseases have declined after control methods for this virus infection, such as vaccination, by the early twenty-first century. HCV-related CLD reduced in industrialized countries while rising in other parts of the world, while HBV-related CLD decreased just slightly[28].

Alcoholic, non-alcoholic steatohepatitis (NASH), and viral cirrhosis, particularly hepatitis C, are all becoming more common in Western countries. Hepatitis viruses B and C are the most common causes in underdeveloped countries. CLD has always had a minor number of intrahepatic biliary tract disorders and autoimmune liver disease. Cryptogenic Cirrhosis is a condition for which the cause is unknown. It is a diagnosis of exclusion[28]. There is a wide number of CLD caused by non-alcoholic fatty liver disease (NAFLD), most of which clinically present as cryptogenic[28&31&32].

Hepatitis B virus-related cirrhosis

Identification of HBV as etiology

The presence of markers of HBV in blood and virus components in the liver tissue are used to make the diagnosis of HBV-related chronic liver disease. The presence of IgG class antibody indicates a previous infection, whereas a current infection is proven by detection of HBsAg. Current infection also proven by detection of HBeAg and HBV DNA as they indicate the presence of active replication of the virus, and the titer of HBV DNA is indicative of the degree of viral replication. In the liver, HBV is randomly distributed in hepatocytes[33]. Therefore, the absence of HBV viral components in liver biopsy does not exclude the presence of the virus in the hepatocytes, as they are or were seen in about 1/50,000 part of the organ[32].

Prevalence and temporal changes

In the mid-1970s , the serological tests for diagnosing HBV infection became accessible and widely used, the prevalence of HBV-related cirrhosis began to be recognized. It was quickly discovered that this viral infection is widespread over the world[34]. These infection rates are mirrored by the prevalence of HBV-related cirrhosis. HBV is transmitted through the hematogenous pathway. Adults who are not immunized can develop acute icteric or non-icteric hepatitis, and most of the patients recover spontaneously and generate an immune response. Only 2-5 percent of infected adults develop chronic hepatitis, which can lead to cirrhosis[35].

From the beginning of 1950s till mid-1990s, the usage of blood transfusions and intravenous drug misuse was widespread and led to increase in HBV infection and liver diseases. At the end of the twentieth century, 2 billion individuals were infected with HBV, 350 million of them were HBV carriers, and 0.5 to 1.2 million people died each year from HBV-related chronic hepatitis, cirrhosis, and HCC. Hepatocellular carcinoma caused by HBV caused about 350,000 deaths per year[36].

Strategies to control and prevent HBV were very important as obligatory vaccination of infants, this will reduce the danger and spread of HBV related cirrhosis and HCC. Liver fibrosis that is prior to liver cirrhosis can be reversed by treatment of HBV. Antiviral drugs and combination therapies are now used to control the HBV infection. Using these drugs in addition to control measures will help in reduction the prevalence of HBV related cirrhosis and HCC[37].

Hepatitis C virus related cirrhosis

Evolution of knowledge

HCV, an RNA virus, can lead to chronic hepatitis, cirrhosis, and HCC. HCV and HBV have several differences in their biological interactions with the host. HCV enters the human body entirely by the hematogenous pathway, primarily through blood transfusions, to a lesser extent through intravenous drug misuse, and very rarely through maternal-perinatal transmission (unlike HBV). HCV infection typically starts much later in life than HBV infection. The beginning of injury of liver by HCV is mainly so mild that mostly shows no symptoms. about 85 percent of individuals suffering from HCV infection develop chronic inflammation, which will proceed to cirrhosis and HCC if not properly treated[38,39].

Identification of HCV as etiology

The confirmation of the role of HCV in CLD is based on detection of the virus infection markers on specific immunological tests in the absence of evidence for other causes. These include anti-HCV antibody and HCV RNA, the anti-HCV antibody is specific as it represents active virus replication. Also, as in the case of HBV DNA, the quantitative assay of HCV RNA units would indicate the degree of virus replication. blood transfusion or intravenous drug misuse is the most common route of HCV transmission, so previous history is additional important proof[40].

In cirrhosis and chronic hepatitis, lymphoid cell aggregates scattered randomly in the fibrous septa are found in the liver in about 85% of these patients. This morphologic characteristic was found in 85.6 percent of HCV seropositive cases versus 13.2 percent of HCV seronegative cases of patients with end-stage CLD who underwent living donor liver transplantation. The other microscopic evidence is focal macro-vesicular fatty change of hepatocytes[41].

Non-alcoholic fatty liver disease related cirrhosis

Patients suffering from chronic liver disease with morphologic alterations of alcoholic hepatitis were termed NASH in the early 1980s[42, 43]. Pathologic changes in hepatic biopsy were found and the defect ranged from steatosis through steatohepatitis to fibrosis[32, 44, 45]. The preferred name for the disease became NAFLD with NASH being the only one of the more important stages in its progression. Increased prevalence of NAFLD is mainly due to lifestyle changes causing diabetes prevalence and obesity.

Autoimmune diseases and cirrhosis

Autoimmune hepatitis is a chronic inflammatory disease that attacks the hepatocytes directly in contrast to the two cholestatic AILDs. Autoimmune hepatitis can appear at any age, mainly in females, although the two peak ages of occurrence are during childhood or adolescence and around the age of 40[47]. Elevated aminotransferase levels, autoantibody positivity, and increased IgG are all biochemical and serological features of autoimmune hepatitis. Autoantibody positivity is a key clinical characteristic of autoimmune hepatitis, allowing for quicker identification and differentiation between two kinds of the illness. Patients with autoimmune hepatitis type-1 have ANA and/or anti-smooth muscle autoantibodies (SMA), but those with AIH type-2 have anti-liver kidney type-1 autoantibody (anti-LKM-1) or anti-liver cytosol type-1 (anti-LC-1)[48,49]. Although the etiology of autoimmune hepatitis is unknown, available research clearly suggests that hereditary and environmental factors interact. The discovery that the hepatitis C virus shares a significant degree of sequence homology with cytochrome P450-2D6, the auto-antigenic target of anti-LKM-1 autoantibodies, has led to the theory that molecular mimicry could cause autoimmune hepatitis in genetically susceptible individuals[50]. Hepatitis B virus, cytomegalovirus, and herpes simplex virus are all potential triggers for autoimmune hepatitis[51].

Budd–Chiari syndrome and cirrhosis

The Budd–Chiari syndrome is a condition that affects humans. According to EASL standards, Budd–Chiari syndrome (BCS) is defined as obstruction of the hepatic venous outflow system in the absence of right-sided heart failure or constrictive pericarditis. Lesions in the large or small hepatic veins (HV) or the suprahepatic section of the inferior vena cava can cause BCS (IVC)[52]

Acute, subacute, chronic, and fulminant Budd-Chiari syndrome are the four clinical variations. Abdominal pain, ascites, and hepatomegaly describe the acute type, which lacks indications of portal hypertension. Fulminant hepatitis can complicate this kind. Regardless of the cause, the chronic form is difficult to distinguish from cirrhosis. The symptoms of acute BCS with portal hypertension describe the subacute variant. It is the outcome of a prior thrombosis progression[53].

The extent and rapidity of hepatic-vein blockage, as well as whether a venous collateral circulation has established to decompress the liver sinusoids, determine the clinical appearance of the Budd–Chiari syndrome[54]. Thrombosis of all main hepatic veins is common in acute Budd–Chiari syndrome, while only one-third of patients have it in sub-acute Budd–Chiari syndrome. The chronic type is manifested as cirrhosis problems[55].

Cryptogenic cirrhosis

Cirrhosis or end-stage CLD are diagnosed in cryptogenic cases where no known cause or causes can be established, meaning that the cause is unknown at the time. As awareness of the different causes of chronic liver illnesses and the probability of cirrhosis progression has increased, this part of "cryptogenic cirrhosis" has diminished over time. The proportion of this group in developed countries has decreased from over 20% in the mid-1990s to around 5% in recent years[56]. Currently, it is recognized that certain cases of NAFLD proceed to cirrhosis, and some cases formerly categorized as "cryptogenic" have been diagnosed as NAFLD[32&56].

Immunological dysfunction in cirrhosis
Innate immune dysfunction

IL-1, IL-3, IL-6, TNF-, transforming growth factor (TGF-), IFN-, and other cytokines are cleared mostly through the liver. Cirrhosis, on the other hand, causes the liver to be unable to remove cytokines, resulting in continuous activation of neutrophils in the peripheral circulation[57] and subsequently impair the neutrophils functions like migration and phagocytosis[58]. In addition, higher endotoxin absorption and bacterial translocation result in a long-term rise in cytokines. Removing endotoxins in vitro[59] and reducing endotoxemia in vivo with probiotics[60] enhances the function of polymorphonuclear leukocytes in cirrhosis.

Cirrhosis impairs innate immunity by lowering the bactericidal potential of the organism by compromising the development and function of pattern recognition receptors (PRRs) and other proteins[61]. PRRs recognize a variety of pathogen-related molecular patterns (PAMPs). TLRs (Toll-Like Receptors) are the most well-studied PRRs, and they play an important role in cirrhosis-related immunological dysfunction (CAID)[62-64]. The acquired modification of TLRs and associated signaling pathways is a significant cause of innate immune failure in cirrhosis[65].

Reduced monocyte HLA-DR expression, often known as immune paralysis, is a well-known feature of acute liver failure and septic shock. It was also recently detected in people with liver cirrhosis. Anti-inflammatory cytokines like IL-6 and IL-10 are up, while pro-inflammatory cytokines like IL-1 and TNF- are down, causing immunological paralysis[66].

Immunomodulatory agents such as the granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon-gamma (IFN-γ) can improve monocyte functions and should be investigated further[67]. Endotoxemia, through an IL-10-mediated mechanism, may lead to HLA-DR downregulation in cirrhotic patients. Low levels of proinflammatory cytokines including TNF and nitric oxide synthase, as well as allostimulatory activity, were found in monocytes with low HLA-DR expression[68].

Classical CD14+CD16 monocytes and non-classical CD14+CD16+ monocytes are the two types of monocytes. In individuals with chronic liver disease, there is a considerable increase in the non-classical subsets, which is linked to collagen-producing hepatic stellate cell activation, pro-inflammatory cytokine production, and clinical progression[69]. A low lymphocyte-to-monocyte ratio has been postulated as an independent prognostic marker in liver cirrhosis[70]. (sCD163) is the soluble form of CD163 marker which is responsible for macrophage activation and it is released in the circulation[71]. It rises with the Child-Pugh score in cirrhosis and has a strong relationship with the hepatic venous pressure gradient, and hence with portal hypertension[72]. Waismann et al.[73] showed that sCD163 had an independent risk factor for death and variceal bleeding in cirrhotic patients, highlighting the possibility of its future development as a new pharmaceutical target. Cirrhotic patients' peritoneal macrophages have been found to produce nitric oxide and angiogenic peptides, which have been linked to SBP in the study[74].

Finally, Tonan et al.[75] reported that Kupffer cell failure contributes to the etiology of non-alcoholic steatohepatitis, since CD14-positive Kupffer cells increase along with necroinflammation grade and fibrosis stage. Cirrhotics also have problems with neutrophils, which are the first line of defense against bacterial infection. On the one hand, this impairs neutrophil delivery to the infective center, while on the other hand, it results in lower neutrophil phagocytic activity as compared to those in the healthy population[67].

Adaptive immune dysfunction

Cirrhotic individuals frequently experience adaptive immune dysfunction. It has long been known that alcoholic liver disease produces several abnormalities in B and T cell activity. In patients with alcoholic liver illness, Nourieta et al. discovered a widespread deficiency of T cells and hyperactivity of B cells. These individuals have circulating IgG and T lymphocytes that identify epitopes against antigens formed from lipid peroxidation, as well as an increase in hepatic synthesis of proinflammatory cytokines and chemokines[76]. Doi et al. found that memory CD27+ B cells were reduced in the peripheral blood of cirrhotic patients, regardless of the cause, and that this reduction resulted in poor TNF- and IgG production, vaccination hyporesponsiveness, and susceptibility to bacterial infection[77].

Because Th1 lymphocytes express antifibrotic cytokines and Th2 lymphocytes express profibrotic cytokines, the Th1/Th2 lymphocyte ratio is critical. Cirrhosis causes an increase in CD8+ cells, which lowers the CD4+/CD8+ cell ratio and favors the fibrogenic process[78]. A study performed by Marquez et al.[79] showed that in patients with liver cirrhosis, the immune system's monocytes and T cells are severely disrupted. Importantly, in cirrhosis, T cells are activated for a longer period of time as a result of the prolonged antigenic input. Apoptosis markers and activation-induced cell death (AICD) are increased in activated CD4+ and CD8+ cells, apparently to maintain lymphocyte homeostasis. Cirrhotic patients have higher levels of the apoptotic marker CD95+ in their memory cell population than healthy controls. These T cells are unable to proliferate after receiving a new antigenic load, resulting in immunological suppression due to the exhaustion of the adaptive immune response[80].

Cytokines and treatment of inflammatory liver diseases

Most acute and chronic liver illnesses are characterized by inflammatory processes characterized by elevated expression of many pro- and anti-inflammatory cytokines in the liver. These cytokines are responsible for a variety of inflammatory liver diseases, including fibrosis and cirrhosis. Many cytokines are thought to play a role in various aspects of inflammatory liver disease and liver tissue repair, according to accumulating evidence.(Table 1)[81].

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Table 1: Summary of cytokines involved in inflammatory liver disease[81]

Group of cytokine	Example of cytokine	Effect
Proinflammatory cytokines	Cytokines of the interleukin-1 (IL-1) type (IL-1 α, IL-1 β, TNF- α)	They're pro-inflammatory cytokines that help with protein synthesis in the acute phase.
	Interferon-g (IFN-γ)	immunoregulatory T-helper cell (Th)1 cytokine, induces TNFα
	Interleukin-12	Th-1-directing cytokine
	Interleukin-18	IFN-g-inducing factor, proinflammatory at a very early step in the immune response
Anti-inflammatory cytokines	IL-1 Receptor antagonist	member of the IL-1 family; blocks binding of IL-1 to cell-surface receptors, prototype anti-inflammatory cytokine
	Soluble IL-1 receptor type II	binds circulating IL-1
	Soluble tumor necrosis factor receptor (TNFR) p55 (I)/p75 (II)	naturally occurring TNF inhibitors, comprised of extracellular domains of the two known TNFRs, p55 and p75, block TNF-regulated inflammatory processes
	IL-18 binding protein	neutralizes IL-18
	Gp130-signaling cytokines (IL-6, IL-11, leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, cardiotrophin)	pro- and anti-inflammatory activities, stimulation of most acute phase proteins. IL-6 regulates hepatic regeneration and immunoglobulin synthesis
	Interleukin-10	prototype anti-inflammatory cytokine, regulates B-cell function
	IL-4, IL-13	Th-2 cytokines, regulate B-cell function, suppress synthesis of proinflammatory cytokines
	Adiponectin	adipokine – induces anti-inflammatory cytokines (IL-10, IL-1RA) and suppresses endotoxin induced TNFa expression
Cytokines involved in immune responses	IL2, IL-4, IL-7, IL-9, IL-12, IL15	
	Th-1 cytokines (IL-2, IFN-γ)	direct anti-viral response, proinflammatory
	Th2-cytokines (IL-4, IL-5, IL-10)	mediate inflammation, allergic responses and immunoglobulin synthesis
Cytokines involved in acute liver failure	TNF and TNFR p55/p75	
	Death receptors (Fas, Fas ligand)	critically involved in liver injury and apoptosis
	IL-18	mediates TNF-and Fas-related experimental liver failure
Fibrogenic cytokines	Transforming growth factor-b	Prototype fibrogenic cytokine, upregulation by proinflammatory cytokines ,Platelet derived growth factor (PDGF) and Fibroblast growth factor (FGF)
Antifibrogenic cytokines	Hepatocyte growth factor (HGF)	anti-fibrogenic ,anti-apoptotic and promotes liver regeneration
	Interferon-a (IFN-α)	anti-viral, immunomodulatory, anti-inflammatory, anti-fibrogenic

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مظاهر التباين في السيتوكينات لمرضى تشمع الكبد الفيروسي والغير فيروسي

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السيتوكينات عبارة عن ببتيدات تنتجها الخلايا في معظم الأنسجة ، بما في ذلك الكبد. هناك أدلة متزايدة على أن العديد من السيتوكينات تتوسط في الالتهاب الكبدي وموت الخلايا المبرمج ونخر خلايا الكبد وتليف الركود الصفراوي وتليف الكبد. تتضمن هذه المجموعة المتنامية من الببتيدات الإنترلوكينات مثل IL10, IL17 ، وعائلة عامل نخر الورم ((TNFمن السيتوكينات مثل TNF-α ، والكيموكينات مثل IL-8 وغيرها. هناك أدلة متزايدة تدعم دورًا رئيسيًا للعديد من السيتوكينات في جوانب مختلفة من أمراض الكبد التي تسببها الفيروسات مثل فيروس التهاب الكبد C وفيروس التهاب الكبد B أو أمراض الكبد غير الفيروسية مثل أمراض الكبد المناعية الذاتية ومتلازمة Budd-Chiari وغيرها من الأمراض غير الفيروسية. أما فيما يتعلق بأمراض الكبد الحادة والمزمنة ، فإن الاستجابة البيولوجية للسيتوكينات المشاركة في الالتهاب وتليف الكبد قد تؤثر على نتائج هذه الأمراض. تصف هذه المراجعة مفاهيم ودور السيتوكينات في الأمراض التي تصيب الكبد ، خاصة في حالات تليف الكبد.