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Stem Cell Therapeutics of Acute Liver Diseases, Transplantation, and Regeneration

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Abstract

Present review article explains various causes of acute liver diseases and their therapeutics. This article describes major reasons of hepatic pathophysiological conditions and diseases including hepatitis, cholestasis, alcoholic and non-alcoholic steatohepatitis, jaundice, liver cirrhosis, carcinogenesis and many others. This article emphasizes use of proliferating hepatocytes, hepatic oval cells, adult human liver mesenchymal stem/progenitor cells, induced pluripotent stem cells (iPSCs) and hematopoietic stem cells in cell transplantation for restoration of liver structure and function. It also justified the therapeutic role of cell secreted growth factors and dietary factors required during natural healing and regeneration liver after surgery or liver transplantation. It sketches out regulatory roles of signaling pathways, expression of cell cycle regulators, growth factors, cytokines, and role of different mitogens in induction of liver stem/progenitor cells (LSPCs) after organ/stem cell transplantation. This article suggests a need for development of new advanced biomaterials, methods, technologies and stem cells for development of targeted therapies to combat and cure liver related diseases and disorders. This article also advice people for avoiding excessive use of alcohol, drugs, fats, salt, high energy diets, and iron as all are responsible of liver cirrhosis, damage and failure.

Keywords: Irreversible liver injury; Cirrhosis; Acute liver damage; Hepatocyte; Growth factors; Mitogens; Stem cells; Liver transplantation; Regenerative medicine

Abbreviations

EGF: Epidermal Growth Factor; TGF Alpha: Transforming Growth Factor Alpha; BAL: Bioartificial Liver; ESLD: End-Stage Liver Disease; ALF: Acute Liver Failure; IRI: Ischemia Reperfusion Injury; Hscs: Hepatic Stellate Cells; LLCC: Large Liver Cell Changes; HGF: Hepatocyte Growth Factor; NAFLD: Nonalcoholic Fatty Liver Disease; PLD: Polycystic Liver Disease; AD-PKD: Autosomal Dominant Polycystic Kidney Disease; HCC: Hepatocellular Carcinoma; BM-HSC: Bone Marrow Derived Hematopoietic Stem Cells; Lsecs: Liver Sinusoidal Endothelial Cells; Spcs: Stem/Progenitor Cells; Hadscs: Human Adipose-Derived Stem Cells; EMT: Epithelial-Mesenchymal Transition; VEGF: Vascular Endothelial Growth Factor; ECM: Extracellular Matrix Scaffold. In Addition; PLLA: Poly-L-Lactic Acid; Mapcs: Multipotent Adult Progenitor Cells; Ipscs: Induced Pluripotent Stem; Hscs: Hematopoietic Stem Cells; Lspcs: Liver Stem/Progenitor Cells; Hybhp: Hybrid Hepatocytes; CSF1: Macrophage Colony-Stimulating Factor; PEDF: Pigment Epithelium Derived Factor; ALF: Anti-Acute Liver Failure; HOC: Hepatic Oval Cells; Pscs: Pluripotent Stem Cells; Hescs: Pluripotent Human Embryonic Stem Cells; Hscs: Haematopoeitic Stem Cells; Mscs: Mesenchymal Stem Cells; Escs: Embryonic Stem Cells.

Introduction

Liver is an important visceral organ that possesses remarkable capacity to regenerate than any organ in the body. Healthy liver can easily replace damaged cells, but severely damaged lost its viability, and stop functioning properly. Though liver enzymatically catabolizes different groups of drugs and toxins, but it is severely damaged due to heavy alcohol drinking, microbial infection, pesticide residues and intake of highly salted food items, fat and minerals in the diet. Other liver damage contributing factors are genetics; gender, over weight and fat deposition. Liver damage depends on type of morbidity and its cause, liver beyond repair needs transplantation, in beginning treatment is possible by alleviating damaging effects using drugs or minor surgical operation. Liver shows self-healing and regeneration capacity after either surgical removal or after chemical injury. It is experimentally proved that as little as 25% of the original liver mass can regenerate back to its full size. End stage liver failure occurs due to virus infection and hepatic carcinoma that is fatal and a major cause of deaths worldwide. Liver transplants are used to treat a wide range of morbidities, including liver cancer, cirrhotic, physically injured, drug or alcohol abused acute liver failure and genetic liver disorders. Though, in pathological circumstances or accidentally damaged liver shows the ability to regenerate itself. But in a condition of severe infection or injury this ability gets disappear and liver transplantation remains only treatment choice. Cirrhotic liver failure may or may not be reversible, but proper medication and therapeutic care can restore its functions.

Liver contains hepatic lobes which are composed of about a million small lobules. Upon intoxication get severely damaged and faces sever inflammation that causes death of large population of liver lobules. These are also disturbed after partial hepatectomy, and surgical removal of liver, and cirrhotic hepatic mass. Though it regenerates quickly and it comes back essentially to its original size. Many biochemicals, genetic, molecular and cellular processes get involved in the regeneration of liver lobules. For treatment of damaged liver cell replacement therapy is proved highly useful therapeutic approach [1].

Moreover, hepatocytes or stem cell-derived hepatocyte-like cells (HLCs) are used for transplantation to replace damaged [2]. Other therapeutic options are liver transplantation and regenerative medicines which are considered best alternatives. Most regenerative medicine strategies have focused on delivering biomaterials and cells, but drug-induced regeneration showed good specificity and safety profiles [3]. More often, for hepatic regeneration stem cell therapy constitutes a promising strategy for liver regenerative medicine. For treatment of liver pathophysiological morbidities both hepatic tissue and *in vivo* cell transplants are needed with integration of all therapeutic approaches available (Figure 1).

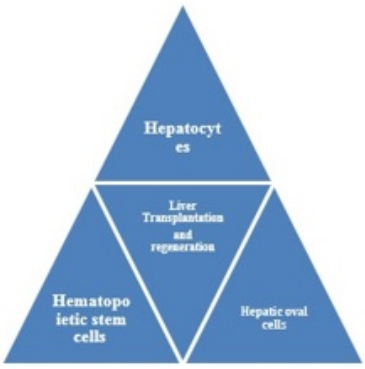

Figure 1: Showing integration of therapeutic uses of various stem cell types in liver transplantation and regeneration mechanism.

Pathophysiology of Liver Diseases

Liver failure results in high mortality in the patients. Though there are so many reasons of liver failure including drugs, toxins, heavy metals, mineral oils, fats, virus infection, chronic injury and physical damage. Physiologically generated diseases are failure of detoxification process that results in addition of waste materials in the blood. Main problems seen in liver are cirrhosis and jaundice. Hepatic microcirculation and cholesterol deposition also causes problems. Other associating factors which display these problems are fatigue, weakness, loss of appetite, nausea, weight loss, muscle loss, itching, bruising or bleeding easily because blood does not clot, bleeding in the stomach, vomiting blood, passing black stools, ascites, the buildup of fluid in the abdomen, forgetfulness or confusion.

Severe liver problems are seen due to defective body metabolism. Oxidative deamination results in the production of ammonia, its normal presence results in a diminution of the blood urea nitrogen level (BUN). Thus, circulating ammonia is highly toxic to blood and its components. Elevated serum ammonia level is extremely toxic, to the brain that leads to hepatic coma. Similarly, defects in protein synthesis also result in severe diffuse chronic and severe acute liver disease. Severe liver disorders are generated due to problems in hepatic lipid metabolism such as diminution in the rate of synthesis of cholesterol and deposition of triglycerides within liver cells makes liver too fatty. In fact, a decrease below the normal level of serum cholesterol is often found in advanced diffuse liver disease or in severe acute liver disease. Besides this, impairment of production of fibrinogen, prothrombin, Factors V, VII, and X leads to coagulation defects. Impairment of detoxification functions also result in severe liver morbidity. Acute hepatitis is a widespread inflammatory reaction throughout the liver. This results in edema and congestion, and compromise hepatic function. Formation and excretion of bile is impaired. The pathologic changes (tissue changes) that occur within the liver itself include hepatocyte necrosis, hyperplasia of the Kupffer cells, and some microscopic anatomic changes. In both conditions hepatitis and cirrhosis impairment of hepatocellular and Kupffer cell occurs, that also derive impairment of hepatic circulation at later stage. Jaundice indicates one of four problems: increased RBC breakdown, failure of hepatocyte conjugation, failure of hepatocyte excretion of conjugated bilirubin into the bile canaliculi extrahepatic obstruction. Acute liver failure is a broad term that encompasses both fulminant hepatic failure and sub fulminant hepatic failure (or late-onset hepatic failure). Diffuse scarring of liver, follows hepatocellular necrosis of hepatitis, Inflammation Loss of normal architecture and function. Cirrhosis is a non-specific end-stage disease towards which various pathologic consequences converge. The differing degrees of functional loss of the hepatocytes results in variable signs and symptoms. In cirrhosis, an unnoticed and unresolved destruction of hepatocytes occur until adequate function can no longer be maintained and reserves are completely depleted leading to liver failure. There are multiple reasons of liver disease which also have specific cause. Important reasons of liver diseases and morbidities are as following:

Physical damage

Liver is severely damaged after sudden jerk due to application of blunt force. It happens during a car accident, or a penetrating foreign object such as a knife [4]. It dissipates through and around the structure of the liver [5]. Normally, sport persons feel a traumatized liver with severe injury during sport events. Sudden force makes liver laceration. Liver injuries constitute 5% of all traumas, making it the most common abdominal injury [6]. Due to position of liver in abdominal cavity and its large size, it is prone to gunshot wounds and stab wounds [6]. Liver located under the diaphragm also makes it especially prone to shearing forces [4]. Virus infection, excess of salt and heavy alcoholic drinks severely injure live. Both carbon tetrachloride (CCl4) and paracetamol use affect liver structure and function. Different primary and secondary causes of liver damage, morbidities and diseases are mentioned in Table 1. Though, liver shows enormous regeneration capacity even after partial intoxication of drugs, poisons and to a mild physical injury. Due to this amazing ability liver can gain its original size but in case of severe viral infection. It is very difficult to regain complex architecture.

Causes primary	Examples	Type of morbidity disease	Diagnosis	Recommendations
Drugs and toxins	Acetamenophen	Hepatocellular carcinoma	Detection of acetaminophen poisoning, acute liver failure	Use of detoxifying agents
		Amanita phalloidins		
		Isoniazid		

		Halothane, birth control pills		
Viral infection	Hepatitis virus A, B, E, Herpes simplex virus, Epstein Barr virus, adenovirus, cytomegalovirus	Hepatitis	Acute liver failure, cirrhosis	Chemotherapy and liver transplantation
Vascular problems	Heavy shock, heat stroke, tumor infiltrating liver	Obstruction of microcirculation, cellular injury, cancer	Determination of hepatic secretions, major blood loss, obstruction in microcirculation	Hepatic surgery
Metabolic	High anabolism and fat utilization, causes inflammation of the liver and a gradual decrease in liver function	Wilson's disease	Family screening	Chemotherapy and hepatic surgery
		Gilbert's disease		
		Alpha-a trypsin deficiency		
Bacterial infection	Jaundice, rocky mountain spotted fever	Toxoplasmosis	Liver injury	Hepatic surgery
Carcinogens	Hepatic fibrosis, ulcer, cancer	Hepatocellular carcinoma	Circulating mitogenic factors and cytokine detection	Hepatic surgery, chemotherapy, liver transplantation
High sodium diet	Levels of excess fluid around abdomen or hands and feet	Pancreatic and liver inflammation	Increased ammonia levels and necrosis	Herbal therapy
High calorie food	Storage of excess of glycogen, minerals and fat	Obesity	Blood pressure, body weight index	Use a healthy, well-balanced diet
Metal toxicity	Adulteration of dietary materials, elemental increase in potable water	Skin and visceral carcinogenesis, acute liver failure	Determination of primary and secondary physiological enzymes and cell metabolism	Safe food and clean potable water
Secondary				
Alcohol abuse	Fragments of liver	Cirrhosis and heavy degeneration of hepatocytes	Loss of regenerating cells histochemistry, serum AST, ALP ratio, CAGE, Audit-C	No alcohol, liver transplantation
NASH or non-alcoholic steatohepatitis	Steatohepatitis, high amount of fat store in the liver, along with inflammation and damage,	Obesity, dyslipidemia, and glucose intolerance. impaired due to poor protein production, tiredness, nausea, vomiting, forgetfulness and mental confusion	Histological examination of liver lobules, liver imaging, serum AST/ALT, elevations in aminotransferase, ultrasonography, CT, and particularly MRI	Use of ursodeoxycholic acid, metronidazole, metformin, betaine, glumatmine infusion.
Hemochromatosis	Iron overload	Liver, pancreas, and heart and can lead to inflammation, cirrhosis, liver cancer, and liver failure	Routine checking of serum Fe, liver biopsy, hematochromatosis genes, polycythimia	Low iron diet
Alpha-1 antitrypsin deficiency	Liver damage	Digestive failure	Serum AAT level, genetic testing for AAT allele deficiency	Genetic testing
Autoimmune hepatitis	Attacks the normal components, or cells, of the liver and causes inflammation and liver damage	fatigue, abdominal discomfort and joint pain, body's own immune system attacks the liver and causes it to become inflamed	ANA, SMA, anti-LKM1, SPEP	Molecular testing
Hepatic encephalopathy	decline in brain function, exposure to alcohol, chemicals, drugs	terminal liver failure, damage and scarring of the liver architecture, forgetfulness, fatigue	head CT scan or MRI, complete blood count, Bilirubin, protein and albumin levels, AST and ALT levels	High-protein foods to avoid include poultry, red meat, eggs, and fish.
Wilson's disease	Inherited disease copper accumulates in brain and another vital organ	Affects the body's ability to metabolize copper	Neurological or psychiatric symptoms and liver disease	Genetic testing and gene therapy

Gilbert's disease	Severe liver damage	Abnormality in bilirubin metabolism in the liver	Elevated bilirubin level	Benign condition and requires no treatment.
High cholesterol	Liver inflammation	Higher risk of developing liver disease	LDL determination in blood serum	Low cholesterol uses and fibrous diet

Table 1: Primary and secondary causes of liver damage, morbidities and diseases.

Cholestatic liver injury

After absorption of lipids are transported to the liver through the systemic circulation. Liver hepatocytes also synthesize cholesterol from acetate and further synthesize bile salts. Oxidative stress and gangliosides change liver metabolism that also start cholestasis [7]. It also appears when bile does not flow from the liver to the duodenum. Sirtuin 1 activation alleviates cholestatic liver injury [8] while galectin-3 regulates inflammasome activation [9]. In addition, inhibition of hepatobiliary transport activity by the antibacterial agent fusidic acid initiates Cholestasis or hyperbilirubinemia [10].

Pruritus is the primary symptom of cholestasis that comes due to interaction of serum bile acids with opioidergic nerves. Jaundice is also one of the important symptoms of cholestasis mainly intrahepatic or metabolic (Table 1). Long time jaundice results in obstructive cholestasis. Pale stool and dark urine are important symptoms of obstructive cholestasis. Formation of gallstones, cystic fibrosis, hepatitis, biliary cirrhosis and intrahepatic cholestasis and severe inflammation in hepatocytes are strong markers of liver cancer.

Among other reasons is over dose of certain herbal and dietary supplements [11] and accumulation of extra cholesterol in liver [12]. Use of birth control, TMP/SMX antibiotics, androgens and over storage of glycogen in liver and abdominal cavity are important risk factors of cholestasis. Other liver related morbidities are biliary atresia, trauma and congenital anomalies of the biliary tract.

Few drugs such as nitrofurantoin, anabolic steroids, estrogen, erythromycin, flucloxacillin and gold salts also cause severe morbidity in liver. Strong antibiotic like acetaminophen with vicodin, chlorpromazine, prochlorperazine, sulindac, cimetidine, and statins can cause cholestasis. Nonalcoholic fatty acids and iron over load are also important causes of cholestasis (Table 1).

Hepatic Microcirculation

The liver not only performs complex functions in biosynthesis, metabolism and clearance, but it also has a dramatic role as the blood volume reservoir. Blood flow to the liver is very unique because it possesses dual supply from the portal vein and the hepatic artery. This hepatic circulation establishes mutual communication through the hepatic artery and the portal vein. Once this hepatic blood supply obstructs this abnormal state displays patho-physiological changes.

There occurs a hepatic arterial buffer response mechanism which controls and allows constancy of hepatic blood flow. This endogenous interrelationship between the hepatic arterial and portal venous inflow is maintained during liver resection, transplantation, as well as inflammatory and chronic liver diseases (Table 1).

Hepatic Blood Flow and Hepatic Pressures

Liver inflammation also increases due to reduced bile flow through the opening of the bile duct into the small intestine. It causes scars in the liver architecture that result in its failure. Gall stones also cause obstruction of the ducts that drain bile from the liver. In addition, blood clots formed in hepatic vein prevent blood leaving from the liver that generates extra pressure within the blood vessels of the liver. A fatty liver is known to have impairment of microcirculation, which is worsened after ischemia reperfusion injury (IRI) [13].

This increased pressure hit liver cells that lead to obstructive cirrhosis and liver failure as well. High blood pressure in venous blood and adjoining hepatic circulation also damage spleen, liver, gallbladder and pancreas [14]. It also lowers down hepatic resistance and lobular micro-circulatory function [15]. Difference in aortic and hepatic artery mean blood pressure is also responsible for slow hepatic morbidities [16,17] (Table 1).

Hepatic Blood Volume

The hepatic blood volume ranges from 25 to 30 mL/100 g liver weight, and accounts for 10% to 15% of the total blood volume. Hepatic blood volume is measured by counting total number of red blood cell in flowing blood in hepatic artery but it gave inaccurate value. Based on method used hepatic blood volume is found always highly variable because hepatic venous pressure largely influences hepatic blood volume [15].

Hepatic venous pressure is elevated to 9.4 mmHg that indicates change in blood volume per unit change in venous pressure [17]. Regulatory processes interact to maintain hepatic blood flow at a constant rate during normal condition. It should be maintained during liver regeneration, to escape from vasoconstriction. Hepatic blood volume may expand considerably in cardiac failure that blood acts as an emergency blood reservoir if bleeding episodes happen. Thus, it compensates up to 25% of the hemorrhage by immediate expulsion of blood from the capacitance vessels [18] (Table 1).

Cirrhosis

Cirrhosis is a slowly progressing diseases that displays permanent scarring of the liver in which normal liver cells are replaced by scar tissue that obstruct normal liver function. It imposes impairment of hepatic function with chronic problems that leads to widespread microscopic, hepatic anatomic changes. Among important causes of cirrhosis are infection of hepatitis virus, use excess of alcohol, and storage of large fat depot in the liver. This also occurs due to rising portal hypertension and hepatic dysfunction. Portal hypertension rises with restricted blood flow through liver to the hepatic veins and then to the inferior vena cava.

Due to reduced blood supply to the cirrhotic liver, the hepatocytes get minimal access to blood. It severely hampers hepatocyte capacity to detoxify harmful chemicals. As a result, toxins become more concentrated in the blood producing damaging effects particularly the production of ammonia (from amino acid breakdown). Thus, large amount of ammonia stays in the blood cause hepatic encephalopathy

and foul breath. Furthermore, the hepatocytes continue to die leading to a progressive deterioration of the liver's regulatory capabilities resulting in hypocoagulation and hypoalbuminemia.

Other reason is formation of scars which stop the flow of blood through the liver. Scars are also formed accumulation of metabolic byproducts after processing of nutrients, hormones and drugs. Liver exposed to these agents produce toxins; and other secondary metabolites which are highly toxic to liver. Increasing severity of cirrhosis causes derangement of the hematopoietic niche and loss of HSCs.

It also results in hematological and immunological dysfunctions and reduced potential for regeneration [19]. For treatment of liver cirrhosis hepatic stellate cells (HSCs) is used. These cells secrete factors which inhibit fibrosis increase degradation of matrix components and reduce activated myofibroblasts.

Fatty liver is associated with obesity and diabetes. Blockage of the bile duct, which carries bile formed in the liver to the intestine get inflamed, blocked, or scarred, due liver disease called primary biliary cholangitis (Table 1).

Hepatitis

Hepatitis is severe inflammation of liver cells that occurs due to hepatitis virus infection. Among different hepatitis types i.e., hepatitis A is infectious and spread primarily through the fecal-oral route when small amounts of infected fecal matter are inadvertently ingested (Figure 2). It results in an acute inflammation of the liver which generally resolves spontaneously. The only remedy to prevent infection is vaccine. Another type hepatitis B spreads by exposure to body fluids mainly by using contaminated needles from drug abusers, contaminated blood, and sexual contact. Virus causes an acute infection, that progress with chronic inflammation.

It gives rise cirrhosis and liver cancer. It is also vaccine preventable. There is no suitable vaccine available for prevention of this virus. Only few anti-viral drugs are available to treat and potentially cure Hepatitis C. Hepatitis D virus needs co-infection of hepatitis B virus for its survival. Hepatitis E is a virus that spread via exposure to contaminated food and water. Other viruses can also cause liver inflammation or hepatitis as part of the cluster of symptoms. Large liver cell changes (LLCC) are characterized by pleomorphic large nuclei frequently found in liver diseases as chronic viral hepatitis and liver cirrhosis [20].

Viral infections with infectious mononucleosis (Epstein Barr virus), adenovirus, and cytomegalovirus also cause severe inflammation in the liver. Non-viral infections such as toxoplasmosis and Rock Mountain Spotted fever are less common causes. The morbidity rate increases with the infectivity of hepatitis and over dosage of steroids, alcohol and toxic drugs (toxic hepatitis) [21]. Pre-emptive antiviral agents can be used to treat hepatitis B before chemotherapy starts to prevent viral reactivation.

More often, potentially hepatotoxic drugs can prevent the development of ACLF. In addition, HGF (hepatocyte growth factor) are also applied for the treatment of acute onset diseases such as fulminant hepatitis [22]. However, for development of targeted therapies for treatment of hepatitis both cellular and molecular drivers of liver dysfunction are to be known before stem cell therapeutics [23] (Table 1).

Figure 2: Showing various factors which can minimize lever damage and cirrhotic risk reduction.

Excessive Use of Alcohol

Alcohol is highly toxic to liver cells because it causes severe inflammation, and results in alcoholic hepatitis. Alcohol abuse is most common cause of liver diseases in most of the countries. In chronic alcohol abuse, fat accumulation occurs in liver cells that affect their ability to function (Table 1). For regeneration of liver one should avoid intake of alcohol in any form because it kills hepatocytes and damage the healthy liver (Figure 2). Alcohol is filtered out of the body through the liver, hence, all forms of alcohol should be avoided until the liver has a chance to regenerate and rebuild. Also avoid medicines containing acetaminophen as these are also filtered through the liver and put necrotic effects. Moreover, microRNA-223 ameliorates alcoholic liver injury by inhibiting the IL-6-p47phox-oxidative stress pathway in neutrophils [24].

Drugs

Broad spectrum drug regimens are proved highly toxic to liver because their catabolic intermediates show residual effect on liver cells. However, excess of acetaminophen use causes liver failure. It should be taken in combination with vicodin, tylenol and lortab which show less toxicity. Certain herbal preparations like comfrey, margosa oil, mate tea and chaparral also toxic to liver. Statin medications are commonly prescribed to control elevated blood levels of cholesterol. Niacin is also used to control elevated blood levels of cholesterol. Patients who take niacin also face liver inflammation and remain under higher risk of liver diseases. Other broad-spectrum drugs i.e., nitrofurantoin, amoxicillin and calvunic acids and isoniazid cause severe liver inflammation. Similarly, methotrexate (Rheumatrex and Trexall) used for treatment of treat autoimmune disorders and cancers causes severe inflammation. Antabuse is used to treat alcoholic patients also cause liver inflammation (Figure 2). Similarly, excess number of vitamins i.e. vitamin A causes hepatitis, cirrhosis and liver failure. Many mushrooms are poisonous to the liver and eating unidentified mushrooms show lethal consequences. Drugs which are provided after partial hepatectomy also cause severe inflammation in aged patients [25]. These drugs after use show an increased number of necrotic hepatocytes and intercalated disc anomalies, resulting in widened inter-hepatocyte and perisinusoidal spaces, smaller hepatocytes and

early-stage microvilli atrophy [25] (Table 1). Hence, only low toxic and easily catabolizable drugs are to be used. Some medications or drugs require an overdose to cause liver injury while others may cause the damage even when taken in the appropriately prescribed dosage.

Oxidative Stress

Oxidative stress contributes to initiation and progression of liver injury. Several risk factors including use of drugs, environmental pollutants and irradiation, induce oxidative stress in liver, which in turn results in severe liver diseases non-alcoholic steatohepatitis [26]. Application of antioxidants signifies a rational curative strategy to prevent and cure liver diseases involving oxidative stress (Table 1).

Non-Alcoholic Fatty Liver Diseases

Nonalcoholic fatty liver disease (NAFLD) is most common cause of chronic liver disease. NASH or non-alcoholic steatohepatitis or a fatty liver shows massive accumulation of fat within the liver that can cause inflammation of the liver and a gradual decrease in liver function. Nonalcoholic fatty liver shows multiple effects on body [27]. Both ethanol and high cholesterol diet causes severe sateathohepatitis and early liver fibrosis in mice [28]. Dietary advanced glycation end-products aggravate non-alcoholic fatty liver disease [29] (Table 1).

Hemochromatosis

Hemochromatosis is a metabolic disorder in which patient shows progressive increase in total body iron stores in liver parenchymal cells. Excess of iron causes severe inflammation in liver, pancreas and heart, and results in toxicity [30] and osteoporosis [31]. It is an inherited autosomal recessive genetic disease [32]. In primary haemochromatosis abnormal accumulation of iron causes signs of fatigue, impotence, arthaligia, hepatomegaly, skin pigmentation and arthritis [33] while in secondary haemochromatosis the spleen become hyper dense (Table 1).

Genetic reasons and syndromes

Wilson's disease is a rare inherited disorder that occurs due to over accumulation of copper in liver, brain and other vital organs [34]. Disease manifests as neurological or psychiatric symptoms and liver disease and life-threatening level. Wilson's disease is treatable, and fully cured people live normal life (Table 1). Gilbert's syndrome is a constitutional hepatic dysfunction and familial nonhemolytic jaundice. It is caused by a heterozygous mis-sense mutation in the gene for bilirubin UDP-glucuronosyltransferase [35,36]. Gilbert syndrome accelerates development of neonatal jaundice [37]. Blood test is done for measuring bilirubin levels. Major symptoms are fatigue, pale yellow skin and whites of the eyes (Table 1).

Metabolic liver disease: Metabolic liver disease is a disorder in which abnormal chemical reactions in the body disrupt the body's metabolism [38]. Most common symptoms of metabolic disease are jaundice, fatigue, bruising, and pain or swelling in the upper right abdomen (Table 1).

Polycystic liver disease: Polycystic liver disease (PLD or PCLD) is an inherited disorder and a rare condition that is characterized by presence of fluid filled cysts scattered throughout the liver. Disease is caused due to chromosomal abnormalities occur in hepatic cysts [39] (Table 1). Disease also appears randomly, with no apparent cause but in most cases, it is evoked due to an inherited autosomal dominant genetic trait. Sometimes, cysts are found in the liver in association with the presence of autosomal dominant polycystic kidney disease (AD-PKD). In PLD abdominal discomfort is also felt by the patient due to swelling of the liver. The main reason of PLD is mutations evoked in two genes, one on the short arm of chromosome 19 (19p-13.2-13.1) and one on the long arm of chromosome 6 (6q21-q23). These genes are not associated with AD-PKD. Dominant genetic disorders also cause severe abnormal conditions to the liver.

Parasitic infection: Few hepatobiliary parasites such as liver fluke causes chronic liver disease of bile ducts. Liver flukes mainly *Clonorchis sinensis, Opisthorchis viverrini and Opisthorchis felineus* infest liver tissue or biliary tree, either during their maturation stages or as adult worms. It leads to formation of pancreatitis, cholecystitis, biliary tree obstruction and recurrent cholangitis [40]. Infection occurs due to eating fluke-infested, fresh-water raw or undercooked fish. Amebic liver abscess [41] and trematode infection also causes hepatic problems [42,43]. Schistosoma mansoni (S. mansoni) infection also causes hepatic granuloma formation around schistosome eggs at acute stage of infection which is further followed by hepatic fibrosis at chronic and advanced stages [44] (Table 1).

Other Diseases and Conditions

Increased level of ammonia is harmful for liver; it shows toxicity and results in morbidity. A functional liver needs higher blood supply, if damage occurs in lobular anatomy or hepatic vein increased pressure within the blood vessels exerts adverse effects on liver other organs. It causes swelling in spleen and veins. Chemical exposure also damages the liver by irritating the liver cells resulting in inflammation. It also cut down bile flow through the liver (cholestasis) and causes accumulation of triglycerides (steatosis). Chemicals such as anabolic steroids, vinyl chloride, and carbon tetrachloride can cause liver cancers (Table 1). Fat rich diet create main problem to the heart. Extra storage of fat not only increases the size of liver but also decrease rate of catabolism of important metabolites (Figure 2).

Liver tumorogenesis

Serine palmitoyltransferase (SPT) is the key enzyme in sphingolipid biosynthesis. SPT deficiency significantly reduces sphingomyelin but no other sphingolipids in hepatocyte plasma membrane. It greatly reduces cadherin, the major protein in adherens junctions and on the membrane. It simultaneously induces cadherin phosphorylation that is an indication for its degradation. SPT deficiency also affects cellular distribution of β-catenin which is the central component of the canonical Wnt pathway.

Sometimes major surgical operation of liver activates occult micrometastases and facilitates tumor growth, and tumor recurrence [44]. Over-expression of single and combinations of genes affect hepatocyte proliferation in response to liver injury. Due to failure of tumor suppressor genes constitutive hepatocyte proliferation is obstructed and liver faces tumor development [45]. Cell cycle activation in hepatocarcinogenesis is directly triggered by some inhibitors mainly toxicants. Intense inflammation is an important hallmark of cancer and chronic hepatitis [46]. Sustained p53 activation subsequent to DNA damage promotes inflammation-associated hepatocarcinogenesis. p53 activation extremely enhance hepatic inflammation during hepatocarcinogenesis [47].

Hepatocellular carcinoma

Hepatocellular carcinoma accounts for most liver cancers, but it is not the same as metastatic liver cancer which starts in another organ and spreads to the liver through the blood stream. Hepatocellular carcinoma (HCC) develops in response to chronic hepatic injury. It is also called malignant hepatoma, which is one of the most common types of liver cancer. It evokes due to viral hepatitis infection (hepatitis B or C), metabolic toxins such as alcohol or aflatoxin, conditions like hemochromatosis and alpha 1-antitrypsin deficiency or NASH. This is a primary form of cancer that arises in liver structures and remains confined within the parenchymal tissue. HCC is quite different from secondary liver cancers; it spread to the liver from other organs. Leukemia and Hodgkin's lymphoma also related to the liver and found more often in men than women. CAPS1 negatively regulates hepatocellular carcinoma development through alteration of exocytosis-associated tumor microenvironment [48]. p53 Protein expression also show its role in Hepatocellular Carcinoma [49]. p18INK4C is also a member of the INK4 family of CdkIs and is a potential tumor-suppressor gene product. Loss of p18INK4C expression also play role in differentiation and development of HCC through the up-regulation of Cdk4 activity [50]. However, the expression of p18INK4C in hepatocellular carcinoma (HCC) and other liver diseases including HCC has relationship with phosphorylation of retinoblastoma protein (pRb), and the activity level of Cdk4 and Cdk6. Normally, cyclins, cyclin-dependent kinases (Cdks), and Cdk inhibitors (CdkIs) are frequently altered in human cancer.

Mechanisms of Liver Regeneration

The liver has the outstanding ability to regenerate itself and restore parenchymal tissue after injury. Human liver grows rapidly after resection of more than 50% of its mass. Liver regeneration is usually attributed to mature hepatocytes, which possess a remarkable potential to proliferate under mild to moderate injury. The most common cell source in liver growth/regeneration is replication of preexisting hepatocytes. Liver also contains non-parenchymal cells and intra-hepatic stem cells which can generate a transit compartment of precursors named oval cells. But after partial hepatectomy liver regeneration does not involve intra or extra-hepatic (hemopoietic) stem cells but solely depends on the proliferation of hepatocytes. More often, a population of fully differentiated hepatocytes continues to carry the burden of maintaining homeostasis for the entire body and assist in restoring liver mass. However, the source of hepatocytes depends on the nature of growth process and the extent of injury. Both bipotent precursor cells (oval cells) and BM-HSC or liver progenitor cells also participate in liver regeneration. Moreover, progeny of BM-HSC share a panel of hematopoietic markers c-kit, CD34, CD45, etc. Oval cells also participate in hepatocyte and cholangiocyte generation [51]. There occurs a conversion of BM-HSC to oval cells in some animal models [52,53]. Hepatocytes can also convert into biliary epithelial cells (BECs) during biliary injury [54]. If any how hepatocyte proliferation is compromised, biliary epithelial cells (BECs) become the source of new hepatocytes [55]. However, for liver regeneration and transplantation participation of different cell types, activation of key metabolic pathways and growth factors are required (Table 2) (Figure 3).

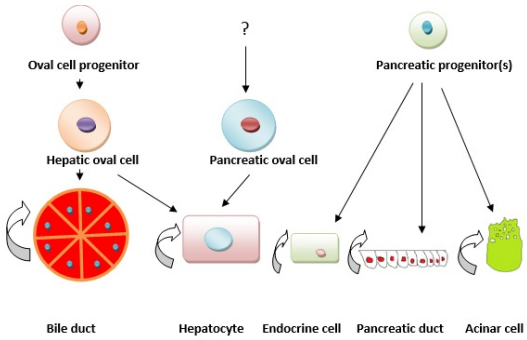

Figure 3: Role of stem cell progenitors in formation of glandular tissues and their organization.

Liver disease	Reason/defect	Method/technology used	References
Injured liver	Metabolic failure	Adipose derived stem cells; C-X-C chemokine receptor type 4; Hepatic ischemia-reperfusion; Homing; Stromal derived factor-1	Saito Y et al. in 2014
Liver damage	Cellular dysfunction	MSC secreted proteins, growthfactor β (TGF-β) and hypoxia-inducible factor 1-α (HIF1-α) signalling	Winkler et al. in 2016
Liver cirrhosis	Aggravated liver fibrosis	Circulating CD34(+) cells, increasingly positive for cell surface markers of VE-cadherin, VEGF receptor-2, and Tie-2	Nakamura et al. in 2016
Sinusoidal endothelial cell injury in liver transplantation	Extravasated platelet aggregation	Thromboxane A2, serotonin, transforming growth factor-beta and plasminogen activator inhibitor-1, released by EPA	Miyashita et al. in 2016
Liver damage	Hypoxia	Interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), hepatocyte growthfactor (HGF), and vascular endothelial growth factor (VEGF).	Lee SC et al. in 2016
Acute hepatic Injury	Low supply of peripheral blood	Expressing hepatocyte markers, including CK8, CK18, CK19, α-fetoprotein	Hu M et al. in 2016
Portal vein embolization	Hepatic circulation	Growth factors (hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), insulin-	Fichtl et al. in 2016

		likegrowth factor 1 (IGF-1), insulin-like growth factor binging protein 3 (IGF-BP3), epidermal growth factor (EGF), transforming growth factor (TGFα), tumor necrosis factor (TNF)] and interleukins (IL2, -6, -8 and -10)	
Acute-on-chronic liver failure (ACLF)	Systematic inflammatory response syndrome and subsequent sepsis due to immune paresis, persistent inflammation, immune dysregulation	Chemotherapy	Sarin et al. in 2016
Fibrosis	Hepatic stellate cell activation	Autologous ASCs-miR-27b enhances liver regeneration and, importantly, preserves hepatic function through paracrine actions	Chen et al. in 2016
Chronic liver disease (CLD) and cirrhosis	Decreased thrombopoietin production and accelerated platelet destruction caused by hypersplenism	Hepatocyte tranplantation	Kurokawa et al. in 2016
Liver damage	Right lobe hepatectomy	Levels of hepatocyte growth factor (HGF), interleukin (IL) 6, tumor necrosis factor α (TNF-α), thrombopoietin (TPO), transforming growth factor β1 (TGF-β1), interferon (IFN) α, and IFNγ	Sasturkar et al. in 2016
Hepatic ischemia/reperfusion	Hemorrhagic shock, or resection	Decreasing proinflammatory mediators, increasing efferocytosis of apoptotic PMNs, endogenous biosynthesis of SPMs and the generation of specific growth factors	Schlegel et al. in 2016
Liver damage	Transplantation of human mesenchymal stem cell-engineered hepatic enhanced liver regeneration and suppressed liver injury	MSCs accelerates liver regeneration through complement C3, EGFR and thioredoxin,	Itaba et al. in 2015
Fatty liver or extra size liver	Hepatocyte burst	Omega-3 polyunsaturated fatty acids (ω-3 PUFAs), Promoted liver regeneration and functional recovery following portal hypertension in the setting of LDLT	Ibrahim et al. in 2015
Liver fibrosis	Failure of hepatocyte function	MicroRNA-125b from CP-MSCs suppressed the activation of Hh signaling, which promoted the reduced fibrosis, suggesting that microRNA-mediated regulation of Hh signaling contributed to liver regeneration by CP-MSCs.	Hyun et al. in 2015
liver-failure or injury	Partial hepatectomy	Both NK cells and IFN-γ were required for BMDH generation	Li et al. in 2015
Liver injury	Mixed factors	OP9-Lhx2 and PSCs	Chen et al. in 2015
Acute-on-chronic liver failure (ACLF)	Increased short and long-term mortality	Granulocyte-colony stimulating factor (G-CSF) accelerates the liver regeneration process and improves survival	Chavez-Tapia et al. in 2015
Liver injury	Acute-on-chronic liver failure	Effect of HADMSC, Liver regeneration	Saidi et al. in 2015
Chronic graft-versus-host disease (cGvHD)	--	Low dose G-CSF-mobilized human PBMCs (G-hPBMCs)	Fujii H et al. in 2015
Liver cirrhosis	Mixed factors	Platelets activate liver sinusoidal endothelial cells, leading to the secretion of growth factors, such as interleukin-6.	Meyer et al. in 2015
End stage liver disease	Cirrhosis	Undifferentiated mesenchymal stromal cells (U-MSCs) or MSC-derived hepatocyte-like cells (DHLCs) from adipose tissue (AT), umbilical cord blood (UCB) and bone marrow (BM) would better restore damaged liver.	Manzini et al. in 2015
Terminal hepatic failure	Failure of microniche and blod circulation	Growth factors (GFs), cytokines, transcription factors (TFs), hormones, oxidative stress products, metabolic networks, and microRNA	Hu C et al. in 2015
Hepatostat	Cellular dysfunction	FGF19, nonparenchymal cells from cholestatic livers produce FGF19.	Naugler et al. in 2015

Hepatic damage	Mixed factors	Matrix metalloproteinase-9 (MMP-9) is an essential factor in liver regeneration	Zhou et al. in 2015
Acute liver failure	Mixed factors	High levels of hepatocyte growth factor and vascular endothelial growth factor,	Chen et al. in 2015
Hepatic surgical injury	Small bowel obstruction and chronic abdominal pain. Postoperative adhesion	Fetal liver mesothelial cells (FL-MCs) to prevent postoperative adhesion	Inagaki et al. in 2015
Injured livers	GalN/LPS-induced fulminant hepatic failure	hUCMSC a potential candidate for stem cell based therapies	Yang et al. in 2015
Acute liver failure	Mixed factors	Receptor for advanced glycation end products binding protein (EN-RAGE), high-mobility group box 1 (HMGB1), and Nε-(Carboxymethyl)lysine adducts (CML)	Basta et al. in 2015
Chronic viral hepatitis and liver cirrhosis.	Virus infection and mixed factors	Telomeric repeat binding factor 1 (TRF1) in liver regeneration	Beier et al. in 2015
Hepatic dysfunction	Failure of pediatric liver transplantation	Gene expression of Bax (pro-apoptotic), Bcl-XL (anti-apoptotic), c-Fos and *c-Jun* (immediate-early genes), ischemia-reperfusion-related inflammatory cytokines (IL-1, TNF-alpha and IL-6, which is also a stimulator of hepatocyte regeneration TGF-beta (a pro-fibrogenic cytokine	Leal et al. in 2015
Liver failure in experimental model	Hepatocyte related deficiency	Both hepatocyte-like cells and un-induced BMSCs had a similarly positively therapeutic efficacy on liver regeneration	Li et al. in 2015
Cirrhosis	Mixed factors	Granulocyte colony-stimulating factor (G-CSF)	Kedarisetty et al. in 2015
Ischemic liver injury	Cellular dysfunction	Stromal cell-derived factor-1 (SDF-1 or CXCL12) and its receptor CXC chemokine receptor-4 (CXCR4)	Wilson et al. in 2015
Massive liver injury and hepatocyte loss	Hepatocyte degeneration	Resident liver stem or progenitor cells (LPCs) or non-liver stem cells, putative cytokines, growth factors, mitogens and hormones in regulating LPC response	Best et al. in 2015
Acute hepatic failure	Mixed factors	Sustained hepatocyte growth factor (HGF) release (HGF-CHC)	Chiang et al. in 2015
Small-for-size liver transplantation (SFSLT).	Liver damage	MSC therapy up-regulated the mRNA expressions of HGF, Bcl-2, Bcl-XL, IL-6, IL-10, IP-10, and CXCR2, increased expressions of *c-Jun* N-terminal Kinase, Cyclin D1, and NF-κB.	Wang et al. in 2014
Chemical-induced hepatotoxicity	Hepatocellular carcinoma	Cyclooxygenase-1 (COX-1) is the constitutive form of the COX enzyme	Xiao et al. in 2014
Liver degeneration	Hepatocyte dysfunction	Sphingosine 1-phosphate (S1P) is a bioactive sphingolipid metabolite released from erythrocytes and platelets, S1P has proliferative and anti-apoptotic effects and promotes the production of IL-6 and VEGF in human LSEC, thereby promoting	Nowatari et al. in 2014
Acute liver damage	Damaged liver	Chemokine CXC receptor 4 (CXCR4) gene (CXCR4-MSC), MSCs expressing CXCR4 showed greater colonization and conferred better functional recovery	Ma et al. in 2014
Damage liver surgery	Clinical factors	F13A treatment promotes early phase liver regeneration after hepatectomy by promoting the activation of Kupffer cells and increasing serum levels of TNF-α and IL-6. F13A treatment	Yoshiya et al. in 2015
Non-alcoholic fatty liver disease	Liver fibrosis in stellate cells	VD and transforming growth factor (TGF)-β	Beilfuss et al. in 2015
Tissue injury		Complement system, platelets, inflammatory cytokines (TNF-a, IL-1b, IL-6), growth factors (HGF, EGF, VGF) and anti-inflammatory factors (IL-10, TGF-b).	Cienfuegos et al. in 2014

End-stage liver disease	Liver transplantation	Insulin-like growth factor 1 (IGF1)	Jara et al. in 2014
--	--	Stromal cell derived factor-1 alpha and vascular endothelial growth factor	Yuan et al. in 2014
Hepatocellular carcinoma	Therapy of REILD	FGF-19 and HGF).	Fernandez-Ros et al. in 2015
Damaged PVP	Hepatic injury	Heme oxygenase-1 HO-1 can induce the expression of HIF-1α, SDF-1α and VEGF, and mobilize the release of EPCs to the peripheral from the bone marrow, promote damaged PVP peribiliary vascular plexus repair and regeneration	Huang et al. in 2014
Chronic liver fibrosis	Hepatic injury	CD34(+) cell therapy	Nakamura et al. in 2014
Acute liver failure	Hepatic injury	Hepatocyte growth factor (HGF)-loaded polylactic acid-O-carboxymethylated chitosan (PLA-O-CMC) nanoparticles in hepatocyte transplantation (HCT)	Chang et al. in 2013
Autoimmune and toxic hepatitis	Inflammatory injury	Type 1 interferons (IFN) protect the host against viruses by engaging a cognate receptor (consisting of IFNAR1/IFNAR2 chains) and inducing downstream signaling and gene expression	Bhattacharya et al. in 2014
Resection or injury	Hepatic injury	Hsp70 to induce TNF-α that assist in Liver regeneration	Wolf et al. in 2014
Fatty liver disease	Hepatic injury	Vascular endothelial growth factor (VEGF) and erythropoietin (EPO)	Gu et al. in 2013

Table 2: Different types of liver related problems, their reasons, growth factors required for liver regeneration and transplantation.

Three distinct restoring levels of regeneration processes have been observed after liver injury i.e. hepatocyte dominant regeneration, LSPCs mediated regeneration, extrahepatic stem cells participative regeneration in which stem/progenitor cells (SPCs)-mediate the regeneration process [56]. Liver sinusoidal endothelial cells (LSECs) also contribute to liver regeneration following an injury. In addition, non-hepatocyte LSECs play an essential role in mammalian liver regeneration by converting to hepatocytes [57]. But in a condition of severely damaged liver, hepatocyte proliferation is greatly inhibited, liver stem/progenitor cells (LSPCs) contribute to the liver regeneration process. Moreover, for restoration of the liver parenchymal tissue hepatocytes or/and LSPCs, or bone marrow (BM) derived cells, such as hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) participate in the wound healing (Figure 3). With extensive proliferation of hepatocytes higher infiltration of immune surveillance cells such as macrophages [58] takes place to attack damaged cells. Macrophage infiltration plays important role in liver regeneration [59] (Table 2). BM-MSCs decreased liver fibrosis and contributed to an increase in oval cells, generation of new hepatocytes and/or to the improvement of resident hepatocytes [43] (Figure 1). Besides, hepatocytes hematopoetic origin HSC also takes part in the regenerative process, originating cells of the hepatocitic lineage and colangiocytes, as well as the oval cell (Figure 3).

Liver regeneration is a well-orchestrated process that allows mature hepatocytes to re-enter the cell cycle to proliferate and replace lost or damaged cells (Figure 3). This process is often impaired in fatty or diseased liver, leading to cirrhosis and other deleterious phenotypes [60]. Cyclin D1 is a cell cycle protein that promotes proliferation by mediating progression through key checkpoints in G1 phase. It is also a proto-oncogene that is commonly over expressed in human cancers. In addition to its canonical role in controlling cell cycle progression, cyclin D1 affects cell physiology through transcriptional regulation [61]. Glycogen synthase kinase 3β (GSK-3β) plays a crucial role in liver development, regeneration, proliferation and carcinogenesis. GSK-3β also plays important role in regulation of growth of hepatic oval cells *in vitro* and in liver regeneration in partially hepatectomized rats [62]. In process of liver regeneration certain complement system and its effector proteins also participate. C3 cascade activates c-fos and promotes the TNF-α signaling pathway, activates acute-phase genes such as serum amyloid proteins and orosomucoids. The complement activation also regulates the efflux and the metabolism of cholesterol, an important metabolite for cell cycle and proliferation [60]. In condition of genetic deficiency in C3, which is a major component of the complement cascade, liver does not regenerate normally.

Stem/progenitor cells (SPCs) have greater clinical applications in liver therapeutics [63]. Non-transgenic protocols are also followed for rapid generation of functional induced hepatocytes (iHeps) from human adipose-derived stem cells (hADSCs). These are considered as good source for obtaining autologous hepatocytes to treat liver disease [64]. Hepatectomy in humans involves physical damage (ie, physical partial hepatectomy, PPHx) which after surgery depends on tissue regeneration process mediated by various cell cycle inducing factors [65] (Table 2). Hepatic regeneration is triggered by the appearance of circulating mitogenic factors. These factors are hepatocyte growth factor, TNF-alpha, norepinephrine Interleukin-6, and insulin which act together. Proliferating hepatocytes initially form clumps while proliferating endothelial cells develop into the type of fenestrated cells typical of those seen in sinusoids. Hepatocytes show enormous regenerating capacity, and are highly differentiated and long-lived cells. These show remarkable capacity for multiple rounds of replication. An array of transcription factors (NF-kB, STAT3, fos and jun) are rapidly induced and probably participate in orchestrating

expression of a group of hepatic mitogens. Proliferating hepatocytes appear to at least partially revert to a fetal phenotype and express markers such as alpha-fetoprotein. These show massive commitment to proliferation during liver regeneration and continuously perform their normal metabolic duties for the host such as support of glucose metabolism (Table 2).

The molecular signals controlling liver regeneration are important gene regulated pathways and physiological factors. Normally, growth in regenerating liver is controlled by serum factors, nutrients, and meaningful gene expression of growth factors. *In vitro* cultures and in regenerating liver, substances EGF, TGF alpha, HBGF-1 (aFGF), and two new substances (HPTA/HGF and Hepatopoietin B) act as complete mitogens for inducing hepatocytes and implicated in control of liver growth. Similarly, 5-hydroxytryptamine signaling pathway genes play important role in liver regeneration [66]. Moreover, apoptosis, cell death, and necrosis were remarkably inhibited through JAK/STAT, ERK1/2, and NF-kB branches in almost every cell type. Osteopontin (OPN) could participate in the occurrence of multiple liver diseases via promoting inflammation, cell activation, proliferation, and migration [67]. Similarly, transforming growth factor-β1 (TGF-β1) induces hepatic progenitors to tumor initiating cells through epithelial-mesenchymal transition (EMT) that is important drawback for stem cell-based therapy [67]. Interaction between sinusoidal endothelial cells and hepatocytes is a prerequisite for liver function. Upon tissue loss, both liver cell populations need to be regenerated. However, repopulation needs regeneration of parenchyma cells (hepatocytes), and production of vascular endothelial growth factor (VEGF) to enable the subsequent angiogenic phase [68]. Hypoxia-driven Hif2a-Vegf factor induce hepatocyte mitosis during liver regeneration [68]. Hif2a acts as a safeguard to initiate sinusoidal reconstruction only upon successful hepatocyte mitosis, thereby enforcing a timely order onto cell-type specific regeneration patterns [68]. Connective tissue growth factor (CTGF), a direct target of miR-133b, also found crucial in the ductular reaction (DR)/oval cell (OC) response for generating new hepatocyte lineages during liver injury in the context of hepatotoxin-inhibited hepatocyte proliferation [69] (Table 2).

Liver regeneration and diet

The primary function of liver is to detoxify toxic substances and to produce the bile used to digest food. It possesses enzyme system that neutralizes poisonous substances, metabolize and filter alcohol and remove bacteria from the flowing blood. Liver also stores certain vitamins, minerals, sugars, and regulates fat storage. It also controls production and excretion of cholesterol. Liver plays an important role in keeping the body healthy by maintaining hepatocytes and Kuffer cells active. After having any injury, degeneration and physical damage various dietary supplements/nutrients mainly vitamins, antioxidants, carbohydrate and fiber rich food, and a well-balanced diet can induce liver regeneration (Figure 2).

Vitamins: Presence of vitamin in diet is essential because they put anti-oxidant effect and assist in membrane permeability function. An excessive number of certain vitamins put additional stress on the liver. Mega-vitamin supplements, especially vitamin A and vitamin D become toxic. Moreover, supplemented food nutrients consist of vitamins B, C, E, minerals, cholesterol, methionine, taurine and histidine become harmful if used above the physiological level. Similarly, efficacy of supplementing the diet with choline or betaine in ameliorating lipid accumulation induced by vitamin B6 (B6) deficiency in rat liver. However, it may be beneficial to supplement a diet designed for liver health with additional vitamin B complexes. In nutrient package serum vitamin D level decreases in children with nonalcoholic fatty liver disease (NAFLD). This low serum vitamin D level is associated with higher stages of steatosis but not with BMI. Vitamin E and their combination significantly ameliorated the fructose-induced metabolic and hepatic disorders.

Calories and carbohydrates: Carbohydrate is a major source of calories in a diet because it provides big nutritional support and important to make liver healthy. But increased consumption of carbohydrate adversely affects major body organs and tissues. Plasma glucose becomes too high and causes catabolic problems. Excess of carbohydrates and fats prevent protein from breaking down, preserving it in the body. After ingestion and digestion of carbohydrate a large fraction is absorbed and stored in the tissues while little is directly processed. Starch is partially digested in the large intestine where it becomes food for the commensal bacterial community. Here, commensal bacteria use available glycans, and work to maximize their energy harvest from these carbohydrates during limited transit time through the gut. With high intake of carbohydrate in the diet it is also important to monitor caloric intake. Excessive of calories, especially in the form of carbohydrates, increases fat deposits to form in the liver, causing further stress to the liver. On average, a person needs about 15 calories a day per pound of weight in order to fulfill his daily caloric needs.

Sodium: Liver removes out excess of sodium by fluid retention in the body, especially around the abdomen or hands and feet. Since sodium aids to increase the amount of fluid in the body, reducing the amount of sodium in a diet can help decrease the levels of excess fluid. One should intake only balanced amount of salt because most foods contain small amounts of sodium and few highly roasted and processed foods contain high amount of sodium. Both conditions are un-tolerable for liver cells. Foods that contain more than 300 mg of sodium per serving are considered high in sodium and should be avoided. Reducing the use of sodium chloride can be a preventive measure for increase in body weight. By controlling the sodium level in blood, one cannot only lower down the risk of nonalcoholic fatty liver disease but cut down chances of hypertensive disease. Normal sodium intake reduces the risk of complications and improves quality of life in patients. Sodium butyrate (SB) is reported to regulate lipid metabolism in mammals. It promotes maternal fat mobilization, which may result in fatty acid uptake and lipid accumulation in the liver of the offspring.

Protein: Presence of proteins in diet is important because they serve as sole source of amino acids and energy source. After digestion, proteins are broken down, and waste products such as ammonia are formed. A healthy liver can remove out wastes and toxins from body. If the liver has been compromised due to damge, toxins can build up in the blood and tissue. This build-up of toxins can cause tiredness, nausea, vomiting, forgetfulness and mental confusion. To avoid this, a diet for liver regeneration may contain only about 1 g of protein per kg of body weight.

Plant based medicines

Plants possess the ability to cure liver damages and injuries and diseases as well. Methanolic extract of Lawsonia inermis leaves showed hepatoprotective effects against on carbon tetrachloride (CCl_4)-induced hepatotoxicity in rats [40]. Polyphenol rich methanolic extract of Amorphophallus commutatus var. wayanadensis also showed

hepatoprotective and antioxidant activity in carbon tetrachloride induced hepatotoxicity in mice model. Phyllanthus urinaria and its bioactive compound LOD work as potent HCV entry inhibitors [70]. Flavonoids isolated from Cichorium glandulosum Boiss seeds have shown hepatoprotective activity both *in vitro* and *in vivo* against carbon tetrachloride-induced hepatotoxic mice [71]. Similarly, turmeric extract and its active compound curcumin were also found protective against chronic CCl4- induced liver damage [72]. Kinesenoside is used for immunosuprssion of auto-immunehepatitic cell population [73]. Saponins extracted from Rhizoma Dioscorea bulbifera [74], nectandrin B, a nutmeg lignan, act against oxidative stress [75]. α-tocopherol protect hepatocytes against oxidative [76] (Figure 2).

Microenvironment: Liver regeneration needs setting of an appropriate microenvironment. Stem cell niches are special microenvironments that maintain stem cells and control their behavior to ensure tissue homeostasis and regeneration throughout life. A well settled microenvironment allows better cell proliferation and differentiation that also assist in hepatic tissue regeneration capacity. A faulty or noxious microenvironment impairs proliferation of cells and diminishes stem cells activity. It will also need favorable gene expression of growth factors to regulate the dynamic balance between normal liver regeneration and repair. In recent years progress has been made in the identification of potential hepatic stem cell niches. By setting microenvironment it is also possible revert back hepatocellular carcinoma (HCC). 3D bio-artificial microenvironments affect function and maturation of hepatocyte-like cells differentiated from iPSCs and grown within an acellular, liver-derived extracellular matrix (ECM) scaffold. If a pro-fibrotic transition and vascular niche is to be maintained it can assist in eradication of liver diseases [77]. In addition, poly-l-lactic acid (PLLA) scaffold allows cell growth and formation of cell-cell contacts [78].

Possible cell therapy treatment: Stem cells are highly useful in various therapies and show wider application in tissue repairing such as hepatic, integument, muscular, neural, adipose and gonadial. However, for restoration purposes genetically altered cells are used to promote liver regeneration and repair. Further, by induction of immune cell function, and inhibition of inflammation and establishment of vasculature regeneration could be accelerated. Bone marrow derived mesenchymal stem cells (BM-MSCs) have been proposed as effective treatment of many diseases owing to their unique ability to differentiate into other cell types *in vivo*. Bone marrow cells (BMC) are progenitors of bone, cartilage, skeletal tissue, hematopoiesis-supporting stroma and adipocyte cells (Figure 3). BMCs have the potential to differentiate into neural cells, cardiac myocytes, liver hepatocytes, chondrocytes, renal, corneal, blood, and myogenic cells. The bone marrow cell cultures from stromal and mesenchymal cells are called multipotent adult progenitor cells (MAPCs). MAPCs can differentiate into mesenchymal cells, visceral mesoderm, neuroectoderm and endoderm *in vitro*. It has been shown that the stem cells derived from bone marrow cells (BMCs) can regenerate cardiac myocytes after myocardial infarction (MI). Adult bone marrow mesenchymal stem cells have the ability to regenerate neural cells. Neural stem/progenitor cells (NS/PC) are ideal for treating central nervous system (CNS) diseases, such as Alzheimer's, Parkinson's and Huntington disease [79].

Hepatic stem cells (HSC) are pluripotent cells which participate in liver regeneration (Figure 3). These cells are found in the ductal plates of fetal livers, and in the Canals of Herring in mature adult livers. Similarly, mesenchymal stem cells (MSCs) inhibit apoptosis of hepatic cells and improve hepatic regeneration in acute liver injury. Secreted molecules from human MSCs could enhance the hepatic function of human iPSC-derived hepatocyte-like cells [80]. Induced pluripotent stem cells (iPSCs) are also found capable of regenerating an injured organ. These stem cells are used to generate hepatocyte-like cells. These cells also show the potential to positively contribute to the maturation of hepatic cells or hepatoblasts derived from human iPSCs [80] (Table 2) (Figure 3).

Hematopoetic stem cells: Hematopoietic stem cells (HSCs) are multipotent stem cells. HSCs are also developed from a specialized subpopulation of endothelial cells known as hemogenic endothelium (HE). HSCs give rise to all the other blood cells through the process of haematopoiesis [81]. HSCs are pluripotent self-renewing progenitor cells that develop from mesodermal hemangioblast cells. These cells reside in adult bone marrow, peripheral blood, and umbilical cord blood. These form two lineages myeloid and lymphoid progenitors [82] and both are capable of self-renewal. HSCs act as both stem cells and precursor cells. HSCs secrete numerous extracellular growth factors known as cytokines which regulate proliferation and differentiation of the precursor cells for various cell lineages. Similarly, cytokines are needed to repair cellular injuries and generate separate immune cell types. For example, erythropoietin is generated that induce formation of erythrocytes which not only act as an erythrocyte precursor but also activates different intercellular signal transduction pathways. Similarly, another cytokine GM-CSF stimulates production of granulocytes, macrophages, eosinophils and megakaryocytic. More specifically, in transplants GM-CSF and BFU-E activate production of terminally differentiated cells, which show unique combination of cell surface protein. However, activation of the *Hoxb4* gene in embryonic stem cells drives the formation of haematopoietic stem cells. The hematopoietic tissue contains cells with long-term and short-term regeneration capacities and committed multipotent, oligopotent, and unipotent progenitors [82]. Both hematopoietic stem and progenitor cells (HSPCs) can be simply characterized by phenotypic markers. Most common marker is CD34 marker which is indicative of stem and progenitor cells (Figure 3).

HSCs are a heterogeneous population [81] basically found in the bone marrow pelvis, femur, and sternum of adults. These also occur in umbilical cord blood and, in small numbers in peripheral blood [83]. HSCs can replenish all blood cell types (i.e., are multipotent) and self-renew. A small number of HSCs can expand to generate a very large number of daughter HSCs. This phenomenon is used in bone marrow transplantation, when a small number of HSCs reconstitute the hematopoietic system. Hematopoietic stem cells progress down a differentiation pathway to committed progenitors in the bone marrow. As soon they get induction for differentiation, they leave the bone marrow and enter the peripheral blood and tissues, where they convert into various mature immune cell types. Intravenously injected bone marrow cells can rescue irradiated mice from lethality by reestablishing blood cell production. These cells convert in to hematopoietic stem cell (HSC) which also become self-renewing multipotent HSCs (Table 2) (Figure 4).

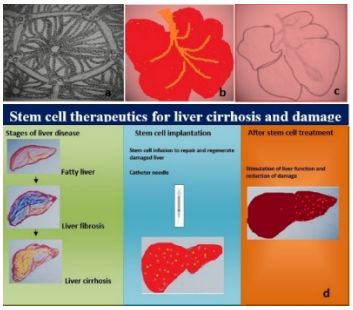

Figure 4: a-c: Histology of liver tissue, d: Showing stem cell therapeutics for liver cirrhosis and damage.

Bone marrow (BM) is a reservoir for immune and hematopoietic cells and critical for tissue repair and regeneration [19]. More often, bone marrow derived hematopoietic stem cells (BM-HSC) also show capacity to act as a source for hepatic regeneration (Figure 4). But it is not still clear that BM- HSC is involved in liver regeneration or not. If it could decide then these cells may work as an alternative donor source for the treatment of liver failure [84]. Cirrhosis patients possess fewer HSCs and show lower hemoglobin. Further, loss of niche in HSCs culture, impose hematological and immunological dysfunctions and reduced potential for regeneration [19].

Adult hematopoietic stem cells (HSCs) found in bone marrow reside within a special microenvironment, or niche. Once these cells are detached from the niche, these cells show cut down in reconstitution capacity because delay in cell cycle progression (Figure 3). In contrast, fetal liver HSCs actively divide without losing their stem cell potentials [85]. A unique CD34(lo)CD133(lo) cell population found in the human fetal liver (FL) give rise cells of hepatic lineage. These CD34(lo)CD133(lo)cells express markers of both endodermal and mesodermal lineages and have the capability to differentiate into hepatocyte and mesenchymal lineage cells by ex vivo differentiation assays. CD34(lo)CD133(lo) cells not only serve as stem/progenitor cells for liver development but are also become an essential component of the HSC niche in the human fetal liver [86] (Figure 3). Hematopoietic stem cells (HSCs) undergo a functional switch in neonatal mice hallmarked by a decrease in self-renewing divisions and undergo in quiescence (Figure 4). However, developmental attenuation of B-1a cell output is a consequence of a shift in stem cell state during ontogeny [87].

Hepatocytes

Hepatocytes are highly specialized cells reside in liver. Hepatocytes perform important functions of protein synthesis, storage and transformation of carbohydrates. These also do detoxification by modifying ammonia into urea for excretion. These cells divide regularly to make copies to replace degenerated or cells die. Transplantation and repopulation experiments have demonstrated that hepatocytes are highly differentiated and long-lived cells. On average, each hepatocyte lives for around 200 to 300 days. These cells have a remarkable capacity for multiple rounds of replication Hepatocytes perform important function of storing vitamins and minerals, removing toxins, and help in regulation of fats and sugars in the bloodstream. Hepatocytes have the ability to metabolize, detoxify, and inactivate exogenous compounds such as drugs, insecticides and endogenous steroids. These also synthesize cholesterol, bile salts and phospholipid and initiate formation and secretion of bile salts. Hepatocytes are dynamic cells that upon injury can alternate between non-dividing differentiated and dedifferentiated proliferating states *in vivo*. However, in 2D cultures primary human hepatocytes rapidly dedifferentiate resulting in the loss of hepatic functions which significantly limits their usefulness *in vitro*. This dedifferentiation occurs due to shut down of hepatic genes related to ncRNAs, in particular miRNAs. Moreover, new cellular models can aid the development of more efficient differentiation protocols for stem cell-derived hepatocytes which can be used for liver regeneration [88]. Functional hepatocytes derived from human stem cells are used for transplantation purposes to get rid of acute liver injury in experimental animal models. They have shown the regeneration effect and increase the survival of mice. A pre-existing group of periportal hepatocytes also found in healthy livers (Table 2) (Figure 4).

Hepatocytes also synthesize apoproteins with which they then assemble and export lipoproteins (VLDL, HDL). Liver also synthesizes carbohydrates from non-carbohydrate precursors like amino acids alanine, glycerol and oxaloacetate through gluconeogenesis. Liver forms fatty acids from carbohydrates and synthesizes triglycerides from fatty acids and glycerol [83]. In liver regeneration process oxygen plays a role of key regulator. Maintenance of portal flow is important to preserve primary hepatocyte functions and liver regeneration *in vivo* [89] (Figure 4). Upon tissue loss, both liver cell populations need to be regenerated. For effective regeneration periportal hepatocytes are the main driving force which expand in large numbers and re-populate the whole liver [90]. But repopulation occurs in a coordinated pattern through regeneration of parenchymal cells (hepatocytes) which produce VEGF to enable the subsequent angiogenic phase [68]. For normal liver function interaction between sinusoidal endothelial cells (SECs) and hepatocytes is a prerequisite. Normally, proliferation of hepatocytes is main process in the hepatectomy-induced liver re-growth; but in case of extensive loss regeneration could be achieved by mobilization of undifferentiated progenitors or resident progenitor cells. More often, hepatic tissue recovery occurs via increasing action of specific mRNA and/or protein expression levels for a panel of genes which implicate in growth, cell differentiation, angiogenesis, and inflammation. Moreover, slight increase in expression levels for Sox9 and two genes encoding tumor necrosis factor-like cytokine TWEAK (Tnfsf12) and its receptor Fn14 (Tnfrsf12a) start differentiation. These genes stimulate mitotic activity of hepatocytes [91] (Table 2). Under normal homeostatic conditions, hepatocyte renewal occurs very slow and complete turnover generally takes least a year.

Liver regeneration increases with the number of proliferating hepatocytes increase [92] but hepatocyte proliferation is blocked after a sever tissue injury as it occurs in fulminant hepatitis. Hepatocytes are main participants in liver regeneration because of remarkable potential to proliferate after an injury. Besides this, mature non-hepatocyte LSECs also play an important role in mammalian liver regeneration by converting in to hepatocytes. [93]. For restoration of liver function hepatocytes or/and LSPCs, or bone marrow (BM) derived cells, such as hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) are used (Figure 5). For therapeutic purposes hybrid hepatocytes (HybHP) are also prepared which express small amounts of Sox9 proteins that are usually enriched in the bile duct. These HybHP undergo extensive proliferation, and give rise mature hepatocytes and bile duct cells, and eventually replenish liver mass [94] (Table 2) (Figure 5). However, in two-dimensional cultures, primary human hepatocytes (PHHs) rapidly dedifferentiate, resulting in loss of hepatic

functions that significantly limits their usefulness *in vitro* model, liver diseases, as well as drug metabolism and toxicity [88] (Figure. 6). Liver weight continuously increased by hypertrophic reaction of hepatocytes, whereas Ki67 staining showed hepatocyte proliferation [65]. Liver precursor cells and bone marrow derived SEPCs participate in proliferation of hepatocytes. Similarly, hepatic oval ells, liver progenitors and certain growth factors like vascular endothelial growth factor assist in repair of liver tissues following an injury (Figure 5). showing use of bone marrow derived SEPCs in proliferation of hepatocytes after engraftment in morbid liver. Macrophages, natural killer (NK) cells, natural killer T (NKT) cells, dendritic cells (DC), eosinophils, gamma delta T (γδT) cells, and conventional T cells, as well as other subsets of the immune cells residing in the liver control liver regeneration [59] (Table 2).

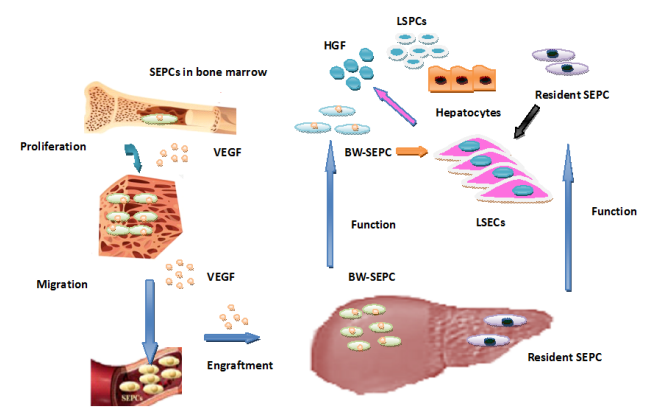

Figure 5: Showing use of bone marrow derived SEPCs in proliferation of hepatocytes after engraftment in morbid liver. SPEC: sca-1+CD31+CD45- cells, VEGF: Vascular Endothelial Growth Factor; LSECs: Liver Sinusoidal Endothelial Cells; LSPCs: Liver Stem/Progenitor Cells.

Few signaling pathways are important for liver regeneration. Among which Hippo pathway is a key regulator of organ size and regeneration by inhibiting cell proliferation and promoting apoptosis [3]. Similarly, P38MAPK signaling pathway involves in cell proliferation, apoptosis, cell differentiation, cell survival, cell death, and is important for liver regeneration [95]. P38MAPK signaling pathway regulated various physiological activities of LR through multiple signaling pathways [96]. Sphingosine 1-phosphate (S1P) participates in migration of bone marrow (BM)-derived mesenchymal stem cells (BMSCs) toward damaged liver via upregulation of S1P receptor 3 (S1PR3) during mouse liver fibrogenesis. HuR is an RNA-binding protein, regulates tumor cell motility. These cells assist in migration of human BMSCs (hBMSCs) in liver fibrosis [96]. Alpha-1 antitrypsin deficiency (A1ATD) imposes cirrhosis and hepatocellular carcinoma in few patients which are susceptible to severe liver disease. A1ATD, a mutation generates insoluble ATZ globules in hepatocytes and induce autophagy, [97]. Macrophage colony-stimulating factor (CSF1) is an essential growth and differentiation factor for cells of the macrophage lineage [58]. CSF1 plays important in steady-state control of monocyte production and differentiation and tissue repair [58] (Table 2).

Ischemia/reperfusion (IR) injury occurs during clinical hepatic surgery. It causes severe inflammation and apoptosis in hepatocytes. Post IR injury nuclear factor κB (NF κB), nitric oxide and the expression levels of inflammatory cytokines, tumor necrosis factor α and interleukin 1 also get increased. These mediate the inflammatory response in the liver. Further, exosomes small membrane vesicles released by hepatocytes also affect proliferation and liver regeneration after ischemia/reperfusion (I/R) injury. Chemokine receptors, CXCR1 and CXCR2, regulate liver recovery and regeneration after I/R injury [98]. Dysregulation of metabolism in hepatocytes leads to hepatic diseases such as hepatitis and non-alcoholic fatty liver disease (NAFLD) [99]. CF102 is a highly selective A3 adenosine receptor (A3AR) agonist that induces an anti-inflammatory and protective effect on the liver via the down-regulation of the NF κB signaling pathway [100]. Similarly, Hippo signaling is a potent *in vivo* growth and tumor suppressor pathway in the mammalian liver and facilitate regeneration [101] (Table 2). MicroRNAs (miRNAs) are potent serum biomarkers that are involved in liver regeneration, and their expression is dysregulated in hepatocellular carcinoma (HCC) [102]. Interleukin 6 (IL6), tumor necrosis factor α (TNFα) and TNF receptor-1(TNFR1) have been shown to involve in oval cell proliferation and inhibit hepatocellular carcinoma (HCC) development. IL6 promotes oval cell proliferation and liver regeneration, while TNFα/TNFR1 does not affect this process [103]. Regeneration is also somehow affected by missing signals. However, elimination of any single extracellular signaling pathway delays and hampers regeneration [104]. c-Met signaling in involved in cholesterol and bile acids toxicity [105]. Receptor tyrosine kinases MET and epidermal growth factor receptor (EGFR) is critically involved in initiation of liver regeneration. Serine peptidase inhibitor, Kazal type 3 (SPINK3) is a trypsin inhibitor, that is identical structure to epidermal growth factor (EGF), work co-jointly and promote cell proliferation [106] (Table 2).

Fibrosis is induced by carbon tetrachloride (CCl4) that causes repeated injury to the liver. It starts reactive regeneration that leads to liver cirrhosis [107]. It can be prevented by pigment epithelium derived factor (PEDF) [107]. TGF-β1 impaired the pathways of cell cycle and cytochrome P450 detoxification. But EGF reverted TGF-β1 effects through activating MAPK and PI3K-Akt pathway in hepatic oval cells, and serve as a protective cytokine to hepatic progenitors [108]. A noxious cell microenvironment is responsible for hepatic cell dysfunction and inflammatory cell activation. It also starts scar tissue deposition in hepatic blood supply that accelerates liver fibrosis [109]. For treatment of fibrosis and injuries rat liver stem cell lines are used as organoid culture system. These can play important role in development of regenerative medicine in liver diseases mainly [110] (Figure 4). Similarly, juglone in combination with hDPSC transplantation effectively treat liver fibrosis. Moreover, hDPSC transplantation with PIN1 inhibition is a novel therapeutic candidate for the treatment of liver injury [111]. However, for restoration of liver mass after hepatectomy both systemic and coordinated changes are needed in gene expression. These starts guiding regenerative responses, activation of progenitor cells, and proliferation of quiescent hepatocytes [112]. The chronic and repeated liver injuries are caused by alcohol, and HBV, HCV, or other pathogens. These directly increase the risk for hepatic cirrhosis and hepatocellular carcinoma (Table 2). However, for new therapeutic targets of the anti-inflammatory immune response cellular molecular mechanisms of TLRs will provide more information [113]. For Anti-acute liver failure (ALF) therapeutics tissue stem cells which supply multiple epithelial cells or cultured hepatocyte are used as important tools. Hepatocyte transplantation is done as an alternative to OLT for the treatment of some liver-based metabolic disorders or acute liver failure [114]. Partial hepatectomy (PH) promotes quiescent

hepatocytes to start cell cycle for regrowth. It can be identified by making miRNA profiles that also give an overall information regarding liver regeneration [115]. Hepatic tissue repair is induced by expression of some original cell mRNAs [116], cytokines (Type 2) [117] and *in vivo* transfer of stem cell progenitors (LPCs) for tissue maintenance [118].

Liver Oval Cells

A small subpopulation of hepatic oval cells found in the liver. Hepatic oval cells display a distinct phenotype and have been shown to be a bipotential progenitor of two types of epithelial cells found in the liver, hepatocytes and bile ductular cells. HOC act as facultative hepatic stem cells (HSCs) that differentiate into hepatocytes and cholangiocytes in severely injured liver [119]. Oval cells constitute an interesting hepatic cell population. They contribute to sustain liver regeneration during chronic liver damage (Figure 4). These cells can be induced to proliferate using a 2-acetylaminofluorene (2-AAF)/hepatic injury (i.e., CCl4, partial hepatectomy (PHx)) protocol. These cells express high levels of Thy-1 and hematopoietic stem cell markers (C-kit and CD 34.6) [120]. These also express α-fetoprotein, gamma-glutamyl transpeptidase (GGT), cytokeratin 19 and OV-6, all are well known markers used in identification of oval cells. Bone marrow stem cells have recently been shown to be a potential source of the hepatic oval cells and that reconstitution of an injured liver from a purified stem cell population is possible. HOCs are implicated in tumorigenesis and undergo malignant conversion and become tumor-initiating cells and drive hepatocarcinogenesis (Figure 3). These cells also originate from fetal hepatoblasts and remain undifferentiated in a stem cell niche within the ducts.

Normally, in the liver, quiescent differentiated cells replicate rapidly after tissue resection, while intra-hepatic precursor cells (oval cells) proliferate and generate lineage only in situations in which hepatocyte proliferation is blocked or delayed. Bone marrow stem cells can generate oval cells and hepatocytes. There also occur transdifferentiation that is very rare and inefficient [121]. Many of the developmental pathways that regulate hepatogenesis in the embryo, use certain growth factors i.e. HGF, FGF, OSM, TNFa and Wnt in oval cell activation. Interleukin-6 and tumor necrosis factor receptor-1 attribute oval cell- mediated liver regeneration and inflammation-associated hepatocarcinogenesis [104]. HGF increases oval cell invasion through extracellular matrix, a process that requires PI3K activation and is at least partly mediated by expression and activation of metalloproteases. HGF/c-Met signaling plays important role during oval cell-mediated mouse liver regeneration [122].

The NF-kB (nuclear factor kB) pathway is involved in the proliferation of many cell types [123]. Branches of the NF-kB signaling pathway regulate proliferation of oval cells in rat liver regeneration. Seven genes have been identified which play vital roles in the NF-kB pathway and regulate oval cell proliferation during rat liver regeneration [123]. Epithelial cell adhesion molecule (EpCAM) is expressed in mouse normal cholangiocytes and oval cells, while, TROP2, is expressed exclusively in oval cells. EpCAM+ cells isolated from injured liver proliferate to form colonies *in vitro*, and the clonally expanded cells differentiate into hepatocytes and cholangiocytes. More often, proliferating mouse oval cells represent transit-amplifying cells rather than HSCs [119]. Hepatic oval cell activation, proliferation, and differentiation are also regulated by physiological conditions during severe hepatic injury [124] (Figure 5). Cyclin D1 is an important protein that participates in cell cycle protein and promotes proliferation hepatocytes by mediating progression through key checkpoints in G1 phase. It also controls cell cycle progression and affects cell physiology through transcriptional regulation [125] (Figure 6).

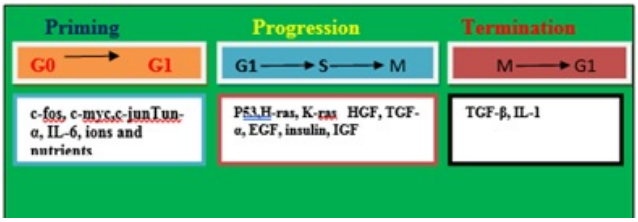

Figure 6: Showing different phases of cell cycle in active hepatocytes during liver regeneration.

Therapeutic role of cell secreted growth factors

For restoration of metabolic failure and injured liver adipose derived stem cells are used. These cells secrete C-X-C chemokine receptor type 4 and stromal derived factor-1 [126]. Transplantation of human mesenchymal stem cells is also used because they enhance liver regeneration and suppressed liver injury. But in restoration of cellular dysfunction MSC secreted proteins, growth factor β (TGF-β) and hypoxia-inducible factor 1-α (HIF1-α) signaling are main participants [127]. MSC therapy is up-regulated the mRNA expressions of HGF, Bcl-2, Bcl-XL, IL-6, IL-10, IP-10, and CXCR2, increased expressions of *c-Jun* N-terminal Kinase, Cyclin D1, and NF-κB. [128]. MSCs accelerate liver regeneration through complement C3, EGFR and thioredoxin [129]. For restoration of portal vein hepatic circulation growth factors [hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), insulin-likegrowth factor 1 (IGF-1), insulin-like growth factor binging protein 3 (IGF-BP3), epidermal growth factor (EGF), transforming growth factor (TGFα), tumor necrosis factor (TNF)] and interleukins (IL2, -6, -8 and -10) play important role [130]. For treatment of chronic liver fibrosis and hepatic injury CD34(+) stem cells are used [131] while in hepatostatic liver, FGF19, secreted from nonparenchymal cells is used [132]. For removing hypoxia induced liver damage interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) are also used [133]. In ischemic liver injury stromal cell-derived factor-1 (SDF-1 or CXCL12) and its receptor CXC chemokine receptor-4 (CXCR4) is used [134]. After right lobe hepatoctomy, for normal regeneration levels of hepatocyte growth factor (HGF), interleukin (IL) 6, tumor necrosis factor α (TNF-α), thrombopoietin (TPO), transforming growth factor β1 (TGF-β1), interferon (IFN) α, and IFNγ are to be normalized [135]. Similarly, partial hepatectomy, both NK cells and IFN-γ were required for BMDH generation [136]. Mixed factors such as OP9-Lhx2 and PSCs [137] and matrix metalloproteinase-9 (MMP-9) are used essential factor for regeneration of injured liver [138]. MSCs expressing CXCR4 showed greater colonization and conferred better functional recovery in injured livers [139]. GalN/LPS-induced fulminant hepatic failure hUCMSC were found potential candidate for stem cell based therapies [103]. Fetal liver mesothelial cells (FL-MCs) to prevent postoperative adhesion [140].

In case of acute liver damage or massive liver injury severe hepatocyte loss occurs due to cell death and degeneration. For

repairing of lost portion resident liver stem or progenitor cells (LPCs) or non-liver stem cells can be used because they synthesize putative cytokines, growth factors, mitogens and hormones in regulating LPC response [141]. For treatment of end-stage liver disease or cirrhosis liver transplantation is only remedy. For cellular transplantation undifferentiated mesenchymal stromal cells (U-MSCs) or MSC-derived hepatocyte-like cells (DHLCs) derived from adipose tissue (AT), umbilical cord blood (UCB) and bone marrow (BM) are used for restoration of damaged liver [142]. For damaged liver granulocyte-colony stimulating factor (G-CSF) is required [143] while enhancement of hepatocyte growth factor or hepatocyte regeneration TGF-beta (a pro-fibrogenic cytokine) is used [144]. Vascular endothelial growth factor accelerates the regeneration process and improves survival and recovery of hepatic tissue [145]. For healing of liver tissue and normalization of hepatocyte function stromal cell derived factor-1 alpha and vascular endothelial growth factor insulin-like growth factor 1 (IGF1) play important role [146]. For restoration of hepatic injury cell secreted TNF-α [147], vascular endothelial growth factor (VEGF) and erythropoietin (EPO) [148] tissue injury complement system, platelets, inflammatory cytokines (TNF-a, IL-1b, IL-6), growth factors (HGF, EGF, VGF) and anti-inflammatory factors (IL-10, TGF-b) are also important for liver regeneration [149]. HADMSC is also used to enhance tissue regeneration [150]. Omega-3 polyunsaturated fatty acids (ω-3 PUFAs), promote liver regeneration and functional recovery following portal hypertension in the setting of LDLT [151]. For stopping degeneration of hepatocytes and its dysfunction Sphingosine 1-phosphate (S1P), a bioactive sphingolipid metabolite released from erythrocytes and platelets was found workable. S1P shows proliferative and anti-apoptotic effects and promotes the production of IL-6 and VEGF in human LSEC, thereby promoting regeneration [152]. Similarly, to remove hepatic dysfunction can be restored by gene expression of Bax (pro-apoptotic), Bcl-XL (anti-apoptotic), c-Fos and *c-Jun* (immediate-early genes), ischemia-reperfusion-related inflammatory cytokines (IL-1, TNF-alpha and IL-6) after pediatric liver transplantation. In deficient experimental model's hepatocyte-like cells and un-induced BMSCs positively show therapeutic efficacy on liver regeneration [153].

Acute-on-chronic liver failure (ACLF) patient feels severe systematic inflammation, subsequent sepsis due to immune paresis, and immune dysregulation [154]. It is diagnosed on the basis of decreasing levels of sustained hepatocyte growth factor (HGF) release (HGF-CHC) [155]. Similarly, severe liver damage can be confirmed on the clinical symptoms of hepatic ischemia/reperfusion, hemorrhagic shock, or resection, decreasing pro-inflammatory mediators, increasing efferocytosis of apoptotic PMNs, endogenous biosynthesis of SPMs and the generation of specific growth factors [156]. Chronic liver disease (CLD) can also be confirmed by decreased thrombopoietin production and accelerated platelet destruction caused by hypersplenism [157]. In case of hepatocellular carcinoma REILD FGF-19 and HGF seems to be important therapeutic markers [158,159]. In case of autoimmune and toxic hepatitis inflammatory injury Type 1 interferons (IFN) protect the host against viruses by engaging a cognate receptor (consisting of IFNAR1/IFNAR2 chains) and inducing downstream signaling and gene expression [160].

Terminal hepatic failure occurs due to failure of microniche and blood circulation, lack of growth factors (GFs), cytokines, transcription factors (TFs), hormones, oxidative stress products, metabolic networks, and microRNA [161] by Hu C et al. in 2015. Fibrosis, hepatic stellate cell activation, autologous ASCs-miR-27b enhances liver regeneration. These also preserve hepatic function through paracrine actions [162]. Similarly, liver cirrhosis platelets activate liver sinusoidal endothelial cells, leading to the secretion of growth factors, such as interleukin-6 [163] and granulocyte colony-stimulating factor (G-CSF) [164]. Similarly, telomeric repeat binding factor 1 (TRF1) [20] and microRNA-125b contribute in liver regeneration. Moreoften, microRNA-125b activates the Hh signaling, that cut down fibrosis, and contribute to liver regeneration by CP-MSCs [165]. Liver cirrhosis aggravates liver fibrosis circulating CD34(+) cells, increasingly positive for cell surface markers of VE-cadherin, VEGF receptor-2, and Tie-2 [166]. Enzyme heme oxygenase-1 HO-1 induce the expression of HIF-1α, SDF-1α and VEGF, and mobilize the release of EPCs to the peripheral from the bone marrow, promote damaged PVP peribiliary vascular plexus repair and regeneration [167]. For promotion of regeneration in injured liver tissue, mixed factors, receptor for advanced glycation end products binding protein (EN-RAGE), high-mobility group box 1 (HMGB1), and Nε-(Carboxymethyl) lysine adducts (CML) [168], hepatocyte growth factor (HGF) play important role [169]. HGF-loaded PLA-O-CMC nanoparticles can steadily release HGF, and exhibits better tendencies in liver regeneration, survival rate and hepatic function compared with intravenous HGF [169]. After surgery of damaged liver clinical factors F13A treatment promotes early phase liver regeneration that also promote the activation of Kupffer cells and increasing serum levels of TNF-α and IL-6 [170]. There are important cellular markers which are used to recognize chemical-induced hepatotoxicity in liver mainly hepatocellular carcinoma. CK8, CK18, CK19, α-fetoprotein work as hepatocyte markers [171]. Cyclooxygenase-1 (COX-1) is the constitutive form of the COX enzyme. In case of rapid hepatocyte burst, sinusoidal endothelial cell injury extravasated platelet aggregation thromboxane A2, serotonin, transforming growth factor-beta and plasminogen activator inhibitor-1, released by EPA are important markers [172]. For non-alcoholic fatty liver disease stellate cells VD and transforming growth factors (TGF)-β are important markers [173].

Liver transplantation

Liver transplantation from living donors is important source of liver grafts. Liver transplantation is surgical method which is used to save the life of a severely diseased patient having more than 50% of injured liver or liver no longer works properly. Liver transplantation is potentially applicable to any acute or chronic condition resulting in irreversible liver dysfunction. It offers patients with liver disease a real chance for long-term survival those who face severe liver morbidity due to infection or due to any type of injury. Surgeons recommend liver transplant from a transplant center. Normally a diseased liver is replaced with a healthy whole liver or a segment of a liver collected or donated by a healthy person, called a donor. It is also known as allograft. Liver transplantation is an effective treatment for irreversible or end stage liver disease when acute liver failure occurs. Liver transplantation is also done in a condition when patient is exposed to any cirrhotic agents, carcinogens, overloaded fat and facing microbial infections in which regeneration is strongly halted [174]. In such patients' incidence of hepatic artery thrombosis remains high. For seeking a liver transplant a team of doctor checks the patient for having a suitable liver donor for transplantationThe most common reason for liver transplantation in developed countries is cirrhosis that is caused by hepatitis C. The second most common reason is cirrhosis caused by long-term alcohol abuse. In children, biliary atresia is the most common cause of liver failure and the need for a liver transplant. A long waiting list is maintained by the Government hospitals at

national level. Normally graft selection is done from family member or from a legally valid living donor, who donate part of their liver. Liver transplant surgery is complex and can take up to 12 hours. Patients usually stay in the hospital from 1 to 2 weeks after a liver transplant. Few common complications after liver transplant surgery are usually happen include bleeding, bile leaks, blood clots in the liver's blood vessels, infection, rejection of the new liver, and side effects from immunosuppressive medications. Liver transplant recipients must take immunosuppressive medications for the rest of their life. Most liver transplants are successful. People who have a liver transplant are usually able to return to normal activities after recovering for several months.

More specifically, organ donation for transplantation if collected from a diseased donor results in systemic infection [175]. Similarly, immunosuppressed SOT recipients remain at risk because they may develop severe forms of strongyloidiasis infection through transmission from an infected donor allograft [176]. SOT recipients also face high mortality. Hence, an effective donor screening and prophylaxis should be followed in high-risk SOT recipients to decrease morbidity and mortality [177]. Liver from aged and diseased patients should be avoided. Advanced age and serious heart, lung, or other diseased donors will not allow for liver donation. Similarly, metastatic liver, drug perturbed, alcoholic abused and septic and HIV infected patients should not consider for liver donation. Donors with bacteremia and sepsis are often considered to be controversial for organ retrieval due to potential transmission of an infectious agent to the recipient. Living donors are faced with risks and/or complications after the surgery.

Orthotropic liver transplantation (OLT) represents the only effective treatment for patients with liver failure. Due to regulatory laws and black marketing of this important organ system, bio-artificial liver (BAL), or bioengineered whole organ liver transplants are also being made available. Donor organ shortage is the main limitation to liver transplantation as a treatment for end-stage liver disease (ESLD) and acute liver failure (ALF) [178]. It can be fulfilled by organ culture or stem cell transplantation and cell fusion methods. Hepatocyte transplantation is a promising alternative to OLT for the treatment of some liver-based metabolic disorders or acute liver failure. But it is very difficult to obtain viable hepatocytes from healthy donors for hepatocyte-based therapies. For better survival of patient's key aspects of intraoperative LT management should improve and standardized perioperative strategies are to be followed. More often, switch toward accurate and tailored preoperative anesthetic care may show steady improvement in recipient survival rates after LT. Further, continuous assessment of fluid status and cardiac performance, strategies promote graft decongestion, rational hemostatic management. Still LT recipients face potential risk of vascular complications in intraoperative management [179]. For outstation patients graft transportation influence on primary dysfunction and graft survival [180].

After a liver transplantation, there remains a possibility of graft rejection. It may happen any time after the transplant. There are three types of graft rejection i.e. hyperacute rejection, acute rejection and chronic rejection. Hyperacute rejection is caused by preformed anti-donor antibodies. It is characterized by the binding of these antibodies to antigens on vascular endothelial cells. Rejection occurs when a person's immune system recognizes the transplanted liver as "foreign" and tries to destroy it. Hyperacute rejection happens within minutes to hours after the transplant procedure. This is B cell mediated. Acute rejection is mediated by T cells that also involves enhancement of direct cytotoxicity and cytokine mediated pathways. Rejection occurs a week or two after a transplant, due to failure of immunosuppressive medications to control the patient's immune reaction. In addition, activation complements system due to foreignness of liver graft. Chronic rejection is the presence of any sign and symptom of rejection after 1 year. The cause of chronic rejection is still unknown but an acute rejection is a strong predictor of chronic rejections. Markers which assist in prediction of transplant rejection are abnormal liver AST, ALT, and GGT enzyme level. Other clinical markers of hepatic health are prothrombin time, ammonia level, bilirubin level, albumin concentration, and blood glucose. Other nonspecific symptoms are malaise, anorexia, muscle ache, low fever, slight increase in white blood count and graft-site tenderness. Rejection does not always cause noticeable symptoms. Elevated liver enzyme levels in the blood may be the first sign that rejection is occurring. Other signs and symptoms of rejection may include fatigue, loss of appetite, nausea, abdominal tenderness or pain, fever, jaundice, dark-colored urine, or light-colored stools. Liver biopsy also helps in finding rejection. Immunosuppressive medications are used to decrease the activity of the recipient's immune response to prevent and treat rejection. Methylprednisolone (Depo-Medrol, Solu-Medrol) is commonly given intravenously after a transplant and during and immediately after surgery. Drugs prednisone, tacrolimus, cyclosporine, sirolimus should not provide for longer time after a liver transplant because it can cause blood clots in the major artery providing blood to the transplanted liver and prevents the surgical wounds from healing.

Future clinical prospects

Regeneration of tissues and cells has wider application in the field of medicine mainly in therapeutics. Both tissue and cell transplantation are boon for liver patients. These not only restore injured lobules but use to replace defective hepatic tissues. Stem cells generate hepatic cells which proliferate enormously and participate in regeneration process and repair injured liver. Further, liver explants grown in the laboratory can be implanted in the diseased liver patients. Hepatocytes can be infused in injured liver or cell transplantation can promote regeneration of tissues or by doing organ transplants. Stem cell transplantation is helpful for anatomically and physiologically deficient patients. Hybrid hepatocyte cells help in generation of different cell types by reprogramming. These can be obtained after transdifferentiation and cytodifferentiation. However, for development of more advanced therapies fine candidate molecules which do make cell programming and assist in real time micro niche formation to obtain highly specific cell types must be identified. However, factors, which can repair structural deformities caused by viruses can be identified and used for regeneration purposes. Though, it is a challenging task to repair and costliest un-imaginable affair how to restore ATPase receptors and other energy or electron accepting ports situated on the membrane surface. For this purpose, new disease and therapeutic markers should identify. Besides, stem cells, progenitors, growth factors, cytokines and inducer molecules which participate in regeneration of liver are to be identified. For establishing better option for treatment of liver diseases immune-modulatory and cell secreted trophic factors, such as growth factors and cytokines which are essentially required for cell must know. New candidate molecules which can suppress inflammatory responses, reduce hepatocyte apoptosis, increase hepatocyte regeneration and enhance liver functionality should identify. Platelets also secrete many growth factors that are required for organ development, tissue regeneration, and repair.

Autologous CD 34(+) cell infusion is also found safe and effective as it restores liver function in a short span of time and can aid in liver transplantation. There is a need to develop a non-cytotoxic, non-immunogenic, and biodegradable hepatic lobe for liver regeneration and bioengineering. Endothelial protective therapy or antiplatelet treatment is useful in the immunosupressive treatment of hepatic ulcer. Cell reprogramming can provide high quality rejuvenated hepatocytes for cell therapy and liver tissue engineering. BDPCs could have potential for liver cell therapies. With the development of novel treatments, newer tissue repairing strategies and biological and synthetic solutions being made available more clinical aids could be possible to patients. However, new promising biomaterial for tissue engineering and stem cell technology are to be developed [181]. Further, inherently suitable scaffolds and matrices are generated for tissue engineering, stem cell propagation and differentiation. Now it become possible to use bio-engineered organs and tissues, though its replacement is very difficult to proceed and practiced for disables [182]. It will lead to the development of strategies to treat age-onset diseases and facilitate stem-cell-based therapies in older individuals [183]. Further, there is an utmost need to have new reagents that could activate recruiting of intrinsic and extrinsic factors to induce or inject or implant progenitor cells into the damaged sites for repairing [184]. Individual tailored stem cells can be used for therapeutic purposes will be new innovative areas of future research [185,186]. Thus, by using or recruitment of intrinsic stem/progenitor cells in to the damaged site suppression of regeneration activity can be improved and organs could make functional. For success of stem cell therapeutics cellular fusion process between the HSC and the hepatic cells may give rise new hopes.

Conclusion

Present review article discussed important reasons of pathophysiological morbidities occur in human liver. This article sketches out all important reasons such as chemical, environmental and genetic factors which alter cellular and metabolic function of liver. All life style behavioral attributes severely affect liver physiology and biochemical functions. This article states and stress upon necessity to change our life style and give up use of alcohols, drugs and narcotics. Excessive intake of chemical drugs and high protein diet lead to severe inflammation of hepatocytes, repetitive alcoholism aids in chronic hepatitis that is a major form of liver cancer. All such agents not only cause severe inflammation of hepatocytes but also cause their death. Liver functions can be restored by using stem cell therapeutics and delivering biomaterials and cells in morbid regions of hepatic tissue but little progress is made to explore drug-induced regeneration to increase the specificity and safety profiles. Though, liver shows greatest regenerative capacity but cirrhotic effects are not easy to manage and only treatment is liver transplantation. From hospital reports and researches done it seems impossible to restore major functions of liver by using conventional drugs or by chemotherapeutics in cirrhotic condition when two third of liver portion get injured. For treatment of end stage liver failure or a cirrhotic or fibrotic liver laboratory generated explants can be used. Among existing methods surgery, liver transplant and use of stem cell therapy are more successful. But there is a shortage of liver transplant donors. *In vitro* organ and cell culture methods can solve the problem of shortage of organs for transplantation and cell replacement therapies. In addition, *in vivo* transplantation of cells can rejuvenate the body and make it able to repair, restore and regenerate damaged hepatic tissues. It will also need use of growth factors, enzymes, signaling molecules and restoration of various pathways involved in transcriptional and translational in-house gene candidates. Moreover, liver regeneration can be induced by a variety of signals, setting of microenvironments, healthy tissue grafts and including, VEGF and hepatocyte growth factor or peroxisome proliferators, and *in vivo* transplantation of liver progenitors, all such events could make liver quickly returns to its normal size. Though there are several stem cells types are available ECFCs which were found capable of forming epithelial colonies in culture at the single-cell level *in vitro*. But *in vivo* do not show such competitiveness. More exceptionally bone marrow derived SEPCs and LPSCs have shown good regenerative capacity. There are several studies done on fetal liver as source of stem cells these have shown much positive results *in vivo* therapeutics. No doubt regenerative medicine is most emerging interdisciplinary field having high biological, clinical and socio-economic importance and is medicine of future. But it will need study of different cell types and cell systems, genetics and biology of bimolecular for better understanding about progression of disease and valuable insights for future clinical therapeutics.

Conflict of Interests

Author has no conflict of interests. The author alone is responsible for the content and writing of the paper.

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