Page 73 to 88

Volume 1 • Issue 2 • 2017

Research Article

Chronicles of Pharmaceutical Science

ISSN: 2572-7761

A Review on Various Approaches on Liver Reprogramming

Pamukuntla Mounika*, Mekala Anusha and Nalini kanta Sahoo

MNR College of Pharmacy, Fasalwadi, sangareddy, Medak, Telangana, India

***Corresponding Author:** Pamukuntla Mounika, MNR College of Pharmacy, Fasalwadi, sangareddy, Medak, Telangana, India.

Received: March 17, 2017; **Published:** April 24, 2017

Abstract

The liver is a gland and plays a major role in metabolism, including regulation, decomposition, protein synthesis, hormone production, and detoxification. Liver failure occurs when healthy cells called hepatocytes are damaged which generate scar tissues from collagen. eventually the liver cannot generate new hepatocytes quickly liver fails, by using new techniques through virus, bacteria, stem cells, gene therapy and few drugs through which we can generate new hepatocytes and liver functions normally and save billions of patients would be given a new lease of life. The health care system is seeing a crippling shortage of organs available for transplant, by using these techniques we can minimize liver transplantation.

Keywords: *Liver; Hepatocytes; Bacteria; Virus; Gene therapy; Virtual technology*

Volume 1 Issue 2 April 2017

Introduction

The liver consist of four lobes of unequal size and shape, it is a reddish brown and wedge-shaped organ. 1.44–1.66 kg (3.2–3.7 lb.) [1] is around human liver weighs. It is the largest and heaviest internal organ of the body. It is Located in the abdominal cavity of right upper quadrant , it is located just below the diaphragm, to the right side of the stomach and down overlies the gallbladder [2].

Two large blood vessels are connected by the liver. One is the hepatic artery and other is the portal vein. Oxygen-rich blood supply is carried by hepatic artery from the aorta, whereas the blood rich in digested nutrients from the entire gastrointestinal tract and also from the spleen and pancreas is carried by portal veins. These hepatic artery and portal veins are subdivide into small capillaries known as liver sinusoids, which can lead to a lobule.

Functional units of the live are lobules. Each functional unit of liver is made up of millions of hepatic cells (hepatocytes) which are the basic metabolic cells. The functional units are held together by fine areolar tissue which extends into the structure of the liver, by accompanying the vessels (veins and arteries) ducts and nerves through the hepatic portal, as a fibrous capsule called Glisson's capsule [3]. The whole surface of the liver is covered in a serous coat derived from peritoneum and this has an inner fibrous coat (Glisson's capsule) to which it is firmly adhered. It is supported by vessels and ducts and fibrous tissue of areolar tissue.

Microscopic anatomy

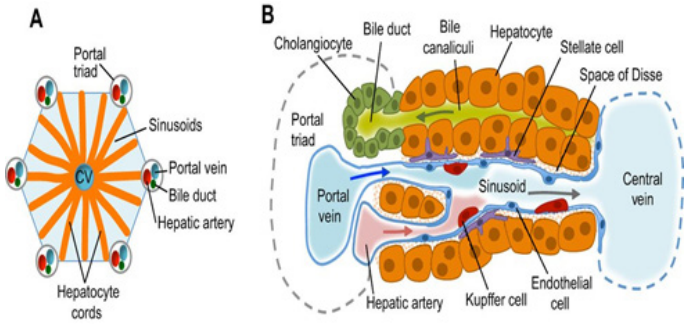


Figure1: *Microscopic anatomy of the liver.*

Microscopically, each liver lobe is seen to be made up of hepatic lobules. The functional units of the liver are radiating from central vein consists of hepatocytes roughly hexagonal in shape. From the liver hepatic vein carries blood out and joins to the central veins. A distinctive component of a lobule is the portal triad, which can be found running along each of the lobule's corners. The portal triad, consists of five structures: a branch of vagus nerve, a branch of hepatic artery, a branch of the hepatic portal vein, and a bile duct, as well as lymphatic vessels. Between the hepatocyte plates are liver sinusoids, which are enlarged capillaries through which blood from the hepatic portal vein and hepatic artery enters via the portal triads, then drains to the central vein it is represented in figure 1.

Histology, the study of microscopic anatomy, shows two major types of liver cell: parenchymal cells and non-parenchymal cells. 70-85% of the liver volume is occupied by parenchymal hepatocytes. Non-parenchymal cells constitute 40% of the total number of liver cells but only 6.5% of its volume [4] The liver sinusoids are lined with two types of cell, sinusoidal endothelial cells, and phagocytic Kupffer cells [5]. Hepatic stellate cells are non-parenchymal cells found in the perisinusoidal space, between a sinusoid and a hepatocyte. Additionally, intrahepatic lymphocytes are often present in the sinusoidal lumen.

Fuctions

The liver is a vital organ of vertebrates and some other animals. In the human, it is located in the upper right quadrant of the abdomen, below the diaphragm. The liver has a wide range of functions, including detoxification of various metabolites, protein synthesis, and the production of biochemical necessary for digestion.

- The liver is a gland and plays a major role in metabolism with numerous functions in the human body, including regulation of glycogen storage, decomposition of red blood cells, plasma protein synthesis, hormone production, and detoxification. It is an accessory digestive gland and produces bile, an alkaline compound which aids in digestion via the emulsification of lipids. The gallbladder, a small pouch that sits just under the liver, stores bile produced by the liver. The liver's highly specialized tissue consisting of mostly hepatocytes regulates a wide variety of high-volume biochemical reactions, including the synthesis and breakdown of small and complex molecules, many of which are necessary for normal vital functions.Estimates regarding the organ's total number of functions vary, but textbooks generally cite it being around 500. The liver stores a multitude of substances, including glucose (in the form of glycogen), vitamin A (1-2 years' supply), vitamin D (1-4 months' supply), vitamin B12 (3-5 years' supply), [35] vitamin K, iron, and copper.
- The liver is responsible for immunological effects-the mononuclear phagocyte system of the liver contains many immunologically active cells, acting as a 'sieve' for antigens carried to it via the portal system.
- The liver produces albumin, the most abundant protein in blood serum. It is essential in the maintenance of oncotic pressure, and acts as a transport for fatty acids and steroid hormones.

- The liver synthesizes angiotensinogen, a hormone that is responsible for raising the blood pressure when activated by renin, an enzyme that is released when the kidney senses low blood pressure. The liver plays a major role in carbohydrate, protein, amino acid, and lipid metabolism.
- The liver is responsible for immunological effects-the mononuclear phagocyte system of the liver contains many immunologically active cells, acting as a 'sieve' for antigens carried to it via the portal system.
- The liver produces albumin, the most abundant protein in blood serum. It is essential in the maintenance of oncotic pressure, and acts as a transport for fatty acids and steroid hormones.
- The liver synthesizes angiotensinogen, a hormone that is responsible for raising the blood pressure when activated by renin, an enzyme that is released when the kidney senses low blood pressure. The liver plays a major role in carbohydrate, protein, amino acid, and lipid metabolism.

The liver performs several roles in carbohydrate metabolism: The liver synthesizes and stores approximately 100g of glycogen via glycogenesis, the formation of glycogen from glucose. When needed, the liver releases glucose into the blood by performing glycogenolysis, the breakdown of glycogen into glucose. The liver is also responsible for gluconeogenesis, which is the synthesis of glucose from certain amino acids, lactate or glycerol. Adipose and liver cells produce glycerol by breakdown of fat, which the liver uses for gluconeogenesis.

The liver is responsible for the mainstay of protein metabolism, synthesis as well as degradation. It is also responsible for a large part of amino acid synthesis. The liver plays a role in the production of clotting factors as well as red blood cell production. Some of the proteins synthesized by the liver include coagulation factors I (fibrinogen), II (prothrombin), V, VII, VIII, IX, X, XI, XIII, as well as protein C, protein S and antithrombin. In the first trimester fetus, the liver is the main site of red blood cell production. By the 32nd week of gestation, the bone marrow has almost completely taken over that task. The liver is a major site of production for thrombopoietin, a glycoprotein hormone that regulates the production of platelets by the bone marrow.

- The liver plays several roles in lipid metabolism: it performs cholesterol synthesis, lipogenesis, the production of triglycerides, and a bulk of the body's lipoproteins.
- There is currently no way to compensate for the absence of liver function in the long term, although liver dialysis techniques can be used in the short term. Artificial livers are yet to be developed to promote long term replacement in the absence of the liver. As of now, liver transplantation is the only option for complete liver failure.

Development of liver

Organogenesis, the development of the organs takes place from the third to the eighth week in human embryogenesis. The origins of the liver lie in both the ventral portion of the foregut endoderm (endoderm being one of the three embryonic germ layers) and the constituents of the adjacent septum transversum mesenchyme. In the human embryo, the hepatic diverticulum is the tube of endoderm that extends out from the foregut into the surrounding mesenchyme. The mesenchyme of septum transversum induces this endoderm to proliferate, to branch, and to form the glandular epithelium of the liver. A portion of the hepatic diverticulum (that region closest to the digestive tube) continues to function as the drainage duct of the liver, and a branch from this duct produces the gallbladder [6]. Besides signals from the septum transversum mesenchyme, fibroblast growth factor from the developing heart also contributes to hepatic competence, along with retinoic acid emanating from the lateral plate mesoderm. The hepatic endodermal cells undergo a morphological transition from columnar to pseudostratified resulting in thickening into the early liver bud. Their expansion forms a population of the bipotential hepatoblasts. Hepatic stellate cells are derived from mesenchyme [7].

After migration of hepatoblasts into the septum transversum mesenchyme, the hepatic architecture begins to be established, with liver sinusoids and bile canaliculi appearing. The liver bud separates into the lobes. The left umbilical vein becomes the ductus venosus and the right vitelline vein becomes the portal vein. The expanding liver bud is colonized by hematopoietic cells. The bipotential hepatoblasts begin differentiating into biliary epithelial cells and hepatocytes. The biliary epithelial cells differentiate from hepatoblasts

around portal veins, first producing a monolayer, and then a bilayer of cuboidal cells. In ductal plate, focal dilations emerge at points in the bilayer, become surrounded by portal mesenchyme, and undergo tubulogenesis into intrahepatic bile ducts. Hepatoblasts not adjacent to portal veins instead differentiate into hepatocytes and arrange into cords lined by sinusoidal epithelial cells and bile canaliculi. Once hepatoblasts are specified into hepatocytes and undergo further expansion, they begin acquiring the functions of a mature hepatocyte, and eventually mature hepatocytes appear as highly polarized epithelial cells with abundant glycogen accumulation. In the adult liver, hepatocytes are not equivalent, with position along the portocentrovenular axis within a liver lobule dictating expression of metabolic genes involved in drug metabolism, carbohydrate metabolism, ammonia detoxification, and bile production and secretion. WNT/β-catenin has now been identified to be playing a key role in this phenomenon [8]. In the growing fetus, a major source of blood to the liver is the umbilical vein which supplies nutrients to the growing fetus. The umbilical vein enters the abdomen at the umbilicus, and passes upward along the free margin of the falciform ligament of the liver to the inferior surface of the liver. There it joins with the left branch of the portal vein. The ductus venosus carries blood from the left portal vein to the left hepatic vein and then to the inferior vena cava, allowing placental blood to bypass the liver.

In the fetus, the liver does not perform the normal digestive processes and filtration of the infant liver because nutrients are received directly from the mother via the placenta. The fetal liver releases some blood stem cells that migrate to the fetal thymus, creating the T-cells or T-lymphocytes. After birth, the formation of blood stem cells shifts to the red bone marrow.

After two to five days, the umbilical vein and ductus venosus are completely obliterated; the former becomes the round ligament of liver and the latter becomes the ligamentum venosum. In the disorders of cirrhosis and portal hypertension, the umbilical vein can open up again.

At birth the liver comprises roughly 4% of body weight and is at average 120g. Over the course of development, it will increase to 1.4–1.6 kg but will only take up 2.5–3.5% of body weight [9].

The liver receives a dual blood supply from the hepatic portal vein and hepatic arteries. The hepatic portal vein delivers approximately 75% of the liver's blood supply, and carries venous blood drained from the spleen, gastrointestinal tract, and its associated organs. The hepatic arteries supply arterial blood to the liver, accounting for the remaining quarter of its blood flow. Oxygen is provided from both sources; approximately half of the liver's oxygen demand is met by the hepatic portal vein, and half is met by the hepatic arteries [10]. Blood flows through the liver sinusoids and empties into the central vein of each lobule. The central veins coalesce into hepatic veins, which leave the liver and drain into the inferior vena cava [11].

The biliary tract is derived from the branches of the bile ducts. The biliary tract, also known as the biliary tree, is the path by which bile is secreted by the liver then transported to the first part of the small intestine, the duodenum. The bile produced in the liver is collected in bile canaliculi, small grooves between the faces of adjacent hepatocytes. The canaliculi radiate to the edge of the liver lobule, where they merge to form bile ducts. Within the liver, these ducts are termed *intrahepatic* bile ducts, and once they exit the liver they are considered *extrahepatic*. The intrahepatic ducts eventually drain into the right and left hepatic ducts, which exit the liver at the transverse fissure, and merge to form the common hepatic duct. The cystic duct from the gallbladder joins with the common hepatic duct to form the common bile duct.

Bile either drains directly into the duodenum via the common bile duct, or is temporarily stored in the gallbladder via the cystic duct. The common bile duct and the pancreatic duct enter the second part of the duodenum together at the hepatopancreatic ampulla, also known as the ampulla of water.

Synthesis of Liver

The liver plays a key role in digestion, as it produces and excretes bile (a yellowish liquid) required for emulsifying fats and help the absorption of vitamin K from the diet. Some of the bile drains directly into the duodenum, and some is stored in the gallbladder.

The liver also produces insulin-like growth factor 1 (IGF-1) a polypeptide protein hormone that plays an important role in childhood growth and continues to have anabolic effects in adults.

The liver is responsible for the breakdown of insulin and other hormones. The liver breaks down bilirubin via glucuronidation, facilitating its excretion into bile. The liver is responsible for the breakdown and excretion of many waste products. It plays a key role in breaking down or modifying toxic substances (e.g., methylation) and most products in a process called drug metabolism. This sometimes results in toxication, when medicinal the metabolite is more toxic than its precursor. Preferably, the toxins are conjugated to avail excretion in bile or urine. The liver breaks down ammonia into urea as part of the urea cycle, and the urea is excreted in the urine.

Liver Failure

liverfailure occurs when large parts of the liver become damaged beyond repair and the liver is no longer able to function.

Liver failure is a life-threatening condition that demands urgent medical care. Most often, liver failure occurs gradually and over many years. However, a more rare condition known as acute liver failure occurs rapidly (in as little as 48 hours) and can be difficult to detect initially.

Causes Liver Failure

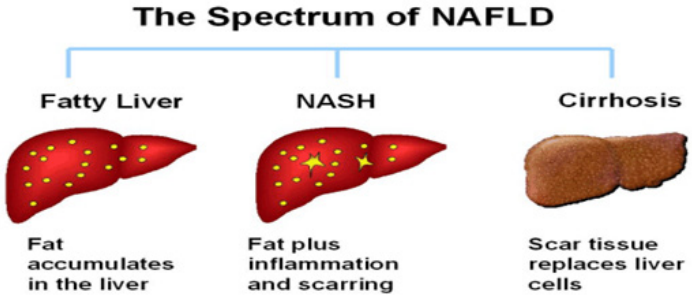
The most common causes of chronic liver failure (where the liver fails over months to years) include:

- Hepatitis B
- Hepatitis C
- Long-term alcohol consumption
- Cirrhosis
- Hemochromatosis (an inherited disorder that causes the body to absorb and store too much iron)
- Malnutrition

The causes of acute liver failure, when the liver fails rapidly, however, are often different. These include:

- Acetaminophen (Tylenol) overdose
- Viruses including hepatitis A, B, and C (especially in children)
- Reactions to certain prescription and herbal medications
- Ingestion of poisonous wild mushrooms

Non alcoholic fatty liver disease:



- Fatty liver is a condition in which the cells of the liver accumulate abnormally increased amounts of fat. Although excessive consumption of alcohol is a very common cause of fatty liver (alcoholic fatty liver), there is another form of fatty liver, termed nonalcoholic fatty liver disease (nonalcoholic fatty liver disease), in which alcohol has been excluded as a cause. In nonalcoholic fatty liver disease, other recognized causes of fatty liver that are less common causes than alcohol also are excluded.
- Nonalcoholic fatty liver disease is a manifestation of an abnormality of metabolism within the liver. The liver is an important organ in the metabolism (handling) of fat. The liver makes and exports fat to other parts of the body. It also removes fat from the blood that has been released by other tissues in the body, for example, by fat cells, or absorbed from the food we eat. In nonalcoholic fatty liver disease, the handling of fat by liver cells is disturbed. Increased amounts of fat are removed from the blood and/or are produced by liver cells, and not enough is disposed of or exported by the cells. As a result, fat accumulates in the liver.
- Nonalcoholic fatty liver disease is classified as either fatty liver (sometimes referred to as isolated fatty liver or IFL) or steatohepatitis (NASH). In both isolated fatty liver and NASH there is an abnormal amount of fat in the liver cells, but, in addition, in NASH there is inflammation within the liver, and, as a result, the liver cells are damaged, they die, and are replaced by scartissue.

Causes of fatty liver disease

The cause of nonalcoholic fatty liver disease is complex and not completely understood. The most important factors appear to be the presence of obesity and diabetes. It used to be thought that obesity was nothing more than the simple accumulation of fat in the body. Fat tissues were thought to be inert, that is, they served as simply storage sites for fat and had little activity or interactions with other tissues. We now know that fat tissue is very active metabolically and has interactions and effects on tissues throughout the body.

- When large amounts of fat are present as they are in obesity, the fat becomes metabolically active (actually inflamed) and gives rise to the production of many hormones and proteins that are released into the blood and have effects on cells throughout the body. One of the many effects of these hormones and proteins is to promote insulin resistance in cells.
- Insulin resistance is a state in which the cells of the body do not respond adequately to insulin, a hormone produced by the pancreas. Insulin is important because it is a major promoter of glucose (sugar) uptake from the blood by cells. At first, the pancreas compensates for the insensitivity to insulin by making and releasing more insulin, but eventually it can no longer produce sufficient quantities of insulin and, in fact, may begin to produce decreasing amounts. At this point, not enough sugar enters cells, and it begins to accumulate in the blood, a state known as diabetes. Although sugar in the blood is present in large amounts, the insensitivity to insulin prevents the cells from receiving enough sugar. Since sugar is an important source of energy for cells and allows them to carry out their specialized functions, the lack of sugar begins to alter the way in which the cells function.
- In addition to releasing hormones and proteins, the fat cells also begin to release some of the fat that is being stored in them in the form of fatty acids. As a result, there is an increase in the blood levels of fatty acids. This is important because large amounts of certain types of fatty acids are toxic to cells.
- The release of hormones, proteins, and fatty acids from fat cells affects cells throughout the body in different ways. Liver cells, like many other cells in the body, become insulin resistant, and their metabolic processes, including their handling of fat, become altered. The liver cells increase their uptake of fatty acids from the blood where fatty acids are in abundance. Within the liver cells, the fatty acids are changed into storage fat, and the fat accumulates. At the same time, the ability of the liver to dispose of or export the accumulated fat is reduced. In addition, the liver itself continues to produce fat and to receive fat from the diet. The result is that fat accumulates to an even greater extent.

Symptoms of liver disorder

Pale stools occur when stercobilin, a brown pigment, is absent from the stool. Stercobilin is derived from bilirubin metabolites produced in the liver.

- Dark urine occurs when bilirubin mixes with urine
- Jaundice (yellow skin and/or whites of the eyes) this is where bilirubin deposits in skin, causing an intense itch. Itching is the most common complaint by people who have liver failure. Often this itch cannot be relieved by drugs.

- Swelling of the abdomen, ankles and feet occurs because the liver fails to make albumin.
- Excessive fatigue occurs from a generalized loss of nutrients, minerals and vitamins.
- Bruising and easy bleeding are other features of liver disease. The liver makes substances which help prevent bleeding. When liver damage occurs, these substances are no longer present and severe bleeding can occur.
- Pain in the upper right quadrant can result from the stretching of Glisson's capsule in conditions of hepatitis and pre-eclampsia [12].
- Abnormal liver tests are found on routine blood testing.
- Fat is seen ultrasonographically when ultrasonography of the abdomen is performed for other reasons, for example, the diagnosis of gallstones
- Infrequently when the liver is enlarged on physical examination.
- Excessive bleeding due to the inability of the liver to make blood-clotting proteins
- Jaundice due to the inability of the liver to eliminate bilirubin from the blood
- Gastrointestinal bleeding due to portal hypertension that increases the pressure in intestinal blood vessels
- Fluid accumulation due to portal hypertension that causes fluid to leak from blood vessels and the inability of the liver to make the major blood protein, albumin
- Mental changes (encephalopathy) due to the liver's inability to eliminate chemicals from the body that are toxic to the brain. Coma may occur.
- Liver cancer.

Diagnosiss

The diagnosis of liver disease is made by liver function tests, groups of blood tests that can readily show the extent of liver damage. If infection is suspected, then other serological tests will be carried out. Sometimes, an ultrasound or a CT scan is needed to produce an image of the liver.

Physical examination of the liver can only reveal its size and any tenderness, and some form of imaging will also be needed.

Liver function tests (LFTs or LFs): are groups of blood tests that give information about the state of a patient's liver [13]. These tests include prothrombin time (PT/INR), aPTT, albumin, bilirubin (direct and indirect), and others. Liver transaminases (AST or SGOT and ALT or SGPT) are useful biomarkers of liver injury in a patient with some degree of intact liver function [14-16]. Most liver diseases cause only mild symptoms initially, but these diseases must be detected early. Hepatic (liver) involvement in some diseases can be of crucial importance. This testing is performed on a patient's blood sample. Some tests are associated with functionality (e.g., albumin), some with cellular integrity (e.g., transaminase), and some with conditions linked to the biliary tract (gamma-glutamyl transferase and alkaline phosphatase). Several biochemical tests are useful in the evaluation and management of patients with hepatic dysfunction. These tests can be used to detect the presence of liver disease, distinguish among different types of liver disorders, gauge the extent of known liver damage, and follow the response to treatment. Some or all of these measurements are also carried out (usually about twice a year for routine cases) on those individuals taking certain medications, such as anticonvulsants, to ensure the medications are not damaging the person's liver.

Although example reference ranges are given, these will vary depending on age, gender, ethnicity, method of analysis, and units of measurement. Individual results should always be interpreted using the reference range provided by the laboratory that performed the test.

Albumin

Albumin (Normal range: 3.5 to 5.3 g/dl) is a protein made specifically by the liver, and can be measured cheaply and easily. It is the main constituent of total protein (the remaining from globulins). Albumin levels are decreased in chronic liver disease, such as cirrhosis. It is also decreased in nephrotic syndrome, where it is lost through the urine. The consequence of low albumin can be edema since

the intravascular oncotic pressure becomes lower than the extravascular space. An alternative to albumin measurement is prealbumin, which is better at detecting acute changes (half-life of albumin and prealbumin is about 2 weeks and about 2 days, respectively).

Aspartate transaminase

AST, also called serum glutamic oxaloacetic transaminase or aspartate aminotransferase (Normal range: 6-40 IU/L), is similar to ALT in that it is another enzyme associated with liver parenchymal cells. It is raised in acute liver damage, but is also present in red blood cells, and cardiac and skeletal muscle, so is not specific to the liver. The ratio of AST to ALT is mostly useful in differentiating between causes of liver damage [17]. Elevated AST levels are not specific for liver damage, and AST has also been used as a cardiac marker. When the AST is higher than ALT, a muscle source of these enzymes should be considered. For example, muscle inflammation due to dermatomyositis may cause AST > ALT. This is a good reminder that AST and ALT are not good measures of liver function because they do not reliably reflect the synthetic ability of the liver and they may come from tissues other than liver (such as muscle).

Transaminases

AST/ALT elevations instead of ALP elevations favor liver cell necrosis as a mechanism over cholestasis. When AST and ALT are both over 1000 IU/L, the differential can include acetaminophen toxicity, shock, or fulminant liver failure. When AST and ALT are greater than three times normal but not greater than 1000 IU/L, the differential can include alcohol toxicity, viral hepatitis, drug-induced level, liver cancer, sepsis, Wilson's disease, post-transplant rejection of liver, autoimmune hepatitis, and steatohepatitis (nonalcoholic). AST/ALT levels elevated minorly may be due to rhabdomyolysis, among many possibilities.

Alkaline phosphatase

Alkaline phosphatase (ALP) (normal range: 30 to 120 IU/L) is an enzyme in the cells lining the biliary ducts of the liver. ALP levels in plasma rise with large bile duct obstruction, intrahepatic cholestasis, or infiltrative diseases of the liver. ALP is also present in bone and placental tissue, so it is higher in growing children (as their bones are being remodelled) and elderly patients with Paget's disease. In the third trimester of pregnancy, ALP is about two to three times higher.

Biliary tract disease produces relatively greater increases in ALP than increases in ALT, AST, or LD. ALP is associated with the plasma membrane of hepatocytes adjacent to the biliary canaliculus. Obstruction or inflammation of the biliary tract results in an increased concentration of the ALP in the circulation. Similar to ALT and AST, ALP is not specific for biliary tract disease. ALP is released by osteoblasts, the ileum, and the placenta. ALP is elevated: 1) in children 2- to 3-fold over adults because the child's skeleton is growing, 2) with bone disease involving osteoblasts (e.g., metastatic cancer or following a fracture), 3) in hyperparathyroidism where parathyroid hormone stimulates osteoblasts through a series of steps that enhances bone resorption (e.g., parathyroid adenoma, hyperplasia, or secondary hyperparathyroidism from vitamin D deficiency or renal disease), 4) in cases of ileal disease, and 5) during the third trimester of pregnancy because the placental isoenzyme is elevated.

Total bilirubin

Measurement of total bilirubin (normal range:0.1 to 1.0 mg/dl) includes both unconjugated and conjugated bilirubin. Unconjugated bilirubin is a breakdown product of heme (a part of hemoglobin in red blood cells). It is very hydrophobic and is mainly transported bound to albumin circulating in the blood. Addition of high-concentration hydrophobic drugs (certain antibiotics, diuretics) and high free fatty acids can cause elevated unconjugated bilirubin. Heme can also come from myoglobin, found mostly in muscle, cytochromes, found mostly in mitochondria, catalase, peroxidase, and nitric oxide synthase. The liver is responsible for clearing the blood of unconjugated bilirubin, and about 30% of it is taken up by a normal liver on each pass of the blood through the liver by the following mechanism: bilirubin is taken up into hepatocytes, 'conjugated' (modified to make it water-soluble) by UDP-glucuronyl-transferase, and secreted into the bile by CMOAT (MRP2), which is excreted into the intestine. In the intestine, conjugated bilirubin may be metabolized by colonic bacteria, eliminated, or reabsorbed. Metabolism of bilirubin into urobilinogen followed by reabsorption of urobilinogen accounts for the yellow color of urine, as urine contains a downstream product of urobilinogen. Further metabolism of urobilinogen into stercobilin

while in the bowels accounts for the brown color of stool. Thus, having white or clay-colored stool is an indicator for a blockage in bilirubin processing and thus potential liver dysfunction or cholestasis.

Increased total bilirubin (TBIL) causes jaundice, and can indicate a number of problems:

- **Prehepatic:** Increased bilirubin production can be due to a number of causes, including hemolytic anemias and internal hemorrhage.
- **Hepatic:** Problems with the liver are reflected as deficiencies in bilirubin metabolism (e.g., reduced hepatocyte uptake, impaired conjugation of bilirubin, and reduced hepatocyte secretion of bilirubin). Some examples would be cirrhosis and viral hepatitis.
- **Post hepatic:** Obstruction of the bile ducts is reflected as deficiencies in bilirubin excretion. (Obstruction can be located either within the liver or in the bile duct).

Direct bilirubin

The diagnosis is narrowed down further by evaluating the levels of direct bilirubin (Normal range: 0.1 to 0.4 mg/dl).

- If direct (conjugated) bilirubin is normal, then the problem is an excess of unconjugated bilirubin (indirect bilirubin), and the location of the problem is upstream of bilirubin conjugation in the liver. Hemolysis, or internal hemorrhage can be suspected.
- If direct bilirubin is elevated, then the liver is conjugating bilirubin normally, but is not able to excrete it. Bile ductobstruction by gallstones, hepatitis, cirrhosis or cancer should be suspected.

Congenital bilirubin disorders

About 5% of the population has Gilbert's syndrome, a mutation (or variation) in the UDP-glucuronyl-transferase promotor that manifests itself as jaundice when the individual is stressed. Autosomal recessive knockouts of UDP-glucuronyl-transferase can lead to Crigler-Najjar syndrome and elevations of unconjugated bilirubin. Defects in CMOAT (MRP2) results in Dubin-Johnson syndrome and elevations of conjugated bilirubin.

High bilirubin in neonates

Neonates are especially vulnerable to high bilirubin levels due to an immature blood-brain barrier that predisposes them to kernicterus/bilirubin encephalopathy, which can result in permanent neurological damage. Neonates also have a low amount of functional UDP-glucuronyl-transferase and can have elevated unconjugated bilirubin, since conjugation is limited. So, newborns are often treated with blue light (420-470 nm) to turn the hydrophobic, albumin-binding unconjugated bilirubin into a form that is more hydrophilic and able to be secreted in urine, sparing the neonate's brain.

Gamma glutamyl transpeptidase

Reference range: 50 to 420 IU/L

Although reasonably specific to the liver and a more sensitive marker for cholestatic damage than ALP, gamma glutamyl transpeptidase (GGT) may be elevated with even minor, subclinical levels of liver dysfunction. It can also be helpful in identifying the cause of an isolated elevation in ALP (GGT is raised in chronic alcohol toxicity). Produce glucose (gluconeogenesis); it is usually the last function to be lost in the setting of fulminant liver failure. The proximal convoluted tubule of the kidney, the liver, the pancreas, and the intestine are sources of GGT, in decreasing order of tissue concentration. Within the cell, GGT is located in microsomes and along the biliary tract plasma membrane, GGT is more commonly measured than 5'-NT because GGT testing is widely available on a variety of laboratory instruments. GGT is typically not elevated with bone disease. Combined elevations of ALP and GGT are compatible with biliary tract disease. However, if the ALP is elevated to a far greater extent than the GGT (or the GGT is normal), ALP sources other than the biliary tract, such as bone, must be investigated. GGT elevations occur in response to alcohol use and anticonvulsants, as GGT is induced by such agents.

International normalized ratio:

- Prothrombin time (PT) and its derived measures of prothrombin ratio (PR) and international normalized ratio (INR) are measures of the extrinsic pathway of coagulation. This test is also called "ProTime INR" and "INR PT". They are used to determine the clotting tendency of blood, in the measure of warfarin dosage, liver damage, and vitamin K status.

Nucleotidase:

- 5' Nucleotidase (5'NTD) is another test specific for cholestasis or damage to the intra- or extrahepatic biliary system, and in some laboratories, is used as a substitute for GGT for ascertaining whether an elevated ALP is of biliary or extrabiliary origin.

Coagulation test:

- The liver is responsible for the production of the vast majority of coagulation factors. In patients with liver disease, INR can be used as a marker of liver synthetic function as it includes factor VII, which has the shortest half life (2-6 hours) of all coagulation factors measured in INR. An elevated INR in patients with liver disease, however, does not necessarily mean the patient has a tendency to bleed, as it only measures procoagulants and not anticoagulants. In liver disease the synthesis of both are decreased and some patients are even found to be hypercoagulable (increased tendency to clot) despite an elevated INR. In liver patients, coagulation is better determined by more modern tests such as thromboelastogram (TEG) or thomboelastrometry (ROTEM).

Serum glucose:

The serum glucose test, abbreviated as "BG" or "Glu", measures the liver's ability to

Lactate dehydrogenase

Lactate dehydrogenase (LDH) is found in many body tissues, including the liver. Elevated levels of LDH may indicate liver damage. LDH isotype-1 (or cardiac) is used for estimating damage to cardiac tissue, although troponin and creatine kinase tests are more preferred [18].

Various approach for liver reprogramming

Failing liver transformed into healthy organ by virus therapy

Liver fibrosis, a form of scarring develops in chronic liver disease when hepatocyte regeneration cannot compensate for hepatocyte death initially collagen produced by myofirbroblasts (MFS) functions to maintain the integrity of the liver, but excessive collagen accumulation suppresses residual hepatocyte function ,leading to liver failure, as a strategy to generate new hepatocyte and limit collagen deposition in the chronically injured liver, we developed in the chronically injured liver, we developed in vivo reprogramming of MFS in to hepatocyte using adeno associated virus (AAV) vectors expressing hepatic transcription factor. Scientist first identified the AAV6 capsid as effective in transducing MFS in a mouse model of liver fibrosis. Scientists then showed in lineage tracing mice that AAV6 vector mediated *in vivo* hepatic reprogramming of MFS generate hepatocytes that replicate function and proliferation of primary hepatocytes and reduces liver fibrosis sanject a bhati as says

Genetically engineered bacteria can fight liver tumors

A new study found that certain strains of bacteria thieve in low oxygen environments, such as tumours and the suppression of hosts immune system also creates favorable conditions for bacteria to flourish. When deployed together with a traditional cancer drug, the bacteria shrank aggressive liver tumours in mice much more effectively than either treatment alone.

Researchers delivered artificial genetic circuits into the bacteria, which allow the microbes to kill cancer cells, in three different ways. One circuit produces a molecule called hemolysin, which destroys tumour cells by damaging this cell membranes. Another produces a drugs that induces the cell to undergo programmed suicide, and tumour.

Gene Therapy

Using gene therapy tyrosinemia type –I and other metabolic disease will allow patients to avoid a liver transplant and save more lives.

The medical research study tested gene therapy in pigs suffering from hereditary tyrosinemia type –I, a metabolic disorders caused by an enzyme deficiency [19]

The common treatment for this disease is a drug regimen

Through gene therapy the corrected liver cells are transplanted into diseased liver, resulting in enzyme production. This treatment is new form of cell transplantation that utilizes the patient own cells. So it does notrequire immunosuppressive drugs. This therapy resulted in improvement of pigs with HtT.1

Liver tissue by manupulating stem cells

Functional human and mouse tissue–engineered liver from adult stem and progenitor cells.

Tissue engineered liver was found to contain normal structural components such as hepatocytes, bile ducts and blood vessels. And the prevention of liver failure. Liver disease affects pediatric and adult patients, imparting linio people in the united states. liver transplantation is the only effective treatment for end stage liver diasease, but scarcity of available organs and the need for life long immunosuppressive medication make this treatment challenging.

Human induced pleuripotent stem (ips) cells are another possibility, so far, ips cells have remained immature developing into the functional and proliferative liver cells called hepatocytes, particularly one that could eliminate the need for immunosuppression.

Stem Cells in Liver Regeneration

The characteristic feature of the liver is its high regenerative capacity, and there has also been debate, with some skepticism, as to whether stem cells are involved in this process. This skepticism is primarily because partial hepatectomy (PHx), the surgical removal of (a) particular lobe (s) of the organ, has long been regarded as the paradigm for experimental analysis of the mechanisms underlying liver regeneration [20]. The PHx protocol does not cause any injury to the remnant hepatic tissue, and the subsequent regenerative process is considered to be achieved by hypertrophy and proliferation of mature hepatocytes, without apparent involvement of any immature stem cell population. Indeed, the results of recent genetic lineage tracing studies in mice support this notion [21], although a small yet significant proportion of newborn hepatocytes generated from cellular sources other than preexisting hepatocytes has also been suggested. Nevertheless, the robust regenerative capacity of hepatocytes manifested upon PHx is quite striking and thus might have contributed to a widespread prejudice that the liver does not require any stem/progenitor cells for its regeneration. While PHx is truly an excellent model to study the process of compensatory growth of the liver and provides useful information relevant to living donor liver transplantation, it does not faithfully recapitulate pathological situations in many human liver diseases, which often involve hepatocyte death and concomitant induction of inflammatory and fibrogenic responses. Under many pathological conditions, such as chronic viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease, unique epithelial cell populations emerge and expand that are not usually observed in a normal liver. These cells typically exhibit immature and intermediate phenotypes between hepatocytes and cholangiocytes as determined by morphology and molecular marker expression, and they are considered to be bipotential progenitor cell populations. Such cell populations have been termed in several different ways, such as ‘‘ductular hepatocytes,’’ ‘‘atypical ductal cells,’’ ‘‘intermediate hepatobiliary cells,’’ or ‘‘hepatic/liver progenitor cells (HPCs/LPCs).’’ The term ‘‘oval cells,’’ which was originally coined to describe a specific, ovoid cell population observed in a rat model of liver carcinogenesis, is also often used, particularly in rodent models. Some researchers consider such disease-activated progenitor cell populations as ‘‘liver stem cells ’’and, indeed, the term ‘‘oval cells’’ is sometimes introduced in literature as a synonym for liver stem cells. Oval cells are the prototype for adult liver stem/progenitor cell populations, which emerge when the liver is injured under conditions.

Diabetes medicine effective against liver disease

The diabetes medicine pioglitazone is effective in stopping the progression of non-alcoholic steaohepatitis (NasH), a liver disease caused by buildup of fat in the organ, in people with type 2 have fat in the liver and nearly one third are estimated to have NasH.

Pioglitazone, a member of the thiazolidinedone class of medicines also known as glitazones works by decreasing insulin resistance in muscle and fat cells and reducing glucose production in the liver.

NasH, which occurs in people who drink little to no alcohol, is often known as "silent" liver diseases because people with the condition frequently have no symptoms.it is characterized by fat in the liver, along with liver inflammation and damage, and is second leading cause of liver transplants.

NasH can lead to liver cancer or cirrhosis. people who have obesity and prediabetes or type 2 diabetes are at greatest risk of developing the condition.

To determine the effectiveness and safety of pioglitazones for their type of liver disease, researchers treated 101 people with prediabetes or type 2 diabetes and NasH with either the medicine or placebo for three year's. The participants were also asked to follow a low–calorie diet. The researchers found that pioglitazone "reduced fatty liver disease activity" in 58% of the subjects and reduced the condition enough that it was no longer consider a threat to the liver in 51% of the participants.

Type 2 diabetes drug prevents cardiovascular disease, it can reduce disease from excess liver fat accumulation and liver inflammation, and halt fibrosis that leads to cirrhosis.

Virtual reality technology to remove liver fibrosis

The sun –yat- sen memorial hospital in guangzhour, south china has successfully removed a liver fibrosis with the help of virtual reality technologies.

In this case, a seven–year old patient underwent a non steatotic liver fibrosis which is a rare child hood liver disease. The growth weighed 1.4 kilograms, three times larger than the liver of a normal child.

As the disease takes up almost the whole of the patient's entire thorasic and abdominal cavity, the medial team used the technique of computerized 3D reconstruction to decide the best surgical slice plane and operation pathway.

By transforming the 2D x-ray film in to a 3D model, doctor were able to define the relation of blood vessels, biliary tract and tissues inside the liver, and so could accurately remove the fibrosis from the liver. Virtual reality technology will be able to boost the success rate of operations in a less invasive way. After the surgery the patient, with a liver only half the size of normal size, is now reportedly recovering well.

Transcription factor-mediated reprograming of fibroblasts to hepatocyte-like cells

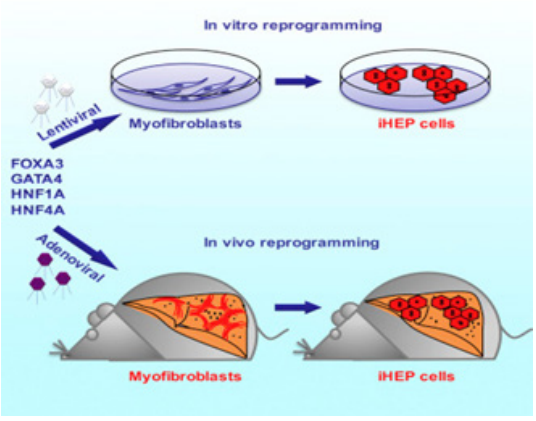
Direct conversion by overexpression of defined transcription factors (TFs) is a promising new method that can generate desired cell types from abundant, accessible cells. While previous studies have reported hepatic generation from fibroblasts, tremendous interest exists in the understanding of hepatic reprograming and its applicability in regenerative medicine. Here, we show that overexpression of Yamanaka factors can induce reprograming of mouse fibroblasts into cells that closely resemble hepatocytes *in vitro* in the presence of an optimized hepatic growth medium. By screening the effects of 20 candidate transcription factors, we identified a combination of three TFs (*Hnf4a*, *Cebpa*, and *Nr1i2*) that can convert fibroblasts into a hepatic fate. These factors in conjunction with Yamanaka factors

increase the efficiency of hepatic reprograming. The induced hepatocyte-like (iHep) cells have multiple hepatocyte-specific characteristics; express hepatocyte-specific markers, glycogen storage, albumin secretion, urea production, as well as low-density lipoprotein and indocyanin green uptake [22].

Direct conversion of mouse fibroblasts to hepatocyte-like cells by defined factor

The location and timing of cellular differentiation must be stringently controlled for proper organ formation. Normally, hepatocytes differentiate from hepatic progenitor cells to form the liver during development [23,24]. However, previous studies have shown that the hepatic program can also be activated in non-hepatic lineage cells after exposure to particular stimuli or fusion with hepatocytes [25-31]. These unexpected findings suggest that factors critical to hepatocyte differentiation exist and become activated to induce hepatocyte-specific properties in different cell types. Here, by screening the effects of twelve candidate factors, we identify three specific combinations of two transcription factors, comprising Hnf4α plus Foxa1, Foxa2 or Foxa3 that can convert mouse embryonic and adult fibroblasts into cells that closely resemble hepatocytes *in vitro*. The induced hepatocyte-like (iHep) cells have multiple hepatocyte-specific features and reconstitute damaged hepatic tissues after transplantation. The generation of iHep cells may provide insights into the molecular nature of hepatocyte differentiation and potential therapies for liver diseases.

Direct Reprogramming of Hepatic Myofibroblasts into Hepatocytes *in Vivo* Attenuates Liver Fibrosis



Direct conversion of mouse fibroblasts to hepatocyte-like cells by defined factor

- Transcription factor induction converts hepatic myofibroblasts to iHeps *in vitro*
- Lineage tracing documents *in vivo* reprogramming of myofibroblasts into iHeps
- iHeps induced *in vivo* closely resemble hepatocytes
- *In vivo* induction of iHeps ameliorates chemically induced liver fibrosis

Contents	Drugs	Dose	Adverse effects
1) corticosteroids	a) prednisone	5 mg	Cushing's syndrome, osteoporosis.
	b) prednisolone	5 mg	Bleeding, dry skin.
	c) dexamethasone	0.1 mg	Insomnia, muscle weakness, spinning sensation.
	d) betamethasone	0.1 mg	Nausea, bruising, bloating.
	c) hydrocortisone	20 mg	Sweating, mood changes, stomach pain, convulsions, glaucoma.
2) Interferon	a) peg interferon α-2a	180 µg	Fatigue, muscle aches.

	b) peginterferone α-2b	1.5 µg	Depression, anxiety, bonemarrow suppression, rash.
3) Antivirals	a) acyclovir	400 mg	Loss of appetite, light headedness, dirrohea
4) Diuretics	a) furosemide	40 mg	Ringing in ears, hearing loss, clay coloured stools, jaundice, itching.
	b) spironolactone	100 mg	Erectile dysfunction, gynaecomastia, dry mouth, thirst.
	c) amiloride	5 mg	Diarrhea, dizziness, hypokalaemia, skin rash.
5) vit k supplements	a) phytonadione	10 mg/ml	Trouble breathing, itching, swelling, allergic reactions.
	b) menadione	2.5-25 mg	Facial flushing, cyanosis, phlebitis Dyspnea
6) antibiotics	a) erythromycin	250-500 mg	Fainting, hearing problems, dark urine, clay coloured stools.
	b) azithromycin	250 mg	Mild rash, sense of taste or smell, insomnia.
	c) chloramphenicol	100 mg/kg/day	Confusion, altered mental status, fever.
7) Albumin		6-8 g/lt	Swelling, fever, vomiting, headache, Flushing

Prevention

Follow instructions on medications: If you take acetaminophen or other medications, check the package insert for the recommended dosage, and don't take more than that.

- **Tell your doctor about all your medicines:** Even over-the-counter and herbal medicines can interfere with prescription drugs you're taking.
- **Drink alcohol in moderation, if at all:** Limit the amount of alcohol you drink to no more than one drink a day for women of all ages and men older than 65 and no more than two drinks a day for younger men
- **Avoid risky behavior:** Get help if you use illicit intravenous drugs. Don't share needles. Use condoms during sex. If you get tattoos or body piercings, make sure the shop you choose is clean and safe. Don't smoke.
- **Get vaccinated:** If you're at increased risk of contracting hepatitis, if you've been infected with any form of the hepatitis virus or if you have chronic liver disease, talk to your doctor about getting the hepatitis B vaccine. A vaccine is also available for hepatitis A.
- **Avoid contact with other people's blood and body fluids:** Accidental needle sticks or improper cleanup of blood or body fluids can spread hepatitis viruses. Sharing razor blades or toothbrushes can also spread infection.
- **Don't eat wild mushrooms:** It can be difficult to distinguish an edible mushroom from a poisonous one.
- **Take care with aerosol sprays:** When you use an aerosol cleaner, make sure the room is ventilated, or wear a mask. Take similar protective measures when spraying insecticides, fungicides, paint and other toxic chemicals. Follow manufacturers' instructions.
- **Watch what gets on your skin:** When using insecticides and other toxic chemicals, cover your skin with gloves, long sleeves, a hat and a mask.
- **Maintain a healthy weight:** Obesity can cause a condition called nonalcoholic fatty liver disease, which may include fatty liver, hepatitis and cirrhosis.

Conclusion

This study showed various techniques used in liver disease such as bacteria, virus, gene therapy, stem cells and diabetes drug are given to improve disease status. Virtual technology are also given daily to improve disease condition. The main purpose of using these technique because for liver transplant we need human volunteer that, the human volunteers should sacrifice their life, so to prevent that we are using these technique to improve liver failure and give new lease of life to many people.

References

1. Vinay Kumar., *et al*. "Robbins and Cotran pathologic basis of disease (7th ed)". *St. Louis, MO: Elsevier Saunders* 23.5 (2005): 482-483.
2. Tortora., *et al*. "Principles of Anatomy and Physiology (12th ed.)". *John Wiley & Sons* (2008): 945.
3. Dorland. "Dorland's Illustrated Medical Dictionary 32nd Edition". Elsevier (2011): 2176.
4. Kmieć Z. "Cooperation of liver cells in health and disease". A*dvances in Anatomy, Embryology and Cell Biology* 161: III–XIII (2001): 1-151.
5. Pocock and Gillian. "Human Physiology (*Third* ed.)". *Oxford University Press* (2006): 404.
6. Gilbert SF. "Developmental Biology (6th ed.)". *American journal of medical genetics* 99.2 (2001): 170-171.
7. Berg T., *et al*. "β-catenin regulates mesenchymal progenitor cell differentiation during hepatogenesis". *Journal of Surgical Research* 164.2 (2011): 276–285.
8. Lade AG and Monga SP. "Beta-catenin signaling in hepatic development and progenitors: which way does the WNT blow?" *Developmental Dynamics* 240.3 (2011): 486–500.
9. Clemente and Carmin D. "Anatomy a Regional Atlas of the Human Body". *Philadelphia: Lippincott Williams & Wilkins* (2011): 694.
10. Shneider., *et al*. "Pediatric Gastrointestinal Disease". *Connecticut*: PMPH-USA (2008): 751.
11. "Human Anatomy & Physiology + New Masteringa & p With Pearson Etext". *Publisher: Benjamin-Cummings Publishing Company* (2012): 881.
12. Extraintestinal Complications: Liver Disease Crohn's & Colitis Foundation of America. Retrieved (2010
13. Lee and Mary. "Basic Skills in Interpreting Laboratory Data". *ASHP* (2009). 259.
14. Johnston DE. "Special considerations in interpreting liver function tests". *American Family Physician* 59.8 (1999): 2223–2230.
15. McClatchey and Kenneth D. "Clinical laboratory medicine". *Lippincott Williams & Wilkins* (2002): 1693.
16. Mengel., *et al*. "Family medicine: ambulatory care & prevention". *McGraw-Hill Professional* (2005): 268.
17. Nyblom H., *et al*. "High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking". *Alcohol Alcohol* 39.4 (2004): 336–339.
18. Nageh T., *et al*. "Cardiac troponin T and I and creatine kinase-MB as markers of myocardial injury and predictors of outcome following percutaneous coronary intervention". *International Journal of Cardiology* 92.2-3 (2003): 285–293.
19. Trary grikschief, Nirmala mavila, Andrew treccastin ,ryan spurier,yixiaw ,xiaongang hou , david james from California institute of regenerative medicine and the European union.
20. Michalopoulos GK. "Liver regeneration". *Journal of Cellular Physiology* 213.2 (2009): 286-300.
21. Espan˜ ol-Sun˜ er R., *et al*. "Liver progenitor cells yield functional hepatocytes in response to chronic liver injury in mice". *Gastroenterology* 143.6 (2012): 1564–1575.e7.
22. Behshad paournasr ,mohammad Hassan Asghari vostikolaee,Hossein baharvand.
23. Zaret KS. "Regulatory phases of early liver development: paradigms of organogenesis". *Nature Reviews Genetics* 3.7(2002): 499-512.
24. Zaret KS and Grompe M. "Generation and regeneration of cells of the liver and pancreas" *Science* 5; 322(5907) (2008): 1490-1494.
25. Scarpelli DG and Rao MS. "Differentiation of regenerating pancreatic cells into hepatocyte-like cells". *Proceedings of the National Academy of Sciences* 78.4 (1981): 2577-2581.
26. Reddy JK., *et al*. "Induction and origin of hepatocytes in rat pancreas". *The Journal of Cell Biology* 98.6 (1984): 2082–2090.
27. Wang X., *et al*. "Liver repopulation and correction of metabolic liver disease by transplanted adult mouse pancreatic cells". *American Journal of Pathology* 158.2 (2001): 571-579.
28. Lee KD., *et al. "In vitro* hepatic differentiation of human mesenchymal stem cells". *Hepatology* 40.6 (2004): 1275-1284.
29. Banas A., *et al*. "Adipose tissue-derived mesenchymal stem cells as a source of human hepatocytes". *Hepatology* 46.1 (2007): 219-228.

30. Wang X., *et al.* "Cell fusion is the principal source of bone-marrow-derived hepatocytes". *Nature* 24;422 (6934) (2003): 897-901.

31. Vassilopoulos G., *et al*. "Transplanted bone marrow regenerates liver by cell fusion". *Nature* 24;422(6934) (2003): 901-904.