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AN INSIGHT INTO THE ORGANOGENESIS OF HUMAN LIVER

***A. Manoj and Annamma Paul**

Department of Anatomy, School of Medical Education, M.G University (Accredited by NAAC with A-Grade), Kottayam, Kerala, India.

***Corresponding Author: A. Manoj**
Department of Anatomy, Government Medical College, Thrissur- 680596, under Directorate of Medical Education of Health and Family Welfare –Government of Kerala, India.

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ABSTRACT

The objective of the current study was to learn the development of liver inorder to strengthen the Gross Anatomy and Microsopic Anatomy studies of liver and also ascertain the congenital anomalies of liver due to disturbance in its organogenesis. Hepatogenesis commence at Fourth week of Intrauterine life by proliferation of endodermal diverticulam at the ventral aspect of the junction between Foregut and mid gut into the septum transversum where it divides into Pars Hepatica and Pars Cystica forms liver and gall bladder respectively. On seventh week of fetal development Pars hepatica differentiates into clusters of liver parenchyma in which billiary capillaries emerges for delivery of its secretions. The trunk of hepatic buds persists as common bile duct and its two branches were right and left hepatic ducts. Haemopoeitic cells, Kuffer cells, Capsule and fibroareolar tissue derived from mesoderm of septum transversum. Fibroblast Growth Factor 2 (FGF2) secreted by cardiac mesoderm induces the development of hepatic bud which generates hepatoblasts, intending the formation of hepatocytes. Pars cystica and its duct give rise to gall bladder and its ducts. The stalk of endodermal diverticulam connected to foregut forms the common bile duct. Umbilical and Vitelline veins of sinus venosus grows into septum transversum which breaks into capillary network eventually forms hepatic sinusoids between the plates of liver cells. The abnormal development of liver leads to absence of left lobe of liver, Reidel's lobe, Supradiaphagmatic liver, ectopic lobes of liver etc.

KEYWORDS: Organogenesis, Pars Hepatica, Septum Transversum, Kupffer cells, Congenital anomalies.

INTRODUCTION

Liver is the largest gland in human which starts to appear as liver primordium on 22 day after conception. It appears at the superior intestinal portal, caudal and ventral to the heart. The foregut endoderm expresses liver specific genes which differentiates into liver tissue by Fibroblast Growth Factor 2 (FGF2) secreted by cardiac mesoderm induces the development of hepatic bud. The hepatoblast nuclear transcription factors (HNF3 and 4) differentiates liver cells/ hepatocytes and billiary cell lineage.[4] On 24 day of gestation the hepatic diverticulam grows into the septum transversum which contains vitelline and umbilical veins. Initially the splanchenic mesoderm spreads anteriorly and meets in the midline beneath the pharynx called hepatocardiac mesoderm, which stimulates the demarcation of the overlying endoderm at anterior intestinal portal. The hepatic bud appears, the hepatic and cardiac mesenchyme become segregated for which hepatic mesenchyme stimulates the proximal part of endodermal cord to differentiates into hepatocytes and intrahepatic bile ducts (IHBD). Simultaneously the endodermal hepatocytes stimulates the mesenchyme to form the endothelial cells of the liver sinusoids. Hepatic bud divides into right and left branches surmounted by solid plates of hepatocytes called Hepatic cylinders. The vitelline and umbilical veins divide into plexus of vessels and invading the endoderm cells move into the spaces around between them forms sinusoids. By day 32 blood flow from umbilical veins has been tapped by the parenchyma that surround the venous channels. These channels become the liver sinusoids. The right umbilical vein regresses in the 6th week. The left vein carries placental blood to the foetus until birth. Its remnant is the round ligament in the free edge of the free falciform ligament. Infraheptic part of right and left vitelline veins are the forerunners of the development of portal vein. The intrahepatic parts incorporates with endodermal hepatocytes give rise to hepatic sinusoids and endothelial cells respectively. The suprahepatic part of right vitelline vein forms the hepatic veins and terminal part of Inferior venacava.[1,3,5,6,7,8]

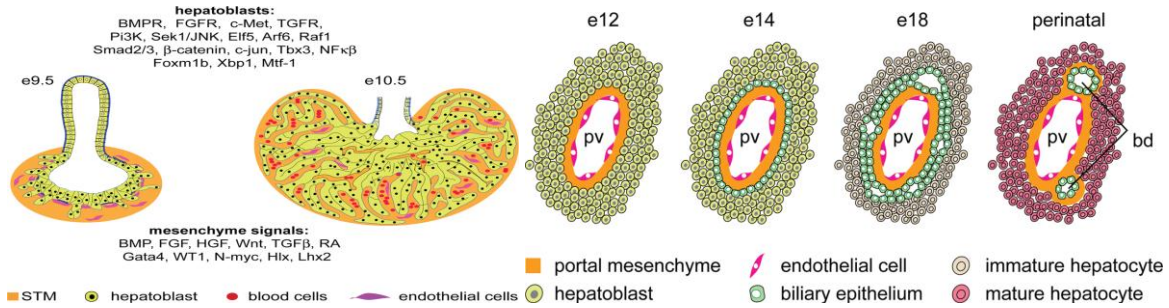

Fig. 1: Showing Hepatogenesis and differentiation of Endoderm into hepatocytes and IHBD.

By day 51, the intrahepatic veins have nearly attained the normal adult distribution and segmentation. The hepatic arteries and bile duct do not advance as quickly towards their adult pattern. The investing cores of parenchyma at first 3-5 cells thickness become reduce to a single layer near term. Growth of liver makes it bulge out of the transverse septum so that the liver becomes a truly abdominal organ lying in the ventral mesentery. The Glisson capsule (GC) of liver and central tendon of diaphragm remains as an indication of the origin of the liver from the transverse septum. By 5th week of gestation the liver embraces as much as 10% of the body weight and the growing liver took most of the spaces of abdominal cavity thus mid gut loop herniates through the umbilicus called physiological hernia. The size of liver got reduces on 10th week of embryonic period resulting reduction of physiological hernia of midgut loop. Its relative size decreases to 5% by term. Simultaneously by 30th day of intrauterine life ventral bud of pancreas develops from proximal part of hepatic diverticulam which fuses with dorsal bud due to rotation of gut leading to formation of pancreas and its ducts system. The roataion bringing the explanation for conjoint opening of main pancreatic duct and common bile duct at hepatopancreatic ampulla papilla of at junction between superior and inferior intestinal portal of duodenum. Adult type of RBC, granulocytes and platelets are produced in the liver between 9th and 24th weeks of prenatal life. Bile is secreted by hepatocytes on 3rd month of gestation. Mean while proximal part being pars cystica which enlarges and canalizes to form gall bladder and cystic duct respectively which unites with hepatic ducts to form bile duct in which bile deliver into the intestine by 5th month. Initially both lobes of liver develops equally, later left lobe regresses, because it suffers from low nutritional status by oblique direction of the left branch of portal vein.[9,10,11]

MATERIALS AND METHODS

The current study was conducted at department of Anatomy ,School of Medical Education Mahatma Gandhi University- Kottyam, Kerala; India for the partial fulfilment of the Post Graduate degree of Medical Anatomy under Mahatma Gandhi University- Kottyam during December 1995 to December 1997. The materials used in this study were clay models of Liver development and Charts to substantiate the Embryology of liver inorder to strengthen liver Gross Anatomy and Microscopy studies.

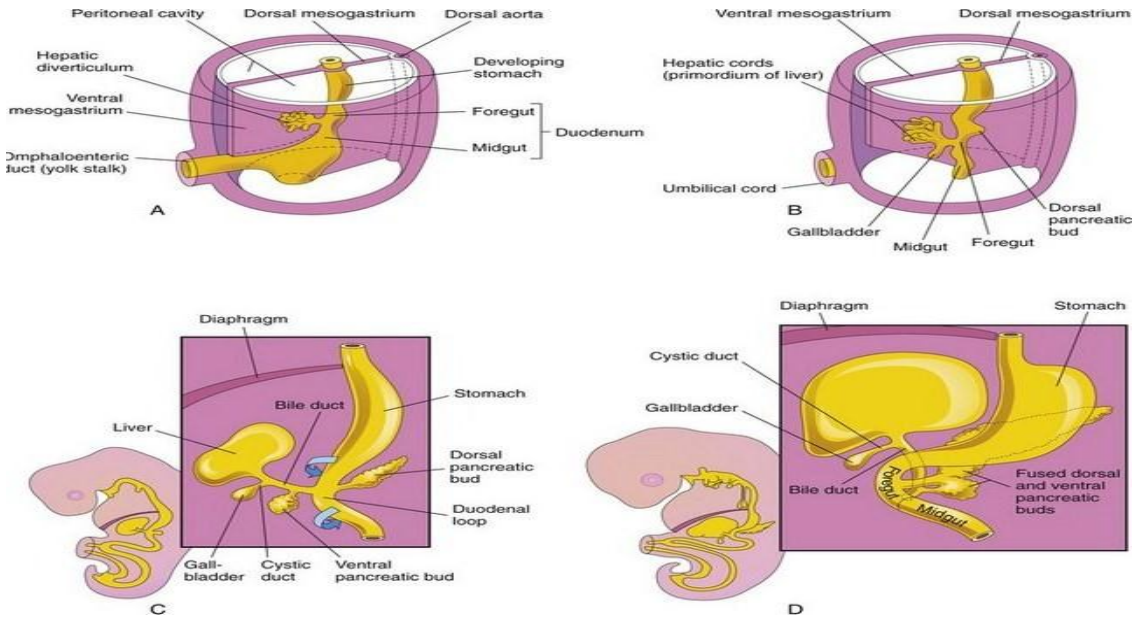

Figure 2: Exhibiting the Development of Liver A. Hepatic diverticulam grows into ventral mesogastrium (Septum transversum), B. Hepatic cords and Gall bladder, C. Origin of Cystic duct, Bile duct and Ventral Pancreatic bud, D. Conjoint opening of Common bile duct and Main Pancreatic duct at Duodenum.

OBSERVATIONS

- The liver and biliary system develops from the hepatic diverticulam.
- The distal end of hepatic diverticulam proliferates rapidly in the septum transversum to form hepatoblasts which further develops hepatocytes and intrahepatic billiary system.
- The proximal part in the ventral mesogastrium does not proliferates rapidly, become relatively narrow and forms the extrahepatic biliary system. A secondary outgrowth as pars cystic from it forms the gall bladder and cystic duct during 4 weeks.
- Simultaneously the ventral pancreatic bud also develops from the proximal part of the hepatic diverticulam which creates the conjoint opening of the bile duct with main pancreatic duct to form hepatopancreatic ampulla during mid rotation of gut.
- The vitelline and umbilical veins disrupted by growth of hepatic cells in the septum transversum, forms the liver sinusoids.
- The septum transversum mesoderm surrounding the hepatic cords forms the Kuppfer cells and haemopietic cells.
- In growing foetus a major source of blood to the liver is the umbilical vein which supplies nutrients to the growing foetus because the infant liver does not perform the normal filteration of digestive and absorptive products hence it receives nourishment from mother via placenta through umbilical veins.
- The foetal liver releases some blood stem cells that migrate to the foetal thymus, so initially the lymphocytes called T-cells are created from foetal liver stem cells. Once the baby is delivered the formation blood stem cells will be shifted to red bone marrow.
- In perinatal stages more functions are acquired by hepatocytes and this driven by hormones which initiates transcription of many liver specific genes.

DISCUSSION

Morphogenesis of liver is believed to be providing essential knowledge of the scientific basis for understanding mechanisms underlying both normal and abnormal development. Conventional study of hepatogenesis gave morphologic clues concerning the patterns of abnormal morphologic development diverge from the normal. Contemporary molecular technology has illuminated the origin of many defects that have a genetic origin, and it has provided some clues concerning the genesis of liver. Grey's et al and Dutta et al reported that hepatic diverticulam begins as a pouch derived from the distal end of foregut on 4th week of gestation[1&7]. The current study agrees with the above findings. However Salder et al reported that hepatic diverticulam develops during the middle of 3rd week of gestation.[4] The source of development of hepatocytes and IHBD is derived from hepatic cylinders reported by Grey,s et al.[1] Neverthless Salder et al, Dutta etal, Singh et al, Ranganathan et al and present study documented that hepatocytes and IHBD is being by differentiation of endoderm of the distal part of hepatic diverticulam.[4,5,7,8] Grey's etal, Salder et al, Dutta et al Singh et al reported that invasion of vitelline vein and umbilical veins incorporates with septum transversum will be the forerunner of hepatic sinusoids.[1,4,5,7] Our study agrees the above reports. According to Salder et al bile synthesis, secretion and its delivery operates during 12th week of prenatal life[4]. We documented bile secretion has been beginning on 3rd month of fetal life. The data of Dutta etal, Ranganathan et al and current study observed that of extra hepatic bile ducts (EHBD) has derived from proxiamal part and trunk of hepatic diverticulam.[7,8] Our study agrees with other datas for showing that ligaments associated with hepar providing its secondary supports has been due to differentiation of ventral mesogastrium. Congenital anomalies of liver such as Absence of left lobe,[12] Hepatic Transposition,[13] Reidel's lobe,[14] Supradiaphragmatic liver,[15] Accessory or Ectopic lobe,[16] Mesenchymal hemartoma,[17] Atresia of Intrahepatic billiary apparatus,[18] Congenital Hepatic Fibrosis,[19] Vascular malformation,[20] and Fibrous appendix of liver,[21] has been evidencing the fact they are due the defect in the FGF2 and HNF3&4 gene expression during hepatogenesis (Table:2).

Table 1: Delineating the Comparison of various Events of Hepatogenesis.

Authors	Events of Organogenesis of Liver					
	Origin of Hepatic Diverticulam	Source of Development of Hepatocytes and IHBD	Invasion of Vitelline vein	Bile secretion and its delivery	Formation of EHBD/ Bile duct	Fate of ventral mesogastrium
H Greys et al	4th week	Hepatic cylinders	Synusoidal system		Intrahepatic ducts Diverticulam of duodenum	Falciiform Triangular Coronary Ligaments Lesser omentum
G.J Romanes et al	-	-	-	-	-	Falciform Hepatogastric ligaments
RMH McMin et al	Y shaped endo.divertic	Branching buds	Hepatic bud	-	Embryologica l centre	-

	ulam					
Sadler et al	Middle of 3rd week	Endodermal cords	Hepatic sinusoid	12th week	Hepatic diverticulam	Ventral mesentry Lesser om. Falciform lig
A.K. Dutta et al	4th week	Endoderm	Sinusoids IVC Ductus venosus Portal vein	-	Trunk of hepatic bud and its branches	Falciform Coronary Triangular Lesser omentum
IB Singh etal	-	Endoderm	Sinusoid Hepato cardiac channel	-		Lesser omentum Coronary Falciform ligaments
Ranganathan et al	Early stage	Endoderm lining of foregut	-	12th week	Proximal pat of diverticulam & branches	Lining cells of sinusoids, kupffer cells Hemopoitic tissue Falciform lig. Lesser omn Central tendon & pericardium
Current study	4th week	Endoderm pouch junction between foregut and midgut	Sinusoids Hepato cardiac Channel & IVC	3rd month of gestation	Trunk of hepatic bud and divisions	Caudal part of septum transversum Become ventral mesogastrium

Table 2: Exhibiting the Congenital Anomalies of Hepar.

Congenital Anomalies	Causes & Manifestations	Authors
Absence of left lobe,[12]	Neoplasia, Chronic damage, Trauma, Surgical resection and Agenesis with Absence of left vessels	Merril et al
Hepatic Transposition,[13]	Pseudoaneurysms after liver transplantation	Fronkalsrud et al
Reidel's lobe,[14]	Downward Tongue like projection of right lobe to the GB	Reidels et al
Supradiaphragmatic liver,[15]	Liver tissue extend into right hemithorax through opening of diaphragm	Organ et al
Accessory or Ectopic lobe,[16]	Large accessory lobe connected to mother liver by a stalk. Ectopic liver not connected to mother liver but to Gall bladder	Bassis et al
Mesenchymal hemartoma,[17]	Benign liver tumor in children due to abnormal expression of microRNA of chromosome19	Maresch et al
Atresia of Intrahepatic billiary Apparatus,[18]	Obstructive cholingiopathy in newborn with hepatomegaly	Ahrens et al
Congenital Hepatic Fibrosis,[19]	Portal tract fibrosis with portal hypertension in children	Murray et al
Vascular malformation,[20]	Abnormal ansatomosis of portal vein, hepatic artery and hepatic veins.	Naganuma et al
Fibrous appendix of liver,[21]	Atrophied remains of left lobe in children	Gao XH et al

CONCLUSION

Hepatogenesis of liver has been pertaining to basic knowledge embryologic development of liver, normal anatomy of biliary tree and its molecular origin will help in understanding and identifying the origin of the anomalies of hepatic morphology occurring in the course of organogenesis. Familiarity of these variants is imperative prior to diagnosis of various congenital anomalies by so far seek.

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