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LIVER GROWTH IN ZEBRAFISH (*DANIO RERIO*)

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ABSTRACT
This study on Zebrafish liver development. Liver is one of the major interior organs in the body and its eminence for the metabolism, purification and homeostasis has been well recognized. In this analysis, I concise current growths in studying the liver initiation and growth through embryogenesis by zebrafish as the model system. We mostly focused on the topics connected to the requirement of hepatoblasts from the endoderm, the creation and development of the liver bud, the variation of hepatocytes and the bile duct cells from the hepatoblasts, and lastly the role of mesodermal indications in directing liver expansion in zebrafish.
KEYWORDS: *Zebrafish, Liver Development, Endoderm, Model Organism.*

1. INTRODUCTION

Liver is a vital organ in the body and executes a number of vital actions including the metabolism, homeostasis, and detoxification. Hepatocytes make up the common of a liver and apply most of this liver's functions, for instance metabolism of the wide range of endogenous and the exogenous matters, synthesis of the blood protein and, also the clotting factors, amino acids, fat, storage of glycogen, and, iron, in addition to secretion of the bile. The liver diseases together with hepatitis B, cirrhosis and the hepatocellular carcinoma (HCC) are global healthiness problems and, cause from top to bottom death toll yearly, making excessive impend to human health and the social expansion. Consequently, it is vital to exemplify liver growth and its cellular and, the molecular mechanism. The facts learned will not lone make new approaches for early monitoring, deterrence and therapy of these liver diseases but also assistance to guide in the vitro culture and the transplantation of this liver. In this analysis, I fleetingly concise the major developments in the zebrafish in the subsequent aspects of the liver development: the beginning and the specification of hepatoblasts within the endoderm, the creation and growth of the liver bud, the discrepancy of hepatocytes and biliary cells from the hepatoblasts and the parts of mesodermal signals throughout the liver expansion.

2. ZEBRAFISH AS AN OUTSTANDING MODEL SYSTEM FOR REVIEWING THE LIVER GROWTH

Zebrafish fit in to teleosts whose liver has unique histological features compared with that in this mammalian. Its gateway veins, hepatic arteries and, the large biliary ducts are disseminated stochastically within this hepatic parenchyma but are not congregated in portal tracts as in this mammalian. In addition, hepatocytes are organized as tubules that enfold small bile vessels sooner than as bilayered hepatocyte plates looked in this mammalian. The intrahepatic of bile ducts are resulting from this bile cannaliculi and, form a system of the biliary channels; the bile is then composed in this gallbladder over large ducts and, the extrahepatic biliary system. In the mammals, liver organogenesis starts with the formation of the population of hepatic ancestor cells in the ventral foregut "endoderm", tracked by the requirement of this definitive hepatoblasts. In conclusion, the hepatoblasts distinguish into the functional hepatocytes and the biliary duct cells. Though the process of the liver beginning and growth at this anatomic level is well recognized, its molecular and the cellular mechanisms are comparatively alternated over genetic tactics, and only inadequate data has been got up to now. The study of this liver growth is mainly forced by the model faunas used for instance mouse and the chicken, which cannot be used for this large-scale genetic study. Zebrafish, conversely, has become a general vertebrate model throughout last decade as both genetic and the experimental embryological methods can be effortlessly applied to this animal. Zebrafish is the small steamy freshwater fish inborn to South Asia and is a communal aquarium fish everywhere the world. In 1981, Streisinger and his co-workers printed a landmark paper relating the genetic procedures for making clones of the homozygous diploid zebrafish. At this Cold Spring Session in the year 1994, zebrafish was officially recognized as a model animal for the vertebrate growth study. In the year 1996, a whole issue of the 'Development' journal stated two sovereign large-scale mutagenesis screens for the phenotypic mutants and the study of some of the gotten mutants in the zebrafish. With increasingly exhilarating findings published in a wide range of the journals, zebrafish has exposed its great potential in the life science. Now it has converted an ideal model organism for this study of the vertebrate development and the disease, functional genomics, organ function, behaviour, toxicology and the drug discovery. This is mostly attributed to some of its compensations, as well as its easy and the economical upkeep, little generation time, outside fertilization, large nos. of fast developing embryos formed per mating, and the external progress of the transparent embryos. Given that fundamental progressive programs are well communal among the vertebrate animals, the studies on zebrafish should logically donate to a better thoughtful of this molecular and genetic mechanisms of growth underlying other classes of the vertebrates with human. Along with the above cited characteristics, zebrafish has some exclusive benefits for studying the liver development. In the mammals, the embryonic liver is an initial hematopoietic organ, so, mutations disturbing liver or blood growth a lot cause anemia and, even timely lethality throughout embryogenesis

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that will obscure the study of liver growth in the mammalian system. Additionally, mammalian embryogenesis happens intrauterine which makes this embryonic liver unreachable for this study of the progressions of liver growth via the direct genetic method. Instead, the blood (primitive) in the zebrafish forms in the intermediate cell mass first and afterward (definitive) in the posterior blood land and finally kidney, not in the liver. For the meantime, subsequently zebrafish gets its nutrient mostly from yolk through embryogenesis, zebrafish can continue to develop comparatively usually for a few days short of the cardiovascular system. These compensations permit the studies on liver growth and disease in the zebrsfish even the mutations upsetting blood growth. Finally, the obtainability of a no. of transgenic fish lines harbouring the reporter genes "gfp" and/or "rfp" driven by the variety of endoderm-specific developers or the heat-shock organizer not only permit researchers to track the growing processes of the liver in vivo but also importantly facilitate mutant screening based on this expression of the correspondent genes.

3. THE ORIGINATION AND DESCRIPTION OF HEPATOBLAST

The endoderm provides rise to this hepatoblast. Fate plotting tests have exposed that, at primary gastrula stage, endoderm cells situated in this ventral part tend to distinguish to liver sprout while endoderm cells located on the dorsal side are suitable to give increase to the pancreas. These liver-only ancestors are positioned significantly additional from the dorsal planner than the pancreas-only forerunners. Clones that donate to both liver and the pancreas are disposed to to lie in more intermediary positions. Presently, there are 2 dissimilar hypotheses concerning the beginning of liver progenitor cells in the zebrafish. Based on the fact that this liver exact marker ceruloplasmin (cp) can be noticed in the dorsal endoderm at the 16 hpf which is prior to this liver morphogenesis, hypothesized that liver forerunners might be distinguished before the beginning of alimentary canal morphogenesis and this liver bud was designed later by immigration and accumulation of these liver progenitor cells. Comparable hypothesis is also useful to the pancreas instigation because the pancreas marker pdx1 is first noticed at the 10-somite stage, which is way in advance of the pancreas morphogenesis. Though, so far there is no real indication to validate that the initial cp positive cells do donate to the establishment of liver bud at the later stage. As for this pdx1 positive cells, it is probable that they mostly underwrite to this endocrine pancreatic cells but not to the exocrine pancreas. The 2nd theory is based on the fact that the appearance of 2 transcription aspects "hhex" and "prox1", 2 key hepatoblast markers, are noticeable in the endoderm area that later provides upsurge to liver bud, signifying that the liver progenitor cells are discriminated from the endoderm cells to form in this situ liver bud after the creation of endoderm rod. The latter premise is reinforced by data from the anatomic studies and by this studies on mutants linked to the liver growth.

4. LIVER BUD CREATION AND PROGRESSION

Liver is an addition organ of the foregut. Based on this outcome perceived in the "GutGFP" transgenic zebrafish Tg, projected that this liver morphogenesis process can be randomly divided into 2 phases: budding and development. The budding phase happens from 24 to 50 hpf and can be additional alienated into 3 stages. At the budding stage I, endoderm cells caudal to the pharyngeal region combined to form the endoderm rod at 24 hpf. At the 28 hpf, the endoderm rod section under this first somite beginnings to thicken, which marks this opening of the liver morphogenesis. From the 28 hpf (budding stage two), the anterior condensing region, which mentions to the liver primordium, upsurges in size and turns to the left side w. r. to the middle line, and then covers this external curvature of the abdominal bulb by 30 hpf. The creation of a furrow amid the liver bud and, this adjacent esophagus marks this start of last phase of liver budding at nearly 34 hpf. Along with the growth of the furrow, the hepatic canal is formed to link liver and the intestine at the conclusion of this budding stage III. The liver now looks to detect among the duct of Cuvier, anteriorly, and this mid-level of fin bud, posteriorly. At this ensuing growth stage, the liver goes through dramatic vicissitudes in its size, shape and also placement because of the speedy cell proliferation. Hepatoblasts as well start to differentiate into the functional hepatocytes and the bile duct cells. By 96 hpf, the liver ranges across this midline ventral to esophagus to usage the 2nd liver lobe. It traces the pericardial cavity anteriorly and overlays with this anterior portion of the remaining yolk.

5. CELLULAR AND THE MOLECULAR MONITOR OF LIVER GROWTH IN ZEBRAFISH

In simply less than a decade, the power of by means of zebrafish to study the liver

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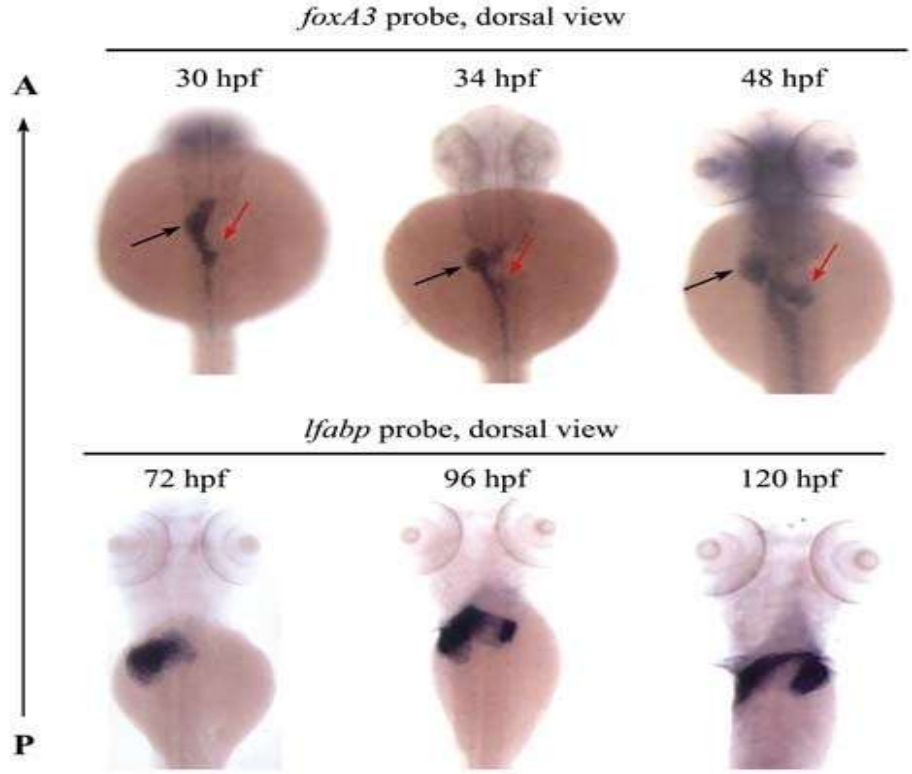

Fig. 1. Dorsal view of the liver growth in zebrafish. This foxa3 probe was used in the whole-mount in the situ hybridization (WISH) for this embryos at 34, 30 and 48 hpf as displayed (black arrow mark: liver and red arrow mark: pancreas). The lfabp probe was used in this WISH for the embryos at 96, 72 and 120 hpf. A, anterior and P, posterior.

growth has been established by a no. of the first-rate publications. In the ensuing, we brief the main accomplishments of these studies. Signalling molecules (Wnt, Shh, Bmp, Fgf and RA) Initial in 1975, Douarin establish that hepatocytes distinguished from endoderm essential interactions with adjacent precardiac mesoderm in the chick, and the similar outcome was established in mouse (Gualdi, 1996). It was attributed to the signalling molecules for instance fibroblast growth factors (Fgfs) from this cardiac mesoderm (Jung, 1999) and the bone morphogenetic proteins (Bmps) from this septum transversum mesenchyme (Rossi, 2001). During this budding stage in the zebrafish, liver cells are detected adjacent to lateral plate mesoderm cells at this dorsal face and, to yolk ball at this ventral face straight (Horne-Badovinac, 2003). So, the query arises whether the zebrafish LPM cells direct signalling fragments functioning to regulate the liver growth alike to Fgf and the Bmp signalling in mouse and the chick. The vital role of this mesoderm tissues for the liver growth in zebrafish has been undoubtedly demonstrated over studying numerous mutants. The fau/gata5 mutant has unadorned defects in differentiation of this precardiac mesoderm (Reiter, 1999) that agreeably correlates with this abnormal liver expansion together with melodramatically lower expression levels of the gata4, gata6, hnf1β and, hhex in these embryonic liver in this mutant. The educations on has mutant also accomplishes that the LPM is essential for the normal liver formation. A current work validates that Mypt1 intercedes coordination between these LPM and endoderm cell activities so as to prudently position liver primordium such that it obtains Bmp signalling that is vital for the liver creation in zebrafish. Stainier's laboratory stated that over appearance of dominant -ve forms of the Bmp or Fgf receptors in this transgenic zebrafish embryos afterward heat-shock treatment relentlessly abridged the countenance of the hhex and prox1, signifying that Bmp and Fgf signalling are vital for hepatic requirement and the liver bud growth. Overexpression of the Bmp2b can moderately rescue the phenotype instigated by the loss of the Fgf signalling through hepatoblast specification, though improved Bmp signalling will randomize the right/left position of the pancreas and also liver. Furthermore, the analysis of prt/wnt2bb mutant, which shows thoughtful but transit fault in liver, initially shows the unforeseen positive role of the Wnt2bb uttered in LPM for this liver specification. Additional studies recommend that the Fgf signalling does not function the downstream of this Bmp signalling in the mouse and zebrafish (Shin, 2007), nor does this Wnt signalling trace downstream of this Bmp or Fgf signalling in this hepatoblast specification (Shin, 2007). Though, little is recognized about how these signalling molecules interrelate with for each other to control the liver organogenesis. In the mouse, liver and also ventral pancreas are initiated from a common ancestor. Fgf signalling released from the contiguous cardiac mesoderm tempts the local face of the sonic hedgehog, which seems to control the fate of this communal bipotential precursor. That is, cells that direct sonic hedgehog form the liver, while cells that do not direct sonic hedgehog form this ventral pancreas (Deutsch, 2001). Though, the role of sonic hedgehog on this liver growth in zebrafish has not hitherto been recognized. In zebrafish, after the blocking this RA signalling by a pan-RA receptor antagonist BMS493, whole mount in the situ hybridization (WISH) displays the countenance of the three liver markers cepb4, cp, and the hhex vanished, which is not instigated by the aberrant cell death. In the meantime, data from

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the nls mutant also expression the absence of or importantly condensed the liver hhex expression. Inhibition of the RA signalling also captures the difference of pancreas, which is an added evidence for this existence of a communal hepatopancreatic precursor. Definitely, cell ancestry tracing outcomes showed that zebrafish liver and the exocrine pancreas share communal endodermal progenitors and this hepatogenic fate is resolute by the Bmp2 signalling (Chung, 2008). Genes vital for the liver budding and development in zebrafish Genetic and in the vitro explant studies in the mouse and chick have presented that the pan-endodermal transcript factors from this Foxa and GATA relations act in performance to found a field of skilled hepatic forerunner cells, and then the Fgfs from cardiogenic mesoderm (Jung, 1999) and the Bmps from this septum transversum mesenchyme (Rossi, 2001) guide this process of hepatogenesis. In following steps, Hhex performances to control this instigation and budding of the liver primordium, however Prox1 is central for the extension of the liver bud and migration of this hepatoblasts into the septum transversum mesenchyme (SosaPineda, 2000). Several other factors have correspondingly been found to control liver growth and this hepatocyte differentiation in the mouse and chick. Consequently, the process of liver organogenesis is exactly measured by a genetic network designed by liver-specific factors, the pan-endodermal factors and, factors from the adjacent mesodermal tissues. In the zebrafish, liver budding and growing stages initiate at the 28 hpf and 50hpf, singly. foxA1-A3, sox17, GATA4-6, hhex, the prox1 and hnf4 are all started to be uttered in the liver primodium throughout the budding stage, signifying that these factors are probable also vital for the liver growth in zebrafish. In the meantime, mutant characterization and the mutant gene cloning have recognized added factors that are convoluted in monitoring liver budding and the development processes in this zebrafish. In the one-eyed pinhead, the encrypting nodal co-receptor mutant, a liver fail to form because of the lack of this dorsal endoderm in the zebrafish. The loss-of-function of gata5 in this faust mutant mains to a liverless or the small liver phenotype. Correspondingly, reduced of the gata4 or gata6 only in zebrafish gives to the faults of heart and the endodermal organs with intestine, pancreas, liver, and swim bladder. Additional lessons reveal that twice knockdown of the gata4 and gata6 in this zebrafish totally eliminate liver growth and leads to the liverless pheno type. Consequently, as found in the mouse, Gata4 and Gata6 have laid off function throughout early stage of the liver growth and are both vital for liver growth in this zebrafish. The retinol binding protein 4 (rbp4) is not only articulated in this adult zebrafish liver, but also noticed in the yolk syncytial layer (YSL). rbp4 is destructively refereed by the Nodal and Hedgehog (Hh) signalling, but definitely controlled by RA signal. It controls liver budding and may be also essential for the migration of liver primordia. The rbp4 morphants display 2 liver buds which may be by reason of indecorous migration of the liver primordia. As rbp4 also controls the movement of fibronectin I, fnI may act on the liver primordia migration unswervingly. Cheap of vegfc in the zebrafish embryos also fallouts in multiple liver and the pancreatic buds; though, the expressions of both anterior liver bud and the posterior pancreatic bud indicators are unaffected, representing that the anteroposterior modelling and organ differentiation of this gut endoderm is standard. Studies on this zebrafish cloche mutant display that endothelial cells do not seem to be vital for the liver budding, which is dissimilar from what have been detected in mouse. Digestive-organ-expansion-factor, a novel nuclear confined protein, is essential for the peptic organ growth but not organ commencement and cell differentiation. Loss-offunction of digestive-organ-expansion-factor selectively up-regulates the appearance of a freshly recognized p53 isoform human counterpart Δ133p53 that mains to up-regulation of the cell-cycle-related genetic factor but not apoptotic-related genes to capture the growth of major peptic organs, together with liver. Two additional factors, nil per os encoding an RNA-binding protein and the liver-enriched gene 1, have also been exposed to play the vital role in the enlargement growth of the embryonic liver in the zebrafish. Pescadillo is extremely preserved from yeast to human and can be spotted firstly at 48 hpf in this liver primordium, tracked by the condensed RNA level at the 72 hpf. Throughout normal growth amongst 72 hpf and 144 hpf, the liver spreads over the yolk superficial and this process is related with the rapid consumption of this yolk. Instead, in the Pescadillo mutant the liver growth is arrested start at 72 hpf, the mutant yolk is not expended and the mutant fish dies at 144 hpf. Appearance of this ubiquitin-like protein comprising PHD and ring finger domains-1 gene is improved in this liver bud and completely advanced liver but is infrequent in this adult zebrafish liver. Study of this zebrafish hi272 line, which stands an addition in uhrf1, make known that uhrf1 controls liver apoptosis and the proliferation but has no pictorial things on hepatocytes the histological exhibition. In this uhrf1 mutant, the liver is designed as a ball while the right form should be crescent-shaped in the wild type at 120 hpf. Furthermore, uhrf1 also functions in this zebrafish liver regeneration. Some other issues have also been acknowledged to play roles in the liver growth. Rai found that DNA methyl transferase 2 but not Dnmt1 was essential for liver growth in the zebrafish. Dnmt2 is a caring protein and its exact expression in liver is only noticeable at 72 hpf. Subsequently the expression of late but not timely liver differentiation markers are lessened in the dnmt2 morphants, Dnmt2 may touch the late stage of the hepatocyte difference through cytoplasmic RNA methylation. Ftz-f1 fits to the nuclear receptor type of the transcript factor and is uttered in dissimilar forms. The IIA form of Ftz-f1 is the main transcript through zebrafish timely liver morphogenesis, representing its potential role in the liver growth. Even though no straight evidence is got up to now, the function of the Ftz-f1 homologs in the human and rat has specified this notion. HNF-1 is a vertebrate transcript factor that comprises a different homeodomain. In this zebrafish hnf1 mutant, liver is ill formed with undistinguishable hepatocytes at 72 hpf. The liver pointer gene hhex, which is also vital for the liver creation, expresses at the low level in this vhnf1hi548 mutant, representing its role downstream of the vHnf1. It is planned that vHnf1 controls liver growth through regulating the balance of this pdx1-shh network. Freshly, Cheng (2006) stated their study of promoter areas of 51 liver-enriched genes by thorough putative binding spots for Hnf1, Hnf3, Hnf4 and Hnf6, and exposed that these 4 liver-enriched record factors form the network to switch the expression of the liver-specific or the liver-enriched genes in this liver. Excitingly, chromatin remodelling factors histone deacetylase 1 (Hdac1) and Hdac3 have also been exposed to play vital but comparatively different roles during liver

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requirement and growth in zebrafish. It looks that Hdac3 acts over constraining its exceptional target development difference factor 11 (Gdf11), a member of the converting progress factor beta family, to indorse liver growth. Genes vital for differentiation of the hepatocytes and the bile duct cells onecut transcription factors play vital roles through zebrafish liver and the pancreas growth. onecut1 and its the downstream gene vhnf1 are together vital for this biliary system growth. Knockdown or overexpression of moreover gene perturbs the growth of intrahepatic but not extrahepatic bile ducts. As the 3rd member of onecut gene family and also the functional ortholog of the mammalian hnf6, onecut3 (oc3) controls the initial stages of zebrafish biliary growth. Expression of oc3 is clearly concentrated in oc1-deficient embryos, and vice versa. Consequently, members of the Onecut family appear to interrelate with each other to control biliary expansion (Matthews, 2004). Furthermore, jagged 1, 2, 3 and notch 1a, notch 1b, notch 2, and notch 5 are apiece stated in liver at 48 hpf and 72 hpf, precisely the time when bile ducts form. Nonappearance of jagged or notch genes touches a series of the zebrafish tissues together with biliary system progress, causing a phenotype similar with the human Alagille Syndrome (AGS). Disruption of this biliary and pancreatic ductular structure also looked in hhex morphant. Genes vital for the hepatopancreatic duct growth all through morphogenesis of liver and the exocrine pancreas, liver bud and the exocrine pancreatic bud are connected by this hepatopancreatic duct. Though, the nature and function of the hepatopancreatic duct have been learned only freshly. In this zebrafish fgf10 mutant, the hepatopancreatic duct epithelium converts malformation and the connecting cells fate is muddled. Based on this thorough molecular and the cellular study, it is recognized that Fgf10 concealed from this adjacent mesenchyme functions not only to upgrade the boundaries among the hepatopancreatic duct and the organs, but also to avoid this differentiation of this proximal hepatic and pancreatic cells into each other. Stimulatingly, as well as its role in the liver organogenesis, a separate role of histone deacetylase 1 (Hdac1) in extra hepatopancreatic duct morphogenesis has also been acknowledged.

6. ZEBRAFISH AS A EXEMPLARY FOR THE LIVER DISEASE STUDY

Along with its contribution to the study of liver growth, zebrafish is progressively being used to these study liver diseases. Lam (2006) engendered liver tumors in the zebrafish by giving the fish with chemicals and then got the gene set for this liver tumors via the microarray hybridization. Subsequent, they cross-compared this zebrafish liver tumor gene set with this gene sets got from 4 cancer kinds (liver, prostate, gastric and, lung) in the human. Amazingly, they found that this zebrafish liver tumor gene set crosses most with this gene set from the human liver tumors and, this lays the underpinning to create zebrafish as the model system to learning the liver tumorigenesis (Lam, 2006). The point that γ-hexachlorocyclohexane, thioacetamide and the alcohol individually can persuade hepatic steatosis in the zebrafish positively convinces the technical community that zebrafish is the good model system to learn steatohepatitis (Braunbeck, 1990; Amali, 2006; Passeri, 2009). More prominently, zebrafish assists as a hereditary model system for learning the molecular mechanism behind schedule hepatic steatosis. e.g. it has been revealed that mutation in the novel gene foie gras chiefs to hepatomegaly prospective due to enflamed lipid-filled hepatocytes in this mutant liver. Full study of this gonzo mutant displayed that alcohol persuaded hepatic steatosis was principally through activation of this pathway arbitrated by the SREBP transcript factors. Instead, mutation in this S-adenosylhomocysteine hydrolase (ahcy) gene upsurges tnfa expression to reason the hepatic steatosis phenotype in this ducttrip (dtp) mutant. In a screen for this zebrafish hepatomegaly mutants, Sadler (2005) found that transformations in a class C vacuolar cataloguing protein gene vps18 and the tumor suppressor gene nf2 together conferred hepatomeglay because of faults in the biliary system growth.

7. CONCLUSION

In current years, zebrafish has revealed a full probable in the studies of this vertebrate liver growth. The grouping of forward and the reverse genetics studies, and the classical genetics study coupled with thru embryos observation and the manipulation, in addition to its specific appropriateness for the study of liver organogenesis, will no hesitation strengthen our accepting of this cellular and the molecular mechanism of liver expansion. Liver formation is a difficult process. Thus, there must be numerous genes and signalling molecules tangled in this process. Until now, we have identified that Fgf, RA, Bmp and, Wnt signalling pathways are intricate in this initiation and the differentiation of hepatocyte in this zebrafish, but the exact relationship among them remains blurred. Additionally, only the handful of factors had been recognized to disturb liver maturing and progress. For instance, hhex acts to control this initiation and, budding of the liver progenitors. prox1 is essential for this outgrowth of liver bud and migration of the hepatoblasts whilst associates of the gata family, as the pan-endodermal factors, are vital for liver growth. Though, these few factors and the pathways are not satisfactory for accepting the whole process of this liver initiation and growth. Consequently, while additional studies of known genes and the existing mutants will deliver us with new info for the understanding of this liver organogenesis, more liver-defective mutants essential to be recognized for exemplifying mechanisms that are behind this mutant phenotype observed. The identification of the such mutants would prime to skimpy the genes that are vital for the liver organogenesis. Though the system for target gene triumph in zebrafish is not classy yet at existing, we trust advance will be made in this near future. Speciously, knowledge gained from the learning liver expansion will help to guide the fields such as liver uprooting, gene therapy and the tissue “engineering”, and to advantage human being as a whole.

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