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Review Article

Role of Fibrinogen-like Protein 1 in Tumor Recurrence Following Hepatectomy

Zahra Shafieizadeh[1#], Zohreh Shafieizadeh[1#], Maryam Davoudi[1], Reza Afrisham[1] and Xiaolei Miao[2*]

[1]Department of Medical Laboratory Sciences, School of Allied Medical Sciences, Tehran University of Medical Sciences, Tehran, Iran; [2]School of Pharmacy, Xianning Medical College, Hubei University of Science and Technology, Xianning, Hubei, China

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Abstract

Partial hepatectomy is a first-line treatment for hepatocellular carcinoma. Within 2 weeks following partial hepatectomy, specific molecular pathways are activated to promote liver regeneration. Nevertheless, residual microtumors may also exploit these pathways to reappear and metastasize. Therapeutically targeting molecules that are differentially regulated between normal cells and malignancies, such as fibrinogen-like protein 1 (FGL1), appears to be an effective approach. The potential functions of FGL1 in both regenerative and malignant cells are discussed within the ambit of this review. While FGL1 is normally elevated in regenerative hepatocytes, it is normally downregulated in malignant cells. Hepatectomy does indeed upregulate FGL1 by increasing the release of transcription factors that promote FGL1, including HNF-1α and STAT3, and inflammatory effectors, such as TGF-β and IL6. This, in turn, stimulates certain proliferative pathways, including EGFR/Src/ERK. Hepatectomy alters the phase transition of highly differentiated hepatocytes from G0 to G1, thereby transforming susceptible cells into cancerous ones. Activation of the PI3K/Akt/mTOR pathway by FGL1 allele loss on chromosome 8, a tumor suppressor area, may also cause hepatocellular carcinoma. Interestingly, FGL1 is specifically expressed in the liver via HNF-1α histone acetylase activity, which triggers lipid metabolic reprogramming in malignancies. FGL1 might also be involved in other carcinogenesis processes such as hypoxia, epithelial-mesenchymal transition, immunosuppression, and sorafenib-mediated drug resistance. This study highlights a research gap in these disciplines and the necessity for additional research on FGL1 function in the described processes.

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Introduction

Known for its 18% 5-year survival rate, hepatocellular carcinoma (HCC) ranks third among cancer-related causes of mortality.[1] Both viral hepatitis and nonalcoholic fatty liver disease are the primary causes of HCC.[2] Chemotherapy and radiotherapy have controlled this malignancy well, but they typically have serious side effects.[3] Hence, liver transplantation and liver partial resection, also known as partial hepatectomy (PH), are considered as the two main therapeutic approaches for HCC.[4] As finding a transplant organ is a time-consuming process in many countries, PH is known as the primary strategy to control HCC at the early stages.[5]

Activation of hepatocyte regeneration pathways is the hepatic response inherent to hepatectomy and other liver parenchymal injuries.[4] Growth factors, endocrine gland effectors, and liver cells work together in this intricate process.[6] Recurrence of tumors is unfortunately always a potential when microtumors remain in patients' liver tissue after PH. Indeed, cancer cells can multiply by exploiting pathways associated with liver regeneration.[3] Tumor recurrence, with a 70% 5-year recurrence, is the most serious PH consequence.[7] The liver secretes proteins called hepatokines, which play crucial roles in diverse medical conditions. As such, fibrinogen-like protein 1 (FGL1) is a hepatokine that communicates between the liver, skeletal muscles, and adipose tissues. It promotes DNA synthesis, inhibits reactive oxygen species production, and causes insulin resistance, steatosis, and inflammation.[8] Thus, FGL1 is important to control liver proliferation factor expression, regenerate liver, and aid liver repair. Overexpression of FGL1 in solid tumors reduces the 5-year survival. It is also present in bone marrow stromal cells, which are responsible for the repair of liver injury and the epithelial intermediate transformation of lung adenocarcinoma cells. Either direct phosphorylation (p) of the epidermal growth factor receptor (EGFR)

Keywords: Fibrinogen-like protein 1; FGL1; Hepatocellular carcinoma; Liver regeneration; Hepatectomy; Lipogenesis; Recurrence.

Abbreviations: ACC, acetyl-CoA carboxylase; ACOX1, acyl-CoA oxidase 1; ACL, ak strain transforming; ACLY, adenosine triphosphate-citrate lyase; BCL, B-cell lymphoma; CCRK, cell cycle-related kinase; CoA, coenzyme A; EGFR, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; FA, fatty acids; FASN, fatty acid synthase; FGL1, fibrinogen-like protein 1; FOXO1, forkhead box protein O1; GSK3, glycogen-synthase kinase-3; HCC, hepatocellular carcinoma; HIF-1α, hypoxia-inducible factor-1 alpha; HNF-1α, hepatocyte nuclear factor-1 alpha; IL6, interleukin 6; JAK2, the Janus kinase 2; LAG, lymphocyte activation gene; LH, lysyl hydroxylase; MAPK, mitogen-activated protein kinases; MEK, mitogen-activated erk kinase; mTOR, mammalian target of rapamycin; MUFA, monounsaturated fatty acids; PD-L1, programmed cell death ligand 1; PLOD3, the procollagen-lysine,2-oxoglutarate 5-dioxygenase 3; PPAR, peroxisome proliferator-activated receptor; PTM, post translational modification; PH, partial hepatectomy; PI3K, phosphatidylinositol-3-kinase; SREBP1c, sterol regulatory element-binding protein 1c; STAT3, signal transducer and activator of transcription 3; TGF, transforming growth factor; TRM, tissue-resident memory T cells.

[#]Contributed equally to this work.

[*]**Correspondence to:** Xiaolei Miao, School of Pharmacy, Xianning Medical College, Hubei University of Science and Technology, Xianning, Hubei 437100, China. ORCID: https://orcid.org/0000-0001-5513-3247. Tel: +86-13720365703, E-mail: 345701500@qq.com

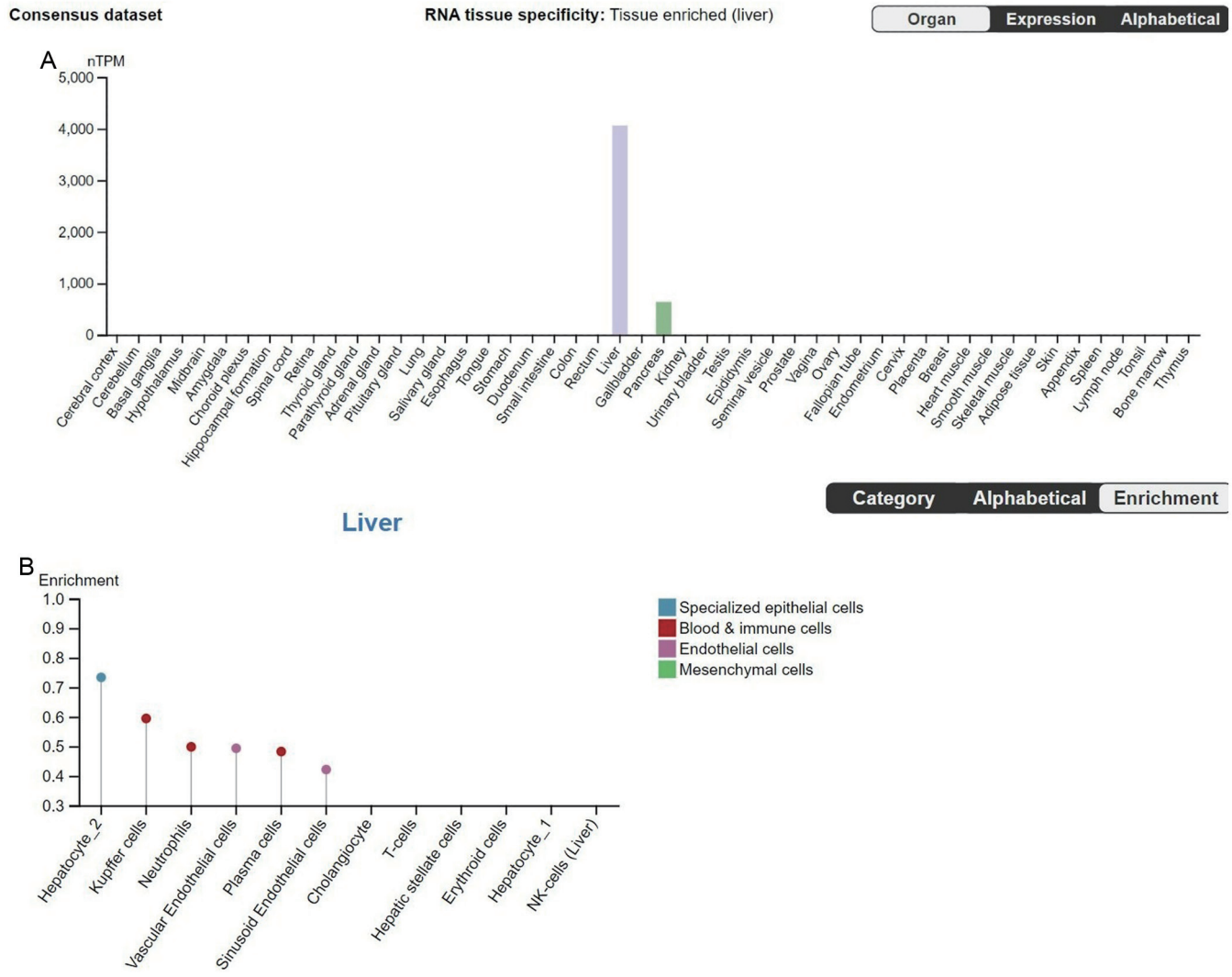

Fig. 1. Tissue-specific and cell type diversity. (A) In The Human Protein ATLAS database, the FGL1 protein is significantly expressed in liver and pancreas. (B) In liver, FGL1 is expressed in hepatocytes, Kupffer cells, neutrophils, vascular endothelial cells, plasma cells, and sinusoid endothelial cells. FGL1, fibrinogen-like protein 1.

or nonreceptor tyrosine kinase Src activates the extracellular signal-regulated kinase (ERK/p-ERK) pathway to promote cell proliferation. Because of the function of FGL1 in cell proliferation pathways, its expression likely regulates tumor cell growth and hepatocyte regeneration. Furthermore, by modulating the poly [ADP-ribose] polymerase 1/caspase 3 pathway, FGL1 bestows drug resistance on certain solid tumors, including non-small cell lung cancer.[9] Therefore, this topic is intriguing, as focusing on one protein allows for deep understanding of mechanisms. This review of recent studies aimed to evaluate the role of FGL1, as a hepatokine associated with metabolic and immune pathways, in each of the processes of liver regeneration and tumorigenesis following hepatectomy.

FGL1

FGL1, a 68-kDa hepatokine that is also referred to as Hepassocin or HPS and hepatocyte-derived fibrinogen-related protein or HFREP-1, is a member of the fibrinogen family. Chromosome 8 (8p22-21.3) in humans contains this protein, and Figure 1A shows its exclusive expression in the pancreas and liver. Figure 1B shows that this protein can be expressed by several types of liver cells, including specialized epithelial cells (hepatocytes), immunological cells (Kupffer cells, neutrophils, and plasma cells), and endothelial cells (vascular and sinusoid endothelial cells).[8,10] The fact that FGL1 plays a significant role in glucose and lipid metabolism and liver regeneration suggests that it may be an important molecule in controlling the reprogramming of lipid metabolism in cancer cells and other proliferative cells.[8,11,12] This protein is linked to an extensive array of cellular signaling pathways, as shown in Table 1.[13] Both gene-gene and protein-protein interactive networks of FGL1 and its coexpression gene network are shown in Figure 2 and Table 1.

It is intriguing to note that FGL1 is typically downregulated in patients with HCC, despite being overexpressed in response to liver parenchymal abnormalities.[13–16] As FGL1 suppresses the phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR), its complete deletion is associated with a poor prognosis in HCC patients.[17–19] As an immunosuppressive receptor typically presents on the surface of activated immune cells, FGL1 is

Table 1. Coexpression genes of FGL1 included in the Coexpedia database

Mechanism	Genes
Transport	*SLC30A2, CELA3A, CACNA1I, SLC22A9, TMEM151B, SERPINA7, NHA, SLC1A2, SHBG*
Inflammatory and immune responses	*MBL2, HSD17B6, AGT, GP2, CEACAM7, CD14, C8G, GFRA4, CFB, HOMER2, C4BPA, C4BPB, JAK3, F13B, HPR, CCL20, TRIM10, SPEF1, F12, RPS24, CPN2, NCR2, APOH, APCS, CRP, CFHR2, C8B, GC, CPB2, F2, F9, TTR, CP, C9, SAA4, RBP4, C8A, CFHR5, CFHR4, C6, CYP8B1, MBL2*
Therapeutic efficacy of drugs	*CYP3A4, SERPINA10, YBX1, CYP3A7, NR1I2, AADAC, SLC28A3, TRIM10, ORM1, ASGR2*
Metabolism-related genes	*PNLIPRP1, A1BG, SERPINA6, ADH1B, CTRC, SERPINA1, GATM, HGD, CPA2, SLC22A1, CELA2B, SYCN, ACSM2A, CEACAM7, CYP2A6, SPP2, PLA2G1B, SERPING1, CELA3B, CLPS, NT5E, PPAP2A, AOX1, MS4A6A, SCAMP1, OPTN, APOC4, PDPR, GYS2, HAL, TMEM97, CYP3A7, ACSM5, CPA1, CBS, VNN1, KIRREL2, CELA3A, HSD11B1, ADH6, PIPOX, KCNK3, RDH16, SULT2A1, PCK1, CEL, SLC51A, TFR2, LEAP2, FTCD, APOA5, RBPJL, CRYBB3, FAM133A, HMGCS2, C10orf10, CSRP3, OR1F1, G6PC, ACADL, CTNND2, CCRN4L, KIAA1467, ALDH8A1, ABCB4, SORD, CYP2B6, DIO1, HBQ1, UPB1, OGDHL, GNMT, FTL, TMPRSS15, HPX, MAT1A, ALDOB, APOC3, APOA2, LBP, UGT2B15, BHMT, HPD, UGT2B28, APOM, FMO3, HAO1, PAH, CPS1, ERP27, LIPC, INSL4, IGFBP1, ADH4, UGT2B4*
Tumor suppressors	*ADH1A, AGXT, HPN, MRPL41, PDIA2, SOX15, GPX3, HABP2, JAK3, SLC10A1, CYP4F2, HOXB5, PON3, GLS2, GATA2, CCDC9, HGFAC, TRIM45, INHBE, ALB, APOB, SERPINC1, KNG1, HRG, ITIH2, ITIH3, CYP2E1, ITIH1, LECT2, AQP8, TEX11, HAMP, FABP1, SERPINA5*
Tumor growth	*KLK1, YBX1, USH1C, CXCR4, PAQR9, AFM, RPL38, SLC39A6, CPLX2, AZGP1, CD44, CHI3L1, ZNF324, IMPA2, NR5A2, PRSS3, FXYD2, TBX6, THBS4, CLDN2, CDH20, MDK, RPS15A, EGF, CLDN1, DLX4, NAT2, FMO5, COL11A2, DRD5, PKHD1, MUC15, GPR31, MUC3A, SFSWAP, FGA, FGB, AMBP, TF, APOA1, CYP2C9, AHSG, CYP2C8, SERPINA3, HP, ANGPTL3, SLC7A2, PON1, SERPIND1, ITIH4, SERPINI2, TM4SF20, MUC5B, A1CF, TM4SF4, CUZD1, MUC5AC, CYP3A4, AHSG*
Related to proteasome	*CTRL*
Epithelial-mesenchymal transition	*YBX1, CDH18, AZGP1, APOC2, EXPH5, VIM, FGA, FGG, PLG, ARG1, VTN, TDO2*

FGL1, fibrinogen-like protein 1.

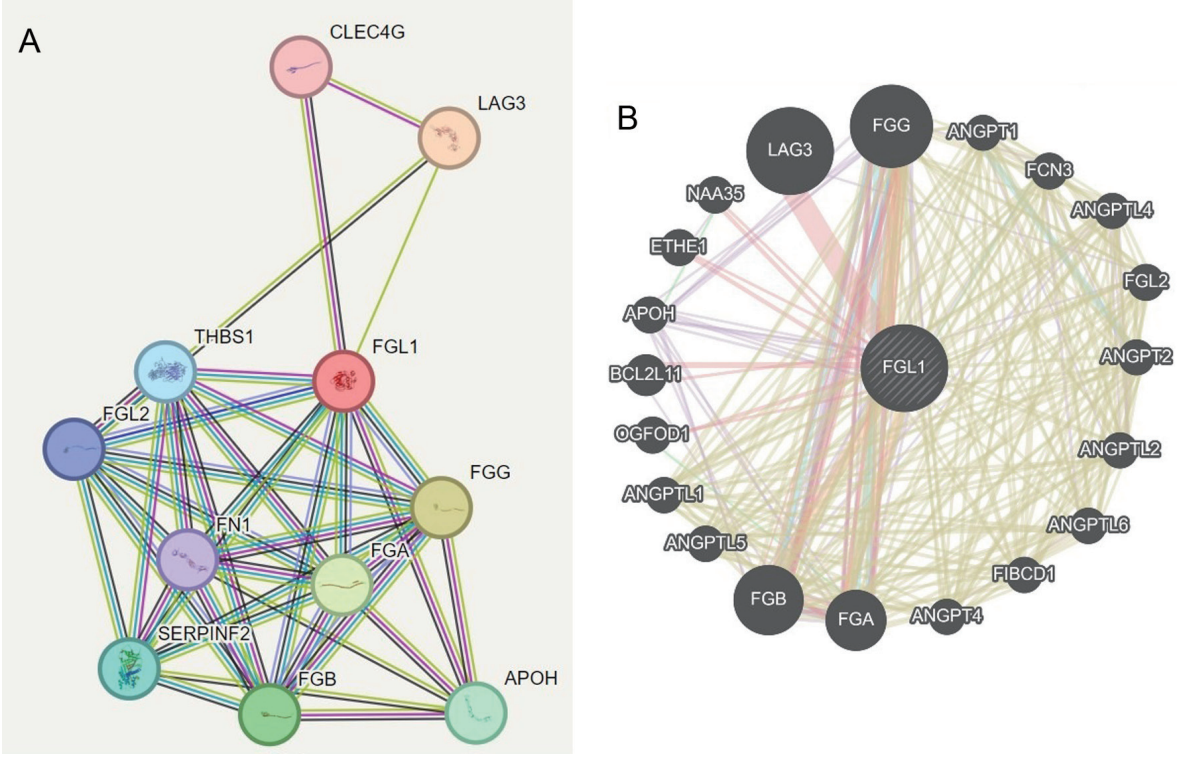

Fig. 2. FGL1 interactions in STRING and GeneMANIA databases. (A) Protein-protein. (B) Gene-gene. FGL1, fibrinogen-like protein 1.

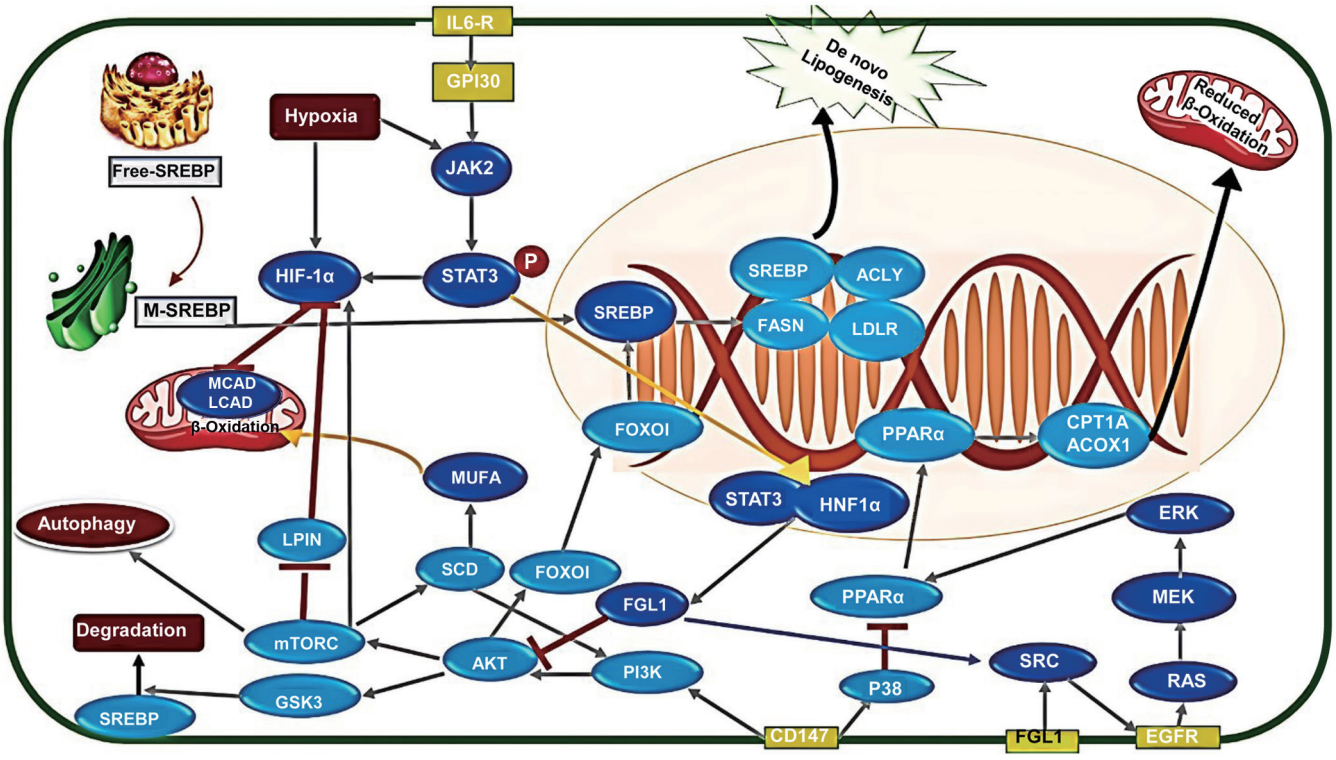

Fig. 3. In proliferative cells, *de novo* lipogenesis is induced by overexpressing the genes involved in FA synthesis. These include ACLY, ACC, and FASN, regulated by transcription factor SREBP1c. In HCC, SREBP1c can be overexpressed by P13K/Akt/mTOR pathway activated by CD147 and its downstream molecules, such as FOXO1, GSK3, and LPIN1. Hyperlipidemia triggers the release of FGL1, which is a suppressor of the Akt/mTOR pathway. On the other hand, beta-oxidation can be suppressed by inhibiting the p38/MAPKs/PPARα/CPT1A/ACOX1 pathway mediated by CD147. In regenerative cells, HNF-1α and phosphorylated STAT3 can upregulate FGL1, triggering proliferative pathways like EGFR/Src/ERK. Nonetheless, in HCC, deletion of HNF-1α downregulates FGL1 promoter, which in turn reduces the secretion of SREBP. Under hypoxic conditions, the JAK2/STAT3 pathway induces HIF-1α, which inhibits beta-oxidation by inhibiting mitochondrial enzymes like MCAD and LCAD. ACC, acetyl-CoA carboxylase; ACOX1, acyl-CoA oxidase 1; AKT, Ak strain transforming; ACL, ATP-citrate lyase; CPT1A, carnitine palmitoyltransferase I; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FASN, fatty acid synthase; FGL1, fibrinogen-like protein 1; FOXO1, forkhead box protein O1; GP130, glycoprotein 130; GSK3, glycogen-synthase kinase-3; HIF-1α, hypoxia-inducible factor-1 alpha; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HNF-1α, hepatocyte nuclear factor-1 alpha; IL6-R, interleukin-6 receptor; JAK2, Janus kinase 2; LDLR, low-density lipoprotein receptor; LCAD, long-chain acyl-CoA dehydrogenase; MAPKs, mitogen-activated protein kinases; MCAD, medium-chain acyl-CoA dehydrogenase; MEK, mitogen-activated ERK kinase; MUFAs, monounsaturated fatty acids; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase; PPARα, peroxisome proliferator-activated receptor alpha; RAS, rat sarcoma; SCD, stearoyl-CoA desaturase; SREBP1c, sterol regulatory element-binding protein 1c; STAT3, signal transducer and activator of transcription 3.

a primary ligand for lymphocyte activation gene (LAG)-3. Hence, its amplification can lead to immunotherapy resistance.[20,21] To better understand tumor recurrence following hepatectomy, it is necessary to identify the function of this multifunctional protein in proliferative cells.

Role of FGL1 in liver regeneration following hepatectomy

After tissue mass loss, the liver is the only organ capable of self repair.[22] This is primarily due to the rapid re-entry into the cell cycle of highly differentiated hepatocytes following liver damage.[6] Within 2 weeks after removing as much as 70% of the liver, hepatocytes start to replenish the lost bulk. A 30% PH is the criterion for liver regeneration.[23] Therefore, liver failure with a significant mortality rate occurs at a PH of 80%.[24,25] While 70% PH has been the most studied model of liver regeneration so far,[22,25] it is important to note that this procedure is not without risk, especially in older patients or those with preexisting liver conditions such as cirrhosis or steatosis.[26] Consequently, liver tumors are surgically removed by hemihepatectomy.[27]

Based on *in vivo* studies in mice, FGL1 is induced 2 h after 70% hepatectomy. Subsequently, it reaches its second peak within 24 h and remains high until 72 h after hepatectomy.[28] As an acute phase reactant, FGL1 can be released by inflammatory effectors like interleukin (IL)-6 and transforming growth factor-beta (TGF-β).[29–31] Following liver parenchymal damage, normal hepatocytes begin to release FGL1 under the regulation of some transcription factors, two of which are hepatocyte nuclear factor-1 alpha (HNF-1α) and signal transducer and activator of transcription 3 (STAT3).[32–34] IL6 regulates FGL1 promoter activity through both STAT3 and HNF-1α.[30–32] The mechanism involves the binding of endogenous HNF-1α to high mobility group box-1 (also known as HMGB1) and cAMP response-element binding proteins in the cytoplasm to form a complex that translocate into the nucleus and binds to the FGL1 promoter together with phosphorylated STAT3.[32] Next, as shown in Figure 3, the expressed FGL1 triggers an EGFR/Src/ERK cascade in hepatocytes through an autocrine process to induce liver regeneration.[16,32,35]

EGFR is a transmembrane glycoprotein receptor that belongs to the ErbB family of receptor tyrosine kinases. It plays a central role in regulating the proliferation of many cell types, including hepatocytes. Upon EGFR dimerization, it activates one or more downstream cascades, including PI3K/AKT, mitogen-activated ERK kinase (MEK)/ERK, mTOR, and STAT. Activation of the ERK pathway is an important step in

FGL1-induced mitogenic signaling. FGL1 induces the phosphorylation of EGFR and the activation of its downstream ERK signaling cascade pathway in a ligand-independent way.[16,36] In addition, FGL1 attaches to a membrane-specific receptor on the surface of hepatocytes and stimulates cell proliferation via an autocrine mechanism that is dependent on the EGFR/ERK/Src pathway. Liver injury also increases FGL1 expression in brown adipose tissue suggesting an interaction between the damaged liver and brown adipose tissues.[8]

In addition to triggering cell proliferation, FGL1 also has anti-apoptosis activity in liver cells via activating STAT3 and inhibiting apoptotic factors, such as B-cell lymphoma 2 (also referred to as Bcl-2)-associated X protein (also referred to as BAX) and caspase-9, as well as overexpressing some anti-apoptotic factors, such as Bcl-2 and B-cell lymphoma extra-large (also referred to as Bcl-xL).[22,35,37] Phosphorylated STAT3 also regulates the expression of genes associated with the cell cycle, including c-fos, c-myc and cyclin.[38] As a result, further study is required to establish the correlation between FGL1 and the genes associated with cell cycle. This aspect was neglected in early studies. It is apparent that a 50% PH can induce changes in the expression of 87 proteins in mouse models, with 37 proteins being downregulated and 50 proteins being upregulated, as determined by a proteome analysis. Given the substantial number of proteins that have both direct and indirect association with c-myc, it is plausible that this protein may have a pivotal influence on the regulation of hepatic regeneration.[27] In proliferative cells such as posthepatectomy hepatocytes and cancer cells, c-myc not only promotes glycolysis, but also assists mitochondria to utilize nonglucose substrates, such as lipids, in order to provide the necessary cellular intermediates to complete the cell cycle.[39] According to several studies, FGL1 is also essential for glucose and lipid metabolism.[8] Given that the Janus kinase 2 (also referred to as JAK2)/STAT3 pathway regulates both FGL1 and c-myc, an unexplored relationship between these proteins is conceivable.[40] Therefore, evaluating the relation between lipid metabolic reprogramming through the FGL1/STAT3/c-myc axis seems to be useful for understanding the underlying mechanisms in liver generation after PH.

Hepatectomy in patients with HCC and the possible role of FGL1

As HCC has similar molecular patterns in rodents and humans, mouse models are usually used to investigate HCC.[41,42] A study on the Mdr2-knockout mice, the most studied of the HCC models, revealed that the stress caused by liver resection can trigger cancer-prone cells to escape from senescence and apoptosis. As a result, they progress through the cell cycle and generate tumors. In other words, it seems that hepatectomy may potentially accelerate carcinogenesis.[43] The potential mechanism includes hepatocytes, which are specialized epithelial cells that are highly differentiated and mitotically inactive under physiological conditions. However, hepatocytes begin to replicate within 1 day after PH, undergoing a cell cycle shift from the quiescent G0 to the G1 phase.[6] On the other hand, nonparenchymal liver cells, i.e. Kupffer cells, hepatic stellate cells, endothelial cells, and biliary duct cells begin to replicate later. Therefore, hepatic cells have an exceptional proliferation capacity to take part in the regeneration process when harmful stimuli like hepatectomy are present.

A study examined *FGL1* expression in different malignant tumor tissues and associated normal tissues and its putative association with HCC prognosis. FGL1 is dramatically downregulated in most HCC-related cell lines and tissues, according to evidence from bioinformatics and western blot studies. In HCC patients, increased FGL1 expression was associated with longer overall survival, suggesting it may suppress tumors. Hence, *FGL1* expression is linked to HCC progression and prognosis, supporting its use as a biomarker.[44] Another study investigated the association of the FGL1-LAG-3 pathway and programmed cell death ligand 1 (PD-L1) with prognosis in HCC. LAG-3, FGL1, PD-L1, and $CD8^+$ T cells were measured in 143 HCC patients. HCC tissue had higher FGL1 and LAG-3 levels than nearby normal liver tissues, but lower PD-L1 and $CD8^+$. Increased populations of cells expressing LAG-3 and $CD8^+$ T cells are detrimental and beneficial prognostic biomarkers for HCC, respectively.[20] Another study investigated how tissue-resident memory T (T_{RM}) cells regulate HCC immunity. Accordingly, FGL1 was determined to have the potential to induce T_{RM} in malignancies, and LAG-3 was identified as a promising next-generation immune checkpoint. In end-stage HCC, $CD8^+$ T_{RM} cells with high LAG-3 expression had a poor prognosis. It seems that FGL1-LAG-3 binding affected HCC $CD8^+$ T_{RM} cell activity, which highlights them as an immunotherapeutic target.[45] The pathogenesis of HCC recurrence following PH seems to involve (1) metabolic reprograming of proliferative cells and (2) alternation of growth factor production and hepatokine release. In the current review, we tried to explain some of these pathways, focusing on the role of FGL1.[6,46–48]

Involvement of FGL1 in tumor proliferation and progression

According to the cBioPortal database, it has been determined that FGL1 is mutated in prostate, pancreatic, breast, lung, liver and bladder cancer, 17 of which have undergone missense mutations and 1 truncating mutation.[13] HCC pathogenesis involves a multistep process with inactivation of tumor suppressor genes (TSGs) and upregulation of proto-oncogenes.[49] Human FGL1 is located on the short arm of chromosome 8, a region rich in TSGs. It seems that the deletion of these TSGs leads to the development of HCC.[50] The heterozygosity loss analysis of cancers has shown that 57.1% of HCCs show a loss of the FGL1 allele on chromosome 8p22.3.[14,51] In fact, knockdown of FGL1 activates Akt/mTOR pathway in mouse models of HCC, which may also be involved in the development and progression of human HCC.[17–19] Several studies have found that 40–50% of human HCCs were associated with increased activity of the Akt-mTOR pathway.[52–54] Therefore, the regulation of FGL1 expression and its downstream signaling pathways play an important role in the proliferation/inhibition of cancer cells.

In the liver, IL6 promotes FGL1 promoter activity through STAT3 and HNF-1α, as described previously.[30,32] Numerous studies have shown that STAT3 is required for HCC development, progression, metastasis, and immunosuppression.[55,56] Indeed, proliferating cells exhibit an upregulation of the STAT3/c-myc pathway.[40] As c-myc facilitates reprogramming of lipid metabolism to maintain energy production in neoplastic cells, its overexpression is linked to poor prognosis in HCC.[57] Residual microtumors in the regenerating liver tissue are highly proliferative. To limit carcinogenesis, modulation of the STAT3-associated pathway can deprive cells of energy content.[58] The next section explains how lipid metabolic reprogramming affects tumor recurrence after hepatectomy.

FGL1 and lipid metabolic reprogramming of tumor cells

By enhancing macromolecular biosynthesis of carbohydrates, lipids, amino acids, phospholipids, and nucleotides, proliferative cells can improve energy output.[59] In proliferative cells, elevated glucose levels increase FGL1 expression by enhancing the activity of STAT3, protein phosphatase 2A (also re-

ferred to as PP2A), and HNF-1α.[12] Overexpression of FGL1 causes insulin resistance, steatosis, and inflammation in the liver through the action of peroxisome proliferator-activated receptor gamma (also referred to as PPARγ).[60] However, when glucose is unavailable, cancer cells rely on lipogenesis for energy. As lipid biosynthesis increases, cell membrane formation and energy generation through β-oxidation of fatty acids (FAs) rise.[61] Unlike cancer cells, which acquire most FAs by *de novo* synthesis, normal mammalian cells primarily acquire FAs by external absorption.[61,62] During *de novo* lipogenesis, the expression of some genes involved in FA synthesis, such as ATP-citrate lyase (also referred to as ACLY), acetyl-CoA carboxylase (also referred to as ACC) and FA synthase (also referred to as FASN), are upregulated following overexpression of a transcription factor, i.e. sterol regulatory element-binding protein 1c (SREBP1c), and its transcription cofactor, i.e. peroxisome proliferator-activated receptor-gamma coactivator-1β (also referred to as PGC-1β) as shown in Figure 3.[63–66] Upregulation of SREBP1c leads to FA production in HCC, which is caused by the Akt/mTOR signaling pathway that is activated by CD147.[66] The PI3K/Akt signaling pathway regulates lipid metabolism in cancer cells.[67–70] As shown in Figure 3, PI3K/Akt overexpresses forkhead box protein O1 (also referred to as FOXO1), which initiates SREBP transcription.[71] Figure 3 also shows that mTOR, a downstream target of PI3K/Akt suppresses lipin-1 (also referred to as LPIN1) activation, which would sequester SREBP and hinder its translocation to the nucleus.[72] Here, Akt can halt SREBP degradation by blocking glycogen-synthase kinase-3 (also referred to as GSK3) activity.[73] At the same time, CD147 alters lipid metabolism and improves cancer cell invasion by blocking the p38/mitogen-activated protein kinases (MAPKs)/PPARα/carnitine palmitoyltransferase I (also referred to as CPT1A)/acyl-CoA oxidase 1 (also referred to as ACOX1) pathway, which in turn slows FA oxidation (Fig. 3).[66] Surprisingly, hyperlipidemia generates FGL1, an Akt/mTOR suppressor.[60]

When HNF-1α is deleted, expression of the FGL1 promoter in HCC is decreased compared with levels found in normal hepatocytes.[32] As FGL1 cannot stimulate the EGFR/Src/ERK pathway, SREBP, and IL6 production are diminished. Thus, partial FGL1 expression in HCC may hinder SREBP1c-mediated lipid reprogramming. Nevertheless, the total elimination of this protein appears to be linked to an unfavorable prognosis as a result of the activation of oncogenes.

On the other hand, unsaturated FAs, such as oleic acid, can activate STAT3, which has a binding site on the FGL1 promoter region.[74] Activated STAT3 cooperates with the androgen receptor to induce the expression of cell cycle-related kinase (CCRK), thereby promoting tumorigenesis.[75] In fact, CCRK enhances *de novo* lipogenesis by maturing SREBP1 via the GSK3β/mTORC1 pathway.[76] In HCC, the enzyme responsible for synthesizing monounsaturated FAs (MUFAs), stearoyl-CoA desaturase (also referred to as SCD) is overexpressed.[77] An increase in MUFAs activates the PI3K/Akt signaling pathway, translocating SREBP from the endoplasmic reticulum to the Golgi. Figure 3 shows how this mechanism boosts *de novo* lipogenesis.[61] High quantities of MUFAs may help highly proliferative cancer cells avoid palmitic acid, a saturated FA that can trigger endoplasmic reticulum stress and apoptosis. Additionally, reducing saturated phospholipids alters cancer cell membrane fluidity, which improves glucose uptake and metastatic capacity. Finally, phospholipase produces pro-inflammatory eicosanoids that boost cell survival and proliferation.[78] Surprisingly, while the liver regenerates, levels of polyunsaturated FAs containing sphingomyelin and phosphatidylcholine decrease and levels of MUFAs containing phosphatidylethanolamine, free cholesterol, short chain triglycerides, and phosphatidylcholine increase.[78] Hepatectomy, hyperplasia, and other models of liver cell proliferation and cancer all appear to involve an increase in MUFAs containing phosphatidylcholine. In most cases, hepatocellular carcinogenesis and altered hepatocyte proliferation appear to be closely linked to an increase in MUFAs containing phosphatidylcholine.[78] Regarding the aforementioned PI3K-mediated lipogenesis in HCC, no studies have examined the function of FGL1 to date.

FGL1, hypoxia and escape from immune checkpoints

In the tumor microenvironment, hypoxia is a major determinant in tumor formation and progression.[79,80] Hypoxia is induced when the rate of tumor growth is accelerated.[81] Under hypoxic conditions, FA synthesis is enhanced in HCC, and beta-oxidation is suppressed to protect cancer cells from the excessive generation of reactive oxygen species.[82–84] The mechanism involves production of hypoxia inducible factor-1 alpha (HIF-1α), which in the tumor microenvironment suppresses the expression of enzymes involved in the first stages of beta-oxidation, i.e. medium- and long-chain acyl-CoA dehydrogenases, as shown in Figure 3.[84] In addition, hypoxia regulates the levels of immune checkpoints, such as CTLA4, PD1, PD-L1, CD47, LAG-3, and TIM3.[81–85] As mentioned above, FGL1 is the primary ligand of the LAG-3 receptor.[21] Although the protein-protein interaction networks obtained through the STRING database do not show any interaction between HIF-1α and LAG-3, HIF-1α interacts with STAT3 as a transcription factor for the promotor of FGL1. As a result, it seems that the study of the correlation between HIF-1α and the metabolic/immune pathways related to FGL1 can be helpful in understanding the underling mechanisms of HCC.

Previously, FGL1 was shown to directly cause drug resistance to HIF-related chemotherapy. Sorafenib is the first systemic drug approved by the United States Food and Drug Administration for HCC, but unfortunately high drug resistance attributed to this compound has made the use of it challenging.[86] Sorafenib suppresses HIF-1α synthesis, shifting the hypoxia response to the HIF-2α pathway. Overexpression of HIF-2α activates the TGF-α/EGFR pathway, resulting in drug resistance.[87] HIF-2α upregulation can also induce HCC progression by stimulating lipogenesis through the PI3K-AKT-mTOR pathway, as shown in Figure 4.[88] To stop cancer growth, targeting HIF-1α and HIF-2α is crucial. Combining TGF-α/EGFR pathway blockers like gefitinib can lower STAT3, Akt, and ERK activation, enabling sorafenib to suppress HCC.[87]

According to studies of sorafenib resistance in HCC, liver cancer cell lines with high FGL1 expression, such as Huh7 and Hep3B, activate autophagy and apoptosis-related signals by decreasing ERK phosphorylation. HCC cells with low FGL1 levels, as SNU387 and SNU475, did not show these alterations. Thus, as shown in Figure 4, assessing FGL1 basal expression levels can predict sorafenib sensitivity.[89] It should be mentioned that HIF-2α can be regulated by both oxygen-dependent and oxygen-independent mechanisms, such as phosphorylation. In low-oxygen environments, ERK1/2 phosphorylates HIF-2α at serine 672, regulating its movement into the nucleocytoplasm and its ability to activate transcription.[90] As a result, manipulating the FGL1/ERK/HIF-2α pathway may be effective in preventing drug resistance in HCC; however, this finding needs to be further investigated.

FGL1 and epithelial-mesenchymal transition (EMT)

Tumor invasion and metastasis are thought to be facilitated by EMT, a process where epithelial cells change into mesenchymal cells.[91] During EMT, cancer cells become motile by

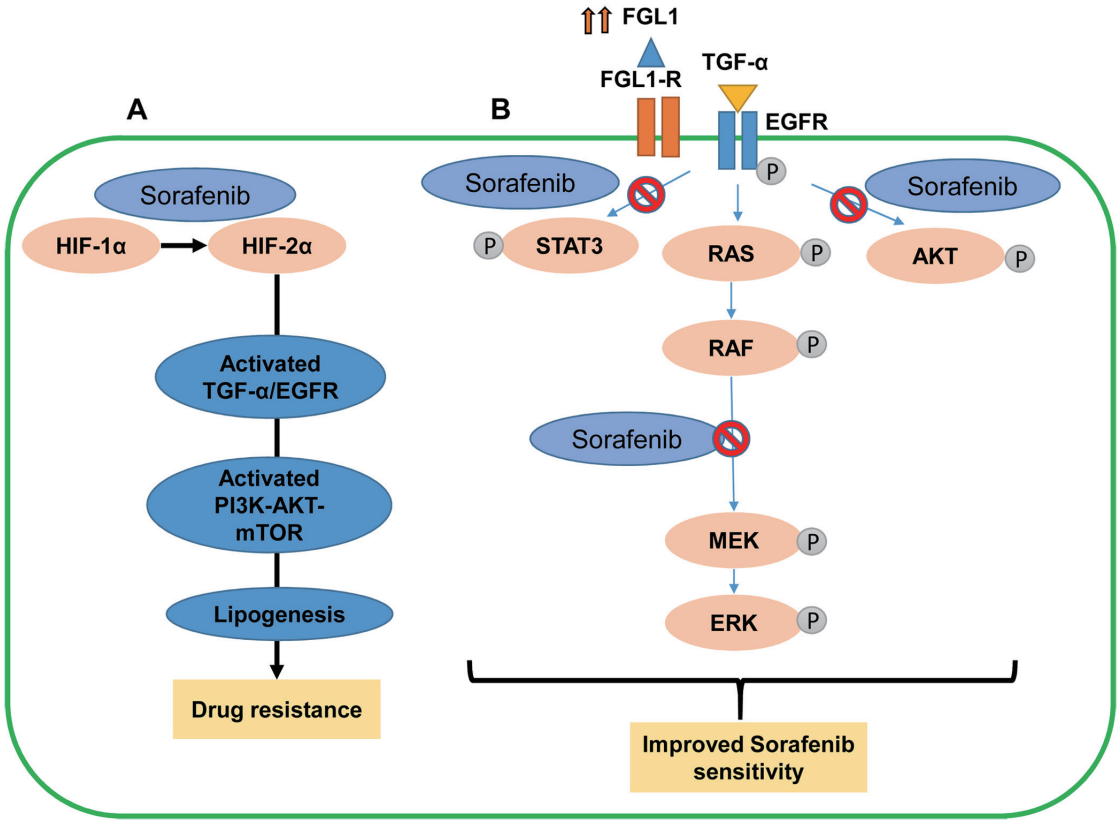

Fig. 4. Impact of FGL1 expression on sorafenib sensitivity in hepatocellular carcinoma. (A) Low FGL1 cells exhibit sorafenib resistance. (B) High FGL1 expression improves sorafenib sensitivity in HCC. AKT, Ak strain transforming; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FGL1-R, fibrinogen-like protein 1 receptor; HIF, hypoxia inducible factor; mTOR, mammalian target of rapamycin; MEK, mitogen-activated ERK kinase; PI3K, phosphatidylinositol-3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; STAT3, signal transducer and activator of transcription 3; TGF-α, transforming growth factor alpha.

upregulation of mesenchymal markers (n-cadherin, vimentin, Snail, Twist, MMP12, and fibronectin) and downregulation of epithelial-like markers (e-cadherin and ZO-1).[92] In one study, FGL1 promoted gastric cancer progression by enabling EMT and another found that FGL1 deletion induced EMT in lung cancer.[93,94] Although our knowledge of FGL1's participation in EMT is limited, we do know that TGF-β is required in this process.[91] Therefore, further clarification is needed about the particular function of TGF-β-mediated FGL1 involvement in the EMT process in HCC.

An important transcription factor for liver-specific FGL1 expression in HCC

According to a meta-analysis on the Oncomine database, FGL1 is upregulated in lung, prostate, melanoma, colorectal, breast and brain tumors and downregulated in pancreatic, breast, liver, and head and neck cancers.[13] In relation to the specific expression of this protein in HCC, the role of HNF-1α should not be neglected. Although HNF-1α can attach to its binding site on the *FGL1* gene promoter in different tissues, it acts as a transcriptional stimulator only when it has histone acetylase activity.[32,95] As overexpression of HNF-1α does not lead to induction of FGL1 gene expression in nonhepatic tissues, the binding of HNF-1α to the FGL1 promoter may be associated with induction of chromatin hyperacetylation in liver tissue owing to the histone acetylase activity of HNF-1α.[95] As mentioned earlier, FA synthesis is necessary for the survival of the tumor. This process involves maintenance of mitochondria cytosolic acetyl coenzyme A (acetyl-CoA) by the mitochondria. Acetyl-CoA is an important metabolite that links metabolic pathways with different histone acetyltransferases regulating gene expression. HNF-1α can overexpress several genes involved in FA synthesis, e.g., ACLY, 3-hydroxy-3-methylglutaryl-CoA reductase and FASN, via chromatin hyperacetylation, which in turn helps tumor growth.[96]

Overall, HNF-1α can specially regulate FGL1 expression at transcriptional level in HCC and the presence of HNF-1α is necessary for the expression of the FGL1 gene. Downregulation of HNF-1α in HCC may cause a reduction in the expression of FGL1. Deletion of the HNF-1α binding site on the FGL1 gene promoter can completely suppress the promoter activity of FGL1. However, re-expression of HNF-1α in HCC leads to the induction of FGL1 expression.[32]

FGL1 and post translational modifications (PTMs)

In addition to transcriptional regulation, PTMs can affect FGL1. FGL1 undergoes glucosyl-galactosyl-hydroxylation at lysine 65, a PTM seen in collagen-like proteins.[97–99] Despite lacking a collagen-like domain, FGL1 can undergo this PTM.[99] During glucosyl-galactosyl-hydroxylation, the lysine residue of FGL1 is initially hydroxylated by lysyl hydroxylase family proteins (also referred to as LHs), and galactose and glucose are then attached to hydroxylated lysine by procollagen galactosyltransferase 1 and 2 (GLT25D1 and GLT25D2). It is noteworthy that the deletion of GLT25D1 can reduce the level of FGL1.[100] However, the expression profile of hydroxy-

lated lysine, GLT25D1 and FGL1 following hepatectomy in patients with HCC has not been investigated. More important, LH3 encoded by the procollagen-lysine,2-oxoglutarate 5-dioxygenase 3 (also referred to as PLOD3) gene is often overexpressed in HCC, which is considered as a potential diagnostic marker of early-stage HCC.[101,102] Deletion of PLOD3 suppressed tumor growth in a spontaneous HCC mouse model.[101] As LH3 plays a key role in the post translational regulation of FGL1, overexpression of this protein may be the cause of the change in FGL1 expression in HCC. Thus, investigating the role of PTMs of FGL1 in both hepatectomy and HCC is recommended.

Successful therapeutic strategies to target HCC via FGL1

Recurrence of microtumors that were undiagnosed following PH can be prevented effectively by targeting the signaling pathways associated with hepatokines and growth factors. Liver regeneration efficiency might also be compromised by these blockers. Oxysophocarpine downregulates FGL1 expression in tumor tissue, which inhibits IL6-mediated JAK2/STAT-3 signaling and improves anti-LAG-3 immunotherapy. This allow enhancement of $CD8^+$ T-cell immunotherapeutic efficacy against HCC.[34] However, when it comes to treating patients with HCC with sorafenib, we need to know that the expression of FGL1 receptors on the surface of cancer cells can increase the sensitivity of these cells to this drug.[89] Therefore, the regulation of FGL1 expression seems to be associated with the type of treatment that we use for HCC.

Conclusion

FGL1 is a hepatokine, and its gene is located on the short arm of chromosome 8, a region rich in TSGs, whose deletion causes tumorigenesis in HCC by inducing the PI3K/Akt/mTOR pathway. In addition, FGL1 as the primary ligand of LAG-3, suppresses host immune responses if it is overexpressed in tumors. Nonetheless, in normal regenerative liver cells following hepatectomy, this acute phase reactive protein is upregulated to induce signaling pathways related to hepatocyte proliferation, such as the EGFR/Src/ERK cascade. Herein, we emphasize the dual roles that FGL1 plays in both normal and cancer proliferative cells by being involved in mechanisms like lipid metabolic reprogramming, response to hypoxia, drug resistance, and EMT-mediated metastasis. We show that the significance of regulating FGL1 in the mentioned pathways is that it can be regulated at both transcriptional and post translational levels.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study leadership and manuscript revision (XM, RA, and ZoS), review conception and manuscript writing (ZoS, ZaS, and MD), and figure design (ZaS and RA). All authors have read and approved the final manuscript.

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