Fibroblast growth factors 19 and 21 in acute liver damage

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Abstract: Currently there are very few pharmacological options available to treat acute liver injury. Because its natural exposure to noxious stimuli the liver has developed a strong endogenous hepatoprotective capacity. Indeed, experimental evidence exposed a variety of endogenous hepatic and systemic responses naturally activated to protect the hepatic parenchyma and to foster liver regeneration, therefore preserving individual's survival. The fibroblast growth factor (FGF) family encompasses a range of polypeptides with important effects on cellular differentiation, growth survival and metabolic regulation in adult organisms. Among these FGFs, FGF19 and FGF21 are endocrine hormones that profoundly influence systemic metabolism but also exert important hepatoprotective activities. In this review, we revisit the biology of these factors and highlight their potential application for the clinical management of acute liver injury.

Keywords: Acute liver injury; fibroblast growth factor 19 (FGF19); fibroblast growth factor 21 (FGF21)

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Introduction

The fibroblast growth factor (FGF) family comprises twenty two members in human and mice, which are classified in six subfamilies according to their structural characteristics and mechanisms of action (1,2). Besides having a key role in embryonic development these polypeptides are involved in a wide variety of biological actions including the regulation of cell growth, differentiation, wound healing, angiogenesis and metabolism (2,3). FGFs signal through four different tyrosine kinase receptors termed FGFR1 to 4, and this interaction is markedly strengthened by heparin or heparan sulphate glycosaminoglycans (4,5). Importantly, depending on the tissue type different splicing forms based on the alterative incorporation of exons IIIb and IIIc of the genes coding for FGFRs can be found. Therefore a total of seven different isoforms of FGFRs have been characterized, namely FGFR1b, FGFR1c, FGFR2b, FGFR2c, FGFR3b, FGFR3c and FGFR4 (6). FGFR binding leads to activation, dimerization and the triggering of intracellular signaling pathways (7). Most of the FGFs interact with heparin moieties and behave as autocrine and paracrine factors, however the members of the FGF19 subfamily of FGFs (FGF19, FGF21 and FGF23) lack a classic heparin binding domain (8). This feature facilitates the diffusion of these proteins from the tissue of production and their secretion

into the bloodstream, thus allowing an endocrine mode of action (9). However, lack of heparin binding domain in the FGF19 subfamily is accompanied by a low affinity interaction with the FGFRs. This situation is compensated by the presence of a transmembrane co-receptor named Klotho, which dimerizes with and contributes to activate the FGFRs (3,10). There are two major Klotho proteins, α-Klotho and β-Klotho, and their tissue-specific pattern of expression restricts to a great extent the target organs on which endocrine FGFs exert their biological activities (11-15).

FGF19, FGF21 and FGF23 are increasingly recognized as important hormones in the systemic regulation of metabolism. The central metabolic pathways controlled by these factors include carbohydrate, lipid and bile acid metabolism, as well as vitamin D and phosphate homeostasis (3,10,16,17). Alterations in the levels of the endocrine FGFs have been described in different pathological conditions, including chronic diseases such as obesity and type 2 diabetes, as well as devastating pathologies like liver cancer and bone diseases (3). Therefore, pharmaceutical strategies aimed at stimulating or inhibiting FGFs signaling are actively being pursued (3,18,19). However, the chronic stimulation, or repression, of the metabolic pathways controlled by these hormones may involve important challenges, including the risk of neoplastic transformation due to the mitogenic potential of factors like FGF19 (18). Therefore, many efforts are being dedicated to design FGF-based molecules with improved physical or pharmacokinetic properties, such as the FGF21-related molecules LY2405319 and CVX-343 (20,21), or the NGM282 FGF19 variant devoid of mitogenic effects (22). The potential application of FGF19, FGF21, and their engineered versions, to treat chronic metabolic conditions has been recently reviewed (3,23). However, the liver, which is a major direct or indirect target organ for FGF19 and FGF21, can also undergo acute episodes of injury and dysfunction which may have fatal consequences. In this review, we briefly revisit the biology of FGF19 and FGF21, outline the several major causes and clinical problems of acute liver injury, and discuss the potential therapeutic applications of FGF19 and FGF21 in acute hepatic damage of selected aetiologies.

Overview of FGF19 and FGF21 biology

FGF19 was cloned by homology to the mouse orthologue *Fgf15* from fetal brain tissues and retina (24). *FGF19* and *Fgf15*, expression is detected mainly in the small intestine, gallbladder, brain, cartilage, skin and kidney (6,25). The fundamental source of endocrine FGF19 is the ileum, from where it is released into the portal circulation. The expression of FGF19 in enterocytes is triggered by bile acids in their enterohepatic circulation through multiple farnesoid X receptor (FXR) binding sites in the *FGF19* gene (26,27). This mechanism makes FGF19 a postprandial hormone, peaking in human serum approximately 2–3 h after a meal (28). More recently, additional studies demonstrated the induction of *FGF19/Fgf15* ileal expression by vitamins A and D (29,30) and other nutrients such as carbohydrates (31) and cholesterol (32). Interestingly, the *FGF19/Fgf15* promoter in mouse ileal enterocytes is also activated by endoplasmic reticulum (ER) stress caused by non-physiological ER stress triggering molecules (33), but also by nutrients like saturated fatty acids at high concentrations (34). Importantly, under excessive accumulation of intrahepatic bile acids *FGF19/Fgf15* expression was observed in human but not in murine liver (34-36). Once in the circulation, FGF19 can interact with its target organs and tissues, which are those expressing FGFR4 and/or FGFR1c together with β-Klotho. Both, FGFR4 and β-Klotho are highly expressed in hepatocytes, where FGF19 has strong effects on the suppression of bile acid synthesis, gluconeogenesis and fatty acid synthesis, while it induces protein and glycogen synthesis (14,16,34,37). The adipose tissue, both white and brown, is also a target of FGF19 as it expresses high levels of FGFR1c together with β-Klotho. FGF19 effects on adipose tissue are believed to be important for glucose and lipid homeostasis (10,16). Finally, recent evidence also points to glucose lowering effects of FGF19 via the central nervous system through still not fully characterized mechanisms (38).

Pharmacological administration, or transgenic overexpression, of FGF19 in mice confirmed the strong physiological effects of this hormone in reducing liver fat accumulation and bile acid synthesis (22,36,39,40). Intriguingly, a recent report demonstrated that the long term pharmacological effects of FGF19 on weight loss and glycemia were mainly mediated at the level of the nervous system (41). Similar pharmacological approaches also evidenced a potent trophic effect for FGF19 in skeletal muscle (42) and hepatocytes (43). Importantly, the persistent activation of FGFR4 by FGF19 on hepatocytes

leads to active proliferation and the eventual development of hepatocellular carcinoma (44). Binding of FGFR4/β-Klotho activates a growing number of downstream intracellular signaling pathways, including the Ras-Raf-Erk1/2 mitogen-activated protein kinase and phosphoinositide 3-kinase pathways, the Jun N-terminal kinase pathway, the glycogen synthase kinase 3β (GSK3β)-β-catenin pathway and the mechanistic target of rapamycin 1 (mTORC1) pathway, among others. These signaling systems are responsible of the metabolic, proliferative and trophic effects of FGF19 in hepatocytes (18,45).

Human and murine *FGF21* were cloned from mouse embryo and fetal brain cDNA libraries respectively (46). In mice, it is predominantly expressed in the liver and adipose tissues, and at much lower levels in other organs like heart, kidney and skeletal muscle (6,47). In humans, under basal conditions, *FGF21* expression is found almost exclusively in the liver (47). Hepatic expression of *Fgf21* is strongly induced in the mouse liver by prolonged fasting. The peroxisome proliferator activated receptor α (PPARα), which is activated by increased circulating free fatty acids, is necessary for *Fgf21* upregulation upon fasting and high-fat low carbohydrate ketogenic diets (16,47). High sugar ingestion also triggers hepatic *FGF21* expression in mice and human, the effect of fructose being particularly strong (48). Other hormones, such as glucocorticoids, also induce *Fgf21* expression in the liver (47,49). Interestingly, stress situations such as amino acid deprivation and protein restriction result in robust FGF21 hepatic production through the ATF4-CHOP axis of the ER stress response pathway in mice (50,51). The notion of FGF21 as a hormone produced by the liver under stress conditions has been substantiated in several models of liver inflammation, liver injury elicited by ethanol, drugs or ischemia/reperfusion (IR), liver regeneration and hepatocarcinogenesis (52-55).

FGF21 exerts potent effects on systemic glucose and lipid metabolism. FGF21 administration to obese mice reduces body weight, fat mass and hepatic triglyceride content, improving glucose tolerance and insulin sensitivity, as reviewed in (3,16,47). Treatment with FGF21 stimulates hepatic fatty acid oxidation and suppresses *de novo* lipogenesis, while FGF21 deficient mice show hepatic insulin resistance and increased glucose production (47). These outcomes are mediated through FGF21 interaction with the FGFR1c receptor in combination with β-Klotho (3). Of note, experimental evidence identified the white and brown adipose tissues as major targets for the metabolic effects of this hormone (56,57), while direct action on liver parenchymal cells could never be observed (58). In fact, while some effects of FGF21 on hepatic metabolism, such as that of cholesterol, might be mediated through FGFR2/β-Klotho signaling in hepatocytes (59), most of the effects of this hormone on liver cells are believed to occur indirectly. One important mediator of FGF21 actions in the liver is the adipocyte-derived hormone adiponectin, which is strongly upregulated by FGF21 (56). Adiponectin-null mice fed a high fat diet are refractory to the metabolic effects of FGF21, including the attenuation of hepatosteatosis (60). Interestingly, a recent study using tissue-specific β-Klotho knockout mice demonstrated that besides adipose tissue the pharmacological long term effects of FGF21 on glucose metabolism were mediated at the level of the nervous system (41).

Acute liver damage: causes and available therapeutic options

Excessive liver injury may lead to acute liver failure (ALF), a rare but life-threatening condition, characterized by a rapid loss of liver function along with coagulopathy and encephalopathy. The incidence of ALF in the US is approximately 2,000 cases per year, accounting for about 6% of all liver injury-related deaths (61). ALF can occur in young adults who have no pre-existing liver disease and thus presents a significant clinical challenge. The effective treatment of ALF remains to be liver transplantation even though advances in critical care management to alleviate symptoms have largely increased the survival rate of ALF patients in recent years. There are a multitude of causes for ALF. Drug-induced liver injury accounts for the majority of ALF cases in developed world (62). In addition, hepatic I/R injury can cause ALF in patients undergoing trauma or liver surgery (63-66). Here, we outline the several major causes and clinical problems of ALF and in the next section we discuss the potential therapeutic application of FGF19/FGF21 in ALF patients.

Acetaminophen (APAP)-induced liver injury (AILI) is the most common cause of ALF in the United States. APAP is the active component in many prescribed and over-the-counter medications commonly used to treat fever and pain (67). Although the hepatotoxicity caused by APAP overdose was discovered over 50 years ago, it was not until

2014 when the US Food and Drug Administration issued a guideline to limit its consumption to less than 4 g per day. This dose is usually safe, but people under certain situations (e.g., alcohol abuse, chronic liver disease, malnutrition, aged) may have lower tolerance to APAP and develop acute liver injury under lower doses (68). A study of 275 patients who developed AILI due to APAP overdose revealed that there were 48% un-intentional overdoes, 44% intentional and 8% of unknown intent (69). In this cohort, 65% survived, 27% died without transplantation and 8% underwent transplantation (69). Another report estimated that 60 million Americans take APAP-containing products weekly and approximately 30,000 patients are admitted to intensive care units every year due to AILI (63,70). The direct cost of APAP overdose-induced liver injury has been estimated to be as high as US $87 million annually (71).

APAP can cause centrilobular hepatic necrosis through bioactivation to form a reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), which depletes glutathione (GSH), binds to mitochondrial proteins, increases oxidative stress and eventually leads to mitochondrial dysfunction and cell necrosis. Once necrosis occurs, the release of damage-associated molecular pattern molecules (DAMPs) induces an inflammatory response that further exacerbates liver injury (72). The timing of hospitalization after APAP overdose is critical for their survival. Gastric lavage, activated charcoal ingestion and ipecacuanha-induced vomiting within 4 h of APAP ingestion are proven effective in attenuating drug absorption (73). *N*-acetylcysteine (NAC), the GSH precursor, can replenish GSH stores and thus detoxify NAPQI (74). However, NAC can prevent hepatic injury only if given within 12 h post APAP exposure. Unfortunately, unintentional overdosing is not often recognized until later (69). If AILI develops into fulminant liver failure, liver transplantation represents the only life-saving procedure. Due to the shortage of donor organs, only a small fraction of patients with APAP poisoning receive transplantation (75). Therefore, it is imperative to explore new antidote strategies, perhaps those that promote liver regeneration.

Liver I/R injury (IRI) is another major cause of acute liver injury. It results from acute cessation of blood supply to liver followed by restoration of blood flow, the latter causing significant cellular injury and subsequent liver dysfunction (76). There are two types of liver IRI: warm and cold. Warm I/R can occur during hemorrhagic shock, trauma, liver surgery and transplantation. If the ischemia time is longer than 15 minutes during warm I/R, reperfusion will greatly contribute to high morbidities (77). Hepatic IRI represents a key risk factor in postoperative recovery (78). Cold I/R occurs during organ preservation. Two-fold increase of liver IRI has been consistently seen if cold preservation of liver is longer than 14 h *in vitro* (79). In the US, there is a significant shortage of donor organs, resulting in approximately 15% yearly mortality of patients waiting for liver transplantation (80). To deal with this problem, marginal organs collected from older, steatotic, or non-heart-beating donors, have been used for liver transplantation. Unfortunately, these marginal organs are more prone to IRI (79). At present, treatment options for liver IRI are extremely limited (81,82). Approaches to reduce liver IRI could improve postoperative/transplant outcomes and help save organs that would be disposed otherwise.

Acute-on-chronic liver failure (ACLF) is recognized as an acute deterioration of liver function in patients with pre-existing chronic liver disease (83). ACLF can be classified into three types. Type A is defined as non-cirrhotic ACLF. However, type B and C occur in approximately 31% of hospitalized patients with liver cirrhosis (84). Type B is defined as compensated cirrhosis with an acute hepatic deterioration caused by infection, surgery or acute alcoholic hepatitis. Type C is decompensated cirrhosis with an acute hepatic deterioration caused by similar etiologies as in type B. The most common cause of ACLF is alcoholic liver disease, accompanied by infection and kidney failure (85). Therapy for severe alcoholic steatohepatitis is currently limited to corticosteroids administration, with an improved effect when given in combination with NAC (86).

ACLF is often associated with failure of one or more organs and has a high short-term mortality (84,87). A clinical survey of 223 patients who were diagnosed with ACLF revealed a 90-day transplant-free mortality rate as high as 62% (84). Clinical managements during early days of hospital stay significantly affect the survival outcome (84). Various devices that support the liver have been explored. Although ineffective in improving overall survival, they could stabilize liver function in certain patients until transplantation (88). Due to the rapid progression of ACLF, a larger proportion of patients are either not eligible for transplantation or die before transplantation. A meta-analysis of 303 patients with ACLF demonstrated that

only 15% underwent transplantation within 90 days (89). A multicentered study from Canada showed that 48% of patients died while waiting for liver transplantation (90). In order to improve survival, introduction of effective interventions to prevent liver deterioration, improve liver function and foster hepatocyte survival and regeneration will be particularly important.

Potential hepatoprotective application of FGF19 and FGF21 in acute liver damage

The biological activities of FGF19 and FGF21 summarized above suggested that these hormones could have a beneficial effect on liver injury, including acute forms of liver damage. Regarding FGF19, early evidence of hepatoprotective potential was obtained in mice that were subjected to acute injury induced upon ligation of the common bile duct (BDL). In these animals, injection of FGF19 markedly reduced the total bile acid pool size and the extent of extrahepatic cholestasis-induced liver necrosis (91). Protection from cholestasis-associated liver injury by recombinant FGF19 administration was confirmed in a model of chemically-induced biliary epithelial cell damage (22). As previously mentioned, FGF19 has strong mitogenic effects in hepatocytes, an effect that may lead to hepatocellular carcinoma development in prolonged treatments (18,92). To avoid this, non-tumorigenic variants of FGF19 have been developed, and these molecules have shown hepatoprotective effects in chronic liver injury associated with alcoholic and non-alcoholic steatohepatitis and cholestasis through the modulation of lipid and bile acid metabolism (93,94). However, the combined metabolic and mitogenic effects of FGF19/FGF15 may be important in clinically relevant situations where liver regeneration is needed. A first evidence in this regard was obtained in a model of ALF due to extensive parenchymal resection (85% partial hepatectomy, PH), where administration of FGF15 expressed from an adenoviral vector markedly improved mouse survival (36). In the clinic, the presence of cholestasis often associated with steatosis existing prior to liver resection, or developing after transplantation, has a negative impact on liver regeneration (95-98). In this context, pre-operative administration of FGF19 from adeno-associated viral vectors to obese db/db mice with fatty liver improved survival after extensive PH (85%). While these effects confirm the efficacy of a FGF19-based therapy, from a translational point of view the use of recombinant factors instead of viral vectors is preferred. In the case of FGF19, one limitation to its clinical application is the short half-life of the protein (3,22). To overcome this limitation, a chimaeric molecule based on the fusion of FGF19 with apolipoprotein A-I (ApoA-I) has been synthesized. This molecule, named Fibapo, demonstrated not only an extended half-life, but also increased hepatotropism owing to the interaction of the ApoA-I moiety with the scavenger receptor class B type I (SR-BI) highly expressed in hepatocytes (99). Pre-operative administration of Fibapo to obese (db/db) mice markedly improved survival and liver regeneration after 70% PH (34). Mechanistically, this effect could be attributed to a marked reduction of liver steatosis and a strong hepatotrophic effect, factors that avoid lipotoxicity and stimulate liver growth, therefore enhancing liver function in the critical hours after parenchymal resection (97,100-102). Similarly, administration of Fibapo prior to PH significantly reduced liver injury and improved regeneration in aged mice (103), in which liver regrowth after partial resection is impaired, as occurs in elderly patients (104). This protective and pro-regenerative effect could be also related to the improvement of the steatosis commonly present in aged livers, as well as to the strong trophic and mitogenic effects elicited by Fibapo (103). Interestingly, delayed administration of Fibapo also protected from APAP-induced liver injury and increased mice survival after lethal doses of the drug, performing better than NAC (103). Mechanistically, the activation of pro-survival and cell growth-related intracellular signaling pathways, along with the inhibition of the pro-apoptotic mitochondria-associated phospho-JNK (p-JNK) (105,106), could be responsible for the beneficial effects of Fibapo on APAP-induced liver injury (103). In view of these findings, it could be interesting to evaluate the hepatoprotective effects of FGF19, or related molecules such as Fibapo, on other models of acute liver injury like acute ethanol intoxication or I/R mediated liver damage.

There are also some recent lines of evidence on the hepatoprotective capacity of FGF21. As mentioned before, FGF21 expression in the liver is increased upon cell stress and injury elicited by different agents, including APAP (55). Indeed, APAP administration results in the fast and strong upregulation of hepatic FGF21 expression and secretion into the circulation (55). Interestingly, APAP-mediated increase in FGF21 expression was independent of PPARα, a major regulator of *Fgf21* gene expression in hepatocytes (47). Of note, in the absence of FGF21, i.e., FGF21 null mice,

APAP hepatotoxicity and mortality was exacerbated, and recombinant FGF21 administration had significant protective effects (55). Moreover, a recent study showed that the beneficial effects of glucocorticoid pretreatment on APAP-induced liver injury required FGF21 expression (107). Regarding the mechanisms responsible for FGF21 hepatoprotection, FGF21 null mice showed marked hepatic oxidative stress upon APAP intoxication, along with increased mitochondrial p-JNK levels, and treatment with recombinant FGF21 restored liver antioxidant activity (55). This response was attributed to the activation of the transcriptional coactivator peroxisome proliferator-activated receptor coactivator protein 1α (PGC1α) by FGF21 administration (55). PGC1α controls the expression of a variety of antioxidant genes, including that of the nuclear factor erythroid 2-related factor 2 (Nrf2), a master regulator of antioxidant gene expression (108). Importantly, hepatic *Nrf2* expression, which is quickly activated upon APAP administration, was markedly impaired in FGF21 null mice (55). Another study also demonstrated a protective effect of FGF21 on D-galactose-induced mouse liver injury, and this was also related to the activation of Nrf2-mediated antioxidant capacity (109). One key unanswered issue in FGF21-mediated hepatoprotection, as well as in FGF21-mediated hepatic metabolic regulation (41,58), is how this hormone exerts its effects on the liver parenchyma. Indeed, treatment of isolated hepatocytes with FGF21 had no effect on PGC1α nor Nrf2 expression (55,58), therefore an indirect mechanism involving the activation of hepatoprotective factor/s by FGF21 must exist.

There is also evidence indicating that FGF21 can ameliorate liver injury caused by chronic alcohol consumption. Indeed, FGF21 null mice develop increased hepatic damage, including inflammation, steatosis and fibrosis, and show higher mortality than their wild type counterparts when fed an ethanol supplemented diet (54). Interestingly, acute ethanol administration markedly increases FGF21 serum levels in mice and humans, and *Fgf21* gene expression in mice (54). On the other hand, the relationship between Nrf2 and FGF21 seems to be reciprocal. Besides the above-mentioned stimulatory effect of this hormone on Nrf2 expression, one study found that the induction of *Fgf21* expression by chronic ethanol feeding was attenuated in Nrf2 null mice, which as expected display increased liver injury when fed an ethanol supplemented diet (110). These findings suggest that the hepatic upregulation of FGF21 expression upon APAP intoxication discussed above could also be mediated in part through Nrf2 activation.

Different engineered forms of FGF21 have been generated with the aim of avoiding protein aggregation, increase conformational stability, avoiding proteolysis or increasing half-life [reviewed in (3)]. The pharmacological activity of some of these variants, such as LY2405319 and PF05231023, has been assessed in experimental models of NAFLD and in patients with obesity and type 2 diabetes, with promising results (3,111,112). It would be very interesting to test the effects of these improved FGF21 variants in experimental models of liver injury elicited by I/R, APAP overdose, acute ethanol intoxication and ACLF.

Conclusions

There are currently very few pharmacological options available to prevent or treat acute liver injury. One potential source of hepatoprotective agents may reside in the endogenous reparative response elicited both locally and systemically upon liver injury. The administration of these agents may enhance the natural regenerative responses of the organism. Moreover, the biological activities of these protective factors can be harnessed in semisynthetic derivatives with improved kinetic and pharmacological properties. In this review, we have summarized evidence suggesting that this could be the case for the endocrine fibroblast growth factors FGF19 and FGF21 (*Figure 1*).

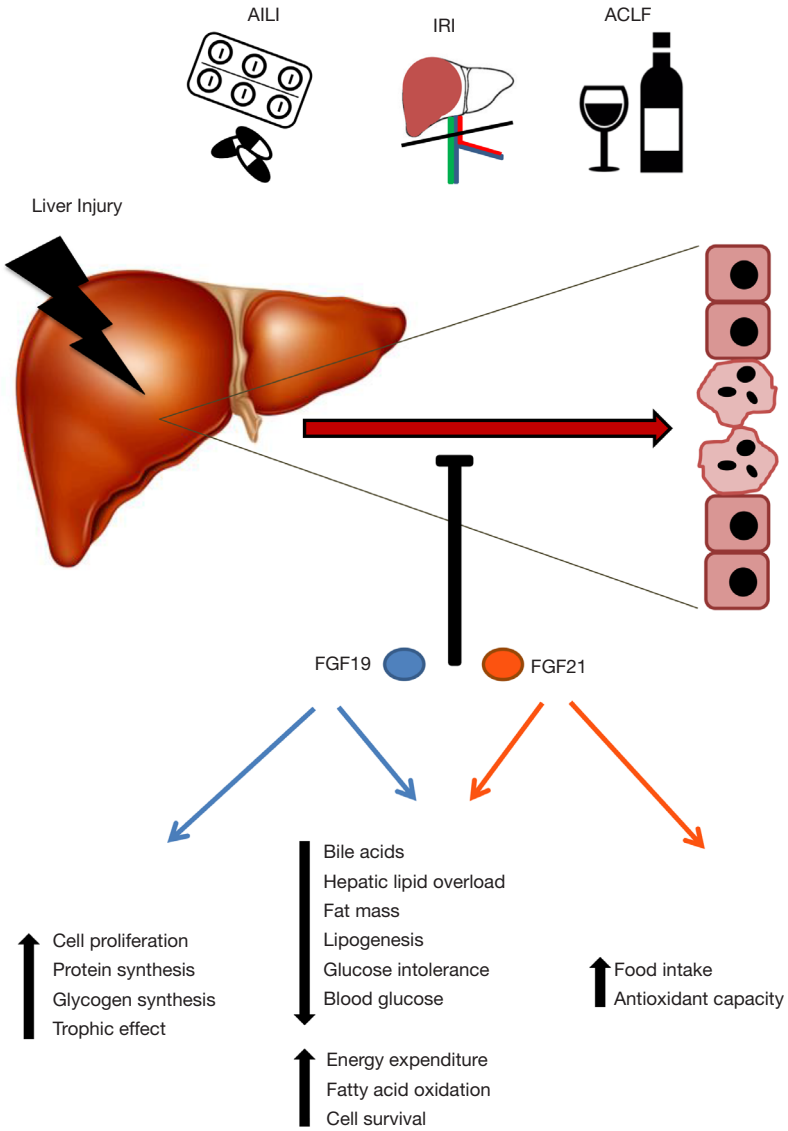

Figure 1 Summary of the biological activities of FGF19 and FGF21 that may participate in the hepatoprotective and pro-regenerative activities of these growth factors. AILI, acetaminophen-induced liver injury; IRI, ischemia and reperfusion liver injury; ACLF, acute-on-chronic liver failure.

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Footnote

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