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REVIEW

Liver−pancreas communication in disease and drug development

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Abstract The liver and pancreas are metabolically intertwined organs whose bidirectional communication is critical for maintaining systemic homeostasis. Dysregulation of this inter-organ crosstalk is a central driver in the pathology of a growing list of prevalent diseases, including metabolic dysfunction-associated steatotic liver disease (MASLD), liver cancer, acute and chronic pancreatitis, and various forms of diabetes. Given the substantial global health burden of these conditions and the lack of effective, Food and Drug Administration (FDA)-approved pharmacological interventions for those diseases, understanding the intricate mechanisms is an urgent and timely endeavor. This review provides a comprehensive synthesis of recent advancements in deciphering the molecular basis of liver−pancreas communication. We explore the multifaceted signaling networks involved, including the roles of liver-derived hepatokines, pancreas-derived hormones, extracellular vesicles, and metabolic exchanges. This axis is further integrated within broader systemic networks involving the gut, neuronal system, adipose tissue, and skeletal muscle. While clinical trials targeting this communication show promise (*e.g.*, FGF21- and bile acid-related drugs), significant challenges remain, particularly the lack of FDA-approved pharmacological treatments for alcohol-associated liver disease (ALD), and acute/chronic pancreatitis. Future research must elucidate specific signaling pathways, identify novel pancreas-derived factors, and develop innovative therapeutic strategies. In particular, small molecule drug discovery based on polypharmacology, for these complex metabolic and organ-specific diseases.

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1. Introduction

Liver disease remains the 11th leading cause of death worldwide, accounting for approximately 2 million deaths annually (4% of all global fatalities)[1]. These figures are likely underestimated due to narrow clinical definitions, coding limitations, the exclusion of liver-related complications, and challenges with multi-morbidity in primary cause attribution[2-4]. Based on data from The Global Burden of Disease (GBD) 2021 study and World Health Organization (WHO) 2024 reports, metabolic dysfunction-associated steatotic liver disease (MASLD) contributes to the highest number of cases among all liver diseases (1.27 billion cases). This is followed by hepatitis B (HBV; 254 million cases), hepatitis C (HCV; 50 million cases), other chronic liver diseases (*e.g.*, drug-induced liver injury, uncommon viral hepatitis, and autoimmune hepatitis; 25.14 million cases), alcohol-associated liver disease (ALD; 3.02 million cases), and liver cancer (739 thousand cases)[5-7]. Importantly, between 2000 and 2022, the disease burden associated with major viral hepatitis has decreased, while that of metabolic liver diseases has drastically increased[8]. To date, several effective treatments have received U.S. Food and Drug Administration (FDA) approval for major viral hepatitis and liver cancer. For instance, antiviral drugs (*e.g.*, lamivudine, entecavir, and tenofovir) are employed for chronic HBV treatment, and direct-acting antivirals (DAAs) have revolutionized HCV treatment, achieving cure rates over 95% across all genotypes[9,10]. Similarly, systemic pharmacological therapy (*e.g.*, sorafenib, lenvatinib, cabotinib, and ramucirumab) and immune checkpoint inhibitors (*e.g.*, nivolumab) have demonstrated significant efficacy in hepatocellular carcinoma (HCC) therapy[11]. Although the thyroid hormone receptor β (THRβ) agonist resmetirom recently gained FDA approval for treating adults with metabolic dysfunction-associated steatohepatitis (MASH), its relatively low response rates (29%−35% for MASH resolution and 30%−35% for fibrosis improvement) underscore the need for superior therapies[12]. Importantly, there is no FDA-approved drug therapy for ALD because of poor understanding of its pathophysiological mechanisms[13]. Therefore, the urgent identification of novel druggable targets for metabolic liver diseases is essential.

While mechanistic knowledge is advancing, pancreatic diseases, including acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic cancer (PC), remain costly and challenging to manage[14]. Recent epidemiological data indicate 122 thousand deaths worldwide from pancreatitis (the sum of AP and CP) and 505 thousand from PC. Notably, the mortality for both pancreatitis and PC significantly rose from 1990 to 2021, with increases of 78.7% and 139%, respectively[14,15]. Although previously considered reversible, patients experiencing a single episode of AP have a higher risk of developing CP and PC[16]. To date, several therapeutic approaches have been FDA-approved for PC. For example, systemic chemotherapy—including regimens such as FOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and fluorouracil), gemcitabine plus nab-paclitaxel, liposomal irinotecan, and NALIRIFOX (liposomal irinotecan, oxaliplatin, leucovorin, and fluorouracil)—remains the mainstay of treatment for pancreatic ductal adenocarcinoma (PDAC). Despite progress in targeted therapies (*e.g.*, erlotinib, olaparib, sotorasib, adagrasib, selpercatinib, larotrectinib, entrectinib) and immunotherapy (*e.g.*, pembrolizumab), PC patients still exhibit suboptimal treatment outcomes, characterized by low objective response rates (ORR) and modest clinical benefits, which necessitates the development of novel therapeutic strategies[17-20]. Notably, owing to a limited understanding of pancreatitis risk factors and pathophysiology, there are currently no FDA-approved pharmacological treatments for AP and CP[21,22]. Current management relies primarily on supportive care, endoscopic interventions, and surgical procedures. Thus, a sustained effort to gain deeper mechanistic insights is required to identify emerging therapeutic agents with broad generalizability, aiming to translate effective treatments into clinical reality sooner[23-25].

Inter-organ communication is essential for maintaining systemic health and underlies the pathology of virtually all diseases, yet its mechanisms remain incompletely understood. As the central metabolic regulation organ, liver-secreted substances are considered to participate in a great number of physiological and pathological events at the systemic level. For instance, albumin is exclusively synthesized by the liver to maintain intravascular oncotic pressure and facilitate the storage and systemic transport of endogenous compounds, including fatty acids, bilirubin, hormones, and drugs[26]. Similarly, urea is uniquely produced by the liver to eliminate toxic ammonia and sustain nitrogen balance[27]. Systemic urea circulation also influences distant organs, such as the heart and kidneys, where changes in its concentration gradient are closely linked to organ function and inter-organ communication *via* the gut−blood barrier[28]. The pancreas complements this systemic regulation through its two major functions: exocrine (aiding digestion) and endocrine (regulating blood glucose). Diabetes mellitus, a metabolic disorder, is characterized by pancreatic endocrine dysfunction, resulting in insufficient insulin production or inappropriate insulin response[29]. Insulin and glucagon are the two key pancreatic hormones regulating energy metabolism, predominantly produced by beta cells (β-cells) and alpha cells (α-cells), respectively[30]. Insulin ensures adequate cellular energy supply by regulating nutrient flux (glucose, free fatty acids, and amino acids) among muscle, liver, and adipose tissue[31]. Conversely, glucagon exerts its effects *via* the glucagon receptor (GCGR) and the glucagon-like peptide-1 (GLP1) receptor, promoting hormone (*e.g.*, fibroblast growth factor 21, FGF21) secretion or activating the sympathetic nervous system to target multiple organs, including the liver, kidneys, heart, and brain[32]. Elucidating the mechanisms of these communicating substances is critical for developing novel drugs capable of simultaneously treating complex metabolic, immunological, and multi-organ end-stage diseases[33,34]. The homology between the liver and pancreas-rooted in shared embryonic origin[35], tissue structure[36], and anatomical association[37] forms the biological basis for their profound pathophysiological interaction. Clinical and mechanistic evidence confirms that the "liver−pancreas−liver feedback axis" constitutes a core pathological mechanism driving mutual organ damage. For example, viral hepatitis significantly increases the risk of severe AP

(SAP)[38], the prevalence of diabetes[39], and the incidence of PC[40]. The underlying mechanisms involve direct viral damage to target cells (acinar/β-cells)[41], persistent viral replication[42], inflammation−fibrosis cascades[43], and genomic integration[44], which collectively drive pancreatic carcinogenesis. Furthermore, hepatitis-associated diabetes can significantly increase the risk of HCC in hepatitis patients, establishing a vicious metabolic cycle of "hepatitis−pancreatic endocrine dysfunction−liver cancer"[45]. Similarly, advanced liver disease leads to pancreatic injury: portal hypertension during liver fibrosis/cirrhosis causes pancreatic congestion and β-cell hypoxia, contributing to hepatogenous diabetes[46]. Conversely, diabetes markedly accelerates the progression of chronic liver diseases, such as MASLD, to fibrosis and cirrhosis[47]. This bidirectional injury is particularly lethal: cirrhosis substantially increases the risk of AP, and when AP occurs in cirrhotic patients, the incidence of hepatic decompensation rises sharply[48]. The mortality rate of SAP is significantly elevated in the context of liver failure, with some SAP cases progressing to fulminant hepatic failure[49]. Moreover, pancreas-derived biomarkers like pancreatic stone protein may hold prognostic value in liver failure, further underscoring the intimate relationship[50]. This bidirectional, self-reinforcing vicious cycle-the "liver−pancreas axis"-constitutes a critical pathological basis for rapid clinical deterioration. A deeper understanding of this framework not only reveals the core mechanism underlying the complexity of chronic liver and pancreatic diseases but also highlights the importance of disrupting such cycles through multi-organ screening and intervention to improve future patient outcomes. The current knowledge of the disease burden and drug therapies of hepatic and pancreatic diseases is summarized in Table 1[5−7,12,14,15,51−61]. Although several important reviews have been published to summarize the liver-oriented or β-cells-oriented communicating mechanisms[62-66], few of them discussed the liver−pancreas axis in disease development and targeted drug therapy. Thus, the aim of the present review is to provide an update of recent advances regarding the communication between the liver and pancreas, with a special emphasis on its role in metabolic diseases.

2. Liver−pancreas crosstalk

As a core metabolic organ, the liver secretes a variety of signaling mediators—including hepatokines, hormones, metabolites, bile acids, and cargos packaged within extracellular vesicles (EVs)—that target and regulate the physiological and pathological functions of the pancreas. These mediators coordinate liver−pancreas communication by regulating key processes in pancreatic cell populations [specifically α-cells, β-cells,

Table 1 Global burden and first-line pharmacotherapy of major liver and pancreas diseases.

Disease	Global burden (data year)	Global mortality (data year)	FDA-approved pharmacotherapy	Mechanism	Ref.
Viral hepatitis-HBV	254 million (2022)	1.1 million (2022)	Nucleoside/nucleotide analogs	Viral replication or DNA synthesis inhibition	6,51
			Interferons	Direct antiviral/immune modulation	
Viral hepatitis-HCV	50 million (2022)	242 thousand (2022)	Direct-acting antivirals	Targeting critical viral proteins essential for HCV replication	52,53
MASLD	1.27 billion (2021)	138 thousand (2021)	Resmetirom	Partial agonist of THRβ that improves steatosis and fibrosis	7,12
ALD	3.02 million (2021)	354 thousand (2021)	N/A	N/A	5,54
Liver cancer	739 thousand (2021)	484 thousand (2021)	Targeted medicines	Targeting angiogenic and proliferative pathways	55,56
			Immunotherapies	Immune checkpoint inhibitors	
Pancreatitis (acute and chronic)	2.75 million (2021)	122 thousand (2021)	N/A	N/A	14
Pancreatic cancer	508 thousand (2021)	505 thousand (2021)	Chemotherapy drugs	Interferes with DNA synthesis, replication and cell division	15,57
			Targeted therapy drugs	Enzyme inhibition, NRG1 targeting	
			Immunotherapy drugs	Regulate tumor microenvironment	
Type 1 diabetes mellitus	8.4 million (2021)	175 thousand (2021)	Insulin therapy	Insulin supplementation	58,59
			Teplizumab	Autoimmune-mediated insulin deficiency targeting	
			Lantidra	Cell therapy	
Type 2 diabetes mellitus	589 million (2024)	723 thousand (2021)	Biguanides	Lowers blood glucose levels	60,61
			Sulfonylureas	Stimulates β-cells to produce insulin	
			GLP-1 receptor agonists	Mimicks natural hormones to maintain glucose levels	
			SGLT2 inhibitors	Works in the kidney to reabsorb glucose	
			DPP-4 inhibitors	Degrades incretin hormones like GLP1 and GIP	

ALD, alcohol-associated liver disease; DPP-4, dipeptidyl peptidase-4; GIP, glucose-dependent insulinotropic polypeptide; GLP1, glucagon like peptide-1; HBV, hepatitis B; HCV, hepatitis C; MASLD, metabolic dysfunction-associated steatotic liver disease; NRG1, neuregulin 1; SGLT2, sodium glucose co-transporter 2; THRβ, thyroid hormone receptor beta.

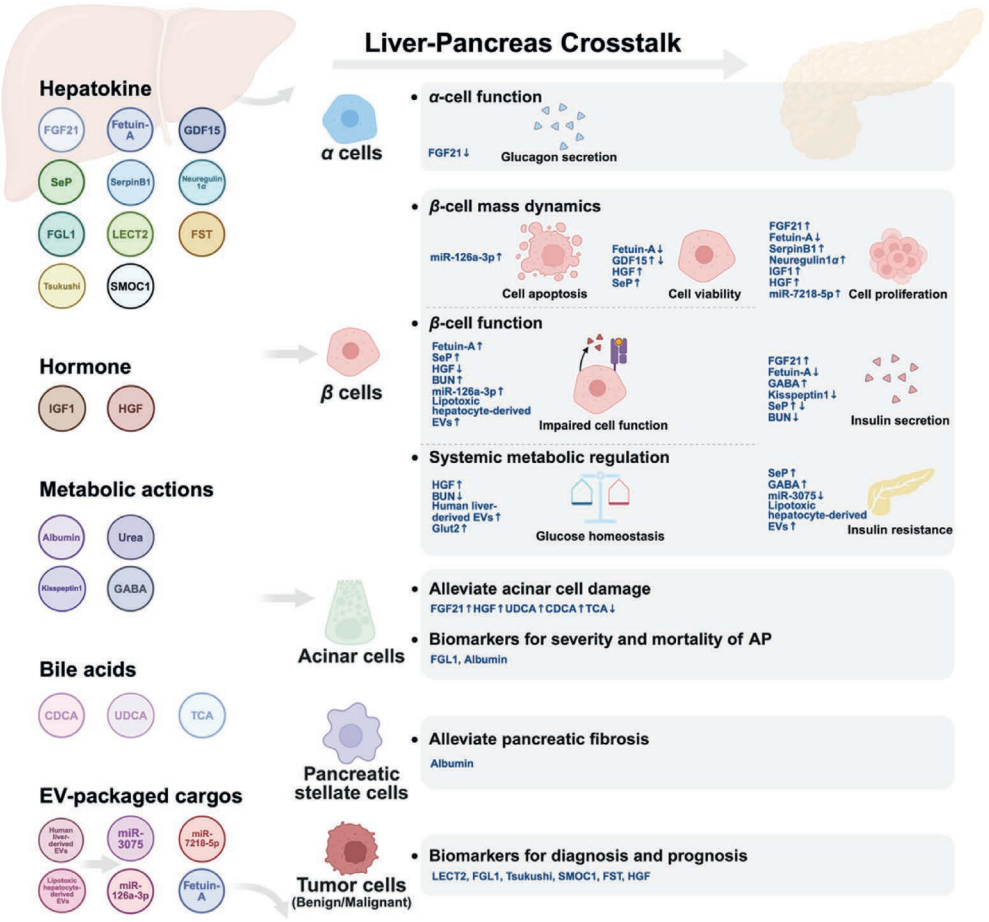

Figure 1 Summary of communicating mechanisms of liver−pancreas axis regulation. Liver secreted several groups of molecules or proteins, including hepatokines, hormones, metabolic actions, bile acids, and extracellular vesicles-packaged cargos (*e.g.*, non-coding RNAs and hepatokines) to target the physiological and pathological functions of pancreatic cells, such as α-cell, β-cell, pancreatic stellate cells, and acinar cells. Dysregulation of those communications contributes to the development of metabolic diseases and pancreatic diseases. This figure is illustrated by using BioRender App.

pancreatic stellate cells (PSCs), and acinar cells], impacting cell proliferation, viability, and secretory function. Dysregulation of this crucial axis, which maintains systemic metabolic homeostasis and pancreatic integrity, promotes the development of both metabolic and pancreatic diseases (Fig. 1).

2.1. *Hepatokine*

Hepatokines are a group of proteins exclusively produced and then secreted by the liver into the systemic circulation, where they function as hormones or messengers across the organism[67]. FGF21 is a prominent hepatokine that largely exerts protective actions across multiple targets, including adipose tissue, the pancreas, muscle, and the hypothalamus[68]. In the liver, FGF21 release from stressed hepatocytes is triggered by nutritional overload, excessive alcohol consumption, and genetic variants, modulating the activity of adjacent Kupffer cells and hepatic stellate cells (HSCs) to promote resolution of steatohepatitis and liver fibrosis[69-71]. Hepatic FGF21 production is also induced during refeeding and overfeeding, where it functions as a key insulin sensitizer to restore glucose homeostasis. This action maximizes peripheral glucose disposal and mitigates peripheral insulin resistance, thereby reducing the chronic metabolic signaling burden on β-cells[72]. The importance of FGF21 in the liver-to-pancreas endocrine axis is evident in various disease models. In a cerulein-induced pancreatitis model, transgenic mice expressing human FGF21 from the apolipoprotein E promoter in the liver showed improved acinar tissue damage and hepatic steatosis[73]. More recently, a study revealed that liver-derived FGF21 is involved in β-cell regeneration under hyperglycemic conditions. The loss of physiologic glucose control and β-cell regeneration was prevented in FGF21 neutralizing antibody-treated db/db mice, *Fgf21* knockout diabetic mice, and hepatocyte-specific $Fgf21^{-/-}$diabetic mice[74]. Furthermore, administration of berberine significantly ameliorated hepatic and pancreatic damage (*e.g.*, insulin resistance and steatosis) in mouse models of type 2 diabetes mellitus (T2DM). This effect was partially mediated by the upregulation of hepatic FGF21 production and the expression of glucose transporter 2 in the pancreas, as *Fgf21* deficiency diminished berberine's protective effects on diabetic mice[75].

Fetuin-A is another important hepatokine that links the liver and other organs during metabolic stress[65]. High circulating levels of fetuin-A have been reported to cause evident damage to murine

islet histoarchitecture, β-cell death, and impede insulin secretion[76]. Mechanistic studies further showed that liver steatosis induced elevated plasma fetuin-A levels, which consequently impaired both β-cell function and adaptive proliferation[77]. Pharmacological inhibition of dipeptidyl peptidase-4 using vildagliptin successfully preserved islet mass and restored β-cell function, partly by reducing high-fat diet-induced fetuin-A secretion mediated by the toll-like receptor 4-nuclear factor kappaB (TLR4−NF-κB) pathway[78].

In type 1 diabetes mellitus (T1DM), the hepatokine growth and differentiation factor 15 (GDF15) exerts pro-survival effects on β-cells during DNA damage-mediated senescence[79]. Knockout of *Gdf15* in mice improved streptozotocin-induced diabetes by preserving β-cell and insulin levels though the endoplasmic reticulum (ER) stress-induced cell death programs[80]. It should be noted that GDF15 may be secreted from both the liver and the pancreas *via* endocrine and autocrine actions, respectively[81], particularly since cytokine-treated human pancreatic islets repressed the local secretion of GDF15[82]. A recent human study further implicated the role of liver-derived GDF15 in liver−pancreas communication, finding that its secretion during exercise or chronic energy deprivation is regulated by the glucagon-to-insulin ratio[83].

In T2DM, the hepatokine selenoprotein P (SeP) causes insulin resistance and metabolic dysfunction by inhibiting insulin secretion through the disruption of pancreatic β-cell functions[84]. Administration of the SeP monoclonal antibody AE2 significantly improved pancreatic insulin secretion and glucose intolerance in a T2DM mouse model[85]. Interestingly, local knockdown of *Selenop* in β-cells decreased cell viability, cellular pro/insulin levels, and insulin secretion, possibly through glutathione peroxidase 4 (GPX4)-mediated ferroptosis[86]. This dual role-where systemic Sep is detrimental but local Sep is protective-positions this hepatokine as an attractive target for novel metabolic disease therapies.

Recently, proteomic and microarray techniques have identified additional hepatokines, serpinB1 and neuregulin1α, that promote pancreatic β-cell proliferation[87,88]. Mechanistically, serpinB1 enhances β-cell proliferation through growth/survival pathways by inhibiting elastase activity. Similarly, neuregulin1α modulates cell expansion in the insulin-resistant state by binding to its receptor ErbB3 and activating the downstream extracellular signal-regulated kinase (ERK) signaling pathway in β-cells. These two hepatokines offer promising avenues for developing therapeutic strategies aimed at restoring functional β-cell mass in metabolic diseases.

Several other hepatokines are reported to participate in pancreatitis and PC development. For instance, in AP patients, the hepatokine fibrinogen-like protein 1 (FGL-1) has been found to be a predictive marker for the incidence of SAP, infectious pancreatic necrosis, and PC[89,90]. Exogenous eicosapentaenoic acid treatment suppressed KRAS mutant PC cell growth by suppressing FGL-1 expression and signal transducer and activator of transcription 3 (STAT3) phosphorylation[91]. Leukocyte cell-derived chemotaxin-2 (LECT2) retarded PC development by inhibiting mesenchymal−epithelial transition and antagonizing forkhead box protein M1[92]. A high expression level of a recently discovered hepatokine Tsukushi was found to be associated with poorer prognosis of PC patients[93]. Positive expression of hepatokine SPARC-related molecular calcium-binding 1 (SMOC1) was reportedly associated with recurrence and a poorer prognosis in pancreatic neuroendocrine tumors[94]. Sequencing of human patient samples revealed the association between high expression level of follistatin (FST) and low apoptotic activity in intraductal oncocytic papillary neoplasm, a rare intraductal tumor of the pancreatobiliary system[95].

2.2. Hormone

Beyond hepatokines, a set of liver-derived hormones has also been identified as key modulators of pancreatic β-cell proliferation, function, and survival. Insulin-like growth factor 1 (IGF1) is primarily produced by the liver, which accounts for about 75% of its circulating, implicating it as a liver-to-pancreas endocrine signal[96]. Studies using inducible hepatocyte-specific insulin receptor knockout mice demonstrated that these mice developed hepatic insulin resistance. This was accompanied by increased hepatic IGF1 expression and circulating levels, leading to compensatory β-cell hyperplasia *via* upregulated insulin receptor A on the β-cell surface. While this adaptation initially maintained glycemic control, it was ultimately insufficient to prevent diabetes progression[97]. Hepatocyte growth factor (HGF) is another liver-secreted hormone that interferes with systemic energy metabolism[98]. An early study identified that HGF administration attenuated pancreatic damage in an AP rat model, possibly by re-balancing interleukins[99]. It has also been proposed to regulate β-cell development and insulin secretory capacity[100]. A screening method identified an HGF activator that responds to metabolic stress to enhance systemic lipid and glucose homeostasis, with potential benefits for β-cell proliferation[101,102]. Importantly, during the development of PC, PSCs are a key source of HGF. PSCs-derived HGF interacts with its receptor, c-Met, on pancreatic cancer cells to activate oncogenic pathways, notably mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)[103]. This pathway is also responsible for conferring resistance to epidermal growth factor receptor (EGFR) inhibition in pancreatic cancer cells[104]. Given this context, whether liver-derived HGF contributes to PC progression remains an important and open research question.

2.3. Metabolic actions

Albumin, the predominant protein found in human serum, performs essential functions, including inflammation modulation, redox equilibrium, and xenobiotic metabolism[105]. A Hungarian clinical investigation revealed that hypoalbuminemia (low albumin levels) serves as an independent prognostic indicator for increased disease severity and mortality in patients with AP. Hypoalbuminemia was proportionally related to the incidence of local complications, organ failure, and prolonged hospital admission[106]. Further studies substantiate that administering albumin infusions leads to a notable reduction in mortality rates for patients with SAP and concurrent hypoalbuminemia[107]. However, the absence of randomized controlled trials means critical details, such as the optimal dosage, appropriate timing, and precise patient cohorts for albumin intervention, remain undefined. Conversely, albumin plays a localized role within the pancreas. Pancreatic fibrosis, a defining pathological characteristic of pancreatic disorders, involves PSCs as key orchestrators. PSCs intrinsically synthesize and store albumin. Elevated intracellular albumin concentrations contribute to maintaining the PSCs quiescent, lipid-storing phenotype by engaging the peroxisome proliferator-activated receptor gamma (PPARγ) and CCAAT/enhancer-binding protein alpha signaling pathways. Research further indicates that retinol enhances albumin synthesis in activated PSCs, and disrupting albumin expression *via* small interfering RNA

(siRNA) effectively abolishes the effects induced by retinol[108,109]. Although the complex of human serum albumin and free fatty acids (FFAs) affects β-cell viability and insulin secretion *in vitro*, the underlying mechanisms and overall physiological relevance of these observations are still largely undefined[110].

Evidence regarding the toxicity of urea on distant organs is beginning to emerge. Large cohort studies show that higher baseline blood urea nitrogen (BUN) is independently associated with an increased risk of incident diabetes and escalated insulin therapy among diabetic patients[111,112]. While these observational analyses cannot establish direct causality or pinpoint pancreatic dysfunction, they highlight the clinical relevance of urea in metabolic disease, referencing experimental findings that underpin a causal relationship. Urea affects cellular functions indirectly by modifying serum or tissue compounds, and directly by increasing oxidative stress[113]. This stress has been shown to impair glucose uptake in adipocytes[114], decrease tight junctions in intestinal cells[115], and induce endothelial dysfunction[116]. In healthy mice, oral urea treatment for three weeks impaired insulin secretion in isolated islets, associated with reduced glucose utilization and decreased activity of phosphofructokinase 1. Similarly, mice with chronic kidney disease showed defective insulin secretion due to the direct action of urea on β-cells, which increased oxidative stress and protein *O*-GlcNAcylation[117]. These adverse effects were reversible with antioxidant or *O*-GlcNAcylation inhibition and were shown to be independent of cyanate, a urea degradation product. A bacterial cocktail was developed for oral delivery in animals with kidney injury to metabolize blood nitrogenous waste products (urea and creatinine) before intestinal diffusion, showing promise without adverse effects[118]. Furthermore, under inflammatory conditions, glucose-mediated activation of the pyruvate carboxylase−urea cycle axis was sufficient to suppress nitric oxide synthesis, thereby shielding β-cells from death in inflammatory and other stress paradigms[119]. However, current evidence is largely restricted to endocrine pancreatic outcomes (β-cell secretion and metabolism), with limited exploration of urea's impact on exocrine function.

Recent findings suggest that hepatocyte-derived gamma-aminobutyric acid (GABA) is released during steatosis and acts as a non-protein mediator of pancreatic function. In mouse models, increased hepatic GABA reduced hepatic vagal afferent nerve firing, which consequently stimulated insulin secretion and promoted systemic insulin resistance. Single-nucleotide polymorphisms in hepatic GABA re-uptake transporters were associated with an increased incidence of T2DM, highlighting a neural−liver−pancreas axis distinct from classical endocrine hormone pathways[120]. Another neurotransmitter, kisspeptin 1, was induced by glucagon and acted on β-cells to suppress glucose-stimulated insulin secretion through the kisspeptin 1 receptor[121].

2.4. Bile acids

Bile acids (BAs), primarily synthesized from cholesterol in the liver and conjugated with glycine or taurine, are indispensable for lipid digestion. Beyond this fundamental role, BAs significantly influence the pathogenesis and progression of diverse gastrointestinal disorders, including chronic liver diseases[122], inflammatory bowel disease[123], and pancreatic diseases[124]. The mechanisms by which BAs inflict injury on pancreatic acinar cells are multifaceted, involving both their detergent and non-detergent properties. The detergent actions of BAs lead to an elevation in intracellular Ca^{2+} concentration, mitochondrial membrane depolarization, and a consequent depletion of intracellular adenosine triphosphate (ATP). Concurrently, the non-detergent effects of BAs initiate PI3K activation, culminating in inappropriate digestive zymogen activation, cellular damage, and ultimately acinar cell death[125]. Intriguingly, pharmacological inhibition of PI3K has been shown to reverse BA-induced intracellular Ca^{2+} increases by promoting Ca^{2+} reuptake into the ER, thereby ameliorating the course of AP[126]. The G-protein-coupled bile acid receptor 1 (GPBAR1, also known as TGR5), a cell surface receptor, also plays a pivotal role in BA-mediated effects. Mouse studies have demonstrated that *Gpbar1* knockout results in a milder form of pancreatitis following challenge with taurolithocholic acid-3-sulfate. This protective phenotype was linked to reduced pathological Ca^{2+} transients and the preservation of physiological Ca^{2+} oscillations despite the pathological stimulus[127]. Moreover, intracellular Ca^{2+} overload, a direct consequence of BA exposure, independently contributes to mitochondrial depolarization, diminished ATP availability, enhanced reactive oxygen species generation, and ultimately acinar cell demise[128]. Beyond their interaction with cell membrane receptors, BAs can also be directly transported into acinar cells *via* specific membrane transporters such as the sodium taurocholate cotransporting polypeptide and organic anion transporting polypeptides[129]. Intracellularly, BAs engage with various receptors, with the nuclear farnesoid X receptor (FXR) and GPBAR1 being the most extensively characterized BA-dependent receptors. The influence of BAs on FXR signaling is pleiotropic: while conjugated BAs generally act as agonists, chenodeoxycholic acid (CDCA) and its metabolic derivatives, taurine- and glycine-β-muricholic acid, exert an inhibitory effect. Notably, FXR activation has been implicated in inhibiting autophagy, thereby sensitizing acinar cells to stress-induced damage[130,131]. In the context of pancreatic inflammation, the transient receptor potential vanilloid 1 (TRPV1), a cell membrane ion channel, is expressed on primary sensory nerves and contributes to the inflammatory cascade in AP. Evidence from mouse models indicates that intraductal BA administration triggers the production of leukotriene B4 by pancreatic acinar cells. This leukotriene B4 subsequently activates TRPV1 on primary sensory nerves, thereby initiating AP. The therapeutic potential of targeting this pathway was underscored by the successful reversal of AP through treatment with the leukotriene B4 inhibitor, MK886[132]. Furthermore, ryanodine receptors (RyR) are critical contributors to BA-induced Ca^{2+} dysregulation and injury, with RyR inhibitors demonstrating protective effects on acinar cells[133]. In pancreatic ductal cells, BAs elicit biphasic responses: modulating secretion at lower concentrations, yet inducing injury, ATP release, and purinergic signaling at higher, pathological concentrations[134].

2.5. EV-packaged cargo communication

EVs serve as a crucial delivery route, facilitating communication between different tissues by delivering their molecular cargo. Non-coding RNAs are frequently packaged and delivered by EVs to link the 'liver−pancreas' axis. In high-fat diet-induced obese mice, miR-7218-5p within hepatocyte-derived EVs targets CD74 on β-cells to mediate compensatory hyperplasia of the islets[135]. Conversely, EVs from steatotic hepatocytes promote β-cell apoptosis and dysfunction, mainly by delivering miR-126a-3p, which downregulates insulin receptor substrate 2 (IRS2). *In vivo*

antagonism of miR-126a-3p preserved β-cell mass and improved glycaemia[136]. In early-onset obesity, hepatocytes secrete EVs containing miR-3075 that inhibit fatty acid 2-hydroxylase, thereby protecting against insulin resistance and islet dysfunction caused by chronic obesity[137]. Hepatokines and metabolic-related proteins constitute another important category of cargo delivered by EVs. For example, chronic administration of exogenous lipotoxic liver-secreted EVs (enriched in Fetuin-A) in lean mice induced hepatic and pancreatic inflammation through the recruitment of immune cells. TLR4-mediated signaling in islet macrophages was identified as a key mediator of the lipotoxic EVs' effects on β-cell function[138]. Conversely, elevated blood glucose levels stimulate the liver to release EVs (enriched in proteins of carbohydrate metabolism) into the bloodstream. This direct EV-mediated signaling from the liver to the pancreas subsequently promoted insulin secretion. Notably, the blood glucose-lowering effects observed with these EVs were replicated when administering liver EVs sourced from humans, regardless of whether they had progressive MASLD or not[139]. Given the complexity and translational potential of these findings, urgent receptor and pathway elucidation is necessary to advance broad EV-based therapies against hepatic and pancreatic diseases[140].

3. Pancreas−liver crosstalk

The pancreas regulates liver function by secreting a variety of regulatory signals. This pancreatic influence on the liver is crucial for coordinating systemic metabolism, immune responses, and organismal homeostasis. The key mediators through which the pancreas communicates with the liver include: hormones (*e.g.*, insulin, glucagon, pancreas-derived factor PANDER, somatostatin, and amylin), metabolites (*e.g.*, Reg3γ), immune factors (*e.g.*, IL-22 and elastase), and EV-packaged cargos (*e.g.*, microRNAs and integrins). These mediators target hepatocytes, Kupffer cells, and cancer cells, thereby modulating the occurrence and progression of metabolic diseases, liver lesions, and carcinogenesis (Fig. 2).

3.1. Hormone

Insulin and glucagon, pivotal peptide hormones secreted by the pancreatic islets of Langerhans, work in a coordinated fashion to maintain glucose homeostasis. The primary role of insulin is to lower blood glucose levels, particularly after meals, by promoting glucose uptake into peripheral tissues like muscle and adipose tissue, and by

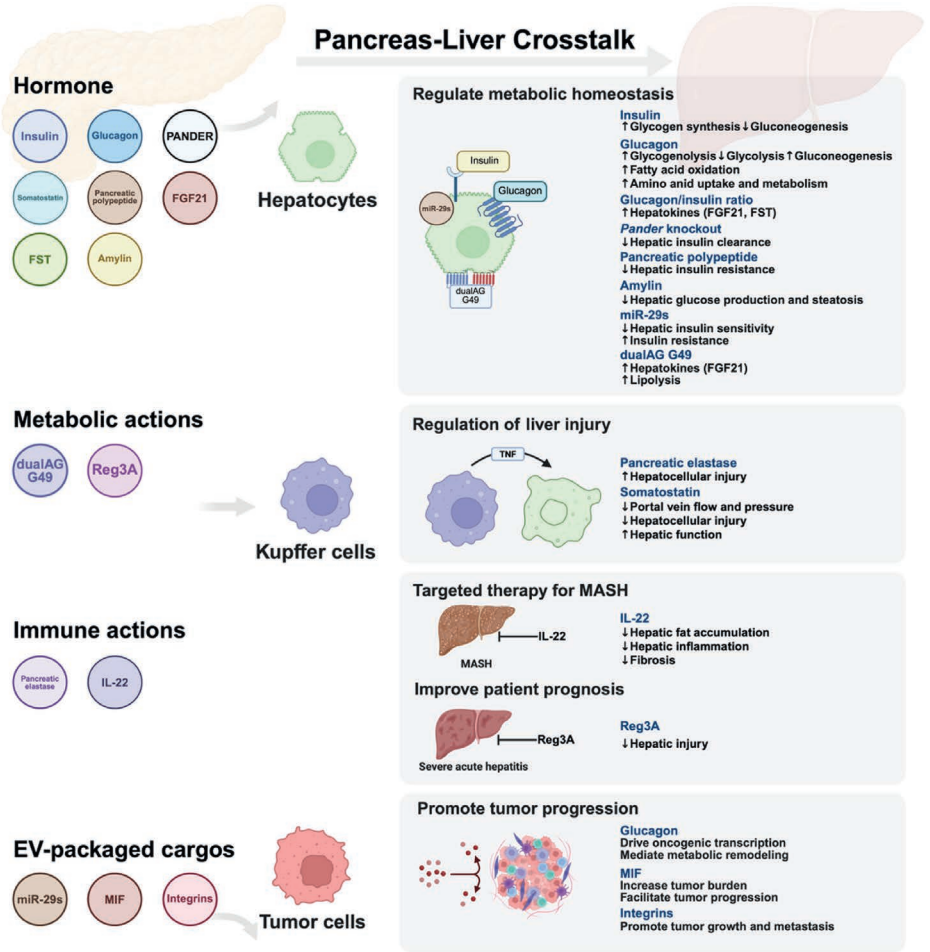

Figure 2 Summary of communicating mechanisms of pancreas−liver axis regulation. Pancreas secretes several kinds of communicating signals, including hormones, metabolic substances, immune actions, and extracellular vesicles-packaged cargos (*e.g.*, non-coding RNAs and proteins) to target hepatocytes, Kupffer cells, and cancer cells to regulate the development of metabolic diseases, hepatic disorders, and carcinogenesis. This figure is illustrated by using BioRender App.

inhibiting glucose production in the liver. This is achieved through either the canonical hepatocyte signaling (*i.e.*, binding to insulin receptor and activates the PI3K−Akt−mTORC1 signaling) or non-canonical effectors (*e.g.*, FoxO1 regulation of fatty acid oxidation and fine-tuning IRS1/IRS2 ratio by peroxisome-proliferator-activated receptor-gamma coactivator-1)[141,142]. Conversely, glucagon, secreted by the pancreatic α-cells, acts to elevate blood glucose, primarily during fasting or hypoglycemia. It targets the liver, stimulating glycogenolysis, gluconeogenesis, amino acid catabolism, and fatty acid oxidation *via* the well-recognized glucagon receptor (GCGR)−cAMP−PKA pathway[143]. This counter-regulatory action ensures a continuous glucose supply to vital organs like the brain. The delicate balance between insulin and glucagon is crucial, as dysregulation is a hallmark of metabolic disorders like diabetes mellitus[32]. Recently, the key roles of glucagon in amino acid turnover and α-cell feedback secretion have been emphasized as the "liver−α-cell axis." Glucagon resistance is now linked to MASLD and associated with hyperaminoacidemia/hyperglucagonemia[144]. Human clinical studies confirming impaired hepatic amino acid metabolism in MASLD *versus* healthy subjects further support the pathophysiological significance of glucagon resistance[145]. Beyond metabolic liver diseases, dysregulation of insulin and glucagon also affects other common liver pathologies. For example, HCV directly infects pancreatic cells, decreasing insulin release *via* β-cell dysfunction[146]. Glucagon secretion, conversely, can promote oncogenic gene expression (*e.g.*, NF-κB, MYC, HIF-1, and STAT3) and metabolic adaptation in HCC cells[147].

Somatostatin (SST) is a peptide hormone released by δ-cells (delta-cells) in the pancreatic islets, as well as the pyloric antrum, duodenum, and neuroendocrine neurons. It directly inhibits the secretion of both insulin and glucagon *via* interaction with G protein-coupled somatostatin receptors[148]. SST content was significantly lower in T2DM patients than non-diabetic subjects[149] but comparable between non-obese and obesity subject[150]. Studies have identified the therapeutic potential of SST analogues in various liver diseases. Exogenously administered SST can treat 'small-for-size' liver by reducing portal blood flow and offering direct protection of liver cells[151]. SST treatment also reduces intracellular cAMP and prevents fluid accumulation in hepatic cysts, thereby attenuating symptoms of polycystic liver disease[152]. Furthermore, SST analogue octreotide intervention significantly improved hepatic steatosis, dyslipidemia, and triglyceride export in obese rats fed a high-fat diet, which reduced plasma SST levels[153]. A clinical trial using long-acting repeatable octreotide (Sandostatin) over three months showed improved portal hypertension in patients with cirrhosis (mostly alcoholic)[154].

Pancreatic polypeptide (PP) is a peptide hormone secreted by PP cells that helps regulate digestion by inhibiting pancreatic and gastrointestinal secretions. It is synthesized and released in response to food ingestion, fasting, and acute hypoglycemia[155]. Fasting plasma PP concentration was reported as a novel predictor of visceral and liver fat content, as well as obesity-related liver injury, in a biochemical study of 104 overweight and obese subjects[156]. Furthermore, PP administration ameliorated hepatic insulin resistance and glucose tolerance in rats with CP by restoring insulin receptor function, which was impaired in this condition[157]. This effect may be linked to the significant upregulation of PP receptor concentration on liver microsomal membranes in CP animals, possibly due to diminished ligand exposure, indicating a blunted response to the fed/fasted state[158]. These results strongly imply a pancreas−liver regulatory axis mediated by PP and its receptor; however, further mechanistic studies are warranted to link PP to other types of liver diseases.

The exocrine pancreas expresses FGF21 to maintain acinar cell proteostasis. In both human patients and animal models of AP and CP, loss of FGF21 expression is associated with activation of the integrated stress response pathway[159]. Pharmacological inhibition or exogenous FGF21 replacement mitigated this pathway and resolved pancreatitis. An indirect communication pathway involves the brain−pancreas axis, as FGF21 administration to the third ventricle improved blood glucose homeostasis in pancreatic denervated rats by increasing insulin secretion while inhibiting glucagon secretion[160]. Interestingly, FGF21 is also an exocrine pancreas secretagogue from acinar cells through an autocrine/paracrine mechanism, requiring signaling *via* both FGF receptor and β-klotho during glucose intolerance and sodium-dependent glucose transporters 2 (SGLT2) inhibition[161,162]. Notably, pancreatic FGF21 is nutritionally regulated (fasting reduces it; obesity enhances it). Mice lacking *Fgf21* exhibited islet hyperplasia and periductal lymphocytic inflammation when fed a high-fat obesogenic diet[163]. In healthy individuals, exercise significantly induced the plasma levels of both hepatokines, FGF21 and FST, which were blunted by the pancreatic clamp. Patients with T2DM showed impaired FGF21 and FST secretions, impairing their sensitivity to pancreatic glucagon and insulin production, which determine the pancreas−liver communication[164]. Local overexpression of FST in the pancreas of diabetic mice increased serum insulin levels and promoted β-cell proliferation[165].

Pancreatic derived factor (PANDER) is a key protein that facilitates communication between β-cells and the liver. This protein is considered a potential bridge between insulin resistance and T2DM, and it might serve as a biomarker for MASLD and diabetes[166]. Knockout of *Pander* in mice significantly increased blood glucose level, disrupted the responses of islets to glucose stimulation, and interestingly, decreased hepatic insulin clearance[167]. Since hepatocytes could also express a small amount of PANDER and overexpression of PANDER in the livers promoted lipogenesis and compromised insulin signaling through the FoxO1-dependent pathway, the metabolic regulation effects of this factor might be bi-directional[168].

Amylin (islet amyloid polypeptide) is co-secreted with insulin from pancreatic β-cells post-ingestion. An early study identified that amylin impaired glucose disposal and elevated glucose output in hepatocytes[169]. It has since been revealed that amylin's suppression of glucagon secretion indirectly reduces hepatic glucose production and steatosis[170]. Administration with exogenous amylin analogue has been tested in several clinical trials to treat metabolic diseases (Table 2[171-192]).

3.2. *Metabolic actions*

Regenerating islet-derived 3 gamma (Reg3γ) is a protein first discovered in the pancreas that exhibits significant upregulation after partial pancreatic resections. Overexpression of *Reg3*γ conferred beneficial effects on β-cell regeneration by activating the Janus kinase (JAK)/STAT pathway in a nonobese-diabetic mouse model of T1DM[193]. Moreover, in a tacrolimus-induced new-onset diabetic mice model, Reg3γ restored glucose-stimulated insulin secretion suppressed by tacrolimus in β-cell by improving mitochondrial functions through the accumulation

Table 2 List of clinical trials targeting liver−pancreas communication substances.

Trial title (brief)	Trial design	Target substance	Study population	Primary outcome (s) of interest	NCT number and starting year	Current status	Ref.
Phase 1 trials							
Safety and efficacy of LY2405319 in T2DM	Double-blinded randomized placebo-controlled trial	Modified human FGF21 expressed in yeast	Patients with T2DM and BMI 25-40.	Safety and fasting glucose change during a 28-day treatment	NCT01869959, 2009	Completed	171
Multiple dose study of PF-05231023 in T2DM	Double-blinded randomized placebo-controlled trial	Two FGF21 joint with an IgG backbone	Patients with T2DM and poor lipid control	Safety, tolerability and pharmacokinetics of multiple doses	NCT01673178, 2012	Completed	172
Safety and effects of AMG 876 (AKR-001) in T2DM	Double-blinded randomized placebo-controlled trial	Fc-FGF21 engineered fusion protein	Patients with T2DM and BMI 25-40.	Safety, insulin sensitivity, and lipoprotein profile	NCT01856881, 2013	Terminated	173
Safety of LY3463251 in healthy people	Double-blinded randomized placebo-controlled trial	Synthetic peptide of GDF15 ligand fused to IgG4-Fc	Healthy participants	Safety, tolerability and pharmacokinetics of multiple doses	NCT03764774, 2018	Terminated	174
Safety and efficacy of follistatin plasmid gene therapy in healthy people	Single group assignment	Follistatin plasmid	Healthy participants	Safety and changes of follistatin serum concentration at 3 months	NCT06411366, 2022	Completed	
Efficacy of BMS-754807 and metformin in healthy people	Single group assignment	IGF1/IR family kinase inhibitor	Healthy participants	Safety and changes of peak plasma glucose concentrations	NCT01525823, 2012	Completed	
Safety of ficlatuzumab with nab-paclitaxel and gemcitabine in advanced pancreatic cancer	Single group assignment	Monoclonal antibody of HGF	Patients with advanced pancreatic cancer	Maximum tolerated dose of ficlatuzumab and response rate	NCT03316599, 2018	Completed	175
Phase 2 trials							
BMS-986036 for treatment obese adults with T2DM	Double-blinded randomized placebo-controlled trial	PEGylated human FGF21	Patients with T2DM and BMI 30-50	Changes of HbA1c, bodyweight, and insulin sensitivity	NCT02097277, 2014	Completed	176
BMS-986036 for treatment MASH and fibrosis	Double-blinded randomized placebo-controlled trial	PEGylated human FGF21	Patients with MASH and stage 3 liver fibrosis	Improvements of NASH and fibrosis at week 24	NCT03486899, 2018	Completed	177
Safety and efficacy of efruxifermin (AKR-001) in MASH	Double-blinded randomized placebo-controlled trial	Fc-FGF21 engineered fusion protein	Patients with biopsy-proven F1-F4 MASH	Improvement of fat fraction and NASH	NCT03976401, 2019	Completed	178
Safety and efficacy of pegozafermin in MASH	Double-blinded randomized placebo-controlled trial	Long-acting glycopegylated FGF21 analogue	Patients with biopsy-confirmed MASH and stage F2 or F3 fibrosis	Improvement of fibrosis and NASH	NCT04929483, 2021	Completed	179
Safety and efficacy of pramlintide in obese patients	Randomized, double-blinded, placebo-controlled, dose ranging trial	Human amylin analogue	Patients with BMI $\geq$30 and $\leq$ 50	Safety and body weight reduction	NCT00112021, 2015	Completed	180
Safety and efficacy of davalintide in obese patients	Randomized, double-blinded, placebo-controlled, dose ranging trial	Amylin receptor and calcitonin receptor dual-agonist	Patients with BMI $\geq$27 and $\leq$ 30 as overweight and patients with BMI $\geq$30 and $\leq$ 45 as obesity	Safety and body weight reduction	NCT00785408, 2015	Completed	181
Safety and efficacy of NGM120 in PC	Randomized sequential assignment trial	Monoclonal antibody blocking GDF15 signaling	Patients with recurrent unresectable PC	Safety and tolerability of NGM120	NCT04068896, 2019	Completed	

Safety and efficacy of MBL949 in obese participants with or without T2DM	Double-blinded randomized placebo-controlled trial	Half-life extended recombinant human GDF15 dimer	Patients with BMI ≥32, weight ≥77 kg, with or without T2DM	Safety and body weight reduction	NCT05199090, 2022	Terminated	
AMG 479 for treatment pancreatic neuroendocrine tumors	Single group assignment	Anti-IGF1R antibody	Patients with locally unresectable or metastatic pancreatic neuroendocrine tumors	Objective response rate	NCT01024387, 2010	Completed	
Efficacy of human albumin in pancreaticoduodenectomy	Randomized controlled trial	Human albumin	Patients undergoing pancreaticoduodenectomy	Overall complications	NCT04418739, 2020	Recruiting	
Safety and efficacy of GABA in T1DM	Open-label randomized clinical trial	Oral GABA treatment	Patients with T1DM	Safety and changes of c-peptide, glucagon response, and HbA1c	NCT03635437, 2018	Completed	182
Safety and efficacy of ALF-5755 in acute liver injury and failure	Double-blinded randomized placebo-controlled trial	Human Reg3α protein	Patients with early-stage acute liver failure or severe acute hepatitis	Safety and changes of prothrombin rate initiation	NCT01318525, 2010	Completed	183
Efficacy of obeticholic acid in T2DM and MASLD	Double-blinded randomized placebo-controlled trial	FXR agonist	Patients with T2DM and presumed MASLD	Insulin resistance and glucose homeostasis	NCT00501592, 2007	Completed	184
Efficacy of GFT505 in obese people	Randomized clinical trial	Dual PPAR-α/δ agonist	Obese people with waist circumference ≥94 cm, BMI ≤45	Changes of glucose infusion rate	NCT01271777, 2011	Completed	185
Phase 3 trials							
Efficacy of VM202 in painful DN	Double-blinded randomized placebo-controlled trial	Plasmid DNA encoding human HGF	Patients with painful DN	Change in the average 24-h pain score	NCT02427464, 2016	Completed	186
Efficacy of UDCA in T2DM	Double-blinded randomized placebo-controlled trial	Naturally occurring BA	Patients with T2DM	Change in oxidative stress biomarkers, BMI, and glucose	NCT05416580, 2022	Completed	187
Efficacy of UDCA in relapsing complications after gallstone AP	Double-blinded randomized placebo-controlled trial	Naturally occurring BA	Hospital admission due to AP with gallstones	Complication due to gallstones and relapse of AP	NCT04924868, 2021	Recruiting	
Efficacy and safety of pramlintide in T1DM and T2DM	Multicenter open-label treatment trial	Human amylin analogue	Patients with T1DM or T2DM who have not achieved glycemic targets with insulin therapy	Changes in HbA1c, glucose profile, body weight and safety	NCT00108004, 2015	Completed	188,189
Efficacy of CagriSema in patients with T2DM and obesity	Quadruple-blinded randomized placebo-controlled trial	Cagrilintide and semaglutide	Patients with BMI ≥27 and diagnosed as T2DM	Changes in HbA1c, body weight, glucose profile, and blood pressure	NCT05394519, 2025	Completed	190
Phase 4 trials							
Efficacy of long-term albumin in cirrhosis and T2DM	Open-label randomized placebo-controlled trial	Human albumin	Patients with decompensated cirrhosis, with or without T2DM	Mortality and complications	NCT01288794, 2011	Completed	191,192

BA, bile acid; BMI, body mass index; FGF21, fibroblast growth factor 21; FXR, farnesoid X receptor; GABA, gamma-amino butyric acid; GDF15, growth and differentiation factor 15; HbA1c, Hemoglobin A1C; HGF, hepatocyte growth factor; IGF1R, insulin growth factor 1 receptor; Reg3, regenerating islet-derived 3; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

of pSTAT3(Ser727)[194]. Intraduodenal Reg3γ infusion in mice significantly decreased liver fat/content and hepatic lipogenic gene expression[195]. A Phase 2a double-blind, randomized, placebo-controlled study confirmed that human C-type lectin Reg3α (Reg3A, also known as pancreatic-associated protein) improved clinical prognosis of patients with HBV- or auto-immune hepatitis-induced severe acute hepatitis[183]. Peptide-guided antifibrotic therapy (using CP-specific pancreatic ligands to direct liposomal apigenin) reduced CP and secondarily protected against markers of hepatic injury (histology and oxidative stress) in mice, suggesting indirect hepatic benefit *via* improved pancreatic health rather than a defined secreted mediator[196].

3.3. Immune actions

Liver injury is a common outcome of the systemic inflammatory response observed in AP. Pancreatic elastase acts as a mediator connecting the localized inflammation in the pancreas to systemic symptoms of pancreatitis and injury to distant organs. This enzyme stimulated the production of TNF-α by Kupffer cells, rather than hepatocytes, and triggered the activation of NF-κB[197]. The interleukin (IL)-22 receptor, IL-22RA1, is abundantly expressed in the pancreas, liver, intestine, and skin. IL-22 is a potent endogenous paracrine suppressor of oxidative and ER stress in pancreatic islets and that in obesity-induced hyperglycemia in mice. Additionally, it could enhance liver function and mitigate steatosis in metabolic disorders[198]. A novel engineered IL-22 fusion protein was specifically designed to target the pancreas and liver, which were critical organs in the progression of MASH. Little effects have been observed in the intestine and skin[199]. Moreover, since obesity is associated with increased severity of AP and IL-18 and IL-12 are elevated in patients with AP or obesity, it was observed that two injections of IL-12 plus IL-18 induced typical AP phenotypes in obese mice *via* the action of the IL-6, which was not secreted from the liver[200].

3.4. EV-packaged cargo communication

Pancreatic β-cell-secreted EVs, specifically those enriched in miR-29s, constitute a novel endocrine route that negatively regulates hepatic insulin sensitivity and glucose homeostasis This effect has been observed both *in vitro* and *in vivo*: elevated EV secretion containing miR-29s in response to high FFA levels leads directly to attenuated insulin sensitivity and insulin resistance[201]. PC cells release EVs enriched in macrophage migration inhibitory factor (MIF), which contribute to the formation of a pre-metastatic niche in the liver, ultimately increasing tumor burden[202]. These EVs modulate the hepatic microenvironment by initiating an inflammatory response and activating fibrotic pathways. Such changes facilitate tumor progression by promoting the uptake of immune cells by liver cells and enhancing the production of transforming growth factor and fibronectin. Additionally, PC-derived EVs enriched with integrin α5β1 exhibit a tendency to migrate specifically to the liver, whereas those enriched with integrins α6β4 and α6β1 are predominantly found in the lungs[203]. This molecular specificity of PC-derived EVs in targeting distant organs, particularly the liver, underscores their critical role as mediators of tumor growth and metastasis. Further studies are required to fully unravel the precise molecular mechanisms through which PC-derived EVs regulate metastasis to distant sites.

4. Liver/pancreas co-crosstalk by other organs

Beyond the direct crosstalk between the pancreas and the liver, organ systems such as the gut, nervous system, adipose tissue, and skeletal muscle secrete a variety of bioactive factors (including metabolites, hormones, neurotransmitters, and cytokines). This forms a complex multi-organ signaling network that regulates the function of the hepato−pancreatic axis and systemic metabolic homeostasis. These mechanisms significantly influence the occurrence and progression of metabolic diseases, hepatic lesions, and pancreatic disorders (Fig. 3).

4.1. Gut

The gut−liver−pancreas axis (GLPA) forms a vital, interconnected system essential for maintaining metabolic stability. Within this axis, substances from the gut, particularly metabolites produced by the gut microbiota, concurrently influence both the liver and pancreas through various mechanisms. This intricate crosstalk is paramount for regulating glucose and lipid metabolism; its dysregulation can precipitate metabolic disorders such as diabetes, MASLD, and certain cancers. Several gut-derived substances drive this interorgan communication. Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are primary metabolites produced when gut microbiota ferment indigestible dietary fibers. They significantly impact both the liver and pancreas. Acetate, for instance, activates GPR43 and GPR41 receptors in insulin-sensitive tissues, including the liver and pancreatic β-cells, thereby modulating insulin secretion[204]. Propionate and butyrate also contribute to insulin sensitivity and glucose homeostasis. Propionate increases insulin release and supports β-cell survival, while butyrate improves insulin sensitivity and offers protection against diet-induced obesity[205,206]. In the liver, SCFAs activate PPARα, which prevents lipid accumulation and promotes energy expenditure[207]. BAs are another crucial group. The gut microbiota converts primary BAs into secondary BAs, which then bind to FXR and Takeda G protein-coupled receptor 5 (TGR5) in both the liver and the pancreas. In the liver, FXR activation improves glucose homeostasis, reduces hepatic steatosis, and enhances glycogen synthesis[208]. In the pancreas, TGR5 activation boosts glucose-stimulated insulin release and reduces glucagon secretion[209]. GLP1, an incretin hormone synthesized by intestinal L-cells in response to luminal SCFAs, critically regulates glucose homeostasis. It enhances insulin secretion from β-cells and suppresses glucagon release from α-cells. In the liver, GLP1 can enhance insulin sensitivity and reduce hepatic steatosis by modulating lipid metabolism[210]. GLP1 receptor agonists (GLP1RAs) have shown promise in treating both T2DM and MASLD by targeting GLPA, improving insulin resistance, and reducing liver fat[211]. Semaglutide is a GLP1RA acting similarly to naturally released GLP1 and has received approval for T2DM, weight management, MASH, cardiovascular risk reduction, and chronic kidney disease in many countries[212]. Its ameliorative effect on T2DM is partly achieved through improved β-cell function[213]. A recent Phase 2b clinical trial demonstrated that a combination of semaglutide and an Fc-FGF21 analogue significantly reduced hepatic fat fraction and noninvasive markers of fibrosis in patients with MASH and T2DM[214]. A recent study revealed that the dual GCGR/GLP1R agonist G49 triggered an inter-organ crosstalk involving adipose tissue, the pancreas, and the liver in a GCGR-dependent manner. This interactome led to elevations in adiponectin and

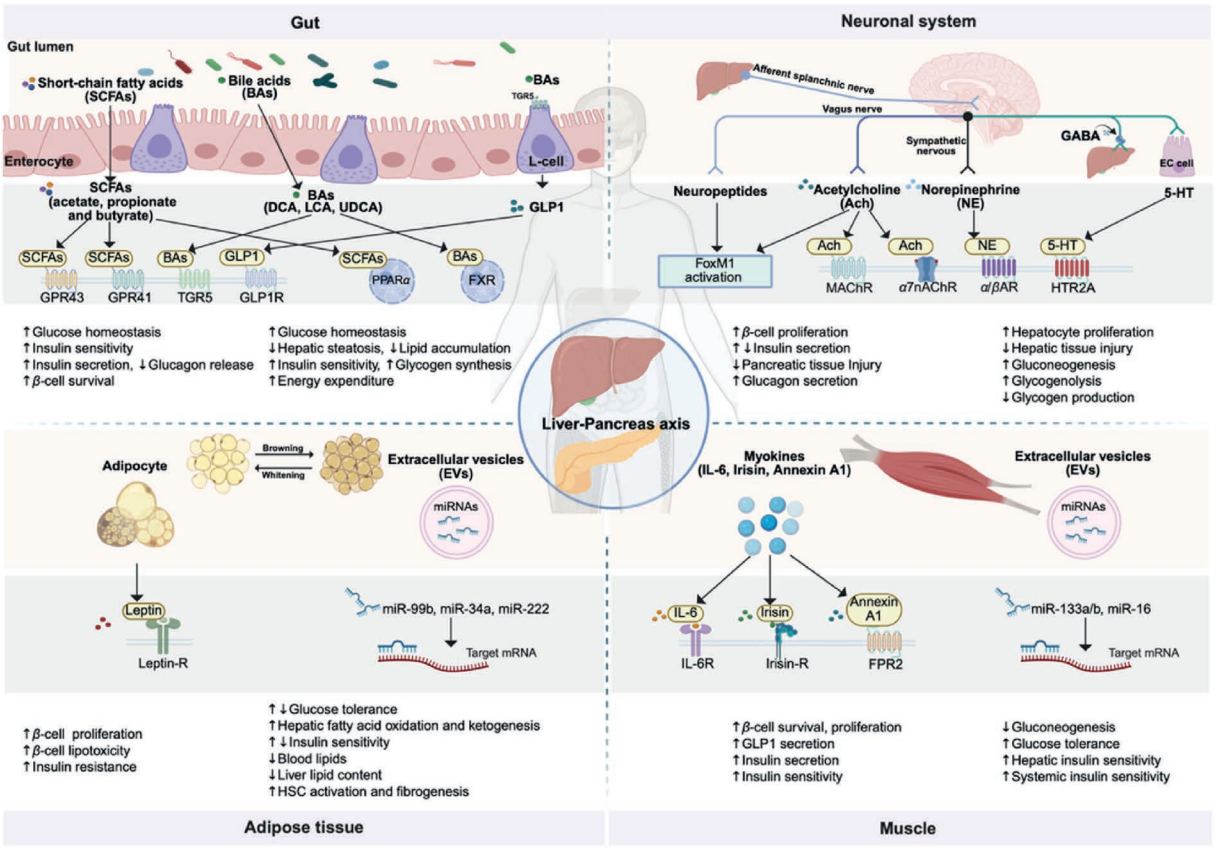

Figure 3 Summary of interorgan communicating mechanisms of pancreas−liver axis regulation by the gut, neuronal system, adipose tissue, and muscle. In addition to the liver−pancreas direct communication, other distant organs, including the gut, neuronal system, adipose tissue, and muscle, also simultaneously regulate the physiological and pathological functions of the liver and the pancreas. Those mechanisms significantly influence the development of metabolic diseases, hepatic disorders, and pancreatic diseases. This figure is illustrated by using BioRender App.

FGF21, which collectively caused brown adipose tissue activation, insulin secretion, and weight loss[215]. Tirzepatide is an FDA-approved drug acting as dual-agonist of the GIP and GLP1 receptors. It is used to treat obesity and T2DM. In head-to-head trials, tirzepatide demonstrated significantly greater weight loss results and superior effects on pancreatic islet function protection and insulin sensitivity improvement compared to semaglutide over a 72-week period[216,217]. Furthermore, a Phase 2 trial showed that 52 weeks of tirzepatide treatment effectively improved MASH without worsening fibrosis[218]. Retatrutide (LY3437943), a triple hormone (GIP, GLP1 and glucagon) receptor agonist, is currently in development for obesity treatment. Phase 2 trials showed that retatrutide achieved up to 17.5% mean weight reduction at 24 weeks in adults with obesity and overweight, along with clinically meaningful improvements in glycaemic control and robust bodyweight reductions in T2DM patients[219,220]. For MASLD patients, 24-week treatment achieved over 80% relative liver fat reduction (at 8 or 12 mg doses) compared with placebo[221]. The possible alleviative effects of this drug on α- and β-cell function and insulin sensitivity in adult participants with T2DM is under investigation by Eli Lilly and Company (NCT06982859). Future research should prioritize unraveling the complex interplay between gut-derived substances and the GLPA to develop personalized and effective treatments for metabolic disorders.

4.2. *Neuronal system*

The regulation of liver and pancreatic function by endogenous neuronal signals and their pharmacological mimics is a complex, multi-organ process with significant implications for metabolic homeostasis, disease adaptation, and tissue regeneration. Increasing evidence demonstrates that the autonomic nervous system-including parasympathetic (vagal) and sympathetic pathways and neuronal circuits originating in the central or enteric nervous systems are central to these processes. A defining feature emerging from these studies is the identification of specialized neuronal circuits that coordinate adaptive responses between the liver and pancreas in metabolic stress and injury. Activation of this circuit by hepatic ERK signaling leads to direct cholinergic and peptidergic neurotransmitter release onto pancreatic islets, which in turn promotes β-cell proliferation and increased insulin secretion *via* upregulation of the FoxM1 pathway[222-224]. These neural mechanisms are shown to be necessary for β-cell adaptive expansion in conditions such as obesity and diabetes, as demonstrated through genetic, surgical, pharmacological, and optogenetic manipulations[225,226]. Parallel investigations have elucidated the role of vagal signaling in liver regeneration and immune modulation. Several studies demonstrated that vagal cholinergic efferent regulated hepatocyte proliferation indirectly by acting on hepatic macrophages, thereby triggering an IL-6- and STAT3-mediated proliferative response required for

effective liver regeneration[227,228]. Furthermore, the literature substantiated a vagal anti-inflammatory reflex in both liver and pancreas, mediated by acetylcholine acting on α7 nicotinic acetylcholine receptors on immune cells, which suppressed inflammatory cytokine release and protected against tissue injury[229,230]. Additional lines of inquiry explore the sympathetic nervous system's contribution to hepatic and pancreatic function, mapping anatomical pathways, receptor subtypes, and functional outcomes such as glucose and lipid metabolism, hormone secretion, and neuroimmune interactions[231,232]. Central integrative pathways—such as those originating from hypothalamic neurons-modulate peripheral organ physiology *via* distinct autonomic efferent, further linking neuropeptidergic signaling and metabolic control[233,234]. Recent studies have also begun to identify novel indirect or non-classical pathways, such as hepatic GABA release affecting afferent vagal activity and downstream insulin secretion[120], or gut-derived serotonin mediated through hepatic local receptors to influence liver metabolism[235]. Although many organ-specific and cell-specific findings have been reported, comparative studies directly analyzing neuronal signaling mechanisms in both liver and pancreas are anchored primarily in the work examining the hepatic neural relay affecting β-cell proliferation and liver regeneration.

4.3. Adipose tissue

Adipose tissue is increasingly recognized as a complex endocrine organ, actively secreting a diverse array of factors—including classical adipokines, EVs, and proteins which exert systemic metabolic effects. These adipose-derived elements are now understood to modulate the function of multiple distant organs, with emerging interest in their capacity to orchestrate crosstalk between adipose depots, liver, and pancreatic islets. This axis is particularly relevant in the context of obesity, insulin resistance, and metabolic diseases. Reported studies reveals strong mechanistic support for adipose-derived factors modulating liver or pancreatic functions. Leptin, a prominent adipokine, has been shown to enhance the liver's insulin sensitivity regarding glucose metabolism, specifically glycogenolysis. It additionally promotes hepatic fatty acid oxidation and ketogenesis[236]. Studies in rodent models of insulin-deficient diabetes, often induced by streptozotocin to destroy pancreatic β-cell, revealed that peripheral leptin administration improved blood glucose levels, reduced circulating lipids, and lowered liver lipid content[237]. Another foundational work using adipose-specific *Dicer* knockout mice demonstrated that adipose tissue was a primary source of circulating exosomal miRNAs that regulated hepatic gene expression, particularly *Fgf21*, and influenced liver-related metabolic phenotypes and β-cell function[238,239]. Similarly, other studies have shown that adipose-derived EVs rich in specific miRNAs, such as miR-106b, miR-222 or miR-34a, regulated hepatic insulin signaling and inflammation in mouse models, with possible beneficial effects on pancreatic islets[240-242]. Collectively, these studies underscore the complexity and specificity of adipose-derived secretome actions. They establish robust frameworks and experimental models for defining adipose−liver and adipose−pancreas signaling through secreted EVs and miRNAs. The elucidation of such dual-organ regulatory mechanisms remains a priority for future research.

4.4. Muscle

Skeletal muscle is increasingly recognized as an endocrine organ that communicates with distant organs through the secretion of myokines, metabolites, and EV-encapsulated molecules. The cross-talk between skeletal muscle and both the liver and pancreas is of particular interest, as these organs are central to the regulation of glucose and lipid metabolism, and their dysfunction underlies prevalent metabolic diseases such as diabetes and MASLD. However, the identification of specific muscle-derived factors mediating these inter-organ effects, and systematic mapping of their actions, remains an evolving scientific challenge. Among these, IL-6 emerges as the most robustly validated myokine with effects on both the liver and the pancreas *in vivo*. White et al.[243] demonstrated that protectin DX, a lipid mediator, induced muscle IL-6 secretion, triggering hepatic STAT3 signaling that suppressed gluconeogenesis and improved insulin sensitivity in mouse models of insulin resistance. This action was absent in *Il6* knockout animals, supporting a muscle−liver−pancreas axis. Complementary findings showed that exercise-induced IL-6 signaling enhanced β-cell viability in a T1DM mouse model[244], while another study linked IL-6 to increased GLP1 secretion from L- and α-cells, further supporting a dual organ role for IL-6 in regulating glucose homeostasis[245]. The role of exosome-mediated transport of muscle-derived microRNAs has also been addressed. Castaño et al.[246] reported that high-intensity interval training in mice modified the miRNA profile of muscle-derived exosomes, notably increasing miR-133a and miR-133b, and that administration of these exosomes to sedentary mice improved glucose tolerance and hepatic insulin sensitivity by downregulating hepatic FoxO1. Although this work established an endocrine muscle−liver pathway, the direct impact of these exosomal miRNAs on pancreatic islet function was not stated in the provided summary. Jalabert et al.[247] further demonstrated that exosome-like vesicles released from lipid-induced insulin-resistant muscle were taken up by β-cell and deliver cargo (including miR-16) that stimulated β-cell proliferation in mice, although corresponding hepatic effects were not reported. Other muscle-derived factors studied include irisin and annexin A1. Several studies found that irisin, secreted by skeletal muscle in response to exercise or to saturated fatty acids, promoted β-cell survival, proliferation, and insulin secretion in both mouse and human islets[248,249]. Nevertheless, the impact of irisin on hepatic metabolism remains unaddressed in these specific studies. Proteomic analysis by Yoon et al.[250] identified annexin A1 as a muscle-secreted protein whose levels decreased in insulin resistance, and showed that activation of its receptor, formyl peptide receptor 2, improved systemic insulin sensitivity in diet-induced obese mice, pointing to a muscle−liver axis. Finally, investigations into fiber-type-specific muscle secretomes have identified potential novel myokines capable of modulating β-cell function; however, these findings are currently limited to *in vitro* analyses, with *in vivo* validation and liver-targeted effects yet to be established[251]. Overall, these studies collectively highlight a growing mechanistic understanding of muscle-derived factors in liver−pancreas cross-talk and underscore IL-6 as the prototypical dual-organ endocrine mediator.

5. Clinical trials targeting the liver−pancreas axis

Clinical intervention trials are actively investigating small molecules and antibodies that target communication substances within the liver−pancreas axis (Table 2). Among these, FGF21—a peptide hormone synthesized across multiple organs—exerts effects on various target tissues through paracrine or endocrine pathways[252]. FGF21 has been proposed as a novel therapeutic agent

for metabolic complications such as diabetes and fatty liver disease. However, native FGF21 exhibits poor pharmacokinetic and biophysical properties[253], prompting the development of numerous long-acting FGF21 analogues. Currently, multiple formulations of human FGF21-including recombinant proteins, IgG-backbone fusion proteins, long-acting human immunoglobulin 1 Fc-FGF21 fusion proteins, and PEGylated/glycopegylated FGF21-have been evaluated for their therapeutic potential. Phase 1 trials primarily investigated their application in T2DM, while Phase 2 trials concentrated on MASH complicated by fibrosis. These trials uniformly verified the bioactivity of FGF21 in humans, suggesting that FGF21-based therapies hold promise for effectively treating specific metabolic disorders while maintaining acceptable safety profiles[171-173,176-179].

BAs are important signaling molecules capable of mediating precise inter-tissue communication. Released from the liver, they act on the intestine and other organs, activating various bile acid receptors (particularly FXR) and modulating signaling pathways involved in a broad network of symbiotic metabolism, including glucose, lipid, steroid, and energy homeostasis[254]. FXR plays a key physiological role in metabolic regulation, inflammation suppression, prevention of cell death, and inhibition of fibrosis[255]. FXR can be activated by both free and conjugated BAs. Among these, CDCA is a well-recognized FXR agonist[256], whereas hydrophilic BAs like ursodeoxycholic acid (UDCA) are unable to activate FXR in this manner[257]. As a 6α-ethyl derivative of CDCA, obeticholic acid (OCA) is a first-in-class selective FXR agonist, exhibiting an FXR agonistic activity 100 times stronger than its natural ligand and high specificity[258]. OCA has demonstrated favorable therapeutic effects in patients with T2DM complicated by MASLD. Similarly, GFT505, a dual PPAR-α/δ agonist, has shown promising efficacy in individuals with abdominal obesity[184,185]. A phase 3 trial of UDCA in T2DM patients further indicated beneficial effects on metabolic and oxidative stress parameters[187]. However, further phase 3 trial results are needed to determine if UDCA can alleviate relapsing complications after gallstone-induced AP.

Amylin analogues were developed to extend half-lives and non-aggregating properties for treating metabolic disorders like diabetes and obesity. Pramlintide is the only approved amylin analogue; it is modified with three amino acids to retain potency while significantly reducing aggregation potential. It is used adjunctively with insulin to treat patients with T1DM or T2DM who fail to achieve desired glycemic control with insulin therapy alone[259]. In obese patients, a Phase 2 trial demonstrated sustained weight loss effects: 43% in the treatment group achieved $\geq$10% weight loss, compared to 12% of the placebo group, following 12-month pramlintide treatment as an adjunct to lifestyle intervention[180]. Another strategy targets the amylin receptor pathway. Davalintide (AC2307), developed by AstraZeneca, is a dual agonist that merges amylin with salmon calcitonin to target the amylin receptor and the calcitonin receptor. A Phase 2 trial showed davalintide displayed comparable weight loss effects but better *in vivo* metabolic activity than native amylin[181]. Most recently, Novo Nordisk reported efficacy and safety data for CagriSema (coadministration of cagrilintide, a long-acting amylin analogue, and semaglutide) in adults with overweight or obesity and T2DM. Once-weekly CagriSema, at a dose of 2.4 mg each, exhibited significantly lower body weight compared to placebo[190].

For GDF15, a Phase 2 trial using a monoclonal antibody to block GDF15 signaling in patients with recurrent unresectable PC demonstrated good tolerance but a limited signal of response. Another Phase 2 trial, which used a half-life extended recombinant human GDF15 dimer to treat obese participants with diabetes, did not show a favorable tolerability-to-benefit ratio based on the maximum weight loss observed. The IGF1 receptor inhibitor ganitumab was tested in patients with pancreatic neuroendocrine tumors (PanNETs). The lack of success for ganitumab aligns with other high-profile disappointments for IGF1 receptor-targeting drugs, which were once considered a promising class in targeted therapy[260]. Human albumin infusions during pancreaticoduodenectomy have been investigated in a Phase 1 trial to assess their ability to reduce fluid overload and improve outcomes. However, preliminary results suggested that preemptive albumin administration did not consistently reduce postoperative complications. Conversely, a Phase 4 trial evaluating the long-term efficacy of albumin in patients with decompensated cirrhosis, with or without T2DM, reported positive outcomes[191,192]. Oral GABA administration and injection of plasmid DNA encoding human HGF have been tested in patients with T1DM (Phase 2) and diabetic nephropathy (DN; Phase 3), respectively. GABA treatment was well tolerated and established a counter-regulatory response to hypoglycemia in long-standing T1DM[182]. The safety and long-lasting pain-relieving effects of HGF gene therapy suggest a novel avenue for DN treatment[186]. Another Phase 1b trials tested the efficacy of a recombinant humanized anti-HGF antibody, and gemcitabine in PDAC patients, which showed durable treatment responses and increased rates of hypoalbuminemia and edema, requiring further optimization before following clinical trials[175]. Finally, a Phase 2a trial using human C-type lectin Reg3α yielded significant clinical benefit in a per-protocol analysis of a subgroup of patients with HBV or autoimmune hepatitis (AIH)-related severe acute hepatitis[183].

6. Future directions

Despite significant advances in understanding the complex interplay between the liver and pancreas, several limitations exist in current mechanistic research and drug development. The intricate molecular and cellular mechanisms governing the liver−pancreas axis are not yet fully elucidated, particularly regarding the precise signaling pathways of various communicating substances. For example, current evidence on urea's impact is predominantly restricted to endocrine pancreatic outcomes (*e.g.*, β-cell secretion and metabolism), with limited exploration of its effects on exocrine function, pancreatic development, or in non-mammalian models. While many communication substances derived from the liver have been unveiled, little is known pancreas-derived signaling molecules that have hepatic regulatory effects, in addition to insulin, glucagon, somatostatin, PP, amylin, PANDER, and Reg family members. Whether there is a group of proteins predominantly or exclusively secreted from the pancreas to exert hormone-like functions on other organs, just like liver-derived hepatokines, adipose tissue-derive adipokines, and muscle-derived myokines, is unknown[261]. Moreover, while EVs are recognized as crucial delivery route for non-coding RNA, hepatokine, and several metabolism-related proteins, other possible interorgan cargos, the specific membrane receptors, and downstream pathways involved in EV-mediated signaling from both liver and pancreas remain largely unknown, hindering their therapeutic exploitation. In terms of systemic communication, while organ-specific neuronal findings abound, comparative studies directly analyzing neuronal signaling mechanisms in both liver

and pancreas, beyond the hepatic neural relay affecting β-cell proliferation, are limited. Unveiling more druggable targets will definitely create more possibilities for the novel drug development for the simultaneous treatment of metabolic, inflammatory, and oncogenic liver/pancreas diseases.

Although FGF21- and BA-related drugs have shown promising clinical results, other attempts—such as the GDF15 antibody for PC (which yielded a limited signal of response) and the GDF15 dimer for obese/diabetic patients (which had an unfavorable tolerability-to-benefit ratio)-as well as the past failures of IGF1R-targeting drugs (*e.g.*, ganitumab), underscore the complexity of drug development in this area. The reasons for these clinical setbacks are multifaceted. For GDF15 receptor antibody therapy of PC and cachexia, while GDF15 receptor antibody therapy increased weight gain, overall activity, and reduced cachexia symptoms, the limited tumor response was likely because GDF15 is only one component of a complex, multi-factorial syndrome. PC progression is driven not just by anorexia, but predominantly by severe systemic inflammation, immune dysfunction, and metabolic reprogramming induced by the tumor. Future trials should co-target the inflammatory and immune components in conjunction with GDF15 antagonism[262,263]. Although MBL949 (a half-life extended recombinant human GDF15 dimer) obtained acceptable safety profiles, the robust weight loss observed in nonclinical species did not translate to efficacy in humans[264]. A key design problem may have been the chronic, sustained activation of the GDF15 receptor complex, which is located primarily in the hindbrain. This long-acting agonist strategy may have induced receptor desensitization or downregulation, making the therapeutic target unresponsive over the dosing period. Furthermore, the high rate of vomiting (poor tolerability) prevented the drug from being titrated to a truly effective therapeutic dose. The failure of the IGF1R inhibitor ganitumab (AMG 479) in Phase 3 trials was probably due to the fundamental biological premise of selective IGF1R antagonism being inadequate to overcome intrinsic tumor resistance mechanisms. Blockade of the IGF1R often leads to the rapid activation of alternative, redundant survival pathways (*e.g.*, EGFR and RAS/MAPK), allowing tumors to escape therapeutic pressure[265]. The failure of the albumin infusion strategy during pancreaticoduodenectomy is rooted in the overwhelming severity of the surgical inflammatory response, which compromises albumin's optimal function. Moreover, the preemptive administration strategy proved incongruent with the successful adoption of current volume-restrictive and goal-directed fluid management strategies now favored in high-risk surgery. While hypoalbuminemia after pancreaticoduodenectomy does not predict or affect short-term postoperative prognosis, rigorous randomized controlled trials are still needed to define optimal dosing, timing, and patient stratification for current interventions like albumin infusions[266]. These failures highlight the need to move beyond single-target interventions and develop strategies that account for receptor desensitization, the multi-factorial nature of disease syndromes, and redundant survival pathways. Further research into gene therapies (*e.g.*, HGF gene therapy for DN) and bacterial cocktails for metabolizing toxic metabolites (*e.g.*, urea in kidney injury) holds promise for broad generalizability and addressing complex multi-organ dysfunctions.

The growing interest in polypharmacology has led to its integration into AI-driven small molecule drug discovery. The conventional "one target−one drug" paradigm, often predicated on a reductionist view of biological systems, frequently encounters obstacles in late-stage clinical trials. These challenges—including a lack of efficacy or unexpected toxicity—are particularly pronounced in multifactorial diseases such as metabolic disorders. In these cases, targeting a solitary node within a complex signaling network can be easily subverted by the system, resulting in a lack of sustained therapeutic benefit or the emergence of resistance[267,268]. Consequently, a polypharmacologic design strategy-targeting multiple critical protein targets within, for example, the liver and pancreas—can yield unexpectedly high therapeutic efficacies. This is exemplified by the success of tirzepatide, a dual GLP1/GIP receptor agonist, and various dual PPAR agonists in treating obesity and dyslipidemia[269,270]. Ultimately, the strategic application of computational polypharmacology promises to dramatically accelerate the identification of promising compounds from massive chemical libraries, while also enhancing multi-task quantitative structure−activity relationships, proteochemometrics, hit-to-lead optimization, and ADMET predictions[271].

In conclusion, thorough research into the liver−pancreas communication axis can pave the way for more effective diagnostic tools and therapeutic interventions for a wide spectrum of metabolic and organ-specific diseases.

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Author contributions

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Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

Statement: During the preparation of this work the authors used Grok 4.0 in order to improve language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Conflicts of interest

The authors declare no conflicts of interest.

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