Journal of Translational Medicine

REVIEW

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Lipid metabolism orchestrates liver regeneration: an integrated metabolic network

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Abstract

Liver regeneration is a tightly regulated biological process driven by the dynamic interplay of lipid metabolism, involving spatially and temporally coordinated pathways of synthesis, degradation, and lipophagy. This comprehensive review delineates the pivotal roles of lipid metabolic networks in liver regeneration and highlights their potential for clinical translation. During the priming phase, transient regenerative-associated steatosis (TRAS) serves important physiological roles which provide energy through β-oxidation and supply substrates for membrane phospholipid biosynthesis, with its regulation orchestrated by transcriptional and post-translational mechanisms. In contrast, chronic lipid dyshomeostasis impairs regeneration through mechanisms including endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and pro-inflammatory signaling. However, protective lipid-handling processes remain active and play pivotal roles in maintaining cellular homeostasis. Lipophagy-mediated selective degradation of lipid droplets (LDs) releases free fatty acids (FFAs), which mitigate oxidative stress and preserve hepatocellular integrity. Furthermore, the gut-liver axis modulates regeneration through microbiota-derived metabolites and incretin hormones that fine-tune the equilibrium between lipid mobilization and storage. Macrophage polarization-metabolic crosstalk emerges as a critical regulator, whereby PPARγ-driven lipogenic networks in reparative macrophages coordinate growth factor secretion and ER expansion via STAT3 activation. Paradoxically, while moderate TRAS supports regeneration through FFA-mediated histone acetylation and membrane raft signaling, pre-existing steatosis exacerbates ischemia-reperfusion injury via lipid peroxidation and necroptosis. Therapeutic strategies targeting lipophagy-ER stress interactions or gut-liver metabolic crosstalk demonstrate therapeutic potential. Future directions include elucidating dynamic lipid metabolic shifts, targeting gut microbiota-liver interactions, and advancing lipidomics-guided personalized therapies. By integrating mechanistic insights with clinical challenges, this review establishes a framework for understanding the metabolic logic underlying liver regeneration and advancing precision medicine in hepatic repair.

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Keywords Liver regeneration, Lipid drops, TRAS, Lipophagy, MASLD, ER stress, Macrophage

Introduction

The liver is unique among mammalian solid organs for its unparalleled regenerative capacity, a process tightly regulated by the hepatostat mechanism to preserve metabolic homeostasis, which refers to an intrinsic regulatory system that maintains liver mass homeostasis through dynamic coordination of proliferative signals (e.g., STAT3), metabolic reprogramming (e.g., lipid synthesis), and cross-organ communication (e.g., gut-liver axis) [1]. Liver regeneration involves the coordinated interplay of multiple cell types and signaling pathways, ensuring effective tissue repair and restoration of function [2]. However, both acute and chronic hepatic injuries can disrupt this intrinsic regenerative capacity. Acute insults, such as partial hepatectomy (PH) or drug-induced toxicity, trigger robust hepatocyte proliferation to restore hepatic mass. Moreover, the remnant liver volume after hepatectomy critically influences the efficiency and outcome of regeneration [3]. In contrast, chronic conditions such as viral hepatitis, metabolic dysfunction-associated steatohepatitis (MASH) or metabolic-associated steatotic liver disease (MASLD) establish a maladaptive microenvironment characterized by impaired hepatocyte proliferation, progressive fibrosis, and increased oncogenic risk [2]. Although surgical intervention remains the cornerstone of managing advanced liver disease, complications such as ischemia–reperfusion injury (IRI) which refers to liver tissue damage caused by the temporary loss and subsequent restoration of blood supply and postoperative liver failure are closely associated with impaired regenerative responses. Elucidating the molecular drivers of liver regeneration is therefore essential for improving clinical outcomes and mitigating life-threatening complications.

Liver regeneration is a tightly regulated process requiring precise coordination of metabolic and cellular events [4]. Following PH, hepatocytes undergo distinct phases of growth: cell size increases within hours (peaking at 36 h) before returning to baseline by 96 h, while cell numbers begin rising at 36 h and continue until regeneration is complete [5]. This regenerative process requires substantial energy, driven by metabolic reprogramming that precedes hepatocyte proliferation. Key early changes include transient hypoglycemia and hepatic lipid droplets (LDs) accumulation [6]. Rodent studies reveal dynamic adaptations in lipid metabolism during regeneration, encompassing de novo lipogenesis, fatty acid transport, oxidation, and systemic lipid mobilization [7, 8]. A regulated surge in lipid flux induces transient steatosis, an essential step for regeneration; experimental blockade of this process delays hepatic recovery [6, 9].

Proper lipid metabolic balance is essential for restoring liver structure and function (Fig. 1). During the priming phase, rapid adjustments in lipid metabolism are initiated especially the early transient regenerative-associated steatosis (TRAS). Fatty acid uptake increase to fuel proliferation [10], while lipogenic enzymes are upregulated to support membrane biosynthesis [11]. During the proliferation phase, lipid synthesis and oxidation peak concurrently, directing fatty acids toward membrane formation and energy production [12]. LDs dynamically expand and contract in this phase, with their pre-mitotic accumulation serving as a critical trigger for regeneration after major liver resection [13, 14]. Finally, during the termination phase, lipid metabolism stabilizes: synthesis and oxidation reach equilibrium, lipid storage normalizes, and gene expression returns to pre-regeneration levels.

Liver regeneration is a tightly orchestrated process in which lipid metabolism functions both as a driver and a modulator of tissue repair. Following acute hepatic injury, transient lipid metabolic reprogramming supplies essential energy and biosynthetic precursors necessary for regeneration. In contrast, chronic dysregulation of lipid metabolism impairs this process and contributes to regenerative failure. Deciphering the crosstalk between lipid metabolism and liver regeneration holds promise for addressing unmet clinical needs in hepatic diseases. This review systematically explores the dynamic regulatory networks of lipid synthesis, catabolism, and lipophagy during liver regeneration, along with therapeutic strategies targeting lipid metabolism to enhance regenerative capacity and define stage-specific lipid metabolic signatures associated with hepatocyte proliferation and tissue remodeling. By mapping these interactions, this review identifies actionable targets for enhancing hepatic repair. Advancing this field requires deeper mechanistic understanding of lipid metabolic regulation and its translation into precision therapies for liver diseases.

Spatiotemporal dynamics of lipid metabolism during liver regeneration

The liver orchestrates systemic lipid homeostasis through its unique capacity to synthesize, store, catabolize, and transport fatty acids and cholesterol. Hepatically derived fatty acids and cholesterol not only constitute structural components of cellular membranes but also serve as essential metabolic substrates for energy production [15, 16]. LDs, the liver's primary lipid storage organelles, dynamically release stored lipids for energy mobilization during physiological demands [17]. Emerging evidence highlights lipid metabolism as a central pathway sustaining the bioenergetic and biosynthetic demands of the

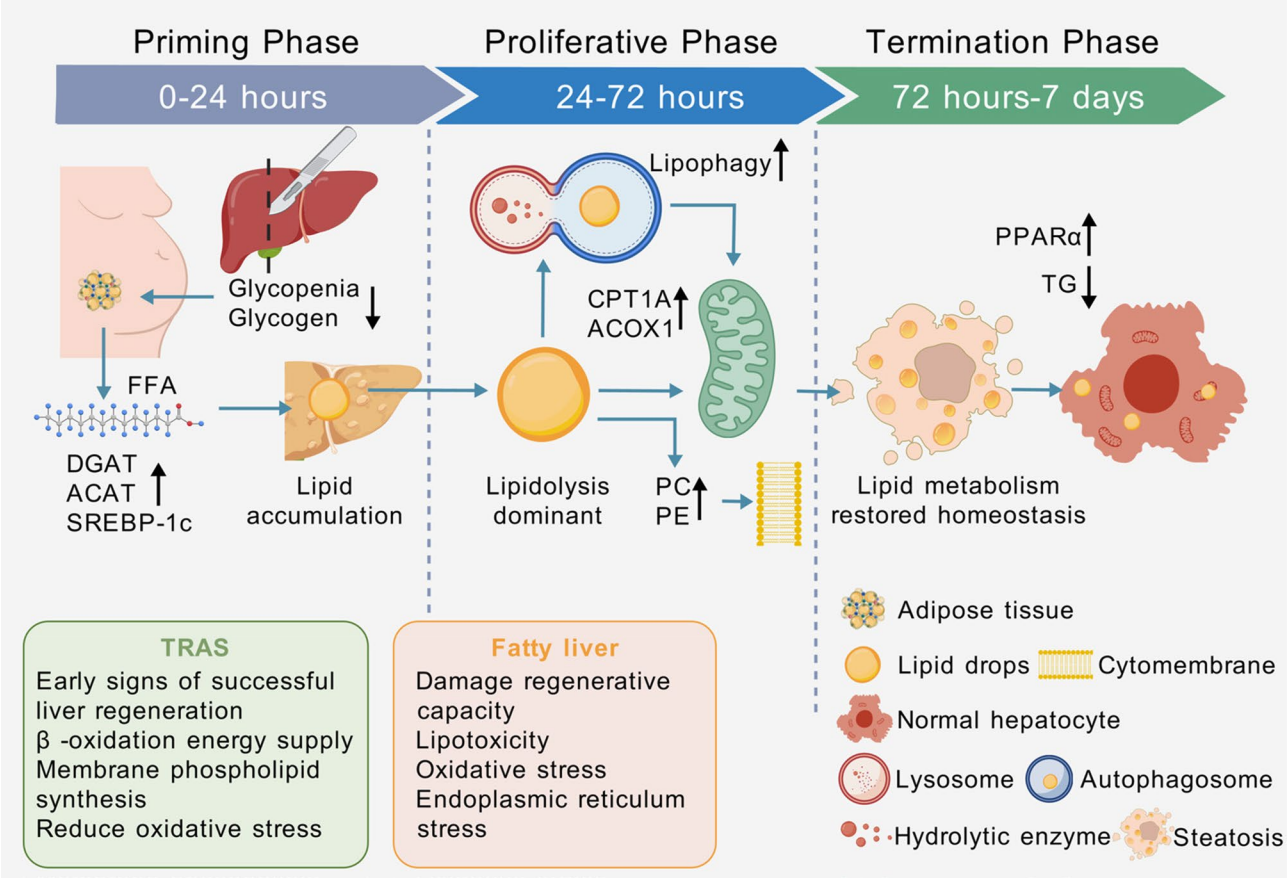

Fig. 1 The Dynamic timeline of lipid metabolism during liver regeneration. Liver regeneration after PH proceeds through three distinct phases—priming (0–24 h), proliferative (24–72 h), and termination (72 h–7 days)—each characterized by dynamic lipid metabolic remodeling. In the priming phase, systemic lipolysis and hepatic uptake of free fatty acids (FFAs) lead to transient lipid accumulation (TRAS) in hepatocytes, facilitated by upregulation of DGAT, ACAT, and SREBP-1c, with suppressed β-oxidation. This stage supports early regenerative signals by providing energy reserves and membrane precursors while mitigating oxidative stress. In the proliferative phase, hepatocytes undergo lipophagy and switch to a catabolic state dominated by β-oxidation, driven by CPT1A and ACOX1, to meet high ATP demands. In the termination phase, lipid metabolic homeostasis is restored via PPARα-mediated signaling, facilitating clearance of excess lipids and resolution of transient steatosis. Throughout regeneration, lipid metabolism not only sustains energy and biosynthesis but also regulates redox balance and cell cycle progression. Pathological lipid accumulation (e.g., pre-existing fatty liver) impairs this tightly coordinated process, whereas TRAS plays a supportive role

regenerating liver. Rodent studies demonstrate that PH induces rapid postoperative depletion of both lean and adipose tissue mass, accompanied by transient hepatic steatosis due to enhanced lipid accumulation in regenerating hepatocytes [6, 9]. Strikingly, β-oxidation accounts for over 70% of ATP generation during the proliferative phase of liver regeneration [18], and experimental disruption of LDs dynamics severely impairs hepatic repair [6].

Functional role and temporal dynamics of TRAS in early liver regeneration

The liver serves as the central regulator of systemic lipid metabolism, maintaining homeostasis through tightly coordination of lipid uptake, storage, catabolism, and export. Under physiological conditions, this network prevents pathological lipid accumulation. However, surgical stress (e.g., PH) or metabolic disorders (e.g., obesity) can destabilize this balance, inducing hepatic steatosis. Notably, TRAS during liver regeneration exhibits distinct biological characteristics, emerging as a consequence of metabolic stress while simultaneously functioning as a critical driver of tissue repair.

Emerging evidence highlights lipid metabolism as the primary energy source for liver regeneration. PH induces a metabolic shift characterized by rapid depletion of body fat stores and transient hepatic lipid accumulation [6, 9]. Animal studies delineate the temporal progression TRAS: triglycerides (TGs) levels increase three- to four-fold within 24 h post-surgery, decline after 48 h, and return to baseline by 72 h—a timeline that coincides with hepatocyte proliferation and the activation of mitochondrial β-oxidation [19–21]. Approximately 70% of TRAS lipids are derived from systemic lipolysis, with hepatic fatty

acid uptake and synthesis contributing the remainder [22, 23]. Strikingly, lipid composition shifts dynamically over time: long-chain fatty acids (C16-C18) dominate early phases [24], while very-long-chain fatty acids (C ≥ 20) increase significantly as regeneration progresses [25], likely reflecting stage-specific demands for membrane remodeling and energy metabolism. Functional divergence in fatty acid profiles is evident: TRAS-phase hepatocytes accumulate both saturated and unsaturated lipids, whereas proliferating cells preferentially utilize unsaturated forms [24]. LDs in TRAS are enriched in TGs and cholesterol esters (CEs), whereas regenerating hepatocytes exhibit reduced CEs content, suggesting dynamic metabolic adaptations across regenerative stages [25, 26]. These compositional changes likely reflect evolving demands for energy production and structural rebuilding across regeneration stages.

While pre-existing hepatic steatosis significantly increases the risk of post-hepatectomy liver failure (PHLF) through endoplasmic reticulum (ER) stress, mitochondrial dysfunction, autophagy defects, and inflammation [27, 28]. TRAS induced by PH may exert protective effects on liver regeneration by supplying energy substrates and membrane precursors [6, 11, 29, 30]. Clinical data show higher hepatic lipid content in recovering PHLF compared to non-recovering PHLF [31], suggesting that TRAS provides essential lipids, membrane components, and mitogenic signals that support regeneration [13, 14, 32, 33]. Inhibition of TRAS, via pharmacological agents (e.g., leptin, clofibrate, propranolol) or genetic models (e.g., Cav1 or Lpin1 knockout), impairs hepatocyte proliferation [6, 34]. Crucially, TRAS differs from chronic steatosis by its transient course versus sustained lipid toxicity in disease states [20].

Mechanistically, β-oxidation supplies over 65% of ATP during regeneration, while lipolysis-derived acetyl-CoA activates cell cycle genes such as Cyclin D1 via histone acetylation [16, 29, 32, 35]. In structural safeguarding, TGs buffer FFAs toxicity via LDs sequestration and supply phospholipid synthesis for membrane expansion [11, 36]. In signaling coordination, PPARα/γ coordinates lipid metabolism with cell cycle progression by regulating CD36 and SCD1 [24], while caveolin-1 organizes growth factor receptors (EGFR/c-MET) in membrane rafts to amplify mitogenic signaling [13].

Interestingly, liver FABP-knockout models show reduced hepatic TG levels without impairing hepatocyte proliferation, challenging the presumed necessity of TRAS [22]. Three non-mutually exclusive hypotheses may explain this discrepancy: (i) selective lipid species (e.g., CE) mediate regeneration-specific signaling independently of bulk TG stores [26]; (ii) extrahepatic compensatory mechanisms, such as intestinal FXR-mediated signaling, may substitute for hepatic lipid reprogramming [37, 38]; and (iii) the subcellular localization of residual TGs, particularly peroxisome-associated LDs, may exert compartmentalized metabolic effects [39]. Notably, transcriptional profiling during TRAS reveals preferential induction of membrane trafficking machinery over lipogenic programs [24, 40], suggesting that lipid redistribution, rather than synthesis alone, orchestrates regenerative metabolism.

Biphasic regulation of lipid oxidation during liver regeneration

Temporal regulation of lipid oxidation is essential for coordinating liver regeneration. During the priming phase, hepatocytes prioritize glycolytic flux by suppressing β-oxidation effectors (CPT1A, ACOX1) and transient LDs accumulation (PLIN2 upregulation). This metabolic configuration shifts sharply during the proliferative phase, where CPT1A-driven β-oxidation becomes the predominant source of ATP [18], further enhanced by CD36-mediated lipid uptake [40]. The functional centrality of this metabolic switch is demonstrated by reduced regeneration efficiency following pharmacological inhibition of β-oxidation [17], highlighting lipid oxidation as a phase-dependent metabolic checkpoint during liver repair.

Dynamic metabolic models based on multi-omics data reveal that lipid catabolism exhibits phase-specific transitions throughout liver regeneration. In the priming phase, lipid storage dominates through upregulation of LD-associated genes with concurrent β-oxidation suppression. This transient lipid accumulation serves dual functions: providing energy reservoirs and supplying substrates for membrane phospholipid synthesis [7, 24]. During the proliferative phase, metabolic priorities shift toward lipid degradation for energy production, characterized by induced β-oxidation genes (CPT1A, ACADL) and enhanced CD36-mediated uptake. In the restorative phase, sustained PPAR signaling activation and elevated fatty acid-binding protein (FABP) expression drive lipid clearance [41]. PPAR-targeted interventions demonstrate therapeutic efficacy. *WY-14,643* treatment accelerates liver regeneration by inducing CPT1A expression and inhibiting SCD1 activity. In *Aqp5*-deficient models, this agonist reverses lipid deposition and restores hepatocyte proliferation, confirming its role in metabolic-proliferative coupling [42, 43]. Similarly, *L-Carnitine* supplementation enhances post-PH regeneration through promoting mitochondrial fatty acid transport and β-oxidation acceleration. This effect is completely blocked by CPT1A inhibitor *etomoxir*, verifying β-oxidation pathway dependency [17]. Epigenetic studies further reveal that *CDK5RAP3* deficiency causes pathological lipid accumulation post-PH via aberrant upregulation of lipid import genes (CD36, LDLR) coupled with

β-oxidation gene suppression (CPT1A, ACADL), leading to proliferative impairment [44]. These findings underscore the pivotal role of maintaining a balanced fatty acid oxidation–synthesis axis in supporting liver regeneration.

Lipolysis-oxidative stress equilibrium

During rapid phases of hepatic regeneration, coordinated activity of growth factors, chemokines, and environmental stressors induces the production of hydrogen peroxide (H_2O_2). Dynamic fluctuations in H_2O_2 levels exert biphasic regulatory effects on the progression of liver regeneration [45–50]. Physiological concentrations enhance hepatocyte proliferation, differentiation, and angiogenesis through redox signaling modulation [51, 52], whereas excessive accumulation triggers oxidative stress-induced cell death [49, 53]. Mechanistic studies reveal reactive oxygen species (ROS) act as molecular switches governing quiescence-proliferation transitions via NF-κB and MAPK pathway regulation [45, 51, 54–56]. Strict maintenance of oxidative stress homeostasis emerges as a crucial regulator ensuring stage-appropriate regenerative responses [51, 57].

FFAs undergo mitochondrial β-oxidation to generate acetyl-CoA, fueling ATP production via the TCA cycle while producing NADH/$FADH_2$ that drive ROS generation [18]. However, excessive lipid catabolism may overload mitochondrial ROS production, inducing oxidative stress that triggers cellular damage and death under pathological levels [58]. For instance, high-fat diet (HFD) or obesity accelerates lipolysis, forcing excessive fatty acids into mitochondrial oxidation pathways that generate ROS overproduction, ultimately impairing cellular function through oxidative stress [59]. Furthermore, ROS stimulate pro-inflammatory cytokine release and FASN and its ligand expression, exacerbating lipid peroxidation and hepatic injury [60]. Conversely, oxidative stress exerts reciprocal control over lipid metabolism by modulating cellular redox states. ROS oxidize critical thiol groups in regulatory proteins, causing conformational changes that disrupt their functions [61]. This redox-mediated interference particularly affects signaling pathways that regulate lipolytic processes, establishing a bidirectional regulatory loop between lipid metabolism and oxidative homeostasis.

PPARα, a key nuclear receptor, coordinates systemic lipid oxidation through three primary pathways when activated by fatty acids or synthetic ligands: mitochondrial β-oxidation (mediated by CPT1A), peroxisomal β-oxidation (involving ACOX1 and ACSL1), and microsomal ω-oxidation (CYP4A family) [62, 63]. PPARα activation upregulates CPT1A to enhance β-oxidation while simultaneously inducing antioxidant enzymes (SOD2, GPx4), effectively balancing energy production with ROS clearance to maintain redox homeostasis [64]. Hepatocyte-specific PPARα deletion disrupts this equilibrium, leading to reduced β-oxidation capacity, TG accumulation, and suppressed Cyclin D1 expression, ultimately impairing hepatocyte proliferation [43, 65]. The endogenous PPARα agonist glucosylceramide further amplifies β-oxidation efficiency via mTORC2-PPARα signaling, enhancing post-surgical hepatocyte regeneration and survival [8]. PPARα also mitigates oxidative stress by accelerating the degradation of lipid-derived inflammatory mediators (e.g., lipid peroxidation products) [66, 67], which suppresses pro-inflammatory cytokines (e.g., IL-6) and reduces apoptosis [68–71].

PPARα serves as a central regulatory hub in liver regeneration by integrating lipid metabolism, ROS scavenging, and cell cycle regulation networks. The development of PPARα-targeted agonists combined with redox modulators offers novel combinatorial therapeutic strategies. This integrated approach optimizes the regenerative microenvironment, showing translational potential for addressing post-PH regenerative failure and metabolism-associated liver diseases.

Hepatic regenerative impairment under lipid metabolic dysregulation

Lipid metabolism disorders exert a bidirectional regulatory effect on liver regeneration, with their mechanisms showing dose-, composition-, and pathology-dependent characteristics. Moderate lipid accumulation can provide energy substrates for hepatocyte proliferation, but persistent metabolic imbalance leads to a vicious cycle of lipotoxicity, oxidative stress, and ER stress, ultimately impairing regenerative capacity. Notably, the impact of hepatic steatosis on regeneration is highly heterogeneous. Mild steatosis or specific lipid compositions may promote proliferation through compensatory mechanisms, while severe fatty degeneration disrupts the regenerative microenvironment due to necrotic cell death and an inflammatory response (Fig. 2). This complexity suggests that the ultimate effect of lipid metabolism disorders on liver regeneration depends on the extent of lipid accumulation, the redox state, and the dynamic balance of compensatory pathways. Therefore, precision therapeutic strategies require integrative analysis of lipidomic signatures with metabolic network modeling to identify critical intervention nodes.

Dual pathological impacts of lipid accumulation and peroxidation

Liver regeneration requires balanced lipid storage to sustain energy demands, yet metabolic imbalance disrupts this finely tuned process. Paradoxically, complete suppression of post-PH lipid accumulation—such as through lipogenesis inhibitors—impairs liver regenerative capacity in murine models [6]. Conversely, pathological lipid

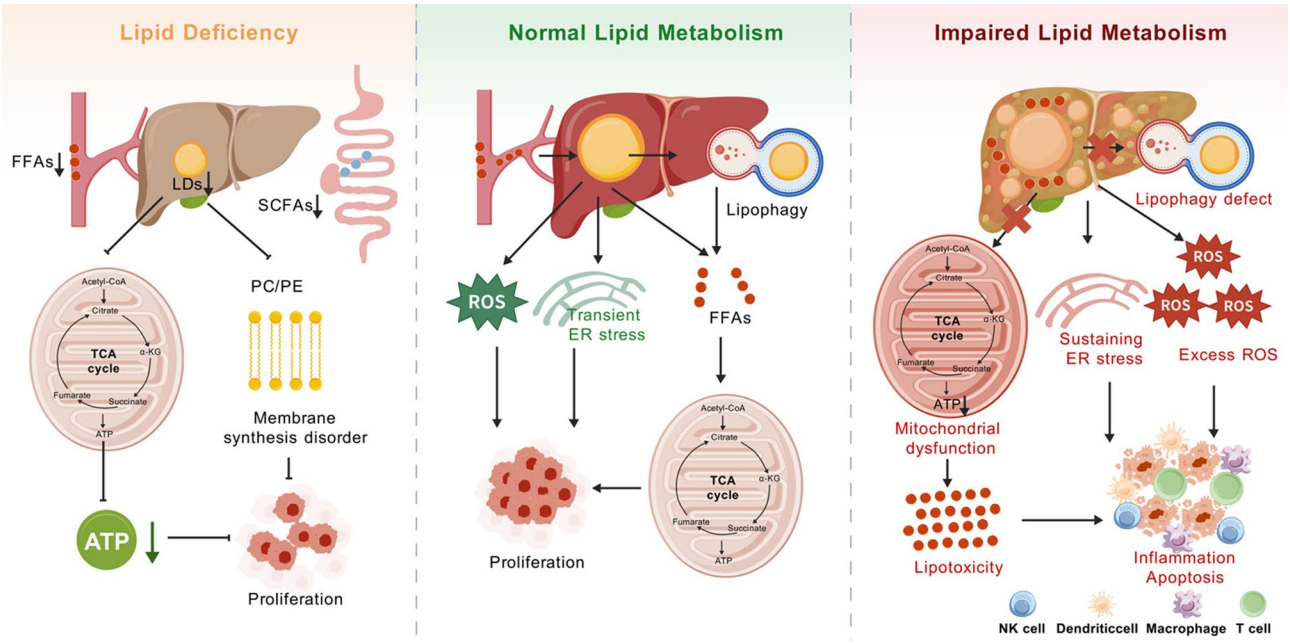

Fig. 2 Comparative diagram of the effects of abnormal lipid metabolism on liver regeneration. This schematic illustrates the contrasting effects of normal versus impaired lipid metabolism on hepatic regeneration following liver injury or partial hepatectomy. Left panel: mechanism of impaired liver regeneration under lipid deficiency. Reduced adipose tissue lipolysis decreases circulating free fatty acids (FFA), while diminished gut-derived short-chain fatty acid (SCFA) synthesis limits hepatic FFA uptake. Insufficient FFA supply impairs CPT1A-mediated mitochondrial fatty acid transport, causing ATP deficiency and subsequent cell proliferation arrest. Concurrent imbalance in the phosphatidylcholine/phosphatidylethanolamine (PC/PE) ratio disrupts new cell membrane assembly, directly compromising hepatocyte regeneration. Middle panel: Under physiological conditions, transient hepatic lipid accumulation and lipophagy support regeneration. Fatty acids (FFAs) released from lipophagy are oxidized via the mitochondrial TCA cycle to produce ATP, facilitating hepatocyte proliferation. Reactive oxygen species (ROS) generation is limited and transient, inducing mild endoplasmic reticulum (ER) stress that promotes compensatory growth. Right panel: In metabolic dysfunction, defective lipophagy and persistent lipid overload induce excess ROS production, sustained ER stress, and mitochondrial dysfunction. These stressors lead to lipotoxicity, inflammation, and apoptosis, ultimately impairing hepatocyte proliferation and liver regeneration. Notably, metabolic disorders such as MAFLD/MASH exacerbate regenerative failure by amplifying oxidative damage and disrupting the regenerative microenvironment. Inflammatory immune cell activation further contributes to impaired regeneration in steatotic livers. This figure emphasizes the dose- and composition-dependent duality of lipid metabolism in liver repair and highlights the importance of lipid homeostasis, mitochondrial integrity, and redox balance in successful regeneration

overload similarly hampers regeneration, as observed in leptin/leptin receptor-deficient mice [72–74] and HFD-induced fatty liver models [75], both of which exhibit significantly delayed hepatocyte proliferation post-PH. This biphasic regulation reflects the delicate balance between energy provision and lipotoxicity. In early regenerative phases, moderate accumulation of TGs and cholesterol supplies critical substrates for membrane synthesis and bioenergetic support. In contrast, in MAFLD, excessive lipid deposition drives mitochondrial dysfunction and ROS overproduction. This initiates lipid peroxidation cascades, leading to hepatocyte apoptosis, sterile inflammation, and impaired tissue repair [10].

The composition of dietary fat plays a crucial role in shaping regenerative outcomes. Although both saturated and unsaturated fat-enriched diets can induce MASH, their post-PH impacts diverge markedly: unsaturated fat-fed animals show reduced hepatic inflammation and improved regenerative capacity compared to saturated fat-fed counterparts [76]. This disparity likely stems from saturated fats exacerbating oxidative stress, lipotoxicity, and ER stress [77, 78]. Moreover, pre-existing fatty liver worsens hepatic IRI via excessive ROS generation, aggravating lipid peroxidation and mitochondrial dysfunction [79]. Chronic lipid overload further shifts cell death modalities from apoptosis to necroptosis or pyroptosis, amplifying pro-inflammatory cytokine release and disrupting the regenerative microenvironment [80, 81].

Heterogeneous steatotic liver phenotypes and divergent regenerative outcomes

The impact of hepatic steatosis on liver regeneration exhibits marked heterogeneity, with outcomes depending on the severity, lipid composition, and metabolic context. Multiple experimental models—including genetically obese mice [72], HFD induced steatosis [75], and leptin receptor-deficient models [73]—exhibit significantly impaired regeneration post-PH, indicating advanced steatosis as a critical risk factor for regenerative impairment [10, 82]. Clinical observations reveal milder lipid infiltration exerts minimal effects on regenerative capacity [30, 83]. Notably, unsaturated fat-enriched diets reduce

inflammatory cytokine levels and enhance regenerative efficiency compared to saturated fat regimens, suggesting lipid composition modulation holds greater therapeutic relevance than mere accumulation control [76].

Clinically, patients with fatty liver are more susceptible to IRI-induced hepatic damage and demonstrate compromised post-surgical regenerative responses [84]. While substantial evidence supports the notion that steatotic livers are suboptimal for surgical resection or transplantation due to impaired regenerative capacity and IRI vulnerability [84–86], regenerative outcomes vary considerably across models. For instance, in certain simple steatosis models (e.g., A20 heterozygous knockout mice), compensatory hepatocyte proliferation is observed, potentially mediated by upregulated hepatocyte growth factor (HGF) signaling [87, 88]. Methionine-choline-deficient (MCD) diet-induced steatosis in rats shows comparable 24-hour post-PH proliferation to controls [30]. Western diet (WD)-fed models exhibit enhanced hepatocyte proliferation with upregulated HGF/leptin signaling and Erk1/2 phosphorylation [88]. Choline-deficient (CD) diet-fed rats display increased DNA synthesis and cellular proliferation compared to choline-supplemented groups [89]. Pathological progression analysis progressive steatosis severity under MCD conditions—from simple lipid accumulation at 1 week to extensive steatosis and necrotic cell death by week 5—underscoring the dynamic nature of steatosis-associated injury and regenerative potential [83].

Collectively, these findings suggest that aberrant lipid metabolism disrupts liver regeneration through multifactorial mechanisms, whose impact is dictated by lipid species, accumulation severity, and microenvironmental plasticity. Therapeutic strategies targeting metabolic reprogramming and redox homeostasis may enhance regenerative capacity in steatotic livers. However, the variability in regenerative responses highlights the need for individualized evaluation of hepatic lipid profiles, oxidative stress markers, and compensatory signaling pathways. Future directions should prioritize lipidomics-guided precision therapies, mechanistic dissection of dietary fat subtype effects (saturated vs. unsaturated), and dynamic mapping of lipid–redox crosstalk.

The unique role of lipophagy in metabolic regulation

Lipophagy is a selective autophagic process devoted to the degradation of intracellular LDs. In hepatocytes, lipophagy governs the turnover of stored lipids through finely tuned molecular mechanisms that intersect with broader metabolic pathways. The morphology and abundance of LDs—specifically their size and number—undergo dynamic changes in response to the cellular metabolic state. Larger LDs are often broken down into smaller droplets via lipolytic processes, which enhances their subsequent recognition and degradation by autophagosomes. Notably, LD size has emerged as a critical determinant in modulating both lipolysis and lipophagy activity [90]. These interrelated pathways enable lipophagy to function as a metabolic switch, linking nutrient sensing to energy mobilization and contributing to the maintenance of hepatic metabolic flexibility.

Basic mechanisms of lipophagy

Lipophagy is governed by a multilayered regulatory network integrating autophagic machinery, LDs surface proteins, and membrane trafficking systems (Fig. 3). Central to this process are autophagy-related (ATG) proteins, particularly Atg7 and the Atg5–Atg12–Atg16L1 complex, which orchestrate autophagosome formation and maturation for the encapsulation and lysosomal degradation of LDs [91, 92]. Notably, LDs surface proteins such as perilipins (PLIN2/PLIN3) contain evolutionarily conserved KFERQ-like motifs recognized by the heat shock cognate 71 kDa protein (Hsc70), thereby directing these proteins for degradation via chaperone-mediated autophagy (CMA) [93]. This proteolytic process exposes the LDs core, enhancing its accessibility to both lipolytic enzymes and autophagic machinery.

The Rab GTPase family orchestrates critical membrane trafficking events in lipophagy [94–96]. Rab7 facilitates LDs degradation by recruiting multivesicular bodies and lysosomes to LDs microdomains [97], while Rab10 promotes autophagosomal engulfment through its association with LC3-positive membranes [98]. These molecular switches regulate membrane tethering, vesicular transport, and fusion events to ensure spatiotemporal control of lipophagic flux.

Lipolysis and lipophagy represent the two principal pathways for LD catabolism [99, 100]. Mounting evidence suggests functional crosstalk between these processes, where lipolytic breakdown may generate upstream signals for lipophagy activation. Specifically, FFAs released through lipolysis can stimulate lipophagy via Sirtuin-1-mediated signaling cascades [101]. This interaction is further supported by direct physical associations between lipolytic enzymes such as adipose triglyceride lipase (ATGL) and autophagosomal marker LC3 [102, 103], highlighting a bidirectional regulatory interface.

Physiologically, lipophagy maintains hepatic homeostasis through two complementary mechanisms: (1) providing substrates for mitochondrial β-oxidation during energy scarcity, and (2) clearing excess or toxic lipid species (e.g., saturated FFAs) to prevent lipotoxicity [90, 104]. However, dysregulated lipophagic flux contributes to metabolic pathologies like MAFLD, where impaired LDs clearance leads to pathogenic lipid accumulation, mitochondrial dysfunction, and inflammatory cascades [105]. Therapeutic strategies targeting key regulatory

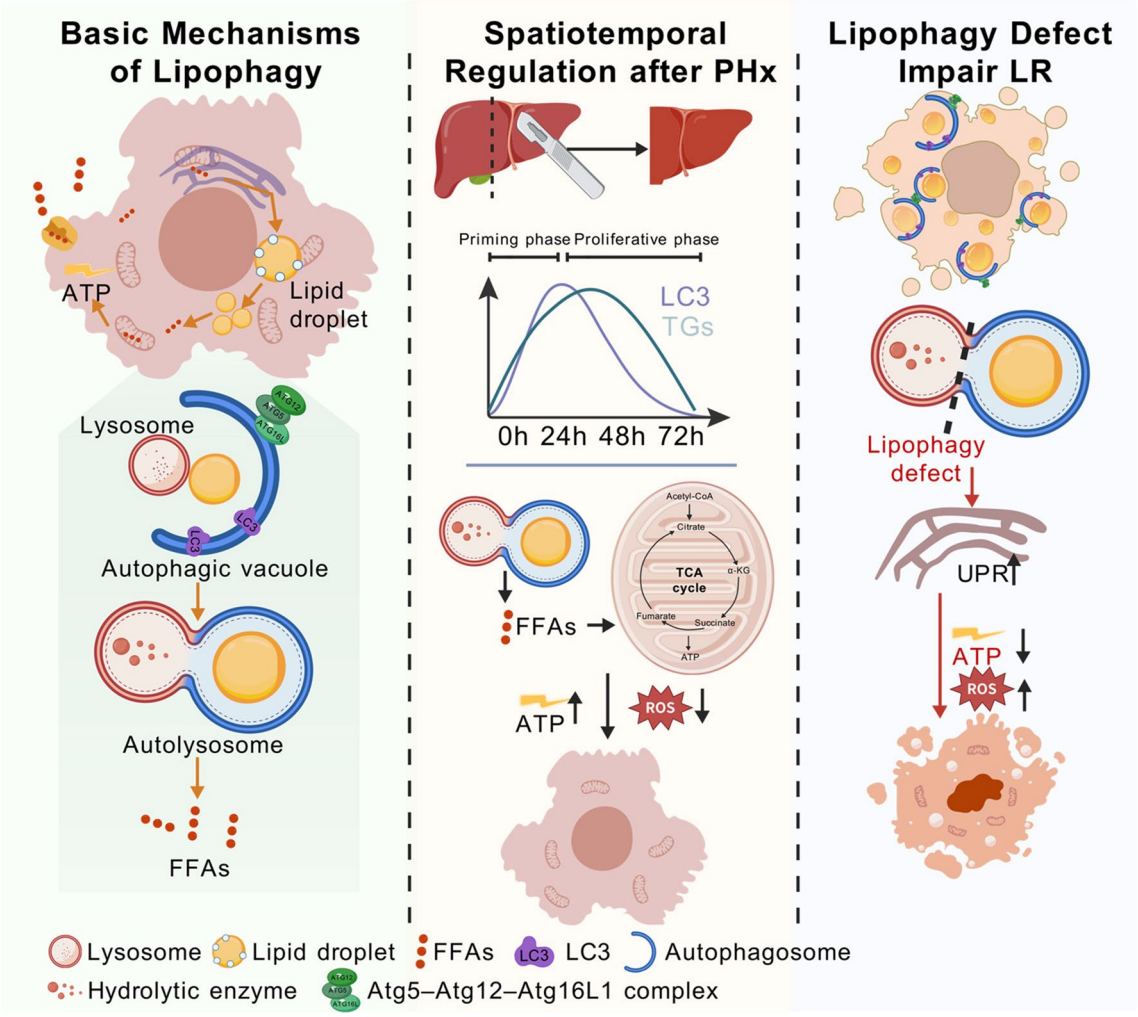

Fig. 3 Lipophagy orchestrates energy homeostasis and regeneration in the liver. This schematic summarizes the mechanisms and pathophysiological relevance of lipophagy during liver regeneration. Left panel: Basic Mechanisms of Lipophagy. Lipophagy is a selective form of autophagy that degrades lipid droplets (LDs) via autophagosome formation and lysosomal fusion, releasing free fatty acids (FFAs) for mitochondrial β-oxidation and ATP production. Key molecular players include Atg proteins, Rab GTPases (e.g., Rab7, Rab10), and perilipin-coated LDs. Middle panel: Spatiotemporal Regulation after Partial Hepatectomy (PHx). Following PHx, triglycerides (TGs) levels increase three- to four-fold within 24 h post-surgery, decline after 48 h, and return to baseline by 72 h and lipophagic activity peaks during early regenerative phases (within 24–48 h), aligning with increased metabolic demands. FFAs liberated through lipophagy fuel the tricarboxylic acid (TCA) cycle, sustaining ATP production and minimizing reactive oxygen species (ROS) accumulation to support hepatocyte proliferation. Right panel: Lipophagy Defect Impairs Liver Regeneration. In steatotic or metabolically impaired livers, lipophagy defects lead to intracellular lipid accumulation, impaired β-oxidation, and excessive ROS generation. This disrupts ER homeostasis and activates maladaptive unfolded protein response (UPR) signaling, ultimately compromising hepatocyte viability and regenerative capacity. Restoration of lipophagic flux ameliorates ATP deficiency and oxidative stress, highlighting its therapeutic potential in fatty liver–associated regenerative failure

nodes—including Rab GTPase activity modulation and CMA pathway activation—has emerged as a promising therapeutic strategy to restore lipid balance and improve regenerative outcomes in metabolic liver disorders.

Spatiotemporal regulation of lipophagy in liver regeneration

Autophagy, a conserved catabolic process, degrades long-lived proteins and damaged organelles (e.g., ER, mitochondria) to provide alternative energy sources during nutrient deprivation [106]. Mounting evidence underscores its pivotal role in liver regeneration, wherein autophagy supports the metabolic and structural demands of DNA replication and cell division. This is achieved via two principal mechanisms: supplying ATP and biosynthetic precursors via degradation products; removing dysfunctional organelles and misfolded proteins to maintain proliferative coordination [107–109]. Toshima et al. demonstrated temporally regulated autophagy activity post-PH, peaking during regenerative initiation and returning to baseline post-regeneration

[108], highlighting its temporal specificity in regenerative progression.

Lipophagy selectively engulfs LDs into autophagosomes, degrading TGs to release FFAs as β-oxidation substrates [110]. Pathological lipid accumulation creates a vicious cycle: excessive LDs suppress autophagic flux, while defective autophagy exacerbates LDs clearance failure, amplifying lipotoxicity [111, 112]. In fatty liver models, autophagosomes aberrantly cluster around LDs during regeneration, indicating lipophagy may fuel regeneration via TGs breakdown rather than proteolysis [113]. Notably, steatotic livers exhibit impaired late-stage autophagic flux, limiting toxic lipid clearance and aggravating regenerative failure [113].

Pharmacological activation of Lipophagy (e.g., rapamycin) reduces LDs accumulation, while Rubicon knockout or FGF21 therapy improves MASLD pathology by enhancing Lipophagic flux [114, 115]. Combining AMPK activators (e.g., AICAR) with autophagy induction alleviates mitochondrial dysfunction and restores β-oxidation capacity [116]. Liver-specific knockout models confirm lipophagy's necessity for regeneration, showing reduced survival and delayed liver mass recovery post-PH [108]. Mas receptor activation via the AKT-FOXO1 axis enhances lipophagic efficiency, improving survival in acetaminophen toxicity models [108]. The development of receptor-targeted therapies is supported by these findings. Mechanistically, the ApoA-1–AMPK–ULK1 axis and the IPMK–AMPK–H4K16 pathway together form the core regulatory network of lipophagy. Phosphorylation of ULK1 dynamically controls autophagosome formation rates, while acetylation of H4K16ac regulates transcription of autophagy-related genes via chromatin remodeling [117]. These insights provide a molecular basis for pro-regenerative strategies that target lipophagy. For example, ApoA-1 mimetic peptides or AMPK agonists might ameliorate regeneration deficits in patients with hepatic steatosis. Furthermore, modulating systemic metabolic responses—such as post-PH hypoglycemia–induced lipid mobilization—represents a novel intervention approach to enhance liver regenerative capacity by optimizing energy substrate availability.

Lipophagy-derived fatty acids maintain energy metabolism and redox homeostasis via β-oxidation

LDs serve as a reservoir for FFAs, which are mobilized for mitochondrial β-oxidation—an essential energy-producing pathway for rapidly proliferating cells, particularly during hepatic regeneration [118]. Notably, selective lipophagy defects correlate with impaired lipid oxidation. Hepatocyte-specific Atg7 or Atg5 knockout disrupts PPARα activation by stabilizing the NCoR1-PPARα complex, which undergoes GABARAP-mediated lipophagic degradation. This mechanism reduces ketogenesis during fasting, revealing lipophagy's regulatory role in β-oxidation and ketogenesis [119].

Lipophagy is also essential for protecting hepatocyte viability under oxidative stress. Atg5 deficiency exacerbates menadione-induced cell death at subtoxic doses and amplifies mortality at toxic concentrations [120]. Crucially, hepatocyte injury arises from β-oxidation dysfunction caused by lipophagic impairment, not FFAs availability per se [119], highlighting lipophagy-derived FFAs as essential regulators of optimal β-oxidation rates.

In obesity and metabolic syndrome, cellular lipid overload—particularly from saturated FFAs—drives hepatocyte cytotoxicity by promoting oxidative stress and mitochondrial dysfunction [121]. Under such conditions, lipophagy mitigates oxidative injury through two synergistic mechanisms: (1) removal of excess or toxic lipid species via autophagic degradation, and (2) generation of ATP through β-oxidation of liberated FFAs [120]. In ethanol-induced liver injury models, autophagy plays a similarly protective role by both degrading peroxidized lipids and reducing reactive oxygen intermediates (ROIs), thereby limiting hepatocellular damage [122, 123]. Collectively, these findings position lipophagy as a critical adaptive mechanism that preserves mitochondrial function and redox homeostasis under metabolic or oxidative stress.

Lipophagy deficiency causes ER stress to impair liver regeneration

The ER, a central hub for lipid metabolism, possesses key enzymatic systems regulating lipid synthesis and processing [124–126]. ER homeostasis is highly sensitive to perturbations such as oxidative stress, calcium imbalance, and increased secretory demands [127–129]. This stress response critically regulates cell fate decisions, including cell cycle progression and metabolic reprogramming [130]. Post-PH, compensatory hyperplasia dramatically increases ER protein-folding loads, creating a stress-prone microenvironment [131, 132]. When ER-associated degradation (ERAD) fails to restore proteostasis, the system will activate the unfolded protein response (UPR). This stress pathway is regulated via three GRP78-regulated branches: (1) IRE1α-mediated XBP1 splicing [33, 133–135]; (2) PERK-dependent eIF2α phosphorylation suppressing translation [136]; and (3) ATF6 proteolytic activation for nuclear gene regulation [134, 137]. During liver regeneration following PH, especially within the first 6 h, UPR markers such as phosphorylated eIF2α, IRE1α activation, and CHOP expression are rapidly upregulated to meet increased demands for ER output [138–140].

Notably, ER stress displays a dynamic equilibrium during liver regeneration. With only 30% of the liver mass remaining, hepatocytes must simultaneously resume biosynthetic functions and maintain systemic homeostasis.

Transient ER stress facilitates lipid synthesis and membrane protein production, both necessary for hepatocyte proliferation and functional recovery [16, 29, 141]. This adaptive process is accompanied by physiological steatosis—characterized by transient LDs accumulation—that typically resolves upon regenerative completion. However, dysregulated or excessive UPR activation can hinder DNA replication and cell cycle progression, ultimately impairing regeneration [133, 142, 143].

Notably, ER stress delays the proliferative potential of residual hepatocytes even in the absence of advanced steatosis or MASLD [144–146]. Mechanistically, ER stress drives de novo lipogenesis through SREBP-1c proteolytic activation. This process promotes SREBP-1c nuclear translocation and subsequent upregulation of lipogenic genes such as FASN and SCD1, establishing a self-reinforcing "ER stress-lipogenesis-regenerative impairment" cycle [147]. Crucially, this pathway operates both in steatosis-associated insulin resistance and chronic ER stress conditions.

Experimental studies demonstrate that HFD-fed mice exhibit significant activation of ER stress markers (GRP78, IRE1α, CHOP) following PH, accompanied by delayed DNA replication and impaired hepatocyte proliferation [28]. Notably, palmitate overload in simple steatosis models specifically activates the IRE1α pathway, inducing ER stress-mediated cell cycle arrest at the G1/S phase [28]. Mechanistic investigations reveal SIRT1 as a pivotal regulator of the ER stress-lipid metabolism axis. Hepatic SIRT1 overexpression ameliorates ER stress through deacetylating XBP1 and eIF2α, concurrently reducing TG accumulation and enhancing regenerative efficiency. Conversely, liver-specific Sirt1 knockout mice display pathological FFAs retention, suppressed PPARα signaling, and delayed regeneration [148, 149].

Lipophagy and the ER stress response form an integrated regulatory axis essential for liver regeneration. Post-PH, IRE1α-XBP1 signaling promotes lipid synthesis for membrane biogenesis, while lipophagy mobilizes FFAs from LDs to fuel mitochondrial β-oxidation and support energy demands [28, 142]. This spatiotemporal interplay ensures synchronized metabolic reprogramming and structural remodeling. In pathological conditions such as MASLD and ALD, chronic lipid accumulation disrupts ER membrane integrity and perpetuates UPR activation [121]. Impaired lipophagy exacerbates this cycle, promoting toxic LD buildup, sustaining ER stress, and suppressing hepatocyte proliferation [28].

Therapeutic enhancement of lipophagy restores regenerative capacity through a dual mechanism: alleviating ER stress by clearing cytotoxic lipids and sustaining ATP production via β-oxidation [150]. These mechanisms highlight lipophagy as a promising therapeutic target for improving regeneration in steatotic livers. Several promising strategies have emerged targeting the ER stress–lipophagy axis: (1) UFMylation pathway modulation, such as UFSP2 activity regulation, to relieve maladaptive ER stress [44]; (2) liver-targeted autophagy activation via resveratrol-loaded nanoparticles, which upregulate SIRT1–AMPK signaling and suppress GRP78 expression [151]; IRE1α inhibition to prevent pathological XBP1s overactivation, normalizing regeneration in steatotic models [143]; and (4) metabolic reprogramming using ω-3 polyunsaturated fatty acids (e.g., DHA), which enhance PPARα-mediated mitochondrial oxidation and attenuate ROS generation [152].

This lipophagy–mitochondria–ER three-way interaction network reveals multiple therapeutic entry points for overcoming regenerative deficits in metabolic liver disease. Notably, AAV-mediated XBP1s overexpression has demonstrated enhanced liver regenerative function in preclinical studies, opening a new regenerative-medicine avenue for end-stage liver disease [16, 141].

Integration of lipid metabolism with regenerative regulatory networks

Liver regeneration involves precisely orchestrated multidimensional metabolic reprogramming, requiring dynamic coordination between metabolic rewiring and cellular proliferation. This coordination extends beyond local hepatic glucose and lipid metabolism to encompass inter-organ communication, particularly through the gut–liver axis and microbiota-derived signaling molecules. Crosstalk with the intestinal microbiome regulates bile acid metabolism, modulates innate immunity, and influences systemic metabolic tone, thereby shaping the hepatic regenerative milieu. In parallel, the immunometabolic network modulates inflammation-resolution dynamics via metabolic plasticity of macrophage polarization states, establishing a tripartite regulatory axis integrating metabolism, immunity, and regeneration. Together, these multilayered interactions define a systems-level framework of regeneration, whereby lipid metabolism is embedded within broader physiological circuits spanning energy homeostasis, immune regulation, and inter-organ communication (Fig. 4). Understanding this integrated network unveils novel systemic principles underlying tissue repair and offers a transformative paradigm for regenerative biology and therapeutic innovation.

Metabolic network dynamics in liver regeneration

Liver regeneration is a precisely coordinated process involving multidimensional metabolic remodeling. In the priming phase, metabolic reprogramming precedes cellular proliferation and is characterized by acute hypoglycemia—driven by rapid glycogen depletion and transient suppression of gluconeogenesis—alongside hepatic

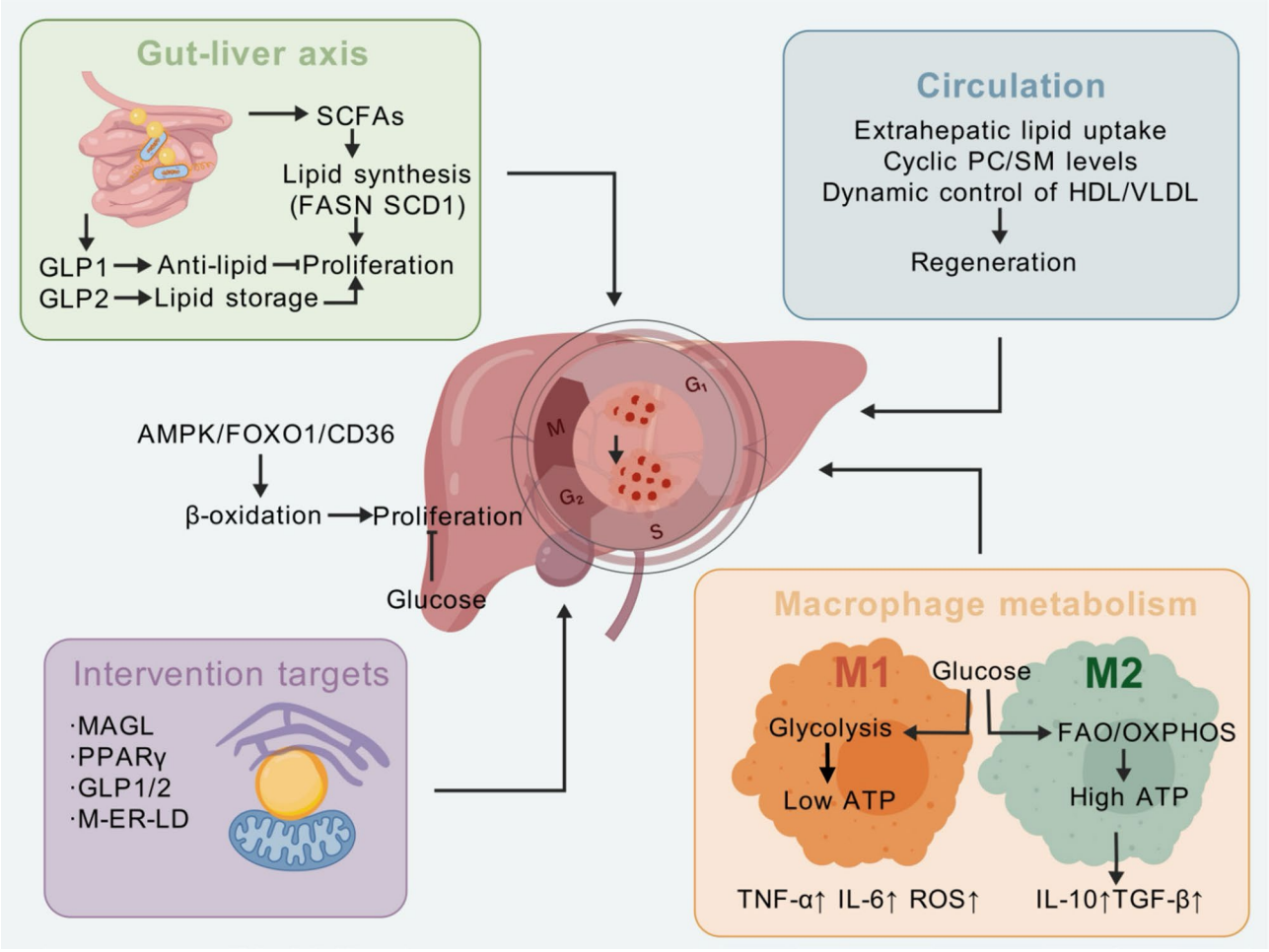

Fig. 4 Multidimensional metabolic crosstalk and cross-system integrated regulatory network in liver regeneration. This schematic illustrates the multilayered interplay between lipid metabolism and systemic regulatory circuits orchestrating liver regeneration. At the core, hepatocyte proliferation is tightly coupled to metabolic reprogramming, including β-oxidation of fatty acids and glucose utilization, coordinated via the AMPK–FOXO1–CD36 axis. Systemic circulatory lipid remodeling—including dynamic shifts in phosphatidylcholine (PC), sphingomyelin (SM), HDL, and VLDL—facilitates membrane assembly and energy supply during regeneration. The gut–liver axis contributes microbiota-derived short-chain fatty acids (SCFAs), which support hepatic lipogenesis (via FASN, SCD1) and provide substrates for membrane biogenesis. Incretin hormones GLP-1 and GLP-2 modulate regenerative outcomes through opposing effects on lipid storage and synthesis. Macrophage metabolism represents a third regulatory layer, where M1-polarized cells rely on glycolysis and generate ROS and pro-inflammatory cytokines (TNF-α, IL-6), whereas M2 macrophages depend on fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) to support reparative programs and growth factor secretion (IL-10, TGF-β1). Therapeutic intervention targets include lipid enzymes (MAGL), transcriptional regulators (PPARγ), incretin pathways (GLP1/2), and multi-organelle interaction hubs (mitochondria–ER–LD complex). Together, this inter-organ and immunometabolic networks define a systemic regenerative framework wherein lipid metabolism is integrated with immune modulation, energy homeostasis, and organ crosstalk

lipid accumulation. Intriguingly, exogenous glucose supplementation corrects hypoglycemia but suppresses regeneration, underscoring the critical balance between glucose metabolism and lipid mobilization [6, 153]. *Pdk4*-deficient models reveal dual regulatory mechanisms: enhanced fatty acid β-oxidation via the AMPK/FOXO1/CD36 axis and improved insulin/Akt pathway sensitivity. This metabolic synergy provides robust energy support for hepatocyte proliferation, accelerating regeneration [154].

Lipid metabolism also plays indispensable roles beyond energy provision, notably in membrane biogenesis. Phosphatidylcholine (PC), a cornerstone of membrane stability, is synthesized through three hepatic pathways: the Kennedy pathway, the Lands cycle and the Phosphatidylethanolamine N-methyltransferase (PEMT) pathway [155–157]. The liver-specific PEMT pathway contributes 30% of hepatic PC production and serves as the primary source of circulating polyunsaturated fatty acid-containing PC (PUFA-PC) [158, 159]. Post-PH, hepatic PEMT activity declines within 24 h, reducing PUFA-PC synthesis. Clinical metabolomics reveals significantly decreased circulating PUFA-PC and sphingomyelin (SM) levels in patients with delayed regeneration, accompanied

by reduced HDL-C and ApoA1. These findings reflect both enhanced hepatocyte lipid uptake and suppressed de novo lipogenesis [7, 160, 161]. Human metabolomic data further confirm that impaired liver regeneration correlates with diminished circulating PC levels, particularly PUFA-PC species [161]. Since hepatic lipid secretion—particularly VLDL assembly and HDL/LDL lipid exchange—is PC-dependent [162], these findings emphasize PC homeostasis as a central determinant of regenerative capacity. Supporting this, choline-deficient diets impair PC synthesis and exacerbate liver injury in experimental models [163–165].

Beyond metabolic pathways, growth factor signaling critically regulates hepatic regeneration. Following PH in mice, ileal FGF15 (human ortholog FGF19) and hepatic FGFR4 expression are coordinately upregulated. The activated FGF15/19-FGFR4 axis promotes regeneration through dual mechanisms: (1) enhancing hepatocyte proliferation through Cyclin D1 and CDK4 upregulation, and (2) attenuating hepatic lipid accumulation during the early regenerative phase [166]. This discovery establishes the gut-liver axis as a pivotal regulator coordinating metabolic reprogramming with proliferative signaling during regeneration.

Gut-liver-microbiota metabolic crosstalk

The bidirectional communication within the gut–liver axis is increasingly recognized as a critical regulator of hepatic regeneration, particularly through its metabolic implications [167]. The gut microbiota, a core component of intestinal homeostasis, ferments dietary fibers into short-chain fatty acids (SCFAs) [168], which not only provide energy and modulate immune homeostasis but also profoundly regulate hepatic metabolism [169–171]. Recent studies highlight the intricate interaction between microbial metabolites and host lipid networks. FAs, derived from either microbial fermentation or host de novo synthesis, function as precursors for lipid signaling molecules and as structural components of membrane phospholipids (PLs) [172, 173]. By altering membrane composition—polyunsaturated fatty acids (PUFAs) enhance membrane fluidity, whereas monounsaturated fatty acids (MUFAs) stabilize biosynthetic membrane structures—FAs directly influence dynamic processes such as cell proliferation, differentiation, and organelle biogenesis [174, 175]. In parallel, de novo synthesis of saturated fatty acids—particularly palmitic acid via fatty acid synthase (FASN)—provides essential substrates for organelle membrane assembly during regeneration [176]. These findings not only clarify how microbial metabolites finely tune the host lipid network but also provide novel molecular insights into the pathological mechanisms of the gut–liver axis in metabolic disorders such as hepatic steatosis and insulin resistance.

SCFAs serve not only as energy substrates but also as direct contributors to hepatic lipogenesis. Experimental data demonstrate that a subset of intracellular fatty acid pools in hepatocytes originates from microbiota-derived SCFAs [177]. Perturbation of gut microbial composition—such as by broad-spectrum antibiotics—reduces intestinal SCFA availability, suppresses hepatocyte proliferation, and downregulates SCD1, thereby impairing MUFA (e.g., oleate) biosynthesis [178]. This SCFA insufficiency leads to disrupted membrane phospholipid production and significantly delays regenerative progression through impaired structural biogenesis [177].

Moreover, the incretin hormones glucagon-like peptides (GLPs), secreted by intestinal L-cells, exhibit contrasting effects on hepatic lipid metabolism. GLP-1 exerts anti-lipogenic effects by reducing intestinal lipid absorption, lowering plasma triglyceride levels, and suppressing hepatic fat accumulation. In contrast, GLP-2 enhances lipoprotein assembly and promotes hepatocyte lipid storage [179]. This hormonal dualism exhibits temporal and spatial specificity in liver regeneration. Rodent models of partial hepatectomy show that GLP-1 administration reduces liver regeneration rates—possibly by limiting early-phase lipid accumulation—whereas GLP-2 enhances regenerative capacity, likely by facilitating lipid supply for membrane synthesis [180, 181]. These findings establish intestinal incretin hormones as pivotal regulators of the lipid mobilization-storage equilibrium, critically shaping hepatic regenerative outcomes through metabolic precision.

Macrophage polarization-metabolic reprogramming synergy in liver regeneration

Macrophages, as highly heterogeneous immune populations, play central regulatory roles in tissue homeostasis maintenance, injury repair, and regeneration [182, 183]. Their functional diversity is governed not only by the dynamic equilibrium between pro-inflammatory (M1) and reparative (M2) polarization states but also through coordinated metabolic reprogramming. Studies have identified the PPARγ-mediated lipogenic network as a critical hub governing macrophage reparative function. Across nine tissue-injury models and in vitro systems induced by IL-10, TGF-β1, or dexamethasone, activation of FASN within reparative macrophages was conserved between mice and humans, underscoring this pathway's translational potential [184]. Mechanistically, injury signals provoke dephosphorylation of PPARγ at threonine 166 (T166), enhancing its binding to regulatory regions of lipogenic genes and thereby driving lipid accumulation. These accumulated lipids serve dual roles: (1) as signaling molecules that activate the STAT3 pathway, thereby upregulating regenerative growth factors such as PDGF, TGF-β1, and VEGF, and (2) as substrates

for phospholipid synthesis, facilitating ER expansion and supporting protein biosynthesis for tissue repair [183, 185]. Consistently, macrophage depletion leads to marked impairment in regeneration, underscoring their indispensable physiological role [186].

Macrophage activation states are tightly coupled to distinct bioenergetic profiles [187, 188]. Pro-inflammatory M1 macrophages favor aerobic glycolysis for rapid ATP production and ROS generation [189], whereas reparative M2 macrophages rely on fatty acid oxidation (FAO) and mitochondrial oxidative phosphorylation (OXPHOS) to sustain long-term reparative functions [190]. This metabolic plasticity is especially relevant in hepatic injury, where an imbalance in M1/M2 polarization exacerbates inflammation or impedes regeneration [191, 192]. For example, M1 macrophages -derived cytokines such as IL-6 and TNF-α can propagate hepatocellular damage [193], though moderate M1 macrophages activation also initiates early regenerative signaling [194, 195]. In contrast, M2 macrophages promote tissue repair by secreting anti-inflammatory mediators [192], and activating PPARγ–STAT3–growth factor axes, while simultaneously supporting ER expansion to accommodate regenerative protein synthesis [184, 185]. Recent work has identified a "tri-organellar interaction unit" (mitochondria–ER–LD, M-ER-LD), in which serve as metabolic signaling hubs in macrophages, mediating inter-organelle crosstalk, and a "quadruple interaction unit" (mitochondria–ER–peroxisome–LD), in which peroxisomes drive lipolysis and release proinflammatory mediators like arachidonic acid [196, 197]. Furthermore, lipopolysaccharide (LPS) activation upregulates hypoxia-inducible lipid droplet-associated protein (HILPDA), inhibits ATGL–mediated triglyceride hydrolysis, and thereby limits production of inflammatory mediators such as prostaglandin E_2 and IL-6—revealing a novel mechanism by which pathogen-associated molecular patterns (PAMPs) modulate immune response strength via metabolic reprogramming [198].

Therapeutic modulation of macrophage metabolism offers promising avenues for regenerative medicine. For example, loss of monoacylglycerol lipase (MAGL) disrupts lipid catabolism, activates type I interferon signaling, and impairs liver regeneration [199]. Meanwhile, exosomes derived from human umbilical cord mesenchymal stem cells (hUC-MSC-exo) enhance hepatic regeneration by improving lipid metabolism and suppressing pro-inflammatory polarization through PPARα activation [200, 201]. Collectively, these findings underscore that macrophages are not merely inflammatory effectors but metabolically reprogrammed regenerative orchestrators, with key roles played by lipogenic transcription networks, organelle crosstalk, and lipid enzyme activities—providing multiple therapeutic targets to modulate inflammation and promote liver regeneration.

Integration and reinforcement of human clinical evidence

The regenerative capacity of steatotic livers in humans remains incompletely understood. While preclinical models have demonstrated that hepatic steatosis impairs liver regeneration [202], corresponding studies in humans are limited. Existing clinical reports—primarily focused on living liver donors—have yielded inconsistent findings [203–205]. Although the clinical implications of steatosis in liver regeneration are yet to be fully elucidated, accumulating evidence suggests that steatosis may increase the risk of poor postoperative outcomes. This increased vulnerability likely results from the metabolic and pathophysiological disturbances induced by excessive lipid accumulation. Notably, even mild hepatic steatosis has been associated with elevated postoperative complication rates and worse prognosis [206].

It is estimated that over 20% of patients scheduled for liver resection present with some degree of steatosis [207]. In the context of transplantation, steatotic grafts are linked to higher rates of primary non-function and inferior survival outcomes [208–211]. Indeed, even mild steatosis significantly increases the incidence of primary graft non-function and lowers patient survival [212]. Steatosis has also been associated with increased morbidity and mortality following liver resection [84, 213]. Behrns et al. emphasized the heightened intraoperative risk associated with steatosis, including increased postoperative mortality, complication rates, and technical difficulty [84]. A study involving 478 patients undergoing elective liver resection identified hepatic steatosis as an independent predictor of postoperative complications, while another report noted that severe steatosis significantly increased the risk of infectious complications [213, 214].

Impaired liver regeneration is a critical consequence of steatosis and has a substantial impact on postoperative outcomes following partial hepatectomy [84, 213]. Experienced surgeons often adopt a more conservative resection strategy in patients with steatosis, reserving more aggressive interventions for those with minimal fat accumulation [215]. A recent meta-analysis concluded that hepatic steatosis doubles the risk of postoperative complications, and in cases of severe steatosis, mortality may increase up to threefold [216]. Although animal studies have consistently shown that steatosis hampers regeneration, clinical studies—though limited—similarly suggest a detrimental effect, particularly in patients with moderate to severe hepatic fat infiltration [202–204, 217].

Species differences pose significant challenges to translational applications. Key lipid metabolic pathways show marked divergence between rodents and humans. For instance, PPARα is robustly expressed and strongly

activates β-oxidation in rodent models, thereby facilitating regeneration; however, in humans, PPARα expression is lower, its activation weaker, and long-term activation may even induce myopathy. For instance, the in vitro EC50 values of *WY-14,643 (a potent agonist of PPARα)* are 0.6 μM and 5.0 μM respectively [218]. These differences necessitate the development of liver-targeted agonists for clinical use. Similarly, the YAP pathway, which mediates liver regenerative proliferation in animal models, is more tightly restricted in human hepatocytes and is associated with hepatocarcinogenic risk, requiring cautious therapeutic modulation [219]. The gut–liver axis also exhibits species-specific features. In rodents, SCFAs primarily promote FFAs uptake; in contrast, primary bile acid–mediated signaling predominates in humans [220]. Within the human hepatic microenvironment, regulation is further shaped by unique cell–cell interactions. For example, secrete WNT2, which activates the FZD5 receptor on hepatocytes to enhance cholesterol uptake and bile acid conjugation—this WNT2–FZD5 axis is absent in mice and represents a human-specific regenerative mechanism [221]. Furthermore, PPARα activation in human hepatocytes appears to exert a more moderate effect on gene regulation compared to rodents. Data indicates that PPARα activation may suppress DNA synthesis while enhancing interferon/cytokine signaling [222]. Finally, metabolomic profiling has identified specific lipid species as potential biomarkers of regenerative capacity. In particular, elevated serum levels of PUFA-PC have been associated with enhanced liver regenerative responses [161].

Conclusions

Lipid metabolism constitutes the energetic and biosynthetic backbone of liver regeneration, with its dynamic regulation exerting a profound influence on regenerative efficacy and clinical outcomes. In the context of acute hepatic injury, TRAS supplies ATP via β-oxidation and supports membrane biogenesis through phospholipid synthesis. Simultaneously, tightly controlled LDs turnover—via storage and catabolism—ensures sufficient energy provision during hepatocyte proliferation and promotes restoration of metabolic homeostasis in the resolution phase. Notably, lipophagy, the selective autophagic degradation of LDs, releases FFAs that fuel mitochondrial respiration and mitigate oxidative stress. In contrast, chronic lipid overload disrupts this homeostatic cycle, precipitating mitochondrial dysfunction, ER stress, and excessive inflammatory signaling—hallmarks of impaired regeneration. Through an integrated "energy–membrane biosynthesis–signaling" framework, lipid metabolism dynamically coordinates regenerative responses: while transient activation is protective and pro-regenerative, sustained dysregulation becomes pathogenic. Beyond hepatocellular metabolism, the gut–liver axis and microbiota-derived metabolites further modulate lipid homeostasis, while macrophage polarization states reshape the immune-metabolic landscape through lipid-centered regulatory programs. Together, these interactions establish a multilayered metabolic–immune regulatory network that orchestrates effective liver regeneration.

Future research directions should prioritize multidimensional approaches to dissect this complexity. First, it is essential to elucidate the temporal dynamics of lipid species transitions during TRAS, and their coupling to cell cycle regulators—particularly lipophagy substrate selectivity and its interplay with mitophagy. Second, efforts should focus on developing metabolic reprogramming strategies aimed at alleviating ER stress and activating the AMPK–ULK1 lipophagy axis, while also investigating how the microbiota–gut–liver axis governs lipid mobilization. Third, there is a need to define the immunometabolic microenvironment by profiling macrophage lipid metabolic states and linking them to cytokine signatures and regenerative outcomes. This includes characterizing how the LD–Mitochondria–ER interaction unit resolves inflammation through lipid flux modulation. Finally, translational advancement will require the integration of lipidomic biomarkers with organoid-based functional models, enabling the validation of lipid metabolism-targeted interventions or lipophagy activators in personalized therapeutic frameworks—ultimately bridging bench discoveries with bedside applications. Importantly, given the species-specific differences in regenerative mechanisms and the current scarcity of human liver regeneration data, future studies should strengthen the human translational connection to ensure clinical applicability.

Abbreviations

TRAS	Transient regenerative-associated steatosis
LDs	Lipid droplets
FFAs	Free fatty acids
ER	Endoplasmic reticulum
PPARα	Peroxisome proliferator-activated receptorα
PH	Partial hepatectomy
MASLD	Metabolic-associated steatotic liver disease
TGs	Triglycerides
CEs	Cholesterol esters
PHLF	Post-hepatectomy liver failure
ROS	Reactive oxygen species
MASH	Metabolic dysfunction-associated steatohepatitis
IRI	Ischemia-reperfusion injury
HFD	High-fat diet
HGF	Hepatocyte growth factor
MCD	Methionine-choline-deficient
WD	Western diet
CD	Choline-deficient
DGATs	Diacylglycerol acyltransferases
ACATs	Acyl-CoA-cholesterol acyltransferases
ATG	Autophagy-related
Hsc70	Heat shock cognate 71 kDa protein
CMA	Chaperone-mediated autophagy

ATGL	Adipose triglyceride lipase
ROIs	Reactive oxygen intermediates
ERAD	ER-associated degradation
UPR	Unfolded protein response
ALD	Alcohol-associated liver disease
PC	Phosphatidylcholine
PEMT	Phosphatidylethanolamine N-methyltransferase
PUFA-PC	Polyunsaturated fatty acid-containing PC
SM	Sphingomyelin
SCFAs	Short-chain fatty acids
PLs	Phospholipids
PUFAs	Polyunsaturated fatty acids
MUFAs	Monounsaturated fatty acids
FASN	Fatty acid synthase
GLPs	Glucagon-like peptides
FAO	Fatty acid oxidation
OXPHOS	Oxidative phosphorylation
PAMPs	Pathogen-associated molecular patterns

Acknowledgements
We would like to thank the authors of the primary studies. The figures in this article were created using Adobe Illustrator, Adobe Photoshop, BioGDP, and Microsoft PowerPoint.

Author contributions
Conceptualization, J.L. X.C.; supervision, L.D. Y.C.; writing–original draft, J.L. J.D.; writing– review & editing, X.C. H.L. W.Z. All authors reviewed the manuscript.

Funding
This work was supported by the funding from Key Research and Development Project of Zhejiang Province (2021C03061 to X.C.).

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
All the authors declare no confict of interests.

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Received: 17 June 2025 / Accepted: 24 September 2025
Published online: 16 October 2025

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