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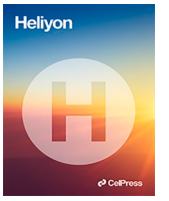

Review article

Lomitapide repurposing for treatment of malignancies: A promising direction

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ABSTRACT

The development of novel drugs from basic science to clinical practice requires several years, much effort, and cost. Drug repurposing can promote the utilization of clinical drugs in cancer therapy. Recent studies have shown the potential effects of lomitapide on treating malignancies, which is currently used for the treatment of familial hypercholesterolemia. We systematically review possible functions and mechanisms of lomitapide as an anti-tumor compound, regarding the aspects of apoptosis, autophagy, and metabolism of tumor cells, to support repurposing lomitapide for the clinical treatment of tumors.

1. Introduction

The incidence of malignancies is gradually increasing [1]. Among them, breast cancer is the most frequent malignant disease worldwide (2.26 million of new cases/year; 11.7 % of total malignancies), followed by lung cancer (2.20 million of new cases/year; 11.4 % of total malignancies), colorectal cancer (CRC) (1.93 million of new cases/year; 10.0 % of total malignancies) and prostate cancer (1.41 million of new cases/year; 7.30 % of total malignancies) [2]. The rapid increase in the global burden of cancer morbidity and mortality is reported to be associated with human economic and social development, with risk factors not limited to reproduction and hormones, but also lifestyles [3–5].

Cancer treatment encompasses various approaches, including surgery, radiotherapy, chemotherapy, immunotherapy, and more. Nevertheless, cancer treatment encounters significant challenges, including drug resistance, toxicity, side effects, recurrence, and metastasis. Hence, extensive research is necessary to investigate the mechanisms underlying tumor occurrence, molecular markers, novel drugs, and treatment strategies, aiming to enhance the quality of life and prognosis for patients with tumors. Therefore, the development of new anti-tumor drugs is increasingly urgent. Drug repurposing provides a very promising approach to address this need by screening 'old' clinically-used drugs for relevant disease targets, and expanding the therapeutic range of existing drugs for new application [6,7]. As the safety, toxicity, and side-effects of such drugs have been investigated already, drug repurposing ensures good bioavailability and suitable physicochemical properties, along with shortened time and reduced cost required for drug development

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Abbreviations

CRC	Colorectal Cancer
HoFH	Homozygous Familial Hypercholesterolemia
MTTP	Microsomal Triglyceride Transfer Protein
HBV	Hepatitis B Virus
Apo B	Apolipoprotein B
VLDL	Very Low-Density Lipoprotein
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
CYP3A4	Cytochrome P450 Isoenzyme 3A4
INR	International Normalized Ratio
FDA	Food and Drug Administration
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
hACE2	Human Angiotensin-Converting Enzyme 2
HTP	High-Throughput
ATP	Adenosine Triphosphate
IC50	Half Maximal Inhibitory Concentration
ER	Estrogen ReceptorERα: Estrogen Receptor alpha
VS	Virtual Screening
mTOR	Mammalian Target of Rapamycin
mLST8	Mammalian Lethal with SEC13 Protein 8
DEPTOR	DEP Domain Containing MTOR-Interacting Protein
PRAS40	Proline-Rich AKT Substrate 40 kDa
raptor	Regulatory Associated Protein of MTOR
rictor	Rapamycin-Insensitive Companion of MTOR
mSin1	Mammalian Stress-Activated Protein Kinase Interacting Protein 1
Protor	Protein Observed with Rictor
PI3K	Phosphoinositide 3-Kinases
PTEN	Phosphatase and Tensin Homolog
HIF1-α	Hypoxia-Inducible Factor 1-alpha
Rheb	Ras Homolog Enriched in Brain
4E-BP1	Eukaryotic Translation Initiation Factor 4E-Binding Protein 1
elF4E	Eukaryotic Translation Initiation Factor 4E
ACC	Acetyl-CoA Carboxylase
GLUT1/4	Glucose Transporter Type 1/4
CPT1	Carnitine Palmitoyltransferase 1
PP2A	Protein Phosphatase 2A
ROS	Reactive Oxygen Species
ADP	Adenosine Diphosphate
MM	Multiple Myeloma
DFG	Asp168-Phe169-Gly170
TSC	Tuberous Sclerosis Complex
GTPase	Guanosine Triphosphatase
TSC2	Tuberous Sclerosis Complex 2
EGFR	Epidermal Growth Factor Receptor
BTK	Bruton's Tyrosine Kinase
SREBP	Sterol Regulatory Element Binding Protein
ATF4	Activating Transcription Factor 4
CMA	Chaperone-mediated Autophagy
LC3	Microtubule-Associated Protein Light Chain 3
ULK1	Unc-51 Like Autophagy Activating Kinase 1
PPM1D	Protein Phosphatase 1D Magnesium-Dependent, Delta Isoform
PARP	Poly (ADP-Ribose) Polymerase
ACD	Autophagy-Mediated Cell Death
PD-1	Programmed Death-1
PLD-1	Phospholipase D1

[8]. For example, the anti-diabetic drug metformin exhibits anti-tumor effects, and is being investigated in phase II/III clinical trials [9], while the antiplatelet drug aspirin has potential therapeutic benefit for patients with prostate cancer [10]. In addition, the anti-allergic drug azelastine [11], antiseptic compound benzethonium chloride [12], anti-hepatitis B virus (HBV) drug adefovir dipivoxil [13], traditional Chinese herb daurisoline [14], and imperatorin [15] have all been used to inhibit malignant tumors.

Lomitapide, an inhibitor of microsomal triglyceride transfer protein (MTTP), has been used in the clinic for treatment of homozygous familial hypercholesterolemia (HoFH) [16]. Recently, lomitapide has been found to have anti-tumor effects in CRC [17]. However, the application potential and molecular mechanism of lomitapide in different types of malignancies is still unclear. To extend the utilization and uncover its mechanism, this article systematically reviews the clinical utilization of lomitapide and its potential mechanism and efficacy, in anti-tumor application, to provide evidence for further investigation of repurposing lomitapide in precision treatment of patients with malignancies.

2. Overview of lomitapide

2.1. Structure and pharmacodynamic of lomitapide

Lomitapide, was initially developed as a lipid-lowering agent, then used as a niche orphan drug for HoFH [18] (Fig. 1). Based on patient tolerance and response, the recommended dose is started from 5 mg once daily, gradually titrated to a maximum of 60 mg/day [19]. As an oral drug, lomitapide targets MTTP to prevent assembly of apolipoprotein B (Apo B)-containing lipoproteins in the liver and intestines [20]. It has been reported that MTTP is involved in the intracellular transfer of lipids required for the assembly and secretion of very low-density lipoprotein (VLDL) (Fig. 2). MTTP inhibition by lomitapide leads to decreased plasma lipid levels through suppressing the secretion of VLDL, and consequently of low-density lipoprotein (LDL) [21].

Lomitapide is primarily metabolized in the liver via cytochrome P450 isoenzyme 3A4 (CYP3A4) into inactive metabolites without MTTP inhibitory activity. Due to a high first-pass metabolism in the liver, the absolute bioavailability of lomitapide is approximately 7 % [22]. As a substrate of CYP3A4, lomitapide also acts as a CYP3A4 inhibitor to the accumulation of other CYP3A4 substrates, such as statins and warfarin. Normally, the time to reach maximum lomitapide concentration after a single dose of 60 mg is approximately 6 h. Lomitapide has a mean volume of distribution in plasma ranging from 985 to 1292 L, a serum half-life of 39.7 h, and is approximately 52.9–59.5 % excreted in the urine and 33.4–35.1 % in the feces [23–25].

Lomitapide can decrease the levels of low-density lipoprotein cholesterol (LDL-C) and very low-density lipoprotein cholesterol (VLDL-C) in the plasma of rabbits with hyperlipidemia, as well as reducing atherosclerotic plaques in Apo E knockout mice [26]. In a long-term (126-week) clinical trial, lomitapide treatment, combined with other lipid-lowering therapies, was shown to be highly effective in reducing the level of LDL-C in patients with HoFH. Meanwhile, the tolerability is acceptable without significant changes in glucose, insulin, homeostatic model assessment of estimated insulin resistance or increased high-sensitivity C-reactive protein [27]. Furthermore, in the clinical studies of up to 246 weeks, more than 70 % of patients received the maximum tolerated dose of the drug, and more than half of the patients benefited by keeping their LDL-C at a low level (<1.8 mmol/L) [20,27,28].

However, lomitapide produces a range of dose-dependent side effects including gastrointestinal disturbances, such as diarrhea, nausea, and dyspepsia [27,29], as well as elevated transaminases [20,28] and fat-soluble vitamin deficiency [20,28,30]. Despite these issues, adverse effects are usually manageable and can often be resolved with dose adjustments or temporary discontinuation [20, 27–30]. It is worth noting that the development of hepatic steatosis is an issue, and although more data are needed to support the effect of more than 5 years of medication on hepatic steatosis [27,29], it is still recommended that regular liver function tests and fat-soluble vitamin monitoring are needed during treatment [20,28].

Regarding special circumstances, such as use during pregnancy and lactation, animal studies have shown lomitapide to be potentially harmful to the fetus. The available human data are insufficient to conclude any drug-related risk of major birth defects or adverse fetal outcomes. Due to its potentially serious side effects and lack of extensive human data, caution is advised [31].

Importantly, lomitapide inhibits P-glycoprotein, an energy-dependent efflux pump responsible for reducing intracellular drug accumulation, thereby increasing the risk of multiple pharmacokinetic interactions and toxicity of co-administered drugs [32,33]. Considering the metabolism and pharmacology of lomitapide, the risks of lomitapide co-administered with certain drugs need to be carefully evaluated.

As lomitapide is metabolized by CYP3A4 enzymes, co-administration of strong or moderate CYP3A4 inhibitors (e.g., fluconazole) significantly increases the concentration of lomitapide in blood, which may result in serious adverse reactions. In addition, co-administration of lomitapide with other drugs that are metabolized by CYP3A4 enzymes (e.g., atorvastatin) may interfere with their metabolism and increase the concentrations of these drugs, which may increase the risk of adverse reactions. Close monitoring the international normalized ratio (INR) is required with concomitant use of warfarin, an oral anticoagulant, as lomitapide may result in an elevated INR [31].

In conclusion, lomitapide, characterized by its manageable side effects and significant reduction in LDL-C levels, is highlighted by long-term clinical experience and continuous post-marketing surveillance, which is consistent with the desirable attributes of the drug to be repurposed for the treatment of other diseases.

2.2. Utilization and potential applications of lomitapide

Lomitapide has been used primarily as a lipid-lowering drug in patients with HoFH, reducing the risk of cardiovascular events, such as myocardial infarction and stroke [24]. Since its approval, other applications of lomitapide have been investigated. Zheng et al.

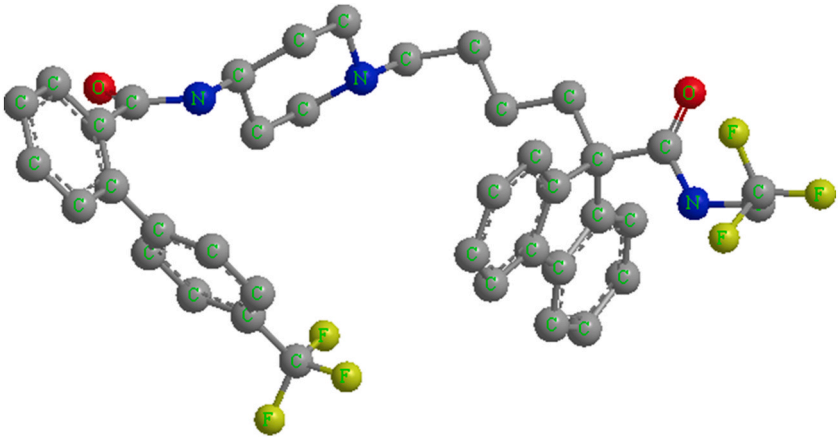

Fig. 1. Structure of lomitapide. Compound ID: 9853053; Molecular Formula: C39H37F6N3O2; Molecular Weight: 693.7 [g/mol] [22].

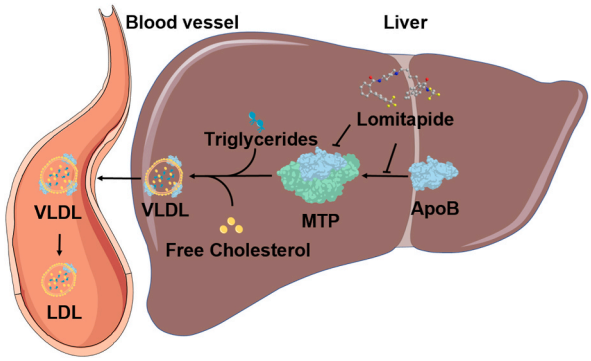

Fig. 2. The lipid-lowering molecular mechanism of lomitapide. Abbreviation: Apo B-apolipoprotein B, MTTP-microsomal triglyceride transfer protein, VLDL-very low-density lipoprotein, LDL-low-density lipoprotein.

found that lomitapide increased patients' survival after middle cerebral artery occlusion, and reduced the neuronal tissue loss through promoting neuronal autophagy and inhibiting microglial migration, resulting in improved neurological function, suggesting repositioning lomitapide for the treatment of stroke [34]. For searching new anti-bacterial agents against multidrug-resistant Gram-positive bacterial infections, Zhang et al. reported that lomitapide displayed broad anti-microbial activities against Gram-positive bacteria, which may be related to cell wall destruction and the inhibition of surface proteins [35]. In addition, an anti-malarial activity of lomitapide was also revealed by inhibition of β-hematin formation and parasite growth [36]. To accelerate the development of COVID-19 treatment, the repurposing of food and drug administration (FDA)-approved drugs against COVID-19 was conducted, applying a new computational protocol against three severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) targets, including protease, papain-like protease and spike protein [37]. With encouraging results of binding between lomitapide and spike protein [37], Olotu et al. observed that allosteric binding of lomitapide perturbed the prefusion spike protein conformation, resulting in displacement of human angiotensin-converting enzyme 2 (hACE2) from the spike protein receptor-binding domain [38].

Lomitapide is supported by *in vitro* and *in vivo* preclinical experiments as a potential anti-tumor agent (Table 1). Lomitapide significantly inhibited the viability of CRC cell lines (HCT116, HT29), with no observed side effects of lomitapide, and normal human colonic mucosal epithelial cell (NCM460) viability was not affected [17]. In addition, Lee et al. utilized a high-throughput (HTP) cancer cell viability assay based on an adenosine triphosphate (ATP) assay to evaluate the effect of lomitapide on the viability of 22 other cell lines (Melanoma, Leukemia, Colon Cancer, Glioblastoma, Lung Cancer, Ovarian Cancer, Breast Cancer, MM, Prostate Cancer, Pancreatic Cancer, Sarcoma, Gastric Cancer, Endometrial Cancer, Lymphoma, Renal Cancer, Neuroblastoma, Esophageal Cancer, Myeloid Leukemia, Bladder Cancer, Liver Cancer, Cervical Cancer, and Thyroid Cancer) with reduced viability of all cancer cells with 1.5–5 μM as half maximal inhibitory concentration (IC50) [39]. The lower IC50 suggests greater sensitivity and selectivity of lomitapide, however, it is unknown whether other forms of necrosis or toxicity alterations occur in cells treated with effective concentrations of the drug.

Similarly, *in vivo* experiments have revealed the therapeutic effects of lomitapide in CRC, where the drug significantly inhibited tumor growth. Tumor mass and volume were significantly reduced after lomitapide treatment compared with control group [17,39]. In terms of safety, no significant drug toxicity of lomitapide was observed in a mouse model based on transplantation of human-derived CRC, and lomitapide treatment did not affect the body weight of mice after treatment with a safe and effective dose (20 mg/kg) [17]. It

Table 1
Anti-tumor effects and mode of action of lomitapide in various types of malignancies.

Mechanism	Malignancy types	Mode of action	References
In vivo			
Syngeneic			
Regulation of immune functions	CRC	Tumor growth↓, antitumor response by $CD8^+$ T lymphocyte infiltration↑	Lee et al., 2022 [39]
Regulation of immune functions	Melanoma	Tumor growth↓, antitumor response by $CD8^+$ T lymphocyte infiltration↑	
Xenograft			
Autophagy	CRC	Tumor growth↓,	Lee et al., 2022 [39]
Autophagy	CRC	Tumor growth↓, *p*-AMPK↑, LC3 I/II↑	Zuo et al., 2021 [17]
Apoptosis	CRC	Tumor growth↓, apoptosis↑	
In vitro			
Autophagy	CRC	Tumor growth↓, apoptosis↑, LC3-II↑, P-ULK1↑	Lee et al., 2022 [39]
Autophagy	CRC	mTORC1↓, Tumor growth↓, autophagy↑, P– S6K1↓, P–S6↓, P-4E-BP1↓	
Autophagy	Breast cancer	Tumor growth↓, P– S6K1↓, P–S6↓, LC3-II↑	
Autophagy	Melanoma	Tumor growth↓, P– S6K1↓, P–S6↓, LC3-II↑,	
Autophagy	Gastric carcinoma	Tumor growth↓, P– S6K1↓, P–S6↓, LC3-II↑,	
Autophagy	CRC	PP2A↓, *p*-AMPK↑, Tumor growth↓, autophagy↑, LC3 I/II↑, p62↓, beclin 1↑, Vps34↑, Atg14↑	Zuo et al., 2021 [17]
Autophagy	CRC	Mitochondrial destruction, Proportion of tubular mitochondria↑, ATP↓, ROS↑, *p*-AMPK↑, *p*-ACC↑	
Apoptosis	CRC	Apoptosis↑, cleaved PARP↑, cleaved caspase 3↑	
Inhibition of tumor proliferation	Lung cancer	Tumor growth↓	
Inhibition of tumor proliferation	Liver cancer	Tumor growth↓	
Inhibition of tumor proliferation	Esophageal cancer	Tumor growth↓	
Apoptosis	MM	Tumor growth↓, disruption of lipid raft microdomains, apoptosis↑, cleaved PARP↑, CD38↓, BTK↓	Saeed et al., 2022 [178]
Cell Cycle Arrest	MM	G0/G1 cell cycle arrest, *TP53*↑, *c-MYC*↑	

Abbreviation: CRC-Colorectal Cancer; MM-Multiple Myeloma.

should also be emphasized that xenotransplantation models involve the transplantation of human tumor cells or tissues into immunodeficient mice, and therefore allow direct assessment of human tumor cell behavior *in vivo*, mimicking the microenvironment of human tumors to a certain extent. Although it is suitable for the screening of new drugs and assessment of anti-tumor effects, the limitation is significant with the insufficient immune response to tumors. Correspondingly, the homotransplantation model uses tumor cells and hosts within the same species. Thus, compared to the former, the growth rate and microenvironment of the homografted tumors more closely resemble those of naturally occurred tumors, while the host retains an intact immune system, making it more suitable for studying the tumor immune response. In mouse CRC and melanoma syngeneic tumor transplantation models, lomitapide treatment was similarly unaffected by body weight in mice and no toxic pathological changes were observed in the liver, kidney or lung [39]. However, it is not known what form of death occurs in cells treated with the drug, such as programmed apoptosis or pathological necrosis, and if necrosis occurs, whether it reaches very high levels of cytotoxicity.

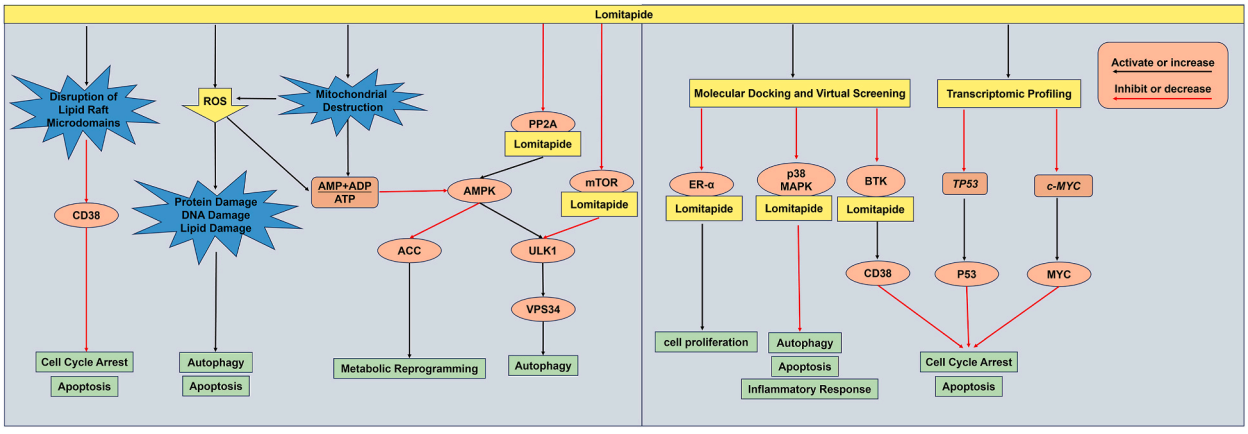

Fig. 3. The molecular mechanism of lomitapide suppressing malignancies.

The use of lomitapide in the treatment of malignant tumors depends not only on its inhibition of tumor growth, but also on the tolerance of normal tissues to it (Fig. 3). Although FDA-approved drugs are usually considered relatively safe, drug toxicity testing during the development of new drugs is still necessary. Therefore, in the future, a series of *in vivo* and *in vitro* experiments need to be carried out to jointly validate the safety of the drug and expand it to more malignant tumors, and only those compounds that show convincing safety and tolerability will be considered further.

3. Underlying molecular mechanisms of the anti-tumor effects of lomitapide

3.1. Potential direct binding to estrogen receptor alpha by lomitapide

As the estrogen receptor (ER)-positive subtype comprises the majority of breast cancers, anti-estrogens and aromatase inhibitors are used in clinic to improve overall survival, but half of them fail [40]. Among the different types of ERs, estrogen receptor alpha (ERα) is expressed in less than 10 % of normal breast epithelial cells, but increases in appropriate 50%–80 % breast cancer patients [41], and has been used as a therapeutic target for breast cancer because of its important role in determining the sensitivity of breast cancer cells to chemotherapeutic agents [42]. In the field of drug discovery, techniques such as molecular docking and virtual screening (VS) have become valuable additions to time-consuming and costly HTP screening experiments [43]. The ability of computational screening libraries of compounds for similarity to known inhibitors (ligand-based) or complementarity to the target structure has been validated [44,45]. Notably, numerous clinical drugs have been identified or optimized with the assistance of computational approaches, such as imatinib [46], zanamivir [47], nelfinavir [48], and erlotinib [49].

To identify novel ERα inhibitory ligands, TilakVijay et al. screened FDA-approved drug molecules by docking pyrazole, bipyrazole, thiazole, thiadiazole and scaffold analogs, revealing that lomitapide showed higher binding affinity for ERα than tamoxifen, which is a clinically used endocrine therapeutic drug targeting ER-positive breast cancer [50]. It was found that the binding of lomitapide to ERα exhibited van der Waals interactions. Thus, ERα may be a key 'bridge' between lomitapide and breast cancer.

Discovery of lomitapide by VS provides new options for personalized breast cancer treatment and may improve the therapeutic efficacy of existing drugs, especially for those patients who perform resistance to tamoxifen endocrine therapy. Importantly, virtual docking initially obtained information on the type of interaction, affinity, selectivity, receptor conformation change, and site of action of lomitapide and ERα, which could help understand the effect of lomitapide on ERα expression and/or activity and the mechanism of interaction between them. Unfortunately, although VS is a powerful tool, there is a lack of relevant *in vitro* and *in vivo* experimental validation to ensure the actual effectiveness and selectivity of lomitapide in the treatment of breast cancer patients. Meanwhile, the study failed to delve into the specific mechanisms by which lomitapide affects ERα, including how it influences downstream signaling pathways and cellular behaviors, such as inhibiting proliferation, invasion and metastasis, or reversing drug resistance in breast cancer. Similarly, this study fails to mention the assessment of potential toxicity and side effects of lomitapide, which is crucial for drug suitability development and clinical application.

3.2. Direct binding to mammalian target of rapamycin by lomitapide

3.2.1. The mTOR signaling pathway in malignancies

The mammalian target of rapamycin (mTOR) is present in all eukaryotic cells [51–55]. It is well known that mTOR plays a key role in the regulation of cell growth, proliferation, motility, autophagy, and metabolism through two distinct complexes (mTORC1 and mTORC2) [56–59]. Both share components such as mammalian lethal with SEC13 protein 8 (mLST8) and DEP domain containing mTOR-interacting protein (DEPTOR) [60,61] but mTORC1 uniquely contains regulatory associated protein of MTOR (Raptor) and proline-rich AKT substrate 40 kDa (PRAS40), whereas mTORC2 contains rapamycin-insensitive companion of mTOR (Rictor), mammalian stress-activated protein kinase interacting protein 1 (mSin1), and protein observed with rictor (Protor) [62–67]. Interestingly, mTORC1 is therefore sensitive to rapamycin treatment, whereas mTORC2 is not [64]. Abnormal activity in mTOR signaling has been associated with oncogenicity and progression of a variety of malignant tumors [68–70]. In prostate intraepithelial neoplasia, inhibition of mTOR activity suppresses the phosphoinositide 3-kinases (PI3K) signaling pathway, while in phosphatase and tensin homolog (PTEN)-deficient cancers, the PI3K signaling pathway can be inhibited by blocking apoptosis and hypoxia-inducible factor 1-alpha (HIF1-α)-dependent pathways [71,72].

Ras homolog enriched in brain (Rheb) is a direct activator of mTOR, and Rheb overexpression promotes oncogenesis in skin epithelial carcinogenesis. These molecular alterations contribute to the promotion of multistage epithelial tumorigenesis, angiogenesis, cytokine production, and stromal-epithelial crosstalk, thereby inducing tumorigenesis and progression [73]. Therefore mTOR inhibitors are considered a promising therapeutic strategy for malignant tumors [74]. The mTOR inhibitor rapamycin has been used in the clinical treatment of a variety of cancers [75,76]. Currently, eight orally effective mTOR inhibitors are undergoing clinical trials (www.icoa.fr/pkidb/).

3.2.2. Binding to mTORC1

Currently, although rapamycin is still a promising anti-tumor agent [77–79], its derivatives mainly act on the mTORC1 isoform, and mTORC2 can reactivate mTOR signaling through other negative feedback pathways, resulting in the development of resistance to mTOR inhibitors through increasing expression of eukaryotic translation initiation factor [77,80]. The increased resistance to mTOR inhibitors limits the therapeutic use of rapamycin derivatives for malignant tumors [78,81].

To investigate the potential novel application of 'old drugs' in a cost-effective way, Lee et al. used a structure-based VS approach on

over 3000 FDA-approved drugs with mTOR druggable potential [39]. Interestingly, although lomitapide was originally not approved for cancer treatment, its specific binding to the ATP-binding catalytic core of mTORC1, including residues H2189, D2190, L2192, Q2194, D2195, D2338, and D2357, evoked further investigation of its anti-tumor activities. The reduced thermal stability of the recombinant mTOR kinase domain indicates that lomitapide selectively binds to the kinase domain of mTOR, disrupting the interaction between the kinase domain and its ligands and leading to a decrease in the thermal stability of the kinase domain [39]. Lomitapide inhibits mTOR activity by binding to the catalytic region of mTOR protein kinase in a manner competitive with ATP, which is different from the binding site of rapamycin-like mTOR inhibitors, targeting the FRB domain [39]. In a CRC animal model, lomitapide nearly completely eliminated the phosphorylation of eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1) and inhibited the viability of cancer cells *in vitro* and *in vivo*, while the anti-tumor effects of other mTOR inhibitors were reduced by eukaryotic translation initiation factor 4E (eIF4E) overexpression [39], supporting the potential advantages of lomitapide as an mTOR inhibitor for the treatment of malignant tumors.

3.3. Activation of the AMPK signaling pathway by lomitapide

3.3.1. AMPK signaling in Malignancy

The AMPK signaling pathway is involved in the control of energy utilization through inhibition of anabolism and stimulation of catabolism, including the metabolism of lipid, glucose and protein [82–85], which is a key factor to ensure energy homeostasis and cell survival in times of energy scarcity [86].

The inhibition of anabolism by AMPK can be achieved through transcription-dependent and transcript-independent pathways [85,86]. AMPK inhibits lipid and sterol synthesis through inactivating the regulatory enzymes in a rate-limiting step of both fatty acid and cholesterol biosynthesis, acetyl-CoA carboxylase (ACC), as well as suppressing the phosphorylation of β-reductase [87,88]. In addition, AMPK regulates biological metabolic processes mainly through mTOR to reduce the consumption of ATP during protein translation and cell growth [89]. Usually, under energy-deficient conditions, the activity of AMPK is increased, whereas mTOR is inactive, and increased AMPK activity could inhibit mTOR signaling pathway [90]. Further, the inhibition of mTOR activity reduces protein synthesis and induces the slowdown of cell growth [91,92]. However, under nutrient-sufficient conditions, mTOR inhibits AMPK activity, which can be considered as a more refined regulation of metabolism by organisms, reflecting the inseparable and close relationship between mTOR and AMPK [93].

To increase energy storage, AMPK stimulates the breakdown of macromolecules to generate ATP, including the utilization of glucose, mobilization of stored lipids and autophagy-induced degradation of macromolecules in yeast and mammalian cells [94–96]. During autophagy, AMPK phosphorylates proteins are involved in glucose transport, which increases plasma membrane localization of glucose transporter type 1/4 (GLUT1/4) and facilitates the uptake of glucose into cells [97,98]. In addition, AMPK also increases the utilization of cellular stored lipids through activating lipases and stimulating the release of fatty acids [99]. The released free fatty acids will be transported to mitochondria by carnitine palmitoyltransferase 1 (CPT1), which can be inhibited by the products of ACC [100–102].

3.3.2. Activation of AMPK to block lipid metabolism by lomitapide

Recently, Zou et al. conducted a screening of 1056 FDA-approved drugs from a small-molecule library with the aim of repurposing them for anti-tumor treatment. Interestingly, lomitapide was found to exhibit anti-tumor properties *in vitro* and *in vivo*, through stimulating mitochondrial dysfunction-mediated AMPK activation [17]. Protein phosphatase 2A (PP2A), a highly conserved and ubiquitous Ser/Thr phosphatase in eukaryotes, is the direct target of lomitapide in CRC cells [17]. AMPK is negatively regulated by PP2A, which mediates high nutrient-induced AMPK inhibition by dephosphorylating AMPKα and interfering with the interaction of the α2 and γ1 subunits of AMPK [103,104]. Not surprisingly, in PP2A-deficient CRC cells, the anti-tumor bioactivity of lomitapide was attenuated accordingly, indicating that the anti-tumor effect of lomitapide occurs in a PP2A-dependent manner, at least partially [17].

Lomitapide interferes with mitochondrial dynamics and increases the levels of reactive oxygen species (ROS), which in turn activates the AMPK signaling pathway [105–107]. Importantly, the activities of AMPK are closely related to the ATP/adenosine diphosphate (ADP) ratio, which is regulated by a variety of physiological conditions, including mitochondrial inhibition, nutritional starvation, and exercise [108,109]. Disruption of mitochondrial network structure, reduction in ATP levels and increases in ROS levels were found in lomitapide-treated CRC cells (HCT116 and HT29), corresponding to an upregulation of AMPK phosphorylation, which supports that the regulation of AMPK by lomitapide occurs through mitochondrial signaling.

In lomitapide-treated CRC cells, the increased AMPK activity phosphorylates and inhibits the activity of ACC, preventing the transport of fatty acids and blocking the energy supply of CRC cells, resulting in an inhibitory effect on the proliferation of cancer cells [17]. The interference of lipid metabolism by lomitapide may be the main mechanism by which lomitapide inhibits cancers.

3.4. Other factors involved in the effects of lomitapide on cancers

3.4.1. The P38 MAPK signaling pathway

P38 MAPK belongs to the MAPK family, an important family of intracellular signal transducers involved in the regulation of various intracellular responses, such as inflammation, cell cycle regulation, cell death, development, differentiation, senescence, and tumorigenesis [110]. Based on its structure, p38 can be divided into four isoforms, those being p38α, p38β, p38γ and p38δ [111]. Among them, p38α is the most comprehensively investigated, and is mainly associated with the inflammatory response [112,113].

When tumor cells are subjected to extracellular stimuli, such as inflammation, cytokines and chemotherapeutic drugs, p38

pathways are activated to exert pro-apoptotic effects and inhibit tumor growth by phosphorylating p53, inducing the translocation of Bax, participating in Fas/FasL-induced apoptosis and enhancing *c-MYC* and *TNF-α* expression [114,115]. In glioblastoma, p38 activation can be attenuated by the small guanosine triphosphatase (GTPase) RND2 through reducing p38 phosphorylation, to inhibit autophagy and apoptosis of glioblastoma cells [116].

In another drug repositioning study, based on computerized virtual molecular docking and molecular dynamics simulations, Suriya et al. verified that lomitapide impedes the anti-tumor function of p38 by binding to the metastable regulatory site of p38 [117,118]. There is no structural overlap between the lomitapide- and ATP-binding sites on p38. The former is spatially distinct by approximately 60° from the ATP-binding site on p38 [119]. The conserved amino acid motif (Asp168-Phe169-Gly170) DFG for the lomitapide-binding site in p38 is allosteric between DFG-in and DFG-out conformations, revealing the potential binding ability of lomitapide with an alternative binding site on p38 [120]. The induced autophagy and apoptosis in CRC and multiple myeloma (MM) cells by lomitapide are indicative of the anti-tumor activity of lomitapide. However, the role of MAPK and its role under lomitapide treatment needs to be verified by further experiments [17,39,121].

3.4.2. Upstream regulators of mTORC1

As the main anti-tumor target of lomitapide, the expression and activity of mTORC1 is regulated by different factors, including growth factors, stress, energy status, oxygenation and amino acids. The tuberous sclerosis complex (TSC) plays a crucial role in inhibiting mTORC1 activities by interacting with and stabilizing the GTPase-activating protein, resulting in the conversion of small GTPase Rheb into an inactive state [122,123]. Activation of mTORC1 occurs primarily through PI3K/AKT signaling pathway, the downstream of growth factors, which phosphorylates and inactivates tuberous sclerosis complex 2 (TSC2) [124–126]. In contrast, the phosphatase PTEN, a tumor suppressor, counteracts the pathway by dephosphorylating PI3K substrates, exerting an inhibitory effect on mTOR [127]. However, the total and phosphorylated protein levels of mTOR upstream factors, such as AKT and PTEN, are not affected by lomitapide treatment [39]. Similarly, knockdown of TSC2 failed to interfere with the inhibitory effect of lomitapide on mTORC1 [91].

As mentioned above, the energy status also regulates mTORC1 through multiple mechanisms [128,129]. Among them, AMPK can directly inhibit mTORC1 activities via phosphorylating Raptor in response to energy depletion [92]. On the other hand, AMPK can phosphorylate and activate TSC2, which indirectly reduces the activation of mTORC1 [91,92,130].

4. The diverse anti-tumor effects of lomitapide

4.1. Disruption of lipid rafts

Lipid rafts are microstructural domains present in a variety of membrane structures consisting of cholesterol, saturated phospholipids, and sphingolipids, and containing a variety of signaling and transport proteins [131]. The composition of lipid rafts in the membrane is highly varied in tumor cells, and is crucial for proliferative signaling, due to processes such as recruiting epidermal growth factor receptor (EGFR) to the rafts [132]. Not surprisingly, lipid raft disruption by the alkyl phospholipid edelfosine displaces all AKT and mTOR from rafts, causing the inactivation of AKT signaling, resulting in apoptosis [133].

CD38, a glycoprotein highly enriched in and considered a biomarker for lipid rafts, and catalyzes the synthesis and degradation of cyclic adenosine diphosphate ribose [134,135]. Inhibition of CD38, which suppresses proliferation and promotes apoptosis of tumor cells, is an effective strategy against MM [136]. As a regulator of CD38, non-receptor bruton's tyrosine kinase (BTK) plays decisive roles in the development, differentiation and proliferation of B-lineage cells [137]. Saeed et al. screened 1230 FDA-approved drugs for targeting BTK, and validated 10 potential components, including lomitapide [121]. In a proliferation assay, more than 80 % of MM cells entered into late apoptosis following treatment with different concentrations of lomitapide. Lomitapide reduced levels of cholesterol, which is highly enriched in lipid raft microregions, leading to the disruption of membrane lipid rafts, and inhibition of adhesion and migration of cancer cells [121]. The disruption of lipid rafts triggers apoptosis through recruitment and aggregation of death receptors [138–140]. To uncover the potential signaling pathways involved in lomitapide-treated MM cells, gene expression profiles were conducted, and showed that both CD38 and its regulator BTK were downregulated, as well as the genes involved in DNA damage, cell death, cell cycle, lipid metabolism, oxidative phosphorylation, and mitochondrial dysfunction [121].

4.2. Inhibition of cellular proliferation

Metabolic reprogramming of tumor cells is an important sign of tumorigenesis, which is characterized by increased intracellular activities, such as protein synthesis, lipid synthesis, carbohydrate metabolism and mitochondrial biosynthesis [141]. It is well known that mTORC1 is a key regulator of energy metabolism [86]. During protein synthesis, mTOR phosphorylates and activates downstream kinases to initiate mRNA translation [142–144]. To investigate the effects of lomitapide on mTOR downstream targets, Lee et al. examined total protein and phosphorylated protein levels, finding that only mTORC1 and its substrates were decreased following lomitapide treatment, while no significant change was found in the phosphorylation and activation of AKT by mTORC2 [39], indicating an inhibitory role of lomitapide on the mTORC1 signaling pathway, which in turn suppressed protein biosynthesis.

Lipids are the basic component of the cell membrane, the formation of which is regulated by mTORC1 activity. De novo synthesis of lipid is promoted by mTORC1, through activating the transcription factor, sterol regulatory element binding protein (SREBP), to meet the needs of membrane formation during cell growth [145–147]. On the other hand, mTORC1 also promotes the synthesis of nucleotides required for DNA replication and ribosome synthesis through promoting the expression of activating transcription factor 4

(ATF4), providing carbon units for purine synthesis [148]. The inhibition of cellular proliferation by lomitapide was also found in skin cancer and gastric cancer cell lines, which was also confirmed to be through inhibiting mTORC1 and its downstream factors [39].

4.3. Induction of cellular autophagy

Autophagy is a lysosome-mediated process of protein degradation that removes damaged organelles, denatured proteins and invading pathogens in cells to meet the requirements of organelle renewal and cell metabolism [149]. Based on the capturing of cargoes to be degraded, autophagy can be divided into three major categories, macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) [150]. Among them, macroautophagy is the predominant and well-studied type, and is the autophagy discussed below.

Microtubule-associated protein light chain 3 (LC3) is recognized as the typical biomarker of autophagy, and is present in the membrane of autophagic vesicles [150]. Currently, it is found that autophagy plays opposite roles in different stages of diverse malignances. At early stages, autophagy inhibits the malignant transformation of cells through maintaining stability of the genome, preventing cell damage from chronic tissue damage or inflammation, and reducing the accumulation of harmful substances. However, in the late stage, autophagy enables tumor cells to cope with hypoxia, malnutrition, and even radiocherapy and/or chemotherapy, resulting in the progression of tumors and chemo-radioresistance [151].

It is noteworthy that lomitapide increased the level of LC3-II in CRC cells, indicating increased autophagy in treated malignant cells [17]. Lee et al. showed that lomitapide decreased mTORC1-mediated phosphorylation of S757 on unc-51 like autophagy activating kinase 1 (ULK1) [39]. The extent of autophagy induction in different cellular environments depends on the relative activities of mTORC1 and AMPK. Under nutrient-sufficient conditions, mTORC1 mediates site-specific phosphorylation of ULK1 via Raptor to prevent the formation of the ULK1-Atg13-FIP200 complex, a key autophagy regulatory complex, which can be reversed by rapamycin through dephosphorylating ULK1 [152]. During periods of starvation and cellular stress, AMPK plays a dual role by inhibiting mTORC1 activity while also phosphorylating ULK1 to activate the enzyme. As a result of AMPK's inhibition of mTORC1 activity, ULK1, PP2A, and the protein phosphatase 1D magnesium-dependent, delta isoform (PPM1D) undergo dephosphorylation [153,154]. Then, the activated ULK1 complex is transferred to the isolated membrane of the endoplasmic reticulum, initiating the autophagy process [153,154].

It is reported that the regulation of lysosomal biogenesis by mTORC1 indirectly inhibits autophagy. For example, nuclear translocation and activity of transcription factor EB, a major transcriptional regulator of lysosomal biogenesis and autophagy genes, is prevented by mTORC1 under normal nutrient conditions [155–157], and is also a potential target for lomitapide treatment in malignancies. In CRC, lomitapide inhibits the progression of tumor cells through promoting cellular autophagy through the AMPK-mTOR signaling pathway. In addition, Zuo et al. showed that lomitapide can also induce autophagy in tumor cells through an AMPK-mTOR-independent transduction pathway in which a large accumulation of ROS in tumor cells is induced to interfere with normal mitochondrial function, along with the induced apoptosis [17].

4.4. Induction of cell apoptosis

Induction of apoptosis is one of the important strategies to inhibit the development of malignancies, and involves changes in nuclear morphology, DNA fragmentation and caspase 3 activation [158]. During apoptosis, the nuclear poly ADP-Ribose polymerase (PARP), a post-translational modification enzyme in base excision repair, nucleotide excision repair and single-stranded base repair, is cleaved by caspases, disrupting cellular DNA repair [159]. Following lomitapide treatment, apoptosis was induced in CRC cells in a dose-dependent manner with increased cleaved caspase 3 and PARP. PP2A, an effective therapeutic target in malignancies [160,161], is suppressed in lomitapide-treated CRC cells, achieving anti-tumor effects through disrupting cellular DNA repair, and inducing apoptosis [17]. In MM cells, the increased apoptosis was also induced by lomitapide treatment, and involved dysregulation of p53 gene [121].

However, in another investigation, the induction of caspase 3/7 activity in CRC cells treated with 2.5 μM and 5 μM lomitapide was negligible, indicating that no significant induction of apoptosis had occurred [39]. Potential variations in experimental conditions between the two studies, such as the cell lines of CRC, cell culture conditions, treatment duration, and the purity and quality of lomitapide, may account for the observed differences in apoptosis induction. It is plausible that lomitapide may exhibit efficacy in inducing apoptosis of CRC cells at higher concentrations. Consequently, lower concentrations of lomitapide may not be sufficiently effective in activating caspase 3/7 and inducing apoptosis. Furthermore, lomitapide might impact the survival or proliferation of CRC cells through alternative mechanisms such as cell cycle regulation, cell migration, and cell differentiation, rather than primarily relying on apoptosis. To gain a more comprehensive understanding of the mechanism of lomitapide action on CRC cells, further investigations are warranted. These investigations should encompass a broader range of lomitapide concentrations, exploration of different CRC cell lines, assessment of alternative apoptosis indicators, and the replication of experiments under varying experimental conditions.

4.5. Induction of cell cycle arrest

Control of the cell cycle is the key regulator during cell growth, differentiation, senescence and even cell death, while uncontrolled cycle progression is one of the hallmarks of tumorigenesis [162]. Studies have demonstrated that treatment with lomitapide induces a significant cell cycle arrest at the G0/G1 phase, thereby impeding cell cycle progression in MM cells [121]. Gene expression profiling showed that lomitapide triggers dysregulation of the tumor suppressor gene p53 and the proto-oncogene *c-MYC*. Downregulation of

c-MYC induced cell cycle arrest and impaired the mitogenic response [163], while p53 responded to a variety of cellular stresses, inducing cell cycle arrest and apoptosis, to inhibit malignant transformation [164]. It is worth noting that different tumor cell lines exhibit varying responses to cell cycle arrest. For instance, the CRC cell line HCT-116 does not show significant cell cycle arrest, while the metastatic melanoma cell line UACC62 undergoes apoptosis when arrested in S phase. On the other hand, no significant apoptosis was observed in the SK-Mel-5 and osteosarcoma cell line HT1080 when they arrested at G2/M phase, but their proliferation was inhibited [165]. Exploring the molecular mechanisms underlying these effects, such as the regulation of cell cycle regulators and apoptotic pathways, will offer valuable insights into the therapeutic potential of lomitapide.

It is worth considering that mTOR also assists regulating cell cycle progression and cell proliferation [166]. mTOR and its downstream factors not only regulate cell growth and tumor size, but also are involved in regulating cell cycle progression [167]. However, Lee et al. did not find any change in cell cycle-related genes in CRC treated with lomitapide [39], although activated AMPK and inhibited mTOR was detected [17,39]. The intricate nature of cell cycle regulation, the heterogeneity of cell types, and the interplay between signaling pathways may contribute to the lack of changes in cell cycle-related genes observed in CRC cells treated with lomitapide. Future studies could investigate the impact of these factors and shed light on the mechanisms by which lomitapide regulates the cell cycle.

4.6. *Increased sensitivity to chemotherapy*

As lomitapide shows effective anti-tumor activity in diverse malignancies, combined therapeutic strategies with chemotherapeutic drugs are emerging as promising treatment methods. The role of autophagy in the development of tumors is controversial, either protecting tumor cells from harmful conditions or inducing autophagy-mediated cell death (ACD) [168–171]. Exploring the regulatory mechanisms of autophagic pathway-related molecules in different types of tumor cells could help the development of targeted drugs. As the role of autophagy in tumor development continues to be clarified, new diagnostic and therapeutic targets could provide new ideas for the study of tumor pathogenesis.

Programmed death-1 (PD-1) is an immune-inhibitory receptor expressed in activated T cells, which plays a critical role in induction

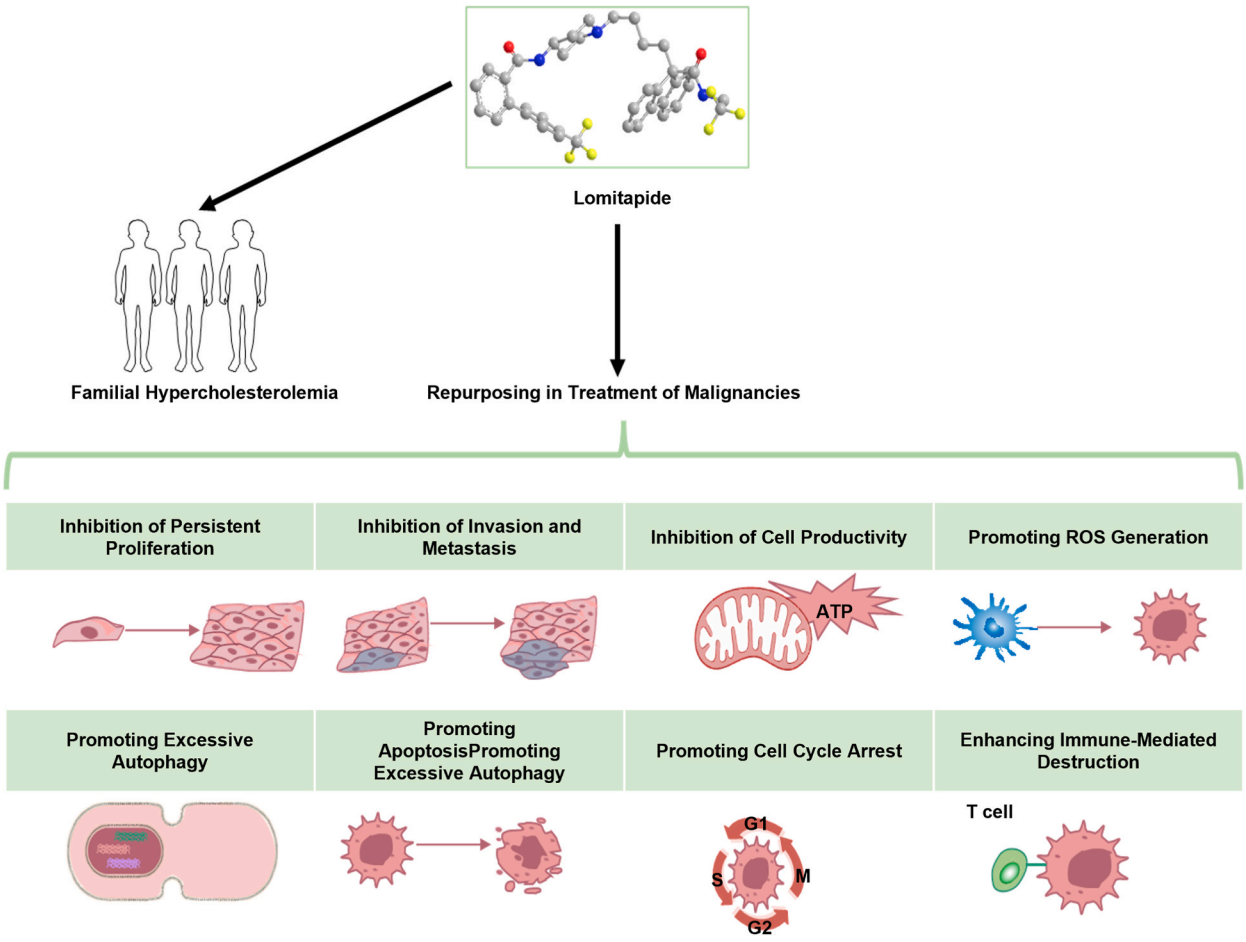

Fig. 4. The graphic abstract of lomitapide in malignancies.

and maintenance of immune tolerance, contributing to the inhibition of effective anti-tumor and anti-microbial immunity [172]. PD-1 blockage is proved to be a prominent anti-tumor immunotherapy [173–175]. However, it is noted no significant improvement during disease progression in the majority of patients who only received anti-PD-1 therapy [173–175]. The improved tumor suppression after co-administration with mTOR inhibitors provides a rationale for the therapeutic strategies of mTOR inhibitors combined with immunosuppressive therapy [176,177]. In mouse colon cancer models, the inhibition of tumor growth was more pronounced in experimental groups treated with lomitapide in combination with anti-PD-1 antibodies than that in single treatment groups [39]. Immunohistochemical staining of tumor tissues revealed that the combination treatment increased the infiltration of $CD8^+$ T cells into tumor. With treatment at a safe concentration of lomitapide at an effective dose of 20 mg/kg, neither significant changes in body weight nor hepatic/renal toxicity was detected, indicating that lomitapide is well tolerated for increasing therapeutic efficacy of other anti-tumor drugs [17,39].

5. Conclusion and perspectives

The anti-tumor efficacy of lomitapide appears promising in preclinical studies, especially for targeting certain molecular subtypes of cancer, and to a lesser extent, for combating drug resistance, as well as synergism with anti-tumor regimens that are already widely used. In conclusion, lomitapide has significant potential as an anti-tumor therapeutic agent in the following areas (Fig. 4).

Molecular docking and VS showed the direct binding of lomitapide to multiple protein receptors, such as BTK, ER-α and p38 MAPK, revealing its potential targets and multiple pharmacological effects, as well as providing new options for the treatment of specific molecular types of cancer. The results of *in vivo* experiments or *in vitro* experiments revealed that lomitapide has the potential to bind or inhibit multiple targets or pathways, such as ER-α, mTOR, AMPK, PP2A, and CD38, and this multi-targeting mechanism of action is of great significance for the treatment of malignant tumors. Meanwhile, preclinical studies of lomitapide with anti-phospholipase D1 (PLD-1) synergistic therapy revealed its clinical application as a novel anti-tumor synergistic drug.

Importantly, the shortcomings and gaps should not be ignored, such as the high-risk situations and side effects of pharmacological interactions with lomitapide still need to be revealed by more *in vivo* experiments and clinical studies. The effect of lomitapide on malignancies includes angiogenesis, invasion and distant metastasis, gene mutation, inflammation-promoted tumors, metabolism, epigenetic reprogramming, tumor microenvironment, antiaging, and immune escape, etc. The mechanisms underlying the effects of lomitapide on these aspects are unclear, and these issues warrant further studies to more fully assess the potential of lomitapide in anti-tumor therapy.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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