The pivotal role of SCD1 in digestive cancers: Bridging lipid metabolic reprogramming and programmed cell death (Review)

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Abstract. Stearoyl-CoA desaturase-1 (SCD1) has emerged as a critical nexus linking lipid metabolic reprogramming to the regulation of cell death. Frequently overexpressed in digestive system malignancies - including gastric, liver and colorectal cancers - SCD1 represents a promising therapeutic target. This review systematically examined how SCD1, through its lipid-modifying functions, governs three key forms of regulated cell death - ferroptosis, autophagy and apoptosis - thereby driving malignant progression and mediating therapy resistance in digestive cancers. Building on this mechanistic framework, the specific contributions of these regulatory pathways to tumor biology and their association with drug resistance were delineated. Current preclinical therapeutic strategies targeting SCD1 were then highlighted, encompassing both monotherapy and combination approaches with ferroptosis inducers, chemotherapeutic agents or targeted drugs. Finally, key challenges and outline future directions for drug development and clinical translation in this rapidly evolving field were discussed.

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1. Introduction

Digestive cancers - including gastric, esophageal, colorectal, liver and pancreatic malignancies - account for a substantial proportion of the global cancer burden. According to the latest Global Burden of Disease data, the incidence and mortality rates of these malignancies rank among the highest of all tumor types (1). Although the global incidence of gastric cancer (GC) has declined in recent decades (2,3), the disease burden associated with colorectal cancer (CRC), liver, pancreatic and esophageal cancers (EC) is projected to increase in the coming years (4-7). Furthermore, a rising incidence of early-onset digestive cancers (occurring in individuals <50 years of age), particularly GC and CRC, has been observed across multiple countries (3,8), with a more pronounced increase among males. More concerning, however, is that the five-year survival rate for certain digestive cancers, such as pancreatic cancer, remains low (9). Despite advances in early diagnosis and comprehensive treatment, drug resistance, metastasis and tumor recurrence persist as core clinical challenges, rendering digestive cancers a major and enduring public health problem.

Metabolic reprogramming is a hallmark of tumorigenesis (10). Unlike normal cells, tumor cells not only rely on aberrant glucose metabolism (e.g., the Warburg effect) but also exhibit heightened dependence on lipid metabolism. Lipid metabolism reprogramming has thus emerged as a hallmark of digestive cancers and a critical driver of their malignant progression. Within this intricate metabolic network, stearoyl-CoA desaturase-1 (SCD1) plays a pivotal role, primarily functioning to maintain cellular lipid homeostasis. Accumulating evidence indicates that SCD1 is highly expressed in various solid tumors (11-13), with particularly pronounced upregulation in digestive cancers (14-18). Elevated SCD1 expression is closely associated with adverse clinicopathological features - including higher TNM stage, larger tumor size and lymph node metastasis - and correlates with poorer overall survival (19-21). Despite considerable heterogeneity in metabolic strategies among digestive tumors, SCD1-driven lipid reprogramming extends beyond conventional energy supply, positioning SCD1 as a core regulator of cell fate determination, including ferroptosis, autophagy and apoptosis (Fig. 1). This SCD1-mediated regulatory network ultimately exerts a profound influence on the malignant progression and therapeutic resistance of digestive cancers.

2. Metabolic cornerstone: SCD1-mediated lipid reprogramming

Enzymatic function of SCD1: Desaturation. SCD is an endoplasmic reticulum (ER)-resident enzyme that catalyzes the rate-limiting step in the biosynthesis of monounsaturated fatty acids (MUFAs) from saturated fatty acids (SFAs). Multiple SCD isoforms exist in mammals: Humans predominantly express two isoforms, SCD1 and SCD5, whereas mice harbor four - SCD1, SCD2, SCD3 and SCD4 (22-24). Among these, SCD1 is widely expressed across various tissues and represents the most extensively studied and functionally dominant subtype to date (24-26).

The primary function of SCD1 is to catalyze the Δ9-desaturation reaction, introducing a cis-double bond at the Δ9 position of saturated fatty acyl-CoAs with chain lengths of 16 and 18 carbons, such as palmitoyl-CoA (C16:0) and stearoyl-CoA (C18:0). This reaction yields the corresponding MUFAs - palmitoleic acid (C16:1 n-7) and oleic acid (OA; C18:1 n-9), respectively. This oxygen-dependent process requires an electron transport chain comprising nicotinamide adenine dinucleotide phosphate (NADPH), cytochrome b5 reductase, cytochrome b5 and SCD1, which coordinately deliver electrons to molecular oxygen. The activated oxygen subsequently abstracts two hydrogen atoms from the fatty acyl substrate, forming a double bond and driving the dehydrogenation of SFAs into MUFAs (24) (Fig. 2).

SCD1: A pivotal hub in fatty acid metabolism. Positioned at a critical downstream node in fatty acid biosynthesis, SCD1 processes SFA intermediates generated by the *de novo* lipogenesis (DNL) pathway - involving ATP-citrate lyase (ACLY), acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN) - and catalyzes their desaturation into MUFAs, which are essential constituents of cellular membrane phospholipids. By modulating the MUFA-to-SFA ratio, SCD1 influences membrane fluidity and integrity, thereby ensuring proper function of membrane-associated proteins and vesicular transport processes.

MUFAs serve as the primary substrates for the synthesis of triacylglycerols (TAGs) and cholesteryl esters (CEs). Compared with SFAs, MUFA-enriched lipids exhibit higher esterification efficiency and superior fluidity, facilitating more effective storage within lipid droplets (LDs). This mechanism not only provides a crucial energy reserve - releasing fatty acids via lipolysis during nutrient deprivation to sustain continuous cell proliferation (27) - but also mitigates lipotoxicity and ER stress triggered by SFA accumulation, thereby protecting cells from apoptosis (28,29). Beyond their structural and energetic roles, MUFAs such as OA can function as signaling molecules or serve as precursors for complex lipid molecules, thereby participating in cellular signal transduction and shaping the tumor microenvironment (TME) (30-32) (Fig. 3).

Context-dependent functions of SCD1: Implications in cancer. The biological functions of SCD1 are highly context-dependent. In metabolic diseases, SCD1 inhibition exerts beneficial effects by ameliorating systemic lipid metabolism, including reductions in body weight and adiposity, as well as improved insulin sensitivity (33-35). During tumorigenesis, however, SCD1 is co-opted by cancer cells and emerges as a critical driver of malignancy. This oncogenic switch is primarily driven by elevated SCD1 expression, which reprograms lipid metabolism by shifting the cellular MUFA/SFA balance. This metabolic adaptation not only provides energy for tumor cell proliferation and substrates for membrane synthesis - thereby alleviating metabolic stress - but also confers protection against lipid peroxidation-induced ferroptosis (29).

These tumor cell-intrinsic effects are well documented across multiple cancer types. For instance, in GC (36), hepatocellular carcinoma (HCC) (37) and CRC (38), SCD1 overexpression exhibits a significant positive correlation with tumor proliferation and invasion. Extending beyond cell-autonomous mechanisms, SCD1 also mediates lipid remodeling - such as LD accumulation - within the TME. This remodeling drives the polarization of tumor-associated macrophages toward an immunosuppressive phenotype and promotes the pro-tumorigenic activation of cancer-associated fibroblasts (CAFs) through signaling pathways including mechanistic target of rapamycin (mTOR) and hypoxia-inducible factor 1α (HIF-1α). These stromal alterations collectively foster a tumor-permissive microenvironment that supports tumor growth, immune evasion and extracellular matrix remodeling (39,40) (Fig. 4).

3. SCD1: The regulator of lipid metabolism

Ferroptosis. Ferroptosis is an iron-dependent form of regulated cell death characterized by lethal accumulation of lipid peroxides, leading to disruption of plasma membrane integrity (41,42). The core regulatory mechanisms of ferroptosis involve intricate interplay among redox reactions, lipid metabolism, and iron homeostasis (43). Four key inhibitory pathways have been identified: the cysteine-glutathione (GSH)-glutathione peroxidase 4 (GPX4) axis, the ferroptosis suppressor protein-coenzyme Q10/vitamin K pathway, the GTP cyclohydrolase 1-tetrahydrobiopterin pathway and the cholesterol biosynthesis pathway (44).

The balance between polyunsaturated fatty acids (PUFAs) and MUFAs critically modulates ferroptosis sensitivity by influencing lipid peroxidation levels (45-47). As the rate-limiting enzyme in MUFA synthesis, SCD1 governs this balance through its enzymatic activity, thereby regulating tumor cell susceptibility to ferroptosis (25,48). At the membrane level, SCD1 modulates the fatty acid composition of phospholipids. PUFAs contain diallylic hydrogen atoms with low bond dissociation energy (~75 kcal/mol), rendering them highly susceptible to free radical attack and prone to initiating lipid peroxidation chain reactions. By contrast, MUFAs synthesized by SCD1 contain monoallylic hydrogen atoms with higher bond dissociation energy (~88 kcal/mol), making them far less susceptible to peroxidation (49). SCD1-generated MUFAs are preferentially incorporated into membrane phospholipids, competitively displacing oxidation-prone PUFAs and thereby inhibiting lipid peroxidation. This mechanism confers robust resistance to ferroptosis inducers [e.g., RAS-selective lethal 3 (RSL3) or erastin] across multiple cancer types, including GC (50), CRC (51), bladder (52) and breast cancers (53). Consistently, exogenous PUFA supplementation (e.g., arachidonic acid or

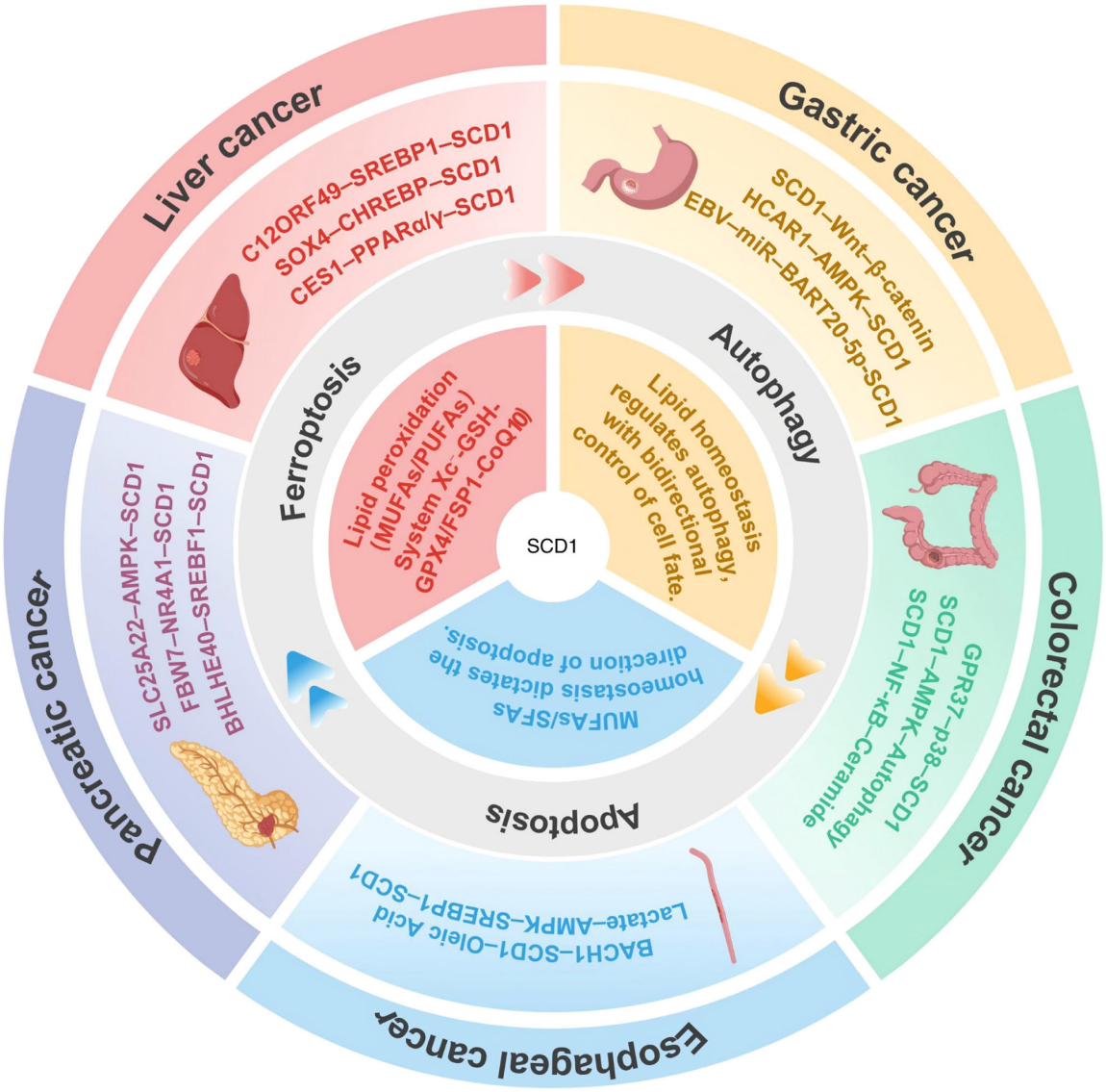

Figure 1. SCD1 integrates oncogenic signals to regulate cell fate and drive cancer progression. In digestive system cancers, SCD1 expression is activated by multiple tumor-specific molecular pathways. The monounsaturated fatty acids generated by SCD1 catalysis modulate key cellular processes, including ferroptosis, autophagy and apoptosis. Through these cell fate-regulating mechanisms, SCD1 functions as a central hub that amplifies pro-tumorigenic signaling and promotes malignant progression. SCD1, stearoyl-CoA desaturase-1; Wnt, Wnt signaling pathway; HCAR1, hydroxycarboxylic acid receptor 1; AMPK, AMP-activated protein kinase; EBV, Epstein-Barr virus; miR, microRNA; BART-20-5p, BamHI-A rightward transcript region 20, 5-prime arm; GPR37, G protein-coupled receptor 37; p38, p38 mitogen-activated protein kinase; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; BACH1, Bric-a-brac, tramtrack, and broad complex and cap 'n' collar homology 1; SREBP1, sterol regulatory element-binding protein 1; SLC25A22, solute carrier family 25 member 22; FBW7, F-box and WD repeat domain-containing 7; NR4A1, nuclear receptor subfamily 4 group A member 1; BHLHE40, basic helix-loop-helix family member e40; C12ORF49, chromosome 12 open reading frame 49; SOX4, SRY-related HMG-box 4; CHREBP, carbohydrate response element binding protein; CES1, carboxylesterase 1; PPAR, peroxisome proliferator-activated receptor; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; System Xc^-, cystine/glutamate antiporter system Xc^-; GSH, glutathione; GPX4, glutathione peroxidase 4; FSP1, ferroptosis suppressor protein 1; CoQ10, coenzyme Q10; SFAs, saturated fatty acids.

adrenic acid) restores ferroptosis sensitivity accompanied by increased lipid peroxidation (46,54).

Beyond modifying membrane lipid substrates, SCD1 indirectly regulates ferroptosis by sustaining the antioxidant defense system. SCD1 enhances redox homeostasis by maintaining key antioxidant components - including CoQ10, GSH and GPX4 activity - thereby diminishing ferroptosis susceptibility. This mechanism has been demonstrated in ovarian (11,55) and triple-negative breast cancers (56,57), where high SCD1 expression facilitates clearance of lipid reactive oxygen species (ROS) and malondialdehyde (MDA), reducing intracellular lipid peroxidation. Conversely, SCD1 inhibition disrupts these antioxidant processes and restores ferroptosis sensitivity (55,56).

Autophagy. Autophagy is a highly conserved lysosome-dependent degradation pathway that maintains cellular homeostasis through the clearance of damaged organelles and misfolded proteins (58). Under stress conditions such as nutrient deprivation or hypoxia, a cascade of autophagy-related (ATG) proteins orchestrates phagophore nucleation, elongation and autophagosome formation, ultimately fusing with lysosomes

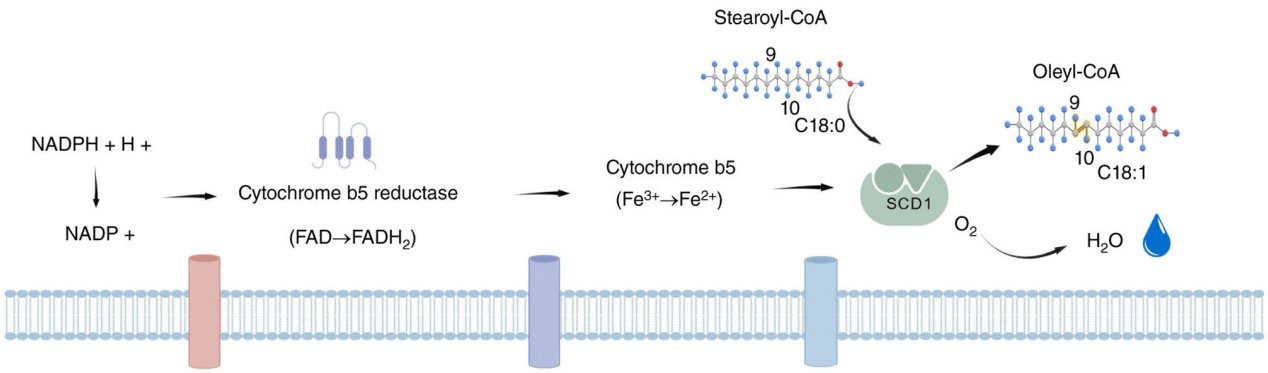

Figure 2. Mechanism of the SCD1 desaturation reaction. The SCD1-catalyzed monounsaturated fatty acid biosynthesis on the endoplasmic reticulum membrane, where saturated stearoyl-CoA (C18:0) is converted to monounsaturated oleoyl-CoA (C18:1 Δ9). NADPH serves as the electron donor, transferring electrons through an electron transport chain comprising cytochrome b5 reductase and cytochrome b5, with O_2 acting as the final electron acceptor to produce H_2O. SCD1, stearoyl-CoA desaturase-1.

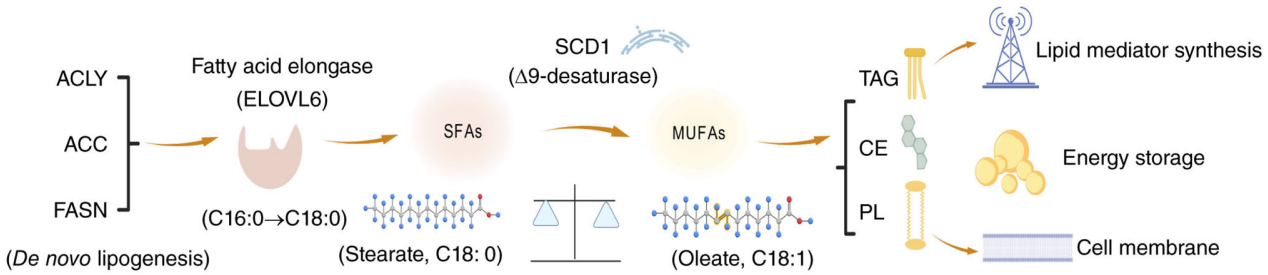

Figure 3. SCD1: A central metabolic and signaling hub. Following *de novo* lipogenesis (ACLY, ACC, FASN) and elongation by ELOVL6, SCD1 converts SFAs to MUFAs. These MUFAs are incorporated into TAGs, CEs and PLs, thereby regulating energy storage, membrane integrity and lipid mediator synthesis. Through these functions, SCD1 modulates membrane fluidity, mitigates lipotoxicity and endoplasmic reticulum stress, and influences signal transduction and tumor microenvironment remodeling. ACLY, ATP-citrate lyase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; ELOVL6, elongation of very long chain fatty acids protein 6; SFAs, saturated fatty acids; SCD1, stearoyl-CoA desaturase 1; MUFAs, monounsaturated fatty acids; TAG, triacylglycerol; CE, cholesteryl ester; PL, phospholipid.

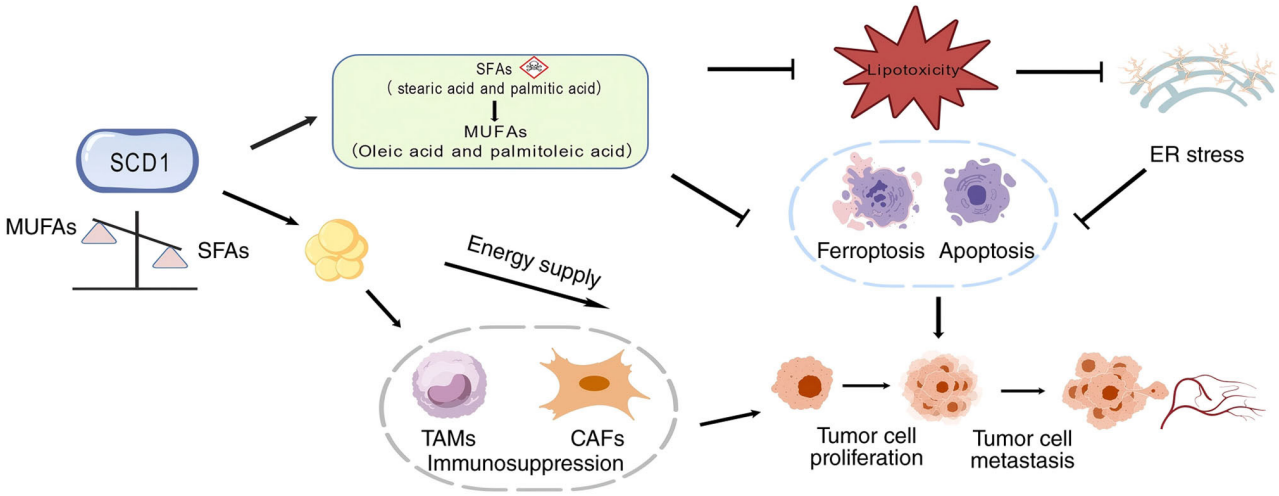

Figure 4. SCD1: A dual-engine mechanism driving tumor progression. By converting SFAs to MUFAs, SCD1 drives tumor progression through dual mechanisms. In tumor cells, this conversion suppresses lipotoxicity and ER stress while inhibiting ferroptosis and apoptosis, thereby enhancing proliferation and metastasis. Within the tumor microenvironment, SCD1-generated lipid droplets drive immunosuppressive TAM polarization and CAF activation. Together, these mechanisms shape a tumor-supportive niche and promote immune evasion. SCD1, stearoyl-CoA desaturase-1; SFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids; ER, endoplasmic reticulum; CAFs, cancer-associated fibroblasts; TAMs, tumor-associated macrophages.

for cargo degradation and material recycling (59-61). This process serves not only as an adaptive survival mechanism but also as a critical quality control system implicated in energy supply, homeostasis maintenance and immune regulation. Consequently, autophagy dysregulation has been closely associated with various diseases, including cancers,

neurodegenerative disorders, and immune and metabolic pathologies (61,62).

Autophagy exerts dual and context-dependent functions in tumor biology. During early tumorigenesis, it acts as a tumor suppressor by maintaining genomic stability through the clearance of damaged organelles and protein aggregates (63,64). Deletion of autophagy-related genes such as *Beclin1* (65,66) or mutations in *Atg5* (67,68) has been shown to promote liver and GC development. Conversely, in advanced stages, tumor cells hijack this protective mechanism to survive under stress and nutrient-deprived conditions (69), facilitating proliferation, migration (70,71), immune evasion (72,73) and chemotherapy resistance (74,75). Notably, the biological outcome of autophagy is determined not simply by its activation or inhibition, but rather by the dynamic regulation of autophagic flux. Current evidence suggests that finely tuning autophagic flux - either by blocking progression to induce cell death (76) or by enhancing flux to accelerate oncogenic protein clearance (77) - can achieve tumor-suppressive effects depending on context.

Alterations in SCD1 expression or activity significantly influence this dual regulation of autophagy, with outcomes similarly contingent on tumor context. In certain malignancies, SCD1 suppresses autophagy to promote tumor progression. For instance, in HCC, elevated SCD1 expression attenuates AMPK-mediated autophagy, whereas SCD1 inhibition restores autophagic activity and facilitates apoptosis (78). Likewise, in non-small cell lung cancer, the small nucleolar RNA SNORD88C drives tumor growth and metastasis by upregulating SCD1 and suppressing autophagy (79). Conversely, in tumors that become reliant on autophagy for survival, SCD1 inhibition-induced autophagy may paradoxically support oncogenicity. In breast cancer, treatment with IC2 - an Icaritin derivative - suppresses SCD1 activity and subsequently activates protective autophagy through the AMPK/mTOR and MAPK signaling pathways, enabling cancer cells to counteract drug-induced lipotoxicity and apoptosis (80). Similarly, in glioblastoma (GBM), SCD1 knockdown triggers autophagy, alleviating lipotoxicity from SFA accumulation and supporting tumor cell survival under serum-deprived conditions (81).

Apoptosis. Apoptosis is a genetically programmed form of cell death that enables the systematic elimination of cells. Its primary function is to remove unnecessary, damaged or potentially harmful cells, a process essential for maintaining tissue homeostasis and normal development (82). Morphologically, apoptosis is characterized by cell shrinkage, chromatin condensation and nuclear fragmentation. Throughout this process, the plasma membrane remains intact, eventually budding outward to enclose cellular contents into apoptotic bodies that are cleared by phagocytes without triggering inflammation (83,84). At the molecular level, apoptosis is governed by two principal pathways. The extrinsic pathway is activated when death receptors bind to their ligands, leading to initiator caspase recruitment. The intrinsic pathway is triggered by intracellular stress signals such as DNA damage or ER stress, which induce mitochondrial outer membrane permeabilization and cytochrome c release. Cytochrome c then forms the apoptosome with apoptotic protease-activating factor 1 (APAF-1), activating caspase-9. Both pathways ultimately converge on effector caspase activation, executing controlled cell dismantling (85).

Dysregulation of apoptosis contributes to diverse diseases. Excessive apoptosis drives tissue degeneration in neurodegenerative disorders such as Alzheimer's disease (86,87), while insufficient apoptosis enables aberrant cell survival and proliferation, facilitating tumor initiation and progression (88). Among the molecular regulators implicated in this process, SCD1 - the rate-limiting enzyme in MUFA synthesis - has emerged as a key modulator of apoptosis, particularly the intrinsic pathway. By maintaining the balance between SFAs and MUFAs, SCD1 preserves the integrity and function of cellular membranes, notably the ER. SCD1 inhibition disrupts this balance, causing SFA accumulation and ER stress, which activates the unfolded protein response (UPR). Although transient UPR promotes survival, persistent ER stress from SCD1 inhibition shifts UPR signaling toward apoptosis via the protein kinase R (PKR)-like endoplasmic reticulum kinase, inositol-requiring enzyme 1 and activating transcription factor 6 pathways, ultimately activating caspases. Thus, by suppressing ER stress-mediated apoptosis, elevated SCD1 expression promotes malignant progression in various cancers, including undifferentiated thyroid cancer (13), acute myeloid leukemia (89) and ovarian cancer (90,91).

The anti-apoptotic function of SCD1 extends beyond ER stress modulation to encompass both direct molecular interactions and broader metabolic crosstalk. At the molecular level, the SCD1-derived lipid PI(18:1/18:1) directly inhibits ER stress-induced apoptosis by stabilizing protein phosphatase 2A (Ppp2ca) (92), revealing a specific effector through which SCD1 promotes survival. At the pathway level, SCD1 inhibition engages additional pro-apoptotic signaling cascades. In CRC cells, MUFA deficiency activates NF-κB signaling, upregulating ceramide synthesis enzymes; ceramide accumulation then induces mitochondrial dysfunction and activates the intrinsic apoptotic cascade (93,94). In HCC, sorafenib-induced energetic stress suppresses SCD1 via the AMPK-mTOR-Sterol regulatory element-binding protein 1 (SREBP1) signaling pathway, and the resulting MUFA reduction exacerbates mitochondrial damage, leading to apoptosis (95). Notably, exogenous supplementation of OA can reverse the apoptosis induced by SCD1 inhibition in both aforementioned models, providing crucial experimental evidence for SCD1-targeted cancer therapy.

4. SCD1 in digestive tumors: Oncogenic mechanisms

GC. SCD1 expression is an independent risk factor for poor prognosis in patients with GC (18). In GC, SCD1 is subject to multilayered regulatory control, which collectively amplifies its pro-tumorigenic effects. At the transcriptional level, the master lipogenic transcription factor SREBP-1c directly binds the SCD1 promoter to upregulate its expression (96). Post-transcriptionally, the circular RNA circTFRC acts as a scaffold, recruiting the RNA-binding protein ELAV-like RNA-binding protein 1 to stabilize SCD1 mRNA (97). At the translational level, the long non-coding (lnc)RNA lncFERO (a ferroptosis regulator) facilitates SCD1 translation by binding the 5' untranslated region (5'UTR) of its mRNA and recruiting heterogeneous nuclear ribonucleoprotein A1 (98). Post-translational stabilization is achieved by the deubiquitinating enzyme ubiquitin-specific protease 7, which directly interacts with the SCD1 protein to remove ubiquitin

tags and prevent proteasomal degradation (99). This multilayered regulatory architecture ensures sustained high SCD1 expression, establishing the molecular basis for its role as a metabolic vulnerability in GC. Notably, SCD1 regulation is context-dependent. In Epstein-Barr virus (EBV)-associated GC, for instance, SCD1 expression is downregulated by the EBV-encoded microRNA (miR)-BART20-5p, which targets the SCD1 3'UTR (100). Consequently, autophagy is activated, and both proliferation and epithelial-mesenchymal transition (EMT) are inhibited, offering a potential explanation for the favorable prognosis observed in this GC subtype (100).

Functionally, SCD1 overexpression drives metabolic reprogramming in GC cells. The lncRNA TENM3-AS1, activated by early growth response 1, promotes lipid synthesis and LD accumulation by upregulating SCD1 (101). Conversely, SCD1 inhibition disrupts endogenous MUFA synthesis, inducing ER stress and apoptosis, which suppresses tumor growth in xenograft models (102). Furthermore, SCD1 inhibition in gastric precancerous cells reduces eicosenoic acid production, leading to energy depletion and activation of the intrinsic apoptotic pathway, thereby selectively eliminating dysplastic cells (103).

SCD1 confers robust resistance to ferroptosis in GC cells through a coordinated network of mechanisms. By catalyzing the synthesis of MUFAs, which are incorporated into membrane phospholipids, SCD1 competitively displaces PUFAs - the primary substrates for lipid peroxidation - thereby reducing ferroptotic cell death. This core metabolic function is reinforced by interactions with key signaling pathways. SCD1 upregulates squalene epoxidase by antagonizing p53-mediated transcriptional repression, promoting cholesterol biosynthesis and activating the mTOR pathway to enhance ferroptosis resistance - a process critical for maintaining GC stem cell stemness (50). Additionally, SCD1 activates the Wnt/β-catenin pathway, leading to upregulation of the ferroptosis inhibitors GPX4 and xCT [solute carrier family 7 member 11 (SLC7A11)] (18,104). Upstream regulators, such as the actin-binding protein tropomyosin 4, further reinforce this network by stabilizing the SCD1 protein without altering its mRNA levels (105). Extending these cell-autonomous mechanisms, SCD1 also acts as a critical molecular hub integrating signals from the TME to modulate ferroptosis. In the GC TME, accumulated lactate activates hydroxycarboxylic acid receptor 1 (HCAR1) on cancer cells, triggering a signaling cascade that promotes ATP production and suppresses AMPK activity. This leads to SREBP1-mediated SCD1 upregulation. The resulting increase in MUFAs suppresses lipid peroxidation, ultimately diminishing the sensitivity of cancer cells to ferroptosis (106).

EC. In EC, SCD1 is subject to multilayered regulation, including direct transcriptional activation by SREBP1 (107) and modulation by ncRNAs such as miR-181a-5p (15), the LINC00514/miR-378a-5p competing endogenous RNA network (108) and peptides derived from KDM4A-AS1 (109). The resulting upregulation of SCD1 drives lipid metabolic reprogramming by catalyzing key fatty acid desaturation reactions, thereby promoting tumor proliferation, therapeutic resistance and metastasis.

A key oncogenic function of SCD1 in EC is to suppress ferroptosis, extending beyond its role in energy metabolism to underlie radiotherapy resistance in esophageal squamous cell carcinoma (ESCC). Ionizing radiation exerts its cytotoxic effects in part by inducing lipid peroxidation (110,111); SCD1 counteracts this process through the synthesis of MUFAs, thereby enhancing cell survival. Pharmacological inhibition of SCD1 has been shown to radiosensitize ESCC cells. Notably, combining the SCD1 inhibitor MF-438 with radiotherapy promotes the release of ATP and high mobility group box 1, thereby enhancing dendritic cell phagocytosis and inducing immunogenic cell death (112). The TME also influences this process. For example, zinc deficiency enhances glycolysis in ESCC, leading to aberrant lactate metabolism and upregulation of HCAR1 and monocarboxylate transporter 1 (MCT1). This suppresses AMPK phosphorylation and subsequently activates SREBP1-mediated SCD1 transcription, reducing ferroptosis sensitivity (113).

The role of SCD1 in EC metastasis is context-dependent. In most cases, SCD1 functions as a pro-metastatic factor by activating the Wnt/β-catenin pathway to induce EMT, thereby enhancing tumor cell migration and invasion (107,114). However, a paradoxical role has emerged from studies on the transcription factor BTB and CNC homology 1 (BACH1): By repressing SCD1, BACH1 reduces MUFA synthesis and exacerbates lipid peroxidation, leading to ferroptosis. While this suppresses the proliferation of primary ESCC cells, the downregulation of SCD1 results in a relative enrichment of OA in the lymph fluid. This establishes an OA concentration gradient between the primary lesion and lymph, which selectively promotes lymphatic metastasis (115).

CRC. In CRC, SCD1 is highly expressed and activated through a multilayered regulatory network that enables tumor cells to resist ferroptosis. This network includes: The tp53-induced glycolysis and apoptosis regulator, which inhibits the AMPK/SCD1 pathway by scavenging ROS (116); transcription factors Nodal (117) and prospero homeobox 1 (118), which upregulate SCD1 expression via the sma- and mad-related protein 2/3 (Smad2/3) pathway and direct transcriptional activation, respectively; and ncRNAs such as LINC01606 (51) and circRHBDD1 (119), which maintain SCD1 protein abundance through competing endogenous RNA mechanisms or by enhancing mRNA stability. Based on this regulatory framework, pharmacological inhibition of SCD1 effectively sensitizes CRC cells to ferroptosis-based therapy. For instance, aspirin downregulates SCD1 by blocking the AKT/mTOR/SREBP-1 pathway and synergizes with ferroptosis inducers, particularly in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit α-mutant CRC (120). Notably, when SCD1 activity is inhibited, cancer cells initiate distinct stress adaptation programs: On one hand, AMPK-mediated protective autophagy is activated to alleviate metabolic stress and maintain survival (121); on the other hand, SCD1 inhibition may trigger mitochondrial dysfunction by initiating *de novo* ceramide synthesis, thereby inducing apoptosis (93).

Beyond its role in ferroptosis resistance, SCD1 promotes CRC invasion and metastasis through multiple lipid metabolism-related mechanisms. Its expression is upregulated by carbohydrate response element binding protein (ChREBP) under high-glucose conditions (38) and can also be directly activated by Nodal via the Smad2/3 pathway (117). Functionally,

SCD1 facilitates CRC metastasis through dual pathways. First, its catalytic products, MUFAs, inhibit phosphatase and tensin homolog, thereby activating the AKT signaling pathway, inducing EMT and enhancing cell invasion (38). Second, SCD1 confers ferroptosis resistance - as detailed above - thereby enhancing tumor cell survival during the metastatic process (117). Additionally, SCD1 regulated by LINC01606 activates the Wnt/β-catenin pathway, upregulates trefoil factor 3 and forms a positive feedback loop that suppresses ferroptosis and maintains cancer stem cell (CSC) stemness (51), further driving CRC invasion and metastasis. Independent of these specific regulatory mechanisms, high SCD1 expression per se is significantly correlated with adverse pathological features, including lymph node metastasis (117,122) and vascular invasion (14), underscoring its pivotal role in CRC malignancy.

The functional role of SCD1 in CRC is context-dependent and exhibits notable plasticity. This dependence manifests at multiple levels. First, in the CAF-enriched microenvironment of CRC peritoneal metastasis, SCD1 downregulation serves as a hallmark of metabolic adaptation, marking a shift from endogenous lipid synthesis to exogenous lipid uptake that enables an invasive phenotype despite low SCD1 expression (123). Second, regarding intestinal homeostasis, studies using intestinal epithelial-specific SCD1 knockout mouse models have demonstrated that SCD1 deficiency results in depleted gut OA, triggering an inflammatory cascade and promoting tumorigenesis; notably, exogenous OA supplementation alleviates these pathological phenotypes, indicating that SCD1 plays a protective role in maintaining intestinal homeostasis (124). Third, in the therapeutic response, the outcome of SCD1 modulation is drug-specific. Under 5-fluorouracil (5-FU) treatment, SCD1 inhibition leads to SFA accumulation, which reduces cell membrane fluidity and may contribute to chemoresistance (125). However, paradoxically, combining the SCD1 inhibitor MF-438 with 5-FU produces a synergistic anti-proliferative effect and reduces the effective 5-FU dose, although the underlying mechanism remains elusive (126). Conversely, under irinotecan treatment, SCD1 overexpression promotes unsaturated fatty acid synthesis, upregulates aldehyde dehydrogenase 1 A1 and reduces ROS levels, thereby maintaining cancer stemness and conferring drug resistance (127).

HCC. SCD1 drives malignant progression in HCC by integrating physical and chemical signals derived from the TME. At the physical level, increased matrix stiffness associated with liver fibrosis or cirrhosis upregulates and stabilizes SCD1 protein expression via the integrin β1/focal adhesion kinase (FAK) signaling pathway (37,128). The MUFAs generated by SCD1, particularly OA, not only enhance plasma membrane fluidity to facilitate HCC cell invasion and migration (37), but also induce the transcription factor CCAAT-enhancer binding protein α (C/EBPα) to upregulate hyaluronan-mediated motility receptor (HMMR). This establishes a positive feedback loop - FAK/SCD1/OA/C/EBPα/HMMR - that continuously amplifies pro-tumorigenic mechanical signals (128), induces EMT and enhances metastatic potential. At the chemical level, aberrant lactate metabolism plays a central role. Lactate activates the PI3K/AKT pathway, upregulating SCD1 and promoting its pH-dependent interaction with peroxisome proliferator-activated receptor α (PPARα), thereby driving fatty acid synthesis and lipid accumulation to support rapid tumor proliferation (129). Following uptake by cancer cells via HCAR1 and MCT1, lactate also enhances ATP generation and suppresses AMPK activity, leading to SREBP1-mediated SCD1 upregulation. Concurrently, lactate downregulates acyl-CoA synthetase long-chain family member 4 (ACSL4), increasing the MUFA/PUFA ratio and reducing lipid peroxidation, thereby conferring ferroptosis resistance and contributing to sorafenib resistance in HCC (130). Additionally, lactate activates the YTH N6-methyladenosine RNA binding protein C1/nuclear enriched abundant transcript 1 epigenetic regulatory mechanism by inducing histone lactylation, further promoting SCD1 transcription (131). Beyond its direct effects on tumor cells, SCD1 contributes to immunosuppression by modulating immune cells within the TME - promoting regulatory T cell and plasma cell enrichment while suppressing natural killer cell activity - thereby facilitating immune evasion (16).

SCD1 serves as a key driver in the transition from non-alcoholic fatty liver disease (NAFLD) or liver fibrosis to HCC, with its expression sustained throughout this pathological continuum (132). During the early compensatory phase, SCD1 upregulation represents an adaptive protective response by hepatocytes to an influx of SFAs. By catalyzing the conversion of SFAs to MUFAs, SCD1 alleviates lipotoxicity, mitigates ER stress and suppresses inflammatory responses. Hepatic SCD1 deletion in mouse models directly induces elevated lipid saturation, triggering inflammation, fibrogenesis and activation of HCC-associated genes (133-135); importantly, these phenotypes are reversible upon OA supplementation (134), indicating that SCD1-mediated MUFA synthesis constitutes a crucial defense mechanism that prevents progression from early liver injury to fibrosis or HCC. However, chronic or excessive compensatory upregulation of SCD1 can drive malignant transformation. In a spontaneous NAFLD-HCC model established via Tmem30a knockout, AKT activation enhances N^6-methyladenosine modification of SCD1 mRNA by upregulating methyltransferase-like 3/14, leading to aberrant stabilization and overexpression of SCD1. This drives uncontrolled *de novo* lipogenesis, inducing severe oxidative stress and ER stress that trigger apoptosis, while persistent tissue damage exacerbates inflammatory responses, DNA damage and compensatory cellular hyperproliferation - ultimately promoting HCC (132). Similarly, in a mouse model bearing activating mutations in hepatic AKT2, SCD1 functions as a core downstream effector; its overexpression exacerbates steatosis and inflammation, accelerating progression from hepatic steatosis to HCC (136). Of note, this function extends beyond hepatocytes: In hepatic fibrosis driven by activation of hepatic stellate cells, SCD1 and the Wnt/β-catenin positive feedback loop it mediates also support the survival and expansion of liver cancer-initiating cells (137).

SCD1 represents a pivotal therapeutic target implicated in treatment resistance in HCC. Frequently overexpressed in HCC tissues (138), elevated SCD1 levels correlate with poor prognosis and are driven by multiple signaling pathways, including SOX4-CHREBP (139) and acyl-CoA thioesterases 9-SREBP1 (140). The MUFAs generated by SCD1 reshape the membrane lipid peroxidation barrier and significantly weaken ferroptosis; this metabolic adaptation is a key contributing

factor to the resistance of HCC cells to tyrosine kinase inhibitors such as sorafenib (141,142). SCD1-derived MUFAs reinforce the chemoresistant phenotype through parallel mechanisms, including mitigation of lipotoxicity (143,144), attenuation of ER stress (145) and maintenance of CSC stemness (146). Given this evidence, combination strategies targeting SCD1 have emerged as a promising approach to overcome drug resistance in HCC. SCD1 expression is elevated in sorafenib-resistant HCC cells and tissues (145,146), and combined inhibition of SCD1 - using agents such as A939572 (94), orlistat (147) or liver X receptor α agonists (144) - effectively restores sensitivity of HCC cells to sorafenib.

Pancreatic cancer. In the pancreatic cancer TME, SCD1 activation can be driven by microenvironmental stresses. On one hand, increased matrix stiffness activates the mechanosensitive ion channel Piezo1, triggering Ca^{2+} influx and initiating the PI3K/AKT signaling pathway. This pathway not only upregulates SCD1 expression but also induces the expression of ACLY, ACC and FASN, promoting lipid accumulation to meet the demands of rapid proliferation. More importantly, this cascade also upregulates ATP binding cassette subfamily C members 1, 3 and 10, enhances drug efflux function and reduces the intracellular gemcitabine concentration, thereby directly leading to chemoresistance (148). On the other hand, metabolic stresses such as nutrient deprivation or hypoxia regulate SCD1 through distinct pathways: Nutrient deprivation upregulates SCD1 transcription via the mTOR-SREBP1 pathway, enhances ferroptosis resistance and helps cells survive under metabolic stress (149); whereas hypoxia upregulates SCD1 through the HIF-1α/PPAR signaling pathway, promotes PUFA synthesis and accumulation of TAGs and CEs, thereby driving pancreatic cancer cell invasion and metastasis (150). Beyond its cell-autonomous functions, SCD1 mediates intercellular communication within the TME. CAFs utilize high SCD1 expression to remodel lipid metabolism, increasing unsaturated fatty acid levels in the microenvironment and providing metabolic protection that enhances pancreatic ductal adenocarcinoma (PDAC) cell resistance to gemcitabine and cisplatin (151). Similarly, SCD1 derived from Schwann cells promotes PDAC cell proliferation and migration in a paracrine manner, potentially through mechanisms involving the p53 signaling pathway (152).

SCD1 provides a critical survival advantage to pancreatic cancer cells by coordinately suppressing both ferroptosis and apoptosis through distinct mechanisms. First, SCD1 confers ferroptosis resistance by modulating membrane phospholipid composition. SLC25A22 maintains high SCD1 expression by inhibiting AMPK phosphorylation, thereby suppressing ferroptosis (153); conversely, ten-eleven translocation 3 inhibition upregulates GATA binding protein 6, leading to SCD1 downregulation and enhanced lipid peroxidation, which increases cellular sensitivity to the ferroptosis inducer Erastin (154). Second, SCD1 suppresses apoptosis by maintaining lipid homeostasis. SCD1 inhibition leads to SFA accumulation, triggering ER stress and the UPR, which activates pro-apoptotic factors such as C/EBP homologous protein; this process can be reversed by exogenous OA supplementation (155). Notably, SCD1 functions as a convergent node in the regulatory networks of apoptosis and ferroptosis. Its expression is suppressed by the F-box and WD repeat domain-containing 7/nuclear receptor subfamily 4 group A member 1 signaling pathway (156) and is directly transcriptionally activated by the oncogene zinc finger protein 488 (157); additionally, dihydrotanshinone I, a natural compound derived from Traditional Chinese Medicine, directly inhibits SCD1 activity (158). Consequently, targeting SCD1 or its upstream regulators concurrently impacts both apoptotic and ferroptotic cell death, establishing SCD1 as a pivotal therapeutic target in pancreatic cancer.

In addition to upregulating drug efflux transporters (148), SCD1-mediated MUFA-dependent ferroptosis tolerance constitutes a critical intracellular mechanism underlying acquired chemotherapy resistance in pancreatic cancer cells, particularly under gemcitabine treatment stress. A small-molecule inhibitor of CD147 disrupts intracellular lactate metabolism, activates AMPK and inhibits the SREBP1/SCD1 pathway while epigenetically upregulating ACSL4. This orchestrated mechanism disrupts MUFA and PUFA homeostasis, inducing ferroptosis in PDAC cells and potentiating the antitumor efficacy of gemcitabine (159). Similarly, knockdown of the nuclear receptor coactivator NCOA6 enhances lipid peroxidation by downregulating SCD1 and upregulating ACSL4, elevating MDA levels and altering the expression of drug resistance-associated genes (upregulation of human equilibrative nucleoside transporter and deoxycytidine kinase, downregulation of ribonucleotide reductase catalytic subunit M1), collectively enhancing gemcitabine sensitivity in pancreatic cancer cells (160). Furthermore, the glutamine transporter SLC38A5 sustains activation of the mTOR/SREBP1/SCD1 pathway by providing glutamine, and cooperates with GSH to inhibit ROS accumulation. Through these dual mechanisms, SLC38A5 suppresses ferroptosis; conversely, silencing SLC38A5 induces ferroptosis and attenuates PDAC resistance to gemcitabine (161).

5. Combination therapy strategies targeting SCD1

SCD1 is frequently upregulated in digestive cancers. By reprogramming lipid metabolism, SCD1 not only enhances the adaptability of tumor cells to adverse microenvironments but also confers comprehensive survival and progression advantages through resistance to multiple forms of cell death, including ferroptosis and apoptosis (Table I) (162-173). Consequently, SCD1 has emerged as a promising therapeutic target for anticancer strategies.

Given its role as a critical nexus between lipid metabolic reprogramming and cell death, and in light of the limitations of monotherapy, combining SCD1 inhibitors with therapeutic agents possessing distinct mechanisms represents a promising direction in oncology therapeutics. Key combination strategies include the following:

i) Combination with ferroptosis inducers: SCD1 inhibitors reduce the threshold of tumor cells to peroxidation damage, thereby significantly enhancing the efficacy of ferroptosis inducers - such as erastin (targeting system Xc^-) (51,157) or RSL3 (targeting GPX4) (141,154) - thereby generating a potent synergistic effect.

ii) Combination with autophagy inhibitors: Under conditions of SCD1 suppression, tumor cells may activate autophagy to recycle lipids, sustaining energy production and resisting

Table I. SCD1 modulates modalities and mechanisms of cell death in digestive tumors.

Cancer type	Mode of cell death	Mechanism	(Refs.)
Gastric cancer	Ferroptosis	SCD1 promotes MUFAs and SLC7A11/GPX4 to suppress ferroptosis.	(18)
		SCD1 derepresses SQLE to boost cholesterol/mTOR for ferroptosis inhibition.	(50)
		CircTFRC recruits ELAVL1 to stabilize SCD1 mRNA, inhibiting ferroptosis.	(97)
		lncFERO upregulates SCD1 via hnRNPA1 to inhibit ferroptosis.	(98)
		USP7 deubiquitinates and stabilizes SCD1 to inhibit ferroptosis.	(99)
		JPYZXZ induces ferroptosis by inhibiting SCD1, Wnt/β-catenin and GPX4/xCT.	(104)
		Lactate inhibits ferroptosis by activating HCAR1/AMPK/SREBP1 axis.	(106)
	Apoptosis	SCD1 upregulated under lipid stress; inhibition induces ER stress/apoptosis.	(102)
		ADAR1 alleviates ER stress and suppresses apoptosis via SCD1 RNA editing.	(162)
		AKAP8L stabilizes SCD1 mRNA to suppress apoptosis.	(163)
	Ferroptosis & apoptosis	TPM4 upregulates SCD1, alleviates ER stress/UPR to inhibit ferroptosis and apoptosis.	(105)
Esophageal cancer	Ferroptosis	SCD1 suppresses lipid peroxidation to inhibit ferroptosis.	(112)
		Zinc deficiency inhibits ferroptosis via lactate production and SREBP1/SCD1 activation.	(113)
		BACH1 inhibits SCD1 to induce ferroptosis.	(115)
Colorectal cancer	Ferroptosis	LINC01606 inhibits ferroptosis via competing for miR-423-5p and SCD1/Wnt/TFE3 loop.	(51)
		TIGAR suppresses ROS/AMPK and upregulates SCD1 to induce ferroptosis resistance.	(116)
		Nodal activates Smad2/3 to upregulate SCD1, inhibiting ferroptosis.	(117)
		PROX1 activates SCD1 transcription to inhibit ferroptosis.	(118)
		CircRHBDD1 stabilizes SCD1 mRNA via ELAVL1 to inhibit ferroptosis.	(119)
		Aspirin inhibits AKT/mTOR and SREBP-1/SCD1 to enhance ferroptosis.	(120)
		GPR37 activates p38-SCD1 axis to inhibit ferroptosis.	(164)
		PPP2CA inhibition activates AMPK to suppress SCD1, enhancing ferroptosis.	(165)
	Apoptosis	SCD1 inhibition induces ceramide/mitochondrial dysfunction/caspase to trigger apoptosis.	(93)
		SCD1 maintains Wnt/NOTCH to promote anti-apoptosis.	(166)
		UPAT/UHRF1 axis inhibition downregulates SCD1/SPRY4 to induce apoptosis.	(167)
	Autophagy	SCD1 inhibition activates lipolysis/lipophagy to reduce LDs/TAGs, affecting cell viability.	(27)
		SCD1 inhibition activates AMPK to induce protective autophagy.	(121)
Hepatocellular carcinoma	Ferroptosis	Lactate suppresses AMPK and activates SREBP1/SCD1 to inhibit ferroptosis.	(130)
		SOX4 activates CHREBP to upregulate SCD1, inhibiting ferroptosis.	(139)
		C12ORF49 activates SREBP1/SCD1 to inhibit ferroptosis.	(140)
		URI promotes p53 degradation to upregulate SCD1, inhibiting ferroptosis.	(141)
		Sorafenib inhibits HBXIP/ZNF263 to downregulate SCD1, inducing ferroptosis.	(142)
		Aurantio-obtusin inhibits AKT/mTOR and Nrf2 to downregulate SCD1/GPX4, inducing ferroptosis.	(168)
	Apoptosis	Sorafenib activates AMPK to suppress SREBP1/SCD1, inducing apoptosis.	(95)
		LXRα + Raf inhibition degrade SCD1 to induce SFA/ER stress, triggering apoptosis.	(143)

Table I. Continued.

Cancer type	Mode of cell death	Mechanism	(Refs.)
		ULK1 deficiency activates RPS6KB1/NCOR1 to inhibit SCD1, promoting apoptosis.	(169)
		CES1 inhibition inhibits PPARα/γ/SCD1 to sensitize cisplatin-induced apoptosis.	(170)
		Zhiheshouwu extract inhibits SREBP1/SCD1 to induce mitochondrial apoptosis.	(171)
	Autophagy & apoptosis	SCD1 inhibition activates AMPK to induce autophagy and apoptosis.	(78)
Pancreatic cancer	Ferroptosis	Nutrient deficiency activates mTOR/SREBP1/SCD1 to induce ferroptosis resistance.	(149)
		SLC25A22 inhibits AMPK to upregulate SCD1, enhancing ferroptosis resistance.	(153)
		TET3 inhibits GATA6 to upregulate SCD1, enhancing ferroptosis resistance.	(154)
		Dracorhodin perchlorate upregulates ACSL4 and downregulates SCD1 to induce ferroptosis.	(159)
		NCOA6 activates SREBP1 to upregulate SCD1 and downregulate ACSL4, inhibiting ferroptosis.	(160)
		SLC38A5 activates mTOR/SREBP1/SCD1 and GSH to inhibit ferroptosis.	(161)
		BHLHE40 activates SREBF1 to upregulate SCD1, inhibiting ferroptosis.	(172)
	Ferroptosis & apoptosis	FBW7 loss activates NR4A1 to upregulate SCD1, suppressing ferroptosis/ apoptosis.	(156)
		ZNF488 downregulation inhibits SCD1 to induce ferroptosis and apoptosis.	(157)
		JPHYD/DHT inhibit SCD1 to induce ferroptosis and activate mitochondrial apoptosis.	(158)
	Apoptosis	SREBP1 knockdown downregulates ACC/FASN/SCD1 to induce apoptosis.	(173)

SCD1, stearoyl-CoA desaturase-1; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; SQLE, squalene epoxidase; mTOR, mechanistic target of rapamycin; CircTFRC, circular RNA derived from transferrin receptor gene; ELAVL1, ELAV-like RNA-binding protein 1; lncFERO, long non-coding RNA FERO; hnRNPA1, heterogeneous nuclear ribonucleoprotein A1; USP7, ubiquitin-specific protease 7; JPYZXZ, Jianpi Yangzheng Xiaozheng Granule; Wnt, Wnt signaling pathway; xCT, cystine/glutamate antiporter subunit; HCAR1, hydroxy-carboxylic acid receptor 1; AMPK, AMP-activated protein kinase; SREBP1, sterol regulatory element-binding protein 1; ER, endoplasmic reticulum; ADAR1, adenosine deaminase acting on RNA 1; AKAP8L, A-kinase anchoring protein 8-like; TPM4, tropomyosin 4; UPR, unfolded protein response; BACH1, Bric-a-brac, tramtrack and broad complex and cap 'n' collar homology 1; LINC01606, long intergenic non-protein coding RNA 1606; miR-423-5p, microRNA 423-5p; TFE3, transcription factor E3; TIGAR, TP53-induced glycolysis and apoptosis regulator; ROS, reactive oxygen species; Smad2/3, sma- and mad-related protein 2/3; PROX1, prospero homeobox protein 1; CircRHBDD1, circular RNA derived from RHBDD1 gene; AKT, AKT serine/threonine kinase; GPR37, G protein-coupled receptor 37; p38, p38 mitogen-activated protein kinase; PPP2CA, protein phosphatase 2 catalytic subunit α; NOTCH, Notch signaling pathway; UPAT, UHRF1-associated protein transcript; UHRF1, ubiquitin-like with PHD and RING finger domains 1; SPRY4, Sprouty 4; LDs, lipid droplets; SOX4, SRY-related HMG-box 4; CHREBP, carbohydrate response element-binding protein; C12ORF49, chromosome 12 open reading frame 49; URI, unconventional prefoldin RPB5 interactor 1; p53, tumor protein p53; HBXIP, hepatitis B virus X-interacting protein; ZNF263, zinc finger protein 263; Nrf2, nuclear factor erythroid 2-related factor 2; LXRα, liver X receptor α; Raf, Raf proto-oncogene serine/threonine-protein kinase; ULK1, Unc-51 like autophagy activating kinase 1; RPS6KB1, ribosomal protein S6 kinase β1; NCOR1, nuclear receptor corepressor 1; CES1, carboxylesterase 1; PPAR, peroxisome proliferator-activated receptor; TET3, ten-eleven translocation methylcytosine dioxygenase 3; GATA6, GATA binding protein 6; ACSL4, acyl-CoA synthetase long-chain family member 4; NCOA6, nuclear receptor coactivator 6; GSH, glutathione; BHLHE40, basic helix-loop-helix family member e40; SREBF1, sterol regulatory element-binding transcription factor 1; FBW7, F-box and WD repeat domain-containing 7; NR4A1, nuclear receptor subfamily 4 group A member 1; ZNF488, zinc finger protein 488; JPHYD, Jianpi Huayu Decoction; DHT, dihydrotanshinone I; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase.

therapeutic stress. Concomitant administration of autophagy inhibitors [e.g., hydroxychloroquine (121)] can block this compensatory pathway, thereby enhancing the efficacy of SCD1 inhibitors.

iii) Combination with chemotherapies or targeted drugs: Many tumors acquire resistance to chemotherapeutic agents such as gemcitabine (157) and targeted therapies such as sorafenib (141) by upregulating SCD1 to drive lipid remodeling. Combining SCD1 inhibitors has been shown to reverse this resistance and restore sensitivity to these agents.

Notably, emerging evidence suggests that traditional Chinese medicinal compounds - such as Jianpi Yangzheng Xiaozheng

Granule (104) and Jianpi Huayu Decoction (158) - can induce ferroptosis by modulating SCD1-mediated lipid remodeling, thereby exerting antitumor effects in GC (104) and pancreatic cancer (158). These findings offer novel perspectives from traditional medicine on SCD1-targeted oncology treatments.

All of the aforementioned combined strategies are based on extensive preclinical studies (using cell lines and animal models), laying the foundation for the translation of SCD1-targeted therapy.

6. Current status and challenges of clinical translation

Preclinical findings. Since the first SCD1 inhibitor was introduced in 2005, research in the field of SCD1 targeting has advanced steadily. A number of SCD1 inhibitors have been evaluated in preclinical models of digestive cancers. This section summarizes the representative inhibitors, the tumor models studied and their principal antitumor effects (Table II) (174-176).

Clinical applicability. To date, no SCD1 inhibitor has been approved for the clinical treatment of digestive system cancers and very few have entered clinical trials specifically for these malignancies. Encouragingly, in the field of metabolic dysfunction-associated steatohepatitis (MASH), the SCD1 inhibitor Aramchol has achieved important progress: An open-label Phase III trial (the ARCON cohort of the ARMOR trial) demonstrated that Aramchol at 300 mg twice daily significantly improves liver fibrosis in a time-dependent manner (177). In addition, another novel SCD1 inhibitor, MTI-301 (formerly SSI-4), is currently being evaluated in a Phase I clinical trial for patients with advanced solid tumors (NCT06911008). Nevertheless, SCD1-targeted therapy for digestive system cancers remains at the preclinical or early exploratory stage, and validated predictive biomarkers are lacking, making it difficult to identify patient populations that may benefit from SCD1-targeted therapy.

Major translational challenges. i) Functional heterogeneity: The biological functions of SCD1 exhibit scenario-dependent characteristics, with its active expression and therapeutic effects correlating with disease type, pathological progression stage, TME components and cellular metabolic status (37,115,124). This functional heterogeneity makes it difficult to establish unified standards for targeted interventions and significantly increases the risk of nonspecific biological effects, thereby posing obstacles to clinical translation.

ii) Expression heterogeneity: Although SCD1 expression is upregulated in most cancers, this gene may exhibit expression heterogeneity across different tumor subtypes (178). Taking GBM as an example, cellular sensitivity to SCD1 inhibitors is strongly correlated with its expression levels: Cells with low SCD1 expression inherently possess intrinsic drug resistance characteristics, whereas those with high expression are more sensitive to therapeutic agents. These differences in expression levels directly lead to variability in drug efficacy, thereby limiting the universal applicability of inhibitors.

iii) Targeted delivery challenges: Currently, the commonly used systemic drug delivery approaches generally lack tumor-targeting specificity, resulting in inadequate drug accumulation at lesion sites and significantly compromising antitumor efficacy. Although previous studies have attempted to address this issue through molecular structure optimization (179), nanodrug delivery systems (180) and prodrug strategies (181), these technologies remain largely at the preclinical stage and have not yet been translated into clinical regimens. Consequently, targeted delivery challenges remain a critical bottleneck in the clinical translation of SCD1 inhibitors.

iv) Off-target toxicity: SCD1 is not only abnormally expressed in tumor tissues but also widely distributed in various normal tissues (24). Systemic inhibition of SCD1 simultaneously disrupts physiological functions in normal tissues and induces multiple toxic side effects. Studies have demonstrated that complete gene knockout of SCD1 can induce hepatic fibrosis and further promote the progression of HCC (134); additionally, loss of this target gene may trigger various cutaneous and mucosal-related adverse conditions, including xerosis and keratoconjunctivitis sicca (182,183).

v) Compensatory drug resistance: Studies have demonstrated that under the pressure of SCD1 inhibitors, tumor cells can upregulate fatty acid desaturase 2 (FADS2) to activate an alternative atypical PUFA synthesis pathway (e.g., producing sapienate), thereby bypassing the SCD1-dependent MUFA synthesis pathway and compensating for metabolic imbalance. Additionally, FADS2 eliminates toxic accumulation of palmitic acid and prevents ER stress-induced cell death. Through these dual mechanisms, tumor cells evade SCD1-mediated metabolic regulation and ultimately develop a drug-resistant phenotype (184,185).

7. Future prospects

To accelerate the clinical translation of SCD1-targeted therapies, future efforts should prioritize the following directions. First, the existing safety data from Aramchol (MASH trials) and MTI-301 (phase I solid tumor trial) should be leveraged to guide trial design and dose selection in digestive cancers. Second, biomarker-enriched basket trials should be implemented to enroll patients with SCD1-high tumors, allowing simultaneous evaluation across multiple digestive cancer subtypes and rapid identification of responsive indications. Third, prespecified futility analysis based on biomarker modulation should be incorporated to enable efficient go/no-go decisions. To support this pathway, future mechanistic and translational research should focus on the following areas: i) highly selective, tissue-specific SCD1 inhibitors, prodrugs or nanoparticle-based delivery systems need to be developed to achieve precise tumor targeting and reduce systemic toxicity, thereby overcoming delivery obstacles and off-target effects; ii) ɑational combination strategies - particularly dual SCD1 and FADS2 inhibition - are warranted to counteract compensatory resistance; iii) predictive biomarkers should be identified and validated to stratify patients according to SCD1 expression levels, pathological stage and microenvironmental features, thereby addressing functional heterogeneity and enabling the biomarker-enriched trial designs described above. Collectively, these research directions target the three major translational bottlenecks - off-target toxicity, compensatory resistance and patient heterogeneity - and will provide critical support for the successful advancement of clinical trials.

Table II. Summary of preclinical studies on SCD1 inhibitors in digestive cancers.

Inhibitor	Cancer type	*In vitro* model	Key *in vitro* findings	*In vivo* model	Key *in vivo* findings	Combination	Core mechanism	(Refs.)
A939572	Gastric cancer	HSC034, GCSCs	Reduced stemness, chemoresistance, migration and invasion; promoted apoptosis	HSC034 subcutaneous xenograft + tail-vein metastasis model in SCID mice	Suppressed tumorigenesis and reduced distant metastasis	Oxaliplatin	SCD1 inhibition → Hippo/YAP suppression → downregulation of YAP/TEAD1 → reduced stemness, chemoresistance and metastasis	(36)
		Organoids	Induced death of dysplastic organoids; rescued by EA	GCK transgenic mice	Selectively eliminated gastric dysplastic cells without damaging normal tissues	-	Blockade of SCD1/EA/FAO axis → energy depletion → apoptosis	(103)
		HGC-27, MKN-45	Downregulated SCD1, β-catenin, GPX4 and xCT	-	-	-	SCD1/β-catenin/GPX4/x CT axis blockade → ferroptosis	(104)
		-	-	MKN-45 subcutaneous xenograft in BALB/c nude mice	Significantly inhibited tumor growth with favorable safety profile	-	SCD1 inhibition → suppression of Wnt/β-catenin/YAP → inhibition of proliferation and migration	(18)
	Colorectal cancer	HCT116, HT29	Suppressed lipid synthesis and glucose metabolism; induced lipolysis and lipophagy	-	-	-	AMPK activation → ACC inhibition and reduced glucose uptake → induction of lipolysis and lipophagy	(27)
		LOVO, Colo205	Inhibited proliferation; increased ceramide levels; promoted apoptosis	LOVO subcutaneous xenograft in BALB/c nude mice	Significantly inhibited tumor growth	-	Induction of endogenous ceramide synthesis → mitochondrial dysfunction → apoptosis	(93)
		Colo205	Decreased MUFA and increased dihydroceramide levels	-	-	-	Upregulation of SPT1/CerS6 via NF-κB → increased dihydroceramide → inhibited proliferation	(94)

Table II. Continued.

Inhibitor	Cancer type	*In vitro* model	Key *in vitro* findings	*In vivo* model	Key *in vivo* findings	Combination	Core mechanism	(Refs.)
		HCT116, LoVo	Inhibited migration and invasion	-	-	-	SCD1 inhibition → reduced MUFAs content → anti-migration/ invasion	(174)
	Hepatocellular carcinoma	Huh7.5, HepG2, Bel-7402	Suppressed cell viability; partially rescued by OA	-	-	Sorafenib	SCD1 inhibition → OA depletion → mitochondrial damage → cell death	(95)
		Myc^{OE}; $Nras^{G12V}$ hepatocytes	Ineffective as monotherapy; combined with LXR agonist induced lipotoxicity	-	-	T0901317	LXR promotes SFAs synthesis; SCD1 inhibition blocks SFAs-to-MUFAs conversion → SFAs accumulation → toxicity	(143)
		SK-Hep1, HepG2	Sensitized RSL3-induced ferroptosis	-	-	RSL3	SCD1 inhibition impairs ferroptosis defense mechanisms	(168)
	Pancreatic cancer	MIAPaCa2, PANC1	Reversed ferroptosis resistance caused by SLC25A22 overexpression	-	-	RSL3, Erastin	SCD1 inhibition → reduced MUFAs → enhanced ferroptosis sensitivity	(153)
		Organoids, PANC-1	Inhibited organoid growth; induced UPR	Pdx1Cre; LSL-$KrasG^{12}D$ transgenic mice	Selectively induced apoptosis in early pancreatic neoplastic lesions	-	SFA accumulation → ER stress-UPR → cell death/growth inhibition	(155)
		MIA PaCa-2, PANC-1	Moderate growth inhibition alone; sensitized to ferroptosis and chemotherapy when combined	-	-	Erastin, Gemcitabine	Inhibition of SCD1 activity; reversal of ZNF488 overexpression effects	(157)
CAY10566	Gastric cancer	GCSCs	Suppressed stemness; synergized with	-	-	Erastin	SCD1 inhibition → downregulation	(50)

Table II. Continued.

Inhibitor	Cancer type	*In vitro* model	Key *in vitro* findings	*In vivo* model	Key *in vivo* findings	Combination	Core mechanism	(Refs.)
			erastin to sensitize ferroptosis				of cholesterol/ mTO R → ferroptosis sensitization and stemness suppression	
		BGC-823, MKN-45	Reversed AKAP8L overexpression-induced stemness and chemoresistance	-	-	Oxaliplatin	SCD1 inhibition → blockade of AKAP8L/SCD1 axis → reversal of stemness and drug resistance	(163)
	Hepatocellular carcinoma	HepG2, SMMC-7721	Suppressed cell viability; induced cell death	-	-	-	AMPK activation → autophagy induction → apoptosis promotion	(78)
		JHH7, HLF	Suppressed proliferation and induced apoptosis in MYCN-high HCC cells	-	-	-	SCD1 inhibition → ER stress → ATF3-mediated downregulation of MYCN → apoptosis	(175)
	Pancreatic cancer	PANC-1	TET3 deficiency confers resistance to CAY10566	-	-	-	TET3 deficiency → low basal SCD1 expression	(154)
		PANC-1, SW1990	Suppressed viability; partially reversed by FBW7 silencing	-	-	RSL3	SCD1 inhibition induces cell death; FBW7 silencing upregulates SCD1 to counteract this effect	(156)
		BxPC-3	Suppressed growth; induced apoptosis; blocked SREBP1-mediated effects	-	-	-	SCD1 inhibition → reduced MUFA → apoptosis induction	(173)
MF-438	Esophageal cancer	KYSE70, KYSE410	Suppressed proliferation; combined with radiotherapy induced ferroptosis +	KYSE70 subcutaneous xenograft in SCID mice	Combined with radiotherapy significantly inhibited tumor growth	Radiotherapy	SCD1 inhibition → MUFAs depletion → ferroptosis + ICD	(112)

Table II. Continued.

Inhibitor	Cancer type	*In vitro* model	Key *in vitro* findings	*In vivo* model	Key *in vivo* findings	Combination	Core mechanism	(Refs.)
			ICD		with favorable safety profile			
	Colorectal cancer	HT29, SW480, HCT116, HCT15	Selectively inhibited CSC sphere formation; induced apoptosis	HT29 tail-vein metastasis model in BALB/c nude mice	Prolonged survival of tumor-bearing mice	-	SCD1 inhibition → blockade of Wnt/Notch → CSCs apoptosis	(166)
	Hepatocellular carcinoma	HepG2	Eliminated CES1 re-expression-mediated chemoresistance; promoted apoptosis	-	-	Cisplatin	SCD1 inhibition → blockade of PUFA/PPARα/γ axis → apoptosis promotion	(170)
PluriSln1	Colorectal cancer	HT29, SW480, HCT116, HCT15	Selectively inhibited CSCs sphere formation; induced apoptosis	-	-	-	SCD1 inhibition → blockade of Wnt/Notch → CSCs apoptosis	(166)
		HCT116, SW620	Reversed CRCMSL knockdown effects: Promoted ferroptosis, reduced membrane fluidity, inhibited migration	-	-	-	SCD1 inhibition → reduced MUFA → decreased membrane fluidity + ferroptosis promotion	(176)
MK8245	Hepatocellular carcinoma	JHH1, HepG2	Ineffective as monotherapy; combined with TKI-induced ferroptosis	-	-	Sorafenib	SCD1 inhibition → reduced MUFAs → enhanced TKI-induced lipid peroxidation → synergistic ferroptosis	(141)
SSI4	Gastric cancer	Organoids, NUGC3, MKN28	Reduced lipid droplets; blocked Wnt signaling; induced apoptosis; decreased stemness; restored chemosensitivity	GX006 organoid subcutaneous xenograft in NSG mice	Inhibited tumor growth; combined with chemotherapy effectively eliminated CSCs	5-FU + Cisplatin	SCD1 inhibition → ER stress → suppression of Wnt/β-catenin → apoptosis + reduced stemness	(162)

Table II. Continued.

Inhibitor	Cancer type	*In vitro* model	Key *in vitro* findings	*In vivo* model	Key *in vivo* findings	Combination	Core mechanism	(Refs.)
T-3764518	Colorectal cancer	HCT-116, HCT-15, HT-29, SW620	Partially inhibited proliferation; feedback activation of AMPK accelerated autophagy, leading to drug resistance	-	-	Bax blocker, Vacuolin-1, Hydroxychloroquine	SCD1 inhibition → feedback activation of AMPK → downregulation of fatty acid synthesis + autophagy promotion → drug resistance	(121)
Aramchol	Hepatocellular carcinoma	JHH1, HepG2	Ineffective as monotherapy; combined with TKI induced ferroptosis	HepG2 subcutaneous xenograft in nude mice	Combined with donafenib synergistically inhibited tumor growth in p53-wild-type models	Donafenib	Reduced MUFA content → donafenib initiates lipid peroxidation → synergistic ferroptosis	(141)
10,12 CLA	Hepatocellular carcinoma	HepG2	Suppressed proliferation; enhanced chemosensitivity	-	-	-	Inhibition of SCD1 enzyme activity → SFAs accumulation → proliferation inhibition and chemosensitization	(138)
DHT	Pancreatic cancer	PANC-1	Directly bound and inhibited SCD1; induced lipid peroxidation and ferroptosis	-	-	-	SCD1 inhibition → pro-oxidation → ferroptosis	(158)

SCD1, stearoyl-CoA desaturase-1; GCSCs, gastric cancer stem cells; SCID, severe combined immunodeficiency; YAP, Yes-associated protein; TEAD1, TEA domain transcription factor 1; EA, eicosenoic acid; GCK, Gif-rtTA, TetO-Cre, KrasG12D; FAO, fatty acid oxidation; GPX4, glutathione peroxidase 4; xCT, cystine/glutamate antiporter subunit; ACC, acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; SPT1, serine palmitoyltransferase 1; CerS6, ceramide synthase 6; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; OA, oleic acid; LXR, liver X receptor; SFAs, saturated fatty acids; RSL3, RAS-selective lethal 3; SLC25A22, solute carrier family 25 member 22; UPR, unfolded protein response; ZNF488, zinc finger protein 488; mTOR, mechanistic target of rapamycin; AKAP8L, A-kinase anchoring protein 8-like; ATF3, activating transcription factor 3; MYCN, N-Myc proto-oncogene; TET3, ten-eleven translocation methylcytosine dioxygenase 3; FBW7, F-box and WD repeat domain-containing 7; SREBP1, sterol regulatory element-binding protein 1; ICD, immunogenic cell death; Wnt, Wnt signaling pathway; Notch, Notch signaling pathway; CSCs, cancer stem cells; CES1, carboxylesterase 1; PPAR, peroxisome proliferator-activated receptor; PUFAs, polyunsaturated fatty acids; MUFAs, monounsaturated fatty acids; CRCMSL, colorectal cancer metastasis-suppressed lncRNA; TKI, tyrosine kinase inhibitor; 5-FU, 5-fluorouracil; 10,12-CLA, trans-10,cis-12 conjugated linoleic acid; DHT, dihydrotanshinone I.

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Availability of data and materials

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Authors' contributions

YF was involved in the conceptualization and writing of the original draft. ZW contributed to the literature investigation and figure preparation. LL and XT contributed to the review and editing of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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