Role of SIRT3 in digestive system diseases and therapeutic prospects (Review)

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Abstract. The family of silent information regulators (sirtuins) constitutes a highly conserved protein family that exhibits two primary enzymatic activities *in vitro*: NAD^+-dependent protein deacetylase activity and adenosine diphosphate-ribose transferase activity. Sirtuin 3 (SIRT3), a member of the sirtuin family, is widely expressed in mitochondria-rich tissues such as the brain, heart, liver and kidney, and functions primarily as a deacetylase. The deacetylations regulated by SIRT3 modulate various metabolic substances and processes within the mitochondrial matrix, playing a crucial role in maintaining normal digestive system function. Therefore, this review focuses on the role of SIRT3 in digestive system diseases to elucidate its function in pathogenic signaling pathways and explore the development of drug targets targeting SIRT3 and related disease pathways, offering new directions for improving the treatment of digestive system-related diseases.

Contents

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1. Introduction

Digestive system diseases are complex and extensive (1). Digestive cancers include gastric, hepatocellular, pancreatic and colorectal cancers (CRC). Among these, hepatocellular carcinoma (HCC) is among the most prevalent cancers worldwide. While existing drug therapies extend patient survival, they have significant side effects (2). Pancreatic cancer, which is difficult to detect early, has low five-year survival rates and remains a highly lethal gastrointestinal malignancy (3). Globally, the incidence of pancreatic cancer is projected to increase to 18.6 cases per 100,000 individuals by 2050, with an annual growth rate of 1.1%, thereby resembling a significant public health burden (4). Given the high prevalence of digestive system diseases, their chronic progression and the substantial burden on patients' quality of life, identifying novel therapeutic strategies for these conditions remains a formidable and urgent challenge.

Mitochondria, which serve as the 'powerhouses' of cells, play crucial roles in cellular energy metabolism, intracellular and extracellular signaling, reactive oxygen species (ROS) production and apoptosis signaling regulation. Within the digestive system-an organ characterized by high turnover rates and metabolic activity-cells demand an exceptional energy supply and precise regulatory control. Consequently, mitochondrial dysfunction can trigger or exacerbate digestive disorders through multiple mechanisms (5,6). The sirtuin family comprises seven members: SIRT1, SIRT6 and SIRT7, which reside in the nucleus; SIRT2, which is localized to the cytoplasm; and SIRT3-5, which are found within mitochondria (7,8). Among these, SIRT3 functions as an NAD^+-dependent deacetylase. Within the mitochondrial matrix, it regulates energy balance and redox status by modifying enzymes involved in metabolic pathways, including the tricarboxylic acid (TCA) cycle, the urea cycle, amino acid metabolism, fatty acid oxidation (FAO) and glucose metabolism (9). In addition to regulating material metabolism, SIRT3

acetylation also modulates numerous mitochondrial proteins involved in metabolic homeostasis, oxidative stress and cell survival. SIRT3 has been demonstrated to control mitochondrial DNA repair, participate in maintaining mitochondrial integrity and regulate apoptosis. Of note, SIRT3 is the only sirtuin reported to influence human lifespan (10). Studies have indicated that SIRT3 also regulates multiple processes critical for mitochondrial structural integrity and function, including oxidative phosphorylation (OXPHOS), mitochondrial dynamics, the mitochondrial unfolded protein response and mitochondrial autophagy (7,9,11). Thus, SIRT3 plays a vital role in maintaining mitochondrial function and homeostasis. Concurrently, SIRT3 is highly expressed in the brain, heart, kidneys, brown adipose tissue and liver-an organ with high oxidative capacity-in which its core enzyme undergoes lysine acetylation (12). In the absence of SIRT3, many of these proteins undergo hyperacetylation. Acetylated proteins induce significant conformational changes in substrate proteins, potentially altering the function and impairing the catalytic activity of most mitochondrial enzymes (13). This disruption may trigger a series of digestive system disorders (14). Therefore, this review describes the role of SIRT3 in digestive system diseases and its potential therapeutic targets, providing new strategies for the diagnosis and treatment of digestive system diseases.

2. Structure and function of SIRT3

Structure of SIRT3. The human SIRT3 protein exists in two forms: A long isoform and a short isoform. Both forms of SIRT3 exhibit NAD^+-dependent deacetylase activity (15). SIRT3 is transcribed in the 11p15.5 chromosomal region of the cell nucleus. The fully transcribed, 399-residue full-length SIRT3 (FLSIRT3) constitutes the long isoform. The mitochondrial targeting sequence located between N-terminal residues 1-25 is crucial for subsequent mitochondrial localization and proteolytic processing. Residues 101, 103, 105, 114, 117 and 118 can prevent substrates from prematurely binding to the SIRT3 active site before mitochondrial transfer (9,12). Upon localization to mitochondria via its mitochondrial targeting sequence, FLSIRT3 is cleaved at residue 142 by mitochondrial proline protease in the mitochondrial matrix, yielding a short isoform with ~28 kDa of class III histone deacetylase activity (16). The conserved catalytic core domain positions SIRT3 as one of the most critical deacetylases, featuring a large Rossmann fold domain that binds NAD^+ and a small domain composed of a helical bundle and zinc-binding motif, formed by two loops extending from the larger domain (8). The remainder of the enzyme core comprises the binding site for SIRT3 substrates (9) (Fig. 1). Each structural feature of SIRT3 directly governs its biological function: The cleft between the Rossmann fold domain and the zinc finger domain forms the substrate binding pocket. Its size and chemical properties determine the ability of SIRT3 to recognize and bind specific acetylated lysine residues; for instance, leucyl-tRNA synthetase 2 specifically binds to SIRT3, and NADH-ubiquinone oxidoreductase subunit V3 specifically binds to SIRT5 (17). The mitochondrial targeting sequence ensures its localization to the mitochondrial matrix, while SIRT3 exclusively deacetylates substrates within mitochondria, guaranteeing its role in regulating mitochondrial activity. The zinc ion-binding domain not only maintains the overall structural stability of the SIRT3 protein but also determines the specific structures of various Sirtuins (18). The highly conserved Rossmann fold domain within SIRT3 perfectly complements NAD^+, initiating the deacetylase reaction by hydrolyzing the cofactor NAD^+. This hydrolysis yields two molecules, nicotinamide and ADP-ribose. The acetylated lysine residue on the substrate protein transfers its acetyl group to ADP-ribose. At this point, the C1'-alkylamide intermediate is converted into a bicyclic intermediate with the assistance of the conserved His 224 residue. This induces a nucleophilic attack by the 2'-OH group of ribose on the amine carbon of the o-alkylamide intermediate. The intermediate is then cleaved by an activated water molecule, ultimately forming 20-acetyl-ADP-ribose to complete deacetylation (8,9). NAD^+, as a cofactor of SIRT3, directly regulates its activity (19). Consequently, SIRT3 expression and activity are modulated by the NAD^+:NADH ratio. Elevated ratios-such as those during starvation, exercise or stress-increase SIRT3 activity and expression, whereas low ratios or aging decrease SIRT3 levels (11,12). Thus, the structure of SIRT3 plays a crucial role in linking cellular metabolic states to mitochondrial functional adaptation. Alterations in SIRT3 structure lead to reduced enzyme activity, causing cellular metabolic reprogramming and increased genomic instability, thereby promoting tumorigenesis (20). Similarly, reduced SIRT3 activity diminishes mitochondrial capacity to adapt to metabolic stress, increasing susceptibility to hepatic steatosis, insulin resistance and oxidative damage. This significantly increases the risk and severity of non-alcoholic fatty liver disease (NAFLD) (21,22).

Functions of SIRT3. SIRT3 performs deacetylation functions because of its conserved enzyme core. Deacetylation by SIRT3 is the most common posttranslational modification of mitochondrial proteins, altering the structure and functional activity of substrate proteins via histone/lysine acetyltransferases (13). Peterson *et al* (23) reported that SIRT3 deacetylates 626 sites across 242 proteins, including 32 sites in 12 FAO proteins, 27 sites in 14 proteins involved in the TCA cycle, 18 sites in 11 proteins involved in the electron transport chain (ETC), 18 sites in 9 proteins involved in protein quality control, and 9 sites in 6 proteins involved in ROS detoxification. In SIRT3 knockout (SIRT3-KO) cells, acetylation levels at mitochondrial protein sites increase twofold (24). These proteins are involved in various pathways, such as the TCA cycle, amino acid metabolism, FAO, ETC/OXPHOS and mitochondrial dynamics. Consequently, they regulate oxidative stress, apoptosis, energy metabolism, inflammation, DNA damage and aging.

Studies reported 283 SIRT3-specific targets among 136 mitochondrial proteins in a SIRT3-KO mouse liver model, particularly within fatty acid metabolism pathways. These include acetyl-CoA synthase 2, long-chain acyl-CoA dehydrogenase (LCAD), and 3-hydroxy-3-methylglutaryl-coenzyme A synthase 2, as well as the stress-responsive enzymes isocitrate dehydrogenase 2, superoxide dismutase 2 (SOD2) and manganese superoxide dismutase (MnSOD) (15,25). When SIRT3 is absent or its activity is reduced, the ability of the liver to oxidize fatty acids decreases. Large amounts of free fatty acids

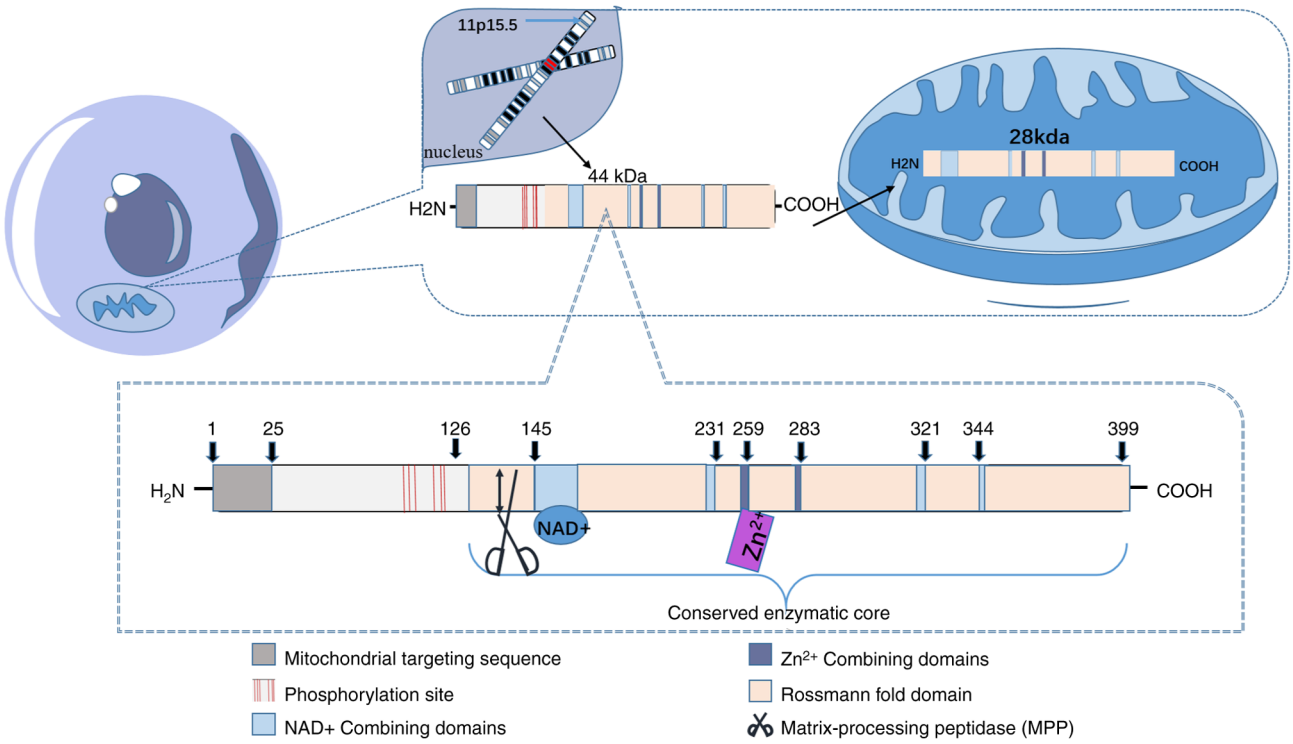

Figure 1. Localization and structure of SIRT3. SIRT3 is transcribed in the chromosome 11p15.5 region in the nucleus, and the mitochondrial targeting sequence between N-terminal residues 1-25 is localized for the next step to enter the mitochondria, and the six serine phosphorylation sites, 101, 103, 105, 114, 117 and 118, prevent the substrate from binding to the active site of SIRT3 in advance prior to transferring to the mitochondria, and are localized to enter the mitochondria according to the mitochondrial localization sequence between residues 1-25 at its N-terminus and its NH_2-terminal 142 residues are hydrolytically cleaved in the mitochondrial matrix by MPP to become the active form of the 28 kDa class III histone deacetylase, whose core region consists of a large Rossmann-folded structural domain that binds to NAD+, and a small structural domain consisting of a helix bundle and zinc-binding motifs. SIRT3, sirtuin 3; MPP, matrix-processing peptidase.

(FFAs) are esterified into triglycerides (TGs) and deposited within hepatocytes, leading to hepatic steatosis. Simultaneously, SOD2 inactivation leads to massive ROS accumulation, triggering oxidative stress that causes hepatocyte injury, ballooning degeneration and cell death. In digestive system cancers, SIRT3 suppresses Bax-mediated mitochondrial apoptosis pathways by deacetylating and activating Ku70, enabling its binding to the pro-apoptotic protein Bax (26). Previous studies revealed that SIRT3 deficiency increases ROS levels, activating hypoxia-inducible factor (HIF)-1α. In mice, this leads to HIF-1α-dependent tumor growth patterns, indicating that SIRT3 suppresses the carcinogenic effects of HIF-1α by regulating ROS, thereby inhibiting tumor growth (27). SIRT3 deacetylation activates pyruvate dehydrogenase, promoting pyruvate entry into the TCA cycle and inhibiting the characteristics of aerobic glycolysis in cancer cells (28).

Increasing evidence has indicated that SIRT3 regulates proteins extensively involved in mitochondrial reactions, including energy production, signaling and apoptosis. When SIRT3 is absent, numerous mitochondrial proteins involved in metabolism and stress undergo hyperacetylation, directly contributing to the onset and progression of various digestive system diseases (11,28,29).

3. SIRT3 and liver disease

SIRT3 and NAFLD. NAFLD encompasses simple steatosis (SS) and non-alcoholic steatohepatitis (NASH) and is characterized by inflammation and ballooning degeneration with or without fibrosis. NASH-associated cirrhosis features the formation of cirrhotic nodules due to fibrotic septa, potentially progressing to HCC (29,30).

Globally, the prevalence of NAFLD and NASH has increased in tandem with that of obesity and metabolic syndrome, indicating that these conditions are becoming serious health threats (31). In NAFLD pathogenesis, hepatocytes exhibit adipocyte-like functions and maintain the balance of lipid metabolism by regulating the production, oxidation, and transport of TGs, FFAs, cholesterol and bile acids (32). When the capacity of hepatocytes is exceeded, lipid metabolism disorders lead to hepatic fat accumulation. Cells exposed to a high-fat environment experience lipotoxicity, which impairs mitochondrial function by activating mitochondrial defects, endoplasmic reticulum (ER) stress and oxidative stress. Concurrently, mitochondria can reduce cellular β-oxidation levels through multiple pathways, including cell division, oxidative stress, autophagy and mitochondrial quality control, thereby promoting hepatic fat accumulation and injury, accelerating NAFLD progression and ultimately causing a rapid decline in liver function (33). Furthermore, disruption of mitochondrial dysfunction-mediated lipid metabolism in patients with NAFLD leads to excessive TG accumulation (>5%) and hepatic steatosis in hepatocytes (34). When obesity remains uncontrolled during the SS stage, innate immune cells within the liver-including Kupffer cells, dendritic cells and hepatic stellate cells-become activated, leading to progressive immune

cell infiltration of the liver (35). In the liver, these immune cells release cytokines that exacerbate the inflammatory process, propelling hepatocytes from the SS stage into the NASH stage and ultimately triggering fibrosis (36). Liver biopsy tissues from patients with NAFLD showed hypermethylation of NADH dehydrogenase-6, which correlated with disease severity (37). These changes in hypermethylation were associated with loss of the inner mitochondrial membrane, deep crista folding and loss of mitochondrial granules, indicating that mitochondrial structural stability is critical for normal hepatic physiological activity. Previous studies revealed reduced SIRT3 expression in animals fed a high-fat diet (HFD). When SIRT3-knockout mice were fed an HFD, hepatic steatosis worsened (25). These findings suggest that SIRT3 plays a role in the pathogenesis of NAFLD. A further study revealed that SIRT3 upregulates β-oxidation and ATP production, suppresses ROS and enhances mitochondrial biogenesis through the activation of peroxisome proliferator-activated receptor (PPAR) gamma coactivator 1 alpha (PGC-1α) (38). Conversely, SIRT3 deficiency leads to excessive acetylation at the K24 site of the mitochondrial metabolic enzyme LCAD. When an acetyl group is covalently modified at this site, the LCAD conformation changes, impairing enzyme activity and obstructing FAO. This results in abnormal lipid metabolism, manifested as massive accumulation of lipid droplets in the liver (25). Furthermore, it affects transcription coactivators involved in FAO, such as PPARα and several target genes involved in FAO, leading to reduced DNA-binding activity and increased acetylation of several hepatic proteins involved in lipid uptake, ultimately resulting in NAFLD development (39). Additionally, SIRT3 promotes β-oxidation by driving LCAD activity and enhancing ketone body production by promoting the deacetylation of 3-hydroxy-3-methylglutaryl-CoA synthase. In SIRT3-deficient mice, hyperacetylation of mitochondrial FAO-related enzymes and reduced enzyme activity lead to increased FFA levels and hepatic steatosis (40). In SIRT3-deficient mice fed an HFD, hepatic steatosis is exacerbated by the activation of oxidative stress-induced nuclear factor erythroid 2-related factor (Nrf)2, which increases the expression and protein levels of genes involved in lipid uptake (very low-density lipoprotein receptor and CD36) in the liver (41). Concurrently, it reduces the activity of respiratory complexes III and IV, exacerbating oxidative stress (42). The administration of adenovirus expressing SIRT3 to mice alleviated obesity, insulin resistance, hyperlipidemia, hepatic steatosis and inflammation in SIRT3-deficient mice (43). Currently, NAFLD treatment relies primarily on lifestyle modifications such as weight reduction, increased exercise and dietary control; however, the adherence to and efficacy of these measures remain suboptimal. Identifying isoenzyme-specific SIRT activators and their target signaling pathways to enhance hepatic mitochondrial function may represent a novel therapeutic strategy for NAFLD. A study revealed that *Polygonum cuspidatum* glycoside (PD), a natural resveratrol precursor isolated from *Polygonum cuspidatum*, activates SIRT3, which in turn activates the deacetylase-activated transcription factor forkhead box (FOX)O3a. FOXO3a induces the interaction between BCL2 and the B19kDa protein-interacting protein 3 (BNIP3), which promotes mitochondrial autophagy (44). This herbal compound, PD, improves NAFLD liver function, histopathology and mitochondrial function through the aforementioned SIRT3-FOXO3-BNIP3 signaling axis and PINK1/parikin (PRKN)-dependent mitochondrial autophagy regulatory mechanism, PINK1 detects mitochondrial damage and recruits PRKN to the mitochondrial surface, thereby mediating ubiquitin-tagging and ultimately initiating the autophagy pathway for the clearance of damaged mitochondria. demonstrating therapeutic efficacy against NAFLD (45). PD has demonstrated broad potential in preclinical studies, but its practical application in clinical settings still faces several challenges (46-48). Although the vitamin D analogue paricalcitol is well-established in clinical treatment for secondary hyperparathyroidism caused by chronic kidney disease, its application in addressing liver inflammation remains in the preclinical stage. The vitamin D analog paricalcitol reduced the acetylation of the transcription factors FOXO3a and NF-κB in the rat liver by increasing SIRT1 and SIRT3 expression, thereby alleviating hepatic inflammation and oxidative stress activation (49).

SIRT3 and HCC. Primary liver cancer includes HCC (accounting for 75-85% of cases) and intrahepatic cholangiocarcinoma (10-15%), along with other rare types (50). During the past decade, most patients were diagnosed at an advanced stage when surgery and local treatments were no longer feasible (51). Although clinical chemotherapy and immunotherapy have demonstrated efficacy in treating HCC, its incidence and prevalence continue to increase (52,53).

Research has indicated that HCC progression and metastasis are associated with altered mitochondrial metabolism (50). Mitochondrial dysfunction, stress responses and protein aberrations in cancer cells lead to mitochondrial defects. In damaged hepatocytes, ROS production, metabolic reprogramming and mitochondrial hormone responses within mitochondria drive tumor growth and metastasis. Previous studies have indicated that when cells lack SIRT3, the inability to deacetylate MnSOD leads to increased ROS levels, readily causing mitochondrial metabolic abnormalities. Under specific intracellular conditions, this triggers genetic instability mutations, ultimately resulting in dedifferentiation and carcinogenesis (54). Compared with that in normal liver cells, SIRT3 expression is downregulated in HCC cells, and this downregulation is associated with tumor size and grade. These findings indicate that SIRT3 plays a tumor-suppressing role in humans and suggest that it can serve as a reliable prognostic indicator (55,56). Cancer cells primarily rely on aerobic glycolysis for energy production, a process that also creates favorable conditions for their survival in the microenvironment-known as the Warburg effect (57). SIRT3 acts as a tumor suppressor gene by promoting oxidative phosphorylation, thereby inhibiting glycolysis and regulating metabolism to suppress the Warburg effect. The most extensively studied mechanism involves the inhibition of HIF-1α by SIRT3. Since many cancer cells extensively consume glucose to produce lactate via lactate dehydrogenase A (LDHA), which is encoded by c-Myc target genes and HIF-1α, HIF1α has been identified as a key factor that activates glycolytic pathways in tumors. SIRT3 modulates HIF1α activity by deacetylating prolyl hydroxylase (PHD). Activated PHDs hydroxylate the substrate HIF-1α, affecting its stability and preventing

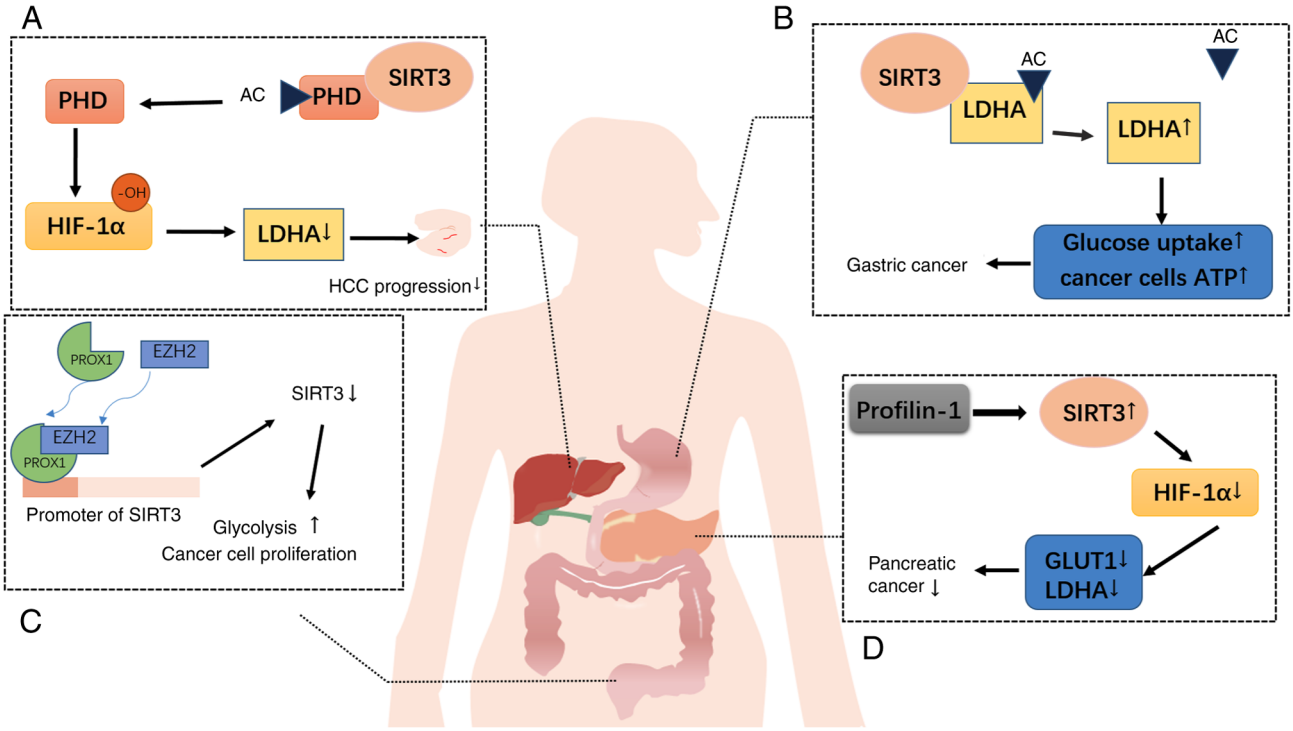

Figure 2. Signaling pathways regulated by SIRT3 in digestive diseases. (A) SIRT3 deacetylates PHD, and activated PHD hydroxylates the substrate HIF-1a to inhibit activity, leading to a decrease in LDHA preventing tumors from undergoing aerobic glycolysis. (B) SIRT3 acts as an oncogenic factor that enhances enzyme activity as well as cellular bioenergetics by deacetylating lactate dehydrogenase A, resulting in rapid tumor cell growth. (C) PROX1 recruits EZH2 to the SIRT3 promoter region in colorectal cancer cells to inhibit SIRT3 transcription and translation, cell proliferation in CRC. (D) Profilin-1 and SIRT3 interact to inhibit HIF1α, and as a result, GLUT1 and LDHA expression is significantly suppressed, affecting glycolysis in pancreatic cancer progression. LDHA, lactate dehydrogenase A; SIRT3, sirtuin 3; HIF, hypoxia-inducible factor; CRC, colorectal cancer; PROX1, proco-related homeobox 1; EZH2, enhancer of zeste homolog 2; PHD, prolyl hydroxylase; AC, acetylation; GLUT1, glucose transporter 1.

aerobic glycolysis in tumors (58,59). Additionally, pyruvate dehydrogenase complexes (PDCs) serve as SIRT3 substrates linked to glycolysis. As an upstream deacetylase of PDCs, SIRT3 deacetylates and activates these substrates, thereby inhibiting tumor cell glycolysis and promoting apoptosis (60) (Fig. 2). SIRT3/SIRT4 reduces the high expression of cyclooxygenase-2 (COX-2) in tumor tissues. Since COX-2 impedes PINK1/PRKN-mediated mitochondrial autophagy, its reduction enhances mitochondrial autophagy, contributing to the early prevention of HCC (61). As HCC is a chemoresistant cancer and its multidrug resistance characteristics contribute to high recurrence and metastasis rates (62). Consequently, drugs that enhance anticancer activity are urgently needed. Given the critical role of SIRT3 in tumors, researchers are now focusing on the function of SIRT3 modulators in HCC. Among these, the small molecule 7-hydroxy-3-(4'-methoxyphenyl)coumarin, a SIRT3 activator, binds to SIRT3 to specifically increase MnSOD deacetylation and activity (63). It also increases sensitivity to HCC treatments such as sorafenib (55,64). Furthermore, the SIRT3 activator resveratrol enables SIRT3 to deacetylate mitochondrial cyclooxygenase-2 (mito-COX-2), thereby inhibiting mito-COX-2/dintenin-1-driven mitochondrial fission, inducing cancer apoptosis and increasing the sensitivity of HCC cells to cisplatin chemotherapy (63). Both of these activators are currently in preclinical trials. Although several effective SIRT3 activators have been identified, further research is still needed to discover and develop specific and potent SIRT3 activators.

4. SIRT3 and intestinal diseases

Inflammatory bowel disease (IBD). The gut serves as a barrier against harmful external substances and pathogenic infections, interacting with the gut microbiome and food antigens. Consequently, the intestinal immune system responds to both internal and external environments to maintain homeostasis. Disruption of this equilibrium can lead to IBD (65). IBD is a chronic, recurrent disease that encompasses ulcerative colitis (UC) and Crohn's disease. Its etiology remains unclear, although it is widely considered an autoimmune disorder in which key pathogenic factors involve the dysregulation of T-cell subsets (66). Compared with healthy individuals, patients with IBD exhibit increased levels of helper T cells (Th17) and the corresponding transcription factor retinoic acid-related orphan receptor gamma-t (RORγt). Additionally, both SIRT3 gene transcription and protein expression are downregulated in the colonic tissue of patients with UC (67). RORγt is a key transcription factor for Th17 cell development. Its signaling is regulated by signal transducer and activator of transcription 3 (STAT3), which directly activates RORγt by modulating STAT3, thereby inducing Th17 cells (68). Thus, STAT3 plays a crucial role in regulating the Th17/T-regulatory cell (Treg) balance and the release of inflammation-related cytokines (69). Increased STAT3 promotes Th17-cell differentiation, disrupting the Th17/Treg balance and triggering inflammatory events (70). Honokiol (HKL), an activator of SIRT3, was used to treat an inflammatory cell model

and a dextran sulfate sodium-induced mouse colitis model. Compared with untreated mice, HKL-treated mice exhibited reduced inflammatory cell infiltration, significantly less structural damage and relatively lower edema levels. As a SIRT3 activator, HKL inhibits STAT3-induced RORγt activity, reduces the Th17 ratio and does not affect Th-cell differentiation, thereby regulating the Th17-cell mechanism to alleviate colitis symptoms (67). Dysregulation of intestinal macrophages also plays a crucial role in the pathogenesis of IBD. Macrophage NAD^+ synthesis exerts immunoregulatory effects by enhancing oxidative phosphorylation (71). This maintains intestinal immune homeostasis by clearing infections while preventing chronic inflammation and inducing tissue repair. During this process, macrophages polarize into classically activated macrophages (M1) and alternatively activated macrophages (M2) (72). SIRT3 deacetylates glutamate dehydrogenase 1 to promote α-ketoglutarate (α-KG) production. α-KG accumulation not only enhances OXPHOS metabolism but also reduces histone H3 K27 trimethylation in the nucleus, leading to the upregulation of genes associated with M2 polarization (73). Given that IBD is a chronic, recurrent disease imposing a significant health burden, the discovery of the role of SIRT3 in IBD potentially reveals a pharmacological target.

The enteric nervous system (ENS). The ENS is a vast, complex and autonomous system distinct from the central nervous system. Neurons within the ENS regulate critical functions such as digestion, nutrient absorption and intestinal motility. The ENS, intestinal epithelium, gut microbiota and immune cells work in concert to ensure the maintenance of normal intestinal function (74). ENS-related neurodegeneration is particularly pronounced in individuals with aging and neurodegenerative diseases. Stress from antibiotic treatment also affects ENS function by altering the gut microbiota (75). ENS dysfunction can lead to numerous disorders associated with motility alterations and inflammation, including primary achalasia (76,77) and irritable bowel syndrome (78). Owing to high energy demands, neurotransmitter autooxidation and limited replication capacity, ENS neurons are highly susceptible to oxidative damage from free radicals. Oxidative stress has also been demonstrated to alter electrophysiological properties, damage neuronal membranes and trigger neuronal death (79). Currently, the known mechanisms of oxidative stress in enteric neurons can be categorized into those associated with endogenous nitrosative damage, mitochondrial dysfunction or inflammation (79). Studies have revealed that SIRT3 protects cortical and dopaminergic neurons from oxidative stress by regulating mitochondrial homeostasis (80). The SIRT3 activator hexafluoromagnol activates SIRT3 and its downstream target PGC-1α to counteract stress-induced ROS production (81). Concurrently, PGC-1α directly enhances SIRT3 transcription to mitigate oxidative damage, thereby promoting intestinal neuronal survival and differentiation (82). Furthermore, SIRT3 significantly increased the density of neural networks and axons in intestinal neurons while increasing neuronal nitric oxide synthase and choline acetyltransferase mRNA levels. SIRT3 exerts neuroprotective effects by inhibiting superoxide release, thereby suppressing palmitate and lipopolysaccharide-induced neuronal pyroptosis, which play crucial roles in promoting intestinal neuronal survival and differentiation (83,84). Beyond regulating host energy balance, the gut microbiota modulates numerous metabolic processes by participating in the complex bidirectional communication system known as gut-brain crosstalk, which is mediated by signaling molecules such as short-chain fatty acids produced by the microbiota (85). Short-chain fatty acids generated by gut bacteria regulate NAD^+ metabolism to influence SIRT3 activity (86). In summary, SIRT3 plays a crucial role in maintaining normal ENS function. Investigating the role of SIRT3 in the ENS provides direction for disease prevention and treatment.

CRC. CRC is a malignant tumor arising from the mucosal epithelium and glands of the large intestine. Its incidence is increasing annually and the 5-year survival rate significantly decreases once tumor cells infiltrate the submucosal layer. Prognosis worsens and survival decreases upon metastasis to extraintestinal organs (87). In CRC, SIRT3 functions as a tumor suppressor to inhibit cancer progression. Compared with those in adjacent normal colorectal epithelium, the expression levels of proco-related homeobox 1 (PROX1) are significantly greater in colorectal tumor cells. As a homologous transcription factor, PROX1 regulates cellular differentiation and development during embryonic growth and is positively correlated with tumor glucose metabolism (88). The mechanism involves the recruitment of the enhancer of zeste homolog 2 (EZH2) to the SIRT3 promoter region in CRC cells by PROX1, thereby inhibiting SIRT3 transcription. This increases glucose metabolism in cancer cells to sustain proliferation (89). When PROX1 is highly expressed, it binds to the SIRT3 promoter region, inhibiting SIRT3 transcription and translation and ultimately leading to low SIRT3 expression. Knocking down PROX1 expression increases SIRT3 expression and reverses the malignant characteristics of CRC (90) (Fig. 2). SIRT3 regulates the expression of PGC1α and NRF1. Reduced SIRT3 expression impairs mitochondrial dynamics and affects the malignancy of CRC cells (91). Of note, SIRT3 may also promote cancer cell growth. Metabolic reprogramming is a hallmark of cancer and is closely linked to cancer progression and metastasis. To enable rapid cell division, cancer cells exhibit abnormal glycolysis, glutamine catabolism and lipid synthesis (92). Previous studies revealed disrupted serine-to-glycine ratios in CRC, where serine/glycine synthesis influences the tumor status by regulating cellular antioxidant capacity (93). The expression of serine hydroxymethyltransferase 2 (SHMT2), a key serine/glycine interconverting enzyme, is significantly elevated in patients with CRC and is correlated with poor survival outcomes. Further study revealed acetylation at the K95 site of SHMT2. Acetylated K95 disrupts the SHMT2 tetrameric conformation to inhibit its enzymatic activity and promotes SHMT2 degradation via the K63-ubiquitin-lysosomal pathway. This leads to reduced serine consumption and decreased NADPH levels, thereby suppressing tumor growth and cell proliferation (94). In the aforementioned SHMT2-K95-Ac pathway, SIRT3 acts as a deacetylase for SHMT2, deacetylating K95. Deacetylation of K95 fails to inhibit SHMT2 activity, leading to SHMT2 overexpression, which promotes

colorectal tumorigenesis. These tumors are highly invasive and have poor prognosis (95). SIRT3 also deacetylates methylenetetrahydrofolate reductase 2, increasing its activity and promoting cell proliferation and cancer progression (96). These studies indicate that SIRT3 influences cancer cell proliferation by controlling whether endogenous regulatory factors undergo deacetylation. In recent years, researchers have been exploring novel therapeutic and preventive strategies against cancer. It should not be overlooked that dietary prevention can reduce the risk of CRC. Apigenin, a natural antioxidant found in fruits and vegetables, reduces the expression of SHMT2, SIRT3 and their upstream long intergenic noncoding RNA LINC01234 when CRC cells are treated. This activity inhibits metabolic reprogramming by regulating the LINC01234/SIRT3/SHMT2 axis (97). Ergothioneine, a dietary betaine, exerts anti-CRC effects by activating SIRT3 (98). Clinically, SGLT2 inhibitors such as canagliflozin, dapagliflozin, tolvogliflozin and empagliflozin are commonly used as hypoglycemic agents. A recent study revealed their novel anticancer activity by reducing glucose uptake and severely impairing cancer-specific cellular metabolism (99). In CRC, canagliflozin can be repurposed to specifically inhibit CRC cell proliferation and induce S-phase arrest through mechanisms of regulating metabolism, mitochondrial function and ER stress via the SGLT2/SIRT3/dipeptidyl peptidase-4 axis (100). It should be noted that the aforementioned drugs remain in the preclinical exploration phase. The findings from preclinical studies provide crucial theoretical foundations and preliminary scientific hypotheses for future formal clinical trials. Radiation therapy is among the primary treatments for cancer patients. However, prolonged radiotherapy can induce radiation resistance in cancer cells, often leading to treatment failure and poor prognosis in patients receiving radiotherapy (101). Research has indicated that SIRT3 promotes radiation resistance in tumor cells by enhancing DNA damage repair through excessive activation of mitochondrial autophagy, which is mediated by PINK1/PRKN (102). In addition to promoting radiation resistance during radiotherapy, SIRT3 modulates chemotherapy resistance in CRC cells via the regulation of SOD2 and PGC-1α during chemotherapy. SIRT3 serves as an independent prognostic factor for colorectal cancer (99). Undoubtedly, the role of SIRT3 in colon cancer is a double-edged sword. Whether its ultimate effect is tumor suppression or promotion depends on a complex decision-making network. Different colon cancer subtypes, tumor microenvironments and tumor stages influence whether SIRT3 promotes or inhibits tumorigenesis in CRC. Therefore, further understanding of the underlying molecular mechanisms is warranted for the future clinical development of SIRT3-targeted therapeutic agents.

5. SIRT3 and pancreatic diseases

Acute pancreatitis (AP). AP is a localized inflammatory response in pancreatic tissue caused by the activation of pancreatic enzymes due to various etiologies. The activation of pancreatic enzymes is a prerequisite for local inflammation in pancreatitis (100). When pancreatic cells undergo necrosis and vascular permeability increases, the pancreas experiences edema, necrosis and hemorrhage. Concurrently, impaired pancreatic function affects other organs, such as through gut microbiota dysbiosis, increased intestinal barrier permeability and bacterial translocation (103). Unlike conventional treatments that primarily reduce disease severity by alleviating pancreatic burden, fecal microbiota transplantation (FMT) achieves similar effects by mitigating tissue damage and inflammation through the reversal of dysbiosis (104). Research has indicated that FMT modulates the intestinal microbiota to concentrate nicotinamide mononucleotide in the pancreas, thereby increasing pancreatic NAD^+ levels and reducing disease severity. This process requires an NAD^+-dependent enzyme for conversion. SIRT3, an NAD^+-dependent deacetylase, mitigates AP-induced oxidative stress and inflammation by reducing the acetylation of the mitochondrial protein peroxiredoxin-5 (PRDX5) in acinar cells and increasing the expression of PRDX5 (105). These findings indicate that SIRT3 exerts an inhibitory effect on AP and that its expression levels in patients may serve as a therapeutic biomarker.

Pancreatic cancer. Pancreatic cancer, particularly pancreatic ductal adenocarcinoma (PDAC), is characterized by late symptom onset, early metastasis and rapid progression, resulting in low patient survival rates. Therefore, identifying potential biomarkers for patients with pancreatic cancer is critically important (106). Studies of sirtuin protein expression profiles in PDAC have revealed that in the absence of chemotherapy intervention, low SIRT3 expression in the tumor cytoplasm is associated with high-grade, poorly differentiated tumors. Low SIRT3 expression is associated with high invasiveness, high recurrence rates and poor prognosis (107). These findings indicate that SIRT3 functions as a tumor suppressor in pancreatic cancer. As an enzyme that regulates macronutrient metabolism, SIRT3 redirects cellular glycolysis toward oxidative phosphorylation and the TCA cycle, suppressing the Warburg effect in tumor cells and reducing proliferation (108). Research has revealed that Profilin1 (Pfn1) expression is downregulated in pancreatic cancer. Pfn1 fails to increase HIF1-α stability by upregulating SIRT3, thereby exerting a growth-inhibitory function in pancreatic cancer. HIF1α promotes metabolic reprogramming and plays a crucial role in maintaining glycolysis in pancreatic cancer (109,110) (Fig. 2). SIRT3 also regulates iron metabolism in PDAC by modulating the activity of iron regulatory protein 1 (IRP1), a key regulator of cellular iron levels that control genes containing iron response elements (IREs) (111). SIRT3 reduces the binding affinity of IRP1 for IREs, leading to decreased expression of iron-related genes such as transferrin receptor and thereby inhibiting pancreatic cancer cell proliferation (112). Furthermore, ZMAT1 belongs to a 5-member family (ZMAT1-5) in humans, in which all encoded proteins contain zinc finger domains, functions as tumor suppressors by triggering cell cycle arrest and apoptosis. ZMAT1 expression is downregulated in PDAC and is associated with tumor differentiation, tumor stage and patient survival. ZMAT1 promotes SIRT3 transcription by binding to three sites on its promoter, subsequently upregulating p53 expression and inhibiting cancer cell proliferation (113). SIRT3 also participates in regulating the ETC in pancreatic cancer, specifically by modulating mitochondrial complex II (CII) activity. Dysfunction of SIRT3 leads to decreased CII activity,

causing mitochondrial dysfunction and promoting tumor progression. Recent research has identified a pharmacological agent, poplar nanocapsules, that targets the ubiquinone site to restore CII activity and SIRT3 expression, thereby inducing apoptosis and reducing pancreatic cancer cell survival (114). Given that pancreatic cancer is characterized by rapid growth and high resistance to chemoradiotherapy, developing novel effective treatments targeting its pathogenesis is critically important (115). Identifying SIRT3-regulated pathways that drive PDAC initiation and progression is important for identifying potential therapeutic targets. Reconstructing SIRT3 activity or activating upstream components of SIRT3-associated oncogenic signaling suppression pathways offers a novel, multifaceted strategy to promote cancer progression and improve patient prognosis.

6. Other digestive system cancers and SIRT3

Gastric cancer ranks fourth among cancer types. Although its global incidence has shown an overall downward trend, long-term trends in incidence and mortality vary significantly across countries (116). Increasing experimental evidence has demonstrated that SIRT3 deficiency leads to increased ROS production and oxidative stress in the body, potentially causing cellular dedifferentiation or carcinogenesis. SIRT3 plays a crucial role in protecting cells and preventing cancer progression during carcinogenesis and tumor development. For instance, SIRT3 regulates MnSOD activity to reduce ROS levels in gastric cancer cells, thereby shielding them from oxidative stress-induced damage (117-119). However, in SIRT3-positive gastric tumor cells, SIRT3 acts as an oncogenic factor. By deacetylating LDHA, it enhances enzyme activity. Increased LDHA activity increases glucose uptake and lactic acid production, reducing mitochondrial oxygen consumption while increasing the mitochondrial membrane potential. This increases overall ATP production and aerobic glycolysis in cancer cells, accelerating tumor growth. Concurrently, the expression of glycolysis-related genes is upregulated in SIRT3-overexpressing gastric tumor cells (119) (Fig. 2). Although the incidence and mortality rates of gastric cancer have generally declined, it remains among the leading causes of death worldwide (120). Decreasing gastric cancer mortality may be achieved by developing drugs through studying the regulatory mechanisms of SIRT3 in gastric cancer.

Gallbladder cancer (GBC) is a common malignant tumor of the biliary tract. Early stages show no specific symptoms, but when significant weight loss, jaundice, abdominal pain and diarrhea occur, the disease has already progressed and is often missing the optimal treatment window. Radical cholecystectomy is the preferred treatment, but owing to its high degree of invasiveness and susceptibility to peritoneal and intrahepatic metastasis, early prevention and treatment are particularly crucial (121). SIRT3 plays a role in the pathogenesis of GBC. Studies have revealed that SIRT3 expression is significantly lower in GBC cells than in adjacent nontumor tissue, and patients with low SIRT3 expression exhibit poorer overall survival than those with high SIRT3 expression (122). As a mitochondrial deacetylase, SIRT3 enhances ferroptosis by inhibiting AKT to increase acyl-CoA synthetase long-chain family member 4 expression (123). When SIRT3 expression is reduced, inhibition of AKT-dependent ferroptosis protects cancer cells from ferroptosis. Simultaneously, activating AKT in GBC cells induces the upregulation of epithelial-mesenchymal transition (EMT) markers, enhancing tumor cell invasion activity and migration capacity (124). Reduced SIRT3 expression promotes tumor cell respiration, ATP production and ROS reduction (122,125). Thus, in GBC pathogenesis, SIRT3 induces Akt-mediated ferroptosis while inhibiting EMT, thereby suppressing tumor progression.

7. Prospects for SIRT3 activator applications

As early as 2003, studies reported an association between SIRT3 expression and lifespan (126). It protects vital human tissues such as the heart, liver, brain and kidneys from disease through the deacetylation of substrates. SIRT3 also participates in the overall progression of cancer. Current research on sirtuin targets has made significant progress. Studies on these targets can be extended to identify sirtuin-activating compounds (STACs) or inhibitory compounds (8). Most STACs belong to the natural product polyphenol family, with resveratrol being the first compound discovered to increase SIRT1 activity nearly 10-fold (127). Compounds such as SRT1720, SRT2183 and SRT3025 have been developed to increase sirtuin enzymatic activity, and these drugs have been shown to limit kidney damage (128). Currently, most SIRT3 activators are natural products. These compounds can deacetylate SIRT3 or regulate its expression levels through various mechanisms. HKL, a SIRT3 activator, is a natural compound that increases SIRT3 expression and deacetylase activity. In mice with cardiac hypertrophy, it inhibits cardiac hypertrophy by regulating the AKT and ERK1/2 pathways (82). HKL exhibits anti-inflammatory effects in mice with enterotoxin-induced diarrhea by promoting intestinal barrier function and regulating intestinal epithelial apoptosis. It can also cross the blood-brain barrier to directly act on neuronal cells in the central nervous system (84). The novel fluorinated synthetic HKL analog hexafluoro-HKL exhibits protective effects against melanoma and enhances SIRT3 expression (129). Dihydromyricetin, which is structurally similar to resveratrol, enhances SIRT3 expression through SIRT3-mediated cell protection and inflammation resistance, thereby treating osteoarthritis (130). In a mouse model of sulfur mustard-induced liver injury, this natural product was shown to exert its hepatoprotective effects via SIRT3 (131). Another natural product, pyrroloquinoline quinone, improves hepatic metabolic disorders by increasing SIRT3 expression (132). In the treatment of HCC, sorafenib is a clinically used drug for treating HCC. Sorafenib has been shown to reduce SIRT3 expression, thereby decreasing drug sensitivity, while upregulating SIRT3 can restore HCC sensitivity to sorafenib therapy (82). These findings indicate that SIRT3 is a promising therapeutic target for liver diseases. However, the dual role of SIRT3 in cancer poses risks to its use as a cancer treatment target (9). In addition to natural compounds, SIRT3 activators can be developed through high-throughput screening and structural optimization. Recent discoveries have identified 2-APQC, a structurally selected SIRT3-targeted small-molecule activator. By activating SIRT3, it modulates the AKT-mTOR and TGFβ-Smad3

Table I. Activating or inhibitory compounds of SIRT3 and their mechanisms of action.

A, SIRT3-activating compounds		
Compound	Effects and diseases	(Refs.)
Honokiol	Increasing the expression of SIRT3 inhibits myocardial hypertrophy by regulating AKT and ERK1/2	(82)
	Promoting intestinal barrier regulation and intestinal epithelial cell apoptosis	(84)
Hexafluoro honokiol	Enhancing the expression of SIRT3 has a protective effect on melanoma	(129)
Dihydromyricetin	Enhancing the expression of SIRT3 for the treatment of osteoarthritis	(130)
Pyrroloquinoline quinone	Improving metabolic diseases in the liver	(132)
B, SIRT3 inhibitors		
Tenovin-6	SIRT3 non-competitive inhibitor	(135)
LC-0296	NAD+ competitive inhibitors, Inhibition of proliferation and promotion of cell apoptosis in head and neck squamous cell carcinoma	(136)

SIRT3, sirtuin 3.

signaling pathways, thereby inhibiting myocardial hypertrophy and alleviating myocardial fibrosis (133). Unlike traditional 'inhibitory' or 'blocking' drugs, SIRT3 activators aim to 'restore and optimize' cellular physiological functions, offering broad and profound application prospects. However, further development through preclinical and clinical studies is needed to address their pleiotropic effects and enhance their specificity. Furthermore, achieving tissue-specific targeting remains challenging, as other members of the sirtuin family are widely expressed in the digestive system and regulate both tumor-promoting and tumor-suppressing processes. Currently, allosteric activators are gaining attention in the design of SIRT-targeting activators (e.g., SIRT1 and -6). Further elucidation of the structure and biological functions of SIRT3 will facilitate the development of small-molecule activators targeting SIRT3 (9).

Compared with the development of SIRT3 activators, the development of inhibitors within the dynamic deacetylation process is somewhat simpler. By leveraging the peptide-binding region within the SIRT3 crystal structure, a structure-based approach can be used to identify novel isoform-specific inhibitors (134). With respect to deacetylation substrates, competitive inhibition of SIRT3 deacetylation activity can be achieved by synthesizing structural analogs of endogenous acetylated substrates. Alternatively, NAD^+ coenzyme competitive inhibitors accelerate the reverse reaction of deacetylation, thereby inhibiting the deacetylation process. Tenovin-6 is a bioactive p53 activator that was later identified as a SIRT3 inhibitor with antitumor activity. Its mechanism of SIRT3 inhibition remains elusive, but it has been demonstrated to act as a noncompetitive inhibitor (135). LC-0296 is a synthetic SIRT3 inhibitor whose mechanism of action is currently unknown. On the basis of its structure, LC-0296 may act as a competitive inhibitor of NAD^+. It exhibits potent antiproliferative and proapoptotic activity against head and neck squamous cell carcinoma (136). As summarized in Table I, an increasing number of natural and synthetic compounds have been identified as SIRT3 activators or inhibitors, providing a critical resource for developing targeted therapeutic strategies (Table I). Research on SIRT3 activators is promising, yet their practical clinical application remains challenging. For instance, precisely delivering drugs to specific diseased organs while minimizing effects on other tissues is crucial for enhancing efficacy and reducing side effects. This precise targeting becomes particularly vital when SIRT3 expression levels exhibit either pro- or antitumor effects across different cancers. Careful monitoring of future research is essential, especially in preclinical and clinical settings, to explore SIRT3-modulating therapies for digestive system diseases.

8. Conclusion

As a member of the sirtuin family, SIRT3 influences mitochondrial energy balance, redox homeostasis and mitochondrial DNA repair by regulating the acetylation status of mitochondrial proteins. The functional integrity of mitochondria is vital for maintaining the health of digestive organs. Dysfunction of SIRT3 leads to mitochondrial disruption and serves as a common pathway linking multiple pathophysiological processes. This review summarizes the structure and deacetylase function of SIRT3, highlighting its vital role in digestive system diseases. In such diseases, loss of SIRT3 activity leads to metabolic disorders, oxidative stress-induced accumulation of energy and substances, cellular damage and mutations, and genomic instability. Ultimately, this leads to tissue carcinogenesis. Notably, however, SIRT3 expression exhibits duality in certain digestive system tumors, such as CRC, and influences chemoresistance

in CRC cells. Therefore, when SIRT3 activators are designed, combining SIRT3 modulators with chemotherapeutic agents or metabolic inhibitors could significantly improve clinically observed chemoresistance. Although a series of SIRT3-targeting small molecules have demonstrated efficacy, the vast majority of SIRT3 activators remain in preclinical stages. SIRT3 remains a largely unexplored therapeutic target, and future research should focus on optimizing SIRT3-targeted therapies by enhancing their specificity and improving their efficacy when combined with conventional treatments. Despite these existing challenges, this approach offers novel therapeutic strategies for digestive system diseases.

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Availability of data and materials

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Authors' contributions

JL was responsible for conceptualization of the review, methodological design, literature search, drafting of the manuscript, and visualization of charts and graphs. QL performed the literature review and data organization and participated in drafting portions of the initial manuscript. SY provided resources and performed quality assessment. XL provided resources and was involved in formal analysis. LZ provided resources and was involved in data curation. YW supervised the study and was responsible for methodology. GW, JA and HJ acquired funding, performed project administration, provided resources and supervision and were involved in writing-review and editing. BT acquired funding and contributed to writing-review and editing. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Zhang Y, Zhao L, Gao H, Zhai J and Song Y: Potential role of irisin in digestive system diseases. Biomed Pharmacother 166: 115347, 2023.
2. Chakraborty E and Sarkar D. Emerging therapies for hepatocellular carcinoma (HCC). Cancers (Basel) 14: 2798, 2022.
3. Menini S, Iacobini C, Vitale M, Pesce C and Pugliese G: Diabetes and pancreatic cancer-a dangerous liaison relying on carbonyl stress. Cancers (Basel) 1: 313, 2021.
4. Hu JX, Zhao CF, Chen WB, Liu QC, Li QW, Lin YY and Gao F: Pancreatic cancer: A review of epidemiology, trend, and risk factors. World J Gastroenterol 27: 4298-321, 2021.
5. Haque PS, Kapur N, Barrett TA and Theiss AL: Mitochondrial function and gastrointestinal diseases. Nat Rev Gastroenterol Hepatol 21: 537-555, 2024.
6. LeFort KR, Rungratanawanich W and Song BJ: Contributing roles of mitochondrial dysfunction and hepatocyte apoptosis in liver diseases through oxidative stress, post-translational modifications, inflammation, and intestinal barrier dysfunction. Cell Mol Life Sci 81: 34, 2024.
7. Zhou L, Pinho R, Gu Y and Radak Z: The role of SIRT3 in exercise and aging. Cells 11: 2596, 2022.
8. Feldman JL, Dittenhafer-Reed KE and Denu JM: Sirtuin catalysis and regulation. J Biol Chem 287: 42419-42427, 2012.
9. Zhang J, Xiang H, Liu J, Chen Y, He RR and Liu B: Mitochondrial sirtuin 3: New emerging biological function and therapeutic target. Theranostics 10: 8315-8342, 2020.
10. Grabowska W, Sikora E and Bielak-Zmijewska A: Sirtuins, a promising target in slowing down the ageing process. Biogerontology 18: 447-476, 2017.
11. Verdin E, Hirschey MD, Finley LW and Haigis MC: Sirtuin regulation of mitochondria: Energy production, apoptosis, and signaling. Trends Biochem Sci 35: 669-675, 2010.
12. Mishra Y and Kaundal RK: Role of SIRT3 in mitochondrial biology and its therapeutic implications in neurodegenerative disorders. Drug Discov Today 28: 103583, 2023.
13. Zhang Y, Wen P, Luo J, Ding H, Cao H, He W, Zen K, Zhou Y, Yang J and Jiang L: Sirtuin 3 regulates mitochondrial protein acetylation and metabolism in tubular epithelial cells during renal fibrosis. Cell Death Dis 12: 847, 2021.
14. Hebert AS, Dittenhafer-Reed KE, Yu W, Bailey DJ, Selen ES, Boersma MD, Carson JJ, Tonelli M, Balloon AJ, Higbee AJ, *et al*: Calorie restriction and SIRT3 trigger global reprogramming of the mitochondrial protein acetylome. Mol Cell 49: 186-199, 2013.
15. Iwahara T, Bonasio R, Narendra V and Reinberg D: SIRT3 functions in the nucleus in the control of stress-related gene expression. Mol Cell Biol 32: 5022-5034, 2012.
16. Onyango P, Celic I, McCaffery JM, Boeke JD and Feinberg AP: SIRT3, a human SIR2 homologue, is an NAD-dependent deacetylase localized to mitochondria. Proc Natl Acad Sci USA 99: 13653-13658, 2002.
17. Yang W, Nagasawa K, Münch C, Xu Y, Satterstrom K, Jeong S, Hayes SD, Jedrychowski MP, Vyas FS, Zaganjor E, *et al*: Mitochondrial sirtuin network reveals dynamic SIRT3-dependent deacetylation in response to membrane depolarization. Cell 167: 985-1000.e21, 2016.
18. Shen H, Qi X, Hu Y, Wang Y, Zhang J, Liu Z and Qin Z: Targeting sirtuins for cancer therapy: Epigenetics modifications and beyond. Theranostics 14: 6726-6767, 2024.
19. Griffiths HBS, Williams C, King SJ and Allison SJ: Nicotinamide adenine dinucleotide (NAD+): Essential redox metabolite, co-substrate and an anti-cancer and anti-ageing therapeutic target. Biochem Soc Trans 48: 733-744, 2020.
20. Ouyang S, Zhang Q, Lou L, Zhu K, Li Z, Liu P and Zhang X: The double-edged sword of SIRT3 in cancer and its therapeutic applications. Front Pharmacol 13: 871560, 2022.
21. Chen LJ, Guo J, Zhang SX, Xu Y, Zhao Q, Zhang W, Xiao J and Chen Y: Sirtuin3 rs28365927 functional variant confers to the high risk of non-alcoholic fatty liver disease in Chinese Han population. Lipids Health Dis 20: 92, 2021.
22. Kane AE and Sinclair DA: Sirtuins and NAD^+ in the development and treatment of metabolic and cardiovascular diseases. Circ Res 123: 868-885, 2018.
23. Peterson BS, Campbell JE, Ilkayeva O, Grimsrud PA, Hirschey MD and Newgard CB: Remodeling of the acetylproteome by SIRT3 manipulation fails to affect insulin secretion or β cell metabolism in the absence of overnutrition. Cell Rep 24: 209-223.e6, 2018.

24. Sol EM, Wagner SA, Weinert BT, Kumar A, Kim HS, Deng CX and Choudhary C: Proteomic investigations of lysine acetylation identify diverse substrates of mitochondrial deacetylase sirt3. PLoS One 7: e50545, 2012.
25. Hirschey MD, Shimazu T, Jing E, Grueter CA, Collins AM, Aouizerat B, Stančáková A, Goetzman E, Lam MM, Schwer B, *et al*: SIRT3 deficiency and mitochondrial protein hyperacetylation accelerate the development of the metabolic syndrome. Mol Cell 44: 177-190, 2011.
26. Liu J, Li D, Zhang T, Tong Q, Ye RD and Lin L: SIRT3 protects hepatocytes from oxidative injury by enhancing ROS scavenging and mitochondrial integrity. Cell Death Dis 8: e3158, 2017.
27. Bell EL, Emerling BM, Ricoult SJ and Guarente L: SirT3 suppresses hypoxia inducible factor 1α and tumor growth by inhibiting mitochondrial ROS production. Oncogene 30: 2986-2996, 2011.
28. Fukushi A, Kim HD, Chang YC and Kim CH: Revisited metabolic control and reprogramming cancers by means of the warburg effect in tumor cells. Int J Mol Sci 23: 10037, 2022.
29. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE and Loomba R: AASLD practice guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 77: 1797-1835, 2023.
30. Paternostro R and Trauner M: Current treatment of non-alcoholic fatty liver disease. J Intern Med 292: 190-204, 2022.
31. Grander C, Grabherr F and Tilg H: Non-alcoholic fatty liver disease: Pathophysiological concepts and treatment options. Cardiovasc Res 119: 1787-1798, 2023.
32. Di Ciaula A, Passarella S, Shanmugam H, Noviello M, Bonfrate L, Wang DQ and Portincasa P: Nonalcoholic fatty liver disease (NAFLD). Mitochondria as players and targets of therapies? Int J Mol Sci 22: 5375, 2021.
33. Zheng Y, Wang S, Wu J and Wang Y: Mitochondrial metabolic dysfunction and non-alcoholic fatty liver disease: New insights from pathogenic mechanisms to clinically targeted therapy. J Transl Med 21: 510, 2023.
34. Pirola CJ, Gianotti TF, Burgueño AL, Rey-Funes M, Loidl CF, Mallardi P, Martino JS, Castaño GO and Sookoian S: Epigenetic modification of liver mitochondrial DNA is associated with histological severity of nonalcoholic fatty liver disease. Gut 62: 1356-1363, 2013.
35. Mazzoccoli G, De Cosmo S and Mazza T: The biological clock: A pivotal hub in non-alcoholic fatty liver disease pathogenesis. Front Physiol 9: 193, 2018.
36. Polyzos SA, Kountouras J and Mantzoros CS: Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. Metabolism 92: 82-97, 2019.
37. Ramanathan R, Ali AH and Ibdah JA: Mitochondrial dysfunction plays central role in nonalcoholic fatty liver disease. Int J Mol Sci 23: 7280, 2022.
38. Kong X, Wang R, Xue Y, Liu X, Zhang H, Chen Y, Fang F and Chang Y: Sirtuin 3, a new target of PGC-1alpha, plays an important role in the suppression of ROS and mitochondrial biogenesis. PLoS One 5: e11707, 2010.
39. Barroso E, Rodríguez-Rodríguez R, Zarei M, Pizarro-Degado J, Planavila A, Palomer X, Villarroya F and Vázquez-Carrera M: SIRT3 deficiency exacerbates fatty liver by attenuating the HIF1α-LIPIN 1 pathway and increasing CD36 through Nrf2. Cell Commun Signal 18: 147, 2020.
40. Chen DD, Shi Q, Liu X, Liang DL, Wu YZ, Fan Q, Xiao K, Chen C and Dong XP: Aberrant SENP1-SUMO-Sirt3 signaling causes the disturbances of mitochondrial deacetylation and oxidative phosphorylation in prion-infected animal and cell models. ACS Chem Neurosci 14: 1610-1621, 2023.
41. Wang Z, Dou X, Li S, Zhang X, Sun X, Zhou Z and Song Z: Nuclear factor (erythroid-derived 2)-like 2 activation-induced hepatic very-low-density lipoprotein receptor overexpression in response to oxidative stress contributes to alcoholic liver disease in mice. Hepatology 59: 1381-1392, 2014.
42. Green MF and Hirschey MD: SIRT3 weighs heavily in the metabolic balance: A new role for SIRT3 in metabolic syndrome. J Gerontol A Biol Sci Med Sci 68: 105-107, 2013.
43. Kendrick AA, Choudhury M, Rahman SM, McCurdy CE, Friederich M, Van Hove JL, Watson PA, Birdsey N, Bao J, Gius D, *et al*: Fatty liver is associated with reduced SIRT3 activity and mitochondrial protein hyperacetylation. Biochem J 433: 505-514, 2011.
44. Lai CS, Tsai ML, Badmaev V, Jimenez M, Ho CT and Pan MH: Xanthigen suppresses preadipocyte differentiation and adipogenesis through down-regulation of PPARγ and C/EBPs and modulation of SIRT-1, AMPK, and FoxO pathways. J Agric Food Chem 60: 1094-1101, 2012.
45. He J, Qian YC, Yin YC, Kang JR and Pan TR: Polydatin: A potential NAFLD therapeutic drug that regulates mitochondrial autophagy through SIRT3-FOXO3-BNIP3 and PINK1-PRKN mechanisms-a network pharmacology and experimental investigation. Chem Biol Interact 398: 111110, 2024.
46. Ren B, Kwah MX, Liu C, Ma Z, Shanmugam MK, Ding L, Xiang X, Ho PC, Wang L, Ong PS and Goh BC: Resveratrol for cancer therapy: Challenges and future perspectives. Cancer Lett 515: 63-72, 2021.
47. Karami A, Fakhri S, Kooshki L and Khan H: Polydatin: Pharmacological mechanisms, therapeutic targets, biological activities, and health benefits. Molecules 27: 6474, 2022.
48. Imtiyaz K, Shafi M, Fakhri KU, Uroog L, Zeya B, Anwer ST and Rizvi MMA: Polydatin: A natural compound with multifaceted anticancer properties. J Tradit Complement Med 15: 447-466, 2024.
49. Malladi N, Lahamge D, Somwanshi BS, Tiwari V, Deshmukh K, Balani JK, Chakraborty S, Alam MJ and Banerjee SK: Paricalcitol attenuates oxidative stress and inflammatory response in the liver of NAFLD rats by regulating FOXO3a and NFκB acetylation. Cell Signal 121: 111299, 2024.
50. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
51. Ladd AD, Duarte S, Sahin I and Zarrinpar A: Mechanisms of drug resistance in HCC. Hepatology 79: 926-940, 2024.
52. Ahmed O and Pillai A: Hepatocellular carcinoma: A contemporary approach to locoregional therapy. Am J Gastroenterol 115: 1733-1736, 2020.
53. Vogel A, Meyer T, Sapisochin G, Salem R and Saborowski A: Hepatocellular carcinoma. Lancet 400: 1345-1362, 2022.
54. Zhang B, Qin L, Zhou CJ, Liu YL, Qian HX and He SB: SIRT3 expression in hepatocellular carcinoma and its impact on proliferation and invasion of hepatoma cells. Asian Pac J Trop Med 6: 649-652, 2013.
55. Wang JX, Yi Y, Li YW, Cai XY, He HW, Ni XC, Zhou J, Cheng YF, Jin JJ, Fan J and Qiu SJ: Down-regulation of sirtuin 3 is associated with poor prognosis in hepatocellular carcinoma after resection. BMC Cancer 14: 297, 2014.
56. De Matteis S, Scarpi E, Granato AM, Vespasiani-Gentilucci U, La Barba G, Foschi FG, Bandini E, Ghetti M, Marisi G, Cravero P, *et al*: Role of SIRT-3, p-mTOR and HIF-1α in hepatocellular carcinoma patients affected by metabolic dysfunctions and in chronic treatment with metformin. Int J Mol Sci 20: 1503, 2019.
57. Liu H, Li S, Liu X, Chen Y and Deng H: SIRT3 overexpression inhibits growth of kidney tumor cells and enhances mitochondrial biogenesis. J Proteome Res 17: 3143-3152, 2018.
58. Le A, Cooper CR, Gouw AM, Dinavahi R, Maitra A, Deck LM, Royer RE, Vander Jagt DL, Semenza GL and Dang CV: Inhibition of lactate dehydrogenase A induces oxidative stress and inhibits tumor progression. Proc Natl Acad Sci USA 107: 2037-2042, 2010.
59. Kwon SM, Lee YK, Min S, Woo HG, Wang HJ and Yoon G: Mitoribosome defect in hepatocellular carcinoma promotes an aggressive phenotype with suppressed immune reaction. iScience 23: 101247, 2020.
60. Fan J, Shan C, Kang HB, Elf S, Xie J, Tucker M, Gu TL, Aguiar M, Lonning S, Chen H, *et al*: Tyr phosphorylation of PDP1 toggles recruitment between ACAT1 and SIRT3 to regulate the pyruvate dehydrogenase complex. Mol Cell 53: 534-548, 2014.
61. Che L, Wu JS, Du ZB, He YQ, Yang L, Lin JX, Lei Z, Chen XX, Guo DB, Li WG, *et al*: Targeting mitochondrial COX-2 enhances chemosensitivity via Drp1-dependent remodeling of mitochondrial dynamics in hepatocellular carcinoma. Cancers (Basel) 14: 821, 2022.
62. Ceballos MP, Quiroga AD and Palma NF: Role of sirtuins in hepatocellular carcinoma progression and multidrug resistance: Mechanistical and pharmacological perspectives. Biochem Pharmacol 212: 115573, 2023.
63. Lu J, Zhang H, Chen X, Zou Y, Li J, Wang L, Wu M, Zang J, Yu Y, Zhuang W, *et al*: A small molecule activator of SIRT3 promotes deacetylation and activation of manganese superoxide dismutase. Free Radic Biol Med 112: 287-297, 2017.

64. De Matteis S, Granato AM, Napolitano R, Molinari C, Valgiusti M, Santini D, Foschi FG, Ercolani G, Vespasiani Gentilucci U, Faloppi L, *et al*: Interplay between SIRT-3, metabolism and its tumor suppressor role in hepatocellular carcinoma. Dig Dis Sci 62: 1872-1880, 2017.
65. Kim YI, Ko I, Yi EJ, Kim J, Hong YR, Lee W and Chang SY: NAD^+ modulation of intestinal macrophages renders anti-inflammatory functionality and ameliorates gut inflammation. Biomed Pharmacother 185: 117938, 2025.
66. Guan Q: A comprehensive review and update on the pathogenesis of inflammatory bowel disease. J Immunol Res 2019: 7247238, 2019.
67. Chen X, Zhang M, Zhou F, Gu Z, Li Y, Yu T, Peng C, Zhou L, Li X, Zhu D, *et al*: SIRT3 activator honokiol inhibits Th17 cell differentiation and alleviates colitis. Inflamm Bowel Dis 29: 1929-1940, 2023.
68. Nistala K and Wedderburn LR: Th17 and regulatory T cells: Rebalancing pro- and anti-inflammatory forces in autoimmune arthritis. Rheumatology (Oxford) 48: 602-606, 2009.
69. Yu R, Zuo F, Ma H and Chen S: Exopolysaccharide-producing Bifidobacterium adolescentis strains with similar adhesion property induce differential regulation of inflammatory immune response in Treg/Th17 axis of DSS-colitis mice. Nutrients 11: 782, 2019.
70. Zhang M, Zhou L, Xu Y, Yang M, Xu Y, Komaniecki GP, Kosciuk T, Chen X, Lu X, Zou X, *et al*: A STAT3 palmitoylation cycle promotes T_H17 differentiation and colitis. Nature 586: 434-439, 2020.
71. Cros C, Margier M, Cannelle H, Charmetant J, Hulo N, Laganier L, Grozio A and Canault M: Nicotinamide mononucleotide administration triggers macrophages reprogramming and alleviates inflammation during sepsis induced by experimental peritonitis. Front Mol Biosci 9: 895028, 2022.
72. Vergadi E, Ieronymaki E, Lyroni K, Vaporidi K and Tsatsanis C: Akt signaling pathway in macrophage activation and M1/M2 polarization. J Immunol 198: 1006-1014, 2017.
73. Zhou W, Hu G, He J, Wang T, Zuo Y, Cao Y, Zheng Q, Tu J, Ma J, Cai R, *et al*: SENP1-Sirt3 signaling promotes α-ketoglutarate production during M2 macrophage polarization. Cell Rep 39: 110660, 2022.
74. Furness JB: The enteric nervous system and neurogastroenterology. Nat Rev Gastroenterol Hepatol 9: 286-294, 2012.
75. Warnecke T, Schäfer KH, Claus I, Del Tredici K and Jost WH: Gastrointestinal involvement in Parkinson's disease: Pathophysiology, diagnosis, and management. NPJ Parkinsons Dis 8: 31, 2022.
76. Gockel I, Müller M and Schumacher J: Achalasia-a disease of unknown cause that is often diagnosed too late. Dtsch Arztebl Int 109: 209-214, 2012.
77. Niesler B, Kuerten S, Demir IE and Schäfer KH: Disorders of the enteric nervous system-a holistic view. Nat Rev Gastroenterol Hepatol 18: 393-410, 2021.
78. Wood JD, Liu S, Drossman DA, Ringel Y and Whitehead WE: Anti-enteric neuronal antibodies and the irritable bowel syndrome. J Neurogastroenterol Motil 18: 78-85, 2012.
79. Brown IAM, McClain JL, Watson RE, Patel BA and Gulbransen BD: Enteric glia mediate neuron death in colitis through purinergic pathways that require connexin-43 and nitric oxide. Cell Mol Gastroenterol Hepatol 2: 77-91, 2016.
80. Shi H, Deng HX, Gius D, Schumacker PT, Surmeier DJ and Ma YC: Sirt3 protects dopaminergic neurons from mitochondrial oxidative stress. Hum Mol Genet 26: 1915-1926, 2017.
81. Zhang X, Ren X, Zhang Q, Li Z, Ma S, Bao J, Li Z, Bai X, Zheng L, Zhang Z, *et al*: PGC-1α/ERRα-Sirt3 pathway regulates daergic neuronal death by directly deacetylating SOD2 and ATP synthase β. Antioxid Redox Signal 24: 312-328, 2016.
82. Pillai VB, Samant S, Sundaresan NR, Raghuraman H, Kim G, Bonner MY, Arbiser JL, Walker DI, Jones DP, Gius D and Gupta MP: Honokiol blocks and reverses cardiac hypertrophy in mice by activating mitochondrial Sirt3. Nat Commun 6: 6656, 2015.
83. Pillai VB, Kanwal A, Fang YH, Sharp WW, Samant S, Arbiser J and Gupta MP: Honokiol, an activator of Sirtuin-3 (SIRT3) preserves mitochondria and protects the heart from doxorubicin-induced cardiomyopathy in mice. Oncotarget 8: 34082-34098, 2017.
84. Balasubramaniam A, Li G, Ramanathan A, Mwangi SM, Hart CM, Arbiser JL and Srinivasan S: SIRT3 activation promotes enteric neurons survival and differentiation. Sci Rep 12: 22076, 2022.
85. Sudo N: Biogenic amines: Signals between commensal microbiota and gut physiology. Front Endocrinol (Lausanne) 10: 504, 2019.
86. Munteanu C, Onose G, Poștaru M, Turnea M, Rotariu M and Galaction AI: Hydrogen sulfide and gut microbiota: Their synergistic role in modulating sirtuin activity and potential therapeutic implications for neurodegenerative diseases. Pharmaceuticals (Basel) 17: 1480, 2024.
87. Dekker E, Tanis PJ, Vleugels JLA, Kasi PM and Wallace MB: Colorectal cancer. Lancet 394: 1467-1480, 2019.
88. Sánchez-Aragó M, Chamorro M and Cuezva JM: Selection of cancer cells with repressed mitochondria triggers colon cancer progression. Carcinogenesis 31: 567-576, 2010.
89. Ku M, Koche RP, Rheinbay E, Mendenhall EM, Endoh M, Mikkelsen TS, Presser A, Nusbaum C, Xie X, Chi AS, *et al*: Genomewide analysis of PRC1 and PRC2 occupancy identifies two classes of bivalent domains. PLoS Genet 4: e1000242, 2008.
90. Gan L, Li Q, Nie W, Zhang Y, Jiang H, Tan C, Zhang L, Zhang J, Li Q, Hou P, *et al*: PROX1-mediated epigenetic silencing of SIRT3 contributes to proliferation and glucose metabolism in colorectal cancer. Int J Biol Sci 19: 50-65, 2023.
91. Torrens-Mas M, Hernández-López R, Pons DG, Roca P, Oliver J and Sastre-Serra J: Sirtuin 3 silencing impairs mitochondrial biogenesis and metabolism in colon cancer cells. Am J Physiol Cell Physiol 317: C398-C404, 2019.
92. Pavlova NN and Thompson CB: The emerging hallmarks of cancer metabolism. Cell Metabol 23: 27-47, 2016.
93. Amelio I, Cutruzzolá F, Antonov A, Agostini M and Melino G: Serine and glycine metabolism in cancer. Trends Biochem Sci 39: 191-198, 2014.
94. Lee GY, Haverty PM, Li L, Kljavin NM, Bourgon R, Lee J, Stern H, Modrusan Z, Seshagiri S, Zhang Z, *et al*: Comparative oncogenomics identifies PSMB4 and SHMT2 as potential cancer driver genes. Cancer Res 74: 3114-3126, 2014.
95. Wei Z, Song J, Wang G, Cui X, Zheng J, Tang Y, Chen X, Li J, Cui L, Liu CY and Yu W: Deacetylation of serine hydroxymethyl-transferase 2 by SIRT3 promotes colorectal carcinogenesis. Nat Commun 9: 4468, 2018.
96. Colloca A, Balestrieri A, Anastasio C, Balestrieri ML and D'Onofrio N: Mitochondrial sirtuins in chronic degenerative diseases: New metabolic targets in colorectal cancer. Int J Mol Sci 23: 3212, 2022.
97. Abdelmaksoud NM, Abulsoud AI, Abdelghany TM, Elshaer SS, Rizk SM, Senousy MA and Maurice NW: Uncovering SIRT3 and SHMT2-dependent pathways as novel targets for apigenin in modulating colorectal cancer: In vitro and in vivo studies. Exp Cell Res 441: 114150, 2024.
98. D'Onofrio N, Martino E, Balestrieri A, Mele L, Cautela D, Castaldo D and Balestrieri ML: Diet-derived ergothioneine induces necroptosis in colorectal cancer cells by activating the SIRT3/MLKL pathway. FEBS Lett 596: 1313-1329, 2022.
99. Colloca A, Donisi I, Anastasio C, Balestrieri ML and D'Onofrio N: Metabolic alteration bridging the prediabetic state and colorectal cancer. Cells 13: 663, 2024.
100. Anastasio C, Donisi I, Del Vecchio V, Colloca A, Mele L, Sardu C, Marfella R, Balestrieri ML and D'Onofrio N: SGLT2 inhibitor promotes mitochondrial dysfunction and ER-phagy in colorectal cancer cells. Cell Mol Biol Lett 29: 80, 2024.
101. Sharma A, Baker S, Duijm M, Oomen-de Hoop E, Cornelissen R, Verhoef C, Hoogeman M and Jan Nuyttens J: Prognostic factors for local control and survival for inoperable pulmonary colorectal oligometastases treated with stereotactic body radiotherapy. Radiother Oncol 144: 23-29, 2020.
102. Wei Y, Xiao G, Xu H, Sun X, Shi Y, Wang F, Kang J, Peng J and Zhou F: Radiation resistance of cancer cells caused by mitochondrial dysfunction depends on SIRT3-mediated mitophagy. FEBS J 290: 3629-3645, 2023.
103. Frost F, Kacprowski T, Rühlemann M, Bülow R, Kühn JP, Franke A, Heinsen FA, Pietzner M, Nauck M, Völker U, *et al*: Impaired exocrine pancreatic function associates with changes in intestinal microbiota composition and diversity. Gastroenterology 156: 1010-1015, 2019.
104. Li X, He C, Li N, Ding L, Chen H, Wan J, Yang X, Xia L, He W, Xiong H, *et al*: The interplay between the gut microbiota and NLRP3 activation affects the severity of acute pancreatitis in mice. Gut Microbes 11: 1774-1789, 2020.
105. Liu LW, Xie Y, Li GQ, Zhang T, Sui YH, Zhao ZJ, Zhang YY, Yang WB, Geng XL, Xue DB, *et al*: Gut microbiota-derived nicotinamide mononucleotide alleviates acute pancreatitis by activating pancreatic SIRT3 signalling. Br J Pharmacol 180: 647-666, 2023.

106. Cai J, Chen H, Lu M, Zhang Y, Lu B, You L, Zhang T, Dai M and Zhao Y: Advances in the epidemiology of pancreatic cancer: Trends, risk factors, screening, and prognosis. Cancer Lett 520: 1-11, 2021.
107. Zhou Y, Cheng S, Chen S and Zhao Y: Prognostic and clinicopathological value of SIRT3 expression in various cancers: A systematic review and meta-analysis. Onco Targets Ther 11: 2157-2167, 2018.
108. Haigis MC, Deng CX, Finley LW, Kim HS and Gius D: SIRT3 is a mitochondrial tumor suppressor: A scientific tale that connects aberrant cellular ROS, the Warburg effect, and carcinogenesis. Cancer Res 72: 2468-2472, 2012.
109. Yao W, Cai X, Liu C, Qin Y, Cheng H, Ji S, Xu W, Wu C, Chen T, Xu J, *et al*: Profilin 1 potentiates apoptosis induced by staurosporine in cancer cells. Curr Mol Med 13: 417-428, 2013.
110. Yao W, Ji S, Qin Y, Yang J, Xu J, Zhang B, Xu W, Liu J, Shi S, Liu L, *et al*: Profilin-1 suppresses tumorigenicity in pancreatic cancer through regulation of the SIRT3-HIF1α axis. Mol Cancer 13: 187, 2014.
111. Jeong SM, Lee J, Finley LW, Schmidt PJ, Fleming MD and Haigis MC: SIRT3 regulates cellular iron metabolism and cancer growth by repressing iron regulatory protein 1. Oncogene 34: 2115-2124, 2015.
112. Chouhan S, Kumar A, Muhammad N, Usmani D and Khan TH: Sirtuins as key regulators in pancreatic cancer: Insights into signaling mechanisms and therapeutic implications. Cancers (Basel) 16: 4095, 2024.
113. Ma Z, Li Z, Wang S, Zhou Z, Liu C, Zhuang H, Zhou Q, Huang S, Zhang C and Hou B: ZMAT1 acts as a tumor suppressor in pancreatic ductal adenocarcinoma by inducing SIRT3/p53 signaling pathway. J Exp Clin Cancer Res 41: 130, 2022.
114. Ragab EM, El Gamal DM, Mohamed TM and Khamis AA: Impairment of electron transport chain and induction of apoptosis by chrysin nanoparticles targeting succinate-ubiquinone oxidoreductase in pancreatic and lung cancer cells. Genes Nutr 18: 4, 2023.
115. Shi S, Yao W, Xu J, Long J, Liu C and Yu X: Combinational therapy: New hope for pancreatic cancer? Cancer Lett 317: 127-135, 2012.
116. Thrift AP, Wenker TN and El-Serag HB: Global burden of gastric cancer: Epidemiological trends, risk factors, screening and prevention. Nat Rev Clin Oncol 20: 338-349, 2023.
117. Kim HS, Patel K, Muldoon-Jacobs K, Bisht KS, Aykin-Burns N, Pennington JD, van der Meer R, Nguyen P, Savage J, Owens KM, *et al*: SIRT3 is a mitochondria-localized tumor suppressor required for maintenance of mitochondrial integrity and metabolism during stress. Cancer Cell 17: 41-52, 2010.
118. Tao R, Coleman MC, Pennington JD, Ozden O, Park SH, Jiang H, Kim HS, Flynn CR, Hill S, Hayes McDonald W, *et al*: Sirt3-mediated deacetylation of evolutionarily conserved lysine 122 regulates MnSOD activity in response to stress. Mol Cell 40: 893-904, 2010.
119. Cui Y, Qin L, Wu J, Qu X, Hou C, Sun W, Li S, Vaughan AT, Li JJ and Liu J: SIRT3 enhances glycolysis and proliferation in SIRT3-expressing gastric cancer cells. PLoS One 10: e0129834, 2015.
120. Arnold M, Park JY, Camargo MC, Lunet N, Forman D and Soerjomataram I: Is gastric cancer becoming a rare disease? A global assessment of predicted incidence trends to 2035. Gut 69: 823-829, 2020.
121. Roa JC, García P, Kapoor VK, Maithel SK, Javle M and Koshiol J: Gallbladder cancer. Nat Rev Dis Primers 8: 69, 2022.
122. Liu L, Li Y, Cao D, Qiu S, Li Y, Jiang C, Bian R, Yang Y, Li L, Li X, *et al*: SIRT3 inhibits gallbladder cancer by induction of AKT-dependent ferroptosis and blockade of epithelial-mesenchymal transition. Cancer Lett 510: 93-104, 2021.
123. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, *et al*: Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell 149: 1060-1072, 2012.
124. Aiello NM and Kang Y: Context-dependent EMT programs in cancer metastasis. J Exp Med 216: 1016-1026, 2019.
125. Osborne B, Bentley NL, Montgomery MK and Turner N: The role of mitochondrial sirtuins in health and disease. Free Radic Biol Med 100: 164-174, 2016.
126. Rose G, Dato S, Altomare K, Bellizzi D, Garasto S, Greco V, Passarino G, Feraco E, Mari V, Barbi C, *et al*: Variability of the SIRT3 gene, human silent information regulator Sir2 homologue, and survivorship in the elderly. Exp Gerontol 38: 1065-1070, 2003.
127. Sinclair DA and Guarente L: Small-molecule allosteric activators of sirtuins. Annu Rev Pharmacol Toxicol 54: 363-380, 2014.
128. Morigi M, Perico L and Benigni A: Sirtuins in renal health and disease. J Am Soc Nephrol 29: 1799-1809, 2018.
129. Akamata K, Wei J, Bhattacharyya M, Cheresh P, Bonner MY, Arbiser JL, Raparia K, Gupta MP, Kamp DW and Varga J: SIRT3 is attenuated in systemic sclerosis skin and lungs, and its pharmacologic activation mitigates organ fibrosis. Oncotarget 7: 69321-69336, 2016.
130. Wang J, Wang K, Huang C, Lin D, Zhou Y, Wu Y, Tian N, Fan P, Pan X, Xu D, *et al*: SIRT3 activation by dihydromyricetin suppresses chondrocytes degeneration via maintaining mitochondrial homeostasis. Int J Biol Sci 14: 1873-1882, 2018.
131. Zhang H, Chen Y, Pei Z, Gao H, Shi W, Sun M, Xu Q, Zhao J, Meng W and Xiao K: Protective effects of polydatin against sulfur mustard-induced hepatic injury. Toxicol Appl Pharmacol 367: 1-11, 2019.
132. Zhang J, Meruvu S, Bedi YS, Chau J, Arguelles A, Rucker R and Choudhury M: Pyrroloquinoline quinone increases the expression and activity of Sirt1 and -3 genes in HepG2 cells. Nutr Res 35: 844-849, 2015.
133. Peng F, Liao M, Jin W, Liu W, Li Z, Fan Z, Zou L, Chen S, Zhu L, Zhao Q, *et al*: 2-APQC, a small-molecule activator of Sirtuin-3 (SIRT3), alleviates myocardial hypertrophy and fibrosis by regulating mitochondrial homeostasis. Signal Transduct Target Ther 9: 133, 2024.
134. Schlicker C, Boanca G, Lakshminarasimhan M and Steegborn C: Structure-based development of novel sirtuin inhibitors. Aging (Albany NY) 3: 852-872, 2011.
135. Nakamura Y, Suganami A, Fukuda M, Hasan MK, Yokochi T, Takatori A, Satoh S, Hoshino T, Tamura Y and Nakagawara A: Identification of novel candidate compounds targeting TrkB to induce apoptosis in neuroblastoma. Cancer Med 3: 25-35, 2014.
136. Alhazzazi TY, Kamarajan P, Xu Y, Ai T, Chen L, Verdin E and Kapila YL: A novel sirtuin-3 inhibitor, LC-0296, inhibits cell survival and proliferation, and promotes apoptosis of head and neck cancer cells. Anticancer Res 36: 49-60, 2016.