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Activation of Sirtuin 3, a Promising "Head Goose Molecule," Triggers the Negentropic Mechanism for Treating Metabolic Diseases

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ABSTRACT

Metabolic diseases, such as diabetes, obesity, and steatotic liver disease, represent a global epidemic. The pathogenesis of these disorders involves systemic disturbances in glucose homeostasis, lipid metabolism, energy balance, and inflammation, yet effective therapeutic strategies to correct these core disturbances remain limited. Silent information regulator 3 (sirtuin 3 (SIRT3)), a major mitochondrial deacetylase that we defined as the "head goose molecule," acts as a central regulator and can initiate a coordinated rescue of metabolic homeostasis. We integrate evidence that SIRT3 activation triggers a "negentropic mechanism," a suite of processes that collectively counteract systemic metabolic disorders by enhancing insulin sensitivity, promoting lipid oxidation, fine-tuning redox equilibrium, optimizing energy expenditure, and suppressing inflammation. The therapeutic potential of SIRT3 activators derived from natural products, synthetic compounds, and nicotinamide adenine dinucleotide (NAD^+) precursors is evaluated, highlighting their promise as safe and sustainable treatment options. This review establishes the role of SIRT3 as a master regulator and suggests that it should be targeted to reconstitute systemic metabolic homeostasis.

1. Introduction

Metabolic diseases include a range of disorders characterized by metabolic abnormalities, most notably diabetes, obesity, steatotic liver disease, cardiovascular disease, and associated metabolic syndromes [1,2]. Over the past two decades, the global prevalence of metabolic diseases has increased significantly, affecting one-quarter of the worldwide population, and is predicted to increase further in the future [3,4]. Complex and shared molecular mechanisms, including interactions between glucose metabolism and lipid metabolism, energy metabolism, inflammation, and oxidative stress, are often responsible for the occurrence and development of metabolic diseases [5–8]. Glucose metabolism disorders and insulin resistance are key mechanisms underlying many metabolic diseases. When the cellular response to insulin decreases, blood glucose levels increase, leading to increased insulin secretion, which can ultimately result in pancreatic failure [9]. Mitochondrial dysfunction can lead to excessive fatty acid accumulation, further disrupting glucose and lipid metabolism and energy homeostasis [5,10]. Oxidative stress, which is primarily associated with mitochondrial energy disorders, further exacerbates metabolic abnormalities by damaging cells and disrupting cellular signaling [6]. Chronic low-grade inflammation and immune cell infiltration associated with metabolic syndrome can also influence insulin signaling pathways, accelerating disease progression [11]. The complexity of metabolic diseases stems from the multifaceted interplay of genetic predispositions, environmental factors, and the gut microbiota, ultimately leading to a state of systemic biological disorder [12,13]. This progression can be viewed through the law of "entropy increase," a concept from physics, denoting the increase in systemic chaos that drives disease deterioration [14–17]. To quantitatively assess this metabolic chaos and overcome the challenges of histopathological heterogeneity, we first employed Shannon entropy to evaluate the efficacy of classic drugs such as berberine (BBR) and metformin, which is based on its prior success in assessing skin disease severity and metabolic syndrome

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risk [15,18,19]. Shannon entropy thus offers a potent and objective tool for evaluating interventions in highly heterogeneous metabolic diseases.

The treatment of metabolic diseases has become a public health challenge. Diseases such as obesity and type 2 diabetes mellitus (T2DM) require comprehensive treatment strategies because of their complicated pathogenesis [20,21]. First-line treatments include lifestyle interventions such as dietary control and increased physical activity. However, patients often struggle to maintain these lifestyle changes [22]. Drug treatments are primarily reserved for severe cases and face several obstacles, as they usually only mitigate symptoms, and no highly effective solutions or single medications that can address most problems have been discovered [23–26]. On the basis of our experience in pharmacological research and drug discovery [27–29], we propose that treating metabolic diseases with complex pathogenic mechanisms requires a systemic approach to regulate multiple signaling pathways through a central or key molecule. Therefore, we have introduced the concept of the "head goose molecule" [30], analogous to a lead goose guiding its flock in migration. An "head goose molecule" can control downstream effectors to systematically remedy dysfunctional pathogenesis. The intricate mechanisms and drug development challenges associated with metabolic diseases undoubtedly require effective and safe "head goose molecule" as front-runners to reprogram cellular networks and effectively suspend or reverse disease progression.

In long-term studies of pharmacological treatments for metabolic diseases, we identified silent information regulator 3 (sirtuin 3 (SIRT3)), a key regulator of mitochondrial function, as a direct target of the multieffect drug BBR [31]. As a nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase, SIRT3 has a conserved catalytic core structure comprising two distinct domains: a large Rossmann-fold domain that facilitates NAD^+ binding and a smaller zinc-binding domain responsible for substrate recognition (Fig. 1(a)) [32]. Through posttranslational deacetylation of various mitochondrial substrates, SIRT3 benefits essential metabolic disorders, such as diabetes mellitus, obesity, and hepatic steatosis. This highlights its potential as a promising therapeutic target for metabolic diseases. However, the translation of SIRT3 into a therapeutic target still presents challenges. These challenges include the potential for context-dependent and even contradictory roles of SIRT3 in different disease stages or tissues, the complexity of its regulation by NAD^+ levels and upstream signals, and the current lack of specific and potent SIRT3 activators suitable for clinical use.

This review aims to systematically summarize the evidence establishing SIRT3 as a pivotal "head goose molecule" that can trigger a negentropic mechanism-coordinated reversal of metabolic disorders by improving glucose homeostasis, lipid metabolism, energy balance, and inflammatory responses. We will critically evaluate the therapeutic potential of pharmacological SIRT3 activation, explicitly address the current challenges and limitations in the field, and provide a balanced perspective on the prospects of targeting SIRT3 for the systemic management of metabolic diseases.

2. SIRT3 appears to be a promising "head goose molecule for inducing negentropy to improve metabolic diseases

In contrast to the mechanism of "entropy increase" observed in metabolic diseases, negentropy refers to the systematic remediation of dysfunctional pathogenesis, in which regulatory networks are organized in an orderly fashion [16,30]. By investigating key regulatory molecules involved in glucose and lipid metabolism, energy metabolism, inflammatory responses, and oxidative stress, as well as the mechanisms of multieffect drugs, such as BBR and metformin [33,34], we identified SIRT3 as a potential "head goose molecule." The sirtuin family (SIRT1–7) is a class III histone deacetylase whose acetylated group is removed from the *N*-acetyllysine residues of histones or nonhistone proteins. They possess an NAD^+-binding catalytic domain and require NAD^+ as a cofactor to act on various substrates. All SIRTs contain N-terminal, catalytic core, and C-terminal structures of varying lengths (Fig. 1(b)). Notably, SIRT3, SIRT4, and SIRT5 possess an additional mitochondrial targeting sequence at the N-terminus, enabling their localization in mitochondria. Deacetylation activity is the predominant physiological role of SIRTs in metabolic regulation, with SIRT1, SIRT2, and SIRT3 exhibiting robust deacetylase activity, whereas other SIRTs display only weak activity (Fig. 1(c)). Similar to sirtuin-mediated epigenetic control in cancer through deacetylation [35], SIRT3 orchestrates multiple key molecules in metabolic pathways through deacetylation, thereby playing a "head goose" role in regulating the progression of nontumor metabolic diseases.

The role of SIRTs in metabolic diseases has been extensively studied (Table 1 [33,34,36–53]). This review focuses on nontumor metabolic contexts, given the documented beneficial and harmful roles of SIRTs in cancer [54,55]. Among all SIRTs, SIRT1, SIRT3, and SIRT6 are the most extensively studied in metabolic diseases, whereas the others are less frequently investigated [34,56,57]. SIRT1 and SIRT2 are generally protective against obesity and hepatic steatosis [34] but play dual roles in diabetes. For example, *Sirt1* knockdown enhances hepatic insulin sensitivity and reduces fasting hyperglycemia in diabetic rats [36], whereas its downregulation impairs insulin signaling and glucose uptake in adipocytes [37]. Similarly, SIRT2 promotes hepatic glucose uptake by deacetylating the glucokinase regulatory protein at K126 [34,38], but its downregulation improves glucose uptake in insulin-resistant Neuro 2a cells [58]. SIRT4 has detrimental effects on obesity and fatty liver disease. Its upregulation in nonalcoholic fatty liver disease (NAFLD) patients reduces fatty acid oxidation and promotes ectopic lipid storage [39]. Conversely, knocking down *Sirt4* in mouse liver alleviates NAFLD by suppressing mitochondrial trifunctional protein (MTP)-mediated fatty acid oxidation [39]. *Sirt4* also plays a contradictory role in insulin resistance; its knockdown enhances glucose-stimulated insulin secretion [40], but it also promotes insulin secretion through adenine nucleotide translocase 2 (ANT2) inhibition and elevated ATP levels [39]. SIRT5 improves obesity and hepatic steatosis; however, its high expression is correlated with elevated blood glucose levels. SIRT5 inhibition promotes pancreatic β-cell proliferation and insulin secretion, suggesting a role in the development of T2DM [41]. SIRT6 has conflicting glucoregulatory effects; SIRT6 improves glucose homeostasis in transgenic mice but also suppresses insulin signaling by targeting insulin receptor substrate (IRS)-1, IRS-2, and protein kinase B [42]. SIRT7 disrupts normal glucose and lipid metabolism by targeting specific sites in white/brown adipose tissue as well as the liver [34,42]. Therefore, the sirtuin family, apart from SIRT3, demonstrates both beneficial and harmful effects and even has dual functions in metabolic diseases such as diabetes mellitus, obesity, and hepatic steatosis.

3. The negentropic mechanism of SIRT3 in metabolic diseases

SIRT3 is predominantly localized in eukaryotic mitochondria, where it interacts with at least 84 mitochondrial proteins, suggesting its close association with multiple human diseases characterized by mitochondrial dysfunction [59]. In contrast to other members of the sirtuin family (Table 1), SIRT3 consistently exhibits protective effects throughout the pathogenesis of metabolic diseases, including glucose homeostasis, lipid metabolism, energy

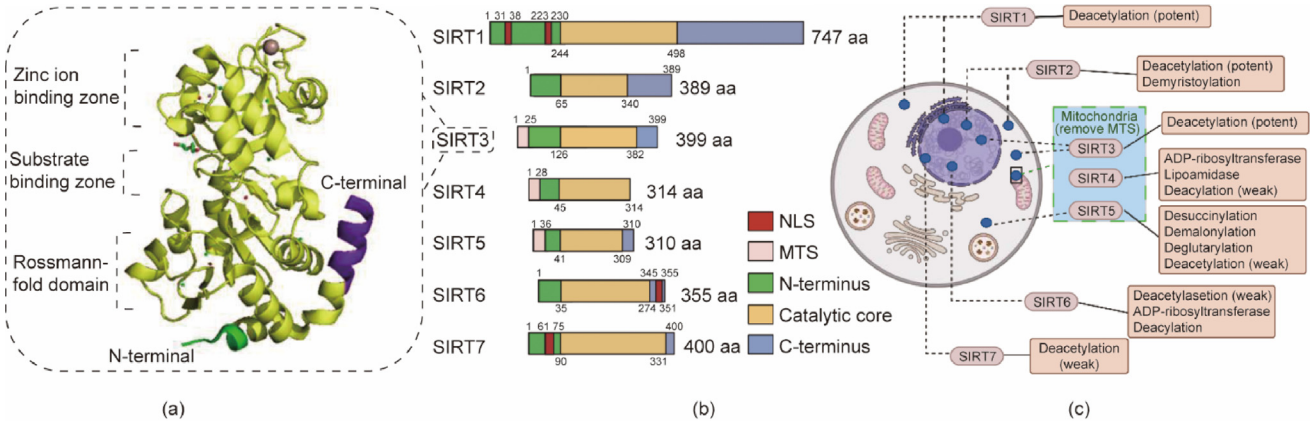


Fig. 1. The structure and function of the sirtuin family. (a) Crystal structure of human SIRT3 (PDB code: 3GLS). (b) The structure of the sirtuin family. (c) The location and function of the sirtuin family. PDB: Protein Data Bank; NLS: nuclear localization sequence; MTS: mitochondrial targeting sequence.

Table 1
Effects of the Sirtuin family on representative metabolic disorders.

SIRTs	Effect on representative metabolic disorders			References
	Diabetes mellitus	Obesity	Hepatic steatosis	
SIRT1	Beneficial role: *Sirt1* knockdown enhances hepatic insulin sensitivity and reduces fasting hyperglycemia in diabetic ratsHarmful role: hepatic *Sirt1* knockdown improves insulin sensitivity	Beneficial role: pharmacological induction of SIRT1 attenuates HFD-induced mitochondrial dysfunction, insulin resistance, and obesity	Beneficial role: pharmacological induction of SIRT1 attenuates HFD-induced mitochondrial dysfunction, insulin resistance, and obesity	[34,36,37,43]
SIRT2	Beneficial role: hepatic SIRT2 overexpression promotes hepatic glucose uptakeHarmful role: SIRT2 reduction in insulin-resistant neuro-2a cells increased insulin-stimulated glucose uptake	Beneficial role: SIRT2 deficiency accelerates the progression of NAFLD; induction of SIRT2 expression inhibits adipogenesis and alleviates the pathological features of NAFLD	Beneficial role: SIRT2 deficiency accelerates the progression of NAFLD; induction of SIRT2 expression inhibits adipogenesis and alleviates the pathological features of NAFLD	[34,38,44]
SIRT3	Beneficial role: *Sirt3* KO aggravated insulin resistance	Beneficial role: SIRT3 overexpression enhances FAO; SIRT3 promotes lipid mobilization in adipocytes	Beneficial role: SIRT3 overexpression enhances FAO; SIRT3 promotes lipid mobilization in adipocytes	[33,34,45]
SIRT4	Beneficial role: SIRT4 promotes insulin secretion by increasing ATP levelsHarmful role: SIRT4 deactivates AMPK and inhibits insulin secretion	Harmful role: *Sirt4* KO mice exhibited resistance to diet-induced obesity; increased hepatic SIRT4 level in NAFLD patients results in decreased FAO and ectopic lipid storage	Harmful role: *Sirt4* KO mice exhibited resistance to diet-induced obesity; increased hepatic SIRT4 level in NAFLD patients results in decreased FAO and ectopic lipid storage	[34,39,40,46,47]
SIRT5	Harmful role: inhibition of SIRT5 promotes pancreatic β-cell proliferation and insulin secretion; high expression of SIRT5 correlates with elevated blood glucose levels	Beneficial role: SIRT5 deacetylates metabolism-related proteins and attenuates hepatic steatosis in ob/ob mice; SIRT5 contributes to the conversion of WAT into BAT	Beneficial role: SIRT5 deacetylates metabolism-related proteins and attenuates hepatic steatosis in ob/ob mice; SIRT5 contributes to the conversion of WAT into BAT	[34,41,48–51]
SIRT6	Beneficial role: whole-body ablation of *Sirt6* in mice promotes diet-induced obesity and insulin resistanceHarmful role: *Sirt6* supra-physiological overexpression in hypothalamic pro-opiomelanocortin neurons promotes obesity	Beneficial role: whole-body ablation of *Sirt6* in mice promotes diet-induced obesity and insulin resistanceHarmful role: *Sirt6* supra-physiological overexpression in hypothalamic pro-opiomelanocortin neurons promotes obesity	Beneficial role: SIRT6 stimulates lipolysis in WAT and attenuates lipid accumulation in the liver	[42,52,53]
SIRT7	Harmful role: SIRT7 stimulates gluconeogenesis and inhibits glycolysis; deficiency of SIRT7 improves insulin sensitivity	Harmful role: *Sirt7* KO mice are resistant to HFD-induced obesity, insulin resistance, and glucose intolerance	Harmful role: *Sirt7* KO mice are resistant to HFD-induced obesity, insulin resistance, and glucose intolerance	[34,42]

BAT: blue adipose tissue; FAO: fatty acid oxidation; NAFLD: nonalcoholic fatty liver disease; KO: knockout; WAT: white adipose tissue; HFD: high-fat diet; AMPK: adenosine monophosphate-activated protein kinase.

balance, and inflammation [33,55,60]. Many studies have demonstrated a causal relationship between SIRT3 deficiency and pathological conditions such as diabetes, cardiovascular disease, and obesity [61,62]. These findings support our hypothesis that SIRT3 functions as a "head goose molecule" capable of initiating a negentropic mechanism to address systemic metabolic disorders in the body (Fig. 2).

3.1. Role of SIRT3 in glucose homeostasis

Glucose homeostasis is intricately linked to metabolic diseases. SIRT3 orchestrates glucose metabolism by ameliorating insulin resistance, optimizing glucose utilization, regulating glycolytic flux, and promoting gluconeogenesis, primarily through the deacetylation of key enzymes in various tissues (Fig. 3).

In diabetic and obese animal models, SIRT3 enhances insulin signaling via the deacetylation of acetyl-CoA synthetase 2 (AceCS2). This posttranslational modification activates AceCS2, promotes the conversion of acetate to acetyl-CoA, replenishes mitochondrial acetyl-CoA pools, and stimulates the tricarboxylic acid (TCA) cycle and ATP synthesis [63,64]. The resulting energy surplus helps reverse insulin resistance in hepatocytes and skeletal muscle [65]. *Sirt3* knockdown in myoblasts increases reactive oxygen species (ROS) levels, activates c-Jun N-terminal kinase (JNK)

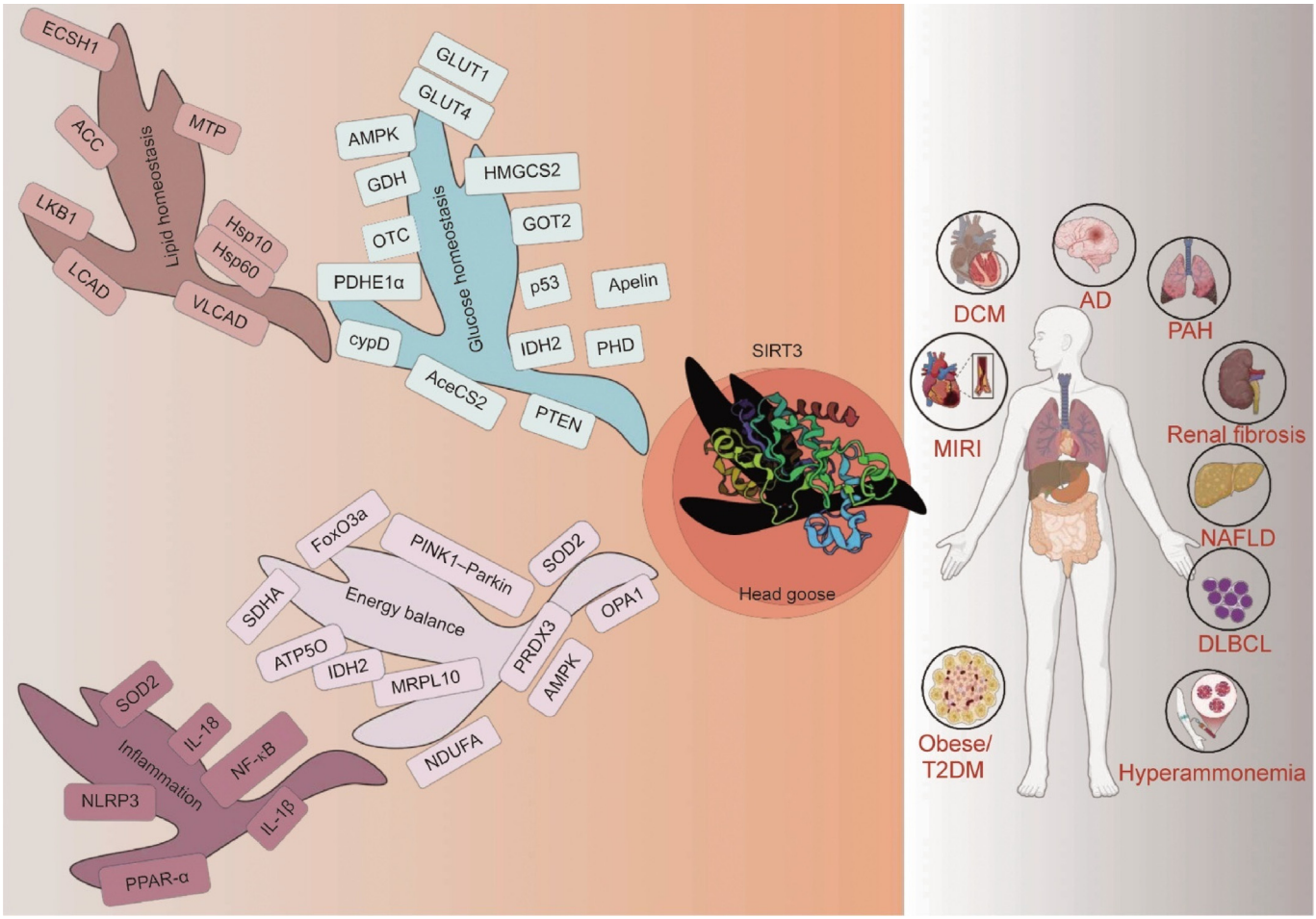


Fig. 2. SIRT3 serves as the "head goose molecule" for fighting metabolic diseases. ECSH1: enoyl-CoA hydratase short chain 1; ACC: acetyl-CoA carboxylase; LKB1: liver kinase B1; LCAD: long-chain acyl-coenzyme A dehydrogenase; VLCAD: very-long-chain acyl-CoA dehydrogenase; Hsp: heat shock protein; GLUT: glucose transporter; GDH: glutamate dehydrogenase; OTC: ornithine transcarbamylase; PDHE1α: pyruvate dehydrogenase E1 subunit alpha 1; cypD: cyclophilin D; AceCS2: acetyl-CoA synthetase 2; PTEN: phosphatase and tensin homolog; IDH2: isocitrate dehydrogenase 2; GOT2: glutamate oxaloacetate transaminase 2; p53: tumor protein 53; HMGCS2: 3-hydroxy-3-methylglutaryl-CoA synthase 2; FoxO3a: forkhead box protein O3; PINK1: phosphatase and tensin homolog-induced putative kinase 1; SDHA: succinate dehydrogenase complex flavoprotein subunit A; ATP5O: ATP synthase subunit O; MRPL10: mitochondrial ribosomal protein L10; NDUFA: NADH:ubiquinone oxidoreductase subunit A1; PRDX3: peroxiredoxin 3; SOD2: superoxide dismutase 2; OPA1: optic atrophy 1; IL: interleukin; NF-κB: nuclear factor kappa B; NLRP3: nucleotide-binding oligomerization domain (NOD)-like receptor thermal protein domain-associated protein 3; PPAR-α: peroxisome proliferator-activated receptor alpha; AD: Alzheimer's disease; DCM: dilated cardiomyopathy; MIRI: myocardial ischemia reperfusion injury; DLBCL: diffuse large B-cell lymphoma; PAH: pulmonary arterial hypertension.

and IRS-1, and impairs insulin signaling, underscoring its role in improving hyperglycemia in diabetes [66]. SIRT3 also optimizes glucose utilization. For example, SIRT3 promotes glucose uptake by upregulating the expression of the glucose transporters GLUT1 and GLUT4 in cardiomyocytes under diabetic energy stress [65]. SIRT3 also increases pyruvate flux into the TCA cycle in renal fibrosis by deacetylating the E1 component subunit-α of pyruvate dehydrogenase and isocitrate dehydrogenase 2 (IDH2), thereby enhancing mitochondrial glucose oxidation [67,68]. In diffuse large B-cell lymphoma, SIRT3 activates glutamate dehydrogenase (GDH) to enhance the TCA cycle and cellular metabolism [60]. With respect to the regulation of glycolysis, SIRT3 has dual effects under different pathological and physiological conditions. In diabetic cardiomyopathy, SIRT3 upregulates 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) via the apelin pathway, promotes tumor protein 53 (p53) deacetylation, and inhibits p53-induced glycolysis regulatory phosphatase (TIGAR), collectively increasing fructose-2,6-bisphosphate levels to activate phosphofructokinase 1 (PFK1) and enhance glycolytic flux [61,69]. Under energy deprivation, decreased ATP levels trigger SIRT3-mediated adenosine monophosphate-activated protein kinase (AMPK) phosphorylation, which promotes glucose uptake and the activation of glycolytic enzymes, ensuring rapid energy replenishment [60].

Conversely, in cancer models, SIRT3 suppresses glycolysis and tumor growth through multiple mechanisms. First, SIRT3 reduces ROS production, stabilizes prolyl hydroxylase (PHD), and promotes hypoxia-inducible factor-1α (HIF-1α) degradation, downregulating HIF-1α-dependent glycolytic gene expression and lactate production [70,71]. Second, SIRT3 deacetylates cyclophilin D (cypD) to dissociate hexokinase II (HKII) from mitochondria, uncoupling glycolysis from oxidative phosphorylation [60]. In addition, SIRT3 stabilizes p53 by deacetylating phosphatase and tensin homolog (PTEN), inhibiting murine double minute2 (MDM2)-mediated nuclear export and degradation and promoting the accumulation of p53 to activate pro-apoptotic signals. Accumulated p53 also controls metabolism by downregulating critical components of the glycolytic machinery at the transcriptional level [60,72]. SIRT3 also suppresses the Warburg effect by deacetylating glutamate oxaloacetate transaminase 2 (GOT2), downregulating the expression of glycolytic genes such as *Glut1* and lactate dehydrogenase A (*Ldha*), and redirecting metabolism toward oxidative phosphorylation [65,73]. During fasting, SIRT3 promotes gluconeogenesis by

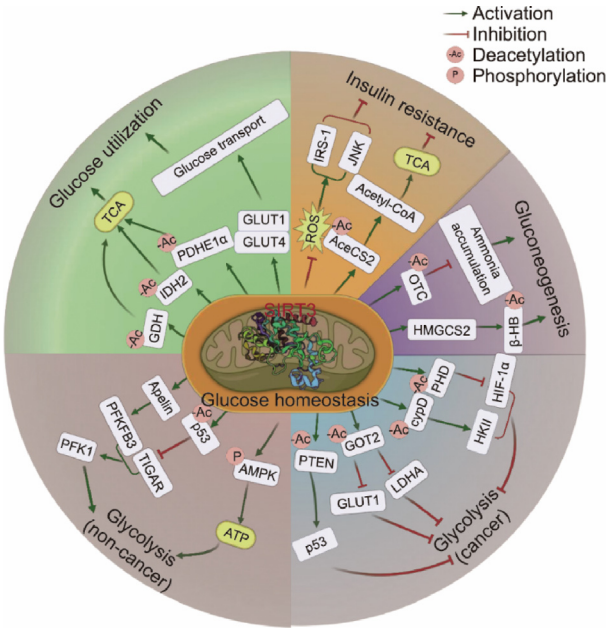


Fig. 3. SIRT3 maintains glucose homeostasis by ameliorating insulin resistance, optimizing glucose utilization, regulating glycolytic flux, and promoting fasting gluconeogenesis. TCA: tricarboxylic acid; JNK: c-Jun N-terminal kinase; PFKFB3: 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PFK1: phosphofructokinase 1; TIGAR: p53-induced glycolysis regulatory phosphatase; LDHA: lactate dehydrogenase A; PHD: prolyl hydroxylase; HKII: hexokinase II; HIF-1α: hypoxia-inducible factor-1α; β-HB: β-hydroxybutyrate.

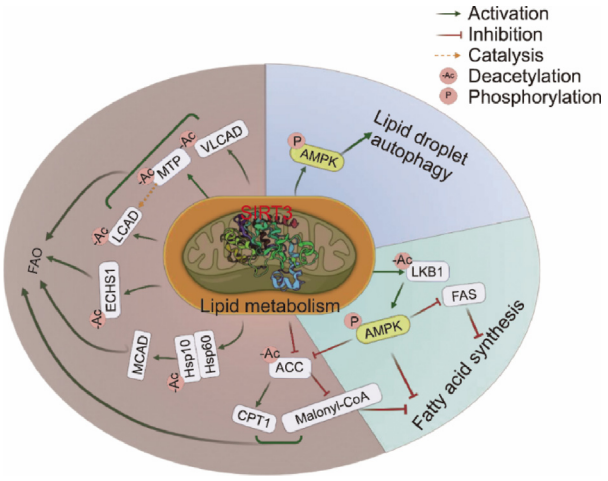


Fig. 4. SIRT3 maintains lipid balance through promoting FAO, inhibiting lipogenesis, and enhancing autophagy-mediated lipid clearance. FAS: fatty acid synthase; LKB1: liver kinase B1; MCAD: medium-chain acyl-CoA dehydrogenase; ECHS1: enoyl-CoA hydratase 1; CPT1: carnitine palmitoyltransferase1; LCAD: long-chain acyl-coenzyme A dehydrogenase; MTP: mitochondrial trifunctional protein; VLCAD: very long-chain acyl-coenzyme A dehydrogenase; AMPK: adenosine monophosphate-activated protein kinase;Hsp10: heat shock protein 10; Hsp60: heat shock protein 60.

deacetylating ornithine transcarbamylase (OTC), facilitating amino acid-derived glucose synthesis and preventing ammonia accumulation. Liver-specific *Sirt3* knockout (KO) mice exhibit hypoglycemia and lethal hyperammonemia, underscoring the physiological necessity of this pathway [74]. SIRT3 also deacetylates and activates 3-hydroxy-3-methylglutaryl-CoA synthase 2 (HMGCS2) to increase β-hydroxybutyrate (β-HB) production, supporting energy maintenance during fasting [75].

3.2. Role of SIRT3 in lipid metabolism

Dysregulated lipid metabolism is a key factor in obesity, NAFLD, and insulin resistance. SIRT3 plays a crucial role in maintaining lipid balance through various regulatory mechanisms, including promoting fatty acid oxidation (FAO), inhibiting lipogenesis, and enhancing lipid droplet autophagy (Fig. 4).

Long-chain acyl-coenzyme A dehydrogenase (LCAD) is a rate-limiting enzyme in FAO and catalyzes the initial step of dehydrogenation [76]. In the absence of SIRT3, increased lysine 42 acetylation in LCAD leads to excessive accumulation of hepatic triglycerides and fatty acid metabolism intermediates, resulting in myocardial hypertrophy and possibly heart failure [73]. In contrast, SIRT3 positively regulates LCAD expression via deacetylation, increasing enzyme activity and promoting FAO [73]. Similarly, SIRT3 deacetylates MTP, restoring FAO, and improving NAFLD in high-fat diet (HFD)-fed mice [77]. Very-long-chain acyl-CoA dehydrogenase (VLCAD) is also activated by SIRT3-mediated deacetylation at lysine 507, enhancing FAO and stabilizing its membrane localization via cardiolipin binding. SIRT3 deficiency in mice impairs this interaction, compromising FAO and contributing to metabolic diseases [78]. During prolonged fasting, SIRT3 deacetylates heat shock protein 10 (Hsp10) at lysine 56 to stabilize the Hsp10–Hsp60 chaperone complex, which maintains medium-chain acyl-CoA dehydrogenase (MCAD) activity and optimizes β-oxidation [79]. In the ischemic heart, SIRT3 inactivates acetyl-CoA carboxylase (ACC) via deacetylation, lowering malonyl-CoA levels, relieving carnitine palmitoyltransferase 1 (CPT1) inhibition, and facilitating mitochondrial fatty acid uptake for β-oxidation [80,81]. Reduced malonyl-CoA also indirectly inhibits *de novo* fatty acid synthesis [82]. Moreover, SIRT3 deacetylates enoyl-CoA hydratase 1 (ECHS1), restoring its activity in oxidizing fatty acids and branched-chain amino acids, reducing oncogenic metabolite accumulation, and inhibiting mechanistic target of rapamycin (mTOR)-driven carcinogenesis under nutrient overload [83].

SIRT3 also suppresses lipogenesis through the deacetylation-mediated activation of liver kinase B1 (LKB1), which subsequently triggers AMPK signaling. This cascade downregulates the transcription of key lipogenic enzymes, including ACC and fatty acid synthase (FAS), thereby reducing lipid synthesis [84]. In HFD-fed *Sirt3* KO mice, cardiac lipotoxicity is exacerbated, indicating that SIRT3 plays a protective role against lipid overload [61]. Notably, SIRT3 also maintains lipid droplet homeostasis via AMPK-dependent autophagy. For example, in NAFLD models, SIRT3 overexpression enhances phosphorylated AMPK and autophagy, reducing hepatic lipid accumulation and lipotoxicity. Conversely, *Sirt3* KO impairs mitophagy and worsens hepatic steatosis, underscoring the therapeutic potential of this axis [62].

3.3. Role of SIRT3 in energy balance

Energy homeostasis is essential for physiology, and its dysregulation underlies numerous metabolic disorders. SIRT3 maintains this balance through three interconnected mechanisms: ATP optimization, redox regulation, and mitochondrial plasticity (Fig. 5).

SIRT3 generally increases ATP production by deacetylating key enzymes involved in energy metabolism. *Sirt3* KO mice exhibit more than 50% reduced basal ATP levels in metabolically active tissues, accompanied by hyperacetylation of ATP synthase and impaired exercise tolerance [59,65,76]. In HFD-induced T2DM mice, SIRT3 downregulation in skeletal muscle leads to hyperacetylation of ATP synthase subunit O (ATP5O) at histidine 135, decreasing electron transport chain (ETC) efficiency and ATP synthesis and accelerating insulin resistance and hyperglycemia. SIRT3 also deacetylates NADH:ubiquinone oxidoreductase subunit

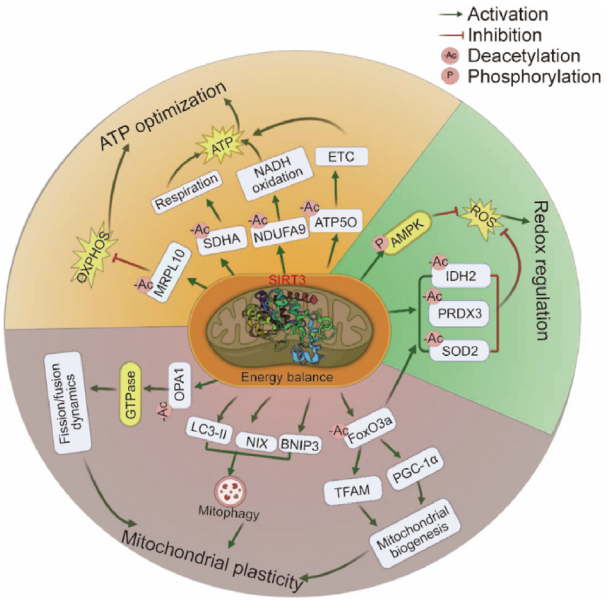


Fig. 5. SIRT3 typically maintains energy homeostasis through a tripartite interconnected mechanism, including ATP optimization, redox regulation, and mitochondrial plasticity. OXPHOS: oxidative phosphorylation; NDUFA9: NADH:ubiquinone oxidoreductase subunit A9; ETC: electron transport chain; LC3-II: microtubule-associated protein 1 light chain 3; BNIP3: B cell lymphoma 2 (BCL2)-interacting protein 3; NIX: BNIP3-like protein X; TFAM: mitochondrial transcription factor A; PGC-1α: proliferator-activated receptor gamma coactivator 1 alpha.

A9 (NDUFA9) and complex II (SDHA), increasing nicotinamide adenine dinucleotide (NADH)oxidation and succinate-driven respiration [73,85]. Paradoxically, excessive SIRT3 activity can impair bioenergetics by deacetylating mitochondrial ribosomal protein L10 (MRPL10), disrupting ribosome assembly, suppressing the synthesis of oxidative phosphorylation (OXPHOS) subunits and ATP production, and exacerbating neuronal dysfunction in Alzheimer's disease models [86].

In redox regulation, the crosstalk between SIRT3 and AMPK forms a redox-sensitive feedback loop. AMPK inhibition diminishes SIRT3-mediated ROS suppression in hyperglycemic models, suggesting that AMPK acts downstream to amplify the antioxidant effects of SIRT3 [87]. Furthermore, SIRT3 maintains mitochondrial redox homeostasis by deacetylating and activating antioxidant enzymes such as superoxide dismutase 2 (SOD2 and MnSOD), IDH2, and peroxiredoxin 3 (PRDX3) through two mechanisms: direct deacetylation and forkhead box protein O3 (FoxO3a)-mediated transcriptional upregulation. In cardiac ischemia reperfusion injury, SIRT3 deficiency worsens oxidative stress and apoptosis, whereas its overexpression reduces infarct size by enhancing ROS clearance, highlighting its therapeutic potential in cardiovascular and metabolic diseases [88].

SIRT3 also regulates mitochondrial plasticity by modulating fission/fusion dynamics, mitophagy, and biogenesis. SIRT3 deacetylates optic atrophy 1 (OPA1) to promote mitochondrial fusion and cristae integrity, a mechanism that is impaired in patients with cardiac hypertrophy [89]. SIRT3 also activates the PINK1–Parkin mitophagy axis, upregulating B cell lymphoma 2 (BCL2)-interacting protein 3 (BNIP3), BNIP3-like protein X (NIX), and microtubule-associated protein 1 light chain 3 (LC3-II) to clear damaged organelles. Diabetic mice with *Sirt3* knockdown develop cardiac hypertrophy because of defective mitophagy, highlighting the role of SIRT3 in adaptation to metabolic stress [90,91]. Additionally, SIRT3 deacetylates FoxO3a to activate proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) and mitochondrial transcription factor A (TFAM), promoting mitochondrial DNA (mtDNA) replication and ETC protein synthesis [92,93]. This coordinated triad of mitochondrial dynamics, mitophagy-mediated quality control, and biogenesis-driven renewal, regulated by SIRT3, collectively protects the robustness of the mitochondrial network from metabolic stress-induced dysfunction.

3.4. Role of SIRT3 in inflammation

Chronic inflammation, a hallmark of metabolic disorders, arises from dysregulated immune responses that disrupt redox homeostasis and exacerbate tissue dysfunction. Preclinical and clinical evidence highlights the ability of SIRT3 to suppress inflammation by inhibiting the activation of inflammatory cells and cytokine production (Fig. 6).

At the cellular level, SIRT3 reprograms immune responses to restrict inflammatory cell activation. Specifically, SIRT3 promotes M2 macrophage polarization, shifting the balance from proinflammatory to anti-inflammatory phenotypes, as indicated by the increased infiltration of inflammatory cells in SIRT3-deficient mice [34]. This anti-inflammatory reprogramming is further reinforced by the SIRT3-mediated increase in mitochondrial antioxidant enzymes such as SOD2 [94], which reduces ROS accumulation, suppresses MAPK signaling, and alleviates lipopolysaccharides (LPS)-induced macrophage hyperactivation [34,95].

SIRT3 also suppresses key cytokines via deacetylation-dependent mechanisms. In aortic endothelial cells, SIRT3 activates peroxisome proliferator-activated receptor alpha (PPAR-α) to upregulate endothelial nitric oxide synthase (eNOS) and suppress inducible nitric oxide synthase (iNOS), thereby attenuating vascular injury [96]. Furthermore, SIRT3 suppresses the nucleotide-binding oligomerization domain (NOD)-like receptor thermal protein domain-associated protein 3 (NLRP3) inflammasome, an effect that is particularly important in early metabolic disease for preventing vascular inflammation via upregulation of autophagy. SIRT3 also reduces the expression of the downstream cytokines interleukin (IL)-1β and IL-18 in hyperlipidemic-induced inflammation and vascular endothelial dysfunction, countering sustained inflammation in later disease stages [97,98]. In cardiac inflammation and fibrosis models, SIRT3 deacetylates nuclear factor kappa B (NF-κB) subunits to attenuate proinflammatory cytokine transcription [99]. Notably, SIRT3 also disrupts the ROS–MAPK–NF-κB axis in free fatty acid-induced renal tubulointerstitial inflammation, underscoring its role in mitigating metabolic stress-driven organ damage [98,100].

Therefore, the regulatory network of SIRT3 is a multitargeted "guardian" molecule that integrates metabolic adaptation with anti-inflammatory signaling, offering transformative potential for addressing the inflammatory underpinnings of metabolic diseases.

In summary, on the basis of the functions and mechanisms of SIRT3 described above, we consider SIRT3 a suitable "head goose molecule" that guides many substrates and targeted molecular networks, which we refer to as detailed negentropic mechanisms. This regulatory network, termed the negentropic mechanism, counteracts the biological entropy increase associated with metabolic diseases. These molecules and pathways are complex and significantly overlap with metabolism-related regulatory molecules, providing a strong basis for the belief that SIRT3 can serve as a lead molecule in reprogramming the biological entropy increase of metabolic diseases [34].

4. Activators of SIRT3 have potential for the treatment of metabolic diseases

The pivotal role of SIRT3 in mitigating metabolic disorders highlights the therapeutic promise of its activators. Unlike specific inhi-

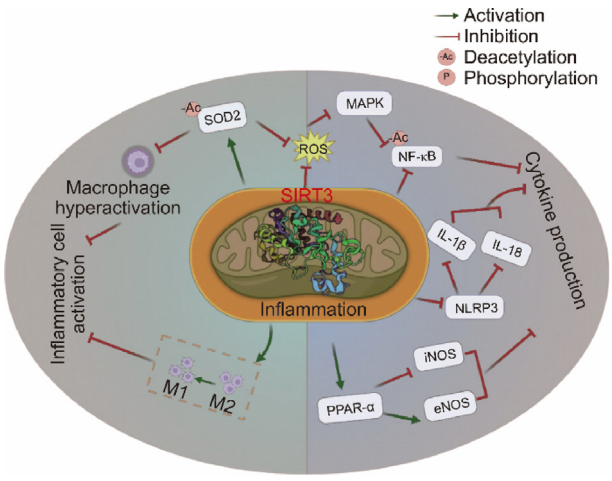


Fig. 6. SIRT3 suppresses inflammation activation in metabolic diseases through the modulation of inflammatory cells and signaling pathways. iNOS: inducible nitric oxide synthase; eNOS: endothelial nitric oxide synthase.

bitors, SIRT3 activators often produce milder, more physiologically tuned responses because of feedback within downstream pathways, making them particularly suitable for long-term management of chronic conditions. A primary challenge, however, is achieving isoform selectivity, given the structural conservation among sirtuins [33]. Notably, tissue-specific expression, distinct subcellular localization, and the recent identification of unique structural pockets in SIRT3 offer promising avenues for developing targeted drugs [101]. SIRT3 activity is also associated with NAD+ availability, genetic background, and disease state, leading to therapeutic variability across patient subgroups. Therefore, precise identification of SIRT3-specific binding sites and the development of highly selective activators are essential for minimizing off-target effects and enabling personalized therapies. The following sections discuss SIRT3 activators, categorized as natural products, synthetic compounds, and NAD+ precursors, with an emphasis on their mechanisms of action and clinical significance (Fig. 7 and Table 2 [31,33,65,101–165]).

4.1. Natural products as SIRT3 activators with multiple mechanisms

Natural products are rich sources of SIRT3 activators and offer significant potential for discovering drugs that enhance the negentropy capacity of the body [16]. These compounds typically activate SIRT3 through one or more mechanisms including upregulating its expression, increasing NAD^+ levels, or directly binding to and allosterically activating the enzyme (Table 2).

4.1.1. Metformin

Metformin, a well-known clinical hypoglycemic drug, can activate SIRT3 and other members of the sirtuin family to treat metabolic, inflammatory, and age-related diseases. Metformin upregulates SIRT3 expression in skeletal muscle, promoting glucose uptake and ameliorating insulin resistance [102], and in cardiovascular models, where it confers protection against hypoxia/reoxygenation injury [103]. Metformin also counteracts oxidative stress and senescence by increasing mitochondrial SIRT3 levels [104] and reversing H_2O_2-induced osteoblast apoptosis [105]. Clinically, metformin attenuates leukocyte oxidative stress in T2DM patients by coordinating the upregulation of SIRT3 and glutathione peroxidase 1 expression [106]. Paradoxically, metformin can suppress SIRT3 expression in the liver via AMPK-independent mechanisms, reducing mitochondrial ATP production and increasing protein acetylation [166]. These contrasting findings highlight the tissue-specific and dose-dependent effects of metformin on SIRT3. Although metformin represents an indirect SIRT3 modulator with proven clinical benefits, such as in a clinical trial (NCT05949008, Phase 4) for the treatment of diabetes, its mechanistic relationship with SIRT3 requires further clarification because no direct binding or disease-dependent complexity has been confirmed.

4.1.2. Berberine

BBR is a natural isoquinoline alkaloid derived from traditional medicinal plants such as *Coptis chinensis*. BBR has been traditionally used in the clinic for its antimicrobial properties and, more recently, for the treatment of metabolic diseases. BBR acts through multiple mechanisms to treat metabolic diseases, including AMPK activation, modulation of the gut microbiota, and upregulation of low-density lipoprotein receptors (LDLRs) [167,168]. The negentropic mechanism is considered the primary target of BBR, with SIRT3 serving as a key "head goose molecule" [16,30]. In general, BBR activates SIRT3 through three pathways: ① Direct binding and activation. Our recent work revealed that BBR is a mitochondria-homing agent that directly binds to and activates SIRT3. This interaction triggers the selective and reversible dissociation of mitochondrial complex I and mediates the deacetylation of its NADH:ubiquinone oxidoreductase core subunit S1 (NDUFS1), ultimately rectifying hepatocellular glucose and lipid metabolism [31]. ② Indirect pathways involving NAD^+ and AMPK. BBR inhibits mitochondrial complex I, increasing the adenosine monophosphate-activated protein (AMP)/ATP ratio and activating AMPK. This activation upregulates nicotinamide phosphoribosyltransferase (NAMPT), increasing the level of intracellular NAD^+, an essential cofactor for SIRT3 activation [107,169]. ③ Upregulation of SIRT3 expression. BBR restores SIRT3 expression and activity in rodents fed a HFD, alleviating mitochondrial dysfunction and promoting fatty acid oxidation via the deacetylation of LCAD [107,170]. BBR also inhibits MAPK/NF-κB signaling in adipose tissue through this mechanism [108].

Clinically, oral administration of BBR to patients with hypercholesterolemia for more than three months reduced the total cholesterol level by 29%, triglyceride level by 35%, and low-density lipoprotein cholesterol level by 25% [171]. In addition, similar to metformin and rosiglitazone, BBR is safe and effective for treating patients with T2DM because of its ability to lower blood glucose levels [172]. These pleiotropic effects, which also involve other targets, such as AMPK, LDLR, insulin receptor (InsR), eukaryotic translation initiation factor 2-alpha kinase 2 (EIF2AK2), and the gut microbiota (conceptualized as a "drug cloud" or dCloud) [16,168], work in concert with SIRT3 activation to activate the negentropy capacity of the body, as indicated by the success of BBR ursodeoxycholate (HTD1801) in clinical trials for metabolic dysfunction-associated steatohepatitis (MASH) and T2DM [173,174].

4.1.3. Silybin

Silybin, a flavonolignan from *Silybum marianum*, is recognized for its antioxidant and hepatoprotective properties [109] and has recently attracted renewed interest as a SIRT3 inducer [110]. In cisplatin-induced models of acute kidney injury, silybin increased *Sirt3* messenger RNA (mRNA) and protein levels in the renal tissue of cisplatin-treated mice and human kidney 2 cells, restoring mitochondrial function and reducing oxidative damage [110]. In addition, the NAD^+/SIRT2 pathway and AMPK/transforming growth factor beta 1 (TGF-β1)/Smad signaling are important mediators through which silybin inhibits NLRP3 inflammasome activation or improves glucose and lipid metabolism in rodent NAFLD models [175,176]. A clinical trial (NCT03538327, Phase 4) is underway to

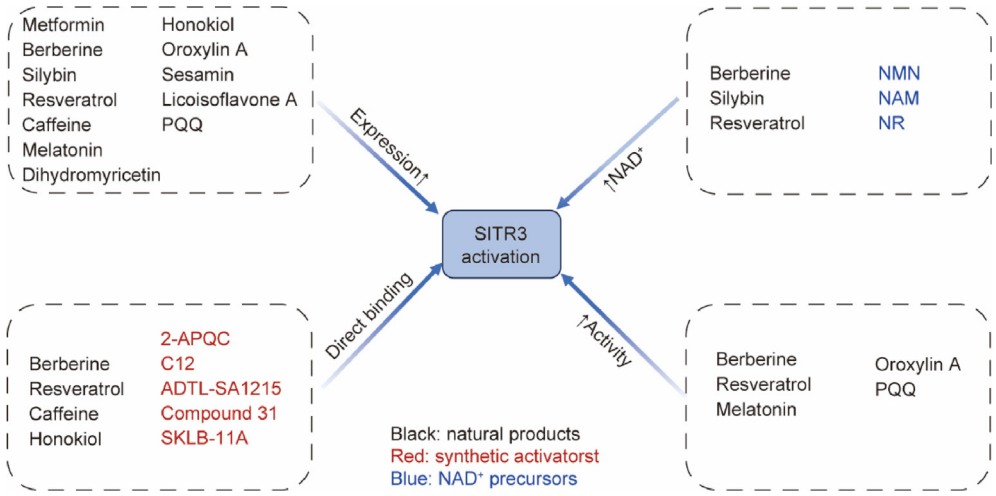


Fig. 7. Representative SIRT3 activators and their mechanisms of action. PQQ: pyrroloquinoline quinone; 2-APQC: 2-aminophenyl pyrazoloquinoline carboxamide; C12: 7-hydroxy-3-(4′-methoxyphenyl) coumarin; ADTL-SA1215: a novel allosteric SIRT3 activator; SKLB-11A: a breakthrough candidate with submicromolar affinity and high selectivity for SIRT3; NMN: nicotinamide mononucleotide; NAM: nicotinamide; NR: nicotinamide riboside.

investigate the metabolic and vascular effects of silybin in hypertensive patients.

4.1.4. Resveratrol (RSV)

RSV is a polyphenolic compound that activates the mitochondrial deacetylase SIRT3, as well as other sirtuin members, including SIRT1 and SIRT5, and thus plays crucial roles in antioxidant protection and metabolic regulation [33]. The mechanisms by which RSV activates SIRT3 are primarily indirect and involve the AMPK–PGC-1α–estrogen-related receptor alpha (ERRα) axis and an increase in the NAD^+/NADH ratio [111,112]. Notably, RSV can also exhibit inhibitory effects by directly interacting with the sirtuin catalytic core to suppress SIRT3-dependent deacetylation of GDH while stimulating SIRT5 [113,114]. In addition to regulating SIRT3, RSV has been shown to activate various transcription factors and antioxidant enzymes and suppress antiapoptotic genes and inflammatory biomarkers in aging-related diseases [177]. Despite challenges such as promiscuous target engagement and extensive first-pass metabolism [33], a clinical trial (NCT04886297, Phase 3) is currently investigating its utility for lipid metabolism disorders.

4.1.5. Other natural products

Caffeine, recognized for its antioxidant properties, directly binds to and enhances SIRT3 activity, promoting SOD2 deacetylation and restoring its antioxidant capacity [115]. In addition, caffeine facilitates the conversion of ADP to ATP, which increases hepatic cyclic adenosine monophosphate (cAMP) levels and cAMP response binding protein (CREB) phosphorylation, potentially enhancing SIRT3 expression and downstream AMPK and ACC phosphorylation [116]. The upregulation of SIRT3 expression by caffeine may be crucial for alleviating high-energy diet-induced hepatic steatosis [116]. On the basis of this well-confirmed mechanism, a clinical trial (NCT02929901, Phase 3) evaluated the effects of supplementation with the main components of coffee (caffeine and chlorogenic acid) on inflammatory and metabolic factors, hepatic steatosis, and fibrosis in NAFLD patients with T2DM.

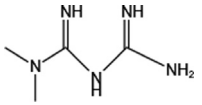
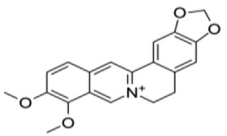
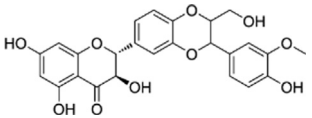
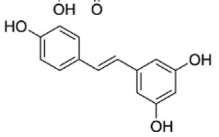
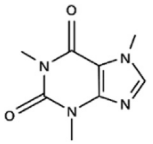
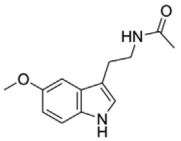
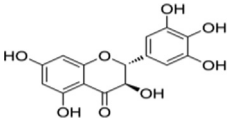
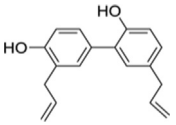
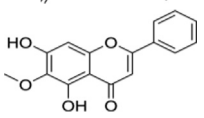
Melatonin, a mitochondrially synthesized indoleamine, has several bioactivities, including the regulation of circadian rhythms, antioxidant defense, and the maintenance of mitochondrial homeostasis through the activation of SIRT3 [178]. Melatonin coexists with SIRT3 in mitochondria [179] and modulates SIRT3 by enhancing its activity without affecting protein expression [180]. Melatonin also upregulates SIRT3 expression through upstream AMPK–PGC-1α–SIRT3 signaling pathways [181]. In addition, melatonin attenuates anoxia/reoxygenation injury by inhibiting excessive mitophagy through the melatonin membrane receptor 2 (MT2)/SIRT3/FoxO3a signaling pathway [117]. Supported by preclinical evidence of metabolic regulation and anti-inflammatory effects, a clinical trial (NCT02681887, Phase 3) for the treatment of diabetes is underway [118].

Dihydromyricetin (DHY), a flavonoid compound from *Ampelopsis grossedentata*, is recognized for its potential therapeutic effects on various metabolic disorders. DHY improves glucose and lipid metabolism, mitigates inflammatory responses, and reduces oxidative stress through several signaling pathways, including AMPK, mTOR/autophagy, PGC-1α/SIRT3, mitogen-activated protein kinase (MEK)/extracellular regulated protein kinases (ERK), and phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) [119,120]. Notably, the increase in SIRT3 protein expression induced by DHY plays a pivotal therapeutic role in diabetic mice [121] and in mice fed a HFD [120,122]. DHY also promotes the binding of activating protein-1 (AP-1), PGC-1α, or other factors to the SIRT3 promoter, thereby increasing SIRT3 expression and suppressing oxidative stress, inflammation, and necroptosis in mice with streptozotocin (STZ)-induced diabetes [123]. A clinical trial (NCT03606694, Phase 2) is registered in Mexico to investigate the effects of DHY on glycemic control, insulin sensitivity, and insulin secretion in individuals with T2DM.

Honokiol, a biphenolic lignan extracted from the traditional Chinese herb *Magnolia bark* (Hou Po), exhibits anti-inflammatory, antioxidant, antidepressant, neuroprotective, and anticancer properties [124,125]. Its therapeutic potential in mitochondrial dysfunction-related metabolic disorders is attributed to the modulation of SIRT3, either through direct binding to SIRT3 [126] or indirect upregulation of SIRT3 expression via the AMPK/PGC-1α signaling pathway [127]. Despite limited clinical evidence, nanoparticle-based delivery systems improve the bioavailability and safety of honokiol, supporting its translational potential [182].

Oroxylin A, a bioactive flavonoid from *Scutellaria baicalensis* and *Oroxylum indicum*, has emerged as a potent SIRT3 activator with broad therapeutic effects in metabolic diseases and cancer [128,129]. Mechanistically, oroxylin A indirectly increases the expression and/or activity of SIRT3, which subsequently deacetylates mitochondrial targets such as cypD to inhibit glycolysis [129]. Compared with other SIRT3 activators, such as RSV, oroxylin A exhibits superior mitochondrial specificity and metabolic stabil-

Table 2
Activators of SIRT3 potential for treating metabolic diseases.

Compound	Molecular formula	EC_{50} for SIRT3 activation	SIRT3 activation mechanisms	Effects	Top study status/conditions	References
Natural products						
Metformin		(196.5 ± 23.0) μmol·L^{-1} (rat hepatocytes)	Increases expression	Promotes glucose uptake; ameliorates insulin resistance; mitigates myocardial hypoxia/reoxygenation (H/R) injury; attenuates leukocyte oxidative stress	Marketed drug	[102–106,147]
BBR		(0.52 ± 0.06) μmol·L^{-1}	Direct binding; increases activity; increases expression; increases NAD^+	Rescues mitochondrial dysfunction; enhances fatty acid oxidation; improves glucose and lipid metabolism; antioxidant; reduces blood glucose; inhibits NF-κB signaling	NCT05647915, Phase 4, obesity| obesity, abdominal| NAFLD	[31,107,108,148]
Silybin		68 μmol·L^{-1} (HepG2)	Indirect binding; increases expression	Restoring mitochondrial function; reduces oxidative damage	NCT03538327, Phase 4, hypertension	[109,110,149]
Resveratrol		(80.3±2.8) μmol·L^{-1} (HepG2)	Direct binding; increases activity; increases expression; increases NAD^+/NADH	Regulates mitochondrial ROS; stimulates ETC efficiency; enhances ATP synthesis; regulates metabolic homeostasis	NCT04886297, Phase 3, dyslipidemias	[33,111,112,114,150]
Caffeine		45.8 μmol·L^{-1} (HEK293-STF)	Direct binding; increases expression	Antioxidant properties; restores SOD2 antioxidative capacity; alleviates hepatic steatosis	NCT02929901, Phase 3, type 2 diabetes|NAFLD	[115,116,151]
Melatonin		(271 ±0.1) μmol·L^{-1} (HepG2)	Indirect binding; increases expression; increases activity	Antioxidant defenses; mitochondrial biogenesis; reinforces mitophagy and metabolic flexibility; improves insulin sensitivity; glycemic control and inflammatory inhibition in diabetic patients	NCT02681887, Phase 3, obesity| prediabetic state	[117,118,152–154]
Dihydromyricetin		32.66 μmol·L^{-1} (BV-2)	Indirect binding; increases expression	Enhances glucose and lipid metabolism; mitigates inflammation; reduces oxidative stress; ameliorates myocardial hypertrophy, fibrosis, and injury	NCT03606694, Phase 2, type 2 diabetes mellitus	[119–123,155]
Honokiol		(34.3 ± 3.4) μmol·L^{-1} (HepG2)	Direct binding; increases expression	Improves insulin sensitivity; attenuates mitochondrial fragmentation, ROS overproduction, and apoptosis in cardiomyocytes	Preclinical	[124–127,156]
Oroxylin A		22.7 μmol·L^{-1} (HepG2)	Indirect binding; increases expression; increases activity	Enhances metabolic reprogramming; suppressing glycolysis; promotes apoptosis; mitigates oxidative damage; reduces hepatic steatosis; inhibits adipogenesis	Preclinical	[128–130,157–159]

(*continued on next page*)

Table 2 (*continued*)

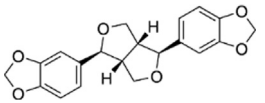
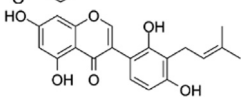
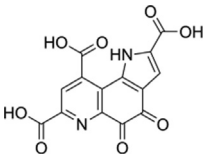
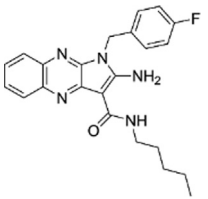
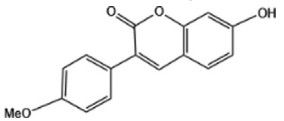
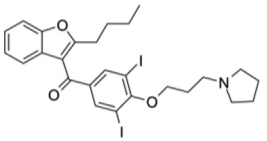
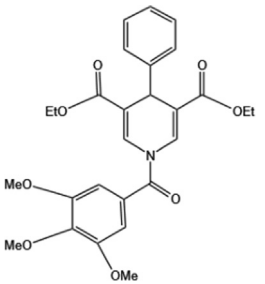
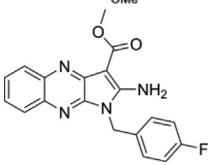
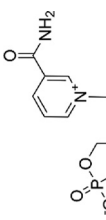
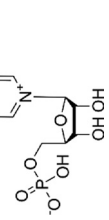
Compound	Molecular formula	EC_{50} for SIRT3 activation	SIRT3 activation mechanisms	Effects	Top study status/conditions	References
Sesamin		(9.4 ± 0.8) μmol·L^{-1} (HepG2)	Increases expression	Improves cardiac function; prevents cardiac hypertrophy; suppresses ROS production	Preclinical	[65,131,160]
Licoisoflavone A		7.2 μmol·L^{-1}	Increases expression	Restrains cardiomyocyte hypertrophy; cardiac hypertrophy therapy	Preclinical	[132,161]
Pyrroloquinoline quinone		(45.71 ± 12.09) μmol·L^{-1} (HepG2)	Increases expression; increases activity	Protects against high glucose-induced oxidative stress and apoptosis; therapy for hyperlipidemia, diabatic cardiomyopathy, and healthy aging	Preclinical	[133,134,162]
Synthetic compounds 2-Aminophenyl pyrazoloquinoline carboxamide		—	Direct binding; selective SIRT3 activator	Therapy for isoproterenol-induced cardiac hypertrophy and myocardial fibrosis	Preclinical	[101]
7-Hydroxy-3-(4′-methoxyphenyl) coumarin		(88.97 ± 1.48) μmol·L^{-1} (BEAS-2B)	Direct binding; high binding affinity and specificity for SIRT3, stabilizing enzyme-substrate complex	Enhances antioxidant and metabolic function; enhances mitochondrial respiration; reduces ROS; rescues mitochondrial dysfunction in ALS	Preclinical	[33,113,135,136,163]
ADTL-SA1215		(2.19 ±0.16) μmol·L^{-1}	Direct binding; allosteric SIRT3 activator	Induces autophagy	Preclinical	[137,138]
1,4-Dihydropyridine compound 31		0.43–3.49 μmol·L^{-1}	Direct binding; SIRT3-specific activators with minimal impacts on SIRT1/2/5/6	Enhances SIRT3 deacetylase activity with minimal impacts on SIRT1/2/5/6	Preclinical	[139,164]
SKLB-11A		(21.95 ± 1.57) μmol·L^{-1}	Direct binding; allosteric SIRT3 activator with high binding affinity and specificity	Restores cardiac ejection fraction and fractional shortening; reduces myocardial injury markers; mitigates mitochondrial dysfunction; decreases infarct size and attenuates fibrosis; improves mitochondrial respiration and ATP synthesis	Preclinical	[140,141]

Table 2 (*continued*)

Compound	Molecular formula	EC_{50} for SIRT3 activation	SIRT3 activation mechanisms	Effects	Top study status/conditions	References
NAD^+ precursors						
Nicotinamide mononucleotide		–	Indirect binding; converts into NAD^+ and activates SIRTs	Attenuates metabolic disorders; increases muscle insulin sensitivity; remodel in women with prediabetes	NCT04903210, Phase 4, hypertension	[143,144]
Nicotinamide		>10 μmol·L^{-1} (RAW 264.7)	Indirect binding; converts into NAD^+ and activates SIRTs	Alleviates diastolic dysfunction; enhances myocardial energetics; reduces cardiomyocyte stiffness; improves calcium-dependent active relaxation; lowers blood pressure and reduces cardiac mortality in patients	NCT04903210, Phase 4, hypertension	[145,165]
Nicotinamide riboside		–	Indirect binding; converts into NAD^+ and activates SIRTs	Therapy for insulin sensitivity and hepatic steatosis	NCT03821623, Phase 2, hypertension| arterial stiffness	[142,146]

EC_{50}: 50% of the maximal binding effect.

ity, thereby minimizing off-target effects [183]. Despite promising preclinical efficacy [130], the clinical translation of oroxylin A has been limited to early-phase safety trials for acute liver injury [184]. Other compounds, such as sesamin (a known antioxidant from sesamin seeds), licoisoflavone A (a bioactive compound from Tongmaiyangxin Pills), and pyrroloquinoline quinone (PQQ; an aromatic heterocyclic anionic orthoquinone), can upregulate the protein expression of SIRT3 [65,131–134,185]. Although these compounds show potential for the treatment of metabolic disorders, they are still in the early stages of development, and their long-term safety and clinical potential require further validation.

4.2. Synthetic compounds for direct binding and activation of SIRT3

SIRT3 is considered a "head goose molecule" that induces negentropy; therefore, researchers are striving to synthesize highly efficient, low-toxicity candidate compounds that directly target SIRT3 (Table 2).

2-Aminophenyl pyrazoloquinoline carboxamide (2-APQC) was developed as a potent and selective activator of SIRT3 on the basis of targeted molecular docking studies on pocket L [101]. The unique selectivity of 2-APQC for SIRT3 contributes to its therapeutic efficacy in both *in vitro* and *in vivo* models of isoproterenol-induced cardiac hypertrophy and myocardial fibrosis [101].

7-Hydroxy-3-(4′-methoxyphenyl) coumarin (C12), discovered in 2017, selectively activates SIRT3-mediated deacetylation of MnSOD, thereby enhancing the mitochondrial antioxidant capacity and metabolic function [113]. Structural studies have indicated that C12 has high binding affinity and specificity for SIRT3 [113]. In models of cardiac hypertrophy, the C12-derived analog SZC-6 reduces left ventricular dysfunction, enhances mitochondrial respiration, and decreases ROS through the SIRT3–LKB1–AMPK pathway [135]. C12 also rescues mitochondrial dysfunction in models of amyotrophic lateral sclerosis by reducing the number of acetylated lysine residues and improving neuronal survival [136].

ADTL-SA1215, a novel allosteric SIRT3 activator, was developed using structure-based drug discovery approaches. ADTL-SA1215 targets a hydrophobic allosteric pocket near the SIRT3 acyl-lysine binding site [137]. Mechanistic characterization revealed that ADTL-SA1215 achieves SIRT3 selectivity through unique molecular interactions that stabilize the allosteric site and increase the deacetylase activity of SIRT3 by approximately twofold in triple-negative breast cancer cells. This activation results in a concentration-dependent decrease in acetylation levels at lysines 68 and 122 of the canonical SIRT3 substrate manganese superoxide dismutase. Furthermore, in mouse xenograft models, ADTL-SA1215 induces autophagy by modulating autophagy-associated regulatory proteins, thereby alleviating triple-negative breast cancer [137,138].

The 1,4-dihydropyridine scaffold was initially identified as a pan-Sirtuin modulator [186]. The subsequent development of potent and selective next-generation SIRT3 activators was achieved through rational structural optimization guided by structure activity relationship analysis [139]. Among these, 1,4-dihydropyridine compound 31 (diethyl 4-phenyl-1-(3,4,5-trime thoxybenzoyl)-1,4-dihydropyridine-3,5-dicarboxylate) enhances the activity of GDH and increases the levels of deacetylated K68- and K122-acMnSOD in cancer cells, both of which are indicators of SIRT3 activation [139,187,188]. Although the current experimental data are limited to cellular models, specifically breast and thyroid cancer cell lines, the observed increase in metabolic enzyme activity in these models aligns with the established role of SIRT3 in metabolic diseases, as demonstrated in HFD and diabetic mouse models. These findings suggest its potential as a therapeutic target for metabolic disorders.

SKLB-11A was recently identified through a hybrid strategy combining computational, structural transformation, and experimental approaches. SKLB-11A was recognized as a breakthrough candidate with submicromolar affinity and high selectivity for SIRT3, offering a first-in-class small molecule as an allosteric SIRT3 activator [140,141]. SKLB-11A binds to a unique allosteric site on SIRT3, distinct from the NAD^+-binding domain, and triggers a conformational rearrangement that is critical for enzyme activation. In preclinical models, SKLB-11A showed robust cardioprotective effects and reduced myocardial ischemia/reperfusion injury [141].

4.3. NAD^+ precursors for SIRT3 activation

NAD^+ is a crucial cosubstrate for sirtuins, particularly SIRT1 and SIRT3, and plays a central role in regulating energy metabolism, oxidative stress, and aging [142,189]. A unique reciprocal relationship exists between SIRT3 and NAD^+ bioavailability [190]. SIRT3 removes the acetyl group from the substrate lysine by transferring ADP-ribose from NAD^+ to the substrate, generating 2′-*O*-acyl-ADP-ribose and nicotinamide. In this mechanism, NAD^+ does not interact directly with SIRT3 but does bind to its ADP-ribose to facilitate the deacetylation reactions of the SIRT3–substrate complex by altering the conformation of the substrate [115]. SIRT3 can bind to and deacetylate nicotinamide mononucleotide adenylyltransferase 3 (NMNAT3), thereby increasing its enzymatic activity and increasing mitochondrial NAD^+ production. This creates a positive feedback loop that further activates SIRT3, a mechanism demonstrated in the mitigation of cardiac hypertrophy [190].

Increasing intracellular NAD^+ levels by increasing the supply of cell-permeable NAD^+ precursors offers an alternative approach for activating sirtuins (Table 2). In addition to diet-derived and endogenous biosynthetic pathways, extrinsic approaches are effective at increasing the NAD^+ pool *in vivo*. These methods include direct supplementation with NAD^+ precursors such as nicotinamide mononucleotide (NMN), nicotinamide (NAM), and nicotinamide riboside (NR) to increase NAD^+ levels and enhance SIRT3 activity. For example, NMN stimulates mitochondrial SIRT3, and its beneficial effects on mitochondrial deacetylation and cardioprotection are blunted in the hearts of *Sirt3*$^{-/-}$ mice [191]. Long-term NMN administration mitigates metabolic disturbances and physiological decline induced by a HFD in aging mice [143] and improves muscle insulin sensitivity, insulin signaling, and muscle remodeling in overweight or obese women with prediabetes [144]. Similarly, NAM restores NAD^+ levels and improves diastolic function in rodent models of aging and hypertension [145], whereas NR enhances insulin sensitivity and reduces hepatic steatosis in models of obesity and type 2 diabetes [142]. Clinical observations corroborate these findings. High dietary intake of naturally occurring NAD^+ precursors, such as NAM, correlated with lower blood pressure and a reduced risk of cardiac mortality in a long-term human cohort study [145]. Compared with low-dose (5 mg·kg^{-1}) and high-dose (900 mg·kg^{-1}) NR, NR at a controlled dosage of 30 mg·kg^{-1} body weight yields better beneficial effects and improved metabolic adaptability [146]. However, dosage and genetic background may influence the experimental phenotypes and should be considered in application [189].

Although the activation of SIRT3 shows promise for treating metabolic diseases, its inhibition represents a viable therapeutic strategy for other conditions, particularly in oncology. For example, 3-(1*H*-1,2,3-triazol-4-yl) pyridine (3-TYP), the first reported selective SIRT3 inhibitor, has been shown to reduce intracellular ATP levels and increase superoxide production. In cardiac models, 3-TYP antagonizes the activating effect of melatonin on SIRT3, decreases SOD2 deacetylation, and impairs its cardioprotective effects. Although 3-TYP exhibits more potent inhibitory activity against SIRT3 than against SIRT1 and SIRT2, its structure is based on a nicotinamide analog, which poses potential off-target risks [55]. Another inhibitor, LC0296, occupies the NAD^+ binding pocket and disrupts the catalytic cycles of enzymes, potentially inducing apoptosis and inhibiting proliferation in cancer cells [192]. Similarly, the SIRT3 inhibitor 2-methoxyestradiol, a natural derivative of 17β-estradiol that binds to both canonical and allosteric sites, has been shown to inhibit mitochondrial biogenesis in an osteosarcoma cancer cell model [193]. These studies underscore the potential of SIRT3 inhibition as a strategy to reduce cancer cell survival. Notably, however, SIRT3 may play distinct roles across various cancer types, and its dual effects should be carefully considered [55].

5. Conclusions and future perspectives

The multifactorial nature of metabolic diseases such as diabetes, obesity, and hepatic steatosis necessitates therapeutic strategies that address systemic pathogenic disruptions [194,195], which we conceptualize as an "increase in biological entropy." Given its central role in regulating glucose/lipid metabolism, mitochondrial energy balance, oxidative stress, and inflammation, we propose that SIRT3 functions as a "head goose molecule." By guiding the realignment of dysregulated metabolic and inflammatory networks, SIRT3 activation promotes a negentropic mechanism essential for the long-term management of these chronic conditions. Activators of SIRT3, including natural products, synthetic compounds, and NAD^+ supplements, represent mild, safe, and sustainable therapeutic modalities. Although substantial preclinical evidence supports the metabolic and tissue-protective effects of SIRT3 activation, translational success depends on overcoming challenges related to compound selectivity, delivery, tissue/organ specificity, and long-term safety. Addressing these hurdles will enable SIRT3 activators to emerge as innovative therapeutics for non-tumor-related metabolic diseases. In conclusion, the regulatory framework, with SIRT3 as the "head goose molecule" that activates the negentropy capacity of the body, can serve as a practical reference for drug repurposing research and treatment strategy selection. We anticipate further practical applications of this framework following future large-scale multicenter clinical trials.

CRediT authorship contribution statement

Hu Li: Writing – review & editing, Writing – original draft, Funding acquisition. **Tong Wang:** Writing – original draft, Visualization. **Biao Dong:** Writing – original draft, Funding acquisition. **Zonggen Peng:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Jiandong Jiang:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

We declare that we have no financial or personal relationships with other individuals or organizations that could improperly influence our work, and that there is no professional or other personal interest of any nature or kind in products, services, or companies that could be construed as influencing the position presented in the revised manuscript entitled "Activation of Sirtuin 3, a promising "head goose molecule," triggers the negentropic mechanism for treating metabolic diseases."

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