

Succinylation modification in diabetes and diabetic complications: Mechanisms and functions (Review)

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Abstract. Despite adequate glycaemic control, diabetic complications frequently progress, underscoring how persistently protein post-translational modifications (PTMs) contribute to disease pathology by sustaining ‘metabolic memory’. Lysine succinylation, a PTM derived from the tricarboxylic acid cycle intermediate succinyl-CoA and primarily regulated by the desuccinylase sirtuin 5 (SIRT5), has emerged as a key metabolic modulator. By introducing a marked shift in lysine charge, succinylation can notably influence enzyme activity and protein stability. The present review integrates current evidence associating the disruption of the succinyl-CoA/SIRT5 regulatory axis with impaired metabolic flexibility in diabetes. The mechanisms by which pathological hypersuccinylation compromises mitochondrial bioenergetics, particularly by inhibiting uncoupling protein 1 in obesity and the pyruvate dehydrogenase complex in diabetic cardiomyopathy, are described, and its implications in neurodegeneration within diabetic retinopathy through modification of optineurin are elucidated. The present review also discusses the mechanistic role of epigenetic dysregulation, highlighting how activation of the lysine acetyltransferase 2A/H3K79 succinylation/spermidine/spermine N1-acetyltransferase family member 2 pathway promotes ferroptosis and inflammation in diabetic kidney disease. The context-dependent duality of SIRT5 function is also examined; although key in limiting lipotoxicity in cardiomyocytes and podocytes, SIRT5 can paradoxically aggravate glomerular fibrosis in renal mesangial cells by suppressing p53 signalling. The present findings suggested that re-establishing succinylation homeostasis represents not simply a metabolic correction but a strategic therapeutic objective. However,

given the tissue-specific and frequently opposing effects of SIRT5, future therapeutic approaches should aim to emphasize organ-targeted delivery rather than systemic modulation to minimize off-target toxicity while effectively addressing diabetic complications.

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1. Introduction

Post-translational modifications (PTMs) operate at the intersection of epigenetic regulation and cellular metabolism, expanding proteomic diversity and fine-tuning biological function by modulating protein activity, stability and intermolecular interactions. Although histone acetylation and methylation have been extensively studied, increasing attention has turned to lysine acylations derived from metabolic intermediates (1,2). Among these, lysine succinylation involves the covalent transfer of a succinyl group from succinyl-CoA to lysine residues. In contrast to relatively neutral modifications such as acetylation, succinylation introduces a marked negative charge that offsets the intrinsic positive charge of lysine (3,4). This charge reversal induces substantial conformational changes, affecting enzymatic activity, protein stability, intermolecular interactions and subcellular localization.

Succinylation is regulated through both enzymatic and non-enzymatic mechanisms (Fig. 1). In the nucleus, lysine acetyltransferase 2A (KAT2A), functioning together with the α -ketoglutarate dehydrogenase (α -KGDH) complex, as well as canonical acetyltransferases such as p300/CREB-binding protein, catalyse histone succinylation at sites including H3K79 and H3K122, influencing transcriptional programs by promoting open chromatin configurations that activate pro-inflammatory and ferroptosis-related genes (5-8). In the mitochondrial matrix, succinylation predominantly

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occurs through non-enzymatic reactions. The mitochondrial microenvironment promotes favourable biochemical conditions-specifically, an alkaline pH and elevated local concentrations of succinyl-CoA-for spontaneous succinyl group transfer, which occurs at rates exceeding non-enzymatic acetylation (9,10). As a result, mitochondrial proteins are particularly vulnerable to this modification.

Given that non-enzymatic succinylation readily occurs under physiological conditions, maintenance of cellular homeostasis depends on efficient removal of succinyl groups by dedicated ‘eraser’ enzymes. Sirtuin (SIRT)-5, an NAD⁺-dependent class III lysine deacylase localized primarily to mitochondria, serves as the principal desuccinylase and displays strong catalytic selectivity for negatively charged acyl modifications (11,12). Although SIRT7 has been reported to desuccinylate specific histone residues (13), SIRT5 serves the dominant role in counteracting the continual, spontaneous addition of succinyl groups. Through this reversible regulation, SIRT5 modulates enzyme function across key metabolic pathways, including the urea cycle (argininosuccinate synthase 1), ketogenesis (HMGCS2), non-shivering thermogenesis [uncoupling protein 1 (UCP1)], carbohydrate oxidation through the pyruvate dehydrogenase complex (PDC) and fatty acid β -oxidation (14-18). These actions preserve proteomic integrity and sustain metabolic flexibility, limiting metabolic dysfunction in preclinical models, such as ob/ob and diet-induced obesity murine models (16,18).

Under physiological conditions, basal succinylation levels are tightly regulated. However, metabolic stress, such as that observed in diabetes and its associated complications, can destabilize this equilibrium (19). Chronic hyperglycaemia and lipid overload affect tricarboxylic acid (TCA) cycle flux by overwhelming oxidative capacity and stalling intermediate turnover, leading to intracellular accumulation of succinyl-CoA. In addition, oxidative stress and NAD⁺ depletion in the diabetic environment compromise SIRT5 activity by inducing transcriptional repression and limiting its essential co-substrate, respectively. The resulting imbalance between succinyl-CoA availability and desuccinylase capacity promotes pathological protein hypersuccinylation. This state establishes a feed-forward mechanism in which hypersuccinylated enzymes exhibit diminished activity, further aggravating metabolic inflexibility and perpetuating ‘metabolic memory’ (20,21).

Emerging evidence has implicated dysregulated succinylation in a spectrum of metabolic disorders, including impaired thermogenesis in obesity, diabetic cardiomyopathy (DbCM), diabetic kidney disease (DKD) and diabetic retinopathy (DR) (22,23). The present review consolidates current mechanistic insights, elucidating how aberrant succinylation associates metabolic imbalance with organ-specific dysfunction (Fig. 2). Through examining the context-dependent functions of SIRT5, the therapeutic importance of targeting the succinyl-CoA/SIRT5 axis in diabetes and its secondary complications are underscored.

2. Dysregulated succinylation in diabetes mellitus (DM)

DM is a chronic metabolic disease defined by inadequate insulin secretion, impaired insulin sensitivity or a combination

of both, leading to sustained hyperglycaemia. Hallmark clinical manifestations include polyphagia, polydipsia and polyuria. DM comprises type 1 diabetes (T1D), T2D, gestational diabetes and a number of less prevalent subtypes, with disease susceptibility influenced by both genetic background and environmental factors (24,25). The global prevalence continues to escalate, with projections indicating that ~783 million individuals will be affected by 2045 (26). DbCM, nephropathy and retinopathy remain the principal causes of morbidity and mortality. Persistent hyperglycaemia promotes chronic low-grade inflammation and oxidative stress (27), with data indicating that protein PTMs serve pivotal roles in regulating the immune and metabolic circuits underlying diabetic complications (28). As gestational diabetes and certain uncommon variants often progress to T1D or T2D, they are not further addressed in the present review.

T1D: Metabolic mismatch and succinyl-CoA:3-ketoacid CoA transferase (SCOT) inhibition. T1D is an autoimmune disorder characterized by progressive immune-mediated destruction of pancreatic β cells, culminating in absolute insulin deficiency (29,30). In the absence of endogenous insulin, glucose homeostasis is markedly disrupted, resulting in chronic hyperglycaemia and lifelong reliance on exogenous insulin therapy. The metabolic consequences of T1D extend beyond impaired glucose regulation, affecting lipid and amino acid metabolism, and increasing vulnerability to systemic complications, including both macrovascular and microvascular damage (31-33). Although β -cell-directed autoimmunity defines T1D, the broader metabolic alterations across peripheral tissues remain insufficiently characterized.

Direct evidence associating lysine succinylation with T1D is currently limited; however, findings from experimental models have implicated the dysfunction of SCOT as a potential mechanistic association (34). SCOT, a central enzyme in ketone body utilization and a key consumer of succinyl-CoA, exhibits reduced activity in T1D models due to inhibitory tyrosine nitration and decreased 3-oxoacid CoA-transferase 1 expression. This impairment is particularly detrimental within the metabolic context of T1D. In contrast to T2D, absolute insulin deficiency in T1D drives unrestrained lipolysis and excessive hepatic ketogenesis. The resulting surge in ketone body production necessitates efficient SCOT-mediated turnover; however, suppression of SCOT activity compromises this process. Such metabolic disequilibrium may limit succinyl-CoA utilization, leading to its accumulation within the mitochondrial matrix, potentially promoting pathological hypersuccinylation in susceptible tissues, including the myocardium (35,36).

Emerging data suggested that mitochondrial succinyl-CoA accumulation is not simply a metabolic by-product, but may foster broader cellular dysfunction (37,38). Beyond SCOT-dependent mechanisms, the characteristics of the T1D inflammatory environment may directly affect succinylation dynamics, specifically the balance between spontaneous modification and SIRT5-mediated desuccinylation. β -cell destruction is orchestrated by pro-inflammatory cytokines, including IL-1 β and IFN- γ , which promote pronounced oxidative stress and mitochondrial injury in pancreatic islets (39,40). Although direct validation in T1D remains limited, evidence from related metabolic disorders, such as non-alcoholic fatty

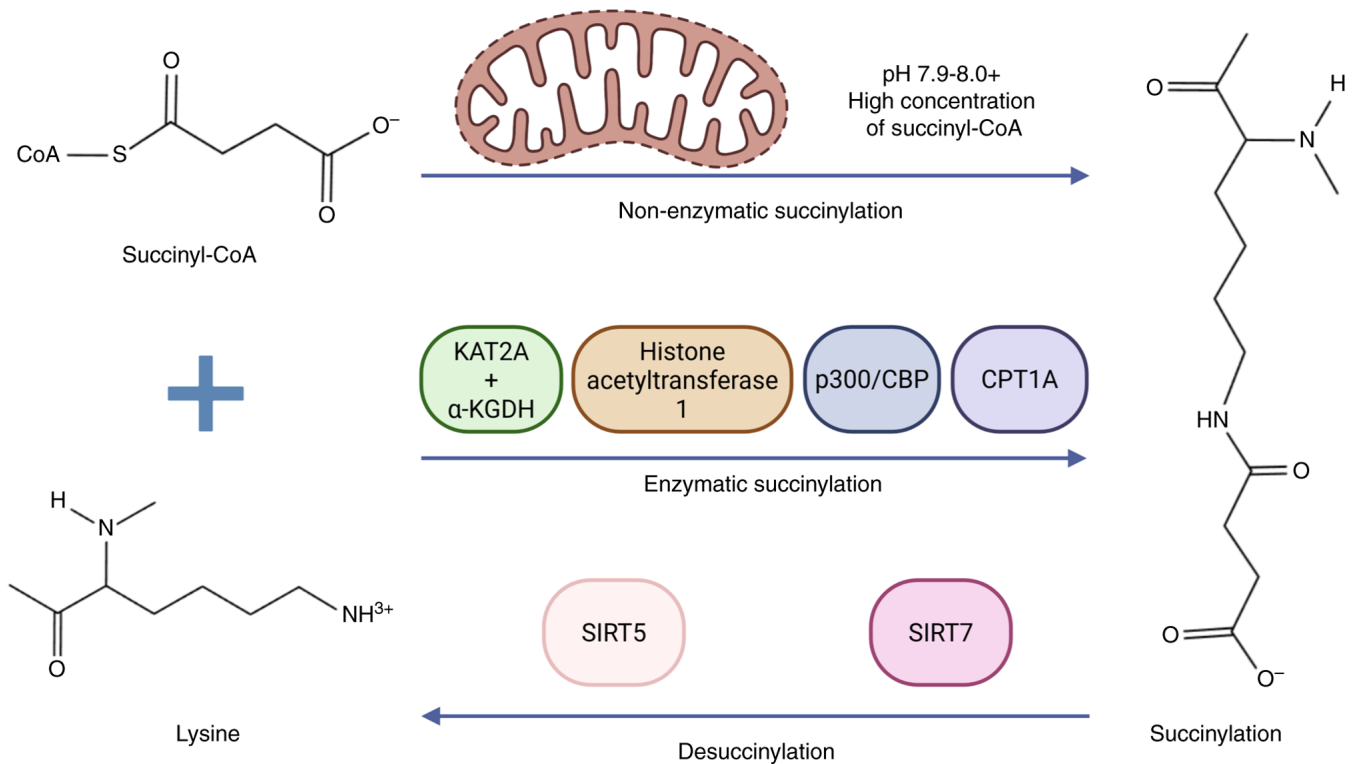


Figure 1. Lysine succinylation and desuccinylation processes, and the numerous enzymes involved. Created with BioRender.com. KAT2A, lysine acetyltransferase 2A; α -KGDH, α -ketoglutarate dehydrogenase; CBP, CREB-binding protein; CPT1A, carnitine palmitoyltransferase 1A; SIRT, sirtuin.

liver disease (NAFLD) and metabolic cardiomyopathy, has indicated that oxidative stress can attenuate SIRT5 activity, diminishing de-succinylation capacity (41,42). It may therefore be hypothesised that cytokine-driven redox imbalance in T1D suppresses SIRT5 function, resulting in the accumulation of hypersuccinylated mitochondrial proteins that further compromise β -cell bioenergetics and viability.

In addition, protein succinylation may contribute to the immunopathogenesis of T1D. PTMs can generate neoepitopes that initiate or amplify autoimmune responses (43,44). As aforementioned, succinylation induces notable structural and physicochemical alterations in target proteins. These modifications may theoretically generate neoantigens or modify antigen processing and presentation by major histocompatibility complex molecules in β cells. In comparison, analogous mechanisms have been established for other PTMs, such as citrullination in autoimmune diseases (45); whether aberrant succinylation functions as a source of neoantigens in T1D remains an important and unresolved question requiring further investigation.

T2D: Insulin resistance and β -cell dysfunction. T2D arises from the interplay between peripheral insulin resistance and an insufficient compensatory increase in insulin secretion (46,47). In the early stages, pancreatic β cells increase insulin secretion to compensate for reduced insulin sensitivity. This adaptive response depends on precise regulation of glycolytic flux, TCA cycle activity and lipid metabolism in response to glucose, incretin signalling and pharmacological stimuli, such as metformin and sodium-glucose cotransporter-2 inhibitors (48). However, persistent exposure to hyperglycaemia and

elevated lipid levels imposes chronic metabolic stress that progressively exhausts β -cell reserve. The ensuing dysfunction is characterized by a depletion of TCA cycle intermediates, including citrate, malate and oxaloacetate, increased oxidative stress and impaired insulin secretory capacity (49). Obesity notably increases the risk of T2D by exacerbating insulin resistance and sustaining low-grade inflammation, which further affects metabolic homeostasis (50). Although classical disruptions in TCA cycle dynamics and fatty acid oxidation (FAO), including metabolic inflexibility and incomplete lipid oxidation, are well documented (51,52), the contribution of emerging PTMs, particularly protein succinylation, to β -cell stress adaptation remains incompletely understood and merits further investigation.

Experimental data have indicated that aberrant succinylation, specifically pathological hyper-succinylation, directly impairs β -cell function in T2D, a central event in disease progression. In Goto-Kakizaki rats, a widely used T2D model, both expression and activity of SCOT are diminished (53). Reduced SCOT function leads to intracellular accumulation of succinyl-CoA, which adversely affects β -cell function by impairing glucose-stimulated insulin secretion (54). Targeted silencing of SCOT in insulinoma cells has been shown to markedly attenuate glucose-stimulated insulin secretion, underscoring its key metabolic role. In addition, chronic glucolipotoxicity, a defining feature of T2D, induces β -cell apoptosis (55,56). Furthermore, experimental overexpression of SIRT5 counteracts this process by upregulating mitochondrial anti-apoptotic proteins Bcl-2 and Bcl-XL, preventing cytochrome *c* release and inhibiting downstream caspase-3/7 activation, preserving β -cell viability and function (57). These

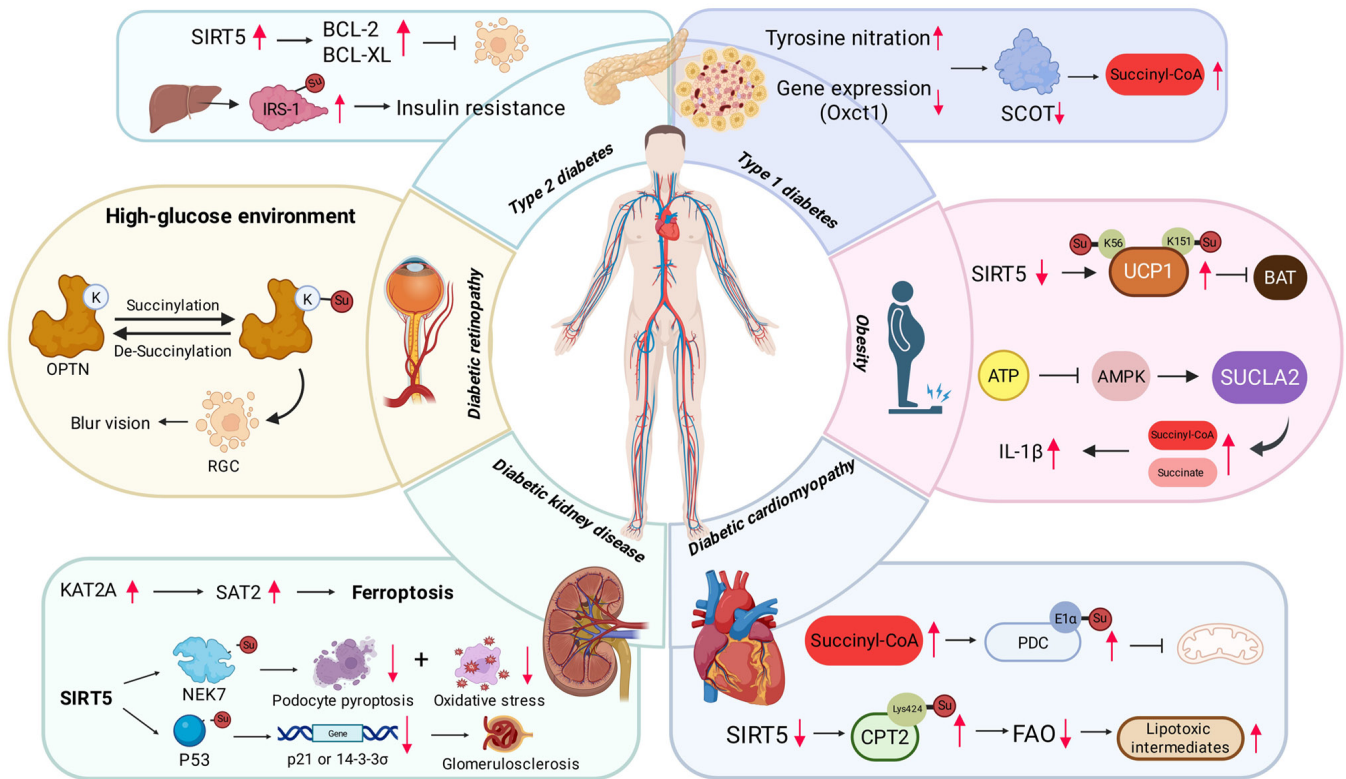


Figure 2. Mechanism of succinylation in diabetes and diabetic complications. Created with BioRender.com. SIRT5, sirtuin 5; IRS-1, insulin receptor substrate 1; Oxct1, 3-oxoacid CoA-transferase 1; SCOT, succinyl-CoA:3-ketoacid CoA transferase; OPTN, optineurin; RGC, retinal ganglion cells; UCP1, uncoupling protein 1; BAT, brown adipose tissue; AMPK, AMP-activated protein kinase; SUCLA2, succinyl-CoA synthetase ADP-forming subunit β ; KAT2A, lysine acetyltransferase 2A; SAT2, spermidine/spermine N1-acetyltransferase family member 2; NEK7, NIMA related kinase 7; PDC, pyruvate dehydrogenase complex; FAO, fatty acid oxidation; CPT2, carnitine palmitoyltransferase 2.

findings support the premise that excessive succinylation is detrimental to β cells under diabetic stress conditions.

Beyond β -cell failure, dysregulated succinylation also impairs insulin signalling in peripheral tissues. In hepatic tissue from diet-induced obesity and diabetes models, abnormal succinylation has been identified on numerous proteins integral to insulin signalling pathways, including insulin receptor substrate 1. Proteomics analyses have mapped nine atypical succinylation sites across 268 metabolically relevant hepatic proteins (58). Such modifications may disrupt downstream signalling from the insulin receptor, reducing cellular insulin responsiveness and aggravating systemic insulin resistance. Pharmacological inhibition of SCOT using diphenylbutylpiperidines (DPBPs) has been shown to improve glycaemic control in experimental animal obesity models, specifically diet-induced obese mice. However, their clinical utility is limited by marked off-target effects. Namely, as potent dopamine D2 receptor antagonists, DPBPs have been associated with extrapyramidal symptoms, sedation and cardiac adverse events, including QT interval prolongation (59,60). Despite these limitations, these observations underscore the therapeutic potential of targeting the succinyl-CoA metabolic axis in T2D (60).

At the molecular level, protein succinylation is primarily determined by the balance between intracellular succinyl-CoA availability and desuccinylase activity. In T2D-associated metabolic stress, increased succinyl-CoA production can overwhelm the regulatory capacity of SIRT5, leading to widespread

hypersuccinylation and subsequent metabolic impairment (61). Enhancement of SIRT5 activity has been shown to ameliorate select metabolic abnormalities, such as β -cell apoptosis, hepatic insulin resistance and cardiac lipotoxicity.

Metabolic memory: A bridge to epigenetic mechanisms. Subsequent to the acute enzymatic disturbances in metabolic pathways, the present review will further discuss more persistent epigenetic alterations that sustain cellular dysfunction. The concept of ‘metabolic memory’ refers to the continued progression of vascular complications even after glycaemic control has been restored. Although this effect has classically been attributed to oxidative stress and the accumulation of advanced glycation end-products, emerging evidence has identified aberrant lysine succinylation as a stable molecular imprint capable of perpetuating dysfunction beyond the initial hyperglycaemic exposure (62–64).

In contrast to transient phosphorylation, succinylation produces a marked charge reversal and steric constraint, changes that can stabilize metabolic enzymes in maladaptive conformations (65). During hyperglycaemia, excessive succinyl-CoA production exceeds the desuccinylation capacity of SIRT5. Restoration of SIRT5 activity is often hindered not only by substrate overload but also by NAD^+ depletion and oxidative stress-induced transcriptional repression (66). This imbalance promotes sustained hypersuccinylation of mitochondrial proteins, such as the PDC and carnitine palmitoyltransferase 2 (CPT2), and contributes to cytosolic

succinate accumulation (16). Elevated succinate functions as an oncometabolite that inhibits prolyl hydroxylases, leading to stabilization of hypoxia-inducible factor-1 α and maintenance of a 'pseudo-hypoxic' state that persists beyond the original metabolic insult (67,68).

Beyond its effects on metabolic enzymes, succinylation associates altered metabolic flux with long-term transcriptional reprogramming. Rather than requiring direct transport of succinyl-CoA into the nucleus, recruitment of the α -KGDH complex enables localized nuclear generation of succinyl-CoA (8). This compartmentalized metabolite pool supplies substrate for histone succinylation. By altering chromatin structure, these epigenetic modifications promote an open configuration at pro-inflammatory gene loci (69). Therefore, prior metabolic stress becomes embedded within the epigenome, sustaining pathogenic transcriptional programs despite subsequent therapeutic normalization of glycemia.

3. Pathological mechanisms in diabetic complications

Obesity: Impaired thermogenesis and macrophage polarization. Obesity is a complex metabolic disorder defined by excessive adipose tissue accumulation resulting from chronic positive energy balance (70). It constitutes a major global health challenge and is a primary risk factor for T2D, cardiovascular disease and NAFLD (71). Obesity induces marked metabolic reprogramming in tissues, including adipose depots in the liver, promoting hepatic steatosis and triggering endoplasmic reticulum stress in adipocytes (72). These disturbances contribute to systemic insulin resistance and broader metabolic dysfunction (73-75). Within this altered metabolic environment, widespread shifts in PTMs occur, with protein succinylation emerging as a key regulatory mechanism.

Brown adipose tissue (BAT), the principal site of non-shivering thermogenesis, is particularly dependent on tightly regulated succinylation dynamics (76,77). Thermogenic capacity in BAT is mediated by UCP1, the stability and activity of which are influenced by succinylation status. SIRT5-mediated desuccinylation of UCP1 (notably, at residues K56 and K151) supports protein stability and thermogenic efficiency. Under obesogenic conditions, reduced SIRT5 activity increases UCP1 succinylation, impairing BAT thermogenesis. The consequent decline in energy expenditure promotes weight gain, highlighting the therapeutic relevance of targeting the SIRT5/UCP1 regulatory axis to restore metabolic flexibility in BAT.

In addition, a parallel succinyl-CoA-dependent pathway operates in adipose tissue macrophages (ATMs), whereby metabolic signalling directly promotes inflammatory activation. In this setting, the glutaminolysis/AMP-activated protein kinase (AMPK)/succinyl-CoA synthetase ADP-forming subunit β (SUCLA2) axis drives pro-inflammatory responses. ATP generated through glutaminolysis suppresses AMPK activity, limiting phosphorylation-dependent inhibition of SUCLA2. Enhanced SUCLA2 activity further increases intracellular levels of succinyl-CoA and succinate, stimulating excessive IL-1 β production. This cascade promotes inflammatory polarization of ATMs, suppresses thermogenic function, reduces energy expenditure and exacerbates obesity (78).

The metabolic consequences of increased succinyl-CoA production are context dependent. When supplied as alternative metabolic fuels, substrates that elevate succinyl-CoA may exert beneficial effects. Dodecanedioic acid (DC12), a medium-chain dicarboxylic acid, undergoes β -oxidation in tissues expressing the acyl-CoA oxidase 1 isoform, generating succinyl-CoA that enters the TCA cycle. Administration of DC12 has been shown to increase whole-body energy expenditure, decrease adiposity, reduce hepatic lipid accumulation and improve glucose tolerance, mitigating obesity by enhancing mitochondrial substrate cycling (79).

The liver further illustrates the context-specific nature of succinyl-CoA metabolism. Hepatic steatosis, a common obesity-associated complication (80), has been shown to be notably attenuated in *ob/ob* mice when hepatic SIRT5 activity is augmented via genetic overexpression (18). These findings underscore how the metabolic impact of SIRT5 is highly dependent on tissue type and pathological context, rather than uniformly protective or deleterious (Fig. 3).

DbCM: Mitochondrial inflexibility and lipotoxicity. Context-dependent metabolic consequences of succinylation extend beyond adipose tissue to the cardiovascular system. DbCM is a distinct myocardial disorder characterized by structural and functional abnormalities in individuals with diabetes, occurring independently of hypertension, coronary artery disease or notable valvular pathology (81). Its development is largely driven by metabolic disturbances, including impaired metabolic flexibility, mitochondrial dysfunction and lipotoxicity, that culminate in myocardial fibrosis, hypertrophy, and progressive impairment of both diastolic and systolic function. Key pathogenic mechanisms include altered substrate utilization, mitochondrial dysfunction, oxidative stress and diminished ATP generation (82,83).

Ketone bodies represent an efficient energy substrate for the heart, particularly under conditions of metabolic stress. In the diabetic myocardium, tyrosine nitration-mediated inhibition of SCOT reduces its enzymatic activity by 24-39% (35). Impaired SCOT function limits the conversion of ketone bodies into acetyl-CoA, aggravating the energetic deficit characteristic of DbCM. As aforementioned, although pharmacological inhibition of SCOT may transiently enhance glucose tolerance, its potential cardiotoxic effects highlight the need to maintain balanced ketone metabolism in the diabetic heart (84).

The PDC, a key association between glycolysis and the TCA cycle, represents an additional metabolic control point disrupted in DbCM (85). Sustained exposure of cardiomyocytes to hyperglycaemia and elevated fatty acids increases intracellular succinyl-CoA concentrations, promoting succinylation of the pyruvate dehydrogenase E1 subunit α -1. This modification suppresses PDC activity, restricting pyruvate flux into the TCA cycle and further compromising metabolic flexibility, the capacity of the heart to alternate between glucose and lipid substrates. Over time, this metabolic inflexibility contributes to myocardial hypertrophy and diastolic dysfunction, establishing a self-perpetuating cycle of metabolic stress, excessive succinylation, PDC inhibition and progressive energetic decline (17).

Regulatory control by SIRT5 is similarly disrupted in DbCM. Mitochondrial impairment and oxidative stress can

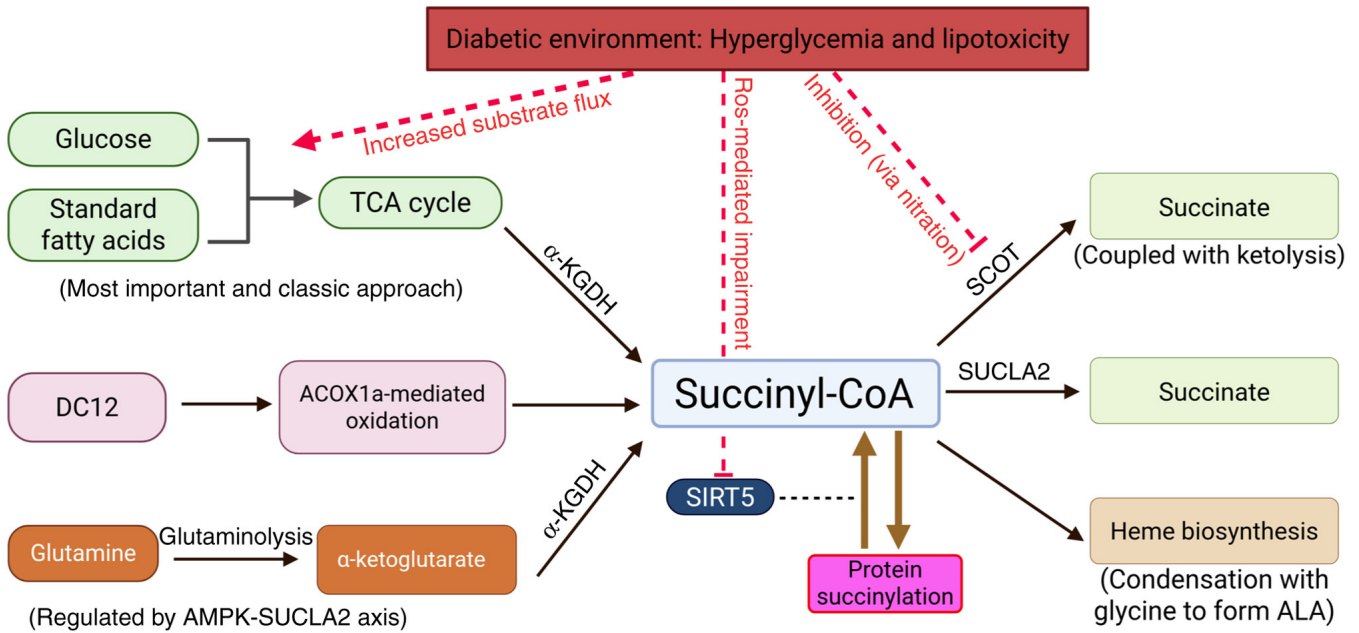


Figure 3. Complexity of succinyl-CoA metabolism and its dysregulation in the diabetic environment. Created with BioRender.com. TCA, tricarboxylic acid; α -KGDH, α -ketoglutarate dehydrogenase; DC12, dodecanedioic acid; ACOX1a, acyl-CoA oxidase 1; AMPK, AMP-activated protein kinase; SUCLA2, succinyl-CoA synthetase ADP-forming subunit β ; ROS, reactive oxygen species; SCOT, succinyl-CoA:3-ketoacid CoA transferase; SIRT5, sirtuin 5; ALA, δ -aminolevulinic acid.

attenuate SIRT5 activity, reducing desuccinylation efficiency and exacerbating mitochondrial metabolic failure (12). SIRT5 also directly regulates CPT2, a key enzyme in mitochondrial fatty acid β -oxidation (86). Deficiency of SIRT5 markedly increases succinylation of CPT2 at lysine 424, suppressing its enzymatic function and impairing FAO. Accumulation of long-chain acylcarnitines subsequently promotes lipotoxic damage and worsens cardiac dysfunction. By comparison, experimental SIRT5 overexpression has been shown to preserve CPT2 activity through desuccinylation, enhancing FAO efficiency and mitigating lipotoxic stress in the diabetic myocardium (61).

DKD: Epigenetic dysregulation and renal cell injury. Similar to the myocardium, the kidneys are highly susceptible to metabolic injury driven by aberrant succinylation, particularly through epigenetic and microvascular pathways. DKD, also termed diabetic nephropathy, is among the most prevalent microvascular complications of diabetes and remains the leading cause of chronic kidney disease and end-stage renal failure worldwide, affecting ~50% of patients with T2D globally (87). It is characterized by progressive damage to both glomerular filtration structures and renal tubular compartments (88). Persistent hyperglycaemia, frequently compounded by hypertension, initiates structural and functional deterioration that culminates in albuminuria, a clinical hallmark of DKD (89). As injury advances, the glomerular filtration rate progressively declines, impairing the capacity of the kidneys to eliminate metabolic waste, often leading to irreversible renal failure (90).

Epigenetic dysregulation has emerged as a central mechanism underlying the aberrant transcriptional programs observed in DKD (91,92). Expression of the histone succinyltransferase KAT2A is notably increased in affected kidneys.

KAT2A mediates succinylation at the spermidine/spermine N1-acetyltransferase family member 2 (SAT2) promoter, enhancing its transcriptional activation. Upregulated SAT2 expression exacerbates renal injury by promoting iron-dependent ferroptosis and amplifying inflammatory signalling, including increased production of IL-1 β , IL-6 and TNF- α (93,94). These processes accelerate glomerular and tubular injury, positioning the KAT2A/H3K79 succinylation/SAT2 axis as a pivotal epigenetic driver of DKD progression (95).

Succinylation dynamics similarly modulate mitochondrial integrity in renal cells. Astragaloside IV, a bioactive natural compound, confers renoprotective effects in part through activation of CPT1A. Enhanced CPT1A activity restores appropriate succinylation of 17 β -hydroxysteroid dehydrogenase 10 (HSD17B10) at lysine 99 (96). Properly succinylated HSD17B10 maintains the structural stability and enzymatic function of mitochondrial ribonuclease P, a key regulator of mitochondrial RNA processing (97), attenuating oxidative stress and reducing tubular epithelial injury.

Podocyte dysfunction represents another hallmark of DKD and desuccinylation appears protective in this setting. The flavonoid quercetin-4'-O- β -D-glucopyranoside upregulates SIRT5 expression in podocytes (98). SIRT5-mediated desuccinylation of NIMA related kinase 7 (NEK7), a kinase key in activating the NLR family pyrin domain containing 3 (NLRP3) inflammasome, disrupts the NEK7/NLRP3 interaction (99). This interference suppresses podocyte pyroptosis, reduces oxidative stress and helps preserve podocyte structure and function (100).

However, SIRT5 activation does not uniformly confer benefit. In mesangial cells under hyperglycaemic conditions, SIRT5 expression is elevated, promoting the desuccinylation of the tumour suppressor p53. Although total p53 protein levels

remain unchanged, desuccinylation attenuates its transcriptional activity (101,102). Diminished p53 function reduces expression of downstream targets such as p21 and 14-3-3 σ , facilitating mesangial cell proliferation and excessive extracellular matrix deposition, including collagen and laminin (103). These alterations directly contribute to glomerulosclerosis and the progression of DKD.

DR: Neurodegeneration and autophagic flux. Although SIRT5 activity may aggravate pathological remodelling in renal mesangial cells, its function in the retina appears consistently protective. DR develops as chronic hyperglycaemia progressively injures the retinal microvasculature within the light-sensitive neural tissue at the posterior segment of the eye. Structural weakening of retinal capillaries increases vascular permeability, permitting leakage of plasma constituents or blood into the retinal parenchyma. The resulting oedema and microvascular damage contribute to progressive visual impairment (104,105).

Aberrant protein succinylation has emerged as an early contributor to neurodegenerative processes in DR. Under hyperglycaemic conditions, increased succinylation of optineurin (OPTN) at lysine 108 has been observed in experimental retinal models. This modification is associated with disrupted autophagic flux in retinal ganglion cells, compromising cellular homeostasis. SIRT5-mediated desuccinylation of OPTN reverses this effect, restores autophagic function and confers neuroprotection. These findings delineate the SIRT5/OPTN axis as a central regulatory mechanism and a promising therapeutic target in early-stage DR (106). A comprehensive overview of organ-specific regulatory mechanisms and their pathological consequences is provided in Table I.

4. Future perspectives

Despite marked advances in characterizing the succinylation landscape, a number of major obstacles remain before these insights can be translated into clinical practice. Current detection approaches rely predominantly on pan-succinyl-lysine antibodies, which may exhibit cross-reactivity with other acyl modifications (such as malonylation and glutarylation) (65,107). Furthermore, conventional mass spectrometry workflows often lack the resolution to determine absolute site-specific stoichiometry (108). The development of highly selective chemical probes and improved quantitative proteomic methodologies will therefore be important in discriminating biologically meaningful, high-occupancy succinylation events from low-abundance background modifications.

In addition, a static catalogue of succinylated proteins does not adequately capture the dynamic nature of metabolic disease. Future studies should aim to integrate acyl-proteomics with metabolomics and metabolic flux analysis within a multi-omics framework. Given that intracellular succinyl-CoA concentrations fluctuate rapidly in response to nutrient status, combining these datasets would enable direct associations to be made between metabolic flux and the kinetics of protein succinylation. Such an approach is key in defining causal associations between metabolic overload and downstream signalling perturbations in diabetes.

Therapeutic targeting of this axis similarly demands precision. As aforementioned, SIRT5 exerts tissue-specific effects that frequently oppose one another. Systemic activation of SIRT5 is associated with adverse renal outcomes, including the promotion of glomerular fibrosis. Accordingly, organ-selective delivery strategies are imperative. Nanoparticle-based encapsulation of SIRT5 modulators or antibody-drug conjugates directed toward cell-specific surface markers may provide the spatial selectivity required for safe intervention. Direct manipulation of the intracellular succinyl-CoA pool is equally challenging, given its indispensable roles in the TCA cycle and haem biosynthesis (109). Future pharmacological strategies must therefore recalibrate the succinyl-CoA/SIRT5 equilibrium without compromising mitochondrial bioenergetics or inducing systemic metabolic toxicity.

At present, the pharmacological repertoire targeting protein succinylation (Table II) remains limited. Numerous SIRT5 inhibitors have been described (such as the non-selective compound suramin and specific mechanism-based thiosuccinyl peptides), yet the majority are peptide-based or non-selective compounds with suboptimal bioavailability or poor cellular permeability (110,111). There is a notable scarcity of specific small-molecule SIRT5 activators. Efforts to enhance SIRT5 activity largely depend on specific NAD⁺ precursors (such as nicotinamide mononucleotide and nicotinamide riboside) that broadly stimulate SIRT function, lacking the specificity needed to minimize off-target effects (112). To address this limitation, a number of emerging specific small molecules, such as the selective SIRT5 activator MC3138, have been developed to provide targeted modulation (113,114). Despite these recent advancements, caution is warranted. The majority of available modulators have not progressed to clinical validation and interpreting reductions in succinylation as an unequivocal therapeutic benefit without a comprehensive safety assessment may be misleading. Emerging strategies such as Proteolysis Targeting Chimeras offer an alternative approach by selectively degrading hypersuccinylated substrates, potentially circumventing the challenges of direct enzymatic modulation (115,116).

Unintended drug effects on the succinylome further illustrate the complexity of therapeutic intervention. For example, lovastatin, a widely prescribed lipid-lowering agent, has been reported to induce succinylation of cytoskeleton-associated proteins in breast cancer stem cells, altering their mechanical properties (117). This observation underscores the potential for pleiotropic and off-target modulation of succinylation in non-intended tissues. Accordingly, rigorous screening for unintended succinylation changes should become an integral component of future drug development pipelines.

5. Conclusion

Protein succinylation has developed from its initial characterization as a metabolic intermediate to emerge as a key regulator of diabetic pathology, orchestrating the important interface between mitochondrial bioenergetics and cellular signalling. Evidence summarized in the present review determined that the breakdown of the succinyl-CoA/SIRT5 regulatory axis is a primary driver of metabolic inflexibility and tissue injury. However, the dichotomy of SIRT5 activity, indispensable in cardiac homeostasis yet paradoxically pathogenic in renal

Table I. Summary of dysregulated succinylation targets and pathological consequences in diabetes and diabetic complications.

Target	Key substrate	Key regulator	Effect of aberrant succinylation/desuccinylation	Pathological consequences	Potential therapeutic implications	(Refs.)
BAT	UCP1 (K56 and K151)	SIRT5 decrease	Increased succinylation reduces UCP1 stability and activity	Impaired non-shivering thermogenesis; accelerated weight gain	Increase SIRT5 activity	(16)
Heart (cardiomyocytes)	PDC (E1 α subunit)		Hypersuccinylation suppresses the activity of PDC	Metabolic inflexibility; myocardial hypertrophy	Restore succinyl-CoA balance	(17)
Liver	IRS-1	SIRT5	Hypersuccinylation disrupts downstream insulin signalling	Systemic insulin resistance; hepatic steatosis	Increase SIRT5 activity	(18,58)
Pancreatic β cells	Unspecified mitochondrial proteins	SCOT decrease; SIRT5	Hypersuccinylation increases cytochrome <i>c</i> release and caspase activation	β -cell apoptosis and impaired insulin secretion	Increase SIRT5 activity; prevent SCOT inhibition	(53-58)
Heart (cardiomyocytes)	CPT2 (K424)	SIRT5 decrease	Hypersuccinylation inhibits the activity of CPT2	Impaired FAO; lipotoxic injury	Increase SIRT5 activity	(61,86)
ATMs	SUCLA2 (upstream pathway)	AMPK-SUCLA2 axis	Elevated succinyl-CoA results in excessive IL-1 β production	Pro-inflammatory ATM polarization; aggravated obesity	Modulate glutaminolysis/AMPK/SUCLA2 axis	(78)
Kidney (epigenetic level)	H3K79	KAT2A increase	H3K79 hypersuccinylation enforces open chromatin at the SAT2 promoter	SAT2-driven ferroptosis and inflammation (IL-1 β , IL-6 and TNF- α)	Inhibit KAT2A/epigenetic modulation	(93-95)
Kidney (tubular cells)	HSD17B10 (K99)	CPT1A (upstream activator)	Loss of proper succinylation destabilizes mitochondrial RNase P	Oxidative stress; tubular epithelial injury	Activate CPT1A to reinstate proper succinylation	(96,97)
Kidney (podocytes)	NEK7	SIRT5 decrease	Hypersuccinylation increases NEK7 interaction with NLRP3	Inflammasome activation; podocyte pyroptosis	Improve SIRT5 activity	(98-100)
Kidney (mesangial cells)	p53 (K120)	SIRT5 increase (paradoxical)	Excessive desuccinylation dampens p53 transcriptional activity (p21, 14-3-3 σ)	Mesangial cell proliferation; extracellular matrix deposition	Organ-targeted SIRT5 inhibition	(101-103)
RGCs	OPTN (K108)	SIRT5 decrease	Hypersuccinylation impairs autophagic flux	RGC neurodegeneration	Improve SIRT5 activity	(106)

AMPK, AMP-activated protein kinase; ATMs, adipose tissue macrophages; BAT, brown adipose tissue; CPT, carnitine palmitoyltransferase; CPT1A, carnitine palmitoyltransferase 1A; FAO, fatty acid oxidation; HSD17B10, 17 β -hydroxysteroid dehydrogenase 10; IRS-1, insulin receptor substrate 1; KAT2A, lysine acetyltransferase 2A; NEK7, NIMA-related kinase 7; NLRP3, NOD-like receptor family, pyrin domain containing 3; OPTN, optineurin; PDC, pyruvate dehydrogenase complex; RGCs, retinal ganglion cells; RNase, ribonuclease; SAT2, spermidine/spermine N1-acetyltransferase family member 2; SCOT, succinyl-CoA:3-ketoacid CoA transferase; SIRT, sirtuin; SUCLA2, succinyl-CoA synthetase ADP-forming subunit β ; UCPI, uncoupling protein 1.

Table II. Overview of agents and compounds affecting protein succinylation and their physiological outcomes.

Agent/compound	Mechanism of action	Target protein/pathway	Effect on succinylation	Functional outcome	(Refs.)
Pimozide	Inhibits SCOT activity	SCOT	Increases (through accumulation of succinyl-CoA)	Improves glycaemic control in obesity models (discontinued due to its cardiac toxicity)	(59-61)
DC12	Increases succinyl-CoA flux through β -oxidation	TCA cycle flux	Increases (by elevating succinyl-CoA production)	Increases energy expenditure; reduces adiposity and hepatic lipids	(80)
Astragaloside IV	Activates CPT1A	HSD17B10 (through CPT1A activation)	Restores physiological levels (at lysine 99)	Mitigates oxidative stress; renoprotective in DKD	(97)
QODG	Upregulates expression of SIRT5	NEK7	Decreases (promotes desuccinylation)	Inhibits NLRP3 inflammasome; reduces podocyte pyroptosis	(99)
Suramin/thiosuccinyl peptides	Directly inhibits enzymatic activity	SIRT5	Increases (inhibits desuccinylation)	Used primarily as research tools; clinical utility limited by off-target effects or poor bioavailability	(111, 112)
NAD ⁺ precursors	Increases the enzymatic activity of SIRT5	Global SIRT targets	Decreases (broad desuccinylation)	Improves mitochondrial function (non-specific, theoretical utility)	(113)
MC3138	Directly activates SIRT5 enzymatic activity	SIRT5	Decreases (promotes desuccinylation)	Emerging SIRT5-selective small-molecule activator (preclinical validation)	(114, 115)
Lovastatin	Off-target metabolic modulation	Cytoskeleton-related proteins	Increases	Alters the mechanical properties of breast cancer stem cells (potential adverse effects)	(118)

CPT1A, carnitine palmitoyltransferase 1A; DC12, dodecanedioic acid; DKD, diabetic kidney disease; HSD17B10, 17 β -hydroxysteroid dehydrogenase 10; NEK7, NIMA related kinase 7; NLRP3, NOD-like receptor family, pyrin domain containing 3; QODG, quercetin-4'-O- β -D-glucopyranoside; SCOT, succinyl-CoA:3-ketoacid CoA transferase; SIRT5, sirtuin 5; TCA, tricarboxylic acid.

mesangial cells, challenges the viability of systemic enzymatic modulation. Ultimately, understanding this context-dependent complexity is not just a theoretical imperative but the prerequisite for developing safe, precision-based therapeutics for diabetes and its complications.

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Authors' contributions

YX, FL, BL and QY contributed to the conception and design of the present review. YX drafted the manuscript, and participated in literature collation and manuscript editing. FL and BL conceptualized the present review and contributed to the writing. QY reviewed and revised the manuscript. All authors commented on previous versions of the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

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The authors declare that they have no competing interests.

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