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Succinate metabolism in cardiovascular diseases

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Abstract

Cardiovascular disease (CVD) refers to a class of diseases related to the heart or blood vessels that have high global incidence. Succinate is generally considered an important intermediate product of the tricarboxylic acid cycle. Recent studies have shown that succinate is related to the pathophysiology of CVD, such as atherosclerosis, acute aortic dissection, hypertension, myocardial ischemia-reperfusion injury, and heart failure. It may represent a potential target or biomarker for CVD. It has been demonstrated that succinate not only participates in various energy metabolic pathways but also plays an important role in various pathophysiological activities as a signaling molecule. Given the significance of metabolism in CVD, it is important to focus on the metabolic regulation mechanism of succinate in CVD. This review outlines the latest evidence pointing to the potential role of succinate in CVD, along with its mechanisms, and updates the current understanding on the role of succinate in CVD. Further studies may focus on identifying succinate, its receptor, and its downstream signaling molecules as new targets for the prevention and treatment of CVD.

Keywords: Cardiovascular diseases; Metabolism; Succinate; Succinate receptor 1

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1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide[1]. It includes atherosclerosis, acute aortic dissection (AAD), hypertension, myocardial ischemia-reperfusion injury (MIRI), heart failure, and metabolic cardiomyopathy[2,3]. The progression of the disease cannot be well controlled with medication and surgery. Therefore, it is particularly important to look for new prevention and treatment targets.

Succinate is an important metabolic intermediate of the tricarboxylic acid (TCA) cycle and glutamine metabolism[4,5]. In addition, it acts as a signaling molecule by binding

to its receptor and regulating metabolism and immune homeostasis in various pathophysiological activities[6]. However, the exact underlying mechanism of succinate in CVD has not been elucidated. As a potential biomarker for CVD, succinate plays an important role in the early diagnosis and treatment. The role of succinate in CVD and the available evidence, including some mechanisms, recent progress, and clinical significance of succinate in CVD, is outlined in this review.

2. Source and metabolism of succinate

Succinate is an important metabolic intermediate that participates in various metabolic pathways, such as the TCA cycle and glutamine metabolism. Succinate is an intermediate metabolite of the TCA cycle, located downstream of α-ketoglutarate. The α-ketoglutarate dehydrogenase complex (OGDH) catalyzes the oxidative decarboxylation of α-ketoglutarate into succinyl-CoA. Under the catalysis of succinyl-CoA synthase, the sulfur lipid bond of succinyl-CoA is broken to form succinate, in which this reaction is reversible. Subsequently, the generated succinate is oxidized into fumaric acid under the action of the succinate dehydrogenase complex (SDH)[7]. Succinate generates a large number of reactive oxygen species (ROS) in the oxidation process. This is a crucial step in the production of ATP in the TCA cycle[8].

2.1. α-ketoglutarate dehydrogenase complex

OGDH is a rate-limiting enzyme in the TCA cycle. It consists of three enzymes (α-ketoglutarate dehydrogenase, dihydrolipoamide succinyltransferase, and dihydrolipoyl dehydrogenase)[9]. While the secretion of inflammatory factors increases in an inflammatory milieu, the increase in OGDH activity in macrophages promotes the decarboxylation of a-ketoglutarate into succinate, resulting in a decrease in the ratio of α-ketoglutarate to succinate. The addition of α-ketoglutarate increases the ratio and decreases the level of cellular inflammation[10].

2.2. SDH

The SDH, also known as mitochondrial respiratory complex II, is located within the inner mitochondrial membrane. It consists of six subunits, namely, SDHA, SDHB, SDHC, SDHD, SDHAF1, and SDHAF2. SDH is also involved in the TCA cycle and electron transport chain[11]. In the TCA cycle, SDH oxidizes succinate into fumaric acid, and subsequently, as a part of oxidative phosphorylation, SDH transfers electrons from succinate to coenzyme Q. SDH is located at the intersection of two important metabolic pathways: The TCA cycle and electron transport chain. Growing evidence reveals that the activity of SDH is regulated by post-translational modifications, such as succinylation, acetylation, deacetylation, and phosphorylation, to cope with various external stimuli[12-14].

2.3. Intestinal flora as a source

The intestinal flora is also an important source of succinate, especially in the fermentation of polysaccharides and oligosaccharides. Microbiota-derived succinate is generally considered an intermediate product of propionate synthesis, and it accumulates less in bacteria in view of its high utilization rate.

Since succinate is produced by microbiota, there are low levels of succinate in the intestinal contents of specific pathogen-free (SPF) mice and almost none in sterile mice[15]. Succinate concentrations range from 1 to 3 mM in human intestinal contents and feces, accounting for 2 – 4% of the total organic anions in feces, which are much higher than the level of succinate in plasma. The high level of succinate in feces implies that succinate is produced by microorganisms and then absorbed into the blood through the intestinal epithelium, participating in host-microbiota interactions and host cell metabolism. The main source of succinate in the intestine is *Bacteroidetes*. *Bacteroides fragilis*, *Prevotella copri*, and *Enterococcus faecalis* produce succinate through the fermentation of dietary fiber[16,17]. Dietary fiber supplements can significantly increase the concentration of succinate in the cecum of mice and participate in the process of small intestinal gluconeogenesis, thus playing an important role in maintaining glucose homeostasis[17]. Succinate levels in the cecum may also increase with dietary fiber supplements during a high-fat diet (HFD)[18]. In the intestinal flora, there are also some succinate-consuming bacteria, such as *P. faecium* and *Ruminococcus*, which convert succinate into propionate[19]. An imbalance in intestinal homeostasis may occur as a result of antibiotics and intestinal inflammation, where there is an increase in succinate-secreting bacteria, but a decrease in succinate-consuming bacteria, thus resulting in the accumulation of succinate in the intestine[20]. In a study, the concentration of succinate in the feces of patients with inflammatory bowel disease was significantly higher than that of the control group; in a dextran sulfate sodium (DSS)-induced colitis mouse model, there was also an increase in the concentration of succinate in feces[21,22].

2.4. Other pathways of succinate production

In addition to the formation of succinate from a-ketoglutarate through the decarboxylation of OGDH, many metabolic pathways are also involved in the production of succinate, such as reverse SDH activity, γ-aminobutyric acid (GABA) shunt, and glutamine metabolism[23].

When a tissue is hypoxic, there will be SDH activity reversal; that is, it mediates the reverse production of succinate from fumarate. Following myocardial ischemia and hypoxia, the SDH activity in cardiomyocytes is reversed. Fumaric acid produced by aspartic acid and adenosine monophosphate (AMP) metabolism generates a large amount of succinate under the action of SDH, resulting in the accumulation of succinate in hypoxic myocardial tissues. Following reperfusion, the accumulated succinate is rapidly oxidized by normally active SDH to produce excess ROS, resulting in further damage to myocardial tissues[24].

When macrophages undergo pro-inflammatory M1 polarization, the glutamine metabolic pathway is activated and the expression of glutamate dehydrogenase is upregulated. The latter catalyzes glutamine to produce a-ketoglutarate and provides the substrate for OGDH to produce succinate. Meanwhile, lipopolysaccharide (LPS) stimulation also leads to an increase in GABA levels and GABA transferase activity in macrophages. GABA is catalyzed by GABA transferase to produce succinic semialdehyde (SSA), which is subsequently converted into succinate by SSA dehydrogenase[25].

2.5. Transport of succinate

Intracellular succinate is involved in mitochondrial TCA cycle and is incapable of crossing the cell membrane. However, when there is an abrupt increase in energy demand and the energy supply cannot be maintained, the anaerobic pathway will be activated, resulting in excessive lactic acid production and cell acidification. The decrease in pH value will lead to the protonation of succinate, which involves the transformation of dicarboxylate trapped in the cell into monocarboxylate so that it can cross the cell membrane and escape into the extracellular matrix. A specific membrane carrier transport is required for succinate to pass through the cell membrane[26]. The solute carrier (SLC) family is composed of a large class of transmembrane solute transporters. SLC25A10 is a mitochondrial dicarboxylate carrier located on the mitochondrial membrane. It mainly transports dicarboxylic acids, such as malic acid and succinate, from the mitochondria to the cytoplasm for the exchange of phosphate, sulfate, and thiosulfate, thus providing substrates for gluconeogenesis and urea synthesis, as well as maintaining the distribution and homeostasis of intermediate products in and out of the mitochondria during the TCA cycle[27]. SLC25A10 transports succinate from the mitochondrial matrix to the cytosol, which is the first step of succinate transport to the extracellular space. Monocarboxylic acid transporter 1 (MCT1), a member of the SLC16 family, is a protein that transports monocarboxylic acids, such as lactic acid and pyruvate, to cells. Recent studies have shown that MCT1 can transfer succinate to the extracellular space through the plasma membrane of myocardium, skeletal muscle, and retina[28,29]. In addition to succinate produced by cells themselves, extracellular succinate uptake is another major source of intracellular succinate. Extracellular succinate can also be absorbed and recovered by sodium-dependent dicarboxylic acid transporters. The plasma membrane transporter of the SLC13 family is responsible for transporting succinate from the circulation into cells and regulating succinate homeostasis.

2.6. Succinate receptor 1 (SUCNR1)

SUCNR1 (also known as GPR91) is a G protein-coupled receptor responsible for succinate signaling and is widely expressed in systemic cell types[30,31]. Emerging evidence suggests that the succinate-SUCNR1 pathway plays an important role in regulating immune homeostasis. In different microenvironments, succinate activates SUCNR1, which leads to different immune cell responses. Therefore, the SUCNR1 pathway can help reduce inflammatory damage in diseased tissues. In chronic inflammation, succinate is released into the extracellular matrix as a signaling molecule to regulate the function of other cells through the interaction with receptors.

SUCNR1 is expressed in various cells of the immune system and plays an important role in regulating cellular immune homeostasis and inflammatory response. SUCNR1 is also widely expressed in the adaptive immune system, such as T-cells (including $CD4^+$ and $CD8^+$ T-cells) and B-cells. Large amounts of interleukin (IL)-10 and succinate are released as a result of the activation of T-cells in patients with systemic lupus erythematosus. When cocultured with B-cells, the activation of T-cells is inhibited by the neutralization of SUCNR1 on B-cells[32]. However, it remains unclear whether succinate acts synergistically with other cytokines to regulate adaptive immunity. The effect of SUCNR1 activation in innate immune cells is environment dependent. For example, in human immature dendritic cells, SUCNR1 controls its chemotaxis in a succinate concentration-dependent manner[33]. SUCNR1 and toll-like receptor-3 (TLR-3) or TLR-7, independent of TLR-2 or TLR-4, act in synergy, increasing the expression of pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and IL-1β, leading to the enhancement of antigen presentation ability and the activation of $CD4^+$ T-cells[33]. However, the activation of SUCNR1 pathway seems to occur only in the acute phase of stimulation, since SUCNR1 is rapidly downregulated following the activation of dendritic cells. In a mouse experimental arthritis model, SUCNR1-mediated chemotaxis of dendritic cells into lymph nodes *in vivo*

resulted in the expansion of Th17 cells, which, further, led to autoimmune diseases[34].

In addition to its effect on chemotaxis, SUCNR1 also plays an important role in macrophage inflammation. However, there are conflicting results in the current research. SUCNR1 plays a pro-inflammatory role in M2 macrophages derived from human peripheral blood monocytes. IL-4 or IL-10 stimulates macrophages, resulting in the upregulation of SUCNR1 expression in macrophages. However, the treatment of macrophages with succinate or SUCNR1 agonists decreases the secretion of IL-10 and increases TNF-α expression in macrophages, thus enhancing the inflammatory response[35]. Macrophages are activated by inflammatory signals release succinate to the extracellular environment, activate SUCNR1 through autocrine and paracrine signaling, and promote the production of IL-1β, thus further aggravating tissue inflammation[36]. Although the previous studies have shown that the knockout of SUCNR1 does not affect the secretion of IL-1β, TNF-α, and IL-6 in peritoneal macrophages stimulated by LPS (10 ng/mL, 24 h)[37], another study found that SUCNR1 knockdown resulted in a significant decrease in IL-1β expression in bone marrow-derived macrophages (BMDMs) when stimulated with a higher dose (100 ng/mL) of LPS. IL-1β stimulation results in an increased expression of SUCNR1 in BMDMs[36]. These results indicate that there may be some positive feedback between SUCNR1 and inflammatory cytokines. Other studies have shown that LPS-stimulated BMDMs of SUCNR1 knockout mice had increased IL-6, TNF-α, and nitric oxide (NO) release compared to the control group[38]. This finding reveals that SUCNR1 may play an anti-inflammatory role, thus contradicting previous studies. Hence, the mechanism needs to be further explored.

In conclusion, succinate is generated and transported through various pathways, and it plays different roles, depending on physiological and pathological conditions (Figure 1). Enzymes, intermediate metabolites involved in succinate metabolism, or SUCNR1 may become potential therapeutic targets for CVD in the future.

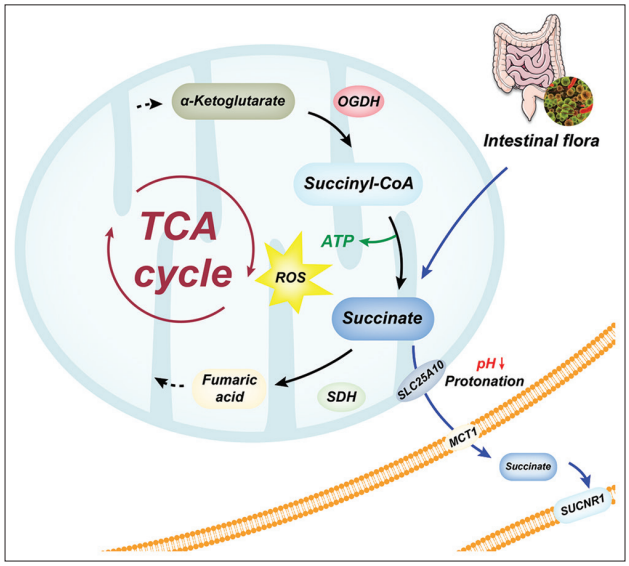

Figure 1. Succinate metabolism and transport. The main source of succinate is the oxidative decarboxylation of α-ketoglutarate by oxoglutarate dehydrogenase in the tricarboxylic acid cycle to form succinyl-coenzyme (Co)A, which is catalyzed by succinyl-CoA synthase to generate succinate. The other source of succinate is derived from the metabolism of intestinal flora through the fermentation of dietary fiber. Succinate generates excessive reactive oxygen species during oxidation. The metabolic pathway of succinate includes the oxidation to fumaric acid in the presence of SDH and then protonation due to the decrease in mitochondrial pH. Succinate is transported to the extracellular level through SLC25A10 and monocarboxylic acid transporter 1.

3. Succinate and cardiovascular disease

3.1. Succinate and atherosclerosis

The pathophysiological mechanism of atherosclerosis involves inflammatory response, endothelial cell dysfunction, and macrophage polarization, all of which eventually lead to plaque formation.

Succinate acts as an inflammatory signal ligand, which can be transmitted through the receptor SUCNR1. SUCNR1 is inactive in normal tissues and can be activated under certain conditions, such as hypoxia and tissue injury[39]. Succinate accumulates in ischemic tissues and is involved in perfusion injury through mitochondrial ROS[24]. The binding of succinate to SUCNR1, which is expressed in human umbilical vein endothelial cells (HUVECs) and macrophages, activates transcription factor hypoxia-inducible factor (HIF)-1α, stimulates the succinate/IL-1β signaling axis, promotes the expression of IL-1β to produce excess pro-inflammatory cytokines, and exacerbates the inflammatory process of atherosclerosis[23,40].

SDHB is one of the six subunits of the succinate dehydrogenase complex. Low shear stress downregulates the expression of tet methylcytosine dioxygenase 2, inhibits the recruitment of histone deacetylase 2, and upregulates the expression of SDHB. SDHB mediates mitochondrial damage, increases the production of ROS, and subsequently induces vascular endothelial cell pyroptosis[41]. Trimethylamine N-oxide (TMAO) promotes the production of ROS in HUVECs and endothelial cell pyroptosis by upregulating the expression of SDHB[42].

Succinate in mitochondria generates a large amount of ROS through the oxidation of SDH, which promotes the conversion of macrophages into M1 pro-

inflammatory macrophages[43]. In macrophages, IFN-β antagonizes JMJD3-IRF4 pathway by controlling the ratio of α-ketoglutaric acid to succinate, thus regulating the activation and polarization of macrophages[44]. In the tumor microenvironment, macrophages are the main cells, and cancer cells secrete succinate, activate SUCNR1, induce M2 polarization of macrophages into tumor-related macrophages, and increase macrophage migration[45]. Succinate pre-treatment enhances IL-1β and pro-IL-1β levels in LPS-stimulated bone marrow-derived macrophages and increases HIF-1α levels. Moreover, the oxidation of succinate produces mitochondrial ROS, which affects the inflammatory phenotype of macrophages[43].

There is significant evidence showing that succinate increases the level of ROS, promotes vascular endothelial cell pyroptosis and macrophage polarization, and ultimately worsens atherosclerosis.

3.2. Succinate and AAD

AAD occurs when the arterial wall is unable to withstand high pressure in the blood vessel, resulting in the tearing of the middle membrane and the formation of a false lumen (arterial dissection). Once it tears, the mortality is as high as 65 – 85%[46]. Untargeted metabolomics studies showed that the level of succinate in plasma was significantly higher in patients with AAD. The direct phosphorylation of cAMP-response element-binding protein (CREB) by P38α in inflammatory macrophages leads to an increase in CREB-mediated transcription of OGDH and an elevated succinate level. The secretion of succinate outside cells leads to an increase in ROS levels in the vascular wall, which aggravates the progress of AAD[47].

3.3. Succinate and hypertension

Hypertension is an independent risk factor for cardiovascular disease. Succinate plays an important role in the regulation of blood pressure and is closely related to the renin-angiotensin system (RAS). Succinate activates RAS through SUCNR1 in the kidney to mediate hypertension[30]. High glucose levels stimulate the paracrine apparatus in the glomerulus and trigger the release of renin through the activation of succinate and its receptor SUCNR1[48]. SUCNR1, which is present in macula densa cells, is activated by succinate and regulates renin release[49]. The intravenous administration of succinate increases plasma renin activity and leads to a dose-dependent increase in blood pressure. This can be prevented with angiotensin-converting enzyme inhibitors[50]. In another study, the level of succinate in the blood of spontaneously hypertensive rats was found higher than that of normotensive rats[51]. A new succinate homeostatic pathway, which may be associated with hypertension, has also been identified, as it leads to the formation of calcium oxalate. The transport of citric and oxalic acids is regulated by the citric and succinate transporter protein Na^+-dependent dicarboxylate (NaDC)-1 and the oxalic acid transporter protein SLC family 26 member 6 (SLC26A6), both of which form a complex. This mechanism regulates the transepithelial transport of succinate. In SLC26A6 knockout mice, calcium oxalate stones, hyperoxaluria, and hypocitraturia are often seen with impaired succinate homeostasis, elevated serum succinate levels, and elevated plasma renin levels, exhibiting activity-dependent hypertension. Succinate acts on SUCNR1 to induce the translocation of the scaffold protein IRBIT and regulate transepithelial succinate transport. IRBIT interacts with SLC26A6-NADC1 complex to inhibit NADC1-mediated succinate transport[52]. In addition, oxidative stress is an important mechanism in the pathophysiology of hypertension, and succinate is known to aggravate oxidative stress *in vivo* by activating HIF-1α, thus leading to hypertension[24]. At present, the molecular mechanism by which succinate activates RAS is not well understood; however, the succinate-SUCNR1 signaling pathway and succinate transport mechanism may become potential therapeutic targets for hypertension.

3.4. Succinate and MIRI

Ischemic heart disease is the leading cause of CVD-related deaths. The main treatment strategy is to restore blood flow to the ischemic area in a timely and effective manner, but reperfusion itself may also lead to myocardial tissue injury, which is known as MIRI.

The release of succinate during reperfusion is mediated by MCT1. In ischemic cardiomyocytes, the intracellular environment acidifies, and succinate transforms into a protonated monocarboxylic form. During reperfusion, succinate monocarboxylate flows out of cells through MCT1, resulting is a reduction in intracellular succinate levels[28]. Blocking MCT1 causes succinate to reside in cells, thus exacerbating ROS production and IR injury[53]. Under hypoxic and ischemic conditions, myocardial extracellular succinate accumulation increases the translocation of dynamin-related protein 1 (Drp1) to mitochondria by SUCNR1 activation of protein kinase C-δ (PKCδ) and induces the phosphorylation of mitochondrial fission factor (MFF) by extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) activation, leading to mitochondrial fission[54]. Succinate drives ROS production during reperfusion. Preventing succinate accumulation or oxidation is a therapeutic target for cardioprotection[55]. Elevated levels of succinate inhibit the proliferation and regeneration of neonatal mouse cardiomyocytes through SDH, while malonic acid (a competitive inhibitor of SDH) inhibits the activity of SDH, preventing succinate

accumulation and inducing cardiomyocyte proliferation and heart regeneration[56]. SDH is the most crucial enzyme for succinate accumulation and oxidation to produce ROS during ischemia-reperfusion. Dimethyl malonate has a protective effect on ischemia-reperfusion injury in pre-ischemia or ischemia[24]. In a porcine ischemia-reperfusion model, coronary administration of dimethyl malonate was found to be cardioprotective[57]. In addition to its role in myocardial infarction, SDH inhibitors can also be used in predictable ischemic processes, such as ischemic stroke, kidney disease, and organ transplantation. Dimethyl malonate has been shown to reduce brain damage after cardiac arrest in rats[58]. Malonic acid may emerge as a potential treatment for reducing injuries during organ transplantation.

Isolated organs are in a state of hypoxia, which leads to the accumulation of succinate in the organs and oxidation after reperfusion, resulting in tissue injury and inflammation. The cold storage solution can slow down the metabolism and the production of succinate, thus reducing the production of mitochondrial ROS during reperfusion and in reperfusion injury[59]. In a recent study related to organ transplantation, a new storage method was designed to preserve the heart for transplantation. Hypothermia oxygenation was used to raise the level of adenosine triphosphate/adenosine diphosphate (ATP/ADP) in the perfusion tissue, which reduced the level of cardiac succinate and cell injury, thus achieving a protective effect on the heart[60]. A large amount of succinate tends to accumulate in ischemic tissue, but following reperfusion, succinate is rapidly oxidized by SDH, and excess ROS are produced through mitochondrial respiratory complex I, resulting in calcium imbalance and ATP depletion, which lead to further damage and myocardial cell death[24].

3.5. Succinate and myocardial hypertrophy and heart failure

Cardiac overload is the primary cause of heart failure. Myocardial hypertrophy is the main compensatory mechanism with an increase in cardiac afterload. The apoptosis of cardiomyocytes has a significant role in the transition from myocardial hypertrophy to heart failure[61]. Pathological myocardial hypertrophy is a major risk factor for various CVDs and sudden death, but there is no effective treatment strategy at present.

Succinate triggers ERK1/2 phosphorylation, Ca^{2+}/calmodulin-dependent protein kinase II delta (CaMKIIδ) expression, and intracellular histone deacetylase 5 (HDAC5 translocation) through SUCNR1, leading to cardiomyocyte hypertrophy[62]. Succinate-SUCNR1 is involved in right ventricular hypertrophy induced by pressure overload through the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway[63]. In a previous study, a patient who presented with congestive heart failure was found deficient in succinate dehydrogenase, which caused succinate to accumulate extracellularly[64]. Succinate activates the cardiomyocyte PKA pathway, regulates cardiomyocyte Ca^{2+} transients through SUCNR1, reduces ventricular cardiomyocyte viability, increases caspase-3 activity, and leads to cardiomyocyte apoptosis[65]. The Ca^{2+} transient is an important indicator of myocardial hypertrophy[66]. These results suggest that succinate promotes cardiomyocyte apoptosis and Ca^{2+} transients, resulting in myocardial hypertrophy and heart failure.

3.6. Succinate and metabolic cardiomyopathy

Metabolic cardiomyopathy is a type of cardiomyopathy caused by metabolic disorders, primarily glucose, and lipid metabolism disorders, some of which include heart failure with preserved ejection fraction, diabetic cardiomyopathy, and Takotsubo syndrome.[67,68] Obesity, body fat, and body mass index are significant risk factors for these cardiomyopathies, and succinate may this condition.

Obesity may lead to metabolic disorders of adipose tissue, leading to macrophage infiltration and chronic inflammation. Succinate-SUCNR1 mediates adipose tissue macrophage infiltration and glucose intolerance in obesity[37]. The knockout of SUCNR1 results in a significant reduction in macrophage infiltration in adipose tissues[37]. In addition to worsening obesity, inflammation and glucose intolerance may occur as a result of macrophage-specific deficiency of SUCNR1[69]. The elevated plasma level of succinate is related to metabolic abnormalities. In obese people, the level of succinate in the circulation increases, while the expression of SUCNR1 in adipose tissue-resident macrophages decreases[70]. The thermogenic activity of brown adipose tissue (BAT) plays a significant role in obesity. Uncoupling protein 1 (UCP1), which is a key thermogenic protein expressed in brown and beige adipocytes, regulates the removal of succinate from the circulation of brown and beige fat. High levels of succinate are rapidly absorbed by adipocyte mitochondria, producing ROS through SDH-mediated succinate oxidation, driving UCP1-dependent thermogenic respiration, and then regulating liver inflammation and glucose intolerance under obesity conditions[71,72]. In a cold exposure mouse model, succinate accumulated in brown adipocytes, reduced HFD-induced obesity, and enhanced thermogenesis in BAT through non-adrenergic signaling pathways[71]. Therefore, succinate can be regarded as an activator of BAT thermogenesis. Interestingly, the exogenous supplementation of succinate to pregnant and lactating female mice was found to promote the development of brown fat in newborn mice

and prevent obesity as well as metabolic dysfunction caused by HFD in newborn mice[73]. It is associated with enhanced succinylation and H3K4me3 modification in the PPARGC1A promoter. These results suggest that succinate can promote energy consumption and counter obesity by activating thermogenic fat, and this effect can be passed on to offspring.

Succinate can increase the differentiation of beige adipocytes. Stearoyl COA desaturase 1 (SCD1) is a rate-limiting enzyme of monounsaturated fatty acids. SCD1 induces the differentiation of preadipocytes into beige adipocytes through mitochondrial complex II activity that is driven by succinate[74]. Succinate inhibits the decomposition of triglycerides in white fat through SUCNR1[75]. The mitochondrial dicarboxylate vector SLC25A10 is mainly expressed in white adipose tissue (WAT), which enhances mitochondrial respiration, promotes succinate transport to the outside of cells, and inhibits lipolysis in adipocytes[27]. The highly expressed SUCNR1 in WAT is significantly higher than that in BAT. In the white adipose tissue of SUCNR1 knockout mice, the inhibitory effect of succinate on lipolysis is weakened. Succinate exerts its anti-lipolysis effect through SUCNR1 in WAT[76]. This is in contradiction with the role of succinate in BAT in promoting fat combustion to counter obesity. Further, exploration of the metabolism of succinate in adipose tissue and its role in obesity is needed, and the study of the role of succinate in metabolic cardiomyopathy is the future research direction (Figure 2).

4. Potential therapeutic targets of succinate metabolism in CVD

In view of the key role of the succinate-SUCNR1 signaling pathway, it is particularly important to develop a SUCNR1 agonist. Using a structural model based on crystal structure, researchers have found that the crystal had 27% homology with the purinergic receptor P2Y1 and further determined its potential ligands through simulation screening[36]. Several agonists have been screened, among which the most effective potential agonist has the structure of the succinate main chain, and its amide-linked hydrophobic structure is connected with the side chamber of the SUCNR1-binding site. Moreover, several potential agonists may be 10 – 100 times more potent than succinate itself and exert effects on SUCNR1 in both, mice and humans. *In vitro*, it may produce a similar effect to succinate on human macrophages. Further experiments have found a new nanomolar agonist with excellent stability *in vitro* but with high hydrophilicity[77]. At present, the best succinate analog found is cis-epoxy succinate, with a half maximal effective concentration

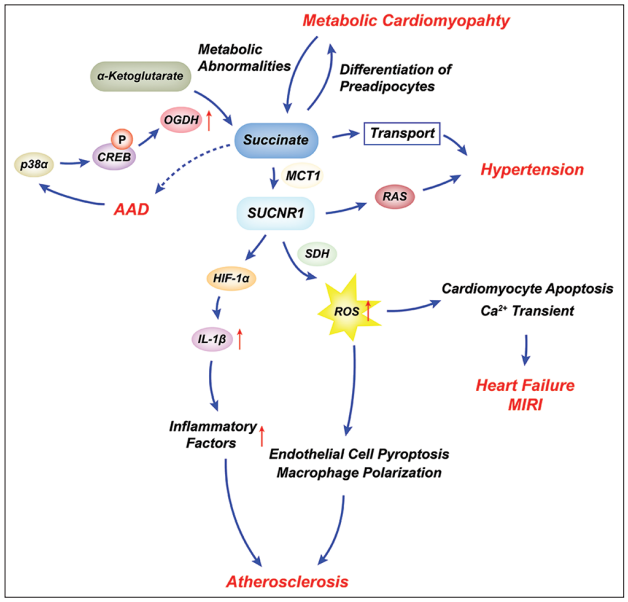

Figure 2. Succinate is associated with various cardiovascular diseases. In atherosclerosis, succinate binds to succinate receptor 1 (SUCNR1), which is expressed in human umbilical vein endothelial cells and macrophages, activates hypoxia-inducible factor (HIF)-1α, promotes IL-1β expression, produces large amounts of inflammatory factors, as well as affects endothelial cell pyroptosis and macrophage polarization; alternatively, through a non-HIF-1α-dependent pathway, succinate upregulates succinate dehydrogenase B (SDHB) expression to promote reactive oxygen species (ROS) production, exacerbating the atherogenic inflammatory process of atherosclerosis. In heart failure and MIRI, succinate accumulates in ischemic tissues. After reperfusion, succinate is rapidly oxidized by SDH, generating excess ROS, which leads to cardiomyocyte apoptosis and calcium ion (Ca^{2+}) transients. In hypertension, succinate is mediated by SUCNR1 through the activation of renin-angiotensin system or the transport mechanism of succinate to increase blood pressure. In acute aortic dissection, p38α in inflammatory macrophages is involved in its pathogenesis by phosphorylating cAMP-response element-binding protein, increasing oxoglutarate dehydrogenase expression, and increasing succinate levels. In metabolic cardiomyopathy, succinate affects the differentiation of preadipocytes. Metabolic abnormalities in obese people are associated with elevated plasma succinate levels.

(EC50) of 2.7 μM. The compound will not be oxidized by SDH but can play the role of succinate as a SUCNR1 ligand. Following intravenous administration, it can significantly increase blood pressure in rats[78]. The EC50 of SUCNR1 activated by succinate is in the range of 17 – 56 μM, and the concentration of succinate in human plasma is about 2 – 30 μM.

Since SUCNR1 plays a key role in the chemotaxis of immune cells and inflammation, SUCNR1 inhibitors may play a protective role in inflammatory diseases. Several potential small molecule inhibitors of SUCNR1 have been screened out from commercial compounds, of which the two most significant compounds are 2c and 4c, with their half maximal inhibitory concentration (IC50) values reaching 30 nM and 7 nM, respectively[79].

Although both compounds have poor bioavailability, they significantly alleviated hypertension in rats induced by succinate intervention. The study also screened several compounds with good bioavailability but poor specificity and used another compound (2d) for intervention. The 2d can inhibit the expression of type I collagen in rat hepatic stellate cells induced by high glucose or succinate[80], suggesting that it may play a certain role in alleviating non-alcoholic fatty liver. High-throughput screening identified another compound, NF-56-EJ40, which may be used as an inhibitor of SUCNR1. Its IC50 for human SUCNR1 is 25 nM, indicating good performance[31]. Through further crystal structure analysis, the structural basis of species differences in this inhibition has been clarified, thus providing direction for the design and selection of inhibitors in the future. The inhibitors studied in the previous stage have poor permeability due to their polar zwitterionic properties. Hence, to design effective drugs with good bioavailability, recent studies have systematically optimized them by adding internal salt bridges.

The therapeutic effect of the SUCNR1 inhibitor has not been reported at present. However, the designer of the SUCNR1 inhibitor based on naphthyridine has applied for a series of patents, in which it has been alluded that SUCNR1 inhibitor may be used in the treatment of non-alcoholic fatty liver disease and other related diseases, revealing a certain potential therapeutic value. Fibroblast growth factor 21 and co-recombinant peptide analogs have been found to inhibit the production of α-smooth muscle actin and reduce fibrosis in mice by inhibiting the succinate-SUCNR1 signaling pathway[81]. Metformin, a miracle drug for the treatment of type 2 diabetes, has also been shown to inhibit the hepatic succinate-SUCNR1 signaling pathway[82].

Exploring the decrease in SUCNR1 expression at the mRNA level is also an important means for researchers to explore the succinate-SUCNR1 signaling pathway. SUCNR1 is an important target of microRNA (miR)-758. Oxidized low-density lipoprotein stimulates the expression of miR-758 in endothelial cells and further downregulates SUCNR1 and its downstream signaling pathway, resulting in human vascular endothelial cell injury[83]. In a rat retinopathy model, the knockdown of rat SUCNR1 by small interfering RNA (siRNA) resulted in decreased vascular endothelial growth factor secretion, abnormal neovascularization, loss of pericytes, and areas without blood vessels[84]. The optimization of the structure and pharmacokinetics of SUCNR1 inhibitors enables researchers to identify new compounds and verify them in animal models (Table 1).

Table 1. Potential therapeutic targets of succinate metabolism

Treatment	Name of compound	Species	EC50/IC50	References
SUCNR1 agonist	cis-Epoxysuccinic acid	Rat	2.7 μM	[78]
SUCNR1 inhibitor	2c 4c	Human/Rat	30 nM 7 nM	[79]
	2d	Rat	40 nM	[80]
	NF-56-EJ40	Human	25 nM	[31]
mRNA	miR-758	Mouse		[83]

Due to the complex environment-dependent functions of SUCNR1, its current research is not thorough enough. Despite the fact that large pharmaceutical companies have submitted patents for screening SUCNR1 regulatory drugs or using SUCNR1 as an immune cell marker, it does not seem to have received enough attention. At present, several research groups and small companies are exploring superior performance regulators of SUCNR1 and their applications in diseases, but more research is needed to explain its complex functions and important role in diseases.

5. Conclusion and perspectives

Numerous clinical diagnoses of CVD have revealed changes in succinate levels. Succinate is regarded as a potential biomarker of CVD. The accumulation of succinate in ischemic tissues indicates the presence of ischemia[24]. Elevated plasma succinate levels are associated with increased cardiovascular risk factors in young adults, and its levels are positively correlated with visceral adipose tissue mass, which may serve as a biomarker for CVD risk in young adults[85]. Serum succinate was found to be significantly elevated in patients with coronary heart disease compared with healthy controls[40]. Circulating succinate levels are elevated in obese patients and are associated with poor metabolic status[86]. In patients with ST-elevation myocardial infarction, the level of succinate in the coronary sinus increases significantly[43]. Serum succinate levels also increase in patients with cardiac hypertrophy associated with acute or chronic obstructive coronary artery disease[62]. Early AAD is usually asymptomatic; hence, it is a challenge for an early diagnosis to be made. Since plasma succinate levels are significantly elevated in patients with AAD, it can be used to distinguish AAD from patients with acute myocardial infarction and pulmonary embolism[47].

This review focuses on the mechanism of succinate metabolism and its related factors in CVD. The existing

evidence reveals that succinate metabolism has a significant role in the pathophysiology of CVD. Succinate, as an important metabolic intermediate and signaling molecule, is a potential biomarker of cardiovascular disease. Further studies on the biological function, signaling pathway, and regulatory mechanism of succinate may provide new strategies and targets for the diagnosis and treatment of CVD in the coming era of precision medicine.

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Conflict of interest

The authors declare that they have no competing interest.

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