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Review

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Emerging roles of the metabolite succinate in bone-related diseases

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Abstract: Bone-related diseases, including osteoporosis (OP), osteoarthritis (OA), rheumatoid arthritis (RA), fracture, and periodontitis, significantly impact human health. Succinate, primarily known as a metabolic intermediate in the tricarboxylic acid (TCA) cycle, has emerged as a regulator of cellular functions beyond its metabolic role. Under stress, succinate accumulates in mitochondria and acts as a signaling molecule, modulating cellular processes. Notably, succinate activates angiogenesis and inflammation by stabilizing hypoxia-inducible factor-1α (HIF-1α). Moreover, it influences various pathophysiological processes by interacting with the succinate receptor 1 (SUCNR1), thereby impacting immune response, inflammation, cancer metastasis, and bone homeostasis. The multifaceted roles of succinate as a signaling molecule vary depending on its cellular location and concentration. Recent metabolomic analyses have revealed elevated succinate levels in bone-related diseases, indicating its potential association with these conditions. The objective of this review is to elucidate the impacts of succinate on different bone-related diseases and to discuss potential therapeutic targets and drug molecules based on its mechanisms of action.

Key words: Succinate; Osteoarthritis; Rheumatoid arthritis; Osteoporosis; Fracture; Periodontitis

1 Introduction

Various bone-related diseases pose a significant threat to human health due to their high incidence and disability rates, which severely limit mobility of patients and decrease their quality of life. The occurrence and development of these diseases are often associated with factors such as bone homeostasis, inflammation, and immunity. Succinate is a metabolic intermediate of the tricarboxylic acid (TCA) cycle, which can be oxidized to fumarate by means of succinate dehydrogenase (SDH) catalysis, which is crucial for adenosine triphosphate (ATP) production in mitochondria. However, recent studies have increasingly revealed regulatory roles of succinate beyond its activity as a metabolic intermediate. Under physiological or pathological stress, disruptions in the TCA cycle may lead to the accumulation of succinate in mitochondria and its secretion into the cytoplasm as a signaling molecule to regulate cellular functions. In particular, by inhibiting prolyl hydroxylase (PHD) activity and stabilizing the expression of hypoxia-inducible factor-1α (HIF-1α), succinate activates downstream signaling pathways, promoting angiogenesis and inflammation. Additionally, succinate can be secreted into the extracellular space and mediate a variety of pathophysiological processes by interacting with succinate receptor 1 (SUCNR1). These processes include immune response, inflammation, cancer metastasis, and bone homeostasis. Succinate also plays a crucial role in energy metabolism by inducing protein post-translational modifications (PTMs) through succinylation, thereby regulating the activity of various metabolic enzymes. It has been found to be involved in the development of many diseases, such as ischemia/reperfusion injury, myocardial infarction, liver fibrosis, obesity, hypertension, neuroendocrine tumor, and hepatocellular carcinoma (Rubic et al., 2008; Hakak et al., 2009; Högberg et al., 2011; Pell et al., 2016). Metabolites are the ultimate functional products that integrate

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external stimuli with intracellular signals (Peng et al., 2015). In recent years, elevated levels of succinate have been observed in metabolomic analyses of bone-related diseases such as osteoporosis (OP), osteoarthritis (OA), rheumatoid arthritis (RA), and periodontitis, suggesting an association between succinate and bone-related diseases.

A comprehensive understanding of the roles of succinate in bone-related diseases is crucial for effectively targeting succinate and related factors as therapeutic interventions to influence the progression of bone-related diseases. This review elucidates the potential roles of succinate in the bone-related diseases listed above. Furthermore, based on its mechanisms of action, we discuss potential therapeutic targets and related drug molecules.

2 Source and structure of succinate and its receptors

2.1 Source of succinate

2.1.1 Generation of succinate by somatic mitochondria or microbial metabolism

Succinate is typically produced in somatic mitochondria as a metabolic intermediate of the TCA cycle, and its levels generally remain stable. However, recent discoveries have identified succinate as a response molecule under stress conditions such as ischemia, hypoxia, bacterial infection, and hyperglycemia (Hohl et al., 1987; Palmieri, 2013; Valls-Lacalle et al., 2016; Wang et al., 2019). Under these conditions, succinate accumulates in mitochondria through various pathways. In addition to somatic mitochondria, succinate can also be produced through microbial metabolism. Succinate is a key metabolic product of the gut microbiota (Connors et al., 2019) and is generated through the metabolism of polysaccharides and amino acids (Fernández-Veledo and Vendrell, 2019). Within the gut microbiota, the genus *Bacteroides* is the main producer of succinate. They utilize specialized carbohydrate-active enzymes to break down dietary fibers and complex polysaccharides into monosaccharide, producing intermediates such as pyruvate and oxaloacetate, which are then converted into succinate (de Vadder and Mithieux, 2018). Moreover, periodontal pathogens have also been found to produce succinate. *Porphyromonas gingivalis* can metabolize asparagine into succinate through fumarate, an intermediate that plays an important role in its energy production and pathogenicity (Shah and Williams, 1987; Takahashi et al., 2000). Likewise, *Prevotella intermedia* utilizes glucose to produce succinate with the aid of bicarbonate (Takahashi and Yamada, 2000). Interestingly, in both gut and oral microbiota, succinate cross-feeding occurs (Fernández-Veledo and Vendrell, 2019; Kin et al., 2020), in which one microorganism produces succinate and another uses it for energy, optimizing metabolic efficiency within the microbial community.

2.1.2 Four pathways of succinate accumulation under stress conditions

2.1.2.1 Activity of SDH in the TCA cycle is inhibited and succinate cannot be converted to fumarate

SDH catalyzes the oxidation of succinate to fumarate, which is an important step in maintaining the normal flow of the TCA cycle. Alterations in SDH activity can impede this oxidation process, leading to succinate accumulation. Mutations in the *SDH* gene have been identified in various cancers (Bardella et al., 2011; Wu and Zhao, 2013; Jiang and Yan, 2017; Zeng et al., 2023), and have been proven to contribute to tumorigenesis (Bardella et al., 2011). The accumulation of succinate under altered SDH activity is a potential mechanism (Dalla Pozza et al., 2020), which is associated with promoting tumor-cell survival, migration, and angiogenesis (Zhang and Lang, 2023). Additionally, SDH function relies on the oxidized forms of flavin adenine dinucleotide (FAD) and nicotinamide adenine dinucleotide (NAD^+) as cofactors. Under hypoxic conditions, these cofactors exist in reduced form, leading to SDH dysfunction and thus elevated levels of succinate (Tannahill et al., 2013). Furthermore, oxidative stress during hyperglycemia generates a significant amount of reactive oxygen species (ROS). This can also reduce SDH activity (Guo et al., 2017).

2.1.2.2 Reverse activity of SDH is activated, converting fumarate to succinate

Mitochondrial ROS-induced oxidative damage is a key factor in the pathogenesis of ischemia-reperfusion injury. Studies have found that succinate is a significant driving factor in ROS production during reperfusion. In contrast to normal conditions, in which succinate mainly comes from the canonical activity of TCA cycle (α-ketoglutarate→succinyl-coenzyme A (CoA)→succinate), succinate is primarily generated through the

reverse activity of SDH under ischemic conditions. Chouchani et al. (2014) first used computer simulations to reveal that under ischemic conditions, reversal of SDH is the optimal solution for succinate production. Subsequently, intravenous infusion of dimethyl malonate (DMM), a competitive inhibitor of SDH, resulted in a reduction in succinate accumulation of more than half under ischemic conditions (Chouchani et al., 2014). In hypoxic synovial fibroblasts (SFs), the use of DMM was also observed to decrease succinate levels (Li et al., 2018). During ischemia or hypoxia, the ability of SDH to oxidize succinate to fumarate is impaired due to a lack of sufficient electron acceptors such as oxygen and FAD. Fumarate can accumulate through the malate-aspartate shuttle (MAS) and the purine nucleotide cycle (PNC) during ischemia (Tomitsuka et al., 2010), and is converted back to succinate by activating the reverse activity of SDH (Pellerin and Magistretti, 1994).

2.1.2.3 Glutamine-dependent anaplerosis

The accumulation of succinate in macrophages stimulated by lipopolysaccharide (LPS) has been observed in many studies. LPS-stimulated macrophages undergo metabolic reprogramming, shifting from oxidative phosphorylation to glycolysis, which leads to decreased activity of the TCA cycle. Under these conditions, glutamine (Gln)-dependent anaplerosis becomes the primary source of succinate production (Tannahill et al., 2013). Gln enters the cytoplasm through membrane transport proteins. In LPS-stimulated macrophages, the levels of the Gln transporter solute carrier family 3 member 2 (SLC3A2) significantly increase after 24 h (Tannahill et al., 2013). The Gln that enters the cytoplasm through this transporter is converted into glutamate (Glu) by glutaminase, and further transformed into α-ketoglutarate (α-KG) by glutamate dehydrogenase (GDH), replenishing the TCA cycle and thus promoting succinate production (Lee et al., 2023).

2.1.2.4 γ-Aminobutyric acid shunt pathway

Besides the Gln-dependent anaplerosis, the γ-aminobutyric acid (GABA) shunt pathway is also a major source of succinate accumulation under LPS stimulation. Tannahill et al. (2013) found that LPS promotes the expression of GABA transporters (SLC6A13 and SLC6A12) and the generation of GABA through gene-expression analysis and metabolomics (Tannahill et al., 2013). Moreover, GABA-transaminase (GABA-T) inhibitors inhibit succinate production, indicating that the GABA shunt pathway also contributes to succinate accumulation (Li et al., 2018). In the cytosol, GABA is decarboxylated from Glu by glutamate decarboxylase (GAD). Subsequently, it enters the mitochondria via GABA transporters (SLC6A13 and SLC6A12) and reacts with α-KG under the action of GABA-T to generate succinic acid semialdehyde, which is then oxidized to succinate.

The four pathways of succinate accumulation under stress conditions are shown in Fig. 1.

2.2 Expression and structure of SUCNR1

Under stress conditions, accumulated succinate in mitochondria is secreted into the cytoplasm as a signaling molecule to regulate local cell metabolism to adapt to stressful environments or promote disease progression. However, continued research has uncovered the fact that succinate can also act as an extracellular signal component to mediate a variety of pathophysiological processes by binding to the succinate receptor SUCNR1.

SUCNR1 is widely expressed in human cells (Wu, 2023), with the highest expression observed in adipose tissue, followed by liver, kidney, pancreas, spleen, and small intestine tissues (Guo YQ et al., 2020). Additionally, SUCNR1 is expressed in immune and hematopoietic lineage cells, especially in mesenchymal stem cells (MSCs), monocytes, and macrophages (Uhlén et al., 2015; Guo et al., 2017). SUCNR1 is closely associated with angiogenesis, bone homeostasis, and immune activation. Studies have also confirmed that there is SUCNR1 expression in human gingival fibroblasts, providing a new perspective on the pathogenesis of periodontitis.

SUCNR1 (or GPR91) is a member of the G protein-coupled receptor (GPCR) family, the largest group of membrane proteins in the human genome. Human SUCNR1 encodes a protein of 334 amino acids, which shares high homology among humans, rats, and mice. The SUCNR1 sequence primarily differs at the C-terminus, being 12 amino acids shorter in rodents (Ariza et al., 2012). SUCNR1 has typical disulfide bonds and two *N*-glycosylation sites in the extracellular region (Gilissen et al., 2016). In addition to succinate, the ligands of SUCNR1 include maleate and methylmalonate, but their activation potency is much lower than that of succinate (Ariza et al., 2012). Antagonists of **2c** and **4c** can bind to remote sites of

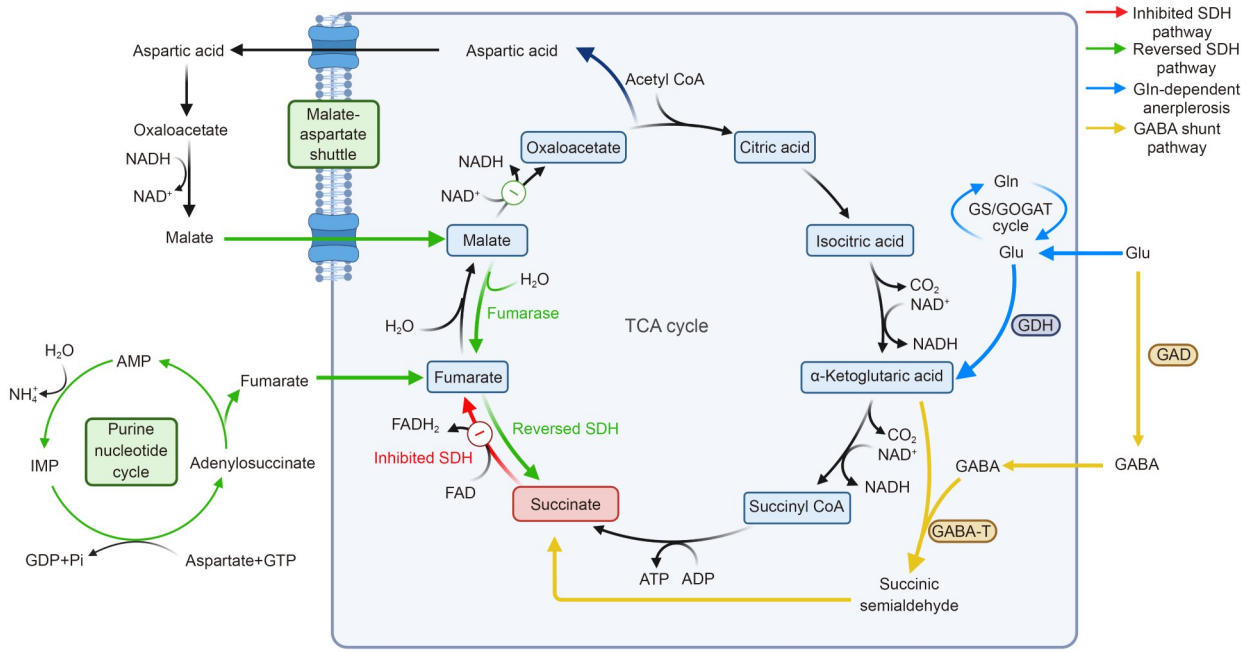

Fig. 1 Four pathways of succinate accumulation under stress conditions. (1) Inhibited succinate dehydrogenase (SDH) pathway: When the activity of SDH in the tricarboxylic acid (TCA) cycle is inhibited, succinate cannot be converted to fumarate and accumulates. (2) Reversed SDH pathway: Fumarate can accumulate through the malate-aspartate shuttle (MAS) and the purine nucleotide cycle (PNC) during ischemia, and is converted back to succinate by activating the reverse activity of SDH. (3) Glutamine (Gln)-dependent anaplerosis: In lipopolysaccharide (LPS)-stimulated macrophages, the Gln that enters the cytoplasm through Gln transporters is converted into glutamate (Glu) by glutaminase, and further transformed into α-ketoglutarate (α-KG) by glutamate dehydrogenase (GDH), replenishing the TCA cycle and thus promoting the production of succinate. (4) γ-Aminobutyric acid (GABA) shunt pathway: In the cytosol, GABA is decarboxylated from Glu by glutamate decarboxylase (GAD). Subsequently, GABA enters the mitochondria via GABA transporters and reacts with α-KG under the action of GABA-transaminase (GABA-T) to generate succinic acid semialdehyde, which is then oxidized to succinate. NAD^+: nicotinamide adenine dinucleotide; NADH: nicotinamide adenine dinucleotide (reduced); AMP: adenosine monophosphate; IMP: inosine monophosphate; GDP: guanosine diphosphate; ATP: adenosine triphosphate; ADP: adenosine diphosphate; CoA: coenzyme A; GTP: guanosine triphosphate; Pi: inorganic phosphate; FADH2: reduced flavin adenine dinucleotide; FAD: flavin adenine dinucleotide; GS: glutamine synthetase; GD: glutamate dehydrogenase; GAT: GABA transporter. Image created with BioRender.com, with permission.

SUCNR1 and act as allosteric antagonists (Bhuniya et al., 2011). The selectivity of SUCNR1 for succinate is mediated by four positively charged key residues in the binding cavity enclosed by the seven transmembrane domains of the receptor, namely Arg99, His103, Arg252, and Arg281 (He et al., 2004).

2.3 Mechanisms of action and related signaling pathways of succinate

2.3.1 Transmembrane transport of succinate

Succinate is typically confined to mitochondria and is generated by the TCA cycle. However, under stress, accumulated succinate in mitochondria can be secreted into the cytoplasm or extracellular space to exert its effects. Succinate has different effects in different cellular locations, making its transport between different locations crucial. Transport of succinate between mitochondria, cytoplasm, and extracellular space relies on various transport channels. Under physiological pH conditions, succinate is a charged molecule and cannot diffuse across membranes. With the accumulation of succinate in mitochondria, it can be exported to the cytoplasm via the dicarboxylic acid translocator SLC25A10 on the inner mitochondrial membrane and the voltage-dependent anion channel (VDAC/porin) on the outer mitochondrial membrane (Selak et al., 2005). During ischemia-reperfusion and intense exercise, succinate efflux is mainly mediated by monocarboxylate transporter 1 (MCT1) (Reddy et al., 2020; Prag et al., 2021). Organic anion transporters (OATs) can also transport succinate from the intracellular space to the extracellular space, but they have low affinity for succinate (Kaufhold et al., 2011).

The plasma membrane-bound Na-dependent dicarboxylic acid transporter Na^+/dicarboxylate cotransporter 3 (NaDC3) (*SLC13A3* gene) is an important pathway for uptake of extracellular succinate (Zhunussova et al., 2015). As a member of the SLC13 family, NaDC3 has a broad transport spectrum for dicarboxylic acid and TCA, with succinate being one of its highest-affinity substrates. The transport process of NaDC3 is dependent on Na^+. When one molecule of succinate binds to three Na^+ ions at the substrate-binding site of NaDC3, the "rocking bundle" mechanism induces a structural change in NaDC3, thereby facilitating the uptake of succinate into the cell (Pajor, 2014). Lithium ions can interfere with this process (Schlessinger et al., 2014).

2.3.2 Succinate-related signaling pathways

In addition to serving as an intermediate in metabolism, succinate can also be secreted into the cytoplasm and extracellular space as a signaling molecule to regulate cellular responses. The primary mechanisms involved are the succinate-HIF-1α axis, succinylation, and the succinate-SUCNR1 axis (Fig. 2).

2.3.2.1 Intracellular signaling pathways of succinate

As an oxygen sensor of cells, HIF-1α is normally activated by hypoxia, thereby initiating the transcription of a series of hypoxia-inducible genes to adapt to the hypoxic environment. It plays an important role in angiogenesis, glycolysis, cancer cell invasion and metastasis, as well as the expression of inflammatory genes (Zhang et al., 2023). Hypoxia induces succinate accumulation and accumulated succinate in mitochondria is transported to the cytoplasm to stabilize HIF-1α in response to hypoxia (Agani et al., 2000). Exogenous addition of succinate can bypass hypoxia and activate HIF-1α-related pathways under normoxic conditions, which is known as "pseudohypoxia." Thus, succinate has been discovered by some scientists to act as a superior pseudo-hypoxia agent, exerting excellent effects in angiogenesis (Löffler et al., 2023). As a substrate of PHD, α-KG produces succinate as a byproduct during the hydroxylation of HIF-1α. Therefore, high concentrations of succinate directly inhibit PHD activity, hindering degradation of HIF-1α and stabilizing it. ROS can impair PHD activity by oxidizing the key PHD cofactor Fe^{2+} to Fe^{3+}. Thus, succinate can also indirectly stabilize HIF-1α by inducing ROS production (Mao et al., 2020). The study by Tannahill et al. (2013) showed that intracellular succinate accumulation enhances the expression of interleukin-1β (IL-1β) by stabilizing HIF-1α in macrophages. Succinate can also promote vascular endothelial growth factor (VEGF) expression through HIF-1α, thereby regulating angiogenesis.

As a post-translational modification, succinylation of lysine is closely related to metabolic regulation. Succinylation of lysine can activate SDH, thereby contributing to the self-regulation of succinate levels in mitochondria (Park et al., 2013). Lysine succinylation participates in the regulation of various metabolic signaling pathways by the desuccinylase sirtuin 5 (SIRT5) and is widespread in mitochondrial energy metabolism. Studies have found that LPS stimulation increases protein succinylation by promoting succinate accumulation and inhibiting the expression and activity of SIRT5 (Tannahill et al., 2013).

2.3.2.2 Succinate-SUCNR1 axis

Extracellular succinate acts on SUCNR1 on the cell membrane through autocrine or paracrine mechanisms, mediating ligand-receptor signaling. For instance, macrophages can migrate and generate cytokines through the autocrine action of succinate. Succinate can also exert its biological effects by binding to SUCNR1 on other cells through paracrine mechanisms. In human skeletal muscle, *SUCNR1* messenger RNA (mRNA) is not expressed in muscle fibers but is highly expressed in subsets of macrophages. Therefore, in the adaptive response of skeletal muscle to exercise, succinate and SUCNR1 may induce a transition from fast to slow muscle fibers through a paracrine mechanism involving M2-like macrophages (Abdelmoez et al., 2023). Additionally, in mice with high blood-sugar levels, succinate that accumulates abnormally in bone marrow stromal cells (BMSCs) exerts its effects by binding to SUCNR1 in osteoclast (OC) precursor cells (Guo et al., 2017). The cascade reactions mediated by SUCNR1 are similar to the Gi and Gq signaling cascades, and lead to the accumulation of inositol trisphosphate (IP3), mobilization of calcium, down-regulation of 3',5'-cyclic adenosine monophosphate (cAMP), and phosphorylation of extracellular signal-regulated kinase (ERK) (He et al., 2004). Activation of SUCNR1 by succinate can also promote calcium-dependent nitric oxide (NO) and prostaglandin E2 (PGE2) production. The succinate-SUCNR1 axis plays a significant role in immune-inflammatory responses

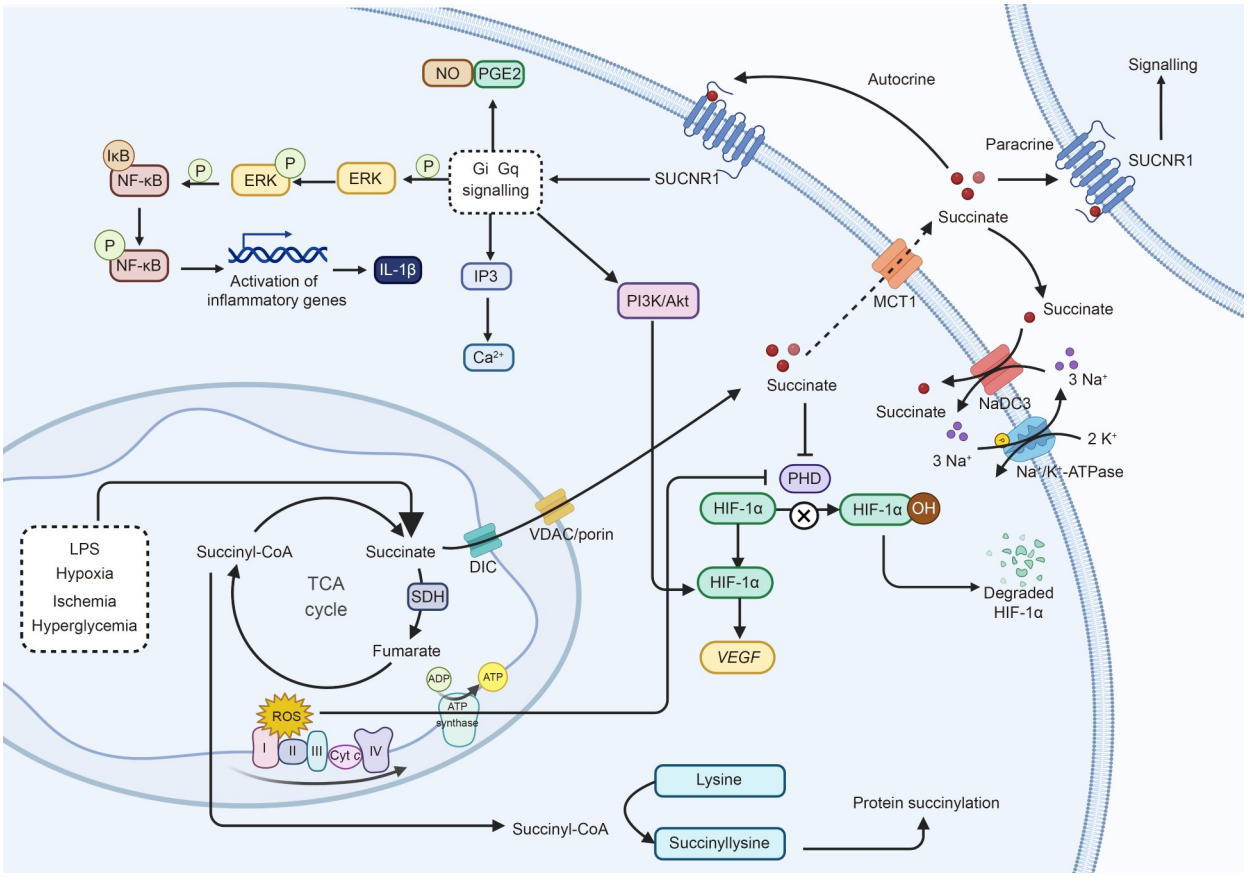

Fig. 2 Mechanisms of action and related signaling pathways of succinate. Under stress conditions, such as lipopolysaccharide (LPS), hypoxia, ischemia, and hyperglycemia, succinate accumulates in mitochondria. With the accumulation of succinate in mitochondria, it can then be exported to the cytoplasm via the dicarboxylic acid translocator SLC25A10 on the inner mitochondrial membrane and the voltage-dependent anion channel (VDAC/porin) on the outer mitochondrial membrane. Succinate in the cytoplasm stabilizes hypoxia-inducible factor-1α (HIF-1α) by inhibiting prolyl hydroxylase (PHD) activity, thereby promoting the transcription of HIF-1α-dependent hypoxia-inducible genes, such as vascular endothelial growth factor (*VEGF*). The succinate in cytoplasm can be exported outside from the cell through the transporter monocarboxylate transporter 1 (MCT1). Extracellular succinate enters the cell through the transporter Na^+/dicarboxylate cotransporter 3 (NaDC3) with the help of Na^+. Extracellular succinate binds to succinate receptor 1 (SUCNR1) through autocrine or paracrine mechanisms and activates downstream signaling pathways. The cascade reactions mediated by SUCNR1 are similar to the Gi and Gq signaling cascades, leading to the accumulation of inositol trisphosphate (IP3), mobilization of calcium, downregulation of 3',5'-cyclic adenosine monophosphate (cAMP), and phosphorylation of extracellular signal-regulated kinase (ERK), which activates the nuclear factor-κB (NF-κB) pathway and leads to interleukin-1β (IL-1β) production. Activation of SUCNR1 by succinate can also promote calcium-dependent nitric oxide (NO) and prostaglandin E2 (PGE2) productions. Lysine succinylation participates in the regulation of various metabolic signaling pathways by the desuccinylase sirtuin 5 (SIRT5). PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; IκB: inhibitor of NF-κB; DIC: dicarboxylate carrier; SDH: succinate dehydrogenase; TCA: tricarboxylic acid; ATP: adenosine triphosphate; ADP: adenosine diphosphate; CoA: coenzyme A; ROS: reactive oxygen species; Cyt *c*: cytochrome *c*. Image created with BioRender.com, with permission.

(Zhang and Lang, 2023) and contributes to the development of various inflammatory diseases by enhancing inflammation. These illnesses include diabetic retinopathy, hypertension, ulcerative colitis, and RA (He et al., 2004; Sadagopan et al., 2007; Toma et al., 2008). Activation of the succinate-SUCNR1 pathway induces M1 macrophages to release pro-inflammatory cytokines and chemokines, thereby aggravating inflammation (van Diepen et al., 2017; Murphy and O'Neill, 2018). Succinate can also promote dendritic-cell migration and activity of antigen-presenting cells by triggering an immune response with SUCNR1. Interestingly, in a mouse model of multiple sclerosis (MS), succinate secreted by MS tissues interacted with SUCNR1

expressed on transplanted neural stem cells (NSCs), inducing the secretion of PGE2 by NSCs and clearance of extracellular succinate, and thereby exerting anti-inflammatory effects (Peruzzotti-Jametti et al., 2018). Simultaneously, the succinate-SUCNR1 axis can control inflammation in the adipose tissue of healthy lean individuals by activating the anti-inflammatory phenotype (M2 type) of macrophages (Keiran et al., 2019). It is worth noting that the succinate-HIF-1α axis and the succinate-SUCNR1 axis are not entirely independent. Extracellular succinate can increase HIF-1α expression through the SUCNR1-phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signaling pathway (Mao et al., 2020).

2.3.3 Roles of succinate in bone and cartilage metabolism

The succinate-SUCNR1 axis has been found to stimulate osteoclastogenesis via the nuclear factor-κB (NF-κB) pathway, thus mediating the bone-resorption process. However, in osteogenesis, succinate appears to exhibit more complex effects. It can inhibit the activity and osteogenic differentiation of MSCs and other osteoprogenitor cells via the HIF-1α pathway. In vitro experiments, though, have also shown that specific concentrations of succinate can promote the migration and osteogenic differentiation of human mesenchymal stem cells (hMSCs). Furthermore, exogenous addition of succinate has been found to play a positive role in angiogenesis by promoting the proliferation and migration of endothelial cells without harming osteoblasts. This difference may be related to the concentration and site of action of succinate. Additionally, research indicates that succinate-induced metabolic remodeling accelerates hypertrophic differentiation of chondrocytes, thereby disrupting the homeostasis of cartilage. Succinate is also associated with the inflammatory phenotype of SFs.

3 Roles of succinate in bone-related diseases

Bone homeostasis is a dynamic balance between bone formation and bone resorption, and is crucial for normal bone development and bone-defect repair. OCs, derived from hematopoietic progenitor cells, participate in bone resorption, playing a vital role in bone homeostasis. When OCs are overactive, the rate of bone resorption exceeds that of bone formation, disrupting bone homeostasis and often leading to metabolic bone diseases. A large number of metabolomic studies have demonstrated an association between elevated levels of succinate and bone-related diseases such as OP, OA, and RA, suggesting that succinate and related factors may serve as therapeutic targets for these conditions. Clarifying the specific roles of succinate in bone-related diseases could provide new insights for treatment.

3.1 Succinate and OP

OP is a systemic metabolic bone disease characterized by reduced bone density and bone-structure deterioration, which is a typical manifestation of bone–homeostasis imbalance. The association between elevated succinate levels and OP is quite evident. Numerous metabolomic studies have observed significantly higher succinate levels in the metabolites of OP patients (Zhao et al., 2018; Yu et al., 2019; Deng et al., 2021). Additionally, a decrease in SDH activity has been observed in the articular cartilage of patients with femoral neck fracture caused by primary OP (Nahir et al., 1990). Studies have found a negative correlation between succinate and bone density (Wang et al., 2023). However, contradictory results exist, with a 4-week dietary supplement treatment based on succinate leading to increased bone mass and calcium content in aging mice (Maevsky et al., 2008). Nevertheless, this study had limitations such as insufficiently controlled variables and a small sample size. Evidence also suggests that succinylation contributes to the development of OP (Su et al., 2017).

In OP patients, OC activity is abnormally high. Guo et al. (2017) found that the succinate-SUCNR1 axis is involved in the activation of OCs and in enhanced bone resorption mediated by OCs in type 2 diabetes (T2D) mice. In T2D mice with concomitant OP, succinate was increased 24-fold in BMSCs. Further research revealed that succinate can stimulate OC generation, differentiation, and maturation, promoting bone resorption. Besides directly stimulating OC generation, succinate can induce OC generation by downregulating the levels of IL-4 and IL-13 and activating the expression of tumor necrosis factor (TNF) and IL-1β. The specific mechanism by which accumulated succinate in BMSCs induces OC generation involves the succinate-SUCNR1 axis. As SUCNR1 is

not expressed on BMSCs but is highly expressed in hematopoietic lineage cells (including OCs and OC precursor cells), accumulated succinate in BMSCs acts on SUCNR1 on the membrane of OC precursor cells through paracrine action, thereby promoting their transformation into OCs via stimulation of the NF-κB signaling pathway (p50/p65).

Mitochondrial dysfunction is associated with aging-related phenotypes such as OP (Guo YQ et al., 2020). Succinate mediates mitochondrial dysfunction, and mitochondrial dysfunction leads to the accumulation of succinate (Nair et al., 2019). The succinate-SUCNR1 axis can promote mitochondrial fission through the downstream extracellular signal-regulated kinase 1/2 (ERK1/2)/dynamin-related protein 1 (DRP1) pathway (Nguyen et al., 2022). In mitochondria with impaired function, metabolic remodeling occurs, with decreased ATP synthesis and increased production of ROS. The transition from oxidative metabolism to glycolytic metabolism in aging bones is a major determinant of bone loss in mice (Liu et al., 2024). During mitochondrial electron transport, complexes I and III generate ROS, whose toxic byproducts damage the mitochondria. This damage then triggers adjacent mitochondria to release more ROS, creating a vicious cycle. Accumulated ROS can act as the second messengers in OC generation (Callaway and Jiang, 2015), inducing bone resorption and thereby playing a role in the onset and progression of OP.

Reduced osteogenic differentiation of osteoprogenitor cells is also one of the contributing factors to OP. Mitochondrial transfer is a novel mode of intercellular communication. Macrophages play an important role in bone homeostasis (Gao et al., 2019). Under normal circumstances, macrophages can promote the osteogenic differentiation of MSCs by transferring mitochondria to MSCs. MSCs that receive functional mitochondria exhibit enhanced osteogenic potential, while those that receive damaged mitochondria experience impaired osteogenic potential. However, in OP, the phenotype and metabolic state of macrophages change, transitioning them from M2-type macrophages to M1-type macrophages. Inflammatory-activated macrophages transfer oxidatively damaged mitochondria to MSCs via microvesicles, causing cellular damage and metabolic reshaping of MSCs. This metabolic disorder leads to the accumulation of succinate in MSCs by inhibiting the activity of SDH, thereby promoting the release of proinflammatory factors (such as IL-1β) and ROS through the HIF-1α signaling pathway and affecting the osteogenic differentiation of MSCs (Cai et al., 2023). Furthermore, mitochondria-derived oxidative damage from M1-type macrophages can increase apoptosis in MSCs and impair their proliferation. In addition to its effect on MSCs, succinate can inhibit the proliferation and osteogenic differentiation of mouse osteoprogenitor cells MC3T3-E1, which may be related to the downregulation of Runt-related transcription factor 2 (RUNX2) and osteocalcin (OCN) (Wei et al., 2019). The role of succinate in OP is illustrated in Fig. 3.

3.2 Succinate and RA

RA is a chronic progressive autoimmune disease characterized by inflammation and angiogenesis. Metabolomic analysis has identified succinate as a potential biomarker for RA (Li et al., 2016). RA patients have abundant succinate in their synovial fluid (Littlewood-Evans et al., 2016). Studies have also shown a correlation between levels of succinate in SFs and the degree of paw swelling in arthritic mice, suggesting that succinate levels could serve as a biological indicator of RA severity (Littlewood-Evans et al., 2016). Succinate was found to be the most differentially expressed metabolite between RA and other joint diseases (Kim et al., 2014).

Angiogenesis in the synovium in RA promotes inflammation and pannus formation, leading to destruction of cartilage and bone (Szekanecz et al., 2010). Succinate can promote synovial angiogenesis, thereby driving the progression of RA. This process involves the HIF-1α-VEGF axis, the succinate-SUCNR1 axis, transforming growth factor-β1 (TGF-β1), and a reversal of SDH activity (Li et al., 2018). In the synovium of RA, due to local hypoxia, TGF-β1 increases succinate production by reversing SDH activity in SFs (Li et al., 2016). Accumulated succinate then induces VEGF expression by stabilizing HIF-1α in the cytoplasm. VEGF can mediate angiogenesis and also promote synovial endothelial cell activation to induce inflammation, thereby establishing crosstalk between angiogenesis and joint inflammation in RA. Additionally, accumulated succinate can be transported to the extracellular space, activating SUCNR1 on endothelial cells to induce VEGF production, further exacerbating angiogenesis. These two pathways work

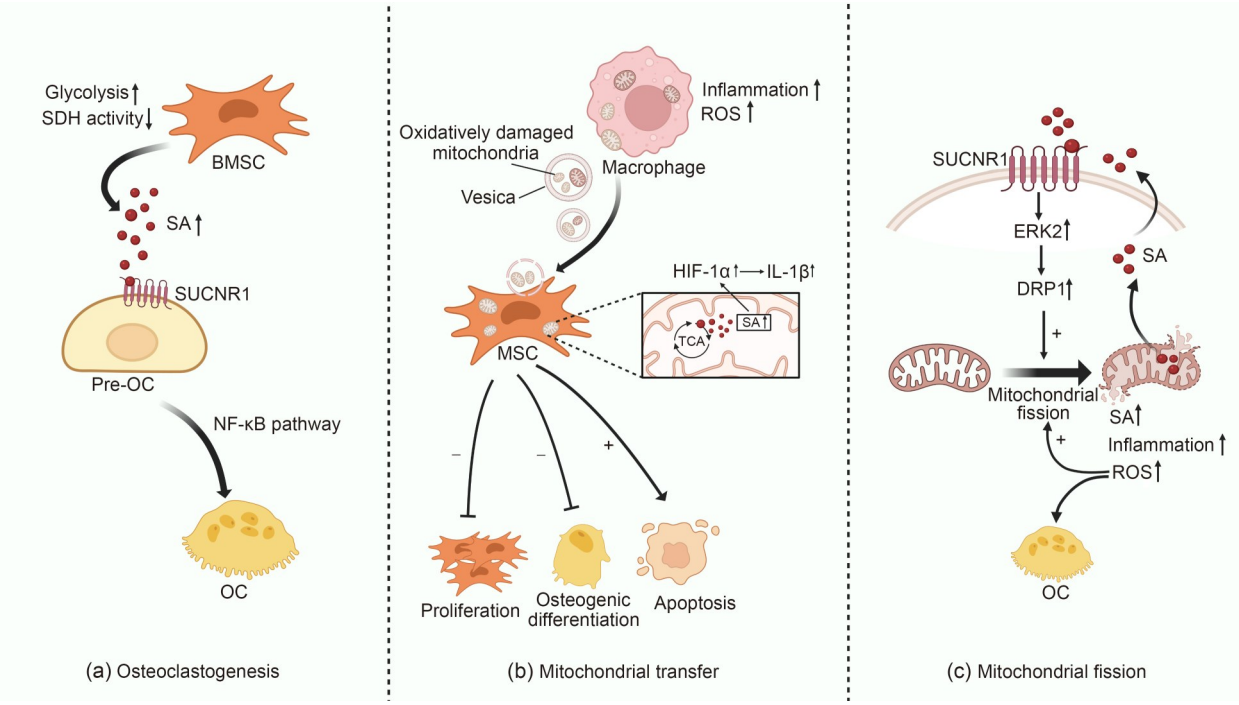

Fig. 3 Role of succinate in osteoporosis (OP). (a) When succinate dehydrogenase (SDH) activity is inhibited, accumulated succinate in bone marrow stromal cells (BMSCs) acts on succinate receptor 1 (SUCNR1) on the membrane of osteoclast (OC) precursor cells through paracrine action, thereby promoting their transformation into OCs via stimulation of the nuclear factor-κB (NF-κB) signaling pathway. (b) During OP, inflammatory-activated macrophages transfer oxidatively damaged mitochondria to mesenchymal stem cells (MSCs) via macrovesicles, causing cellular damage and metabolic reshaping of MSCs. This leads to accumulation of succinate in MSCs by inhibiting the activity of SDH, thereby promoting the release of interleukin-1β (IL-1β) and reactive oxygen species (ROS) through the hypoxia-inducible factor-1α (HIF-1α) signaling pathway. This promotes the apoptosis of MSCs and inhibits the proliferation and osteogenic differentiation of MSCs. (c) The succinate-SUCNR1 axis promotes mitochondrial fission via the extracellular signal-regulated kinase 1/2 (ERK1/2)/dynamin-related protein 1 (DRP1) pathway. In addition, mitochondrial dysfunction can lead to accumulation of succinate, inflammation, and ROS generation, creating a vicious cycle. These ROS act as the second messengers, inducing osteoclast generation and bone resorption. SA: succinate; TCA: tricarboxylic acid. Image created with BioRender.com, with permission.

together to exacerbate inflammation and angiogenesis in RA synovium. Moreover, succinate can induce dysfunctional angiogenesis by inducing basic fibroblast growth factor (Biniecka et al., 2016). Inhibitors of SDH such as DMM can attenuate angiogenesis and inflammation in RA synovium by reducing succinate production.

The proinflammatory effect of succinate is also significant in the progression of RA. Synovial hypoxia in RA leads to succinate accumulation in SFs. IL-1β is released from macrophages triggered by succinate in an SUCNR1-dependent manner, and thus serves as a core driver of arthritis inflammation. Maturation of IL-1β is mediated by the nucleotide-binding oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome (Wen et al., 2011). Accumulated succinate in SFs can activate the NLRP3 inflammasome with the involvement of HIF-1α, inducing IL-1β secretion and promoting inflammation. IL-1β-mediated inflammation, in turn, induces fibroblast activation by inducing TGF-β1. Activated fibroblasts further stimulate the generation of IL-1β, thus perpetuating a cycle that leads to sustained polarization of fibroblasts, ultimately resulting in fibrosis of the synovial tissue. Therefore, the accumulation of succinate serves as a metabolic signal that connects IL-1β and TGF-β1 and establishes crosstalk between inflammation and fibrosis, further exacerbating tissue damage in RA (Li et al., 2016). Additionally, succinate can exacerbate synovial tissue hyperplasia and inflammation by promoting the invasion and migration capacity of fibroblast-like synoviocyte (FLS) (Hu et al., 2024). The role of succinate in RA is illustrated in Fig. 4.

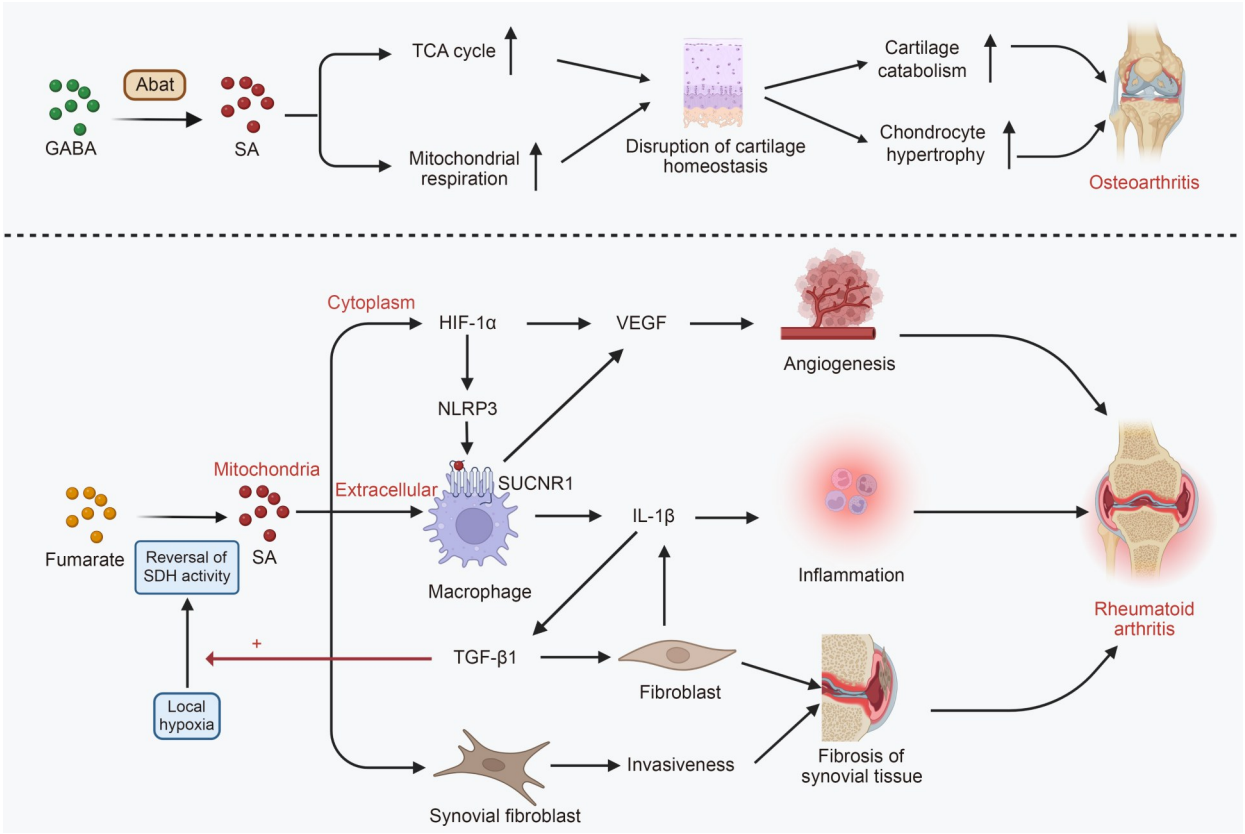

Fig. 4 Roles of succinate in osteoarthritis (OA) and rheumatoid arthritis (RA). 4-Aminobutyrate aminotransferase (Abat) is an enzyme that metabolizes γ-aminobutyric acid (GABA) to succinate. Increased succinate levels enhance the tricarboxylic acid (TCA) cycle and mitochondrial respiration, which disrupts cartilage homeostasis, thereby promoting cartilage catabolism and chondrocyte hypertrophy. Synovial hypoxia in RA leads to reversed succinate dehydrogenase (SDH) activity, resulting in succinate accumulation in synovial fibroblasts (SFs). Succinate promotes angiogenesis via the hypoxia-inducible factor 1α (HIF-1α)-vascular endothelial growth factor (VEGF) and succinate-succinate receptor 1 (SUCNR1) pathways. Accumulated succinate triggers macrophages to release interleukin-1β (IL-1β) via the SUCNR1 pathway. IL-1β release is mediated by the nucleotide-binding oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome and activated by succinate with HIF-1α involvement. This process promotes inflammation and fibroblast activation through transforming growth factor-β1 (TGF-β1), creating a cycle of inflammation and fibrosis. Succinate also enhances synovial-tissue hyperplasia and inflammation by increasing the invasiveness and migration of fibroblast-like synoviocyte (FLS). Thus, succinate links IL-1β and TGF-β1, exacerbating RA progression. SA: succinate. Image created with BioRender.com, with permission.

3.3 Succinate and OA

As an inflammatory joint disease, OA progresses significantly through inflammation-driven degeneration of joint cartilage (Jones et al., 2009; Cao et al., 2024). Some evidence suggests a link between succinate and OA. Reduced activity of SDH and alterations in the TCA cycle have been observed in OA (Nahir et al., 1990; van Pevenage et al., 2023), indicating changes in the succinate-related metabolic pathways. However, when it comes to the changes of succinate levels in OA, various metabolomic studies have failed to reach a consensus. While Huang et al. (2020) reported decreased succinate levels in OA patients compared to healthy individuals, most studies affirmed the crucial role of excess succinate in OA. Qualitative analyses of metabolic profiles in OA patients have revealed elevated levels of succinate in urine and blood samples (Liao et al., 2023).

Synovitis is an early manifestation of OA, and SFs are the primary effectors in synovitis (Nanus et al., 2020). Many lines of evidence suggest that the inflammation-activated phenotype of fibroblasts is closely related to their metabolic status (Yin et al., 2018; Farah et al., 2021). For instance, obese OA patients have significantly higher levels of succinate

in their synovial fluid compared to those with normal body mass index (BMI) (Farah et al., 2022). While glycolysis is increased in obesity, this metabolic remodeling induces a phenotype of inflammation-activated SFs, which in turn secrete more IL-6, thereby promoting synovial inflammation (Xie et al., 2015). Additionally, succinate treatment in SFs can induce activation of the NLRP3 inflammasome and increase intracellular inflammatory responses (Li et al., 2016).

Chondrocyte homeostasis is related to the occurrence and development of OA, and involves changes in metabolism. While healthy articular chondrocytes primarily utilize glycolysis for energy, hypertrophic chondrocytes rely more on oxidative phosphorylation and mitochondrial respiration (Pollesello et al., 1991). Increased mitochondrial respiration can cause catabolism and progression of OA in mouse articular cartilage (Shen et al., 2017). 4-Aminobutyrate aminotransferase (Abat) is an enzyme that metabolizes GABA to succinate. Overexpression of Abat was found to cause chondrocyte hypertrophy in vitro and accelerate OA progression in mice. Treatment with vigabatrin, an US Food and Drug Administration (FDA)-approved small-molecule Abat inhibitor, can prevent OA progression caused by injury (Shen et al., 2019). Elevated levels of Abat lead to increased succinate levels, thereby enhancing the TCA cycle and mitochondrial respiration, which disrupts cartilage homeostasis and promotes OA progression. The role of succinate in OA is illustrated in Fig. 4.

3.4 Succinate and fractures

Bone regeneration after fracture is a complex process, and successful bone regeneration depends on the balanced interaction of anabolic and catabolic processes, including inflammation and angiogenesis, matrix formation, and tissue remodeling, which have high dynamic energy requirements (Schmidt-Bleek et al., 2014). However, the influence of metabolism on the progression and outcomes of bone healing remains insufficiently studied. Several studies suggest that succinate may contribute to fracture healing. Scientists have found that during the early stages of bone-healing inflammation, the levels of succinate are higher in rats with successful bone regeneration compared to those with impaired bone regeneration (Löffler et al., 2023). Additionally, succinate has been discovered to accelerate the healing of mandibular fractures in guinea pigs (Faustov et al., 2001).

Angiogenesis is crucial in early osteoinduction. Compared with cobalt chloride, succinate is a safer pseudohypoxic agent, and the pseudohypoxia induced by succinate contributes to bone regeneration by promoting angiogenesis. An in vitro study found that the cultivation of Saos-2 (osteoblasts) on succinate-alginate xerogel films promoted the proliferation of osteoblasts, with the effective succinate concentrations ranging from 10 to 100 mmol/L (Deering et al., 2022). Moreover, 1 and 10 μmol/L of succinate can promote angiogenesis and maintain long-term vascular stability (Deering et al., 2022). This indicates that succinate at a lower concentration (10 μmol/L) can promote angiogenesis and early osteoinduction without damaging osteoblasts.

Succinate plays a significant role in successful bone healing, stimulating hMSC migration in the fracture gap and supporting osteogenesis and bone formation. It can activate macrophages via SUCNR1, inducing expression of IL-1β. It has been found that sustained exposure to IL-1β in osteogenic cultures of hMSCs leads to attenuated osteogenic differentiation, whereas stimulation with IL-1β at the beginning of differentiation can promote osteogenic differentiation of hMSCs (Löffler et al., 2023). The specific effects of succinate are concentration-dependent. In the study by Löffler et al. (2023), 50 μmol/L succinate acted as a significant VEGF inducer, mediated by the succinate-SUCNR1 axis. The process involved upregulation of signal transducer and activator of transcription 3 (STAT3) and ERK1/2, and expression of VEGF, independently of HIF-1α. Moreover, higher concentrations of succinate (200–800 μmol/L) were found to promote tubular structure formation in vitro and in zebrafish (Mu et al., 2017). Treatment with 400 or 800 μmol/L of succinate significantly increased the vitality of human umbilical vein endothelial cells. Addition of succinate (50 or 500 μmol/L) in vitro promoted the migration of primary hMSCs, with 500 μmol/L of succinate particularly inducing osteogenic differentiation and intense mineralization of hMSCs. Notably, in the absence of other osteogenic stimuli, paracrine signals from succinate-stimulated macrophages, especially M2-type macrophages stimulated with 50 μmol/L succinate, directly induced osteogenesis in hMSCs. There is a direct connection between succinate, SUCNR1, and

tissue healing, as treatment of 50 μmol/L succinate accelerated the healing of skin incisions in mice (Ko et al., 2017). In addition, succinate can play a positive role in fracture healing by activating macrophage responses and neovascularization, as well as reducing fibrosclerosis in damaged muscle areas (Faustov et al., 2001).

3.5 Succinate and periodontitis

Succinate plays a significant role in the progression of periodontitis. Elevated levels of succinate have been found in the gingival crevicular fluid of periodontal patients (Ohwaki, 1988; Lu et al., 2015). Targeted metabolomic analysis of 28 gingival plaque samples found that individuals with severe periodontitis had elevated succinate levels and dysregulated oral microbiota in their dental plaque (Guo et al., 2022). Additionally, succinate levels in periodontal pockets are significantly correlated with clinical indicators of disease severity (Lu et al., 2014). These pieces of evidence suggest the potential involvement of succinate in the progression of periodontitis.

The development of periodontitis begins with colonization by pathogenic bacteria, and microbial metabolism is a major source of abnormal succinate accumulation (Gao et al., 2014). Many periodontitis-related bacteria produce succinate through metabolism, for example *P. gingivalis*, *P. intermedia*, and *Treponema denticola* (Shah and Williams, 1987; Takahashi and Yamada, 2000; Takahashi et al., 2000; Kin et al., 2020). Succinate can mediate the pro-inflammatory response of periodontal ligament stem cells (PDLSCs) triggered by *P. gingivalis* (Su et al., 2020). PDLSCs undergo metabolic reprogramming in response to *P. gingivalis*, shifting from oxidative phosphorylation to glycolysis and accumulating succinate, which triggers the inflammatory response in PDLSCs through the succinate-SDH-HIF-1α axis and ROS production. However, in contrast to LPS-stimulated macrophages (reduced SDH activity), PDLSCs infected with *P. gingivalis* show increased SDH production, SDH activity, and succinate levels. Therefore, the source of succinate accumulation in PDLSCs infected with *P. gingivalis* still requires further investigation. Succinate also enhances the expression of inflammatory cytokines, particularly TNF-α and IL-1β, by activating SUCNR1, thereby inducing alveolar bone loss (Guo et al., 2022). Given that dysbiosis of the oral microbiome is a key phenotype and cause of periodontitis, the impact of succinate on the periodontal microbiota also contributes to the development of periodontitis. In vitro experiments have shown that succinate can directly stimulate the growth and virulence gene expression of *Fusobacterium nucleatum*, leading to an imbalance in the oral microbiota (Guo et al., 2022; Li, 2023). Guo et al. (2022) found through 16S sequencing that systemic application of succinate significantly increased the abundance of periodontal-associated bacteria such as *Bacteroidetes*, whereas these changes were not evident in *SUCNR1*-knockout mice. The use of an SUCNR1 antagonist reduced the abundance of periodontal-related bacteria, indicating that succinate affects the microbiota composition through the SUCNR1 receptor. Additionally, a metabolic cooperation has been found between *P. gingivalis* and *T. denticola*, and is known as succinate cross-feeding. *T. denticola* produces succinate, which is utilized by *P. gingivalis* and converted into toxic metabolites. This cooperation may exacerbate the progression of periodontal disease and help bacteria more efficiently acquire energy and carbon sources in nutrient-limited environments (Kin et al., 2020).

Nevertheless, in the absence of bacteria-mediated effects, exogenous addition of succinate can act as a pseudo-hypoxic agent to promote proliferation, migration, and osteogenesis of human periodontal ligament stem cells (hPDLSCs) by activating the HIF-1α pathway (Mao et al., 2020). The role of hypoxia in osteogenic differentiation of MSCs remains controversial. The reason why succinate promotes osteogenesis of hPDLSCs may be that in addition to serving as a hypoxia mimetic, it can also enhance oxidative capacity, thereby enhancing bone matrix protein biosynthesis in later stages. It is worth noting that hypoxia-mediated proliferation of hPDLSCs depends on the SUCNR1 pathway, while hPDLSC proliferation mediated by exogenous succinate includes the SUCNR1-dependent and SUCNR1-independent pathways. High levels of exogenous succinate can bypass SUCNR1 and directly induce cellular effects through the cell membrane. The metabolic changes induced by succinate in cell metabolism depend on its concentration. Exogenous succinate at concentrations of 1 and 5 mmol/L (mainly 5 mmol/L) can promote proliferation, migration, and osteogenic ability of hPDLSCs, while high concentrations of succinate (25 mmol/L) can decrease cell viability (Ko et al., 2017). This inhibitory effect of

high-concentration succinate may be associated with the succinate-induced apoptotic pathways (caspase3/7) (Wentzel et al., 2017), the induction of DNA hypermethylation, epigenetic silencing (Jiang and Yan, 2017), protein succinylation, and the induction of oxidative damage by ROS (García-Prat et al., 2017). The role of succinate in periodontitis is illustrated in Fig. 5.

3.6 Other findings

Jin et al. (2022) found that succinate can also stably bind to collagen fibers through hydrogen bonds, enhancing the ability of the collagen matrix to attract more calcium ions and thus accelerating the mineralization of collagen fibers. This process is crucial for both tooth and bone formation. Succinate promotes dentin restoration and remineralization of demineralized dentin, and enhances its mechanical properties, which suggests potential for application of succinate in dental caries restoration.

4 Treatment targets

Abnormal accumulation of succinate is associated with changes in SDH activity, and the succinate-SUCNR1 axis and succinate-HIF-1α axis mediate the pathogenesis of bone-related diseases. Succinate also mediates the mitochondrial transfer from macrophages to MSCs, promoting OP development. Moreover, the multifaceted actions of succinate as a signaling molecule vary depending on its cellular location and concentration. Therefore, targeting key points in succinate-induced pathogenesis may offer new insights into the treatment of bone-related diseases.

4.1 SDH inhibitors

Activation of the reverse activity of SDH is known to lead to succinate accumulation (Chouchani et al., 2014), which plays a role in synovial inflammation in the joints (Li et al., 2018). SDH inhibitors (such as

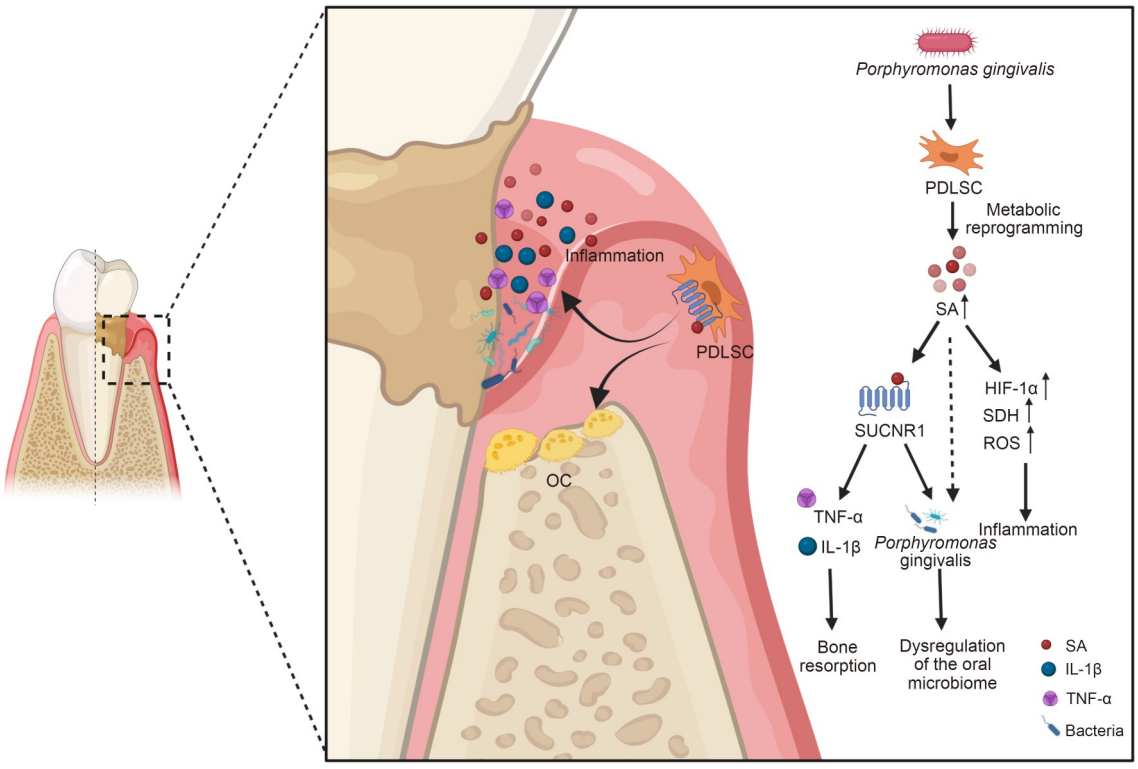

Fig. 5 Role of succinate in periodontitis. Succinate can mediate the pro-inflammatory response of *Porphyromonas gingivalis* to periodontal ligament stem cells (PDLSCs). PDLSCs respond by shifting from oxidative phosphorylation to glycolysis, accumulating succinate, and triggering inflammation via the succinate dehydrogenase (SDH)-hypoxia-inducible factor 1α (HIF-1α) axis and reactive oxygen species (ROS) production. *P. gingivalis*-infected PDLSCs show increased SDH production and activity. Succinate also supports the growth of periodontal pathogens through succinate receptor 1 (SUCNR1), disrupting the balance of oral microbiota. Additionally, succinate activates SUCNR1, enhancing tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) expression and inducing alveolar bone loss. SA: succinate. Image created with BioRender.com, with permission.

DMM) can prevent abnormal succinate accumulation and inhibit synovial angiogenesis by blocking the HIF-1α/VEGF axis (Li et al., 2018), and thus they serve as therapeutic targets for RA.

4.2 SUCNR1 antagonists

The succinate-SUCNR1 axis mediates various pathological processes, and the use of SUCNR1 antagonists can effectively block this pathway, hindering succinate-driven effects on OP, OA, RA, and periodontitis. In the K/BxN serum transfer-induced arthritis model and the antigen-induced mouse arthritis model, the absence of SUCNR1 has been shown to alleviate arthritic inflammation and lesions (Rubić-Schneider et al., 2017). Currently, the compound **4c** appears to be the most effective SUCNR1 antagonist in vitro (Ariza et al., 2012), and has the potential to become a drug for treating inflammation-related diseases and cancer metastasis. Local application of the SUCNR1 antagonist gel formulation of compound **7a** effectively inhibits inflammation, microbial dysbiosis, and bone loss in mice with periodontitis (Li et al., 2018). This effect is mediated by inhibiting host SUCNR1 signaling, rather than through direct interaction with the host microbiota (Thomas et al., 2024).

4.3 Mitochondrial transfer

Mitochondrial transfer plays a crucial role in maintaining bone homeostasis and preserving bone cell vitality. Artificial mitochondrial transfer to damaged cells or tissues can effectively repair the damage (Cai et al., 2023). Guo YS et al. (2020) reported that mitochondrial transplantation therapy enhanced the proliferation, migration, and osteogenic differentiation of BMSCs, improving bone defect healing. In OP, the mitochondrial transfer from pro-inflammatory M1 macrophages to MSCs inhibits MSC osteogenic differentiation. Utilizing artificial mitochondrial transfer by transferring healthy mitochondria into MSCs could serve as an effective therapeutic target for enhancing osteogenic differentiation in OP treatment.

4.4 Abat inhibitors

Abat is a key enzyme responsible for the metabolism of GABA to succinate (Osei and Churchich, 1995). Elevated Abat levels can lead to succinate accumulation, thereby enhancing the TCA cycle and increasing mitochondrial respiration. This affects chondrocyte homeostasis and causes OA. Treatment with Abat inhibitors (such as gabaculine) can prevent OA progression caused by cartilage injury in mice (Shen et al., 2019).

4.5 Exogenous addition of succinate

The effects of succinate vary depending on the concentration. Exogenously adding specific concentrations of succinate has potential as a microbial therapy. Lower concentrations have a positive effect on fracture healing, with 10 μmol/L of succinate promoting early bone induction and 50–500 μmol/L of succinate aiding in the migration and osteogenic differentiation of hMSCs within the fracture gap (Löffler et al., 2023). However, lower concentrations (primarily 5 mmol/L) of exogenous succinate, like hypoxia, can act as a pseudohypoxic agent by activating the HIF-1α pathway to promote proliferation, migration, and osteogenic capacity of hPDLSCs, while higher concentrations of succinate (25 mmol/L) may decrease cell viability (Mao et al., 2020).

5 Conclusions

Succinate plays a significant role in bone-related diseases. Abnormal accumulation of it is closely associated with pathological processes such as OP, OA, RA, and periodontal diseases through the succinate-SUCNR1 axis and succinate-HIF-1α axis, and links mitochondrial dysfunction to the pathogenesis of OP. Current research suggests that inhibiting succinate generation or modulating its metabolism, for example with Abat inhibitors, SDH inhibitors, or SUCNR1 antagonists, may provide new avenues for treating these diseases. However, translating the results of these novel compounds from in vitro and animal models to human trials is challenging. There are issues such as low drug exposure at target sites and clinical safety concerns. Systemic administration of SUCNR1 antagonists may attenuate the anti-inflammatory properties of macrophages, potentially leading to other adverse reactions (Keiran et al., 2019). Additionally, exploring the regulatory role of succinate in stem cell function and developing more precise drug-targeting strategies may bring further breakthroughs in the treatment of bone diseases in the future.

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Author contributions

Zuping WU and Qiaoli DAI were involved in conceptualization, visualization, writing – original draft, and writing – review & editing. Ying WANG, Na WU, and Chenyu WANG were involved in writing – review & editing. Jiejun SHI was involved in writing – review & editing, supervision, and conceptualization. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Zuping WU, Qiaoli DAI, Ying WANG, Na WU, Chenyu WANG, and Jiejun SHI declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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