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Review

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Metabolic regulation for the treatment of ischemic heart disease with stem cells and extracellular vesicles

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Ischemic heart disease (IHD) is a leading cause of mortality worldwide, primarily driven by coronary artery stenosis. Current therapies predominantly slow disease progression, with limited capacity to restore functional myocardium. Worsening metabolic disorders significantly drives heart failure. Emerging evidence suggests that stem cell therapy may improve cardiac metabolism. This review examines metabolic dysregulation in IHD and explores how stem cells and extracellular vesicles could modulate these pathways to support tissue repair.

Ischemic heart disease (IHD), which is primarily caused by coronary atherosclerosis or dysfunction[1], leads to myocardial ischemia and hypoxia, manifesting as angina pectoris, myocardial infarction (MI), and other related disorders. IHD poses a substantial disease burden globally, with over 1 million annual deaths attributed to IHD in China alone[2]. Acute myocardial infarction (AMI) is the most severe manifestation of IHD, progressing to heart failure (HF) in 14–36% of cases due to adverse remodeling; The five-year survival rate for advanced HF following treatment is only 50%[3,4], with IHD being a primary risk factor[5] and the most frequently reported cause of the trend toward younger onset of HF[6]. The regenerative capacity of cardiomyocytes is notably low and decreases with age[7]. Therefore, reducing myocardial loss or promoting regeneration is a potential approach to treating IHD. Stem cells, with their unique self-renewal and differentiation properties, are considered potential therapeutic agents[8], particularly for AMI and refractory angina pectoris[9].

Recent research into the pathophysiology of IHD has established that metabolic remodeling occurs in the ischemic heart. This remodeling not only leads to energy deficiency but also plays critical roles beyond energy metabolism, closely linking to cell growth, antioxidant defense, and apoptosis. Consequently, regulating myocardial cell metabolism has emerged as a novel therapeutic direction[10–12]. Risk factors for IHD induce metabolic disorders in the myocardium even before the onset of the disease, such as hyperglycemia-induced insulin resistance, which decreases glucose utilization while increasing fatty acid utilization[13]. Following myocardial ischemia, metabolic processes become more complex; for instance, disturbances in lipid and carbohydrate metabolism are observed after transient ischemia[14,15]. Therefore, metabolic interventions in cardiomyocytes may represent a pivotal therapeutic strategy. The role of stem cells in regulating myocardial metabolism has been supported by several studies, and this article reviews the pathometabolic alterations in IHD and how stem cells, along with their extracellular vesicles (EVs), can facilitate cardiac repair by improving pathological metabolism.

Metabolic disorders in ischemic heart disease

Cardiac contraction and relaxation requires constant ATP supply, fundamentally supported by substrate metabolism. Fatty acids contribute about 70–90% of ATP, with the remainder derived from carbohydrates and small amounts of ketone bodies and amino acids[10]. Disruption of energy metabolism is now widely recognized as a central aspect of IHD progression[16,17], classified into disorders of substrate metabolism and mitochondrial dysfunction. The endocardial region at the infarct border zone exhibits the most significant reduction in phosphocreatine (PCr)/ATP[18]. Additionally, this area experiences higher wall stress, potentially driving progressive metabolic and functional impairments, which is a key factor in the progression to HF[19].

Disorders of substrate metabolism

Glucose metabolism. Exogenous glucose enters cardiomyocytes via glucose transporter type 1 (GLUT1) and glucose transporter type 4 (GLUT4)[20]. The glucose taken up is phosphorylated to glucose-6-phosphate (G-6-P) by hexokinase (HK), with a portion synthesized into glycogen and another entering glycolysis to generate pyruvate for anaerobic or aerobic oxidation to produce ATP. Increased glucose uptake and glycolysis in cardiomyocytes following myocardial ischemia have been shown to be important for cell survival[21]. Enhanced glycolytic flux not only provides rapid energy under hypoxic conditions but also supports myocardial anabolic metabolism, inducing hypertrophic responses[22]. Following myocardial injury, glucose uptake increases in neonatal mice overexpressing GLUT1, enhancing mitotic activity through increased

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nucleotide synthesis[7]. After 10 min of myocardial ischemia in mice, glucose oxidation increased in the ischemic border zone, accompanied by lactate utilization for energy compensation[14]. Isolated heart perfusion experiments revealed increased glycolytic flux and reduced glucose oxidation upon reperfusion[23]. In chronic coronary artery disease in swine, ischemic tissue exhibits elevated levels of mitochondrial pyruvate carrier (MPC), citrate synthase (CS), and complex II, indicating increased aerobic glucose oxidation following ischemia[24]. Ischemia-reperfusion injury (IRI) downregulates GLUT4 expression, whereas pyruvate dehydrogenase E1 α subunit overexpression or dopamine receptor D4 activation upregulates GLUT4, mitigating cardiac injury[25,26]. Conversely, the RabGTPase-activating protein TBC1D4 knockout exacerbates IRI[27]. Additionally, metaxin 2, which promotes PKM2 tetramerization and aerobic glucose oxidation, is downregulated in I/R hearts, further impairing metabolic recovery[28].

Endogenous glucose is stored as glycogen, which serves as a crucial reserve to withstand hypoxia-induced stress[29]. The dynamic cardiac glycogen pool comprises 2% of the adult cardiomyocyte volume[30]. Myocardial glycogen content decreases following ischemia in rabbits, while transcription of pyruvate kinase (PK) and lactate dehydrogenase (LDH) increases, highlighting glycogen's crucial role in sustaining glycolysis and short-term metabolic balance during ischemia[31].

Enhancing glucose uptake, glycolysis, and aerobic oxidation represents a critical therapeutic mechanism in IHD. Danqi Pill treatment upregulates the expression of GLUT4 and PKM2 via the HIF-1α signaling pathway, protecting the heart from ischemic injury[32]. The sodium-glucose co-transporter 2 inhibitor (SGLT2i) canagliflozin enhances cardiac output and ejection fraction by increasing glycolysis and mitochondrial oxidative phosphorylation[24]. Fatty acids are substrates with lower oxygen utilization efficiency compared to glucose, with palmitic acid yielding an ATP/O2 ratio of 2.33, while glucose yields 2.53[33–35]. Glucose-insulin-potassium (GIK) therapy promotes a shift from fatty acid metabolism to glucose metabolism. However, a meta-analysis indicates that GIK administration after symptom onset in acute coronary syndromes patients does not reduce mortality[36]. Additionally, genetic variations may influence the response of glucose, potassium, and free fatty acid levels to GIK[37,38]. Increased glucose metabolism enhances cardiac mechanical function without adversely affecting cardiac economy, rendering it beneficial. However, the increased energy turnover may exacerbate IRI[39]. Enhanced glycolysis may lead to uncoupling from aerobic oxidation, and the accumulation of toxic glycolytic intermediates could contribute to pathological hypertrophy and the progression of HF[40].

Fatty acid metabolism. Fatty acids are transported into cells, converted to acyl-CoA by acyl-CoA synthetase (ACS) and subsequently transported into the mitochondrial matrix through the carnitine palmitoyltransferase (CPT) system. After undergoing β-oxidation, acetyl-CoA is produced and enters the TCA cycle[33]. Carnitine palmitoyltransferase 1 (CPT1) serves as the rate-limiting enzyme in fatty acid oxidation. Malonyl-CoA, produced by acetyl-CoA carboxylase (ACC) from acetyl-CoA, inhibits CPT1, suppressing fatty acid oxidation. Moreover, malonyl-CoA can be converted back to acetyl-CoA by malonyl-CoA decarboxylase (MCD)[41,42]. AMP-activated protein kinase (AMPK) is activated under conditions of energy deficiency. AMPK phosphorylates and activates downstream pathways that promote the catabolism of glucose and fatty acids while inhibiting anabolic processes, thus restoring energy balance[43]. The activation of AMPK is recognized for its crucial protective role in ischemic myocardium[44], and peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) can be phosphorylated and activated by AMPK[45]. PGC-1α plays a pivotal role in energy metabolism and mitochondrial function. Activation of PGC-1α promotes fatty acid oxidation via PPARα and lipid droplet formation via PPARγ, thereby limiting the accumulation of toxic lipids[46].

Cardiac lipid metabolism is markedly dysregulated following myocardial ischemia. In isoproterenol (ISO)-induced rat myocardial infarction models, significant elevations in serum and cardiac total cholesterol, triglycerides (TGs), and free fatty acids (FFAs) were observed, accompanied by intramyocardial lipid accumulation. Moreover, correction of these metabolic abnormalities was associated with reduced inflammation and apoptosis, while myocardial injury was also alleviated[47,48]. In canine models of AMI, the uptake of FFAs and the concentration of long-chain acyl-CoA, as well as FAT/CD36 mRNA expression, are elevated[49]. Similarly, increased fatty acid uptake and oxidation have also been documented in MI mice and patients with IHD. In terminal IHD, the heart exhibits increased AMPK-induced phosphorylation of ACC, along with upregulated expression of MCD and FAT/CD36[50]. The isolated heart perfusion model demonstrates that myocardial fatty acid oxidation rate increases during post-ischemic reperfusion, but only leads to a 41% recovery of cardiac function[23]. Notably, in severe end-stage HF, fatty acid oxidation is downregulated, whereas it remains unchanged during compensated HF[51].

Current understanding of fatty acid metabolism regulation remains controversial. While some studies have demonstrated that inhibiting fatty acid metabolism benefits ischemic myocardium, emerging evidence suggests more complex mechanisms. The transcription factor GATA zinc finger domain protein 1 mitigates IRI by suppressing β-oxidation genes acetyl-CoA acyltransferase 2 and medium-chain acyl-CoA dehydrogenase[52]. Beyond transcriptional regulation, elevated serum levels of 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid (CMPF) in chronic heart failure patients and mice enhance PGC-1α, CPT-1, and MCD expression. Inhibiting CMPF reduces fatty acid oxidation, thereby alleviating ischemia-induced chronic heart failure[53]. Pharmacologically, the SGLT2i canagliflozin has been shown to reduce ACC phosphorylation and inactivation, exerting beneficial effects in chronic myocardial ischemia[54]. However, a recent systematic evaluation of preclinical models demonstrated that stimulating (rather than inhibiting) fatty acid oxidation improves cardiac function[55]. Supporting this paradigm, Sang Lee et al. demonstrated that progesterone receptor membrane component 1 deficiency protects against isoproterenol-induced cardiac injury by upregulating key enzymes in fatty acid and glucose oxidation, including CPT2, very long-chain acyl-CoA dehydrogenase, acyl-CoA oxidase 1 and PDH[56].

Branched-chain amino acid metabolism. Branched-chain amino acids (BCAAs), comprising leucine, isoleucine and valine, undergo catabolism to yield acetyl-CoA and succinyl-CoA, thereby entering the TCA cycle and contributing to ATP synthesis[57]. The rate-limiting enzyme in BCAA catabolism is branched-chain α-ketoacid dehydrogenase (BCKDH). This enzyme is phosphorylated and inactivated by branched-chain α-ketoacid dehydrogenase kinase (BCKDHK), while it is dephosphorylated and activated by protein phosphatase 2Cm (PP2Cm)[58].

The catabolic activity of BCAAs is intricately linked to cardiac function. For instance, the knockout of the branched-chain α-ketoacid dehydrogenase E1α subunit (BCKDHA) leads to cardiac dysfunction and significant transcriptomic reprogramming[59]. Following AMI, a notable decrease in circulating BCAAs is observed, accompanied by an accumulation of myocardial BCAAs and impaired BCAA catabolism, which responds to chronic ischemia and contributes to heart dysfunction and remodeling[60]. In HF models, similar impairments in catabolism and an accumulation of branched-chain α-keto acids (BCKAs) have been documented[61]. Elevated levels of BCAAs have been shown to directly inhibit PDH activity, thereby reducing aerobic glucose oxidation and exacerbating IRI[62].

Promoting BCAA catabolism represents a promising therapeutic strategy. For instance, a high-dose combination of Salvia miltiorrhiza and Panax notoginseng has been shown to ameliorate rat AMI by activating 3-MST and inhibiting BCKDHK[63]. Additionally, exercise has been demonstrated to protect the heart from IRI by enhancing PP2Cm expression[64]. However, a study by Danielle Murashige et al. revealed that BCAA oxidation is actually elevated in both human and mouse models of HF. The activation of BCAA catabolism appears to confer protective effects by lowering blood pressure[65]. Moreover, the modulation of BCAA levels

serves as an additional therapeutic avenue. Although the contribution of BCAA oxidation to cardiac ATP production is relatively minor—~1%[66]—it plays a significant role in regulating the mechanistic target of rapamycin (mTOR) signaling pathway[67]. The activation of mTORC1 promotes protein synthesis and inhibits autophagy[68]. Both in vitro and in vivo studies indicate that BCAA treatment confers cardiomyocyte and mitochondrial protection via mTOR pathway activation. For example, 160 μM leucine has been shown to enhance the survival rate of isolated rat cardiomyocytes under simulated IRI conditions and to induce mitochondrial biogenesis[69,70]. Nevertheless, evidence also suggests that oral administration of BCAAs may be detrimental to myocardial health. In murine models, BCAA supplementation has been shown to upregulate PPAR-α transcription, leading to increased fatty acid oxidation, exacerbation of lipid peroxidation, and elevated reactive oxygen species (ROS) levels, all contributing to myocardial damage[71,72].

Ketone metabolism. Ketone bodies are synthesized in the liver through the process of ketogenesis, including acetoacetate (AcAc), β-hydroxybutyrate (β-OHB), and acetone. β-OHB is converted to AcAc by the enzyme β-hydroxybutyrate dehydrogenase 1 (BDH1), which is subsequently metabolized to acetyl-CoA, allowing it to enter the TCA cycle[73]. In advanced HF, the utilization of ketones is markedly increased, primarily due to elevated serum levels of fatty acids and ketone bodies, which enhance substrate delivery to the failing myocardium[74]. During pressure overload and myocardial infarction-induced HF, the key enzyme in the β-OHB oxidation pathway, BDH1, is upregulated. This increase in ketone body oxidation is considered adaptive, as it occurs in response to a reduced capacity for fatty acid oxidation. Similar metabolic adaptations have been observed in non-ischemic HF as well[75,76].

The ATP/O_2 ratio for ketone bodies is ~2.5, indicating that their oxidation is more oxygen-efficient than that of palmitic acid and more efficient than glucose metabolism. Consequently, enhancing ketone metabolism presents a promising therapeutic strategy. BDH1 overexpression in murine models has been shown to alleviate contractile dysfunction and oxidative stress in failing hearts[77]. Additionally, treatment with ketone esters has been found to upregulate the expression of genes involved in ketone utilization, thereby enhancing ATP production and improving cardiac function in rodent models of HF[78].

Mitochondrial dysfunction

Mitochondria are indispensable organelles responsible for ATP production and coordination of calcium homeostasis, hormone synthesis, signal transduction, and apoptotic regulation[79,80]. Mitochondrial quality control is critical for maintaining mitochondrial homeostasis, encompassing mitochondrial dynamics and autophagy to prevent dysfunction[81]. IRI induces significant mitochondrial abnormalities, including reduced mitochondrial numbers, aggregation, swelling, rupture of the outer membrane and cristae, vacuolization, and ectopic lipid droplet accumulation[82,83]. The AMPK/PGC-1α axis serves as the central regulator of mitochondrial adaptations[84,85].

Oxidative stress. ROS are chemically unstable compounds that contain oxygen, encompassing both free radicals (e.g., superoxide and hydroxyl radicals) and non-radicals (e.g., hydrogen peroxide). The primary sources of cardiac ROS include the mitochondrial electron transport chain (ETC), xanthine oxidase, NADPH oxidases (NOX), and nitric oxide synthases. In cardiovascular diseases, the majority of ROS is generated by Complexes I and III of the ETC[86–88]. Antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), serve to protect biological systems from ROS toxicity[89]. Oxidative stress arises when ROS production exceeds the capacity of the antioxidant defense system[90].

Oxidative stress is a significant contributor to the onset and progression of IHD. High-fat environments and elevated ROS levels enhance lipid peroxidation, potentially accelerating arterial thrombosis and leading to AMI[91]. Phospholipid peroxidation increases the susceptibility of cardiomyocytes to cell death[92]. Notably, 15-lipoxygenase accumulates in the infarcted myocardium following IRI, catalyzing the production of lipid peroxidation intermediates, such as 15-hydroperoxyeicosatetraenoic acid. This compound promotes the ubiquitin-dependent degradation of PGC-1α, impairing mitochondrial biogenesis and inducing ferroptosis[93]. During myocardial ischemia, sustained hypoxia, reduced perfusion, and acidosis compromise mitochondrial function and disrupt redox homeostasis. In the reperfusion phase of IRI, the significant increase in oxygen concentration enables the ETC to resume activity, resulting in excessive ROS production that exacerbates myocardial injury[94]. ROS also play a critical role in mediating the opening of the mitochondrial permeability transition pore (mPTP), leading to loss of mitochondrial membrane potential, intracellular calcium overload, and the release of apoptotic factors such as cytochrome c, ultimately triggering cell apoptosis[95–99].

Inhibiting ROS production represents a viable strategy for mitigating mitochondrial damage. One approach involves suppressing mitochondrial complex activity. Activation of the PERK/eIF2α signaling pathway has been shown to reduce the activity of mitochondrial complexes, thereby slowing electron transport and lowering ROS production, which protects cardiomyocytes from IRI[100,101]. The Kelch-like ECH-associated protein 1 (Keap1)/Nuclear respiratory factor 2 (Nrf2) signaling pathway serves as a crucial endogenous mechanism for combating oxidative stress. Under normal circumstances, Keap1 functions as an E3 ubiquitin ligase that ubiquitinates and degrades Nrf2. However, in response to elevated ROS levels, the interaction between Keap1 and Nrf2 diminishes, promoting Nrf2's translocation to the nucleus and upregulating the expression of antioxidant genes. Enhancing Nrf2 nuclear translocation has been shown to protect against IRI-induced cardiomyocyte apoptosis and oxidative stress[102–105]. Fibronectin type III domain-containing 4 (FNDC4) promotes Nrf2 nuclear translocation via ERK1/2 signaling; however, plasma levels of FNDC4 are significantly reduced in IRI mouse models and patients with AMI[106]. SIRT3 is another important regulatory protein in the context of oxidative stress, with its activation contributing to the mitigation of oxidative damage[107]. For instance, tetrahydrocurcumin has been shown to modulate the Nrf2-SIRT3 signaling pathway, where SIRT3 deacetylates SOD2 to enhance its activity and deacetylates FOXO3a to activate the expression of antioxidant genes[108]. Additionally, fibroblast growth factor 21 has been found to ameliorate diabetes-induced mitochondrial dysfunction and oxidative stress by activating the AMPK/FOXO3/SIRT3 pathway[109].

Mitochondrial dynamics. Mitochondrial dynamics, which encompass the processes of biogenesis, fusion and fission, are essential for the formation of a robust mitochondrial network[110]. PGC-1α is a pivotal regulator of mitochondrial biogenesis, activating nuclear respiratory factor 1 (Nrf1) and Nrf2 to induce the transcription of mitochondrial transcription factor A (TFAM), with Nrf1 exerting a more substantial influence on TFAM promoter activity compared to Nrf2[105]. Sirtuin 1 (SIRT1) activates PGC-1α through deacetylation[111]. The activation of AMPK signaling pathway further activates PGC-1α, thereby promoting mitochondrial biogenesis[112,113]. Additionally, perm1, a regulator induced by PGC-1α and estrogen-related receptors, is abundant in ventricular muscle but is significantly reduced in failing hearts. Perm1 interacts with PGC-1α, promoting the expression of mitochondrial biogenesis and oxidative phosphorylation genes[114]. Activation of PGC-1α is also frequently associated with reduced oxidative stress, enhanced mitochondrial fusion, and restored membrane potential[115].Following MI and IRI in murine models, cardiac levels of SIRT1, PGC-1α, Nrf1, and TFAM significantly decrease[116], while ATP and mtDNA levels are markedly reduced[117]. Furthermore, mitochondrial-related genes, including COX1, Nrf1, TFAM, and SIRT1, are downregulated in ischemic cardiomyopathy-induced HF[118]. These results reveal that mitochondrial biogenesis is impaired during myocardial ischemia.

Multiple studies suggest that -Research indicates that certain -various bioactive compounds can promote mitochondrial biogenesis to facilitate

myocardial repair. For instance, Notoginsenoside R1 has been shown to attenuate hypoxia/reoxygenation (H/R) injury in H9c2 cells by upregulating PGC-1α, Nrf1, and Nrf2[119]. Melatonin restores mitochondrial biogenesis via the AMPK/PGC-1α pathway, suppresses mitochondrial oxidative stress, and prevents cardiomyocyte apoptosis[120]. Additionally, M6a demethylase FTO enhances PGC-1α mRNA stability through demethylation, and its overexpression upregulates TFAM and COX1 genes, mitigating the effects of IRI[121]. These findings underscore the protective effects of promoting mitochondrial biogenesis on myocardial health.

Mitochondrial fusion plays a crucial role in repairing damaged mitochondria, thereby protecting cardiomyocytes from further injury. The key proteins mediating mitochondrial fusion include mitofusins 1 and 2 (MFN1/2) located on the outer mitochondrial membrane (OMM) and optic atrophy 1 (OPA1) on the inner mitochondrial membrane (IMM). OPA1 undergoes constitutive proteolytic processing and exists in two isoforms: the long N-terminal transmembrane-anchored isoform (L-OPA1) and the short form (S-OPA1). Key proteases involved in the processing of OPA1 include OPA1 Mitochondrial Antiviral Signaling Protein 1 (OMA1) and YME1 Like 1 (Mitochondrial AAA Peptidase, YME1L). YME1L cleaves OPA1 into L-OPA1, which directly interacts with cardiolipin to promote mitochondrial membrane fusion. In contrast, OMA1 cleaves OPA1 into S-OPA1, facilitating mitochondrial fission[122,123].

Mitochondrial fission is mediated by dynamin-related protein 1 (Drp1), which is recruited from the cytosol by various mitochondrial outer membrane proteins, including fission 1 (Fis1), mitochondrial fission factor (Mff), and MID49/51. Upon activation, Drp1 relocates to the fission site, facilitating mitochondrial division[124,125]. Keap11, a novel mitochondria-associated membrane (MAM) protein, accumulates in the MAM under hypoxic conditions and recruits Drp1 to promote mitochondrial fission and autophagy during hypoxia[126]. While mitochondrial fission serves to separate damaged mitochondria from the mitochondrial network, excessive fission can lead to mitochondrial outer membrane permeabilization, resulting in caspase-dependent DNA damage[127].

Mitochondrial fission increases in response to cardiac stress or injury, such as ischemia or oxidative stress. Drp1 is a key factor in the morphological changes of mitochondria following MI, primarily through its interaction with the cytoskeletal regulator filamin, which enhances Drp1 activity and promotes mitochondrial fission[128]. Enhancing mitochondrial fusion while reducing fission has been observed to improve mitochondrial morphology and function, thereby alleviating cellular damage[129]. In models of IRI, both MFN2 and Drp1 levels are significantly decreased in mitochondria. In cardiomyocytes treated with cryptochlorogenic acid, the restoration of Drp1 expression is slightly less pronounced than that of MFN2, which promotes mitochondrial fusion[116]. Secreted frizzled-related protein 5 (Sfrp5) has been identified as protective against IHD. In MI mouse models, Sfrp5 expression is downregulated in cardiac tissue. Overexpression of Sfrp5 has been shown to increase phosphorylated AMPK (p-AMPKThr172), upregulate MFN1/2, downregulate mitochondrial fission proteins, and enhance mitochondrial biogenesis while reducing oxidative stress[130]. Additionally, omentin-1, a novel adipokine, has been found to have reduced circulating levels in HF patients. Omentin-1 upregulates MFN2 and OPA1 expression while downregulating p-Drp1, thereby regulating mitochondrial morphology and offering potential therapeutic benefits in HF[131].

Mitophagy. Mitochondrial autophagy, or mitophagy, is a specialized form of cellular autophagy that facilitates the recognition, separation, and degradation of damaged mitochondria by lysosomes, thereby contributing to the balance of mitochondrial quantity and quality within cardiomyocytes[132–134]. Mitochondrial fragmentation can promote oxidative stress or release pro-apoptotic factors into the cytoplasm, leading to mitochondrial-dependent apoptosis. Mitophagy aids in the removal of fragmented mitochondria, exerting both antioxidant and anti-apoptotic effects[97].

The PINK1/Parkin pathway represents a widely studied mechanism of mitophagy. Under normal conditions, PINK1 is degraded by the mitochondrial protein PARL. However, upon mitochondrial damage, PINK1 degradation is inhibited, resulting in its accumulation on the OMM. There, it phosphorylates and activates Parkin, an E3 ubiquitin ligase that facilitates the ubiquitination of mitochondrial proteins, thus triggering mitophagy. Microtubule-associated protein 1 light chain 3 (LC3-II) serves as a marker for autophagic activity, as it is commonly found on the membrane of autophagosomes[135]. Nuclear dot protein 52 kDa (NDP52) acts as a key receptor in PINK1/Parkin-mediated mitophagy, linking ubiquitinated mitochondria to LC3-II and facilitating the fusion of mitochondria with the phagophore. Notably, hypoxia-induced mitophagy primarily occurs through PINK1/Parkin-independent mechanisms[126]. In these cases, ULK1, a Ser/Thr kinase, is upregulated and translocates to fragmented mitochondria during hypoxia-induced mitophagy. It phosphorylates FUNDC1, enhancing its interaction with LC3 and thereby regulating mitophagy[136]. AMPK regulates ULK1 activity, as supported by empagliflozin-induced activation of the AMPKα1/ULK1/FUNDC1 axis and associated mitophagy enhancement in IRI models[97].

Additionally, PGC-1α is known to play a regulatory role in autophagy; its disruption can lead to reduced autophagic activity, consequently suppressing mitochondrial biogenesis. Under stress conditions, increased autophagy has been shown to inhibit apoptosis[137]. Notably, an increase in mitophagy has been identified as an early event before the onset of global cardiac dysfunction[94]. Ischemia-reperfusion significantly increases apoptosis, mitochondrial fission, and autophagic flux[138].

Moderate enhancement of mitophagy exerts protective and stabilizing effects on stressed cardiomyocytes, promoting their survival[139]. For instance, phosphorylation of AMPK at Thr172 is elevated in cardiomyocytes under conditions of oxygen and glucose deprivation. The treatment with asiatic acid further enhances AMPK activation, promoting mitophagy and protecting cardiomyocytes[29]. Additionally, gerontoxanthone I and maclurax-anthone have been shown to alleviate IRI in H9c2 cells by inducing Parkin puncta accumulation, leading to the degradation of the OMM protein Tom20 and the IMM protein Tim23[140]. Omentin-1 treatment enhances PINK1/Parkin-dependent mitophagy by upregulating the SIRT3/FOXO3a signaling pathway, thereby improving mitochondrial quality[131]. However, excessive mitophagy may cause energy crisis and signaling dysregulation, potentially contributing to the loss of cardiomyocytes. Thus, inhibiting excessive mitophagy may offer cardiac protection[141]. In mouse models of doxorubicin-induced HF, mitochondrial transfer from mesenchymal stem cells (MSCs) has been shown to suppress AMPK-mTOR-mediated excessive autophagy[142].

Stem cells and extracellular vesicles in metabolic therapy for ischemic heart disease

Stem cell therapy primarily involves the use of human pluripotent stem cells derived from blastocyst-stage embryos or reprogrammed somatic cells (induced pluripotent stem cells, iPSCs), as well as MSCs, which are predominantly sourced from bone marrow, adipose tissue, and umbilical cord[143]. Among these, bone marrow-derived MSCs (BMSCs) are the most commonly utilized cells for the treatment of cardiovascular diseases. Originating from the mesoderm, BMSCs facilitate the repair of damaged cardiomyocytes through mechanisms such as differentiation, anti-fibrosis, angiogenesis, and immune modulation[144]. While the safety of MSC treatment has been well established, its efficacy in clinical studies has yielded inconsistent results, which may be attributed to factors such as stem cell type, dosage, delivery route, and timing of administration[143,145].

Additionally, stem cell-derived EVs have emerged as a promising cell-free therapeutic approach. These lipid bilayer-enclosed particles contain a variety of biomolecules, including DNA, proteins, lipids, mRNA, and siRNA. They primarily mediate the paracrine effects of stem cells, offering enhanced biocompatibility while mitigating risks associated with tumorigenicity and immunogenicity[146,147].

Targeting substrate metabolism

Several studies demonstrate that stem cells can enhance cardiac function by modulating glucose and fatty acid metabolism. In a swine MI model, BMSCs promote glucose metabolism, leading to improved cardiac contractile function. By four weeks post-transplantation, the expression of glucose transporter proteins GLUT1 and GLUT4, as well as glucose metabolism-related enzymes such as phosphofructokinase (PFK) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH), are significantly upregulated in the injection area[148]. Recent studies involving lung spheroid cell-derived exosomes indicate that these EVs can inhibit fatty acid oxidation to treat MI. Specifically, the exosomal microRNA-100 targets endothelial cell CD36 to reduce fatty acid metabolism while significantly upregulating compensatory expression of glucose metabolism genes like HK and PDH, thereby increasing ATP levels[149].

In insulin-resistant and MI mouse models, MSC treatment has been shown to enhance cardiac glucose uptake and mitochondrial oxidative phosphorylation, while also improving insulin signaling and GLUT4 expression[150]. Notably, the endometrium serves as a site of active physiological angiogenesis; studies suggest that human endometrial mesenchymal stem cells (hEMSCs) exhibit greater angiogenic potential and higher glucose uptake compared to BMSCs, contributing to improved cardiac function[151]. Both iPSCs and ESCs demonstrate the ability to improve glucose metabolism when treating myocardial infarction. Throughout the therapeutic process, iPSCs exhibit more stable therapeutic effects compared to ESCs[152]. While stem cell therapy targeting ketone or BCAA metabolism in IHD remains largely unexplored, further investigations are needed to confirm its potential. The effects of stem cells on substrate metabolism in ischemic myocardium are summarized in Table 1. Collectively, Fig. 1 provides an overview of the substrate metabolic pathways, their alterations in ischemic myocardium, and the role of stem cells in metabolic modulation.

Targeting mitochondria

Ameliorating mitochondrial dysfunction. Stem cells and stem cell-derived EVs play a significant role in inhibiting mitochondrial fission, promoting mitochondrial biogenesis, and alleviating oxidative stress, thereby exerting therapeutic effects in IHD. Exosomes derived from adipose-derived stem cells (ASCs) contain miR-196a-5p and miR-425-5p, which promote mitochondrial fusion in cardiomyocytes by increasing the levels of MFN1/2, and also enhance mitochondrial biogenesis[153]. Additionally, miR-9-5p present in MSC-derived exosomes mitigates mitochondrial fragmentation in cardiomyocytes by inhibiting the VPO1/ERK signaling pathway, ultimately improving cardiac function[154].

The conditioned medium from MSCs has been shown to enhance mitochondrial biogenesis and reduce oxidative stress through the SIRT1/PGC-1α/Nrf2 pathway[155]. Similarly, exosomes from ASCs protect H9c2 cardiomyocytes from H_2O_2-induced damage by reducing apoptosis and hypertrophy in vitro[156]. However, the results of studies on autophagy remain controversial. In a rat IRI model, SIRT6-enriched ASC-derived exosomes improved cardiac function and reduced infarct size by increasing levels of p62 and Beclin-1, which enhance mitophagy[141]. Conversely, exosomes derived from MSCs, which contain miR-143-3p, inhibit autophagy via the CHK2-Beclin-2 pathway[157]. Despite mechanistic differences, both interventions confer cardioprotection.

Mitochondrial transfer. Mitochondrial transfer between cells often occurs in response to conditions such as hypoxia or oxidative stress in recipient cells, which can recruit donor cells to provide mitochondria[158]. This transfer helps restore mitochondrial respiration[159] and regulates cellular signaling, promoting the recovery of damaged myocardium[160,161]. Damaged cardiomyocytes release mitochondria as rescue signals, which induce the expression of the cytoprotective enzyme heme oxygenase-1, stimulate mitochondrial

Table 1 | Stem cells in the treatment of ischemic heart disease via modulation of myocardial substrate metabolism

Type of stem cells	Route of delivery	Model	Key mechanism	Outcome	References
Bone marrow mesenchymal stem cells	Intramyocardial injection	Chinese mini-swine, MI	Activate mTOR pathway, upregulate the protein expressions of GLUT1, GLUT4, PFK and GAPDH	Enhance myocardial function	148
Lung spheroid cell-derived exosomes	Nebulization therapy	C57BL/6 mice, MI	Downregulate CD36 in endothelial cells, decrease Fatty acid, metabolism genes expression, increase glucose utilization compensatorily	Improve left ventricular function, reduce fibrotic tissue, promote cardiomyocyte proliferation	149
Mesenchymal stem cells	Intramyocardial injection	C57BL/6 mice, insulin resistance/MI	Improve insulin signaling, enhance oxidative phosphorylation efficiency	Increase systolic function	150
Human endometrium-derived stem cells	Intramyocardial injection	Female nude rats, MI	Increase ^{18}F-FDG uptake at the infarction area, upregulate angiogenesis-related factors	Induce angiogenesis, improve cardiac function	151
Induced pluripotent stem cell and derived cardiomyocytes	Intramyocardial injection	Male Sprague–Dawley rats, MI	Increase glucose metabolism (^{18}F-FDG)	Improve cardiac function	152
Human umbilical cord mesenchymal stem cell-derived exosomes	Tail vein injection	Male sprague–dawley rats, IRI	Facilitate GLUT4 membrane translocation, enhance glucose uptake and ATP production	Ameliorate cardiomyocyte injury	202

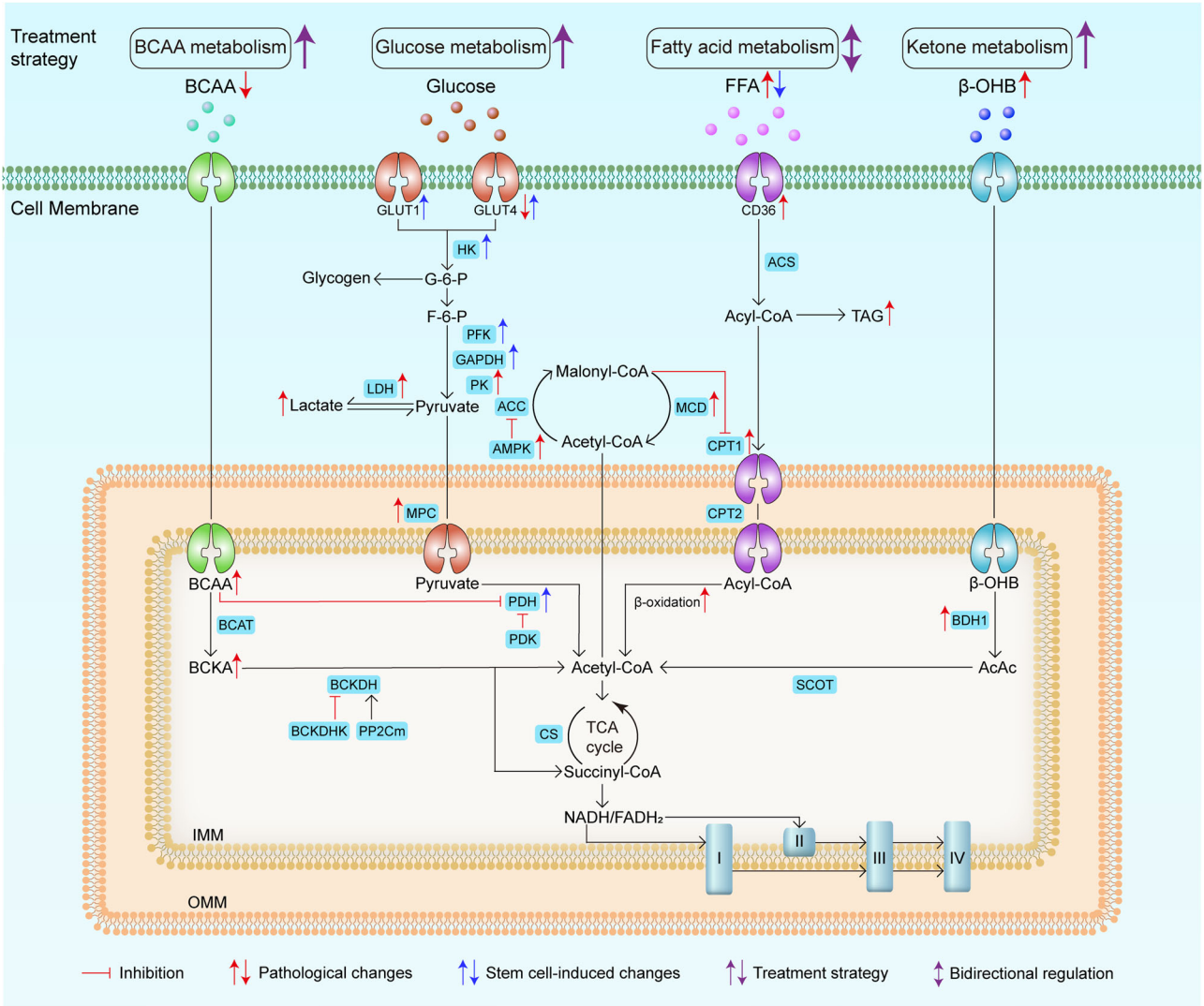

Fig. 1 | Substrate metabolic changes in cardiomyocytes in ischemic heart disease, treatment strategies and the role of stem cells in regulation of metabolism. Glucose, free fatty acids, β-hydroxybutyrate, and branched-chain amino acids enter cardiomyocytes and are metabolized to generate acetyl-CoA, which then enters the tricarboxylic acid cycle. This cycle generates reducing equivalents that fuel the electron transport chain, ultimately producing large amounts of ATP. Enhancing glucose, BCAA and ketone metabolism can provide cardioprotective effects in ischemic myocardium. Current research on stem cell therapy for ischemic heart disease mainly focuses on regulating glucose metabolism. Enzymes highlighted in blue-background boxes represent key regulatory points in the pathway. Red, blue, and purple arrows indicate pathological metabolic changes in IHD, stem cell-induced metabolic changes, and treatment strategies, respectively. Double-headed arrows represent bidirectional regulation.

biogenesis, and facilitate mitochondrial transfer in MSCs[162]. Additionally, mitochondrial transfer can occur remotely; for instance, under conditions of intense energetic stress, adipocytes can release small EVs containing mitochondrial particles, which are absorbed by cardiomyocytes via circulation, thereby limiting myocardial IRI[163].

Mitochondrial transfer is a crucial mechanism through which stem cells exert their therapeutic effects. MSCs can transfer mitochondria through tunneling nanotubes and cell fusion[164]. Leveraging this property, some studies have explored mitochondrial transplantation as a treatment for IHD, either through direct mitochondrial transplantation or spontaneous transfer via the administration of stem cells or their EVs. Direct mitochondrial transplantation has been shown to restore mitochondrial membrane potential in HF cardiomyocytes, inhibit excessive autophagy mediated by the AMPKα-mTOR pathway, reduce cardiomyocyte apoptosis, and alleviate oxidative stress. The therapeutic efficacy of mitochondrial transplantation is influenced by the source of the cells, likely due to variations in membrane potential and free radical levels following mitochondrial isolation from different cell types using the same separation technique[142,165]. For instance, Gentaro Ikeda et al. isolated mitochondria-rich EVs (M-EVs) from iPSC cell-derived cardiomyocytes (iPSC-CMs) and transplanted them into mouse models of MI. They found that compared to mitochondrial injection alone, M-EVs enhanced mitochondrial resistance to oxidative stress and calcium overload, improved mitochondrial uptake, and resulted in better recovery of cardiac function[166]. Collectively, stem cell-mediated regulation of mitochondrial metabolism in ischemic myocardium is summarized in Table 2 and the key pathways modulating mitochondrial metabolism are depicted in Fig. 2.

The impact of myocardial microenvironment on transplanted stem cells

Accumulating evidence indicates that the cardiac repair effects of stem cells and their EVs primarily occur through paracrine mechanisms, as transplanted stem cells typically survive for no more than four weeks[148,167,168]. The ischemic and inflammatory environment following MI significantly reduces

stem cell viability, increases apoptosis, and lowers survival rates. Under conditions of hypoxia and serum deprivation, MSCs demonstrate increased glycolytic enzyme activity and decreased levels of tricarboxylic acid cycle enzymes, leading to diminished survival and proliferation[169]. Additionally, mitochondrial dysfunction induces MSC apoptosis via a caspase-dependent pathway[170]. Although the injection of MSCs into the myocardium of IRI mice improves cardiac function, these cells still exhibit greater mitochondrial dysfunction and reduced viability compared to the sham-operated group[171].

Exposure to hypoxia upregulates the expression of Sug1 in MSCs, which interacts with class II transactivator proteins to upregulate MHC-II expression while simultaneously downregulating COX2 and PGE2 levels. This interaction results in a loss of immunoprivilege for allogeneic MSCs. Knockout of Sug1 and preservation of COX2 levels maintain immunoprivilege, thereby improving the survival rate of transplanted MSCs[172,173]. M1 macrophage-mediated necroptosis in IRI hearts presents similar environmental cues that contribute to extensive cardiac cell death, potentially leading to the acute death of transplanted stem cells[174]. Furthermore, pro-inflammatory cytokines released after AMI, such as TNF-α and IL-1β, hinder stem cell proliferation and differentiation[175].

Metabolic disorders within the microenvironment also limit the therapeutic effects of stem cell treatment. Diabetes and heart disease frequently coexist, with the incidence of IHD in diabetic patients being 1.66 times higher than in non-diabetic individuals[176]. Type 2 diabetes mellitus may increase susceptibility to IRI[177–179] and worsen outcomes following MI[180]. In a high-glucose environment, both stem cells and cardiomyocytes exhibit increased glycolytic activity and reduced oxidative phosphorylation. Consequently, the benefits of SGLT2 inhibitors and MSC transplantation on cardiac function may be diminished or completely lost[24,181]. Additionally, metabolic disorders induced by a high-fat diet impair the therapeutic angiogenic effects of MSC-derived EVs in chronic myocardial ischemia[182]. Elevated circulating BCAAs can render MSCs more sensitive to stress-induced cell death and premature senescence via the mTORC1/DUX4/KDM4E axis, further limiting the efficacy of MSC transplantation[183]. Summarily, Fig. 3 shows the impact of the myocardial microenvironment on transplanted stem cells.

Enhancing stem cell adaptation to the microenvironment

To address the low engraftment efficiency of stem cells, three major strategies have been developed to enhance implantation, survival, and paracrine function. These strategies include preconditioning, stem cell-based 3D tissue (e.g., cell spheroid formulations, cardiac patches), and gene modification[184–188]. As native MSCs reside in hypoxic niches (2–9% O_2 concentration)[189], hypoxic preconditioning prior to transplantation can significantly enhance stem cell survival[190]. For example, hypoxic preconditioning has been shown to protect mitochondrial membrane potential, enhance migration, and reduce apoptosis in MSCs by upregulating Pim-1[191]. This approach also improves angiogenesis and engraftment capacity in stromal vascular fraction cells[192]. Utilizing a cardioplegic solution enriched with conditioned medium from BMSCs under hypoxic conditions to preserve donor hearts has been found to enhance post-transplant cardiac function[193].

Laminin-conjugated engineered cardiac tissue improves both the mechanical function and hypoxia tolerance of iPSC-CMs[194]. Inhibition of soluble epoxide hydrolase in iPSC-CMs enhances resistance to the inflammatory microenvironment, significantly improving retention rates while reducing oxidative stress and apoptosis in host cardiomyocytes[195].

Enhancements in stem cell survival and engraftment are often associated with the maintenance of mitochondrial homeostasis and resistance to oxidative stress. Specifically, treatment of MSCs with ELA, a peptide hormone, enhances their anti-apoptotic properties under hypoxic and ischemic conditions by increasing ATP levels and inhibiting the loss of mitochondrial membrane potential[196]. Leptin inhibits OMA1 activity, and leptin-overexpressing umbilical mesenchymal stem cells effectively increase

Table 2 | Stem cells in the treatment of ischemic heart disease through modulation of myocardial mitochondrial metabolism

Type of stem cells	Route of delivery	Model	key mechanism	Outcome	References
MSCs-conditioned medium	Intramyocardial injection	Male Wistar rats, IRI	Upregulate SIRT-1/PGC-1α/Nrf-2 profiles	Upregulate mitochondrial biogenesis, improve myocardial function, decrease infarct size	155
Mesenchymal stem cells	An epicardial patch during coronary artery bypass graft	Juvenile swine, chronically ischemic myocardium caused by coronary artery disease	Increase in expression of PGC-1α and key components of the ETC (complex II and V)	Improve contractile function and mitochondrial size, number and morphology	203
Mitochondria derived from human umbilical cord mesenchymal stem cells	Intravenous injection	C57BL/6N male mice, HF	Inhibite excessive autophagy mediated by AMPKα-mTOR	Restoring ATP production, reduce cell apoptosis	142
Mitochondria-rich extracellular vesicles from iPSC-CMs	Intramyocardial injection	Female CD1 mice, MI	Upregulate the protein expressions of PGC-1α and ETC complexes	Restore bioenergetics and activates mitochondrial biogenesis	166
Adipose-derived mesenchymal stem cells	Intramyocardial injection	F344/NJcl-rnu/rnu rats, MI	Exhibite mitochondrial transfer, increase mitochondrial DNA and ATP	Improve myocardial function	159
SIRT6-enriched adipose stem cell-derived exosomes	Tail vein injection	Male Sprague Dawley rats, IRI	Increase p62 and Beclin-1 (target proteins of mitophagy), decrease AIM2 and GSDMD (associated with pyroptosis)	Improve myocardial function, decrease infarct size	141
Mesenchymal stem cell-derived exosomes	Intramyocardial injection	Sprague Dawley rats, IRI	MiR-143-3p inhibite CHK 2-Beclin 2 pathway and autophagy	Reduce cell apoptosis and infarct size	157
Exosomes from induced pluripotent stem cell-derived cardiomyocytes	Intramyocardial injection	Female severe combined immunodeficient beige mice, MI	Upregulate autophagy and autophagic flux	Improve myocardial function, reduce apoptosis and fibrosis	204

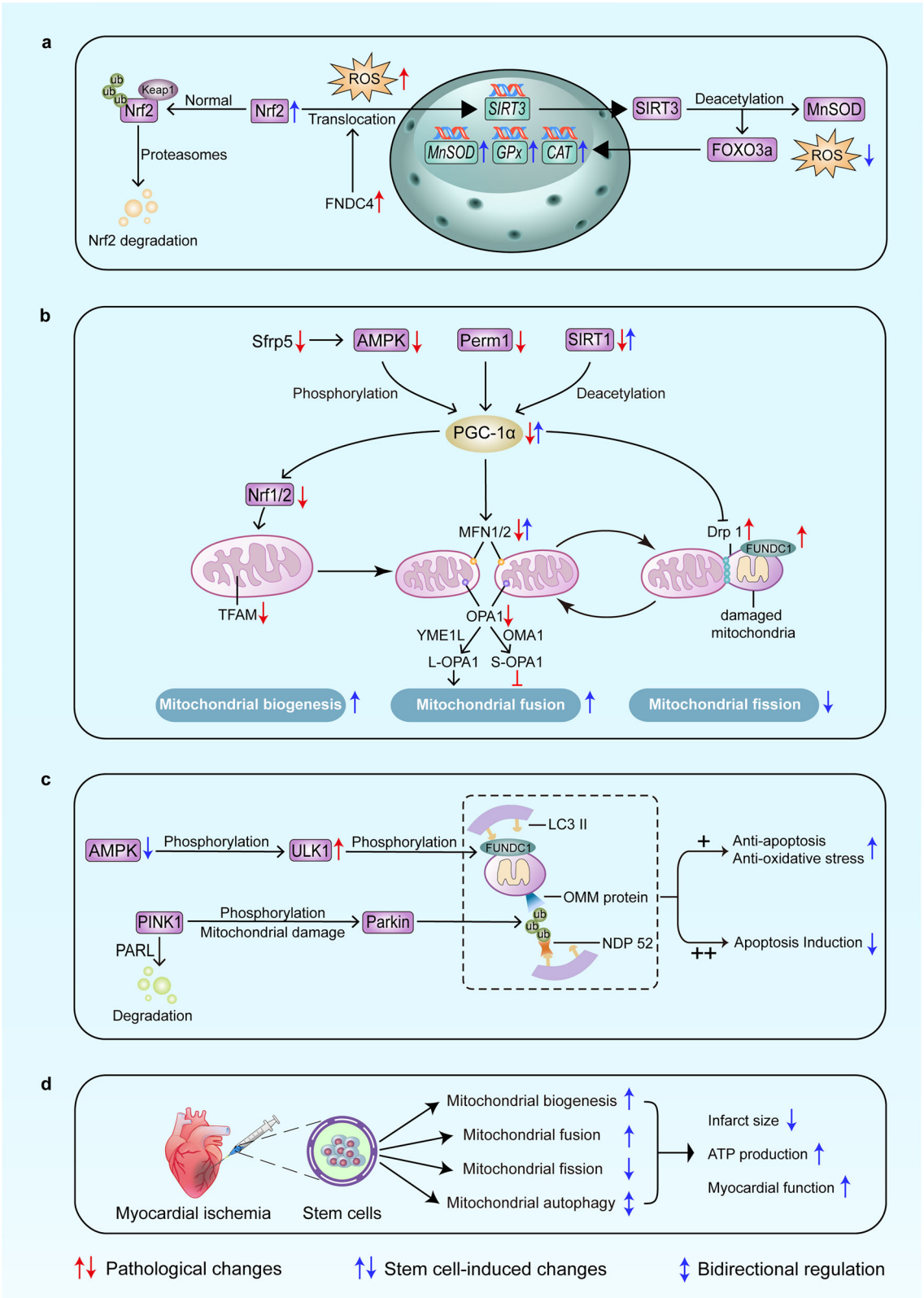

Fig. 2 | Regulatory mechanisms of mitochondrial metabolism and the role of stem cells. a Regulatory targets of mitochondrial oxidative stress. Keap1/Nrf2 alleviates oxidative stress by promoting the expression of antioxidant enzymes; **b** Regulatory targets of mitochondrial dynamics. Nrf1 activates mitochondrial biogenesis; MFN1/2 facilitates fusion, while Drp1 promotes fission; **c** Regulatory targets of mitophagy. ULK1 enhances autophagy. Notably, AMPK/PGC-1α plays a crucial regulatory role in these processes. **d** Stem cells contribute to reducing infarct size and restoring ATP levels by increasing mitochondrial biogenesis, promoting fusion, decreasing fission and mitigating oxidative stress. However, their impact on autophagy remains controversial. Red and blue arrows indicate pathological metabolic changes in IHD and stem cell-induced metabolic changes, respectively. Double-headed arrows represent bidirectional regulation.

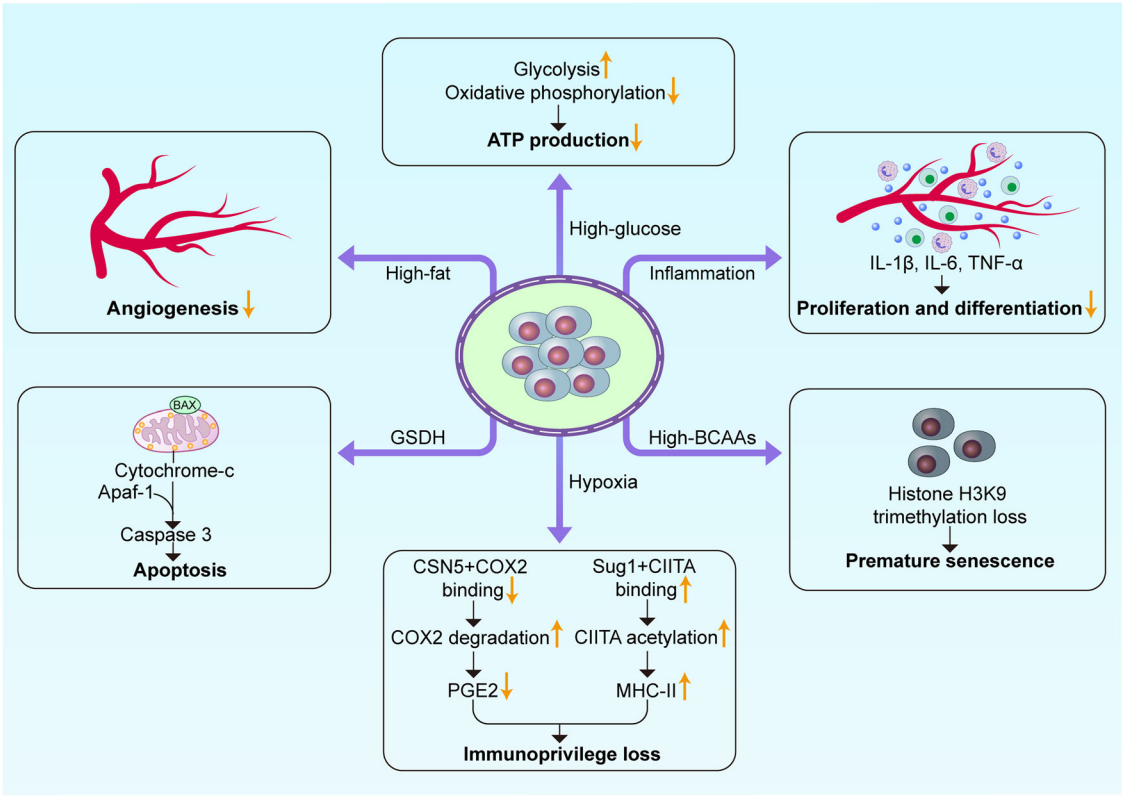

Fig. 3 | The impact of myocardial microenvironment on transplanted stem cells. The post-ischemic myocardial microenvironment (e.g., high-fat conditions, inflammation) compromises the survival and reparative function of transplanted stem cells by inducing metabolic disorders, loss of immunoprivilege, apoptosis, premature senescence, impaired angiogenic capacity and diminished proliferation/differentiation potential. Yellow arrows denote upregulation (↑) or downregulation (↓).

L-OPA1 accumulation, promoting mitochondrial fusion[123]. Similarly, GDF11-overexpressing MSCs upregulate YME1L through the TGF-β receptor/Smad2/3 pathway, enhancing mitochondrial fusion, alleviating mitochondrial dysfunction, and improving outcomes in MI[197]. In parallel developments, surface-anchored cell engineering with a nanogel coating helps preserve MSC mitochondrial integrity and function by blocking TNFα-induced apoptosis[198]. Additionally, andrographolide promotes a shift in BMSCs from glycolysis to oxidative phosphorylation, enhancing ATP production and activating Nrf2 to reduce the expression of oxidative stress-related genes, thereby minimizing cell damage under hypoxic conditions with glucose and serum deprivation[169]. Meanwhile, overexpression of SIRT3 in MSCs upregulates the expression of antioxidant enzymes, such as manganese superoxide dismutase (MnSOD) and CAT, via the FoxO3a pathway, thereby enhancing the antioxidant capacity of aging human MSCs[199]. NOX is a crucial producer of ROS, and the knockout or inhibition of Nox2 in MSCs reduces ROS accumulation, promoting MSC retention and survival[200]. Overall, to address the low engraftment efficiency of stem cells, Fig. 4 illustrates a strategy to enhance implantation, survival, and paracrine function of stem cells during adaptation to the microenvironment.

Limitations

Metabolic disorders in IHD manifest early and persist throughout disease progression, extending beyond energy metabolism to include the regulation of signal transduction, cell growth, and survival. Intervening in ischemic myocardial metabolism is crucial for promoting myocardial repair. However, the intricate network of substrate metabolism, the varying metabolic disorders at different stages of IHD, and the discrepancies between preclinical and clinical trial findings create controversy surrounding intervention strategies.

Cardiac metabolism research requires careful alignment of experimental models and analytical methods with specific scientific questions. The integration of complementary techniques is essential to enhance data reliability. Interpretation of results necessitates multidimensional validation due to: (1) substantial baseline metabolic differences among various cellular models, and (2) the challenges in capturing dynamic metabolic reprogramming during stress responses[201].

Although stem cell therapy has been demonstrated to modulate cardiomyocyte metabolism, the available literature remains relatively scarce. Existing studies predominantly focus on glucose metabolism enhancement, while comprehensive investigations into other critical pathways (e.g., fatty acid metabolism, ketone metabolism) are notably lacking, potentially leading to an incomplete understanding of their metabolic modulatory functions.

Conclusion

Stem cell therapy, particularly in the context of modulating myocardial metabolism, has emerged as a promising research direction for treating IHD. Current investigations primarily focus on enhancing myocardial glucose metabolism and mitigating mitochondrial dysfunction to improve myocardial survival and contractile function. Clinical and preclinical studies have yielded inconsistent therapeutic outcomes with stem cell therapy, likely due to factors such as the type of stem cells used, their quantity, delivery methods, and timing of administration. These observations highlight the need to establish standardized treatment protocols.

The adverse myocardial microenvironment induced by ischemia and metabolic disruption further diminishes stem cell engraftment and survival. On one hand, extracellular vesicle-based therapies present a viable alternative; on the other hand, cell engineering approaches can enhance stem cell

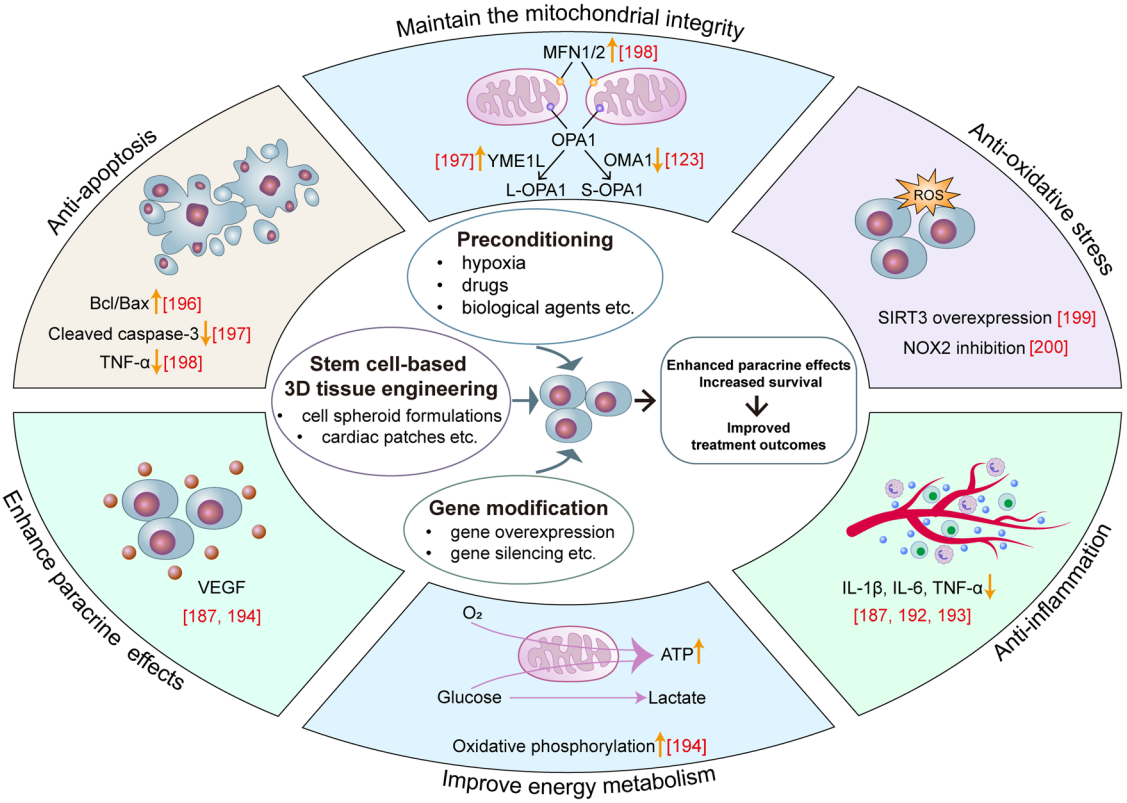

Fig. 4 | Enhancing stem cell adaptation to the microenvironment. Prior to stem cell transplantation, preconditioning, gene modification or stem cell-based 3D tissue engineering can enhance survival and paracrine effects, thereby improving therapeutic outcomes. Key mechanisms include anti-inflammation, metabolic enhancement, anti-apoptosis, and anti-oxidative stress. Relevant references are indicated in the figure for detailed methodologies. Yellow arrows denote upregulation (↑) or downregulation (↓).

adaptability, thereby improving their survival and paracrine functions. Overall, stem cell intervention aimed at modulating cardiomyocyte metabolism offers a promising new avenue for the treatment of IHD. While these approaches show preclinical potential, their clinical translation requires further validation through standardized protocols and larger controlled trials.

Data availability

The data are available upon request to the corresponding author.

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Author contributions

S.L. and L.J. contributed to write the paper, J.Z. contributed to draw the figures, X.Z., Y.S. and Z.T. contributed to researching data for the article, discussion of content the paper. J.X. conceived the hypothesis, designed, supervised and written the paper. All authors read the manuscript and agree with its contents.

Competing interests

The authors declare no competing interests.

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