Review

Metabolic remodeling induced by mitokines in heart failure

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ABSTRACT

The prevalence rates of heart failure (HF) are greater than 10% in individuals aged >75 years, indicating an intrinsic link between aging and HF. It has been recognized that mitochondrial dysfunction contributes to the pathology of HF. Mitokines are a type of cytokines, peptides, or signaling pathways produced or activated by the nucleus or the mitochondria through cell non-autonomous responses during cellular stress. In addition to promoting the communication between the mitochondria and the nucleus, mitokines also exert a systemic regulatory effect by circulating to distant tissues. It is noteworthy that increasing evidence has demonstrated that mitokines are capable of reducing the metabolic-related HF risk factors and are associated with HF severity. Consequently, mitokines might represent a potential therapy target for HF.

INTRODUCTION

Heart failure (HF) is an urgent global public health problem because of its high morbidity, high mortality, and high rehospitalization rate [1]. The proportion of HF may rise [2] because of prolonged life, increased prevalence of risk factors, and improved survival rates from other cardiovascular diseases (CVDs) [3, 4]. Currently, advancements in the treatment of ischemic and valvular heart disease have greatly improved the survival rates; however, residual cardiac dysfunction and postoperative complications lower the quality of life, ultimately leading to the development of HF [5]. In addition, therapeutic strategies for HF rehospitalization are mainly limited to symptom reduction, such as regulation of the neuroendocrine function and reduction in heart rates. These strategies aim to unburden the heart and reduce the myocardial oxygen demand in order to rebalance energy production and consumption at a low efficacy as well as prevent or slow ventricular remodeling [6]. Despite symptom reduction, the patients' quality of life and long-term prognosis may be favorable [5]. Consequently, therapeutic strategies that improve myocardial contractility and pumping function without causing adverse effects similar to those caused by inotropic drugs are required in clinical practice [7]. Unfortunately, stem cell therapy for HF does not appear promising [8, 9], and novel therapies are under research.

Although a normal heart accounts for only about 0.5% of the total mass of human body, the proportion of cardiac adenosine triphosphate (ATP) consumed each day reaches 8% [5]. Moreover, energy consumption is increased exponentially under cardiac stress [10]. Consequently, insufficient myocardial energy supply [11], substrate utilization disorder [12], and oxidative stress (OS) [13] are considered to be responsible for the progress of HF. However, it appears difficulty to treat HF from a metabolic perspective, considering the flexibility of cardiac substrate metabolism [14] and the complex metabolic network [15]. It has been validated that small molecules derived from mitochondria have capability to serve as cellular and systemic signals, such as adenosine monophosphate (AMP), adenosine diphosphate (ADP),

reactive oxygen species (ROS), Ca^{2+}, NAD^{+}, cytochrome c, succinate and metabolites (Figure 1) [16–19]. It is noteworthy that moderate mitochondrial dysfunction or stress reduce risk factors of HF [20], partly owing to the metabolic regulation of mitokines produced via cell non-autonomous responses [21, 22]. In detail, fibroblast growth factor 21 (FGF21), growth differentiation factor 15 (GDF15), adropin, and irisin are encoded and released by the nucleus, regulating inter-tissues metabolism [22, 23]. In contrast, mitochondria-derived peptides (MDPs) and mitochondrial unfolded protein response (UPR^{mt}) are encoded by mitochondrial genomes that upregulate the expression of chaperones, proteases, and mitochondrial biogenesis by acting as retrograde signaling [24, 25]. Furthermore, mitokines are also capable of improving cell metabolism via indirect methods [26–28], such as inhibition of inflammation, alleviation of OS damage, reduction of autophagy, and delay in cellular aging (Table 1). This review outlines the significance of the mitochondria for cardiac function maintenance, highlighting the metabolic characteristics in healthy and diseases heart with a summary of the possible roles and mechanisms of mitokines in CVDs. Finally, we discuss the possibilities and challenges of mitokines as a potential target for HF and indicate important research areas.

CHARACTERISTICS OF MYOCARDIAL METABOLISM

The mitochondria are critical for the maintenance of adult cardiac function, given its potent capacity to

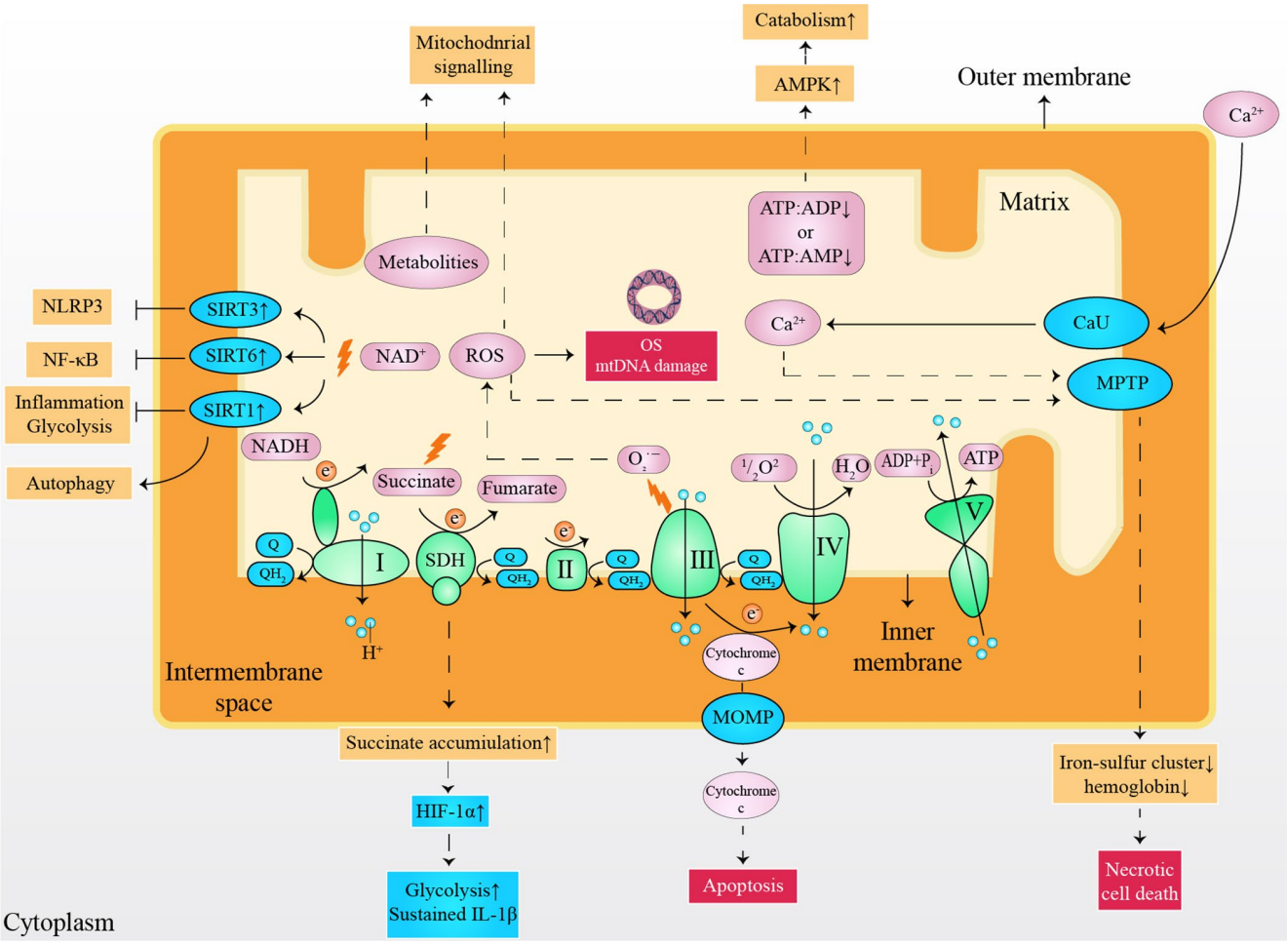

Figure 1. Small molecules arising from the mitochondria served as cellular and systemic signals. ATP: adenosine triphosphate; ADP: adenosine diphosphate; AMP: adenosine monophosphate; AMPK: 5' adenosine monophosphate-activated protein kinase; CaU: calcium uniporter; e^{-}: electron; HIF-1α: hypoxia-inducible factor 1-alpha; IL-1β: interleukin 1 beta; mtDNA: mitochondrial deoxyribonucleic acid; MOMP: mitochondrial outer membrane permeabilization; MPTP: mitochondrial permeability transition pore; NLRP3: nucleotide-binding oligomerization domain-like receptors pyrin domain containing 3; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NADH: nicotinamide adenine dinucleotide; OS: oxidative stress; Q: ubiquinone; QH_2: ubiquinol; ROS: reactive oxygen species; SIRT1: sirtuin1; SIRT3: sirtuin3; SIRT6: sirtuin6; SDH: succinate dehydrogenase.

Table 1. The role of mitokines in heart failure.

Mitokine	Encoded	Signaling pathway	Function	Application
Nucleus-derived				
FGF21 [81–100]	FGF21 gene	Akt1-GSK-3β-caspase3; ERKs; Ucp3; ATF4	Anti-OS; Autophagy protection	HF prevention
GDF15 [120–129]	GDF15 gene	GFRAL	OXPHOS improvement	HF biomarker
Adropin [130–136]	ENHO	GPCR-MAPK-PDK4; VEGFR2-ERK1/2	Endothelial protection	HF biomarker
Irisin [137–142]	FNDC5 gene	AMPK-ULK1	Autophagy protection	HF biomarker
Mitochondria-derived				
Humanin [106–112]	Mt 16S rRNA	STAT3	Anti-OS; Anti-apoptosis OXPHOS improvement	HF prevention
SHLPs [104, 113]	Mt 16S rRNA	STAT3; ERKs	Similar to humanin	HF prevention
MOTS-c [114–119]	Mt 12S rRNA	folate-AICAR-AMPK; MAPKs; NF-κB	Anti-inflammatory; Endothelial protection	HF prevention
UPR^{mt} [143–159]	bZIP domain	ATFS-1; ATF5; SIRT3-AMPK	Protein regulation; Anti-OS; OXPHOS inhibition	HF biomarker; Therapeutic target

Abbreviations: AMPK: 5′-AMP-activated protein kinase; AICAR: minoimidazole-4-carboxamide ribonucleotide; ATFS-1: activating transcription factor associated with stress-1; ATF: activating transcription factor; bZIP domain: the basic leucine zipper domain; ERKs: extracellular signal-regulated kinases; FGF21: fibroblast growth factor 21; FNDC5: fibronectin type III domain-containing protein 5; GDF15: growth differentiation factor 15; GSK: glycogen synthase kinase; GFRAL: glial cell-derived neurotrophic factor (GDNF) family receptor α-like; GPCR: G protein-coupled receptor; HF: heart failure; MOTS-c: mitochondrial open reading frame of the 12S rRNA-c; mt: mitochondrial; MAPK: mitogen-activated protein kinase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; OS: oxidative stress; OXPHOS: oxidative phosphorylation; PDK4: pyruvate dehydrogenase lipoamide kinase isozyme 4; rRNA: ribosomal ribonucleic Acid; SHLPs: small humanin-like peptides; STAT3: Signal transducers and activators of transcription 3; SIRT3:sirtuin3; UPR^{mt}: mitochondrial unfolded protein response; Ucp3: Mitochondrial uncoupling protein 3; ULK1: Unc-51 like autophagy activating kinase1; VEGFR2: vascular endothelial growth factor receptor 2.

produce ATP, ability to regulate Ca^{2+}, and the ability to induce myocardial pathological inflammatory responses and apoptosis [29, 30]. The mitochondria account for approximately 25%–30% of the volume of cardiomyocytes, widely distributed in the subsarcolemmal, perinuclear, and intramembranous regions [5]. Mitochondria support > 95% of the myocardial ATP demand through oxidative phosphorylation (OXPHOS) [14]. Mechanistically, glycolysis, fatty acid (FA) β-oxidation (FAO), and tricarboxylic acid cycle are the main sources of H^+ and electrons. Nicotinamide adenine dinucleotide (NADH) and reduced flavin adenine dinucleotide ($FADH_2$) transfer H^+ and electrons to the electron transfer chain (ETC) composed of complex I to complex IV [31]. Correspondingly, the energy released by the protons is pumped from the mitochondrial matrix into the intermembrane space across the inner membrane [32]. Considering the high impermeability of the mitochondrial inner membrane, a chemical gradient (ΔpH) and an electrical gradient (ΔΨm) are built up across the inner membrane [33]. The proton motive force (PMF), the collective name of ΔpH and ΔΨm, drives the phosphorylation of ADP to form ATP at F_0F_1-ATP synthase, along with the generation of a small amount of ROS [32].

Myocardial metabolism has its own characteristics. First, the metabolic substrate of a healthy heart is flexible. FA (60%–90%) and ketone bodies (10%–40%) are the main substrates under physiological conditions [12]. Despite a higher utilization efficiency of glucose, glucose merely accounts for 5% of the cardiac oxidation [34]. In-vivo and in-vitro experiments have demonstrated that glucose metabolism is restrained by FAO and is related to dietary and physical activity [35]. However, glucose oxidation instead of FAO takes charge of myocardial metabolism during cardiac overload [12]. Furthermore, ketone bodies might become the main substrate for fasting or poorly controlled diabetes. Second, myocardial metabolism has a specific regulation mechanism. 5′-AMP-activated protein kinase (AMPK)

activates along with the increased AMP content during ATP shortage [36]. ATP content is increased via AMPK-mediated inhibition of ATP consumption, promotion of FA, and oxidation of glucose [37]. In addition, peroxisome proliferator-activated receptors (PPARα) are validated to regulate the long-term cardiac metabolism [14]. PPARα is capable of upregulating the transcription of genes related to FA uptake and OXPHOS, enhancing the cardiac oxidation ability. Its activation depends on PPARγ co-activator 1α (PGC1α) or PGC1β [14, 38]. Third, the buffer between the mitochondria and the cytoplasm guarantees heart energy supply during cardiac stress. Excess ATP shifts the phosphate bond to creatine via the action of creatine kinase (CK) to form phosphocreatine (PCr) that is rapidly transferred to the cytoplasm [14]. PCr has the ability to transfer the phosphate bond to ADP, forming ATP again during the first 7 *s* of cardiac stress [39]. These mechanisms ensure ATP supply during a sudden cardiac attack [40].

The most prominent metabolic change in HF is the conversion of FAO to hypoxic carbohydrate metabolism, such as glycolysis [41]. It is noteworthy that the alterations in myocardial metabolism depend on the HF stage (Figure 2). In the early stage of HF, FAO remains

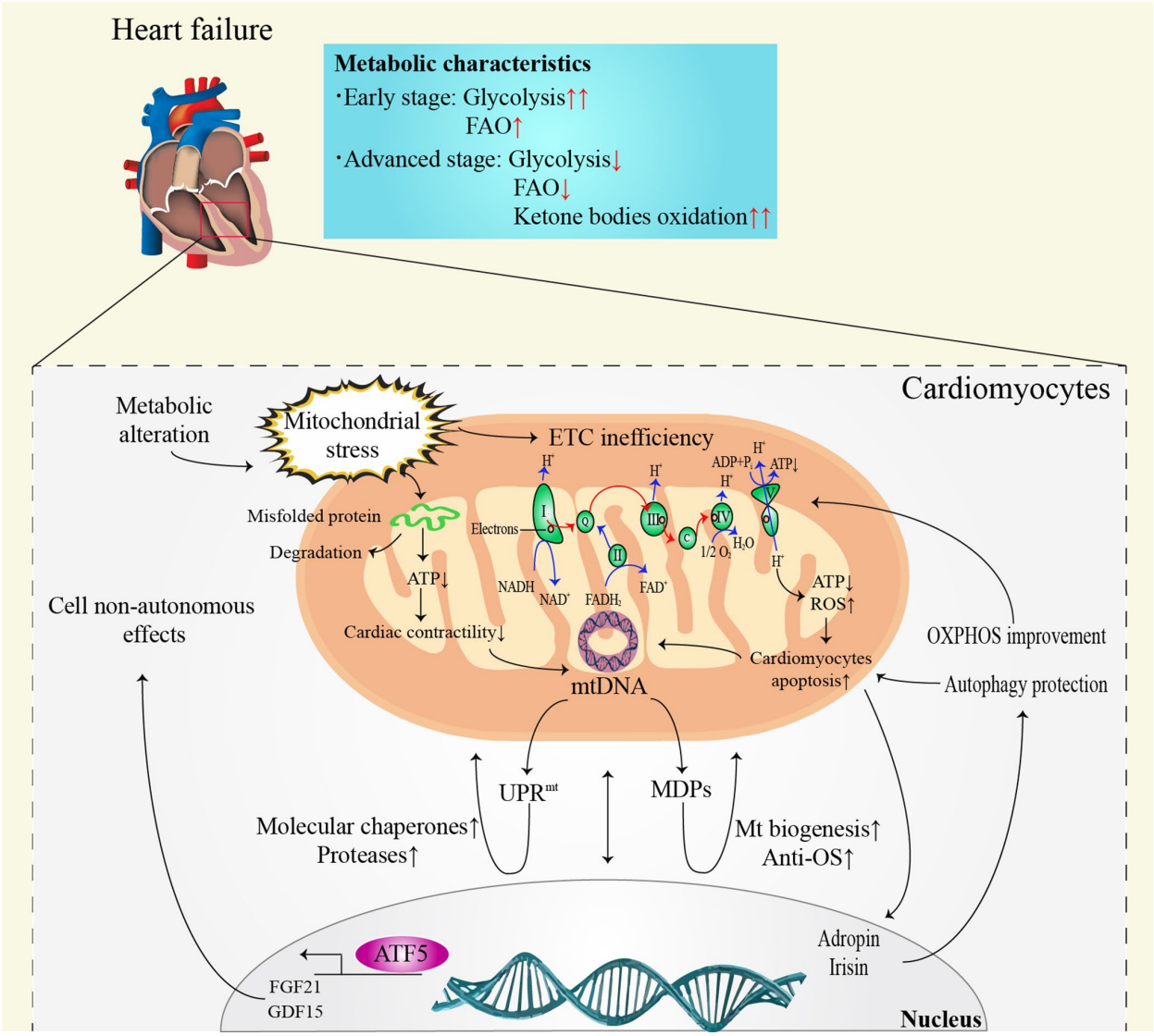

Figure 2. Communication between mitochondria and nucleus in heart failure. ATP: adenosine triphosphate; ADP: adenosine diphosphate; ATF5: activating transcription factor 5; DNA: deoxyribonucleic acid; ETC: electron transfer chain; FAO: fatty acid β-oxidation; $FADH_2$: reduced flavin adenine dinucleotide; FGF21: fibroblast growth factor 21; GDF15: growth differentiation factor 15; Mt: mitochondrial; MDPs: mitochondria-derived peptides; NADH: nicotinamide adenine dinucleotide; OS: oxidative stress; OXPHOS: oxidative phosphorylation; ROS: reactive oxygen species; UPR^{mt}: mitochondrial unfolded protein response.

unchanged or slightly elevated [42], while glucose uptake and glycolysis increase significantly [43]. However, both FAO and glucose metabolism efficiency decrease in advanced or end-stage HF [42]. It is noteworthy that ketone bodies seem to become the main metabolic substrate in advanced stage HF [41, 44]. The oxidation of ketone bodies has been validated to improve the efficiency of myocardial metabolism and cardiac function in HF [45]. Despite the positive function, the long-term impacts of ketone body metabolism on HF patients still need to be elucidated.

NOVEL INSIGHTS INTO THE HIGH-RISK FACTORS OF HF

Obesity and insulin resistance (IR)

It is clear that IR plays an essential role in atherosclerosis and hypertension [46]. Type 2 diabetes and obesity are independent risk factors that increase the morbidity of HF [47]. However, whether obesity and IR induce HF remains controversial. Moderate IR might be beneficial to the heart by exerting a protective effect against the damage caused by excessive accumulation of myocardial substrate [14]. In addition, it seems that the alteration of substrate rather than a high-fat diet (HFD) is more likely to increase metabolic stress and induce cardiac dysfunction [48]. These differences might be attributable to the dietary styles, duration of therapy, and species. Although obesity has been validated as an independent risk factor for HF [49], overweight is related to lower HF mortality [50]; this is called the obesity paradox. It is hypothesized that overweight and obesity have the potential to exert protective effects in the aged and those with chronic diseases [51, 52]. Obesity paradox was first observed in 1999 in patients undergoing hemodialysis who were overweight and obese [53]. More importantly, obesity paradox was also found in patients with HF [54, 55]. Hemodynamic changes [56] and cytokine responses [57] in HF are associated with impaired gastrointestinal function [58], anorexia [56], and hypermetabolism [59], contributing to the development of cardiac cachexia. Consequently, patients with HF commonly exhibit weight loss [60]. Furthermore, obesity is capable of increasing the muscle mass in patients who have HF with reduced ejection fraction (HFrEF) [61]. In contrast, 239 prospective studies have disproved the obesity paradox, suggesting that obesity and overweight are closely related to higher all-cause mortality [62]. However, there remains considerable debate whether obesity paradox contributes to cardiac remodeling and the risk of HF with preserved ejection fraction (HFpEF) [63]. The discrepancy might be related to age, sex and other comorbidities [64]. Objectively, obesity increases the morbidity and mortality of HF. However, it appears reasonable for patients with advanced HF to gain weight properly to offset the weight loss caused by HF. Further optimized studies that aim to assess this difference are urgently required.

Oxidative stress (OS)

Conventionally, the abnormal release of ROS induced by OS is considered the main cause of cell senescence and apoptosis [65], manifesting metabolic abnormalities [66]. However, recent studies have demonstrated that the mitochondrial theory of aging appears to have been overestimated [67, 68], indicating no necessary connection between aging and mitochondria-derived ROS production [67]. In fact, cardiomyocytes appear to focus on injury tolerance and repair [69] instead of apoptosis and regeneration [70]. Interestingly, mild ROS are validated to be beneficial to the heart to some degree [71], such as ischemic preconditioning (IPC) [72] and the protective effects induced by physical exercise [73]. A probable mechanism might be the mitohormesis [74] and AMPK/Unc-51 like autophagy activating kinase1 (ULK1)-mediated pro-autophagy pathway [75]. Moderate ROS within mitochondria may develop an adaptive reaction, finally causing cellular stress resistance and OS inhibition. Mitohormesis, an inhibitory process for OS, is beneficial for extending lifespan induced by physical exercise [73, 76]. Despite the protective effect, excessive ROS might be harmful during ischemic-reperfusion injury (IRI) [77]. Long-term exposure to ROS is capable of promoting cardiac hypertrophy by inducing cardiomyocytes apoptosis, necrosis, and fibrosis [78, 79]. In conclusion, low dose of ROS contributes to health-promoting capability while higher dose and sustained stimulation of ROS may lead to OS [80]. Further studies on the impact of ROS are still needed.

PROTECTIVE FACTORS FOR HF

FGF21

FGF21, a novel member of fibroblast growth factors (FGFs), was first isolated from mouse embryos by Nishimura et al [81]. FGF21 is mainly expressed in the liver, pancreas, and adipose tissues [82, 83], partially expressed in the myocardium [84]. The endogenous receptors of FGF21 include FGF receptor 1 (FGFR1) and β-Klotho [85] that are also highly expressed in the myocardium [84]. Clinical studies have shown elevated levels of circulating FGF21 in patients with atherosclerosis or those at high risk of atherosclerosis [86]. The application of exogenous FGF21 is capable of significantly improving the lipid metabolism disorder in mice and reducing the area of atherosclerotic plaque [87]. Mice lacking FGF21 are more prone to hypercholesterolemia and atherosclerosis [88], suggesting the cardioprotective effect of elevated

FGF21. In IRI models, FGF21 bound to cardiac receptors to activate the Akt1-glycogen synthase kinase-3β-caspase 3 (Akt1-GSK-3β-caspase 3) signal pathway [89], then phosphorylating phosphoinositide 3-kinase (PI3K), p85, Akt1 and BCL-2/BCL-XL-associated death promoter (BAD), consequently reducing the activity of caspase 3 and apoptosis of cardiomyocytes [90]. Mitochondrial uncoupling protein 3 (UCP3) exerts an anti-OS function by activating FGF21 under myocardial hypertrophy condition [91]. Similarly, genetic deletion of UCP3 exaggerates the expression of apoptotic signal, leading to HF [92]. Additionally, FGF21 is also capable of inhibiting the ROS production by activating superoxide dismutase 2 (SOD2) via extracellular signal-regulated kinases (EPKs) on the basis of sirtuin1 (SIRT1) overexpression [84, 93]. Correspondingly, patients with HF showed upregulation of UCP3 and SOD2 [26].

Autophagy deficiency is associated with modifiable factors of atherosclerosis [46], such as IR, dyslipidemia, and abdominal obesity [27, 94]. FGF21 is activated by activating transcription factor 4 (ATF4) induced by autophagy deficiency [95], protecting mice against diet-induced obesity [96] by enhancing the mitochondria oxidative efficiency [97], increasing fatty acid utilization, promoting lipid excretion [98], and lowering the level of blood glucose and triglycerides [99]. Accordingly, the deficiency of FGF21 enhanced myocardial lipid accumulation in mice [27]. As per a clinical study, advancements were preliminarily obtained in patients with obesity which ameliorates dyslipidemia by applying FGF21 analogues [100].

MDPs

MDPs are a class of peptides encoded by mitochondrial deoxyribonucleic acid (DNA), mainly including humanin, mitochondrial open reading frame of the 12S rRNA-c (MOTS-c), and small humanin-like peptides (SHLPs) [101, 102]. As the first member of MDPs, humanin has been validated to induce positive metabolic activities, such as reduction in visceral fat and increase in glucose-stimulated insulin release [101]. MOTS-c and SHLPs further complement the role of MDPs in cell metabolism [103, 104]. Recently, the metabolic protection mechanism of MDPs in CVDs has been gradually recognized [105].

Humanin and SHLPs

Humanin is a micropeptide encoded by the 16S ribosomal ribonucleic acid (RNA) gene of mitochondrial genome, discovered by Hashimoto Yuichi [106]. Humanin was initially thought to be a specific neuronal protective peptide for AD [107]. Recent studies demonstrated that humanin plays an essentially protective role in cardiac stress [108]. In IRI models, humanin protects left ventricular function [109] by promoting mitochondrial biogenesis [110] and the expression of endothelial nitric oxide synthase (eNOS) [111]. Additionally, [Gly14]-humanin (HNG) can reduce the risk of atherosclerosis by increasing cholesterol efflux and reducing the uptake the oxidized low-density lipoprotein (ox-LDL) by macrophage-derived foam cells [112]. Small humanin-like peptides (SHLPs) are also a class of polypeptides encoded in the mitochondrial 16S rRNA region. Six peptides (SHLP1~6) have been identified so far, each of which is 20–38-amino acids long [104]. SHLP2 exhibits a similar effect to HN in anti-apoptosis, insulin sensitization, and glucose homeostasis maintenance [104]. In addition, in-vitro studies have demonstrated that SHLP2 are capable of improving mitochondrial metabolism by increasing the oxygen consumption rate (OCR) and ATP generation [113]. SHLP2 reportedly activate the signal transducers and activators of transcription 3 (STAT3) pathway in a time-dependent manner; however, the specific mechanism remains still unclear [104].

MOTS-c

MOTS-c is encoded by mitochondrial 12S rRNA [103] that is activated by metabolic stress signals and transferred to the nucleus, regulating adaptive nuclear gene expression [114]. The polymorphism of MOTS-c is related to longevity [28], playing a vital role in regulating obesity and diabetes [115]. MOTS-c is capable of reversing age-dependent and HFD-induced insulin resistance, preventing diet-induced obesity [116]. Mechanistically, MOTS-c regulates cell metabolism by inhibiting the folate cycle, new purine biosynthesis, and endogenous aminoimidazole-4-carboxamide ribonucleotide (AICAR) aggregation via the folate-AICAR-AMPK pathway [103]. In addition, MOTS-c also plays an important role in protecting vascular endothelial function [117] by inhibiting the activity of mitogen-activated protein kinases (MAPKs) and reducing the expression of inflammatory factors (TNF-α, IL-6, IL-1β) induced by nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [118]. Consequently, lower endogenous MOTS-c level is thought to be associated with impaired coronary endothelial function [119].

POTENTIAL DIAGNOSTIC AND THERAPEUTIC TARGETS FOR HF

GDF15

GDF15, first identified as macrophage inhibitory cytokine 1 (MIC-1), belongs to the transforming growth factor (TGF)-β superfamily [120] that plays a significant role in regulating the inflammatory pathway, cell growth, cell repair, and apoptosis [121]. Similar to FGF21,

GDF15 is also considered a marker of mitochondrial respiratory chain deficiency [122]. Activated GDF15 combines with glial cell-derived neurotrophic factor (GDNF) family receptor α-like (GFRAL) [123] to regulate appetite and energy metabolism by affecting mitochondrial biogenesis, calorie production, and fatty acid metabolism [124]. Preliminary studies have considered GDF15 as a biomarker and prognostic indicator for HF [125]. Lok et al. [126] first reported that GDF-15 has the potential to estimate the prognosis of possible therapeutic interventions, such as left ventricular assist device (LVAD) implantation. Similarly, another clinical study demonstrated that GDF15 and N-terminal pro-brain natriuretic peptide (NT-proBNP) are both core biomarkers for patients with HFrEF and patients with HFpEF [127, 128]. However, the expression of GDF15 appears to be related to a variety of pathological states, suggesting that GDF15 might act as a general stress factor [129].

Adropin and irisin

Adropin is a novel membrane-bound protein containing 76 amino acids encoded by an energy homeostasis-related gene (ENHO) [130]. It is mainly expressed in the liver, brain, coronary arteries, vascular endothelium, and heart [131]. Adropin is capable of improving cardiac glucose metabolism in mice with HFD [132] and regulating pyruvate dehydrogenase in cardiomyocytes via the G protein-coupled receptor-MAPK-pyruvate dehydrogenase lipoamide kinase isozyme 4 (GPCR-MAPK-PDK4) signal pathway [133], suggesting an important role of adropin in cardiac substrate utilization. Furthermore, adropin upregulates the expression of eNOS and protects endothelial function [134] via the vascular endothelial growth factor receptor 2 (VEGFR2)-phosphatidylinositol 3-kinase-Akt and VEGFR2-ERK1/2 pathways [135]. Clinically, lower level of adropin is an independent risk factor for CVDs, and circulatory adropin level increases along with HF severity [136]. Collectively, these findings suggested that elevated adropin in HF patients improves cardiac function by regulating metabolism and protecting the vascular endothelium; further, adropin has the potential to be a serum biomarker for early diagnosis of CVDs.

Irisin is a polypeptide hormone that contains 112 amino acids and was discovered by Boström et al [137]. It is cleaved from Fibronectin type III domain-containing protein 5 (FNDC5) when activated by PGC-1α after exercise or stress [138]. Irisin is highly expressed in the myocardium, skeletal muscle, brain, and spinal cord [139]. Irisin is capable of converting white adipose tissue into brown adipose tissue by upregulating the expression of Ucp1 [137]. Elevated level of irisin has been recognized to highly correspond with many CVDs, suggesting poor prognosis [140]. Mechanistically, irisin protects against pressure overload-induced myocardial hypertrophy and ameliorates angiotensin II-induced cardiomyocyte apoptosis by activating AMPK-ULK1 signaling and inducing protective autophagy and autophagy flux [141]. Clinical studies have demonstrated that both adropin and irisin are related to HF severity [131] that might be an emerging marker of cardiac cachexia in HFrEF patients. Interestingly, a study has demonstrated that plasm level of irisin in HFpEF was obviously higher than patients with HFrEF. In addition, the negative relationship between irisin and total antioxidant capacity (TAC) was only observed in patients with HFpEF, suggesting a distinct mechanism of irisin secretion in the two HF subtypes [142].

UPR^{mt}

UPR^{mt} was first identified as a crucial regulatory pathway for mitochondrial protein homeostasis and quality control in Caenorhabditis elegans (C. elegans) [143]. Physiologically, nuclear-encoded proteins are transported to mitochondria by ribosomes [144] where they are properly folded and assembled [145]. During mitochondria stress, lower ATP or transmembrane potential in the cells slows down the process of precursor proteins entering the mitochondria, leading to a large number of misfolded proteins or protein precursors accumulating in the cytoplasm [146]. UPR^{mt} is subsequently activated by the mitochondrial proteasome to upregulate the expression of molecular chaperones, proteases, and antioxidant genes, restoring mitochondrial function [25]. Noticeably, UPR^{mt} is mainly regulated by activating transcription factor associated with stress-1 (ATFS-1) in models of worm and C. elegans [147]. ATFS-1 contains a mitochondrial targeting sequence (MTS) and a nuclear localization sequence (NLS), guaranteeing its regulation for communication from the mitochondria to the nucleus [148]. In the case of mitochondrial dysfunction, the mitochondrial importing ability decreases [149], leading to ATFS-1 accumulation in the cytoplasm. Subsequently, ATFS-1 enters the nucleus through NLS, activating nuclear transcription reaction [150] that weakens the expression of OXPHOS-related genes and strengthens the expression of molecular chaperone and proteasome-related genes to reduce ROS toxicity and increase mitochondrial importing ability, consequently reconstructing mitochondrial protein homeostasis [148]. Recent studies have demonstrated that mitochondrial stress induced by knockdown ETC subunits in C. elegans activates UPR^{mt} both in neurons and gut, improving health and prolonging life [20].

Recently, the metabolic regulation of UPR^{mt} has been gradually recognized [151]. Interestingly, the metabolic effects of UPR^{mt} on proliferating and post-mitotic cells

are different. In proliferating cells, sustained UPR^{mt} promotes glycolysis while maintaining the mitochondrial function [152]. However, in mitotic or post-mitotic cells, such as muscle cells, UPR^{mt} inhibits the expression of tricarboxylic acid cycle and OXPHOS-related genes and reduces the metabolic load and cell damage caused by secondary product ROS while increasing the expression of glycolysis and amino acid decomposition genes to meet the cellular needs for ATP [153]. It seems to be a temporary way for muscle cells to respond to mitochondrial stress without permanently rewiring cell metabolism [154]. Notably, Smyrnias et al. [10] concluded that the pharmacodynamic enhancement of myocardial UPR^{mt} is capable of improving mitochondrial and systolic dysfunction, using vitro myocardial cell test, a mouse heart overload model, and plasma marker analysis of patients with aortic stenosis. They also demonstrated that UPR^{mt} activation is negatively correlated to lower plasma levels of high-sensitive cardiac troponin (hs-cNT) and N-terminal pro B type natriuretic peptide (NT-pro BNP) [155] in patients with aortic stenosis. UPR^{mt} is regulated by ATF5 in mammals [10], and NAD^+ supplementation has the potential to improve UPR^{mt} activity [156]. Similar to ATFS-1, ATF5 is also a transcription factor containing the basic leucine zipper (bZip) domain [150]. Additionally, studies have confirmed that choline attenuates myocardial hypertrophy by modulating the expression of UPR^{mt} [157]. However, excessive prolongation or lack UPR^{mt} regulation might cause harm by contributing to the accumulation of defective mitochondria [158] and the formation of neurodegenerative phenotypes [159].

POSSIBILITIES AND CHALLENGES

Non-invasive evaluation of mitochondrial function remains unresolved [160]. Clinically, biomarkers with a high specificity and short-term sensitivity are urgently needed [32]. The lactate: pyruvate ratio [161] and oxidative damage markers [162] can be referenced to evaluate systemic mitochondrial function. Additionally, FGF21 [163] and GDF15 [122] have been validated as biomarkers for mitochondrial diseases in mouse models and patients. However, the specificity of these methods remains unsatisfactory [32]. Noticeably, it seems more meaningful to focus on the protective effects on the heart rather than distinguish the origins of mitokines. Mitokines secreted by other tissues reduce the HF risk by ameliorating IR and regulating glucose and lipid metabolism [96, 104, 124]. Damaged myocardial cells or endothelial cells simultaneously secret mitokines into the circulation, regulating lipid metabolism and protecting against oxidative stress or inflammatory injury by affecting the cell surface receptors, consequently improving atherosclerosis, protecting the ischemic myocardium and reducing IRI [90]. These findings suggest that mitokines protect against cardiac damage by systemic metabolic regulation effect (Figure 3). Mechanistically, the nucleus regulates mitochondrial

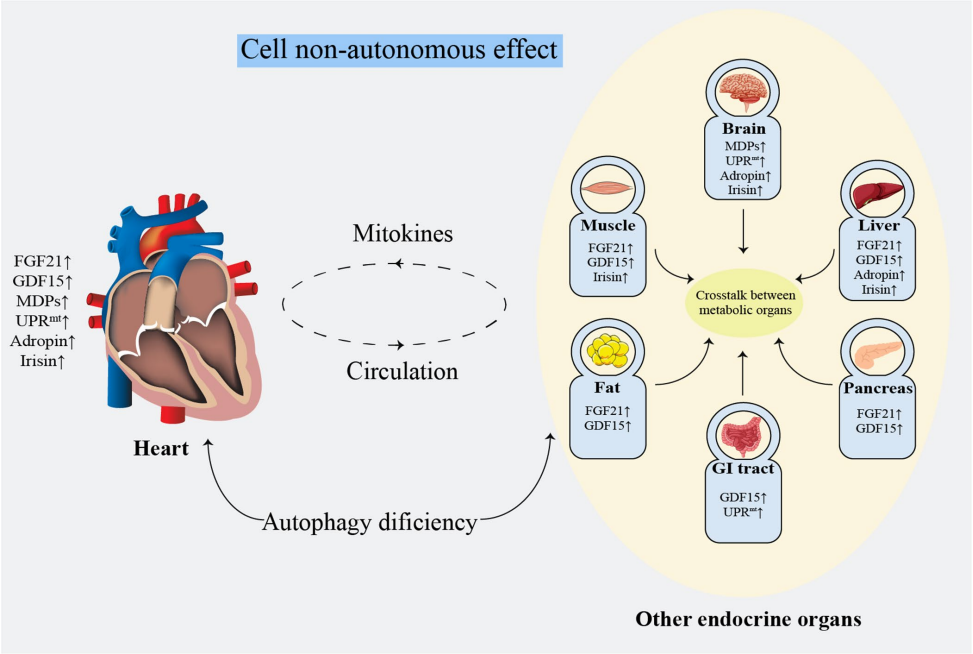

Figure 3. Systematic metabolism regulated by cell non-autonomous effect. FGF21: fibroblast growth factor 21; GDF15: growth differentiation factor 15; GI: gastrointestinal; MDPs: mitochondria-derived peptides; UPR^{mt}: mitochondrial unfolded protein response.

metabolism through FGF21, GDF15, adropin, and irisin, while the mitochondria retrogradely regulates nuclear metabolism-related gene expression by MDPs and UPR^{mt} [164] that changes the traditional understanding of the mitochondria as terminal functional organelles that receive cell signals (Figure 2).

The existing literature shows differences in the research results for partial mitokines. Circulating levels of FGF21 have been reported to be positively correlated with age, causing premature aging and death in mice [165]. Similarly, it is suggested that the beneficial results of muscle mitochondrial stress might be independent of endogenous FGF21 activation [166]. Furthermore, several observations have indicated that the effect of GDF15 might highly depend on the state of the cell and its environment [167]. Despite the positive effects of mitokines [97, 98, 121, 129], the specific metabolic mechanism of mitokines requires greater clarification. In addition, obesity has been validated to be a FGF21 resistance state, and that further studies on addressing FGF21 resistance are needed [168]. Decreased activity of FGF21 has been observed in heart samples from obese rodents and white adipose tissue of human due to the decreased expression of beta-klotho [169, 170]. Although this conclusion was under challenge [171], the signal response of ERK1/2 phosphorylation was significantly weakened when using exogenous FGF21 to treat obese mice, along with the impaired induction of FGF21 target genes (cFos and EGR1) [168]. Objectively, the differences in the experimental data of animal models and human HF patients might be owing to the diversity in the species and dietary styles [172]. Furthermore, alterations in metabolism tend to occur in late stages in animal HF models. In addition, gross and micro differences in metabolic changes might be observed in the left ventricle [12]. Hence, drawing a general conclusion from a single point in time or from a single animal model needs careful considerations [173].

OUTLOOK

The importance of metabolic alterations in the myocardium for the subsequent development of HF has been previously highlighted [12]. The interactions between mitochondrial dysfunction and HF have been continuously examined [14, 32]. It is difficult to evaluate mitochondrial function noninvasively, achieve targeted drug delivery, and reduce drug toxicity [160, 174]. Noticeably, the emerging concept of mitokines might represent a novel prospect for HF therapy. It has great potential in the diagnosis and treatment of CVDs if these processes are well understood and the related genes and peptides are further identified. Currently, adropin and irisin have shown a correlation with HF severity and might be emerging markers of HF [131]. FGF21 and GDF15 have already been investigated in pre-clinical studies [128, 175], especially in the treatment of adrenergic nervous system (ANS) hyperactivity-induced HF [176]. It has been reported that up-regulation of GDF15 negatively regulated norepinephrine-induced myocardial hypertrophy by inhibiting epidermal growth factor receptor (EGFR) transactivation [177]. Similarly, FGF21 reduced angiotensin II (Ang II)-induced myocardial hypertrophy through SIRT1 [178]. Given the fact that the influential effects of physical exercise and Ang II type 1 (AT_1) receptor antagonists on GDF15 and FGF21 [179, 180], whether GDF15 and FGF21 have the potential to evaluate the prognosis of patients with HF treated by angiotensin receptor-neprilysin inhibitor (ARNI) has not yet been determined. MDPs [105] and UPR^{mt} [157] are typical examples of mitochondrial reverse regulation of nuclear metabolic gene expression, providing a novel therapeutic approach. As previously mentioned, FGF21 [90], MOTS-c [103], and irisin [181] are regulated by AMPK; ATFs activates UPR^{mt} [10] and FGF21; ERK1/2 is activated by HNG, SHLPs [104], and FGF21 [90]. Furthermore, MOTS-c also reduces the myocardial immune response and protects endothelial function by inhibiting MAPKs [117, 118]. Hence, studying the metabolism-related signaling pathways and transcription factors can deepen our understanding of mitokines-mediated cardiac protection.

Considering the current progress with mitokines [165], we hope to establish a validated class of biomarkers and predictive algorithms that are capable of screening patients with risk factors of HF before clinical symptoms emerge, assisting subsequent treatment. We have only discussed a small fraction of the possibilities of mitokines as a therapeutic target for HF. For example, the secretion of partial mitokines is influenced by circadian and nutritional factors [182] that might lower its specificity. In addition, high-risk factors, such as diabetes, obesity, and liver diseases should be carefully evaluated. However, we still encourage clinicians to explore the possibilities in appropriate patient populations.

The communication among the adipose tissue, skeletal muscle, liver, heart, pancreas, intestine, and other major endocrine organs plays a crucial role in regulating energy metabolism [183, 184]. The effect of mitokines on cardiac and overall metabolic levels provides a novel hope for HF therapy (Figure3).

AUTHOR CONTRIBUTIONS

All authors critically reviewed and approved the final version of the paper.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interests.

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