Review

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Review

Adipokines as Cardioprotective Factors: BAT Steps Up to the Plate

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Abstract: Cardiovascular disease is the leading cause of death throughout most of the industrialized world. Metabolic syndrome (MetS) and its associated pathologies are underlying factors in the etiology of cardiovascular disease, as well as a plethora of other maladies which cause excess morbidity and mortality. Adipose tissue (AT) has come to be regarded as a *bona fide* endocrine organ which secretes specific molecular entities constituting part of a complex web of inter-organ crosstalk that functions as a key determinant of whole-body metabolic phenotype. Brown adipose tissue (BAT) has classically been regarded as a thermogenic tissue exerting its metabolic effects primarily through its capacity to oxidize substrate decoupled from ATP resynthesis, thereby resulting in increased energy expenditure (EE) and heat production. However, in recent years, BAT has begun to receive attention as a secretory organ in its own right. The molecules secreted specifically by BAT have been termed "batokines" and currently available evidence supports the notion that batokines exert favorable metabolic effects on multiple organ systems. While maintenance of healthy body composition by conferring resistance to excessive adiposity is a rather obvious mechanism by which BAT operates via increased EE, effects on critical organs such as the heart remain unclear. This narrative review focuses on four types of batokines for which evidence of modulation of cardiovascular function exists, namely FGF21, neuregulin 4, 12,13-diHOME, and microRNAs. Given the overwhelming burden of cardiometabolic disease, further study of the functions of BAT and its secretome is warranted and will intensify in the future.

Keywords: adipokines; brown adipose tissue; batokines; cardiovascular disease; metabolic syndrome; insulin resistance; obesity; type 2 diabetes; atherosclerosis; hypertension

1. Introduction

Obesity and type 2 diabetes constitute global epidemics and are crucial underlying factors in a host of chronic diseases that play a causal role in excess morbidity and mortality, particularly in the industrialized world [1]. For decades, advice intended to combat obesity has revolved around repeated exhortations to "eat less and move more" and yet the incidence of obesity and its associated pathologies continues to spiral upward in an alarming trajectory despite these admonitions [2,3]. The unsatisfactory results of this conventional advice aimed at preventing and reversing obesity can be at least partially attributed to its erroneous underlying assumption which holds that dietary energy intake and energy expenditure (EE) are independent variables and thus can be manipulated at will in efforts to alter body composition without regard to complex biochemical regulatory pathways governing energy homeostasis [4–6]. This is evidenced by the observation that changes in body weight invariably result in changes in energy expenditure in a process known as adaptive thermogenesis [7–9]. While the exact origin of the collective failure of efforts to interrupt current trends toward ever-increasing rates of obesity remains a source of vigorous debate [10], the necessity of finding new and effective methods to prevent and treat obesity is irrefutable.

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Adipose tissue (AT) has long been recognized as a regulator of nutrient status given its capacity to store excess dietary substrate as triacylglycerols (TGs) in the fed state and export fatty acids and glycerol during fasting [11,12]. However, the discovery of secretory factors specifically derived from adipocytes in the mid-1990s has led to an appreciation of adipose tissue beyond its function solely as a storage site for excess dietary substrate [13,14]. Indeed, the roughly concurrent discoveries of leptin, adiponectin, TNF-α, adipsin, and other adipocyte-derived factors termed "adipokines" has given rise to a surge in interest in adipose tissue as a *bona fide* endocrine organ situated at the nexus of energy homeostasis [15].

The recognition that adipocytes play an indispensable role in metabolic function also provided an impetus for the development of pharmacologic agents targeting adipose tissue specifically in efforts to improve insulin sensitivity and blood glucose control [16,17]. The anti-diabetic drugs targeting adipose tissue exert their effects primarily by modulating the activity of the transcription factor PPAR-γ, which is the master transcriptional regulator of adipogenesis [18]. These PPAR-γ agonists constitute the thiazolidinediones (TZDs), which have potent insulin sensitizing effects but are known to result in weight gain and can also have adverse effects on cardiac function [19]. Given that cardiovascular disease (CVD) is one of the leading causes of death globally [20,21] and that obesity-related metabolic dysfunction is a critically important contributor to CVD [22], there has never been a more urgent time to increase understanding of the complex relationships between adipose tissue of all types and cardiovascular function [23].

The discovery that functional brown adipose tissue (BAT) is present in adult humans [24] led to a groundswell of research interest in this unique tissue. BAT had been long recognized as a physiological defense against cold temperatures in small mammals and human infants given its capacity to generate heat by dissipating the normally tight coupling between substrate oxidation and ATP synthesis [25]. However, in recent years an appreciation of BAT as a tissue with secretory function has developed in parallel with our current understanding of WAT as an endocrine organ with potent effects on whole body metabolic function [15,26,27]. Notably, several studies have indicated that diminished BAT activity and non-functional BAT are contributors to obesity and cardiometabolic syndrome [28–30]. Conversely, expansions in BAT mass and increases in the circulating levels of BAT-derived secreted molecules (batokines) have been demonstrated by a growing literature to beneficially affect key parameters such as glucose homeostasis, insulin sensitivity, and total energy expenditure, all of which confer resistance to the development of obesity-related metabolic dysfunction [31–33].

While the discovery of functional BAT in adult humans constituted a major leap forward in our understanding of adipose tissue in general as a nexus of metabolic control in concert with the actions of WAT, the recognition of BAT-derived secreted factors as modulators of cardiovascular function is a relatively newly emerging field [34–37]. Recent studies have identified several batokines that modulate the heart in a generally favorable manner; these include FGF21, neuregulin 4 (NRG4), 12,13-diHOME, and microRNAs specifically derived from BAT [38]. This review will focus specifically on these batokines for which experimental evidence exists demonstrating a heretofore relatively unknown function of BAT as a tissue acting in a cardioprotective manner and will aim to briefly summarize the state of the field in understanding the mechanisms by which BAT-derived humoral factors could act advantageously in combating CVD. The new recognition of BAT as a cardioprotective tissue is certain to stimulate vigorous investigation in the future, with a view towards targeting BAT expansion and enhanced secretory function as a therapeutic strategy in combating cardiometabolic disease.

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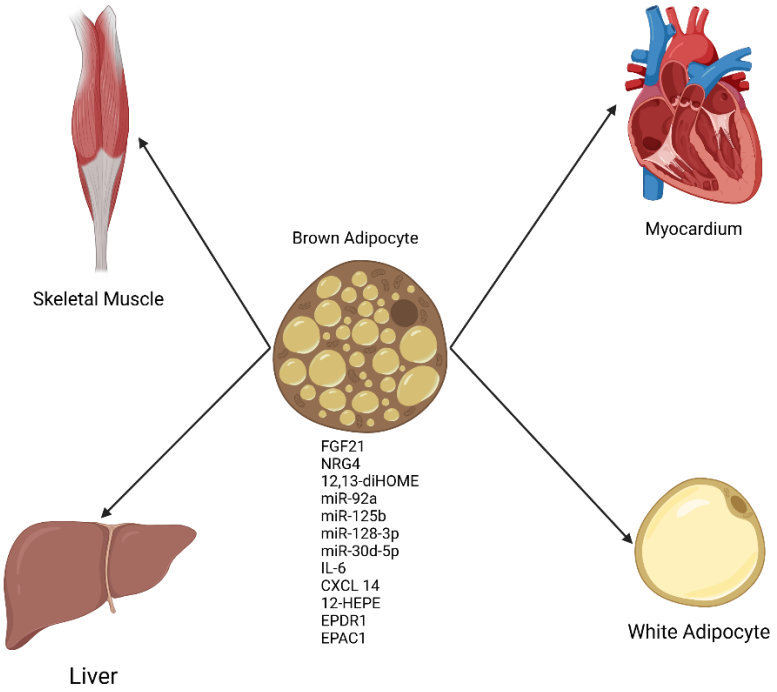

Figure 1. General schematic of factors secreted from BAT (Batokines) with effects on multiple organs. Batokines appear to be uniformly beneficial in organ systems studied thus far [38]. Created in BioRender.

2. Batokines Affecting Cardiac Function

2.1. FGF21

Fibroblast growth factor 21 (FGF21) is expressed primarily in the liver, although recent evidence inidicates that this peptide is also produced by cardiomyocytes and BAT [39–41]. FGF21 has received intense attention in the scientific literature in the context of metabolic syndrome due to the generally beneficial effects observed on systemic parameters such as glucose homeostasis, insulin sensitivity, and systemic inflammation [42]. Moreover, FGF21 is involved in the adaptive responses to prolonged fasting and ketogenic diets, which include enhanced insulin sensitivity and cognitive effects [43–45]. FGF21 is therefore viewed as a key integrator of a diverse range of physiological responses to states of energy restriction, many of which underlie desirable alterations in metabolism that confer resistance to clinical manifestations of the metabolic syndrome.

While the centrality of FGF21 as a factor underlying physiological adaptations to challenges in whole-body energy status has been widely recognized, appreciation of the role of FGF21 as an important mediator of many of the beneficial effects of increased activity of BAT thermogenesis has only recently emerged. This is particularly relevant in terms of cardiac function since the discovery that the heart both produces FGF21 in cardiomyocytes and is in turn stimulated by FGF21 derived from distant tissues; therefore FGF21 exerts endocrine, paracrine, and intracrine effects on the cardiovascular system in a complex system of inter-organ crosstalk [46–51]. As early as 2013, transgenic mice studies demonstrated that FGF21 KO mice suffered maladaptive cardiac hypertrophy and dilatation in response to isoproterenol challenge and that the maladaptive responses were reversed by treatment with exogenous FGF21 [51]. More recent studies indicate that BAT is a source of FGF21 [40] and that FGF21 derived specifically from BAT exerts a protective effect on the heart by acting as a preventative against deleterious cardiac remodeling in response to hypertension in mice [41]. Experiments from this study revealed a crucial role for FGF21 from

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interscapular BAT in attenuating hypertensive cardiac remodeling which was intertwined with BAT adenosine A_{2A} receptor signaling, which was obligatory in mediating FGF21 protection against pathological hypertensive cardiac remodeling. Moreover, this study showed that the beneficial cardiac effects of BAT-derived FGF21 were dependent on AMPK/PGC1α pathway activation which was necessary for induction of FGF21 secretion from iBAT. The conclusions of this study were consolidated by the finding that administration of recombinant FGF21 in iBAT depleted mice improved cardiac remodeling and that intact BAT-specific A_{2A} receptor signaling was required to diminish cardiac damage in hypertensive mice [41]. Importantly, BAT-derived FGF21 has also recently been demonstrated as a cardioprotective factor in C57BL/6J mice subjected to myocardial ischemia/reperfusion injury (I/R), which is a major causative factor in myocardial damage resulting from infarction [52]. Data from a study by Ding et. al. provided evidence from in vitro experiments that the protective effect of BAT-derived FGF21 in the context of dexmedetomidine administration was modulated by the Keap/Nrf2 pathway, whereby FGF21 stimulation of Nrf2 signalling attenuated the oxidative stress and inflammation typically observed in myocardial I/R injury [53].

Year	First Author	Citation	FGF21 Effects on Cardiac Function (Systemic or Direct)	Model
2010	Hondares	39	↑Hepatic FGF21 expression, ↑thermogenic activation of neonatal brown fat	Neonatal mice
2011	Hondares	40	↑ FGF21 expression and release in BAT, ↑ systemic protective effects	Mice
2018	Ruan	41	↑BAT-derived FGF21 protects against maladaptive cardiac remodeling in hypertension	Mice with induced hypertension
2016	Fisher	42	↑ Glucose homeostasis ↑ insulin sensitivity, ↓ Systemic inflammation	General Physiological studies
2013	Bookout	43	↑ Adaptive responses to fasting, ↑ Insulin sensitivity, ↑ Cognitive effects	General studies on fasting and metabolism
2014	Laeger	44	↑ FGF21 signaling during protein restriction, ↑ endocrine adaptation to dietary changes	Mice and rats on low-protein diets
2024	Khan	45	↑ FGF21-driven metabolic adaptations, ↑ behavioral motivation changes in response to diets	Mice; Studies on brain reward signaling and dietary preferences
2013	Planavilla	51	↓ Maladaptive cardiac hypertrophy and dilatation in FGF21 KO mice, reversal with exogenous FGF21	FGF21 KO Mice subjected to isoproterenol-induced cardiac stress

2.2. NRG4

Neuregulin 4 (NRG4), a lesser-known but emerging batokine secreted by brown adipose tissue (BAT), has received significant attention for its key role in cardioprotection through its multifaceted involvement in energy metabolism and homeostasis [54]. Initially detected in the pancreas [55], NRG4 belongs to the epidermal growth factor family and preferentially binds to the receptor tyrosine kinase ErbB4, predominantly expressed in adipose tissue [56]. Recent studies point to NRG4's potential cardioprotective properties, indicating its crucial role in mitigating the adverse impacts of obesity, insulin resistance, and metabolic dysfunction on heart health [57]. Insulin resistance, defined

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by disrupted insulin-mediated glucose metabolism, is recognized as an early indicator of cardiovascular disease [58]. Strong evidence supports the role of BAT in alleviating insulin resistance [59], with NRG4 playing a pivotal role in enhancing glucose metabolism and reducing inflammation in metabolic tissues [54]. Hyperinsulinemic-euglycemic clamp studies have demonstrated that NRG4 increases glucose metabolism in peripheral tissues, significantly improving systemic insulin sensitivity [60]. Furthermore, NRG4 reduces chronic inflammation in white adipose tissue by decreasing macrophage accumulation in high-fat diet-induced obese mice, further supporting its role in improving metabolic health [61].

Obesity significantly contributes to cardiovascular disease risk by dysregulating lipid metabolism, leading to the ectopic accumulation of lipids in various tissues and promoting cardiovascular complications [62,63]. Cai et al. demonstrate that mRNA expression of NRG4 is reduced in adipose tissue in human models of obesity [64], while Chen et al. observe similar findings in mouse models [60]. Activating NRG4 in adipocytes has been shown to enhance adipose tissue angiogenesis, suggesting a pro-angiogenic role for NRG4 [65]. Furthermore, overexpressing NRG4 through hydrodynamic gene delivery significantly reduces diet-induced obesity in mice [61], demonstrating NRG4's therapeutic potential and contribution to cardiovascular disease reduction.

NRG4's role in metabolic regulation forms the foundation of its external cardioprotective effects; however, it also exerts a direct, internal cardioprotective influence. In vivo and in vitro studies have revealed its ability to restore cardiac function and attenuate pathological remodeling [66]. Specifically, in an isoproterenol-induced cardiac remodeling model, Nrg4 treatment was shown to significantly restore cardiac function, mitigate pathological hypertrophy, and suppress myocardial fibrosis [66]. These therapeutic effects were mechanistically linked to its modulation of inflammatory responses and apoptosis via activation of the AMPK/NF-κB signaling pathway [66]. The AMPK/NF-κB pathway primarily suppresses inflammation and apoptosis, thereby preventing tissue damage and reducing pathological remodeling of cardiac tissue [66]. Complementary to this, the AMPK/Nrf2 pathway plays a pivotal role in regulating oxidative stress and ferroptosis by enhancing antioxidant defenses [67]. In a diabetic myocardial injury model, NRG4 alleviated high-glucose-induced ferroptosis in cardiomyocytes by activating the AMPK/Nrf2 signaling pathway [67]. Notably, inhibition of this pathway diminished NRG4's beneficial effects, emphasizing the importance of AMPK signaling in cardiovascular protection. Both AMPK-mediated pathways have been linked to the amelioration of cardiovascular disease.

At the vascular level, NRG4 has been shown to prevent endothelial dysfunction and vascular inflammation [68]. In a mouse model, BAT-specific Nrg4 deficiency exacerbated atherosclerosis, whereas restoring Nrg4 levels reversed these effects, demonstrating its crucial role in maintaining vascular health [68]. Beyond experimental models, clinical studies have identified profound serum NRG4 levels as a promising biomarker for cardiovascular protection [69]. Lower serum NRG4 has been associated with early detection of vascular abnormalities, such as increased carotid intima-media thickness and atherosclerotic plaque, particularly in individuals at high risk of subclinical cardiovascular disease [69,70]. Reduced NRG4 levels have also been observed in patients with coronary artery disease [71]. In line with these findings, a recent Mendelian randomization study found that elevated serum NRG4 plays a protective role in atherosclerosis, mediating lowered LDL-C levels linked to a reduced risk of peripheral atherosclerosis [72]. By enhancing insulin sensitivity, regulating lipid metabolism, and protecting against cardiac remodeling, NRG4 represents a promising therapeutic target in addressing heart disease, particularly in populations affected by obesity and type 2 diabetes [57,73]. While NRG4 has demonstrated cardioprotective effects, its exact role in the cardiovascular system is not yet fully understood, and further investigation is needed to uncover its complete potential.

Year	First Author	Citation	NRG4 Cardioprotective Outcomes (Systemic or Direct)	Model

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2017	Chen	[52]	↑Energy expenditure, ↑Whole-body glucose metabolism, ↑β-oxidation, ↑Glycolysis, ↓Hepatic steatosis, ↓Inflammation (eWAT),	Nrg4 transgenic obese mice
2016	Ma	[53]	↓ Diet-induced weight gain, ↓ Inflammation, ↓ Macrophage infiltration, ↑BAT thermogenesis, ↑ Insulin sensitivity, ↓Hepatic steatosis, ↓Nrg4 mRNA (AT, pre-delivery)	Hydrodynamic gene delivery of Nrg4 in obese mice
2016	Cai	[56]	↓ Serum Nrg4, ↑MetS, ↑Blood glucose and BP	Human (obese)
2018	Nugroho	[57]	↑ Adipose tissue angiogenesis, ↑ WAT vasculature, ↑ Systemic metabolic health, ↓ Adipose hypoxia, ↓ Inflammation, ↑ Glucose homeostasis	Nrg4 transgenic obese mice
2024	Wei	[58]	↑ Cardiac function, ↓ Cardiac hypertrophy, ↓ Fibrosis, ↓ Cell apoptosis, ↓ Inflammatory factors, ↑ Cardioprotection via AMPK/NF-κB pathway	ISO-induced myocardial injury in mice
2024	Wang	[59]	↓ Myocardial injury, ↓Oxidative stress, ↓ Ferroptosis, ↑ AMPK/Nrf2 signaling, ↑ Cardiac function, ↓ Cardiac fibrosis, ↑ Mitochondrial integrity	Nrg4-Treated T1D Mice
2022	Shi	[60]	↓ Atherosclerosis, ↓ Vascular inflammation, ↓ Endothelial dysfunction, ↓ Leukocyte homing, ↓ Apoptosis, ↓ Inflammation	Humans and Mice
2016	Jiang	[62]	↓ Serum Nrg4 levels associated with ↑ CIMT and carotid plaque, ↑Nrg4 levels associated with ↓ BMI, ↓ Systolic BP, ↓ Total cholesterol	Human (Obese with CIMT and carotid plaque)
2023	Taheri	[63]	↓Nrg4 levels in CAD, ↑BMI, ↑Waist circumference ↑Fasting blood glucose, ↑Triglyceride-glucose index	Human (CAD)
2014	Zheng	[64]	↓Athereosclerosis, ↓LDL-C levels ↓Peripheral atherosclerosis	Human

2.3. 12,13-diHOME

In 2008, Cao and colleagues identified a novel lipid hormone connecting adipose tissue to organism-wide metabolism; these investigators termed this newly discovered hormone “lipokine” [74]. Recent experiments have provided evidence that a novel lipokine secreted from BAT, 12,13-diHOME (12, 13-dihydroxy 9Z-octadecenoic acid), exerts beneficial cardiac effects [75,76]. Interestingly, 12,13-diHOME is increased independently of ambient temperature by a single bout of exercise in humans and mice, with evidence demonstrating that the tissue source of 12, 13-diHOME is BAT, as shown by surgical ablation of interscapular BAT negating the exercise-induced increase in 12,13-diHOME [77]. These experiments revealed the mechanistic insight that 12,13-diHOME increases skeletal muscle fatty acid uptake and oxidation via induction of genes involved in fatty acid transport and mitochondrial activity and biogenesis. Other experiments demonstrate that 12,13-diHOME treatment increases mobilization of fatty acid transporters CD36 and FATP1 to the membrane in mature brown adipocytes, thereby increasing uptake of fatty acids and setting the stage for increased fat oxidation [75].Given that exercise is an indispensable cardioprotective modality, the close linkage between exercise and lipokine secretion from BAT indicates that 12,13-diHOME can be thought of as an “exerkine,” a term referring to humoral factors induced by exercise that confer pleiotropic metabolic benefits [78–80].

From the perspective of specific cardioprotection, 12, 13-diHOME has been shown in mice to favorably modulate cardiac function directly via increasing mitochondrial respiration, induction of nitric oxide synthase 1 (NOS1), and increasing cardiomyocyte contractility by NOS1-dependent

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activation of the ryanodine receptor [76]. These findings were consistent with previous data demonstrating that NOS1 modulation of cardiac contractile function is mediated by calcium cycling via interation with the ryanodine receptor [81,82]. Moreover, this study provided evidence that 12,13-diHOME is positively correlated with ejection fraction in human patients with heart disease [76]. While previous studies have indicated that 12,13-diHOME could be deleterious to cardiac health, the applicability of these results are vitiated by methodological issues, including the use of ex vivo models and high concentrations of 12,13-diHOME that are toxic to cardiomyocytes [76,83–85]. A retrospective study undertaken by Cao and colleagues on T2DM patients with and without acute myocardial infarction (AMI) employed untargeted metabolomics and subsequent validation with ELISA to demonstrate that 12,13-diHOME was elevated in T2DM patients with AMI compared to those who did not suffer AMI [86]. However, this study is retrospective and correlational therefore it is difficult to impute a causal role for 12,13-diHOME in AMI from these data alone [86].

Further evidence of beneficial effects of 12,13-diHOME on cardiovascular function was shown in experiments demonstrating a linkage between insulin signaling and differentiation of perivascular progenitor cells (PPCs) into BAT, with conseqential increases in BAT mass and 12,13-diHOME secretion which in turn reduced inflammation and atherosclerosis in mice [87]. These experiments indicated that inhibition of eNOS by L-NAME resulted in a failure of PPCs to differentiate into beige/brown adipocytes and abrogation of weight loss and beneficial effects on bioenergetics which were reversed by infusion of 12,13-diHOME, which improved endothelial function and decreased atherosclerosis [87]. These recent results in preclinical studies are encouraging; however, future research in humans with and without diagnosed CVD are needed to more throughly understand the effects of 12,13-diHOME on cardiovascular function.

Year	First Author	Citation	12,13-diHOME Cardioprotective Outcomes (Systemic or Direct)	Model
2017	Lynes	75	↑BAT activity, ↑Fat oxidation, ↑Cold tolerance ↓Serum triglycerides, ↑fatty acid uptake, ↑lipid metabolism	Human and Mouse
2021	Pinckard	76	↑Mitochondrial respiration, ↓Cardiac remodeling, ↑NOS1 activity, ↑Cardiomyocyte contractility, ↑Systolic function, ↑Diastolic function, ↓12,13-diHOME in heart disease, ↑Glucose tolerance, ↑Fatty acid uptake, ↑Ejection fraction	Human and Mouse
2018	Stanford	77	↑Baseline 12,13-diHOME in active individuals, ↑Circulating 12,13-diHOME post-exercise, ↑Fatty acid uptake, ↓RER, ↑Mitochondrial respiration, ↑Fatty acid oxidation	Human and Mouse
2007	Gonzales	81	NOS1 deficiency → ↓RyR2 S-nitrosylation, ↑SR Ca^{2+} leak, ↓SR Ca^{2+} content, ↑ventricular arrhythmias, ↑sudden cardiac death	Mouse
2022	Park	87	↑BAT mass, ↑12,13-diHOME secretion, ↓Inflammation, ↓Atherosclerosis, ↑Endothelial function, ↑Insulin signaling, ↑ Thermogenesis	Mouse

2.4. BAT-Derived miRNA Affects Cardiac Function

Small extracellular vesicles (sEVs) are secreted from various tissues upon exposure to physiological and pathological stimuli, whereupon they enter the circulatory system and constitute an important biological mechanism by which diverse organ systems communicate with one another [88,89]. Also known as exosomes, sEVs have become acknowledged as playing a major role in regulating inter-organ crosstalk in an expanding literature in which experimental evidence in numerous paradigms indicate that sEVs are obligatory in mediating the beneficial effects of

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interventions such as exercise [88–92]. As our understanding of the pleiotropic benefits of BAT activation expands, it is notable that sEVs are emerging as key mechanistic players mediating the beneficial effects of BAT. This section of the review will summarize the latest findings providing evidence for a specific role of BAT-derived sEVs in cardioprotection, which is a relatively new field of exploration that offers great potential in unraveling the mechanisms by which BAT can communicate not only with the heart but with other distant organs as well.

A seminal set of experiments performed by Zhao and colleagues revealed that a subset of sEVs from BAT exerted potent direct cardioprotective effects of exercise in a model of myocardial infarction/reperfusion (MI/R) injury in mice [91]. Specifically, the findings of these experiments demonstrated that a particular set of miRNAs contained in the sEVs from BAT (miR-125b-5p, miR128-3p, and miR30d-5p) favorably modulated the heart's response to MI/R injury via suppression of the proapoptotic MAPK pathway [91], thereby promoting cardiomyocyte survival. Mechanistic insights from this study from in vivo proof of concept experiments and detailed investigation from in vitro studies interrogated the mechanisms by which the miRNA cargo of the BAT conferred exercise -induced cardioprotection. The data from these experiments revealed that the main biological mechanism by which sEVs from BAT advantageously modulated cardiac response to MI/R injury were by inhibition of several genes in the proapoptotic MAPK and caspase pathways, including Map3k5, Map2k7, and Map2k4. The conclusions of the study were consolidated by data indicating that direct delivery of BAT sEVs into hearts or cardiomyocytes inhibited MAPK pathway activation and that this protective effect was abolished by BAT miRNA inhibitors [91]. Collectively, the results of these in vitro and in vivo experiments revealed a novel pathway by which the cardiovascular benefits of aerobic exercise are mediated by activation of the BAT secretome, specifically miRNAs encapsulated by sEVs.

The effect of miRNAs on heart function remains complex and is an emerging field of study. A particular miRNA, miR-92a, has been investigated and reveals a complicated relationship with BAT and cardiac function which has yet to be fully unraveled. The circulating levels of miR-92a are negatively correlated with BAT activity in humans; however, currently it is not possible to definitively conclude whether or not miR-92a is an independent causal factor in cardiac pathology [93–96]. Chen and colleagues, for example, demonstrated that miR-92a abundance in exosomes was markedly decreased in both humans and mice in conditions with high BAT abundance or activity, such as in mice subjected to cold exposure or cAMP treatment, both of which are known to activate BAT [96]. Plasma miR-92a levels were also shown to be elevated in patients with diabetes with comcomitant increased expression of the inflammatory factors NF-κB, MCP-1, ICAM-1, and endothelin-1 [97]. Another study indicated that in a porcine experimental model inhibition of miR-92a resulted in protection against MI/R injury, with improved ejection fraction, left ventricular end-diastolic pressure, and reduced infarct zone size [94].

While the previously cited studies implicate miR-92a in myocardial damage, drawing definitive conclusions is complicated by a recent study showing that overexpression of miR-92a-5p attenuated myocardial damage in rats with induced diabetic cardiomyopathy [93]. In these rats, the principal mechanism which conferred cardioprotection was reduction in oxidative stress injury, with reduced apoptosis levels, increased glutathione, reduced malondialdehyde accumulation, and inhibition of MKNK2 expression which in turn reduced activation of p38MAPK signaling [93]. Taken together, the divergent results of these studies might indicate that a physiological secretion of miR-92a from activated BAT could be cardioprotective, while in a different context this miRNA could be damaging to the heart. Any conclusions currently remain speculative until more detailed mechanistic experiments can be performed that can clarify the biological conditions under which miR-92a acts beneficially versus adversely.

Year	First Author	Citation	MiRNA Cardioprotective Outcomes	Model

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2022	Yu	93	↑MiR-92a results: ↑Glutathione level, ↓myocardial oxidative stress, ↓ROS, ↓malondialdehyde, ↓apoptosis, ↓MAPK signaling	Rats
2022	Zhao	91	↑MiR-125a-5p, miR-128-3p, miR-30d-5p results: ↑Protection against MI/R injury, ↓signaling of TRAF3, TRAF6, TNFRSF1B, BAK1, ↓activation of caspases, MAPK pathway, ↓apoptosis	Mice

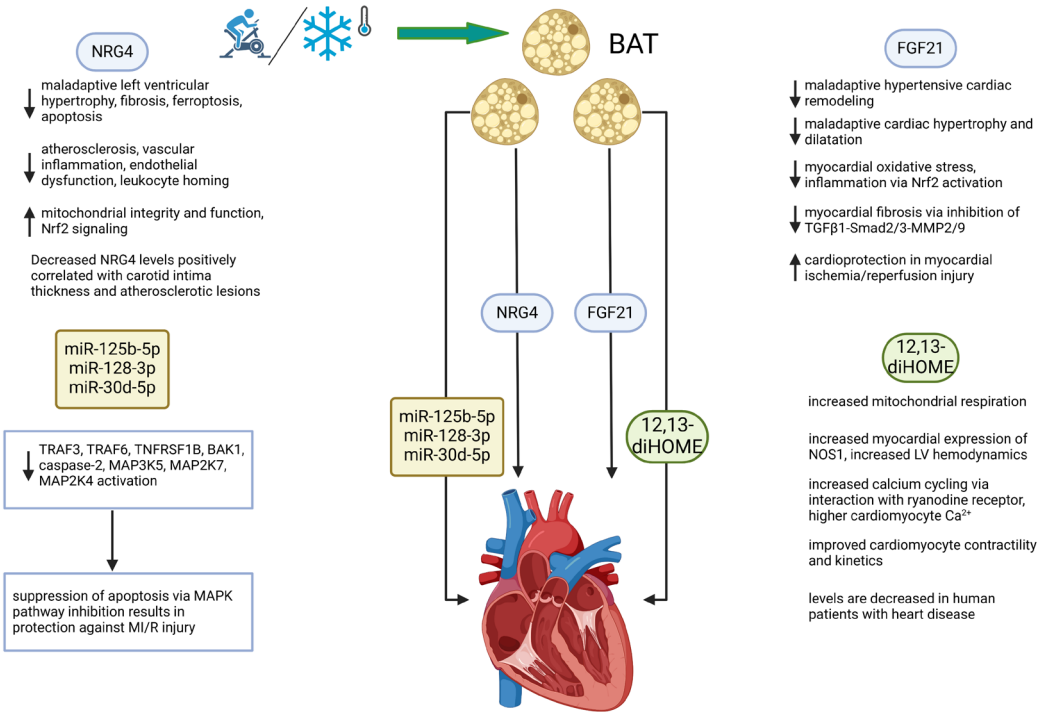

Figure 2. BAT directly and favorably modifies cardiac function through the secretion of batokines. The BAT secretome operates through at least four types of secreted molecules. These include the proteins FGF21 and NRG4, the lipokine 12,13-diHOME, and a set of miRNAs. Mechanisms of action include those that are indicated under the 4 factors diagrammed. Stimuli that activate BAT include exercise and cold exposure, both of which operate systemically and by direct targeting of multiple organ systems. See list of abbreviations for definitions of abbreviations used in the diagram. Created in BioRender.

3. Conclusions and Future Directions

The discovery of functional BAT in humans entailed a profound shift in our understanding of adipose tissue in general as a multifunctional tissue serving not only to store energy substrate but as a thermogenic organ with endocrine, paracrine, and autocrine effects that play key roles mediating interorgan metabolic communication [15,98–104]. BAT has been shown over the last decade to act not solely as a thermogenic organ but as an endocrine organ with pleiotropic effects in distant tissues that appear to be almost uniformly beneficial in all model systems studied thus far [38]. The mechanisms by which BAT communicates with distant tissues include proteins, lipokines, and exosomes carrying a cargo of miRNAs that alter the metabolic functions of various organs, which, notably, includes the heart [104].

This review has focused on elements of the BAT secretome which have been shown to affect the heart, specifically FGF21, neuregulin-4, 12,13-diHOME, and exosomes encapsulating miRNAs that exert cardiac effects. Given that CVD continues to be the primary cause of death globally, the urgency of discovering new preventative and therapeutic modalities for CVD is readily apparent [105]. BAT has received relatively little attention compared to other tissues with endocrine function in terms of

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its relevance as a cardioprotective organ and it is notable that BAT is activated by exercise, an intervention with irrefutable beneficial effects on the cardiovascular system [102–104]. The recognition of BAT as an endocrine organ has stimulated recent investigation into its potential in promoting heart health and the mechanisms by which BAT modulates cardiovascular function are only beginning to be elucidated. The data summarized in this review offer new mechanistic insights into how BAT affects the heart.

BAT modulates cardiovascular function systemically by increasing EE and thereby acting in opposition to the development of obesity and clearing lipids from the circulation, which are two mechanisms by which ectopic lipid accumulation can be abrogated or at least minimized. However, the data from studies summarized in this review provides evidence of a direct line of communication between BAT and the heart, with various beneficial direct effects on the heart specifically and the cardiovascular system more generally. FGF21 specifically of BAT origin protects the heart from maladaptive remodeling in hypertension, myocardial ischemia/reperfusion injury and acute myocardial infarction [41,51–53]. NRG4 has been shown to decrease cardiac fibrosis, apoptosis, ferroptosis, oxidative stress, and atherosclerosis, while also inducing protective adaptations including increased mitochondrial function and enhancement of anti-inflammatory activity via Nrf2 signaling [66,70,72,106,107]. 12,13-diHOME, a novel lipokine of the oxylipin class, exerts beneficial cardiovascular effects via enhanced calcium cycling with consequent improvements in systolic and diastolic function, with concomitant augmentation of cardiomyocyte shortening and kinetics [76,87]. MiRNA contained in small extracellular vesicles also has been shown to favorably modulate cardiac function. Specifically, miR-125b, miR-128-3p, and miR-30d-5p exhibited cardioprotective effects by inhibition of apoptosis in MI/R injury via suppression of the pro-apoptotic MAPK pathway [91]. While findings are divergent in terms of the effects of miR-92a on the cardiovascular system **[93–95,97**], one study found that in rats subjected to MI/R injury, overexpression of miR-92a resulted in improved systolic function and reduction of infarct size [93].

Future research should include both females and males in rodent studies to clarify whether there are sex-specific differences in circulating batokines and responsiveness to batokines in a diverse range of tissues, including the heart [104]. It is reasonable to hypothesize that sexually dimorphic patterns of batokine activity might exist in humans, considering the evidence that young lean women have a higher percentage of BAT than age-matched young, lean men [108]. It is an exciting time to study BAT and its effects on cardiometabolic health; many questions remain surrounding the exact interventions utilizing expansion of BAT mass and batokine levels/activity and the techniques available to disentangle the complex interactions between BAT and other organ systems are robustly suited to the task. Exercise and intermittent cold exposure are physiological means by which BAT mass can be expanded and it is reasonable to infer that expansion of BAT would lead to consequent increases in batokines. Modalities such as pharmacological adrenergic stimulation and direct exogenous delivery of BAT derived secretory factors merit further exploration, although the risk of side effects and dosing issues must be carefully considered.

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Abbreviations

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12,13-diHOME	12,13-dihydroxy 9Z-octadecenoic acid
AMI	acute myocardial infarction
AMPK	adenosine 5′-monophosphate (AMP)-activated protein kinase
$A_{2A}R$	adenosine 2a receptor
BAT	brown adipose tissue
Batokines	brown adipose tissue adipokine
CAD	coronary artery disease
CD36	cluster of differentiation 36
CIMT	carotid intima media thickness
CVD	cardiovascular disease
EE	energy expenditure
eWAT	epididymal white adipose tissue
FATP1	fatty acid transport protein 1
FGF21	fibroblast growth factor 21
iBAT	interscapular brown adipose tissue
ICAM-1	intercellular adhesion molecule 1
L-NAME	N(ω)-nitr-L-arginine methyl ester
MetS	metabolic syndrome
MiR	micro-RNA
MI/R	myocardial ischemia/reperfusion
MKNK2	MAP kinase-interacting serine/threonine-protein kinase 2
NF-κB	nuclear factor kappa B
NOS	nitric oxide synthase
eNOS	endothelial nitric oxide synthase
iNOS	inducible nitric oxide synthase
MAPK	mitogen-activated protein kinase
MCP-1	monocyte chemotactic protein 1
Nrf2	nuclear factor erythroid 2-related factor
NRG4	neuregulin 4
PPC	perivascular progenitor cell
PPAR-γ	peroxisome proliferator activated receptor-gamma
ROS	reactive oxygen species
RyR	ryanodine receptor
sEV	small extracellular vesicle
SR	sarcoplasmic reticulum
TG	triacylglycerol
TNF-α	tumor necrosis factor-alpha
TNFRSF	tumor necrosis factor super family
TRAF	tumor necrosis factor receptor-associated factor
WAT	white adipose tissue

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