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REVIEW

Cardiomyokines from the heart

Ayano Chiba[1] · Haruko Watanabe-Takano[1] · Takahiro Miyazaki[1] · Naoki Mochizuki[1,2]

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Abstract
The heart is regarded as an endocrine organ as well as a pump for circulation, since atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) were discovered in cardiomyocytes to be secreted as hormones. Both ANP and BNP bind to their receptors expressed on remote organs, such as kidneys and blood vessels; therefore, the heart controls the circulation by pumping blood and by secreting endocrine peptides. Cardiomyocytes secrete other peptides besides natriuretic peptides. Although most of such cardiomyocyte-derived peptides act on the heart in autocrine/paracrine fashions, several peptides target remote organs. In this review, to overview current knowledge of endocrine properties of the heart, we focus on cardiomyocyte-derived peptides (cardiomyokines) that act on the remote organs as well as the heart. Cardiomyokines act on remote organs to regulate cardiovascular homeostasis, systemic metabolism, and inflammation. Therefore, through its endocrine function, the heart can maintain physiological conditions and prevent organ damage under pathological conditions.

Keywords $sPLA_2$ · FSTL1 · ET1 · CHGA · FGF21

Introduction

The heart functions not only as an essential pump but also as an endocrine organ to maintain homeostasis of the circulatory system [1]. The discovery of atrial natriuretic peptide (ANP) indicates the heart as an endocrine organ. In the middle of 20th century, researchers who used electron microscopes observed granules in atrial cardiomyocytes that resembled those found in endocrine glands. These observations let them consider the possibility that atrial cardiomyocytes might function as hormone-secreting cells [2]. In 1981, de Bold et al. demonstrated endocrine properties of the heart [3]. The extract of rat atrial cardiomyocytes contained peptides that exerted potent natriuretic and diuretic effects when it was injected in rats. The peptide was identified by several groups and named ANP or atrial natriuretic factor (ANF) [4–7]. The identification of ANP acting on kidneys revealed that the heart functioned as an endocrine organ. After the discovery of ANP, structurally and functionally related peptides including brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) were identified [8, 9]. These peptides are referred to as the natriuretic peptide (NP) family.

Cardiomyocytes also secrete other peptide hormones besides natriuretic peptides (NPs) through secretory granules [10]. In addition to peptides, lipids and genetic materials including mRNAs, DNAs, and non-coding RNAs are secreted from cardiomyocytes through extracellular vesicles [11]. The word 'cardiokine' is used to describe proteins secreted from cardiomyocytes, cardiac fibroblasts, endothelial cells, and smooth muscle cells in response to changes in the cardiac environment [10, 12]. Particularly, proteins secreted from cardiomyocytes are referred to as 'cardiomyokines' [13]. Therefore, ANP and BNP are considered to belong to cardiomyokines. Cardiomyokines are predicted to play physiological and pathological roles in the heart and remote organs. Although most of cardiomyokines act on the heart in autocrine or paracrine fashions, some of them exert endocrine actions (Fig. 1). In this review, by focusing on the regulation and function of cardiomyokines, we overview the current knowledge of the heart as an endocrine organ.

✉ Naoki Mochizuki
nmochizu@ri.ncvc.go.jp

[1] Department of Cell Biology, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

[2] AMED-CREST, National Cerebral and Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan

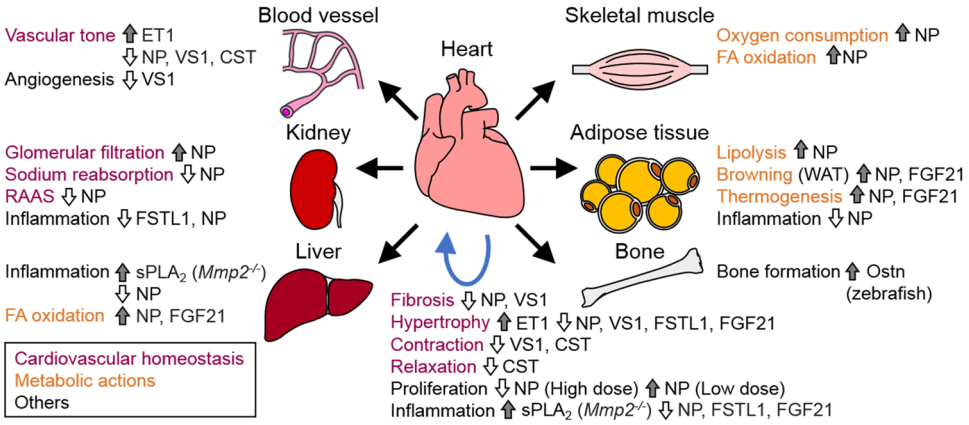

Fig. 1 Target organs of cardiomyokines. Cardiomyokines act on blood vessels, kidney, liver, skeletal muscle, and adipose tissue. Cardiomyocyte-derived osteocrin (Ostn) might act on bone in zebrafish. Cardiokines exert biological functions (cardiovascular homeostasis and metabolic actions) in an endocrine manner (black arrows) and in an autocrine/paracrine manner (blue arrow). *CST* catestatin, *ET1* endothelin 1, *FA* fatty acid, *FGF21* fibroblast growth factor 21, *FSTL1* follistatin-like 1, *Mmp2* matrix metalloproteinase 2, *NP* natriuretic peptide, *sPLA*$_2$ secreted phospholipase A$_2$, *RAAS* renin angiotensin aldosterone system, *VS1* vasostatin 1, *WAT* white adipose tissue

Natriuretic peptides

Natriuretic peptides are mainly secreted from the cardiovascular system. Although they are primarily known as natriuretic, diuretic, and vasodilator factors, NPs also possess metabolic activities [14]. ANP is the first cardiac endocrine factor identified in rat hearts [4, 5] and human atrial tissues [6]. Following the discovery of ANP, BNP was identified in the brain [8]. Although isolated from the porcine brain, BNP is mainly produced in the heart [15]. Because ANP and BNP are expressed predominantly in the heart, they are called cardiac NPs [1]. CNP was identified as the third NP from the porcine brain [9]. CNP is mainly expressed in vascular endothelial cells [16] and the central nervous system [17, 18]. CNP acts locally as an autocrine/paracrine factor [19].

NP receptors and signal transduction

NP receptor family consists of NP receptor 1 (NPR1), NPR2, and NPR3 [20–23]. Because NPR1 and NPR2 have guanylate cyclase (GC) domain in their cytoplasmic domain, upon binding to those receptors, NPs increase intracellular cyclic guanosine monophosphate (cGMP) and subsequently activate cGMP-dependent protein kinase (PKG). On the other hand, NPR3 does not induce intracellular cGMP accumulation, because it lacks the GC domain and instead has a short 37-amino acid cytoplasmic domain. NPR3 acts as a clearance receptor for NPs by binding to all NPs. It is still controversial whether NPR3 triggers the intracellular signaling via $G_{i/o}$ proteins [24]. NPs have 17-amino acid ring structure formed by a disulfide cysteine bridge between two cysteine residues that is necessary for binding to NPR1 and NPR2 [1]. Both ANP and BNP preferentially bind to NPR1, while CNP binds to NPR2 [25]. All the NPs bind to NPR3. Binding affinities are ranked as follows; NPR1 = ANP > BNP ≫ CNP; NPR2 = CNP ≫ ANP > BNP; NPR3 = ANP > CNP > BNP [26].

Secretion of ANP

Cardiomyocytes store ANP in secretory granules. ANP is secreted through the classical secretory pathway, a secretory pathway dependent on the endoplasmic reticulum (ER), coat protein complex II-coated vesicles, and the Golgi apparatus [10, 27]. ANP is secreted in a basal manner as well as inductive manners, such as agonist-stimulated and stretch-stimulated manners [1]. ANP secretion is induced by the stimulation of agonists including endothelin1 (ET1) and alpha adrenergic agents [28, 29]. Agonist-stimulated ANP secretion is mediated through the activation of G_q proteins [30]. Mechanical stretch also promotes the release of ANP from cardiomyocytes [31]. Although the mechanisms how stretch stimulation exerts secretion of cardiac granules have not been fully clarified yet, the secretion is mediated through pertussis toxin-sensitive $G_{i/o}$ proteins [30]. Stretch-sensitive ion channels function as mechanosensors in cardiomyocytes [32, 33]. Stretch-activated non-selective cation channels and swelling-activated Cl^- channels contribute to stretch-activated ANP secretion [32, 34].

ANP secretion from cardiomyocytes is increased under pathological conditions, such as ventricular hypertrophy, hypertension, heart failure, and myocardial infarction (MI) [35–38]. In these conditions, myocardial stretch and hypoxia induce ANP secretion. Hypoxic conditions stabilize hypoxia inducible factor 1 alpha (HIF1A). HIF1A promotes ANP transcription in neonatal rat cardiomyocytes [39]. In addition, cardiomyocytes in hypoxic conditions develop intracellular acidosis. The intracellular H^+ increment increases intracellular Na^+ and Ca^{2+} via H^+–Na^+ and Na^+–Ca^{2+} exchange [40], which is also observed in hyperosmolar conditions. The resulting ion imbalance results in an increase of ANP secretion [41, 42].

Secretion of BNP

ANP and BNP are co-stored in the same secretory granules in cardiomyocytes [43]. They are co-released from cardiomyocytes, suggesting common mechanisms for the secretion of ANP and BNP [44]. On the other hand, in physiological conditions, plasma BNP is much lower than plasma ANP. Thus, separate NP-specific mechanisms of secretion and synthesis must be present. Plasma BNP reflects the severity of the pathological conditions [45]. Specific cytokines that are increased in pathological conditions including tumor necrosis factor alpha (TNFα) and interleukin 1 beta (IL1β) selectively promote BNP expression through a p38 mitogen-activated protein kinase-dependent (p38MAPK-dependent) pathway [46]. Moreover, BNP synthesis and secretion might be regulated by ER stress. ER stress under pathological conditions induces the secretion of various cardiomyokines from cardiomyocytes. ER stress promotes the expression of transcription factors, such as activating transcription factor 4 (ATF4), ATF6, and X-box binding protein 1 (XBP1), thereby inducing the expression of the genes involved in protein folding and secretion as well as the genes encoding cardiomyokines [10, 47–49]. In failing human hearts, the expression of active XBP1 and BNP is increased. In cultured neonatal rat cardiomyocytes, pharmacological ER stress induces BNP expression through an XBP1-dependent pathway [50].

NPs inhibit cardiac hypertrophy in autocrine/paracrine fashions

ANP inhibits hypertrophy in cultured neonatal rat cardiomyocytes [51]. NPR1-deficient ($Npr1^{-/-}$) mice show cardiac hypertrophy as well as systemic hypertension [52]. Moreover, although cardiac-specific $Npr1^{-/-}$ mice show cardiac hypertrophy, the blood pressure of these $Npr1^{-/-}$ mice is slightly below wild type. These data suggest that NPs directly inhibit cardiac hypertrophy [53].

NPs also inhibit cardiac inflammation. Pro-inflammatory cytokines are associated with the development of cardiac hypertrophy. Expression of pro-inflammatory cytokines is increased in the $Npr1^{-/-}$ mouse hearts, while it is decreased in the NPR1 gene-duplicated mouse hearts [54]. The NPR1-dependent signaling pathway suppresses the expression of pro-inflammatory cytokines through the inhibition of the transcription mediated by nuclear factor kappa B (NFκB) and activator protein 1 [54].

NPs regulate cardiomyocyte proliferation in autocrine/paracrine fashions

Natriuretic peptides show an anti-proliferative effect on cardiomyocytes. ANP suppresses angiotensin II-stimulated (ANGII-stimulated) proliferation of cultured fetal sheep cardiomyocytes through a cGMP-dependent pathway [55]. On the other hand, there are controversial reports demonstrating that NPs promote cardiomyocyte proliferation probably through an NPR3/$G_{i/o}$ protein-mediated signaling pathway. In developing zebrafish, cardiomyocyte proliferation is increased by simultaneous knockdown of *npr1* and *npr2*, whereas it is decreased by knockdown of *npr3*. In cultured neonatal rat cardiomyocytes, a low concentration (10 nM) of ANP triggers an NPR3-dependent pathway to promote cardiomyocyte proliferation, while a high concentration (10 μM) of ANP induces NPR1- and NPR2-dependent pathways to inhibit cardiomyocyte proliferation [56].

NPs inhibit cardiac fibrosis in paracrine fashions

Natriuretic peptides inhibit proliferation of cardiac fibroblasts and their collagen syntheses in a cGMP-dependent manner [57, 58]. The endogenous ANP released from cultured cardiomyocytes inhibits collagen synthesis in cardiac fibroblasts [59]. Consistently, both $Npr1^{-/-}$ mice and BNP-deficient ($Nppb^{-/-}$) mice show more cardiac fibrosis than the control [52, 60]. Cardiac fibrosis is also regulated by the expression of matrix metalloproteinases (MMPs). The expression of MMP2 and MMP9 is increased in the $Npr1^{-/-}$ mouse hearts. The treatment of a MMP inhibitor reduces cardiac fibrosis in $Npr1^{-/-}$ mice [61]. These data suggest that ANP suppresses cardiac fibrosis by the inhibition of MMP expression.

NPs inhibit hypertension in endocrine fashions

When NPs are given to animals, NPs exert natriuretic and vasodilator effects, thereby decreasing intravascular volume and blood pressure. NPs reduce vascular tone through a relaxant effect on vascular smooth muscle cells [62]. NPs also reduce intravascular volume through a direct effect on endothelial permeability [63]. Furthermore, NPs

regulate blood pressure by counteracting the renin–angiotensin–aldosterone system, by reducing sympathetic tone, and by suppressing the secretion of ET1, a potent vasoconstrictor [35]. In the kidney, NPs regulate electrolyte and fluid balance by increasing glomerular filtration rate [64, 65] and by decreasing sodium reabsorption in the proximal tubes and the collecting duct [66, 67]. NPs reduce renin release, peritubular ANGII, and ANGII-dependent reuptake of sodium [64]. These mechanisms lead to natriuresis that was the origin used for the naming of these peptides.

NPs regulate metabolism in endocrine fashions

Natriuretic peptides directly act on adipose tissues, resulting in the inhibition of the proliferation of human primary adipocytes [68]. NPs induce the synthesis of free fatty acid (FFA) through promoting lipolysis in adipose tissues by NPR1/cGMP/PKG-mediated activation of hormone-sensitive lipase [69, 70]. Indeed, ANP infusion increases plasma FFA and glycerol in young men. These increments are independent of the activation of the sympathetic nervous system [71]. Moreover, exercise training improves ANP-induced lipolysis in human adipose tissues [72, 73].

NPs modulate thermogenesis. Adipose tissues consist of white adipose tissue (WAT) and brown adipose tissue (BAT). The former is the main fat reservoir, while the latter is another fat reservoir and is able to generate heat through mitochondria-uncoupled respiration. NPs induce a transition from WAT to BAT-like tissue. In both BAT and WAT, NPs increase the expression of thermogenic genes, such as peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC1α) and uncoupling protein 1 (UCP1). The expression of those genes by NPs in the adipocytes is mediated by an NPR1/cGMP/PKG/p38 MAPK and subsequent ATF2-dependent pathway [74]. These data suggest that NPs might increase energy expenditure through the regulation of lipolysis and thermogenesis. The heart needs a huge energy supply to maintain continuous beating. To this end, the adult heart mainly uses either FFA or glucose as its energy source to generate ATP. Under normal conditions, most of ATP is generated from mitochondrial oxidation of FFA [75]. NPs increase FFA availability and mitochondrial biogenesis. These effects might contribute to more efficient FFA oxidation in the heart [76].

NPs also regulate skeletal muscle oxidative capacity. Skeletal muscle in which either BNP or PKG is overexpressed in mice shows higher oxygen consumption, greater FFA oxidation, and higher expression of mitochondrial oxidative genes [77]. Interestingly, exercise training upregulates *NPR1* transcripts in human skeletal muscles [78]. Therefore, NP signaling may also contribute to exercise training-induced fat oxidation in skeletal muscle.

NPs control satiety

Natriuretic peptides might regulate the gastro-intestinal system through modulating satiety hormone levels. Ghrelin, a gut-derived hormone, increases appetite and energy balance [79–81]. Plasma ghrelin is decreased after an administration of somatostatin, a peptide produced in the gastric oxyntic mucosa [82]. ANP stimulates somatostatin secretion via NPR1 activation [83]. Considering these data, NPs might indirectly inhibit ghrelin secretion through somatostatin secretion. Indeed, intravenous BNP administration inhibits the fasting-induced increment of plasma ghrelin in healthy volunteers [82]. In addition, BNP decreases the subjective rating of hunger and increases the feeling of satiety [84]. These results support the existence of a mutual regulation mediated by peptide hormones between the heart and gut.

NPs suppress inflammation in an endocrine fashion

Natriuretic peptides exhibit anti-inflammatory actions. As nitric oxide (NO) produced in the activated macrophages is toxic for microorganisms [85], an excess of NO production can cause damage in neighboring tissues. ANP inhibits the lipopolysaccharide-induced expression of inducible nitric oxide synthase (iNOS) that is required for NO production in macrophages [86]. In addition, ANP stimulation inhibits the secretion of pro-inflammatory cytokines, chemokines, and adipokines from cultured human adipose tissues [87]. Similarly, BNP has protective effects on acute lung, kidney, and intestinal tissue injury by down-regulating the expression of pro-inflammatory cytokines, such as TNFα and IL6. These anti-inflammatory effects of NPs are mediated through the suppression of NFκB inhibitor (IκB) phosphorylation and NFκB expression [88–91]. Because the chronic low-grade inflammation state is a risk factor for cardiovascular and metabolic disease [87], those anti-inflammatory effects of NPs seem to be beneficial to suppress the onset of those diseases.

Secreted phospholipase A_2

Secreted phospholipase A_2 ($sPLA_2$) is a class of enzyme that catalyze *sn*-2 ester of glycerophospholipids to release FFAs and lysophospholipids. PLA_2 family consists of intracellular PLA_2 and $sPLA_2$ [92]. In mammals, there are 11 $sPLA_2$s (groups IB, IIA, IIC, IID, IIE, IIF, III, V, X, XIIA, and XIIB) [93].

Secretion of $sPLA_2$s

$sPLA_2$s are stored in secretory granules. $sPLA_2$s have distinct tissue distributions. Group V $sPLA_2$ (PLA2G5) is

expressed mainly in the heart [94]. Cardiomyocytes secrete $sPLA_2$s through the classical secretory pathway. The release of $sPLA_2$ from hearts is enhanced by the ex vivo incubation with pro-inflammatory C-C motif chemokine ligand 7 (CCL7). CCL7 binds to and is inactivated by MMP2. In MMP2-deficient ($Mmp2^{-/-}$) mice, the plasma $sPLA_2$ that is presumably released from cardiomyocytes is elevated [95, 96].

$sPLA_2$s induce inflammation in autocrine/paracrine fashions

Cardiomyocyte-derived $sPLA_2$s function as autocrine/paracrine factors. The elevation of cardiomyocyte-derived $sPLA_2$s in the $Mmp2^{-/-}$ mice induces cardiac inflammation. The expression of pro-inflammatory cytokines is increased in the $Mmp2^{-/-}$ mouse hearts. The pro-inflammatory cytokine expression induced in the $Mmp2^{-/-}$ mice is down-regulated by the knockdown of *Pla2g5* gene and the treatment of a pan-$sPLA_2$ inhibitor, respectively [95]. Therefore, cardiomyocyte-derived $sPLA_2$s induce cardiac inflammation.

$sPLA_2$s induce inflammation and metabolic dysregulation in endocrine fashions

In addition, cardiomyocyte-derived $sPLA_2$s work as endocrine factors. $sPLA_2$s derived from the $Mmp2^{-/-}$ mouse hearts induce hepatic inflammation and metabolic dysregulation. A pan-$sPLA_2$ inhibitor normalizes the expression of lipid metabolic genes and pro-inflammatory cytokines in the liver of $Mmp2^{-/-}$ mice [96]. Therefore, liver functions are regulated by cardiac $sPLA_2$s in $Mmp2^{-/-}$ mice.

Follistatin-like 1

Follistatin-like 1 (FSTL1), also referred to transforming growth factor beta-stimulated (TGFβ-stimulated) clone-36 (TSC-36), is a secreted glycoprotein identified originally as a molecule induced by TGFβ stimulation [97]. FSTL1 belongs to follistatin family, because it shares a domain structure, which is called the FS domain [98]. Although other members of follistatin family proteins antagonize the binding of TGFβ superfamily proteins to their receptors, FSTL1 does not act on cells through its ability to inhibit the actions of TGFβ superfamily proteins [99].

FSTL1 receptor and signal transduction

Despite of inhibiting TGFβ superfamily proteins, FSTL1 activates Disco-interacting protein 2 homolog A, a cell surface receptor, and induces AKT serine/threonine kinase (AKT) phosphorylation [99]. In neonatal rat cardiomyocytes, FSTL1 induces extracellular signal-regulated kinase1/2 (ERK1/2) phosphorylation and AMP-activated protein kinase (AMPK) activation [100, 101].

Secretion of FSTL1

FSTL1 is secreted from cardiomyocytes through the classical secretory pathways [10]. The expression of *Fstl1* is ubiquitous in early mouse embryos, whereas it becomes restricted and is mostly found in the mesenchymal tissue later during development [102]. Although FSTL1 is expressed in epicardial cells of the normal adult mouse heart, FSTL1 is expressed in cardiomyocytes and disappears from epicardial cells in the mouse heart with MI [103]. Serum FSTL1 is increased in mice with MI [101]. FSTL1 protein in the heart and plasma is increased in the mice with transverse aortic constriction (TAC) and ischemia/reperfusion (I/R) injury [100, 104]. Furthermore, FSTL1 expression is increased in patients with heart failure [105].

FSTL1 improves cardiomyocyte survival and inhibits cardiac hypertrophy in autocrine/paracrine fashions

FSTL1 secreted from the cardiomyocytes inhibits myocardial apoptosis and hypertrophy. FSTL1 knockdown exacerbates hypoxia/reoxygenation-induced apoptosis in neonatal rat cardiomyocytes through an AKT-dependent mechanism [101]. Cardiac-specific FSTL1-deficiency exacerbates cardiac hypertrophy following TAC. Cardiac FSTL1 inhibits TAC-induced cardiac hypertrophy through an AMPK-dependent mechanism [104]. On the other hand, epicardial cell- but not cardiomyocyte-derived FSTL1 improves cardiac functions after MI [103]. Although the role of cardiomyocyte-derived FSTL1 remains to be resolved, these data indicate the cardioprotective role for FSTL1.

FSTL1 inhibits systemic inflammation in endocrine fashions

FSTL1 works as an endocrine factor. In mice with kidney injury, plasma FSTL1 is increased. An increase of FSTL1 seems to be dependent on its secretion from cardiomyocytes. Given that cardiac-specific FSTL1-deficient mice show the exacerbation of renal injury after nephrectomy and that cardiomyocyte-derived FSTL1 exerts anti-inflammatory effects in kidneys via an AMPK-dependent mechanism, FSTL1 might function as a mediator involved in inter-organ communication between the heart and kidney [106].

Endothelin 1

ET1 is the most potent and long acting vasoconstrictor [107]. In 1988, ET1 was identified as an endothelium-derived blood vessel-constricting factor using the supernatant of cultured porcine aortic endothelial cells [108]. The ET peptide family consists of three structurally similar 21-amino acid peptides, ET1, ET2, and ET3 [109].

ET1 receptors and signal transduction

In 1990, two ET receptors, endothelin receptor type A (ENDRA) and type B (ENDRB), were identified [110, 111]. ENDRA has higher affinity to ET1 and ET2 than ET3. ENDRB has equal affinity to all ETs. Both ET receptors belong to the G-protein-coupled receptor family. ET receptors activate phospholipase C, inositol triphosphate, diacylglycerol, and intracellular calcium-dependent pathways [112].

Secretion of ET1

Cardiovascular systems predominantly express ET1 [113]. In coronary endothelial cells, ET1 is stored in secretory granules. ET1 secretion follows the classical secretory pathway [114]. Although the primary source of ET1 is vascular endothelial cells [115], ET1 is also expressed in cardiomyocytes [116]. Mechanical stretch and low oxygen conditions lead to ET1 secretion in cultured neonatal rat cardiomyocytes [117, 118]. Plasma ET1 concentration and cardiac ET1 synthesis are increased in patients with ischemic cardiomyopathy [119].

ET1 promotes cardiac hypertrophy and cell survival in autocrine/paracrine fashions

Autocrine/paracrine effects of cardiomyocyte-derived ET1 have been demonstrated by cardiac-specific ET1-deficient mice. ET1 exacerbates tri-iodothyronine-induced cardiac hypertrophy [120]. On the contrary, ET1 is essential for aged mice to survive and to maintain cardiac functions [121].

ET1 controls blood pressure

ENDRA is expressed on vascular smooth muscle cells and cardiomyocytes. The activation of ENDRA results in vasoconstriction and vascular smooth muscle cell proliferation through a phospholipase C-dependent pathway. On the other hand, ENDRB is expressed on endothelial cells and is involved in the clearance of ETs. ENDRB also shows a vasodilator effect through the release of NO and prostacyclin from endothelial cells [112, 122]. Although the role of cardiomyocyte-derived ET1 for the systemic regulation remains to be resolved, it appears to work as an autocrine or a paracrine factor in the organs where ET1 is produced.

Chromogranin A

Chromogranin A (CHGA) is an ubiquitously expressed acidic secretory protein, which belongs to the granin family. Because CHGA has several cleavage sites, the proteolytic cleavage of CHGA results in several biologically active CHGA-derived peptides, such as vasostatin1 (VS1), pancreastin, and catestatin (CST) [123].

Secretion of CHGA

Chromogranin A is found as a chromaffin granule protein secreted from the catecholamine- stimulated adrenal medulla [124, 125]. CHGA is co-stored and co-secreted with other secretory factors, such as catecholamines and NPs. Immunohistochemical analyses show that CHGA co-exists with ANP and BNP in cardiac secretory granules [126, 127]. Circulating CHGA levels are increased in patients with heart failure and essential hypertension [128, 129].

Vasostatin1

VS1 is an N-terminal fragment of CHGA. CHGA fragments containing VS1 are detected in rat heart extracts [130]. VS1 binds to heparin sulfate proteoglycans and activates phosphoinositide 3-kinase (PI3K) through a caveolae endocytosis-dependent mechanism [131].

VS1 inhibits cardiomyocyte hypertrophy in autocrine/paracrine fashions

VS1 treatment shows anti-adrenergic effects in cardiomyocytes. VS1 abolishes the isoproterenol-induced (ISO-induced) positive inotropism in the perfused rat heart [132]. Consistent with this action, chronic VS1 treatment inhibits ISO-induced cardiomyocyte hypertrophy in rats [133]. The anti-adrenergic effect of VS1 might depend on the activation of a PI3K/endothelial NOS (eNOS)/NO-dependent signaling pathway in endothelial cells rather than in cardiomyocytes [134]. Cardiomyocyte-derived VS1 might work as a paracrine factor and inhibits cardiomyocyte hypertrophy by targeting endothelial cells.

VS1 inhibits hypertension and angiogenesis

Although VS1 treatment suppresses vascular tension and inhibits angiogenesis [135, 136], it is unclear whether cardiomyocyte-derived VS1 acts as an endocrine factor.

Catestatin

CST is a C-terminal fragment of CHGA. CHGA fragments containing CST are detected in the mouse heart [137]. CST acts as a nicotinic cholinergic antagonist to inhibit catecholamine release [138]. While plasma CHGA is increased, plasma CST is decreased in patients with cardiovascular disease, such as hypertension [139] and heart failure [140]. Therefore, low plasma CST might increase the risk for cardiovascular disease.

CST controls heart function

In the Langendorff-perfused rat heart, CST stimulation counteracts ISO-induced positive inotropism and lusitropism through a $G_{i/o}$ protein and eNOS-dependent mechanism [141].

CST inhibits hypertension

CST Catestatin prevents blood pressure elevation. Intravenous administration of CST results in a decrease of blood pressure in rats through an increment of plasma histamine, a potent vasodilator [142]. CHGA-deficient mice show high blood pressure, increased heart rate, and high plasma catecholamines. This phenotype is rescued by exogenous injection of CST [143, 144]. Although these data suggest that CST is involved in the cardiovascular maintenance, it is unclear whether cardiomyocyte-derived CHGA acts as an endocrine factor.

Fibroblast growth factors

Fibroblast growth factor (FGF) family consists of 22 FGFs, FGF1–FGF23 (FGF15 and FGF19 are orthologous peptides). FGFs can be classified as paracrine, endocrine, and intracrine FGFs [145]. Seven major FGF receptors (FGFRs) are translated from 4 FGFR genes, *FGFR1-FGFR4* [146]. Paracrine FGFs including FGF1-FGF10, FGF16-FGF18, FGF20, and FGF22 bind to FGFRs with heparin/heparin sulfate as a cofactor. Endocrine FGFs comprising FGF15/19, FGF21, and FGF23 require either αKlotho or βKlotho as a cofactor to bind to FGFRs. Because of their low heparin-binding affinity, endocrine FGFs are capable of targeting remote organs through the blood stream [147]. Intracrine FGFs, FGF11–FGF14, are intracellular proteins that regulate voltage gated sodium channels through intracrine fashions. Among FGFs, FGF3, FGF8, FGF9, FGF10, FGF15/19, and FGF16 work as paracrine factors during heart development. On the other hand, FGF2, FGF9, FGF10, FGF16, and FGF21 act on the heart in pathological conditions as paracrine factors [148].

FGF21 receptors and signal transduction

FGF21, an endocrine FGF, activates FGFR1c, FGFR2c, and FGFR3c with βKlotho [145]. Cardiomyocytes express both FGFR1 and βKlotho [148]. FGF21 activates ERK1/2, p38MAPK, AMPK, and PI3K/AKT pathways in mouse hearts and in rat cardiomyocytes [149, 150].

Secretion of FGF21

FGF21 is mainly expressed in the liver and acts as a metabolic regulator [151, 152]. FGF21 increases glucose uptake [153], regulates lipid metabolism [154, 155], and improves insulin sensitivity in the liver and adipose tissues [156]. Because FGF21 is also produced in cardiomyocytes, it is regarded as a cardiomyokine [157]. Its expression is up-regulated in H9C2 cardiomyotubes by ER stress and in mouse hearts by mitochondrial dysfunction, respectively [158, 159]. FGF21 mRNAs in mouse hearts are also up-regulated after ISO-induced cardiac hypertrophy, TAC, and MI [160].

FGF21 inhibits cardiac hypertrophy in an autocrine/paracrine fashion

Cardiomyocyte-derived FGF21 works as an autocrine/paracrine factor. It prevents cardiac hypertrophy through the inhibition of metabolic dysregulation and pro-inflammatory signaling in cardiomyocytes. FGF21 activates FFA oxidation through an ERK1/2-, cAMP-responsive element binding protein-, and PGC1α-dependent pathway. FGF21 suppresses pro-inflammatory gene expression through the inhibition of NFκB activity [160].

FGF21 protects cardiomyocytes in autocrine/paracrine fashions

FGF21 protects the heart from oxidative stress through up-regulating antioxidant factors, including UCP2, UCP3, and superoxide dismutase 2 [161]. In addition, FGF21 inhibits cardiac apoptosis in an ERK1/2-, p38 MAPK-, and AMPK-dependent manner [150].

FGF21 controls systemic metabolism in endocrine fashions

Although the endocrine function of cardiomyocyte-derived FGF21 remains to be elucidated, mice overexpressing FGF21 in the heart show a decrease in body weight [158]. Moreover, mitochondrial dysfunction-induced FGF21 up-regulation in the mouse heart seems to be responsible for systemic changes in metabolism [159]. These data suggest that cardiomyocyte-derived FGF21 has a potential to work as an endocrine factor.

Osteocrin

Osteocrin (OSTN) was originally identified in muscles and bones by signal-sequence trap methods [162, 163]. OSTN is proposed to belong to the NP family, because it has two NP-like motifs. OSTN binds to NPR3, but not NPR1 and NPR2, because NP-like motifs of OSTN lack disulfide cysteine bridges that are essential for the circle structure of NPs [164, 165].

Cardiomyocyte-derived Ostn might promote bone formation in zebrafish

Recently, we reported that Ostn is expressed in zebrafish cardiomyocytes and that Ostn-deficient fish show the shortening of membranous bone and cartilage lengths. This impairment of bone growth was rescued by the myocardium-specific overexpression of Ostn. Although it is unclear whether the amount of endogenous cardiomyocyte-derived Ostn is enough to regulate bone formation, cardiomyocyte-derived Ostn might contribute to bone formation [166]. These data suggest that the cardiomyocyte-derived peptide has a potential to regulate bone growth at least in zebrafish.

Cardiomyokines have a potential to regulate bone formation

In mammals, OSTN is mainly expressed in bones and skeletal muscles, whereas subtle expression is detected in cardiomyocytes. Besides Ostn, several peptides known to regulate bone formation have been reported to be secreted from cardiomyocytes, although they are thought to work as autocrine factors. TGFβ superfamily peptides, such as activin A, bone morphogenetic protein 2 (BMP2), growth differentiation factor 15 (GDF15), and myostatin (MSTN) are secreted from cardiomyocytes [167–170]. Cardiomyocyte-derived TGFβ superfamily peptides might target bones, because some of them contribute to systemic increment of these peptide levels in pathological conditions. Cardiomyocyte-derived MSTN contributes to skeletal muscle atrophy in heart failure [171]. An increase of GDF15 in the blood that is presumably derived from cardiomyocytes acts on the liver to inhibit body growth [172]. In addition, FGFs have a potential to regulate bone formation. Cardiomyocyte-derived FGF21 might affect bone formation, because it has been reported to enhance the osteogenic activity of BMP2 [173]. Moreover, parathyroid hormone like hormone, a peptide known to regulate bone formation, has been reported to be secreted from cardiomyocytes [174]. Therefore, bone formation might also be regulated by cardiomyokines in mammals.

Secretion through cardiac extracellular vesicles

Besides the secretory pathway released from secretory granules, cardiomyocytes secrete proteins using extracellular vesicles, such as exosomes and micro-vesicles [11].

Cardiomyocyte exosome-derived proteins work as paracrine factors

Under hypoxic conditions, cultured adult rat cardiomyocytes secrete HSP20 via exosomes. Serum HSP20 in mice are increased after myocardial I/R. Cardiomyocyte-specific HSP20-overexpressing mice show increased circulating HSP20 and enhanced capillary density in hearts. Cardiomyocyte-derived HSP20 might induce angiogenesis through its paracrine effects [175].

Cardiomyocyte exosome-derived microRNAs work as paracrine factors

Extracellular vesicles carry not only proteins but also other bioactive mediators, such as lipids, DNAs, mRNAs, and non-coding RNAs including microRNAs (miRNAs) [11]. Exosomal miRNAs work as paracrine factors. In adult Goto-Kakizaki rats, an animal model of type 2 diabetes, cardiomyocytes release exosomes containing miR-320. Cardiomyocyte exosomal miR-320 regulates its target genes and inhibits proliferation, migration, and tube formation of cultured cardiac endothelial cells [176].

Cardiomyocyte exosome-derived microRNAs are detected in systemic blood

miRNAs are reported to play roles in progression of cardiovascular diseases and are recognized as potential biomarkers and novel drug targets [177]. miR-1, miR-133a/b, miR-208a, and miR-499 are highly expressed in cardiomyocytes. Plasma levels of these miRNAs are increased after acute MI [178]. These miRNAs regulate cardiac function. For example, miR-1 and 133 inhibit cardiac hypertrophy in mice [179]. On the other hand, the inhibition of miR-208a improves cardiac function and survival during hypertension-induced heart failure [180]. Although the function of circulating miRNA remains to be resolved, the systemic elevation of cardiomyocyte-derived miRNAs has the potential to target remote organs.

Conclusion

The fact that the heart is an endocrine organ was demonstrated by the discovery of ANP. Besides ANP, several peptides have been reported to be secreted from cardiomyocytes. Although most of such cardiomyokines act as autocrine or paracrine factors, several cardiomyokines, including those introduced in this review, target remote organs as endocrine factors. These peptides act on not only blood vessels and kidneys, but also liver, skeletal muscles, and adipose tissues. In addition, bone formation might also be regulated through cardiomyokines. Therefore, these peptides regulate various biological functions, such as cardiovascular homeostasis and metabolism. Cardiomyokines are synthesized in stress environments, such as pressure overload and ischemia through hypoxia- and ER stress-induced up-regulation of transcripts and are subsequently released in stretch- and agonist-induced manners. The heart contributes to general homeostasis of the body by regulating circulation and by secreting peptides. Although there are many cardiomyokines that have potentials to work as endocrine factors, their endocrine function is not fully demonstrated because of the lack of cardiac-specific knockout data. Further investigation will lead to a better understanding of the heart as an endocrine organ.

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