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New Technologies of Peptide Therapy in Bioregenerative Cardiology

Yuriy Nalapko[1,*], Aljafri Abdul Majid[2], Jonathan RT Lakey[3], Thomas Skutella[4], Glen Alvin[1], Simon Yefimov[1], Svetlana Yartseva[1], Michelle BF Wong[1] and Mike KS Chan[1]

[1]*European Wellness Biomedical Group, Malaysia, Germany*

[2]*The Heart Foundation of Malaysia, Malaysia*

[3]*Department of Surgery, University of California Irvine, USA*

[4]*Institute for Anatomy and Cell Biology, III Medical Faculty, University of Heidelberg, Heidelberg, Germany*

[*]**Corresponding Author**: Yuriy Nalapko, European Wellness Biomedical Group, Malaysia, Germany, E-mail: dr.yuriy@european-wellness.com

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Abstract

Short- and long-chain peptides play an important role in regulating cardiovascular effects. Some of these peptides are synthesized in the heart by different cells of the muscular (cardiomyoblasts, cardiomyocytes) or epicardial and endocardial tissues. It has recently been revealed that some extracardiac peptides demonstrate actions effective in heart contractility and muscle tissue repair. For instance, ghrelin, cholecystokinin, gastrin and other biomolecules synthesized in the intestine and adipose tissue could potentially help to modulate heart functions. Peptide treatment early after heart attack and myocardial infarction dramatically reduces life-threatening arrhythmia and mortality. Also, its hemodynamic effects are revealed. Thus, being signalling messengers, peptides are promising tools for cardiology and antiaging medicine.

These findings suggest that cardiac and non-cardiac peptides could be promising novel therapeutic agents in cardiology. The ability of the cells to produce these peptides opens new frontiers for the bioregenerative approach in heart and vessel disorders.

Keywords: Cardiology; Peptide; Regenerative Medicine; Stem Cells

Introduction

A peptide is a short string of amino acids (usually 2 to 50) formed by a condensation reaction. Peptides are essential in fundamental physiological processes and are necessary for many biochemical reactions. The nature of peptides, as the building blocks of proteins, allows for the synthetic and in vitro mimicking of these endogenous substances to regulate specific cellular functions and facilitate an innumerable amount of biochemical processes in the body. Extensive research has shown the multi-faceted role of bioactive peptides has demonstrated effectiveness in anti-inflammatory, anti-thrombotic, anti-apoptotic, anti-ageing therapy, etc [13].

Peptides are used widely in the medicine. Historically, insulin was the first medicinal peptide synthesized in 1921. Further, other peptides with anti-diabetic activities were discovered, including, among others, liraglutide, dulaglutide, and semaglutide, the analogues of human glucagon-like peptide 1 [19]. Vasopressin, oxytocin, somatropin, thyrotropin, corticorelin, and many other peptides with hormonal activities are widely used as therapeutical substances. Having relatively small molecular weights of 500 to 5000 Dalton, peptides as medicinal ingredients could be easily delivered into the cells through the cell membranes. The obvious advantages of the use of peptides include activation of the well-characterized receptors and avoiding off-target actions associated with small molecules [30]. Based on the fact that peptides possess a larger surface area than small molecules, it optimizes receptor activation and efficacy.

Peptides play a significant role in transmitting information to and from one cell/tissue to another. Their structural complexity has challenged medicine due to the lack of understanding of peptide organ and tissue specificity.

Some peptides demonstrate their anti-inflammatory and regenerative potentials locally and in the whole body or systemically. The endogenous peptide and specific receptor binding mechanism is principally designed for peptides acting as imaging probes and receptor-binding peptides for overexpressed receptors. Since some of these receptors are organ-specific or tissue-specific, the activity of such peptides is also targeted to the selected organs. Another scenario is with the tissue- (organ-) non-specific peptides, e.g., insulin, which works in cells of diverse organs with insulin receptors [10].

Endogenous peptides also play a role as modulators of tissue repair. They could induce the mesenchymal cells to differentiate and promote healing of the damaged tissues. Therefore, some peptides (e.g., syndecan, a cell surface heparan sulphate proteoglycan) possess tissue-regenerative functions. Syndecan activates the heparin-binding growth factors and tissue matrix substances to facilitate wound repair in damaged tissues [15].

There are organ-specific peptides active in some organs only and non-selective peptides working in the whole body. Their functions are extensive; they relay information, modulate cell metabolism, activate pro- or anti-inflammatory mechanisms, and regulate the cell membrane channels. Some peptides ultimately act as biomarkers and allow for the detection of bacterial infection or a tumor. As a result, tissue-specific peptides play crucial roles in regeneration, inflammatory response, and anti-ageing.

Peptides and Their Cardiac Functions

The heart has long been regarded as a pumping organ composed of muscles. In the 1980s, it was discovered that cardiomyocytes secrete peptides with hormonal activity (cardiomyokines) [7]. About 40 years have passed since the atrial natriuretic peptide (ANP), the first cardiac peptide, was discovered [9]. Subsequently, the brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP) were found, and natriuretic peptide receptor-A (NPR-A), NPR-B, and NPR-C receptors were also identified [34]. Both ANP and BNP bind to their receptors expressed on remote organs, such as kidneys and blood vessels; therefore, the heart, via the secretion of its endocrine peptides, control the circulation by pumping blood and regulating the blood flow through the kidneys, adrenal glands, gut, brain, liver, etc.

Endothelin was discovered in 1988 as a potent vasoconstriction and pressor peptide isolated from the culture supernatant of

porcine heart and aortic endothelial cells. Endogenous endothelin is involved in the progression of various cardiovascular diseases, and as a result, a variety of endothelin antagonists have been developed [46].

Adrenomedullin is a peptide consisting of 52 amino acids demonstrating potent vasodilatory potential. It was discovered initially in human pheochromocytoma tissue. Subsequent studies showed adrenomedullin was highly expressed in heart tissue, and adrenomedullin has the inhibitory effect of proliferation and collagen production in fibroblasts and cardiac hypertrophy in myocytes, and it also has a positive inotropic effect. Highly expressed cardiac adrenomedullin in heart failure may regulate cardiac function and cardiac hypertrophy [36].

The first gastrointestinal peptides discovered were gastrin and cholecystokinin. They are commonly involved in digestive processes, including gastric acid secretion, pancreatic enzyme release, gallbladder motion, gut motility, and energy homeostasis. Gastrin and its receptor, cholecystokinin 2 receptor (CCK2R), are highly and widely expressed in the heart [33]. Recently, the trophic actions of gastrin were demonstrated by a sequence of in vivo studies. One previous study showed that a synergistic interaction between renal CCK2R and D1-like dopamine receptors is crucial in maintaining normal blood pressure [6]. Plasma gastrin concentration is associated with low cardiovascular mortality risk, the opposite of that found with plasma cholecystokinin level.

Cholecystokinin (CCK), a gut–brain peptide, is expressed at the mRNA and protein levels in both atrial and ventricular cardiomyocytes. Interestingly, the post-translational processing of proCCK in cardiomyocytes is substantially different from intestinal and cerebral CCK peptides. The porcine cardiac tissue extracts analysis showed that cardiac proCCK expression shifted from the right atrium in newborn piglets to include the left atrium in adolescent pigs. The plasma proCCK level is increased during exercise in parallel with proBNP. Furthermore, the plasma proCCK level — but not the CCK level — is increased in severe heart failure patients [17]. In addition, the ability of CCK to induce pancreatic hyperplasia and hypertrophy was also reported by in vivo studies [11].

Apelin is an endogenous peptide ligand, which exerts various physiological functions, including vasodilation, inotropic effects, heart development, the control of fluid homeostasis, and obesity. Both apelin and angiotensin II are substrates for angiotensin-converting enzyme 2 (ACE2). In addition, endogenous apelin negatively regulates the renin–angiotensin system via the upregulation of ACE2 [41].

Adrenomedullin (AM) and proadrenomedullin N-terminal 20 peptide (PAMP) are two peptides causing vasodilation, angiogenesis, or anti-inflammation, and other bioactive effects. AM and PAMP are predominantly expressed in the gastrointestinal tract. They act as gastrointestinal hormones, regulating numerous physiological processes – gastric acid release, insulin secretion, gastric emptying, bowel movements, and intestinal barrier function. AM also improves vascular and lymphatic regeneration, function, and epithelial repair. It also regulates cytokine production in the intestinal mucosa [28].

Heart Peptides in Cardiology

As biochemical sciences and therapeutic design progress, peptide synthesis and design are studied with implications for some therapies (e.g., oncology, infection diseases, etc.) as the pharmaceutical industry continues shifting more toward biologicals for new drug candidates [40]. Although most such cardiomyocyte-derived peptides act on the heart in autocrine/paracrine fashions, several peptides target remote organs.

The pleiotropic actions of the natriuretic peptides make this humoral mechanism attractive in patients with heart failure. Carperitide (ANP) and nesiritide (BNP) have been approved in Japan and the US for acute decompensated heart failure, respectively. Cenderitide is a potent peptide that has renal-enhancing and cardiac unloading effects. It has a lesser reduction of blood pressure than BNP. Also, cenderitide has antiproliferative, anti-fibrotic, and anti-hypertrophic properties [21].

A new ligand for NPR-C, osteocrin, was also discovered from bone. Osteocrin is vital in suppressing the progression of heart failure by inhibiting NPR-C.

Plasma level of another type of natriuretic peptide, BNP, is also increased according to the severity of heart failure, and guidelines worldwide recommend using BNP in diagnosing heart failure. In addition, recombinant ANP and BNP are effective in improving the hemodynamics of heart failure and have been used in the treatment of acute decompensated heart failure [35].

Ularitide is the form of the human natriuretic peptide produced in distal renal tubule cells [31]. This cardiovascular peptide regulates water and sodium reabsorption through the natriuretic peptide receptor-A (NPR-A) that is presented in the myocardium, kidneys, and vascular smooth muscle tissue. Therefore, ularitide stimulates diuresis and sodium excretion. Also, it inhibits the activity of the renin–angiotensin–aldosterone system. In Phase II randomized, double-blind, placebo-controlled trial of ularitide in patients with decompensated heart failure, ularitide statistically significantly reduced systemic vascular resistance and increased cardiac index [32]. Such findings suggest that this peptide may play a role in the management of heart failure.

Experimentally, endothelin antagonist is a very effective drug in the treatment of heart failure. Still, clinical trials have failed to improve mortality or heart failure hospitalisation rates in heart failure patients [8]. As was shown in EARTH Study [1], patients with chronic heart failure have shown no difference in the effect of darusentan on left ventricular end-systolic volume, probably as plasma levels of endothelin-1 increased dose-dependently, suggesting that the doses were not endothelin antagonists selective [23]. Treatment with darusentan in the EARTH studies did not reduce the plasma level of norepinephrine, suggesting that endothelin antagonists do not inhibit the sympathetic nervous system in chronic heart failure.

However, endothelin receptor antagonists are effective in treating pulmonary arterial hypertension, and guidelines approved the use of endothelin antagonists in treating pulmonary arterial hypertension [39].

The intravenous administration of adrenomedullin to patients with heart failure improved hemodynamics in heart failure [2]. The adrenomedullin receptor is formed by a complex of seven-transmembrane calcitonin receptor-like receptors and single-transmembrane receptor activity modifying protein (RAMP) 2. When cardiomyocyte-specific RAMP2 deletion was induced, mice exhibited dilated cardiomyopathy-like heart failure with cardiac dilatation and myofibril disruption, supporting the hypothesis that increased cardiac adrenomedullin in heart failure may compensate for a failing heart [48].

It is well known that the human heart has limited regenerative capacity and repairs itself poorly after injury. After the ischemic injury, acute or chronic, patients often progress to heart failure despite the decrease in direct mortality by reperfusion therapies. In contrast to the adult human heart, neonatal hearts can substantially regenerate from injury or disease via the induced proliferation of cardiomyocytes [38].

Damaged adult cardiomyocytes in the human heart show upregulation of genes involved in heart development. Induction of cardiomyocyte proliferation in regenerating hearts has been linked to paracrine signaling, often attributed to the peptide secretion from the epicardium [4,18]. Furthermore, efficient cardiac regeneration is accompanied by revascularisation induced by epicardial-derived endothelial and smooth muscle cells [27].

Some peptides are focused on stimulating cardiomyocyte proliferation, while others aim to restore vascularisation and prevent extensive fibrosis. Studying regenerative factors that can promote angiogenesis, target fibroblast behavior, and function in intercellular communication could be a promising approach. FSTL1 can double or triple the expression of multiple proliferation markers in human cardiomyocytes. This makes it a good candidate factor to target cardiac repair. By decreasing both cell death and secretion of pro-inflammatory cytokines, the regenerative potential of FSTL1 might also be linked to increasing cardiomyocyte proliferation and survival in a less hostile (i.e., less inflammatory) infarct microenvironment.

The epicardium peptides have been identified to mediate cardiac regeneration initially in the zebrafish heart. One more peptide, follistatin-like 1 (FSTL1), increases cardiomyocyte proliferation and decreases cardiomyocyte apoptosis. It also prevents cardiac rupture in animal models of ischemic heart disease. To explore its therapeutic potential, Peters et al. (2022) used a human in vitro model of cardiac ischemic injury with human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) and assessed regenerative effects of two differently glycosylated variants of human FSTL1 [37]. Also, they investigated the FSTL1-mediated interaction of human cardiac fibroblasts (cFBs) and iPSC-CMs in hypoxia. FSTL1 increased viability, while only hypo-glycosylated FSTL1 increased the proliferation of cardiomyocytes after the hypoxia issue. Scientists revealed that human fetal cardiac fibroblasts (fcFBs) secreted FSTL1 under non-hypoxic conditions. Combined treatment of iPSC-CMs and cFBs increased FSTL1 secretion compared with cFB monoculture. Taken together, the authors confirm that this cardiac peptide in a human cardiac in vitro hypoxia damage model induces proliferation of the iPSC-CM. In hypoxic conditions, FSTL1 secretion by human cFBs and indications for FSTL1-mediated intercellular communication between cardiomyocytes in response to hypoxic conditions.

Also, follistatin-like-1 peptide has been confirmed to act as myogenic cardiokine in murine and porcine cardiac injury models [44]. Furthermore, cardioprotective and angiogenic effects of FSTL1 have been reported.

Ghrelin was discovered in 1999. It is a ligand for the receptor of growth hormone secretagogues. Besides its powerful effect on the growth hormone secretion, ghrelin stimulates food intake. It transduces signals to hypothalamic regulatory nuclei that control energy homeostasis. Subsequent studies demonstrated that ghrelin also has cardiovascular functions [20].

Also, ghrelin has a potential therapeutic role in the treatment of heart disorders. In both heart failure animal models and human patients, repeated subcutaneous administration of ghrelin improves cardiac function and remodelling. Moreover, ghrelin treatment early after myocardial infarction effectively reduces fatal arrhythmia and, consequently, mortality. The beneficial effects of ghrelin result from a growth hormone increase, an orexigenic effect, direct actions to the cardiovascular cells and its potent inhibitory action on sympathetic nervous activity, which is excessively activated in cardiac diseases. These results suggest that ghrelin could be a promising novel therapeutic agent for cardiac diseases [24,25].

In a myocardial infarction and followed chronic heart failure model, ghrelin chronic administration improved cardiac function and left ventricular remodelling. Moreover, the long-term administration of ghrelin improves left ventricle function, exercise capacity, and muscle wastage in patients with heart failure [24]. Similar data were obtained by Tokudome et al. (2014) [42]. They confirmed again that in animal models of chronic heart failure, ghrelin administration improves cardiac function and remodelling. Notably, such data were replicated in human patients with heart failure. In part, in an animal study, ghrelin administration seriously reduced pulmonary hypertension induced by long-term hypoxia. Repeated administration of ghrelin to end-stage patients with chronic obstructive pulmonary disease positively affected the integrative body function, e.g., muscle wasting, functional capacity and sympathetic activity. In the post-myocardial infarction stage, administration of ghrelin reduced life-threatening arrhythmia and attributed mortality. In rodents with low ghrelin expression, exogenous and endogenous ghrelin promoted remodelling after myocardial infarction and were protective against fatal arrhythmia [43].

The exact mechanisms underlying the effects of ghrelin on the cardiovascular system still remain unclear. Nevertheless, evidence shows that its beneficial effects are mediated through direct physiological actions, including regulating autonomic nervous system activity, improved energy balance and direct actions on cardiovascular cells. Therefore, ghrelin is a promising novel therapeutic agent for cardiovascular disease.

Ischemia/reperfusion injury is one of the complications of chronic ischemic heart disease. Gastrin is another regulator of cardiovascular function. It plays a critical protective role in hypoxia. Blood serum concentrations of gastrin are elevated in patients with myocardial infarction, but the pathophysiological significance of this finding is still unknown [47]. The expression of gastrointestinal hormones has been reported to modulate reflex cardiovascular responses, although the role of gastrin is yet unknown. In their ani-

mal study, Grossini et al. (2011) discovered the primary in vivo effect of gastrin 17 on coronary blood flow and cardiac function [18]. Intracoronary gastrin 17 administration caused dose-related increases in both coronary blood flow and cardiac function. The intracoronary co-administration of CCK33 and gastrin 17 potentiated the coronary effects seen when these agents were given alone. Authors concluded that gastrin 17 primarily increases coronary blood flow and cardiac function through the NO release, involvement of β-adrenoceptors and CCK receptors [18].

Summarizing, many cardiotropic peptides are secreted by cardiomyocytes, epicardial cells, and endothelial cells of the heart and aorta; also, some extra-cardial cells produce peptides with cardiovascular effects. They demonstrate their promising potential as therapeutic agents in vitro and in vivo in preventing and treating cardiac diseases and normal heart ageing.

Cell Peptide Therapy in the Ageing Heart

The low endogenous regenerative capacity of the human heart renders cardiovascular diseases a significant health threat, thus motivating intense research on in vitro heart cell generation and cell replacement therapies. Various strategies to foster cellular maturation provide some success, but fully matured cardiomyocytes are still to be achieved. Several peptides are recognized today for their effects on cardiomyocyte proliferation, differentiation, and function. Due to their pleiotropic effects, peptides may be valuable in improving in vitro heart cell generation and beneficial for in vivo heart regeneration [16].

The secretion of cardiokines plays essential roles in intercellular communication during physiology and disease by mediating paracrine cross-talk inside the heart and facilitating communication with peripheral organs. To illustrate, the release of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) has been found to enable dynamic motion of the ventricular wall, while cardiokine IL-33 released by cardiac fibroblasts regulated CM hypertrophy [45].

As cardiac hypoxia impairs endoplasmic reticulum (ER) protein synthesis, protein secretion is decreased for most proteins [12]. Maintained or increased protein secretion during ER stress suggests important functions for these proteins in the post-ischemic heart repair response.

Adrenomedullin and its receptor components (e.g., calcitonin receptor-like receptor (CRLR), receptor activity modifying protein (RAMP)2 and RAMP3) are placed in peripheral tissues – heart, kidney, and vasculature, etc. It suggests an essential role for adrenomedullin as a regulator of cardiovascular function. Adrenomedullin gene expression and/or immunoreactivity are increased in the cardiac hypertrophy and heart failure ventricles. Also, CRLR, RAMP2 and RAMP3 mRNA levels are increased in cardiac hypertrophy and failing heart [36]. Together, these data support a protective role for increased adrenomedullin in cardiac hypertrophy and heart failure. Also, adrenomedullin has hemodynamic effects, including vasodilation and an increase in cardiac contractility, cardiac output, diuresis, and natriuresis. Apart from its cardiovascular action, the acute administration of adrenomedullin in the models of experimental and human heart failure demonstrated complex hormonal and renal effects. Such effects incorporate plenty of the therapeutic goals of heart failure management.

Proteomic studies have detected the expression of over 150 distinct mature peptides. Recently, heart-oriented nanomized organopeptides (NOP) have been manufactured and tested for cardiac patients. According to the data of its manufacturer, NOPs are organ-specific, thus making it possible to choose the range of the NOP needed for a particular patient. It could be injected intramuscularly and via noninvasive routes (sublingual, intranasal).

The manufacturer offers a wide range of NOP. The new formulation implemented in 2023 has a three-time higher dose of the active peptides (NOP triple strength). It is especially important for heart patients as they usually require multifunctional activities: cardiac, epithelial, endothelial, renal, pulmonary, neuronal, immune, etc. The list of the available organ- and tissue-specific NOP products is given in Table 1.

Importantly, non-cardiac organs also secrete cardiotropic peptides. In our practice, we usually use the combinations of the NOP taken from the intestine, kidneys and endothelial cells. Some peptides, such as cholecystokinin and vasoactive intestinal peptide, have been detected in the brain cortex. Peptides obtained from the hypothalamus harmonize the brain-adrenal-heart axis, thus playing an essential role in cardiology.

Table 1: Nanomized organ-specific peptides (NOP) are used for cardiac patients. (Source: fctiinc.com). Courtesy of FCTI company.

Cardiomyocytes	Brain
Cardiomyoblasts	Hypothalamus
Fibroblasts	Pituitary gland
Endothelial cells	Hippocampus
Epithelial cells	Brain stem
Mesenchyme	Spinal cord
Placenta	Stomach
Smooth muscle	Adrenal cortex
Skeletal muscle	Intestinal mucosa
Liver	Spleen
Lungs	Bone
Kidneys	Bone marrow
Testis	

Mitochondria are the core organelles producing the energy for any cell. In heart hypoxia/ischemia, mitochondrial dysfunction is detected at the pre-clinical stage of the disease. Thus, mitochondrial autophagy (mitophagy) is the high-sensitive test of the cardiomyocyte dysfunction. On the other hand, mitochondrial dysfunction (insufficiency) promotes ROS activation, peptide malfunction, cell damage and apoptosis. Together with a nucleus, mitochondria contain genetic information. In human cells, mitochondria are the only organelles containing DNA besides the nucleus. Mitochondrial DNA (mtDNA) comprises 37 genes, 13 of which encode proteins, and the remaining genes encode RNA molecules involved in the translation of proteins. The number of peptides and polypeptides encoded by mtDNA is very small compared to that encoded by nuclear DNA. Therefore, mtDNA and mitochondria are vital for proper cellular function. Mitochondrial RNA contains information about the organ-specific peptides secreted by cardiomyocytes, fibroblasts, epicardium, endothelial cells, etc. Therefore, restoration of heart mitochondria is a new and perspective technology in bioregenerative cardiology.

Heart failure is related to redox reactions and abnormal mitochondrial metabolism of different severities. Although mitochondria are classically associated with oxidative phosphorylation and ATP synthesis, it is important to note that these organelles are also essential for normal calcium homeostasis, redox signalling cascades, and regulation of neurotransmission. There is strong scientific evidence that mitochondria are highly concentrated in presynaptic terminals. Thus, loss of redox control can negatively affect the neurotransmission and synaptic plasticity in the autonomous nervous system of the heart. The injection of the organ-specific mitochondrial peptides is new bioregenerative technology.

Methods to isolate mitochondria rely on differential centrifugation. The tissue is homogenized and centrifuged at low speed, cell debris is discarded, and the mitochondria contained in the supernatant are collected at high speed in a second centrifugation step. The obtained mitochondrial fractions show adequate purity [14]. Moreover, density gradient centrifugation or affinity purification of the organelle is used to purify mitochondria further or separate different organelle populations [26].

Mitochondrial organ and tissue specificity should be considered when choosing the donor mitochondria. Isolating mitochondria

from a cell could prime the mitochondria and influence their impact on recipient cells' mitochondrial networks or their ability to fuse with endogenous mitochondria. The transfer procedure has been studied using mitochondria from differentiated cells like heart fibroblasts, cardiomyocytes, mesenchymal stem cells, and others [22]. Testing different cell states will be important to understand how exogenous mitochondria interact with the endogenous organelles, how the cell's phenotype changes after transfer, and if metabolic reprogramming is possible [3].

In 2015, the principal new technology of manufacturing cell-expressed peptides was established [5]. Such peptides are known as "Mitochondrial organelles" or Mito Organelles (MOs). Authors suppose that the efficacy of MOs is related to substituting the damaged native mitochondrial organelles, provision of the organ-specific mitochondrial peptides, and organ-specific growth factors (e.g., neuropeptides, neuronal growth factors, etc.).

One of the critical advantages of Mito Organelles is their organ specificity. As the leader in the cell therapy field, the manufacturer offers organ- and tissue-specific products (Table 2).

In summary, mitochondria are a promising tool for the development of new medical technologies. Mitochondrion-to-mitochondrion DNA transfer is one of the fundamental biological processes that restore its function. Moreover, the pioneering studies of the xenogeneic cell transfer of mitochondria open new horizons for stem cell medicine.

Table 2: Mitochondrial organelle peptides (MO) are used for cardiac patients. (Source: fctiinc.com). Courtesy of FCTI company.

Heart	Oligodendrocytes
Lungs	Pituitary gland
Placenta	Hypothalamus
Mesenchyme	Hippocampus
Microglial cells	Bone marrow
Adrenal cortex	Spinal cord
Adrenal medulla	Kidneys
Endothelial cells	Ovary
Smooth muscle	Testis
Gastric mucosa	Lungs
Intestinal mucosa	Brain
Parasympathetic nervous system	

Studying the safety of mitochondria transplantation in 2013, Masuzawa et al. proved that mitochondria can be safely used in vivo to repair damaged tissues. Because ischemic damage affects the mitochondria, the authors hypothesized that replacing affected mitochondria with healthy ones would significantly improve postischemic recovery [29]. The authors observed that the transplantation of mitochondria was safe and had no side effects after 28 days of the procedure.

Conclusion

The heart is regarded as an endocrine organ and a pump for circulation since ANP and BNP were discovered to be secreted as hormones in cardiomyocytes. It is clear that the heart, as an endocrine organ, secretes many bioactive peptides and hormones acting in the cardiovascular system, brain, gut, liver, lymphatic system, and others. Importantly, these cardiomyocyte-derived peptides (cardiomyokines) work on the remote organs and the heart. Cardiomyokines act on remote organs to regulate cardiovascular homeostasis, systemic metabolism, and inflammation. Therefore, through its endocrine function, the heart can maintain physiolog-

ical conditions and prevent organ damage under pathological conditions. At the same time, many hormones and peptides considered non-cardiac could promote heart tissue regeneration and antiarrhythmic, anti-inflammatory, immunomodulatory, and remodelling effects. The cardiomyocytes, myoblasts, and other cells synthesize most of these peptides. Its endoplasmatic reticulum is the main "plant" where this synthesis happens. Since this process is energy-cost, mitochondrial function is crucial. Also, mitochondria (together with the cell nucleus) contain genetic information about these peptides to be synthesized in the heart. Thus, the organ-specific mitochondrial peptides and nanomized organ-specific peptides (MO and NOP) play an important role in treating the cardiac patients. Anti-inflammatory, immunomodulating and remodelling effects of MO and NOP promote both heart repair and cardiac antiagieng effects. Further additional study of the efficacy of this technology of the bioregenerative therapy in different cohorts of the cardiac patients is needed.

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