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Potential applications of natriuretic peptide system in cardiovascular regenerative medicine

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Abstract

Cardiovascular diseases are among the major causes of death worldwide. These diseases can be described as circumstances in which cell loss and injury exceed the capacity for regeneration and repair. Many therapeutic approaches have been developed to prevent and cure these diseases. Because the adult mammalian heart has limited regenerative capacity, harnessing the power of stem and progenitor cells could be one of the most promising approaches to regenerate and repair injured cardiac and vascular tissue. The natriuretic peptide system plays a key role in orchestrating the mammalian heart development. Studies have reported that the natriuretic peptide system has been implicated in the proliferation and differentiation of cardiomyocytes derived from embryonic stem cells, cardiac progenitor/stem cells, and mesenchymal stem cells. After cardiac damage and ischemic events, the revascularization of the ischemic areas improves cardiac function and delays the onset of heart failure in myocardial ischemia patients. Studies have shown that the natriuretic peptide system can promote vascular regeneration and repair, resulting in improved heart function after an ischemic event. Combining the exogenous administration of natriuretic peptide with stem/progenitor cells differentiating into cardiovascular system cells could be one of the most effective therapies for replenishing and replacing lost or injured cardiac and vascular tissue and cells. As a result, the natriuretic peptide system may play a role in cardiovascular protective and regenerative processes, as well as the proliferation and differentiation of relevant stem cells into cardiomyocytes, endothelial cells, and smooth muscle cells, via their receptors. In this review, we provide an overview of cardiovascular regenerative medicine and examine the potential applications of the natriuretic peptide system in cardiovascular repair and regeneration.

Introduction

Cardiovascular diseases (CVDs) are among the deadliest diseases that humans have suffered in the twenty-first century, affecting over 37 million people globally. CVDs were responsible for about 19 million deaths worldwide in 2020, representing an increase of 18.7% from 2010. CVDs are predicted to be the cause of more than 23 million deaths globally by 2030[1-3]. CVDs not only affect people worldwide, but they also place a significant social and economic burden on developing-country economies due to high death and hospitalization rates linked to poor patient quality of life and high healthcare costs[1,4]. Among the myriad of disturbances that could result in CVDs, atherosclerosis and ischemic heart disease contribute to more than two-thirds of the cases that proceed to severe heart failure (HF) and eventually mortality. The aging population, sedentary lifestyle, poor nutrition, and smoking are all likely factors in the continual rise in ischemic HF incidence in the 21st century[5]. Many alternative therapeutic approaches for preventing and treating CVDs have been developed over a few decades.

These approaches include cell therapy, gene therapy, nanomaterial-based drug targeted therapy, beta-blocking pharmaceuticals, angiotensin-converting enzyme inhibitors, non-invasive and invasive techniques to re-open occluded coronary vessels, antiplatelet and anticoagulant medications for the prevention and treatment of coronary thrombosis, to mention but a few[6-13]. The survival rate of CVD patients has been increasing promisingly in tandem with the development of preventative and treatment methods[3]. Therefore, deciphering the underlying cellular and molecular mechanisms behind CVDs will enhance the chance of survival for people suffering from these diseases. In this review, we first provide the overall information about cardiovascular regenerative medicine. We next discuss the possible effects of the natriuretic peptide system on cardiovascular repair and regeneration, which is our main focus.

An overview of cardiovascular regenerative medicine

Studies have revealed that only a small percentage of mammalian cardiomyocytes undergo turnover, with the majority appearing to cease the cell cycle. Most cardiomyocytes enter cell cycle arrest at birth due to the downregulation of cyclins, cyclin-dependent kinases (CDKs), and E2F transcription factors[14-17] and the upregulation of cyclin-dependent kinase inhibitors (Cdkn1a, Cdkn1b, Cdkn1c, and Cdkn2c)[18]. The existence of functional growth factor receptors on the plasma membrane of adult myocytes gives them the ability to undergo physiologic and/or pathologic hypertrophy in response to pathologic loads, when combined with foetal gene expression reprogramming[19]. This phenomenon has spurred researchers to investigate novel strategies and methods for repairing damaged hearts. Various bench-to-bedside approaches have been developed for that purpose[6,8,20,21]. These regenerative medicine approaches are considered promising for patients seeking to repair or replace their injured hearts. The minor improvements provided by cell-based[22-25] and cell-free[26-28] modalities have been linked to inadequate treatment efficacy[29], as well as improper administration and retention.

Over a few previous decades, researchers have made considerable progress in the realm of tissue engineering, notably related to stem cell engineering, the production of functional biomaterials and biomimetic nanofibrous scaffolds, and the use of biomanufacturing technologies to create complex, high-resolution biological structures[30]. This progress has laid a solid foundation for revisiting current therapy techniques and developing novel bioengineering therapies[31]. However, *in vitro* fabrication of completely grown and functioning heart tissue remains challenging. Despite these hurdles, it is becoming feasible to successfully design miniature tissue replicas that can compete and partially replace the state-of-the-art platforms for assessing drug safety, imitating human physiopathology, and allowing for efficient drug development[32]. We leave these developments out of the scope of the current study. We here address the possible effects of natriuretic peptides on the proliferation and differentiation of cardiovascular system cells in the field of cardiovascular regenerative medicine.

Possible effects of natriuretic peptides on cardiac repair and regeneration

Natriuretic peptides (NPs) perform key functions during embryonic heart development[33-39]. NPs are highly expressed in the embryonic heart during mid-gestation. Cardiac development coincides with the time window at which NPs production peaks, indicating their role in cardiac organogenesis[38]. In the developing zebrafish embryo, atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) may orchestrate cardiomyocyte proliferation and differentiation[40]. ANP and BNP are sensitive markers for the differentiating functional myocardium[41,42]. Crucial cardiogenic transcription factors regulate their expression[43]. Both genes are postnatally expressed in the heart, with ventricular ANP expression being significantly reduced[35,44,45]. Hypertrophy and cardiac failure lead to the ventricular overexpression of ANP and BNP, which is often called the reprogramming of foetal gene expression[34,46,47]. Exactly deciphering the molecular mechanisms of reprogramming would help us better understand why NPs are overexpressed in clinically relevant disease conditions and whether they hold promise for future cardiac regenerative medicine applications.

NPs are necessary for the proliferation of embryonic stem cells (ESCs) and their differentiation into cardiomyocytes[48,49]. ANP fulfils a local paracrine

function in orchestrating the balance between proliferation and differentiation of cardiac progenitor cells (CPCs) in embryonic mammalian ventricles via NPRA/cGMP-mediated signalling pathways[39]. An investigation into whether BNP plays an age-dependent role in the regeneration of neonatal and adult mouse hearts provided the first evidence for its involvement in the proliferation and differentiation of CPCs into cardiomyocytes[50]. In their study, Bielmann and co-workers found a few key findings concerning the involvement of BNP and its receptors in the proliferation and differentiation of CPCs into cardiomyocytes[50]. CPCs exhibit NPR-A and NPR-B expression, indicating that they are capable of responding to BNP[50]. NPR-A is necessary for the self-renewal and pluripotency maintenance of CPCs, whereas NPR-B participates in the proliferation of CPCs, suggesting that NPs are involved in those processes[51]. ANP, BNP, and CNP drive the proliferation and differentiation of CPCs into new cardiomyocytes through binding to NPR-B, increasing cGMP and activating PKG[52]. Exogenous BNP causes an increase in proliferating CPCs and new cardiomyocytes, which is linked to better cardiac function and remodelling following MI. Positive BNP staining indicates that CPCs can synthesise and release BNP in an autocrine manner to control their proliferation and differentiation into new cardiomyocytes[50]. Because NPs are cardiac hormones that can activate the proliferation and differentiation of CPCs both *in vivo* and *in vitro*, these results would be of great relevance to regenerative therapy of cardiac diseases.

Beltrami and co-workers were the first to reveal that the adult heart harbours cardiac progenitor/stem cells, which are identified by the proto-oncogene c-Kit expression on their cell surfaces[53,54]. c-Kit$^+$ cardiac stem cell (CSC) niches reportedly exist throughout the atrial and ventricular myocardium, with a higher density in the ventricular apex. When isolated and *ex vivo* cultured, c-Kit$^+$ CSCs were found to be self-renewal, clonogenic and multipotent, indicating that they are able to differentiate into cardiomyocytes, endothelial cells and smooth muscle cells. More importantly, transplantation of c-Kit$^+$ CSCs expanded in culture conditions resulted in their multilineage differentiation into cardiomyocytes, endothelial cells, and smooth muscle cells[53-56]. If adult CSCs could be genetically modified to enhance their therapeutic potential in response to myocardial damage, their use would become more prevalent in the stem cell-based therapeutic methods for augmenting cardiac regeneration in patients suffering from cardiac diseases. Accordingly, some studies have reported that CSC transplantation reduced infarct size and improved cardiac performance in a rat model of myocardial infarction, indicating that CSCs are involved in cardiac regeneration[53,57]. Mesenchymal stem cells (MSCs) have emerged as a major breakthrough treatment that harnesses paracrine signalling to regenerate damaged cardiomyocytes and restore endogenous tissue, as well as possessing unique immunomodulatory capabilities[58]. MSCs produce numerous paracrine factors, including ANP, BNP, and vascular endothelial growth factor (VEGF)[59-63]. These factors functionally recover the infarcted heart from ischemic injury through retaining contractile properties of the myocardium, preventing cell death of cardiomyocytes, and inducing angiogenesis in the infarcted heart[64-66]. In this direction, MSCs could be an ideal candidate for cardiac repair and regeneration research. It has been investigated if MSC transplantation could have a paracrine effect on the proliferation, migration, and differentiation of isolated CPCs into cardiomyocytes[67]. They found that CPCs initially were unable to express late phase markers of cardiac lineage (ANP and β-myosin heavy chain (β-MHC)) but expressed some early phase markers of cardiomyogenic lineage (myocyte-specific enhancer factor 2C (MEF-2c) and GATA-binding protein 4 (GATA-4)[67]. After two to four weeks of treatment with MSC-derived conditioned medium, there was an increase in ANP and β-MHC mRNA expression in CPCs. This activation promoted the proliferation, differentiation, and migration of CPCs in a paracrine manner[67]. However, spontaneously beating cells were not observed even after four weeks, in contrast to those reported previously[68,69]. Overall, these results showed that cardiomyogenesis of CPCs may be induced by MSC-derived conditioned media, but the potential for MSC-derived conditioned media to stimulate the differentiation of CPCs into mature cardiomyocytes may be limited[67]. Transplantation of MSCs into the infarcted heart does produce beneficial paracrine effects on endogenous cardiac stem/progenitor cells. Additionally, activation of endogenous CPCs through MSC transplantation and exogenous NP administration might have substantial clinical implications and open up promising therapeutic avenues for the treatment of cardiac diseases.

It has been reported that bone marrow derived mesenchymal stem cells (BMSCs) have the ability to differentiate into cardiomyocytes and endothelial cells[70-74]. BMSC transplants have proven effective in animal trials, and transplanted BMSCs have been reported to enhance heart function[75-78]. The interaction between BMSCs and neonatal rat ventricular cardiomyocytes can alleviate the phenotypes of pathological cardiac hypertrophy through suppressing the unfavourable remodelling processes in hypertrophic myocardium and ventricular cells[74]. In a study based on the fact that BMSCs possess the ability to differentiate into cardiac cells[70], recombinant human BNP (rhBNP) treatment and BMSC transplantation for treating cardiac failure in rats led to a significant increase in GATA-4 expression, which is linked to myocardial cell differentiation. This treatment also increased the expression levels of cardiac troponin I (cTnI) and connexin 43 (Cx43), which are responsible for cardiac systolic and diastolic function. As a result, these data on the survival rate of the BMSCs in cardiac tissue and the expression levels of proteins specific to the myocardium have put a new perspective on cell-based therapy to treat heart failure[79]. Given that myocardium-generating cells are of mesodermal origin[80] and that NPs play important roles during cardiac development[33-38], using BMSCs in the presence of NPs may be an effective cell-based therapy option of replenishing and restoring cardiomyocytes lost or damaged during myocardial infarction.

In vivo incorporation of BrdU into new-born and adult infarcted hearts (non-infarcted region) and cell culture experiments revealed that an increase in the number of CPCs in BNP-treated hearts was due to the stimulation of CPC proliferation[50]. However, the BNP administration did not enhance the proliferation of CPCs in the infarcted zone in pathological situations while appearing to affect the destiny of exogenous $CD45^+$ infiltrating cells. In the infarcted area of BNP-administered mice hearts, more NK2 homeobox 5 $(Nkx2.5)^+$ $CD45^+$ cells were found than that in the same zone of BNP-untreated mice hearts[50]. The findings reported by Bielmann and co-workers[50] showed that infiltrating bone marrow cells in a damaged heart could differentiate into the CPCs under *in vivo* conditions, as evidenced in cultured cell studies[81,82]. An increase in the number of $Nkx2.5^+$ $CD45^+$ cells in BNP-administered hearts could be explained by either enhanced mobilisation and migration of the $CD45^+$ cells from the bone marrow to the heart or enhanced differentiation of these bone marrow cells into CPCs[50, 83]. An increase in the number of $Nkx2.5^+$ cardiomyocytes in BNP-administered neonatal and adult hearts was demonstrated using immunohistochemistry, western blot and cell counting despite the unknown source of increased number of $Nkx2.5^+$ cardiomyocytes[50]. The cardiomyocytes that express the nuclear transcription factors Nkx2.5 in healthy and infarcted adult hearts could derive from the differentiating CPCs, proliferating mature cardiomyocytes or de-differentiating cardiomyocytes[84]. An *in vitro* study reported that ANP might induce the proliferation of new-born murine cardiomyocytes in a concentration-dependent manner. The low concentration of ANP (10 nM) increased the number of EdU-positive cardiomyocytes, but its high concentration (10 μM) decreased the number of EdU-positive cardiomyocytes, suggesting that increasing concentrations of ANP suppressed the proliferation of neonatal rat ventricular cardiomyocytes[40]. Therefore, the lower concentration of BNP is able to induce the proliferation of cardiomyocytes, taking into account approximately 200 nM concentration of BNP that was given to adult mice[50]. Collectively, these data show that using BNP as part of a therapeutic approach to induce cardiac regeneration may be beneficial.

The pathway triggered by BNP is vital to the function of CPCs and might be a target for inducing myocardial regeneration. Thus, the identification of relevant receptors would be critical to its possible role in cardiovascular regeneration. It is clearly evident that the BNP/NPR-B axis was necessary for the differentiation of CPCs into mature cardiomyocytes, in addition to the significance of the BNP/NPR-A axis for the induction of CPCs proliferation[50]. BNP receptors have already been reported to perform different roles in embryonic stem cells (ESCs)[48, 49, 51, 85]. Therefore, the interaction between BNP and NPR-B in the CPCs differentiation would be of great relevance for cardiovascular medicine applications. A low amount of NPR-A has been detected in the myocardial and coronary arteries of failing human hearts[86]. NPR-B has been found to be the most common natriuretic peptide receptor in the failing mice hearts secondary to transaortic constriction[87]. The chimeric natriuretic peptide CD-NP exerting cardioprotective effects without causing hypotension might be used instead of BNP therapy[88, 89].

The ability of BNP administration to enhance the number of Sca-1$^+$ cells, particularly Sca-1$^+$ Nkx2.5$^+$ cells, is of great relevance for cardiac cell therapies targeted at inducing heart regeneration. The general view is that Sca-1$^+$ Nkx2.5$^+$ cells are cardiac precursor cells capable of differentiating into mature and functional cardiomyocytes[90-93]. Nevertheless, a study revealed that Sca-1 is expressed by around 70% of cardiac fibroblasts and Nkx2.5 could be expressed by half of the Sca-1$^+$ fibroblasts[94], indicating that the Sca-1$^+$ Nkx2.5$^+$ cells represent a heterogeneous cell population and Sca-1+ cells are impure precursor cells[52]. In this context, the protective effect of BNP *in vivo* must be due to its action on these cells or a subset of them[50, 95-97]. Consistent with a previous study[50], administration of BNP into neonatal or adult mice following MI resulted in an increase in Sca-1$^+$ Nkx2.5$^+$ cells[52]. Those findings support a previous study in which Sca-1$^+$ cells differentiated into cardiomyocytes following MI[92]. Given that some of these Sca-1$^+$ cells are CPCs able to differentiate into cardiomyocytes following BNP delivery[50], future research should be focused on the role and function of fibroblasts that express both Sca-1 and cardiogenic markers[52]. An interesting finding is that T-box transcription factor 20 (Tbx20)-knockout specific to these fibroblasts influenced cardiomyocyte differentiation in the process of cardiac development[94]. This subpopulation of fibroblasts may promote cardiac regeneration through secreting particular substances, including prostaglandin E2 (PGE2) and fibroblast growth factor 2 (FGF-1), that are able to help differentiate endogenous Sca-1$^+$ cells into cardiomyocytes following MI[91,92]. Administration of three NPs (ANP, BNP and CNP) had an inducible effect, with an increase in the number of Sca-1$^+$ cells. NPs exert their effects on Sca-1$^+$ cells through different mechanisms[52]. The inducible effects of BNP and CNP were clearly suppressed by P19 (an NPR-B antagonist), indicating that BNP and CNP triggered Sca-1$^+$ cell proliferation merely through binding to NPR-B. On the contrary, Anantin (an ANP antagonist) and P19 impeded the stimulative action of ANP on Sca-1$^+$ cell proliferation, demonstrating that ANP can function through both NPR-B and NPR-A[52]. Additionally, Anantin weakened the proliferation of unstimulated Sca-1$^+$ cells by a ratio of 20 percent. These observations imply that NPR-A is implicated in cellular proliferation[52]. However, more research is needed to understand the exact role of NPR-A in ANP-induced Sca-1$^+$ cells.

Infarcted myocardium is proximally to distally characterised by three zones, namely the infarct zone (IZ), border zone (BZ) and remote zone (RZ). Among these zones, the BZ, which is hypocontractile and undergoes electrophysiological remodelling, might be more vulnerable to ischemic insults[98]. After MI, its hypocontractility seems to spread to neighbouring myocardium, which progressively diminishes contractile function as the cardiac remodelling occurs[98]. However, studies of zebrafish and transgenic mouse models have resurfaced the significance of BZ myocardium as a putative player in post-injury heart regeneration. These studies showed that the proliferation of cardiomyocytes in the zone bordering the injury enhances cardiac regeneration, implying a role of BZ cardiomyocytes specifically involved in cardiac regeneration[99-103]. Recent studies have uncovered a transcriptionally distinct BZ conserved in mice and humans that expresses ANP and BNP genes[43,46,104], indicating that these two genes are closely linked in post-myocardial infarction survival[43]. It has been reported that regulatory element 1 (RE1) highly influences the ventricular expression of ANP and BNP genes. When the BNP gene is knocked out, augmentation of ventricular ANP expression confirms that RE1 may activate ANP and BNP genes in a competitive manner[43]. Further studies are needed to discover the precise role of NPs in cardiac regeneration in general, and in the proliferation and differentiation of cardiomyocytes in the BZ in particular, and their functional relationship with regulatory elements, including RE1.

Possible effects of natriuretic peptides on vascular repair and regeneration

Improved vascularization is a critical step in accelerating cardiac recovery and function following ischemic events[105,106]. In this regard, the creation of new blood vessels in the ischemic regions improves blood flow, supplies nutrients and oxygen to the surviving cells, and provokes new cell migration, proliferation, and engraftment[107]. Suppression of the angiogenic events leads to heart failure in animal models of cardiac injury. However, immediate reperfusion or enhanced angiogenesis would improve cardiac function and delay the onset of heart failure in individuals with myocardial ischemia[108-110]. Therefore, it would be noteworthy to figure out which factors promote neovascular growth after myocardial infarction (MI).

Recent studies have provided novel evidence for the regional and temporal effects of BNP in the infarcted hearts[50,107]. BNP administered intraperitoneally increased myocardial vascularization and endothelial cells in both the infarct zone and border zone and the remote zone of infarcted mouse hearts. BNP increased the proliferation of endogenous pre-existing endothelium cells through binding to NPR-A and activating the p38 MAP kinase[107]. BNP promoted and/or expedited the re-expression of the Wilms' tumour 1 transcription factor (WT1) in cardiac cells in the aftermath of the MI. The proliferation of $WT1^+$ epicardium-derived cells (EPDCs) and their differentiation into endothelial cells contributed slightly to neovascularization in the infarcted region of untreated damaged hearts. BNP caused the proliferation of $WT1^+$ EPDCs, resulting in a marked increase in the number of endothelial cells stemming from $WT1^+$ EPDCs in BNP-administered infarcted mice hearts[107]. These findings corroborated previous findings that natriuretic peptides promote vasculogenic and angiogenic events throughout development and in ischemic adult organs[111,112]. Furthermore, BNP administration enhanced vascular regeneration in a mouse model of hindlimb ischemia[83]. Adenovirus-mediated BNP gene delivery into the myocardium had improved the formation of capillary networks in the healthy, but not infarcted, rat hearts[97].

Differentiation of some immature precursor cells, including human or murine endothelial precursor cells (EPCs) and mouse embryonic stem cells, might be stimulated by BNP administration[83]. In humans, BNP levels in the blood correspond with the quantity of EPCs in the peripheral blood, but BNP administration causes a large increase in bone marrow EPCs expressing stem cell antigen-1 (Sca-1) and Flk-1 (a receptor for VEGF) in mice[83]. A more interesting finding of alteration in angiogenic processes came from the ischemic hind limb model established in NPR-A-deficient mice, showing that NPR-A was involved in angiogenesis[113,114]. It has been shown that BNP is released by activated satellite cells, but not quiescent satellite cells, in the ischemic hindlimb model[50,114]. Taken together, BNP stimulates vascular growth by increasing the quantity of endothelial progenitors and improving their functional characteristics. The involvement of BNP in the pro-vasculogenic process might be beneficial for chronic heart failure patients and for the improvement of collateral formation in ischemic patients.

The modulatory function of CNP in the vasculature has been well reviewed[112]. CNP administration has been shown to expedite re-endothelialization and mitigate harmful neointimal hyperplasia in animal models of vein grafts and balloon angioplasty[115-117]. Studies reviewed by Moyes and Hobbs[112] have demonstrated that CNP promotes endothelial and smooth muscle cell growth via NPR-C independently of cGMP. Although both cell types generate a significant amount of cGMP, extracellular signal-related kinase 1/2 (ERK 1/2) mediates pro- and anti-mitogenic effects of CNP, which may be suppressed by M372049 (an NPR-C antagonist) and Pertussis toxin (a $G_{i/0}$ G protein inhibitor)[118,119]. Activation of ERK 1/2 via CNP causes endothelial cells to express more cell cycle promoters (cyclin D1) and smooth muscle cells to produce more inhibitory cell cycle proteins (p21 and p27)[119]. Augmentation of CNP-driven endothelial cell proliferation requires phosphorylation of ERK1/2 in an NPR-C–dependent manner[119]. The capacity of CNP to stimulate endothelial tubule formation and aortic sprouting was prevented in the presence of the specific phosphoinositide 3-kinase (PI3K) inhibitor wortmannin[120], indicating that PI3K is required for endothelial cell migration[121]. In addition, *in vivo* studies revealed that endothelial-derived CNP and NPR-C deficient animals experience slower wound healing and more intimal hyperplasia after vascular damage. In summary, CNP produced by the endothelium is important for vascular repair and regeneration following ischemia[120]. Therefore, pharmacological targeting of NPR-C would improve vascular restoration following damage and open up a new therapeutic avenue for the treatment of vascular diseases.

Both cell loss and insufficient angiogenesis are local causes of serious myocardial remodelling after a MI. *In vivo* investigations have revealed that the presence of capillary density led to an impairment in myocardial perfusion throughout the left ventricular (LV) areas of infarcted hearts[122, 123]. Despite the evidence that vasculogenesis is functionally ineffective, a few pre-clinical gene therapy studies have revealed that over-expression of cardiac VEGF could prevent or constrain late myocardial remodelling by inducing angiogenesis[124,125]. A study on the vasculogenic role of CNP in myocardial remodelling demonstrated that VEGF and CNP were upregulated in the left ventricular border zone

(LVBZ). Four weeks after MI, CNP and VEGF expression were linked to enhanced LV capillary density, elevated BNP levels, and extracellular matrix remodelling. However, CNP expression was not enhanced in the non-infarcted RZ in a comparable manner to that of sham-operated swine myocardium[126]. These results show that CNP serves as an endogenous mediator in VEGF-dependent vasculogenesis during post-ischemic remodelling, in addition to the vasorelaxant effect yielded by BNP[127].

In vivo CNP administration has been shown to considerably reduce myocardial collagen deposition in infarcted LV areas[128]. Cardiomyocytes submerged in a solution rich in collagen type III and I fibres exhibited higher CNP expression. Thus, it seems plausible that an ischemic milieu causes cardiomyocytes to express CNP in an adaptive manner[126]. Despite the fact that CNP safeguards cardiomyocytes against ischemia insult via the NPR-C receptor[129], CNP predominantly interacts with the NPR-B in the heart[130,131]. NPR-B mRNA expression was acceptable in LV remodelling areas of the swine heart, yet NPR-C mRNA expression was more than three times higher than in RZ[126]. The size of the angiogenic response through which VEGF-A is mostly mediated in the healing area determines regional cardiac remodelling[132,133]. LVBZ is characterised by swift VEGF-A expression that could continue up to three months after MI[134]. Enhanced VEGF expression is localised to coronary endothelial cells throughout the LV remodelling in which CNP expression is also present. These findings suggest that the interaction of CNP-VEGF between cardiomyocytes and endothelial cells is required for cardiac remodeling[126]. Taking into consideration that CNP is implicated in vascular protective and regenerative processes through its receptors NPR-B and NPR-C[112], pharmacological and genetic targeting of these receptors would bring considerable therapeutic benefits for vascular diseases.

CONCLUSIONS

There are various investigations harnessing the power of progenitor/stem cells to treat and curb CVDs. The growing consensus is that progenitor/stem cells could be used as effective mediators of cardiac and vascular repair and regeneration. Stem cells have a high degree of plasticity and the ability to modulate regenerative and angiogenic processes. Considering the myocardial cells are of mesodermal origin and the natriuretic peptide system is involved in cardiac development, harnessing the power of mesenchymal stem cells in the presence of natriuretic peptides may be a potent cell-based therapy candidate for replenishing and restoring cardiomyocytes lost or damaged during myocardial infarction. In addition, the pharmacological and genetic manipulation of C-type natriuretic peptide and its receptors would promote angiogenic processes and provide considerable therapeutic insights into the treatment and prevention of vascular diseases. Compelling evidence shows that natriuretic peptides and their receptors could orchestrate regenerative and compensative processes following cardiac and vascular injuries. Overall, the evidence demonstrates that exogenous natriuretic peptide administration could trigger the regenerative and restorative processes in the cardiovascular system following experimental and inherent cardiac and vascular damage. It is clearly evident that although we have achieved tremendous progress in the interaction of stem cells with the natriuretic peptide system in cardiac and vascular regeneration and repair, we still have a long distance to cover in efficiently harnessing their power in the field of cardiovascular regenerative medicine. Therefore, deciphering the exact role of the natriuretic peptide system in the proliferation and differentiation of stem cells and better understanding the pharmacological activation and genetic manipulation of the natriuretic peptide system could be touted as novel approaches to curing, mitigating, and preventing cardiovascular diseases.

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