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Heme oxygenase in cardiac repair and regeneration

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TABLE OF CONTENTS

1. ABSTRACT

The incidence of cardiac complications such as myocardial infarction and congestive heart failure is increasing. Once congestive heart failure emerges, little can be done to improve long-term cardiac function. The cellular basis of this downward spiral may be the dramatic loss of viable cardiomyocytes following acute ischemia and/or chronic apoptosis/necrosis which are not adequately replaced. Contrary to the old postulates of developmental biology, tissue self-renewal is not limited to blood, intestines and skin, but other organs including the heart have some capabilities of self-renewal. However, the intrinsic ability of self-renewal of adult myocardium or cardiomyogenesis is limited and thus novel paradigms capable of potentiating this process of regenerative organogenesis should be sought. Several strategies and paradigms are being currently explored, and among these is the heme-oxygenase system. Emerging evidence indicate that the heme-oxygenase system could be explored in regenerative medicine given its unique ability to concomitantly suppress apoptosis and necrosis, while facilitating tissue regeneration/repair and the formation of new blood vessels. This review highlights the recent development of heme-oxygenase in myocardial repair and regeneration.

2. INTRODUCTION

In industrialized and developing countries, cardiovascular disease remains a challenging problem with huge socio-economic burden to healthcare systems (1-8). In spite of the advances in early management and longer-term therapy, heart-related diseases still carry an undesirably high rate of morbidity and mortality (1,4,5,8-14). For example, in 2010, the overall rate of death in the United States attributable to cardiovascular disease was 235.5 per 100 000, and 1 in 9 death certificates (279 098 deaths) was due to heart failure (1). This was not limited only to the male gender, but amazingly, a wide body of evidence suggests greater vulnerability of females to many cardiovascular complications (15-22). Generally, males are at higher risk of developing cardiovascular complications including myocardial infarction than females (8,16,23-27), and it is widely documented that males are also more likely to have myocardial infarction earlier in life (23,27-29). However, recent epidemiological data indicates that heart disease kills more females each year than any other disease, including breast cancer (1,8,30). In a 2014 publication by the *American Heart Association* (AHA), cardiovascular death rates in the United States were 278.4 per 100 000 for white males, 369.2 per 100 000 for black males, 192.2 per 100 000 for white females, and 260.5 per 100 000 for black females (1,30). Similarly, a 2014 Lancet publication showed that the total number of cardiovascular deaths registered worldwide for 2013 was 17 297 500, while that of all cancers combined was 8 235 700 (8), indicating a 2.1-fold increase in cardiovascular deaths as compared to all cancers. Consistently the AHA report indicates that 1 in 4.5 females died of cancer in 2010, whereas 1 in 3.1 died of cardiovascular disease (1). Furthermore, the 2010 mortality data of the United States indicates that cardiovascular disease caused about 1 death per minute among females (1,30). By the same token, the 2014 AHA report revealed that the number of female deaths attributable to cardiovascular disease represents approximately the same number of female lives claimed by cancer, Alzheimer disease and chronic lower respiratory disease combined (1). Thus, a significant number of females die from cardiovascular disease each year, and this is twice the number of

deaths from all cancers combined (1,8,30). Moreover, females undergoing isolated coronary artery bypass graft surgery have increased risk for postoperative morbidity and mortality (31). Similarly, recovery from myocardial infarction is better in men than women (27,31-34). Furthermore, women recovering from myocardial infarction are more likely to die of a recurrent heart attack or a related complication earlier than men (27,35). Thus, cardiovascular complications remain a challenging issue in both genders and novel studies tailored to address this problem in both genders are needed.

With aging of the population and the epidemic of chronic conditions like hypertension, obesity and diabetes, the incidence of cardiac complications such as myocardial infarction and congestive heart failure will further increase (8,36-55). Although various treatment strategies are available, once congestive heart failure emerges, little can be done to improve long-term cardiac function. The cellular basis of this downward spiral trend of cardiomyocyte loss is the dramatic reduction of viable cells following acute ischemic injury and/or chronic cell apoptosis/necrosis, which are not adequately replaced (56-66). With the exception of heart transplantation and implantation of mechanical ventricular devices, current therapies do not address the central problem of decreased pumping capacity owing to a depleted pool of cardiomyocytes. Thus, the only cure to effectively restore myocardial function is cardiac transplantation. However, with the low number of available hearts for transplantation, the search for alternative ways of recovering myocardial function is indispensable. Currently, several strategies including regenerative therapy are under consideration.

3. PROSPECTS OF REGENERATIVE MORPHOGENESIS

For decades, many adult organs have been considered post-mitotic organs without regenerative capacity. It was generally believed that the myocardium from early postnatal life until death was constituted by myocytes with the same chronological age as the individual, and the concept of new myocyte formation and/or regeneration did not fit into this picture. Contrary to the old postulates of developmental biology, tissue self-renewal is not limited to blood, intestines and skin, but other organs like the heart and kidney have some capabilities of self-renewal (67-70). This has re-enkindled great hopes an immense interest in regenerative organogenesis in medicine. However, the intrinsic ability of self-renewal of the adult myocardium or cardiomyogenesis is limited (71-78), and thus novel paradigms capable of potentiating this process of regenerative organogenesis should be sought.

Emerging evidence suggest that the adult mammalian myocardium has great innate potential for regenerative morphogenesis following severe injury although this regenerative process is slow (71-78), suggesting the need for novel strategies capable of amplifying this intrinsic regenerative capacity of the myocardium. Although transplantation of cultured cardiac stem cells into the infarcted heart leads to the formation of *de novo* cardiac tissue, the effect on cardiac regeneration is still marginal (79,80). This unsatisfying outcome may be due to physiological differences arising during tissue morphogenesis *in vitro* as opposed to *in vivo* conditions. Since *in vitro* conditions may not be optimal for *in vivo* tissue morphogenesis, *in situ* activation of resident progenitor cells within the heart or mobilization of endogenous progenitors from other extra-cardiac sources might be an attractive approach to enhance the limited endogenous regenerative capacity of the injured myocardium. The epicardial layer of the heart provides cardiac progenitor/stem cells during development (81-97). Given that this layer regains embryonic characteristics in the adult heart after cardiac injury, it could serve as a potential source for resident cardiac progenitor/stem cells (81-97).

Generally, myocardial regeneration or cardiomyogenesis of the adult heart may occur by several processes including; (i) the re-entry of cardiomyocytes into the cell cycle, (ii) dedifferentiation of pre-existing cardiomyocytes, (iii) transdifferentiation of hematopoietic stem cells and cardiac fibroblast into cardiomyocytes, and (iv) cardiomyocytes derived from resident cardiac stem cells (71-73,76,98-126). However, the relative input of each of these processes to cardiac regeneration following cardiac injury is not fully understood. Therefore, future studies should be designed to fully investigate the contribution these processes on cardiac morphogenesis. On the other hand, the impact of these regenerative processes on cardiac morphogenesis may be affected by a wide variety of different factors including; (i) the type of cardiac injury (ischemic vs fibrotic), (ii) underlying chronic conditions such as diabetes, obesity and hypertension, (iii) genetics and epigenetics, (iv) gender, ethnicity and aging, and (v) life styles. The diversity of these factors renders the complexity of the challenge to find a universal answer.

4. THE HEME OXYGENASE SYSTEM

Heme oxygenase (HO) is a microsomal enzyme that cleaves the α-methene bridge of heme moiety to produce equimolar amounts of carbon monoxide, bilirubin and iron that is rapidly sequestered into ferritin (127,128) (Figure 1). The cytoprotective products of the HO system include carbon monoxide, biliverdin, bilirubin and ferritin, and are known to abate apoptosis, necrosis, inflammation and oxidative stress (128-177) (Figure 1). HO has three major isoforms of which HO-1 is inducible, HO-2 is constitutive, and HO-3 is a

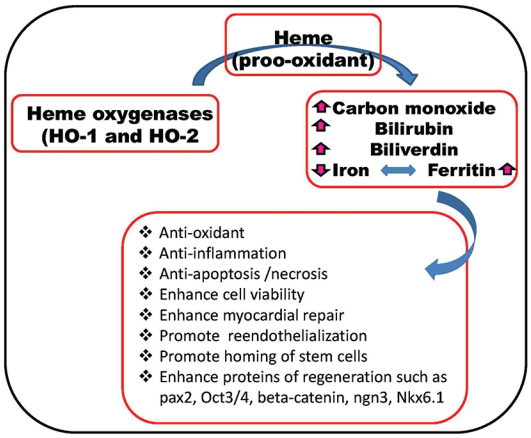

Figure 1. The Heme oxygenase (HO) system and its cytoprotective products. HO catalyses the breakdown of pro-oxidant heme to produce cytoprotective products such as carbon monoxide, biliverdin, bilirubin and ferritin. The HO system enhance the recruitment of stem/progenitor cells to injured tissue, facilitates tissue regeneration/repair and the formation of new blood vessels.

pseudotranscripts of HO-2 with no functional genes, so HO-1 and HO-2 are largely responsible for HO enzymatic activity (127,128,178-181). Generally, the basal HO activity is maintained by HO-2 (127,128,178,179,182), while HO-1 is stimulated by a diversity of chemical, pathological and physical stimuli (127,128). Seen in this light, HO-1 is considered a sensitive index that is triggered during adverse conditions. However, the pathological activation of HO-1 is generally subthreshold and may not be able to activate the major downstream signaling pathways like the soluble gyanylyl cyclas/ cGMP secondary messenger system through which HO elicits most of its effects, suggesting the need for a more robust and surmountable increase with HO-inducers for cytoprotection (128,131-135,140-175,183,184).

Although HO-substrates like hemin, heme arginate and cobalt protoporphyrin are widely used to upregulate the HO system for cytoprotection (128,129, 131-134,140-147,154,155,160,167,169,183,185-190), recent evidence indicate that other compounds such; (a) statins like simvastatin, fluvastatin, lovastatin atorvastatin, pitavastatin, pravastatin, cerivastatin and rosuvastatin (191-207), (b) phytochemicals like polyphenols, resveratrol, α-Viniferin, ellagic acid, ε-Viniferin, phytoestrogens, polydatin, pinosylvin, carotenoids, ginsenoside, flavonoids, curcumin and stilbenoids (208-268), (c) omega-3 polyunsaturated fatty acids (222,269-284), (d) methotrexate (217,285), (e) flaxseed (283), and (f) aspirin (286,287) are capable of inducing HO-1. Given that the HO system is beneficial in cardiomyopathy (132,135,144,149-153, 156,159,161,162,165,175,184,288-310), this array of pharmacological and naturally occurring compounds may be explored for the induction of the HO system is the restoration of cardiac morphology and function.

5. THE HO SYSTEM AND TISSUE REGENERATION

The HO system has a wide variety of different functions in physiological system. More-recently, the HO system has been shown to modulate angiogenesis (311-314), cell proliferation and cell-cycle progression (315,316). Although the HO system modulates the pro-angiogenic factor, VEGF and enhance the process of angiogenesis, the levels of VEGF should be carefully controlled because excessive angiogenesis is at the basis of many proliferative disorders including cancer (317,318) (. Since VEGF is generally stimulated by oxidative stress and (inflammatory cytokines (319,320) and the HO system has anti-inflammatory and anti-oxidative properties (136-138,321), HO may attenuate excessive stimulation of VEGF to promote healthy angiogenesis.

The processes of neovascularization and angiogenesis are important for tissue repair. Angiogenesis is a fundamental process by which new blood vessels are formed. Angiogenesis is increased during embryogenesis and in pathological events like ischemia, inflammation, tumor growth, and wound healing in response to angiogenic factors. Generally, angiogenic factors increase vascular permeability, cell activation, migration, proliferation and capillary formation. After injury, ineffective capillary repair/angiogenesis may lead to chronic disease, whereas effective repair attenuates the injury process. Accordingly, the process of myocardial repair and regeneration may depend on an intricate balance between angiogenic and anti-angiogenic factors to maintain the myocardial microvasculature. These processes lead to the production of different mediators including cytokines and acute phase response proteins such as HO (314).

Besides angiogenic factors, the preservation of cell vitality is essential. Necrosis and apoptosis are processes that reduce the availability of cells for regeneration and repair (322,323). Thus substances that preserve cell vitality may facilitate repair. Amongst the physiological cytoprotective pathways with effects against inflammation, apoptosis and necrosis is the HO system (136-138,176,177,321,324-329). HO is ubiquitously distributed and expressed in different tissues including cardiac tissue (135,144,149). Importantly, the HO system improved cardiac xenograft survival by abating necrosis, apoptosis, inflammation during ischemia (326,328). Similarly, HO suppressed nitric oxide-induced necrosis and lipid peroxidation in human lung epithelial cells (325). Furthermore, the HO system reduced apoptosis (327) by concomitantly potentiating anti-apoptotic agents like Bcl-2, Bcl-xl and the p38MAP kinase pathway, while suppressing pro-apoptotic agents such as caspase-3, caspase-9 and Bax (327,330-332). Therefore, by abating apoptosis and necrosis through

multiple mechanisms, the HO system preserves cell vitality (329,333), which in turn, may enhance regeneration by stem/progenitor cells and myocytes. Accordingly, recent evidence indicates that the HO system promoted reendothelialization (334). Similarly, the HO system facilitated the recruitment of stem cells to injured tissue (335) and promoted myocardial neovascularization (336). Furthermore, the HO inducer, hemin, enhanced the proliferation and differentiation of endothelial progenitor cells via activation of Akt and extracellular signal-regulated kinase (337). Interestingly, mesenchymal stem cells transfected with adenovirus carrying human HO-1 gene were shown to reduce myocardial infarct size, abate apoptosis of cardiomyocytes, increased microvessel density and improved left ventricular function (338). Consistently, the overexpression of HO-1 in mesenchymal stem cells resulted in the suppression of apoptosis and oxidative stress, with the reduction of myocardial infarction and the enhancement of VEGF (339). Moreover, HO-1 overexpression has been shown to enhance mesenchymal stem cells differentiation (340,341). Furthermore, we recently showed that the HO-inducers like hemin or heme-arginate, restored myocardial morphology and function by attenuating myocardial damage in a several hypertensive and diabetic models including; (i) spontaneously hypertensive rats (SHR), (ii) uninephrectomized (UnX) deoxycorticosterone acetate (DOCA-salt) hypertensive rats, (iii) Nω-nitro-L-arginine methyl ester (L-NAME)-induced hypertension, (iv) Zucker diabetic fatty (ZDF) rats and (v) insulin resistant obese Zucker rats (132,135,144,149,150,153,165,175). Interestingly, the restoration of the damaged myocardium was accompanied by increased expression of several proteins of dedifferentiation and transdifferentiation such as pax2, Oct3/4, beta-catenin, ngn3, Nkx6.1 and the stem cell marker, cKit (Figure 2).

Collectively, these studies suggest that the HO system has unique qualities that facilitate tissue regeneration/repair and the formation of new blood vessels. The cytoprotective qualities of HO include its ability to suppress apoptosis/necrosis and enhance the recruitment of stem/progenitor cells to injured tissue (334,335). In addition to these qualities, the anti-oxidant and anti-inflammatory effects of the HO system would create an optimum environment for tissue regeneration/repair.

6. CONCLUSION

Cardiovascular disease remains a challenging problem with huge socio-economic burden to healthcare systems (1-8). With aging of the population and the epidemic of chronic conditions like hypertension, obesity and diabetes, the incidence of cardiac complications such as myocardial infarction and congestive heart failure will further increase (8,36-55). Although various treatment strategies are available, once congestive heart failure emerges, little can be done to improve long-term cardiac function. Thus, novel strategies of recovering myocardial functions are needed. Amongst areas of significant interest is regenerative therapy. The adult mammalian myocardium has great innate potential for regenerative morphogenesis following severe injury although this regenerative process is slow (71-78), suggesting the need for novel strategies capable of amplifying this intrinsic regenerative capacity of the myocardium. Emerging evidence indicate that the HO system could be explored in regenerative medicine given its unique ability to concomitantly suppress apoptosis and necrosis, while facilitating tissue regeneration/repair and the formation of new blood vessels (334-341).

7. FUTURE DIRECTIONS

Generally, myocardial regeneration or cardiomyogenesis of the adult heart may occur by several processes including; (i) the re-entry of cardiomyocytes into the cell cycle, (ii) dedifferentiation of pre-existing cardiomyocytes, (iii) transdifferentiation of hematopoietic stem cells and cardiac fibroblast into cardiomyocytes, and (iv) cardiomyocytes derived from resident cardiac stem cells (71-73,76,98-126). However, the actual contribution of each of these processes to cardiac regeneration following cardiac injury is not fully understood. The relative input of each of these processes to cardiac regeneration should be assessed to understand the process with the greatest impact on cardiac morphogenesis. Should this knowledge become available, then strategies to optimize the processes with significant contribution towards cardiac morphogenesis should be sought. On the other hand, the impact of these regenerative processes on cardiac morphogenesis may be affected by a wide variety of different factors including; (i) the type of cardiac injury (ischemic vs fibrotic), (ii) underlying chronic conditions such as diabetes, obesity and hypertension, (iii) genetics and epigenetics, (iv) gender, ethnicity and aging, and (v) life styles. The diversity of these factors renders the complexity of the challenge to find a universal answer. Thus, without precise and adequate knowledge on all these factors, a universal solution may be far. Nevertheless, any acquired knowledge on the impact of some of these factors either as a single entity or in combination with another factor about the effect on cardiomyogenesis, would greatly increase the prospects of optimizing cardiac regeneration in a specific population group or groups with the ultimate goal of improving cardiac morphogenesis.

Since hemin and heme arginate are the traditional HO-1 inducers used clinically in humans (342-346), a wide of other compounds including statins (191-207), phytochemicals (208-268), (**c)** omega-3 polyunsaturated fatty acids (222, 269-284), are capable of inducing HO-1, more-in-depth studies about the HO-1 inducing capabilities of these compounds should be investigated

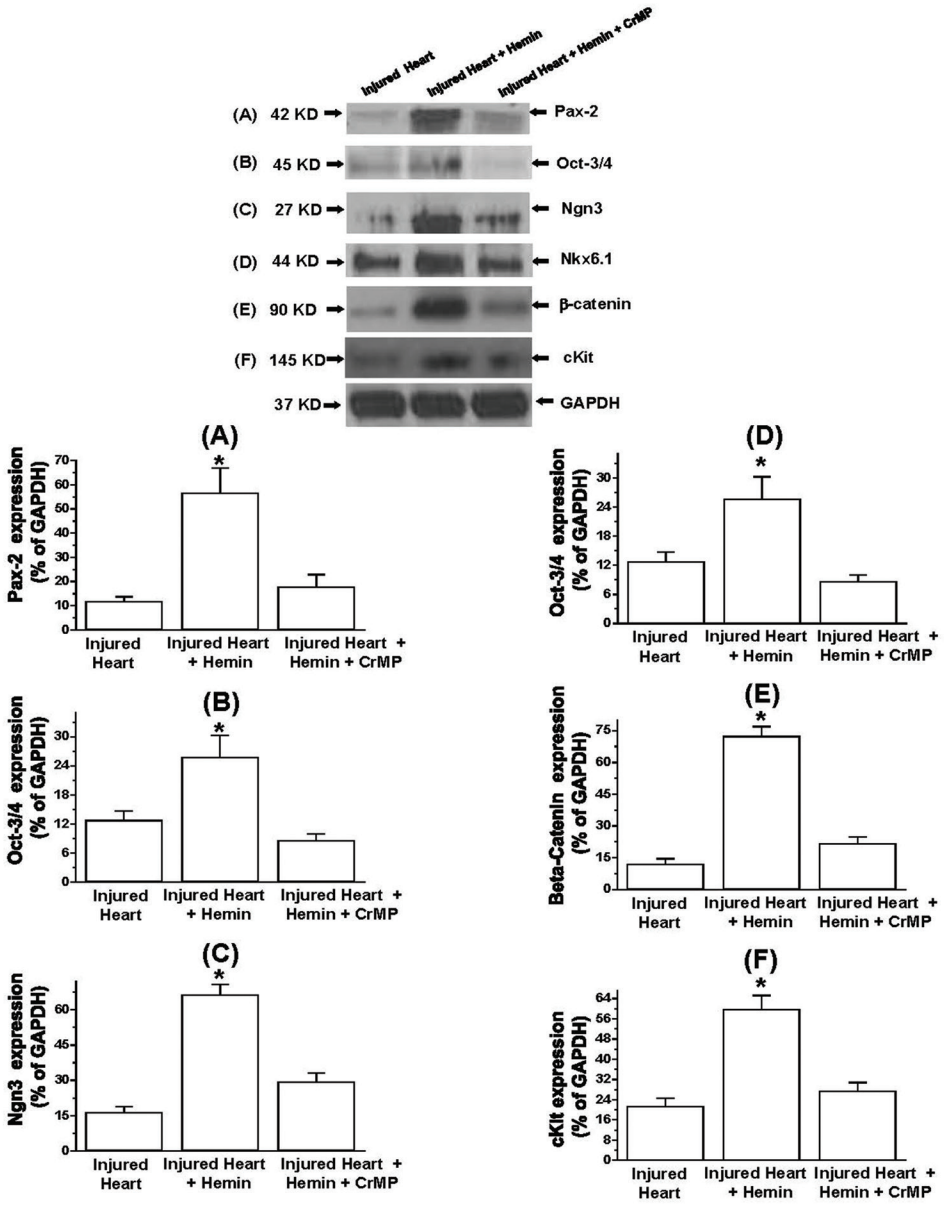

Figure 2. Western immunoblotting indicates that the HO-inducer, hemin poentiates proteins of regeneration such as pax2, Oct3/4, beta-catenin, ngn3, Nkx6.1 and the stem cell marker, cKit in injured hearts from uninephrectomized (UnX) deoxycorticosterone acetate (DOCA-salt) hypertensive rats.

given that the traditional HO inducers like hemin and heme arginate which are used clinically can only be administered via intravenous route. New HO-1 inducers that can be administered via alternative routes with greater efficacy and reduced collateral effects are needed for cardiprotection. Besides searching for alternative HO inducers with clinical application, further studies should investigate the threshold level of HO-1 induction that evokes optimal cardioprotection with less side effects. These are some of the hurdles that must be cleared for HO-inducers to be formally accepted as a class of cardioprotective drug.

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