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Chapter 16

Role of Prokineticin in Epicardial Progenitor Cell Differentiation to Regenerate Heart

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http://dx.doi.org/10.5772/48234

1. Introduction

Cardiovascular diseases are one of the most common health-care problems throughout the world and carry a high rate of mortality (Zannad, et al., 2009). New strategies are urgently needed to replace cardiomyocytes and increase circulatory support for the treatment of cardiovascular diseases.

Over the last decade, stem/progenitor-cell therapy has emerged as an innovative approach to provide cardiac repair and regeneration (Zimmermann, et al., 2006). Several stem- and progenitor-cell types from autologous and allogeneic donors have been analyzed to find the most appropriate candidate. Although embryonic stem (ES) cells can differentiate into most cardiac cell types (Mummery, et al., 2002) , their clinical use is severely limited due to ethical concerns and immunogenic and teratogenic side effects (Blum and Benvenisty, 2008). Adult bone marrow-derived stem cells avoid the ethical and clinical issues associated with ES cells (Bianco, et al., 2001). However, animal studies have demonstrated a variable degree of cardiomyogenesis, and improvement in heart function by bone marrow-derived stem cells (Murry, et al., 2004). Thus, the utility of adult bone marrow-derived stem cells is hampered by their limited population size and restricted potential for cardiovascular differentiation (Assmus, et al., 2010).

Recently, therapies based on cardiac progenitor cells (CPC) have emerged as promising potential cardiac therapeutics (Gonzales and Pedrazzini, 2009). For cardiovascular therapy, pluripotent cardiac progenitor cells (CPCs) resident in the epicardium offer distinct advantages over other adult stem-cell types (Wessels and Perez-Pomares, 2004). They are autologous, tissue-specific and pre-committed (Dube, et al., 2012) to a cardiac fate, and display a greater propensity to differentiate towards cardiovascular lineages (Cai, et al., 2008), (Smart and Riley, 2012). Epicardial derived cardiac progenitor cells (EPDCs) exist in the heart of several species, including mice (Limana, et al., 2007) and humans (van Tuyn, et

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al., 2007). Due to cardiogenic and angiogenic abilities, epicardial CPCs represent an ideal candidate for cardiac regeneration. However, we do not know the mechanisms underlying epicardial CPC self renewal, proliferation and differentiation, which are prerequisites for cardiac regenerative therapy. An optimal paradigm of cardiovascular therapy may therefore consist of identifying the most effective factors that trigger the restoration of epicardial CPCs for healing heart injuries, with an emphasis on small molecule-based therapy over cell-based therapy.

It is therefore imperative to obtain a better understanding of the biology and regenerative potential of endogenous epicardial CPCs. The race is still on to find the "best" factor or drugs to reprogram endogenous epicardial CPCs to reconstitute the myocardium and improve function after myocardial damage.

2. Epicardium as a source of multipotent progenitor cells

Epicardium derived from proepicardium has an essential modulating role in the differentiation of the compact ventricular layer of the myocardium and the development of cardiac vessels during embryogenesis (Zhou, et al., 2008). Deletions of selected genes expressed in the epicardium (i.e. VCAM-1, α4-integrin) resulted in severe defects in the developing heart and its vasculature. The zebrafish epicardium promotes cardiac regeneration through epithelial to mesenchymal transition (EMT) and subsequent migration into the myocardium to form neovasculorization (Lepilina, et al., 2006). Signalling from the myocardium to the epicardium (i.e. Tβ4, FOG-2) (Smart, et al., 2007; Tevosian, et al., 2000) also leads undeveloped ventricle with vascularisation defects.

The epicardium through EMT generates a population of Epicardial Derived Progenitor Cells (EPDCs) that invade the underlying myocardium, and differentiate into various cardiac lineages (Smart and Riley, 2012; Zhou, et al., 2008). Williams Tumour (WT1) gene has been shown to regulate epicardial EMT through beta-catenin (Zamora, et al., 2007) and retinoic acid signaling pathways (von Gise, et al., 2011). EPDCs can either form endothelial cells, in response to a combination of myocardial vascular endothelial growth factor and basic-fibroblast growth factor signalling (van Wijk, et al., 2009), or differentiate into smooth muscle cells, upon exposure to platelet-derived growth factor (Kang, et al., 2008), transforming growth factor beta and bone morphogenetic protein-2 (Sanchez and Barnett, 2012).

However, Tβ4 (Smart, et al., 2007) and PKR1 (Urayama, et al., 2008) signaling appear to be a necessary and sufficient signaling factor for adult EPDC differentiation into the endothelial and smooth muscle cells to induce neovascularization. Thymosin beta-4 can activate adult epicardial cells (Bock-Marquette, et al., 2009) acting through reactivation of embryonic signalling pathways (Smart, et al., 2007).

In a regenerative context, the adult epicardial progenitor cell population also mediates cardiac repair after injury. Tβ4 can activate adult epicardial cells (Bock-Marquette, et al., 2009; Smart, et al., 2007) to promote revascularization of the injured mammalian heart by forming endothelial and vascular smooth muscle cells. Tβ4 treatment before myocardial

infarction alters the responsiveness and fate of activated epicardial cells (WT1+ progenitor cells), to differentiate into cardiomyocytes (Smart, et al., 2011). However Tβ4 treatment after myocardial infarction induces epicardial expansion and coronary capillary density without affecting migration or alteration of $WT1^+$ progenitor cell fate into cardiomyocytes (Zhou, et al., 2012). Tβ4 treatment of mice after MI activates cardiac progenitor cell fate to induce cardiomyocyte linage (Bock-Marquette, et al., 2009). However, the cardiac progenitor subpopulation remains to be characterized. Further, a sub-population of adult epicardial cells retains the potential to give rise to cardiac precursors or endothelial cells (Limana, et al., 2007). The regenerative potential of EPDCs has been tested in the injured myocardium. The injection of human EPDCs was reported to enhance cardiac repair (Winter, et al., 2007). When the cardiomyocyte progenitors were co-transplanted with EPDCs into infarcted myocardial tissues, they improved functional repair as compare to single cell type supplementation (Zhou, et al., 2011). The effect was shown to be caused by paracrine effects from both cell types. Nevertheless, signals and cellular contributions from the EPDCs are indispensable for the establishment of normal coronary vasculature and myocardial architecture (Smart and Riley, 2012; Winter, et al., 2009).

3. GPCRs and cardiovascular system

Many hormones and neurotransmitters use GPCRs to exert their cardiovascular effects (Marinissen and Gutkind, 2001; Tang and Insel, 2004). Relatively little information is available regarding the role of GPCRs in the functional activities of cardiac stem/progenitor cells, both in normal and disease conditions. The well-studied cardiac role of GPCRs via Gαq signalling (Gutkind and Offermanns, 2009) is to promote cardiac hypertrophy (Wettschureck, et al., 2001) or protect cardiomyocytes against hypoxic insult (Nebigil, et al., 2003). Gα12 signaling can interact with the cytoplasmic domain of cadherins (Kaplan, et al., 2001), resulting in the release of the transcriptional activator β-catenin. Gα13 signaling is involved in vessel formation (Offermanns, et al., 1997). Gαs signaling regulates heart rate and contractility in response to catecholamine stimulation, but excessive Gαs signaling in heart eventually induces myocardial hypertrophy, fibrosis and necrosis (Gaudin, et al., 1995). Given the important roles of GPCRs in cardiac regulation, a key question is how many different GPCRs exist in the heart and what is their physiologic significance? Since forty percent of these GPCRs represent viable drug targets (Schlyer and Horuk, 2006) and also many of GPCR is involved in regulating cardiovascular system, unraveling of novel GPCR in cardiac progenitor/stem cells is very important to develop novel therapies for limit cardiovascular disease.

3.1. Prokineticins and cognate receptors:

Prokineticins are structurally homologues of amphibian or reptilian peptide toxins (Kaser, et al., 2003). They were first identified in the gastrointestinal tract as potent agents mediating muscle contraction (Hoogerwerf, 2006; Li, et al., 2001), and have been isolated from bovine milk (Masuda, et al., 2002) . They comprise two classes: Prokineticin-1 (PK1), originally called endocrine gland-derived vascular endothelial growth factor (EG-VEGF)

(LeCouter and Ferrara, 2002) based on the functional similarity to VEGF and prokineticin-2 (PK2, also called Bv8). PK1 and PK2 are approximately 50% homologous and contain carboxyl-terminal cysteine-rich domains that form five disulfide bridges (Bullock, et al., 2004). N terminal hexapeptide (AVITGA) and cysteine residues in the carboxy-terminal domain are crucial for their biological activities . Prokineticins and their receptor are widely distributed in mammalian tissues (Soga, et al., 2002). Prokineticins induce cell excitability such as gut spasmogen (Wade, et al., 2009), pain sensitization (Negri, et al., 2006), circadian rhythm (Li, et al., 2006), and sleep (Hu, et al., 2007)). They also induce cell motility such as angiogenesis (LeCouter and Ferrara, 2002), neurogenesis (Ng, et al., 2005), hemotopoiesis (LeCouter, et al., 2004), neovasculogenesis (Urayama, et al., 2008). Prokineticins regulate complex behaviors such as feeding (Negri, et al., 2004), drinking (Negri, et al., 2004), anxiolity (Li, et al., 2009). Moreover, prokineticins are potent survival/mitogenic factors for various cells including endothelial cells , neuronal cells (Kisliouk, et al., 2005; Ngan, et al., 2007a), lymphocytes, hematopoietic stem cells (LeCouter, et al., 2004), and cardiomyocytes (Nebigil, 2009). Table 1 summarize the involvement of prokineticin in the diseases.

Prokineticins bind to two cognate 7-transmembrane G-protein-coupled receptors. PKR1 and PKR2 share about 85% amino acid identity and encoded within distinct chromosomes in both mouse and human (Masuda, et al., 2002). Prokineticin-2 is the most potent agonist for both receptors (Masuda, et al., 2002). PKR2 is the dominant receptor in the adult brain, particularly in the hypothalamus, the olfactory ventricular regions, and the limbic system. However, PKR1 is widely distributed in the periphery. These receptors couple to G◎q, G◎i and G◎s to mediate intracellular calcium mobilization, activation of MAPK, Akt kinases and cAMP accumulation, respectively (Ngan and Tam, 2008). Although prokineticin signaling has been implicated as a survival/mitogenic factor for various cells including endothelial cells (Guilini, et al., 2010), neuronal cells (Ngan, et al., 2007b), enteric neural crest cells (Ngan, et al., 2007a), granulocytic (Giannini, et al., 2009)and monocytic lineage (Dorsch, et al., 2005) , lymphocytes and hematopoietic stem cells (LeCouter, et al., 2004), until recently, little was known about the underlying molecular and cellular events to regulate cardiovascular function.

3.1.1. A novel role for prokineticin in regulating cardiovascular system

PK2/PKR1 signaling pathway seems an important cardiovascular regulatory pathway, because of the following aspects: Prokineticins are potent angiogenic factors (LeCouter and Ferrara, 2003), which have beneficial effects on cardiac repair by inducing angiogenesis to improve coronary circulation or regenerating the cardiomyocytes (Bellomo, et al., 2000). They exert their biological effects via activating GPCRs that couple to diverse G proteins. Mutations in the gene encoding prokineticin-2 cause Kallmann syndrome (hypogonadotropic hypogonadism) in human (Abreu, et al., 2008; Canto, et al., 2009; Cole, et al., 2008), with congestive heart failure and dilated cardiomyopathy. Prokineticins induce differentiation of murine and human bone marrow cells into the monocyte/macrophage lineage and activate monocyte proliferation, differentiation and macrophage migration (Denison, et al.,

2008; Dorsch, et al., 2005; Giannini, et al., 2009). In human end-stage failing heart samples, reduced PKR1 and prokineticin-2 transcripts and protein levels implicate a more important role for PK2/PKR1 signaling in heart (Urayama, et al., 2007). Therefore, we reasoned that PK2/PKR1 signaling should contribute to heart repair by inducing angiogenesis or repairing cardiomyocytes.

3.1.2. Role of PKR1 signaling in cardiovascular system

In cultured capillary endothelial cells derived from heart, PK2 via PKR1 induces proliferation, migration and vessel-like formation, activating Gα11/MAPK and Akt kinases (Guilini, et al., 2010). In cardiomyocytes, activation of overexpression of PKR1 protects cardiomyocytes against hypoxic insult, activating the PI3/Akt pathway (Urayama, et al., 2007).

Transient PKR1 gene transfer after coronary ligation in the mouse model of myocardial infarction reduces mortality and preserves heart function by promoting cardiac angiogenesis and cardiomyocyte survival. This result suggests that PKR1 may represent a novel therapeutic target to limit myocardial injury following ischemic events (Urayama, et al., 2007).

Transgenic mice overexpressing PKR1 specifically in the heart under the control of cardiac α-myosin heavy chain (α-MHC) promoter displayed no spontaneous abnormalities of cardiomyocytes, but showed increased neovascularisation (Urayama, et al., 2008). Thus, these data suggest that PKR1 is involved in post-natal de novo vascularization, rather than vasculogenesis during embryogenesis.

Genetic inactivation of PKR1 in mice (PKR1-knockout mice) exhibit dilated cardiomyopathy and reduced angiogenesis in heart (Boulberdaa, et al., 2011). The heart pathology in PKR1 knockout mice is due to increased apoptosis in cardiomyocytes and reduced epicardial progenitor cell numbers. These data was consistent with an endogenous role of PKR1 signalling in stimulating epicardial progenitor cell proliferation and differentiation. All together these findings show that PKR1 signalling is involved in regulating cardiomyocyte survival signalling, and progenitor cell proliferation and differentiation.

3.1.3. Role of PKR2 signaling in cardiovascular system

Since PKR1 and PKR2 are 85% identical and are both expressed in cardiovascular tissues, PKR2 may also contribute to cardiomyocyte growth and vascularization. Transgenic mice overexpressing PKR2 specifically in the heart under the control of cardiac (α-MHC) promoter exhibit eccentric hypertrophy in an autocrine regulation and impaired endothelial integrity in a paracrine regulation without inducing angiogenesis (Urayama, et al., 2009). These transgenic PKR2 mice may provide a new genetic model for heart diseases. We found that in the endothelial cells PKR2 couples to Gα12 signaling pathway and downregulates ZO-1, thereby inducing endothelial cell fenestration (Urayama, et al., 2009).

3.1.4. Prokineticin signaling in cardiac stem/progenitor cell activation

Prokineticin-2 has been shown to modulate mobilization of bone morrow-derived cells and also promote angiogenesis. Systemic exposure to prokineticins promoted the survival of hematopoietic cells and enhanced progenitor mobilization (LeCouter, et al., 2004). Recently, we found that prokineticin-2 induces significant outgrowth from mouse epicardial explants and quiescent EPDCs, restoring epicardial pluripotency and triggering differentiation of endothelial and vascular smooth muscle cells (Urayama, et al., 2008). Co-culturing EPDCs with cardiomyocytes overexpressing PKR1 increased prokineticin-2 levels as a paracrine factor, thereby promoting EPDC differentiation, mimicking our PKR1-transgenic mice model (Urayama, et al., 2008). These prokineticin-2 effects were abolished in EPDC derived from PKR1-null mutant hearts, demonstrating PKR1 involvement. Prokineticin/PKR1 signaling can reprogram adult EPDCs to induce neovascularization. These studies provided novel insight for possible therapeutic strategies aiming at restoring pluripotency of adult EPDCs to promote neovasculogenesis, by induction of cardiomyocyte- PKR1 signaling. Whether epicardial-PKR1 signaling contributes cardiomyocyte function and metabolism, and it determines lineage choice decision in EPDCs remained to be investigated.

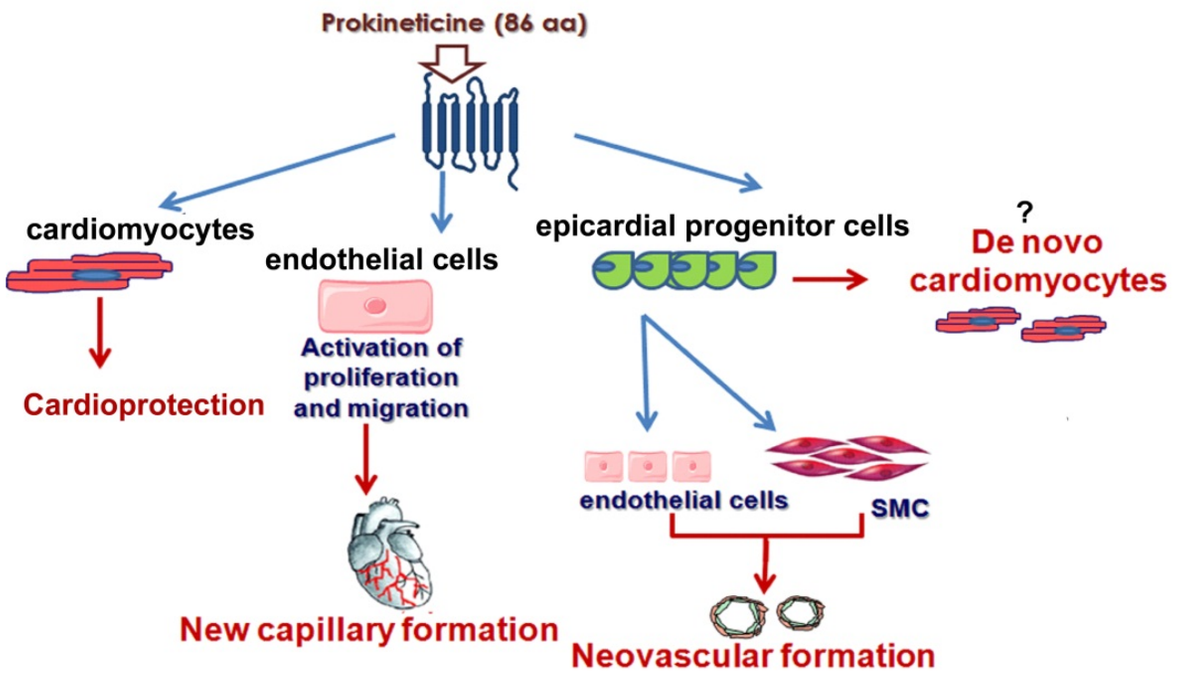

Figure 1. Role of prokineticin PKR1 signaling in cardiac regeneration.

PKR1 signaling protects cardiomyocyte against hypoxia-mediated apoptosis, activates endothelial cells for angiogenesis, activates EPDC differentiation into vasculogenic cell type to induce neovascular formation, activates EPDC differentiation into new cardiomyocytes.

DOMAIN	ROLE/EXPRESSION in human organs	REFERENCE
Reproduction		
Menstrual cycle	Progesterone induces elevation of prokineticin-1 expression during the secretory phase indicating a role of prokineticins and their receptors in endometrial vascular function	(Battersby, et al., 2004)
	Prokineticin-1 is derived from granulosa lutein cells and its synthesis is elevated during the mid- to late luteal phase	(Fraser, et al., 2005)
	Alteration of prokineticin-1 can induces several biochimical abnormalities characterizing eutopic endometrium in endometriosis	(Tiberi, et al., 2009)
Placentation and pregnancy	Prokineticin-1 and PKR1 expression is elevated in human decidua during early pregnancy. Prokineticin-1 via PKR1 regulates expression of host implatation-related gene.	(Evans, et al., 2008)
	Dysregulation of Prokineticin signaling in fallopian tube could affect fallopian tube smooth muscle cells contractility and embryo-tubal transport providing a potential cause for ectopic pregnancy	(Shaw, et al., 2010)
	Prokineticin-1 and its receptor gene polymorphism and haplotype were associated with idiopathic recurrent pregnancy loss. These three gene contribute to recurent pregnancy loss in the Taiwanese Han population	(Su, et al.)
Kallman syndrome	Insufficient prokineticin signaling leads to abnormal development of the olfactory system and reproductive axis in man	(Dode, et al., 2006)
	Mutation in prokineticin-2 and PKR2 genes underlie both Kallman sydrome and idiopathic hypogonadotropic hypogonadism	(Cole, et al., 2008)
Behaviour	Prokineticin-2 may play a role in the pathophysiology of mood disorders in the Japanese population	(Kishi, et al., 2009)
	Prokineticin-2 may play a role in the pathophysiology of methamphetamine dependance in the Japanese population	(Kishi, et al., 2010)
Cancer	Prokineticins and their receptors are expressed in human prostate and their levels increased with prostate malignancy	(Pasquali, et al., 2006)
	Prokineticin-1 favors neuroblastoma progression	(Ngan, et al., 2007b)

DOMAIN	ROLE/EXPRESSION in human organs	REFERENCE
	Prokineticin-1 derived from islet and/or pancreatic stellate cells act through its receptor on endothelial cells to increase angiogenesis in pancreatic disease	
	Prokineticin-2 play a role in pathophysiological in human tumors and inflammatory disorders	(Zhong, et al., 2009)
	Prokineticin-1 is significantly increased in papillary thyroid cancer and its expression in papillary thyroid cancer is related to BRAF oncogen	(Pasquali, et al., 2011)
Vascular	Prokineticin-2 is involved in immune and inflammatory response at abdominal aortic aneurysms site	(Choke, et al., 2009)
Inflammation	Prokineticin-1 was found in the controls in the patients with temporomandibular joint disorders	(Herr, et al.)
Cardiology	Prokineticin-2 and PKR1 were reduced in human end stage failure heart sample	(Urayama, et al., 2007)

Table 1. Involvement of prokineticins in human diseases

4. Conclusion

All together these data showed that PK2 via PKR1 signaling has important roles on heart physiology and pathophysiology. PKR1 is involved in postnatal cardiac vascularization by activating epicardial progenitor cells. These studies also raise numerous questions for further investigation. Do EPDCs differentiate into functional (beating) cardiomyocytes in vitro or in vivo? Do EPDCs differentiate into cardiac lineages in vivo in the damaged adult? Does the activity or potential of EPDCs decline with age? The identification of factors which stimulate endogenous cardiac progenitor cells to induce neovascularization and cardiomyocyte replacement is an evolving paradigm towards therapeutic intervention in cardiac diseases. The race is to facilitate drug discovery for targets acting on cardiomyocytes or EPDCs to invoke new coronary vessels and cardiac tissues as a significant step toward cardioprotection and cardiovascular regeneration.

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Acknowledgement

I acknowledge all the members of my laboratory and Dr. Laurent Désaubry for their fruitful discussion during preparation of this article.

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