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1. Introduction

In this chapter we will explore the current understanding about the dynamics of myocardial cell populations after birth and how they may contribute to homeostasis and response to injury. Recent investigations of myocardial cell biology have revealed that the heart is not the terminally differentiated organ it was once thought to be. We now know that myocardium contains limited populations of cardiac progenitor cells (CPC) that are capable of generating all myocardial cell types. The changes in myocardial cell populations with time and the role these changes play in neonatal myocardial tissue expansion will be discussed. The contribution of CPC to heart growth and therapeutic strategies for congenital cardiac diseases will be explored.

2. Stem cells and heart development

2.1 Stem cells: The perspective has evolved

Pluripotent embryonic stem cells (ESC) are derived from the inner cell mass of an embryonic blastocyst (primitive ectoderm). The pluripotency of ESC defines that they are capable of differentiation into one of the three germ layers: ectoderm, mesoderm, or endoderm; reviewed in (Rossant, 2008; Bolli & Chaudhry, 2010). Embryonic mesoderm cells (identified by the expression of Brachyury T) in the developing primary heart field undergo committed differentiation into a pre-cardiac lineage (expressing Mesp-1) and have the potential to form committed cardiac progenitor cells (CPC, expressing Nkx2.5), which are capable of differentiation into cardiomyocytes, vascular smooth muscle cells, and endothelial cells; reviewed in (Sturzu & Wu, 2011). A cardiac progenitor cell is thus defined as a multipotent progenitor cell of the pre-cardiac lineage.

Originally it was thought that only ESC are pluripotent, and they could only be obtained from living embryos. Consequently, studies of human ESC have been impeded by ethical concerns. However, continued research has led to the realization that pluripotency is in fact a plastic multidirectional state. It has now been clearly demonstrated that a pluripotent state can be induced in adult somatic cells from humans, and other species; reviewed in Yamanaka (Yamanaka & Blau, 2010). The biochemical methods through which so-called induced pluripotent cells (iPSC) may be derived from adult cells are numerous and still expanding. Several recent reviews (Rossant, 2008; Yamanaka & Blau, 2010) of both the technology and the biology of iPSC may be consulted for the interested reader; the topic will not be further discussed here.
A variety of techniques have been used to induce the differentiation of ESC into a specific cell type of interest. The directed differentiation of ESC into cardiomyocytes has been achieved by several methods and has enabled the use of this approach to produce a large enough number of cells for repairing the injured heart to restore myocardial function (Gonzales & Pedrazzini, 2009; Laflamme & Murry, 2011). A large number of studies have been conducted and are still being conducted with the goal of restoring the function of infarcted myocardium using stem cell therapy with ESC-derived cardiomyocytes and also other cell types, with the expectation that they would continue to differentiate into cardiomyocytes after being delivered to the injured heart tissue (Murry et al., 2005). As this therapy is less relevant to congenital heart disease, it will not be further discussed here.

2.2 How cardiac progenitor cells form the developing heart

A brief review of cardiac development illustrates how cardiac stem cells are identified and how multiple distinct populations of pre-cardiac cells coalesce to form the distinct subregions of the heart.

2.2.1 Heart fields and cardiac progenitor cells

The development of the multi-chambered heart is complex and requires a precise regulation of cell migration, proliferation, and differentiation in a highly organized positional and temporal order. Several distinct CPC populations contribute to the formation of different heart fields. The first heart field (FHF) of cardiac progenitor cells is localized in the primitive streak and mostly contributes to formation of the left ventricle and part of the atria (Garcia-Martinez & Schoenwolf, 1993; Tam et al., 1997). A second heart field (SHF) of CPC from the pharyngeal mesoderm migrates into the arterial pole of the heart and is a major source of the cardiac progenitors that form the outflow tract (OFT), the right ventricle and the atria (Abu-Issa & Kirby, 2007). Continued development of the OFT and heart valves is achieved by migration of a population of non-mesodermal neural crest cells (NCC) from the neural fold into the arterial pole and endocardial cushion (Kirby & Waldo, 1995; Hutson & Kirby, 2007). Another population of mesenchymal CPC, the proepicardium, has been demonstrated to be an additional cell source contributing to the formation of coronary arteries and cardiac fibroblasts (Dettman et al., 1998). CPC from both FHF and SHF act in a close collaboration during the formation of the embryonic heart. During heart morphogenesis, CPC directed by different signaling pathways differentiate to mature cardiac cells. However, CPC of the postnatal heart have been shown to express markers common to both FHF and SHF. Whether these postnatal resident CPC contribute to remodeling and growth of the heart is considered likely but is still unsettled.

2.2.2 Second heart field and congenital heart disease

Studies of heart development in mice have shown that mutation of genes expressed by cells of the SHF causes congenital heart disease (CHD). Mutations in Nkx2.5 cause a spectrum of congenital heart defects including cardiac conduction abnormalities and ventricular- and atrial-septal defects (VSD, ASD) (Basson et al., 1997). Deletion of Tbx1 results in malformations of the cardiac outflow tract and VSDs due to failure in the migration of NCC to the heart (Jerome & Papaioannou, 2001; Merscher et al., 2001). Mutations in GATA4, some of which disrupt its interaction with Tbx5, cause ASDs and VSDs (Garg et al., 2003). Hand2 is essential for survival of second heart field progenitors and loss of Hand2 function in this cardiac progenitor population can cause a spectrum of congenital heart malformations.
Myocardial Self-Repair and Congenital Heart Disease

(Tsuchihashi et al., 2011). Cai (Cai et al., 2003) reported that Isl1+ cells are mostly localized in the SHF and give rise to the outflow tract. They demonstrated that disruption of Isl1 results in a complete failure to form the outflow tract in the mutant mice. The role of Fgf8 in early and late heart development has also been studied (Sun et al., 1999; Abu-Issa et al., 2002). Fgf8 is required for migration of mesoderm out of the primitive streak (Sun et al., 1999). In addition Fgf8 plays an important role in development of all the pharyngeal arches and in NCC survival (Abu-Issa et al., 2002). Cardiac NCC are multipotent and after migration to the SHF contribute to cardiovascular patterning (Kirby & Waldo, 1995). Ablation of the pre-migratory cardiac NCC causes numerous outflow tract septation defects: persistent truncus arteriosus, double-outlet right ventricle, tricuspid atresia, straddling tricuspid valve, and the absence of a varying combination of aortic arch arteries derived from pharyngeal arches 3, 4 and 6 (Nishibatake et al., 1987; Hutson & Kirby, 2007). Studies of interactions between cells of SHF origin with NCC in the pharyngeal region of mice (Vitelli et al., 2002; Moraes et al., 2005) have shown that mutation in Tbx1 disrupts formation of the pharyngeal arch arteries and causes septation defects due to failure in NCC migration. Bradshaw (Bradshaw et al., 2009) showed that abnormal distribution of Isl1-expressing cells in a neural crest-deficient mutant mouse causes instability of posterior arch arteries and outflow tract septation defects, leading to a double outlet right ventricle. Discovery of the presence and role of CPC in the normal and abnormal development of heart fields and their possible role in postnatal life suggests that targeting these cells is a valuable approach for both understanding the ontology of CHD and developing therapeutic approaches.

The implications of resident CPC expressing neural markers in the heart are manifold for congenital heart disease repair. First, the secondary heart field of cells creates the structures most affected by congenital disease: the outflow tracts and pulmonary and aortic trunks (Dyer & Kirby, 2009; Jain et al., 2010). Second, the resident CPC-derived from this field (i.e. Isl1+ or Nestin+ CPC) may form the primary cardiac stem cell pool that would potentially be mobilized to participate in the repair (cell replacement) of structures derived from the anterior/secondary heart field such as the OFT. Thirdly, therapeutics aimed at CPC mobilization may act more effectively on the right heart if they target NCC-derived CPC.

2.2.3 Postnatal distribution of CPC in the heart

Resident CPC have been localized in small groups or clusters in a unique microenvironment known as a “stem cell niche” which provides conditions for stem cells to maintain their multipotency and renewal capacity (Morrison & Spradling, 2008). Niches comprise a specific arrangement of stem cells, supporting cells, and extracellular matrix. The niche environment provides a paracrine signaling influence that maintains stem cells in their quiescent state and also responds to conditions outside the niche to initiate activation of stem cell replication and/or differentiation, for example in response to tissue injury (Morrison & Spradling, 2008). Classically, three well-characterized stem cell niches have been identified: germline, hematopoietic, and epithelial (Lemischka, 1997; Xie & Spradling, 2000; Spradling et al., 2001). However in the past decade, identification of resident stem cells in most mammalian organs suggests local tissue-specific niches are a general rule. Discovery of CPC niches in the adult mouse heart strengthens the growing appreciation that the heart is not a terminally differentiated organ and resident CPC might play a role in the postnatal remodeling and repair of cardiac tissue (Urbanek et al., 2006). The early study of Messina (Messina et al., 2004) demonstrated that cardiac stem cells are present in both atrial and ventricular human samples and in a wide range of ages (1 to 80 years old). According to this
study and mouse studies by Beltrami (Beltrami et al., 2003) and Oh (Oh et al., 2003), cardiac stem cells can be isolated from adult myocardium and differentiated into different cardiac cell lineages. Our own studies (Amir et al., 2008) have investigated the number and characteristics of CPC in human neonatal myocardium from patients with congenital heart disease. We demonstrated that CPC comprise a high percentage relative to cardiomyocytes in the human neonate and that their fractional representation declines as the heart grows in size, suggesting a dilutional effect. In other words, an apparently fixed population of CPC resides in the heart postnatally. Pouly (Pouly et al., 2008) reported that CPC concentration in the right atrium is greater than that of the septum of transplanted hearts. Other myocardial niches have been reported. Schenke-Layland (Schenke-Layland et al., 2011) reported that in human and mouse heart endogenous, multipotent Isl1+/Flk1+ CPC reside within niche clusters in the right ventricular free wall, the atria and outflow tracts. They were tightly circumscribed by the basement membrane proteins collagen V and laminin. However, systematic mapping of the complete heart to localize major niches and determine the distribution of these regions of high CPC density has not been reported. A general concept is that cardiac regions protected from greatest mechanical stress (atria, septum, apex) appear to contain the highest density of CPC. A more useful perspective may be consideration of the cardiac developmental sequence in which fields of CPC undergo migration and strategically controlled distribution, since the niches may constitute remnants of specific precursor fields in the primordial heart anlagen.

The role of niche-associated cells in regulating the stability and activation of resident stem cells is still poorly understood, especially in the heart. Recently, it has been shown that Notch-1 of murine CPC interacts with surrounding cells via the Jagged ligand. Through a Jagged-mediated activation signaling process induced in vitro, notch signaling, downregulation of c-Kit and upregulation of Nkx2.5 were found to be associated with increased myocyte proliferation (Boni et al., 2008). These data support the concept that interaction of CPC with supporting cells and matrix regulates their commitment to the myocyte lineage.

2.2.4 Postnatal Characterization of CPC fates

2.2.4.1 Prenatal formation of the heart from different fields

During heart development CPC express field-specific markers (Figure 1.) for FHF, SHF, and neural crest (Vincent & Buckingham, 2010). Mesp1 is one of the earliest markers for cardiac primordial cells (Saga et al., 1999). Depending on the stage of cell differentiation, genetic markers will be upregulated or down regulated in the CPC, which complicates clear classification of CPC originating from FHF and SHF based on markers. Nkx2.5 is a critical cardiac transcription factor in the first lineage, and Isl1 along with Foxh1, GATA factors, and Hand2 are key regulators in the second heart progenitor field (Moretti et al., 2006). The earliest differentiated cells in the cardiac crescent express GATA4 and Nkx2.5 (Vincent & Buckingham, 2010). The final differentiation to cardiomyocytes is controlled by Tbx (Takeuchi & Bruneau, 2009). Known markers for SHF CPC are Isl1, Tbx1 and Fgf10 (Kelly et al., 2001; Cai et al., 2003; Xu et al., 2004). Pax3 is recognized as a major regulatory gene for NCC, having an important role in their migration (Bradshaw et al., 2009). There is considerable overlap between the heart field-specific genetic markers. This issue is more evident in the case of the proepicardial organ, which gives rise to coronary arteries and epicardium. Both Isl1 and Nkx2.5 are expressed in the CPC from the proepicardial organ (Dettman et al., 1998), the cells of which also express Tbx18 and Wt1 (Martinez-Estrada et al., 2010).
2.2.4.2 Markers of CPC in the postnatal heart

In the postnatal heart, identification of CPC is based primarily on the cardiac lineage markers Nkx2.5, Mef2c, and Isl1. Identification of c-Kit+ cells in adult mammalian heart suggests another postnatal source of CPC, however, the origin of these cells is unsettled. Although expression of the key CPC markers is preserved both in rodents and humans, species-specific markers limit translation of animal studies to human studies. Our studies of human infant RVOFT myocardium showed a mixed population of c-Kit+, Isl1+, and Nkx2.5+ CPC (Amir et al., 2008). The neonatal human heart is a rich source of CPC bearing markers such as SSEA4, Isl1, Nkx2.5, and c-Kit. In addition to our report of myocardial SSEA4 localization (Amir et al., 2008), SSEA4 expression has been previously only reported in adult human kidney (Ward et al., 2011). Isl1+ CPC have also been localized to the atrium (Laugwitz et al., 2005). Stem cell antigen-1 (Sca-1) is a marker for mouse resident CPC. In the mouse and human studies performed by Messina (Messina et al., 2004) and Beltrami (Beltrami et al., 2003) c-Kit+ cells are considered to be CPC, whereas Oh (Oh et al., 2003) used c-Kit, Sca-1+ cells as a marker for CPC. This apparent controversy may be explained by the existence of heterogeneous pools of cardiac stem cells in different stages of differentiation rather than multiple populations of distinct resident CPC. In addition, the anatomical location (i.e., heart field of origin) of the heart regions studied may determine the markers expressed by postnatal CPC.

Fig. 1. Overview of myocardial CPC Markers in relation to their ontology. Pre-cardiac mesoderm cells express Mesp1 until differentiation to cardiogenic mesoderm, marked by the expression of Nkx2.5. The cardiogenic mesoderm differentiates to form two heart fields. Cells in the first heart field (FHF) express GATA4 in addition to Nkx2.5. Cells of the secondary heart field (SHF) express Isl1 and Nkx2.5. The SHF also becomes populated by neural crest cells (NCC) expressing Pax3. Markers associated with the heart field cells but showing greater variation in their expression are indicated in blue type. In addition to cardiogenic mesoderm, cells from the pro-epicardial organ and also of hematopoietic lineage have been identified in the myocardium. Abbreviations: NCC, Neural crest cells; SHF, Second heart field; FHF, First heart field.
Mouse studies have demonstrated homing of bone marrow-derived stem cells into the infarcted myocardium, suggesting a hematopoietic origin for c-Kit^+ CPC. However, transdifferentiation of these cells into cardiomyocytes is controversial (Orlic et al., 2001; Murry et al., 2004; Bearzi et al., 2007). On the other hand, Tallini (Tallini et al., 2009) reported that c-Kit is expressed by immature cardiomyocytes as well as endothelial cells during development of mouse heart and that the populations rapidly expanded during the first 2 days of postnatal life. Their study compared the difference between the multipotency potential of CPC derived from the neonatal heart and the adult injured heart. They concluded that the neonatal c-Kit^+ cells showed an ability to differentiate into cardiomyocytes, smooth muscle cells, and endothelial cells. In contrast, they found that c-Kit^+ cells in the adult injured mouse heart had no myogenic capacity. The co-expression of c-Kit and neuronal marker Nestin in neonatal CPC (Tallini et al., 2009) suggests a transitional status of NCC in postnatal life and the potential for NCC contributing to cardiac repair and remodeling (Drapeau et al., 2005).

2.3 Postnatal heart growth
The infant heart grows rapidly after birth. The pulmonary valve annular diameter doubles in the first 7 years of life and plateaus by age 14 (Sairanen & Louhimo, 1992) while left ventricular volume doubles over approximately the first 10 years of life (Nielsen et al., 2010). Although cardiomyocytes increase in volume (hypertrophic growth), in part by cellular fusion into very large multinucleate myocytes, there is also an overall increase in cellularity (cell number) in the heart during this rapid expansion phase of heart growth. That the number of myocytes continues to increase after birth has only recently been demonstrated. For decades, it was taken as fact that cardiomyocytes were incapable of dividing postnatally, if only because mitosis of a multinucleated cell is considered impossible.

One of the earliest reports of new cardiomyocytes appearing in the postnatal human heart was provided by studies of adult aortic stenosis patients, in which cells co-expressing cardiac and stem cell markers could be localized (Urbanek et al., 2003). Additionally, studies of transplanted adult donor hearts revealed the appearance of new cardiomyocytes in the donor heart by the presence of sex chromosomes opposite to that of the recipient host (Bayes-Genis et al., 2007). Highly compelling further evidence that new myocytes are added to the heart over time arises from carbon isotope data (Bergmann et al., 2009) showing that nearly 50% of myocytes are replaced over a lifetime. Studies of the hearts of dogs with advanced dilated cardiomyopathy performed by Leri (Leri et al., 2001) showed postnatal proliferation of cardiomyocytes, documented by the expression of cell proliferation marker Ki67 and telomerase. Telomerase activity is not only required for cardiac growth and survival but it also suppresses cardiomyocyte apoptosis (Oh & Schneider, 2002). We (Amir et al., 2008) also demonstrated that the neonatal human heart contains cardiomyocytes expressing Ki67. We also determined that the number of these proliferating myocytes declines nearly 6-fold in the first two months of life.

2.4 Summary: CPC in the postnatal myocardium
Work by a number of investigators has demonstrated that a population of multipotent cardiac lineage-determined cells (i.e., CPC) capable of further differentiation to all cardiac cell types is present in all hearts. Hence, continued cardiomyocyte renewal has slowly been gaining acceptance as both an important aspect of normal myocardial biology and a potential strategy to assist with repair of a diseased heart. The ability to expand the
population of cardiomyocytes presents a potentially vast opportunity for therapeutic intervention for congenital heart diseases.

3. CPC and Therapy for CHD

3.1 Cardiac repair using CPC

3.1.1 Role of CPC in homeostatic repair and postsurgical healing

If the heart can add new cells, then the question arises regarding why it doesn’t always heal itself? The generally offered explanation for the fact that resident CPC are unable to naturally rescue a moderately infarcted adult heart is that the region of damaged tissue is too great for this mechanism to work rapidly enough to restore function. Although not widely recognized, “silent” repair by CPC has been observed (see section 3.2.1). It is probable that small lesions in the myocardium are actually self-repaired silently through expansion of the resident CPC population. Large ischemic lesions would be expected to also result in the loss of resident CPC in the infarcted region, further impairing self-repair. However, progress has recently been reported. Intra-myocardial injection of autologous bone marrow derived stem cells has been used in adults with chronic ischemic heart disease (i.e. not infarcted) to achieve functional recovery and reverse ventricular remodeling (Williams et al., 2011). Such reports of success strengthen the concept that endogenous stem cells can provide clinically significant benefits to heart disease patients of all ages.

3.1.2 Therapies using CPC for tissue engineering

3.1.2.1 Tissue engineered myocardial grafts

Presently, many investigators are attempting to use cardiac stem cells to produce engineered myocardial sheet grafts for myoplasty of larger regions of infarct-damaged adult myocardium. Success has been limited to moderate. Major limiting factors to this approach remain. For example, integration of the graft into the existing myocardium so that it provides clinically significant augmented force development has been problematic. Additionally, achieving sufficient revascularization of the grafts to sustain viability has been difficult; see review by Sui (Sui et al., 2011). Although the potential utility of such grafts in congenital heart disease is not expectedly large, marked progress in this approach could conceivably provide alternative therapies for patients with failing Fontan circulations or possibly for those with cardiomyopathies.

3.1.2.2 Tissue engineered myocardial vascular and valve grafts

One area of potentially beneficial therapy that has previously received little attention in congenital heart disease patients is the engineering of vascular and valve grafts that are capable of meeting the rapid growth rate typical of the neonatal heart and great vessels during the first decade of life. The availability of graft materials with the ability to grow along with the young patient is highly desirable, but thus far not available. This is an area of recently increasing research interest, and one in which further research could provide enormous benefit to CHD patients.

3.1.3 Mobilizing resident CPC

3.1.3.1 Alternatives to cell delivery: “Activation” of resident CPC

Given the apparent difficulty in achieving clinically valuable augmentation of cardiac performance through the delivery of cardiomyocytes to a damaged heart, therapeutic
approaches that are designed to mobilize resident CPC to expand the population of cardiomyocytes in situ are being given much more consideration. Therapeutic exploitation of the paracrine environments of the CPC niche and enhancing homing to sites of repair is a very attractive alternative approach to cell-based therapies. In concept, it is a matter of using biomolecules to mimic or enhance endogenous CPC “awakening” mechanisms to obtain greater quantities of cells to differentiate into functional cardiomyocytes. Recent reports reveal that this general approach has a high potential for success and is quite worthy of further investigation. High mobility group box protein 1 (HMGB1), an endogenous chromatin-associated protein, and Thymosine Beta4, a G-actin monomer binding protein, have been identified as paracrine factors potentially able to promote regeneration of myocardium. HMGB1 is released from necrotic cells and has been shown to stimulate the homing of fibroblasts and smooth muscle cells. It has been identified as a potential mediator of resident stem cell activation/mobilization (Palumbo & Bianchi, 2004). Limana (Limana et al., 2005) demonstrated that injection of HMGB1 into the infarcted region of mice induced the appearance of new myocytes and an increase in ventricular performance, leading these investigators to conclude that HMGB1 is a “potent inducer of myocardial regeneration.” They demonstrated that c-kit+ CPC express the receptor for HMGB1 and that treatment increased the number of c-kit+ cells in mouse heart. Thymosine Beta4 has been shown to stimulate epicardial-derived cells (EPDC) to migrate and potentially promote neovascularization in the infarcted mouse heart (Smart et al., 2010); see review by (Bollini et al., 2011). Although there was no proof that EPDC were a source of the new cardiomyocytes, they may facilitate collateral vessel growth and thereby support the cardiomyocyte regeneration process. Damaged myocardium has a different paracrine environment, which if properly understood and exploited, may provide unique approaches for therapy via resident CPC activation.

Growth factor treatment has also been used to activate resident CPC populations for myocardial repair. Linke (Linke et al., 2005) used a canine MI model to show that IGF-1 and HGF treatment (intra-myocardial injection) could increase the density of proliferating (Ki67+) CPC following MI. These same investigators recently extended their observations, showing that CPC aging is related to a decline in signaling through IGF-1 and HGF, which in turn reduces their effect to antagonize the aging effect that the local renin-angiotensin system induces on CPC. They found that IGF-1 and HGF were able to partially reverse age-related decline in cardiac function in rats (Gonzalez et al., 2008). Consistent with these reports of IGF-1 stimulation of CPC proliferation, D’Amario (D’Amario et al., 2011) has proposed that CPC senescence is regulated by paracrine and autocrine signaling: positive through IGF-1 & -2, and balanced by an opposing signal mediated primarily by angiotensin II, all acting via their cognate receptors. Accordingly, they propose that IGF-1 promotes CPC proliferation and survival via IGF-1 receptor signaling, CPC differentiation via action on both IGF-1 and -2 receptors, and increasing angiotensin signaling and reduced IGF-1 receptor signaling with aging promotes CPC and cardiomyocyte apoptosis.

CPC from the secondary/anterior heart field (i.e., Nestin+) are resident in the secondary heart field regions of the rat heart (Drapeau et al., 2005). The recent review by Di Felice (Di Felice & Zummo, 2009) surveyed the many mutations of secondary heart field cells that are associated with human Tetralogy of Fallot. They concluded that potentially improved approaches to therapy would be better informed by a clearer understanding of the behavior and patterns of migration of CPC of the secondary heart field. That neural stem cells (CPC
from the secondary heart field) may participate in recovery from myocardial injury in a region-specific manner has also been shown. These cells apparently migrate and home to infarcted region of rat hearts, although they differentiate into neuronal, not myocardial cells (Beguin et al., 2011). Tamura (Tamura et al., 2011) used a mouse transgenic approach to tag neural crest cells and show that these cells migrated to the ischemic border zone of an infarct and transdifferentiated into cardiomyocytes. Although evidence for Nestin+ cells in the human heart is lacking, it is worth considering the different heart field lineages in the context of devising strategies for therapeutic targeting of human CPC. The targeting of neural crest-derived CPC to correct late ventricular arrhythmias occurring in patients after surgical repair operations for TOF is a potential therapeutic strategy (Di Felice & Zummo, 2009).

3.2 Potential roles of CPC in therapy for CHD
3.2.1 CPC silently contribute to therapy
3.2.1.1 (Pre-) Failing Fontan rescue via activation-RV strengthening

In the setting of failing Fontan physiology the potential for boosting cardiac performance through manipulation of cell number represents a new horizon. Ventricular assist devices (VAD) are presently used as a bridge to transplant in pediatric Fontan patients (Fynn-Thompson & Almond, 2007). VAD are also used to reduce ventricular load with the objective of enhancing the ability of the ventricle to support a greater load, i.e., to “rest” or re-train the ventricle of patients with dilated cardiomyopathy (CMP), even restoring function to the point of enabling pump removal (Birks et al., 2011). It is conceivable that the use of VAD may increase cardiomyocyte number, and evidence of this comes from recent prospective studies of myocardial biopsies showing an increased number of diploid myocytes in end stage congestive heart failure patients supported as a bridge to transplant with LVAD (Wohlschlaeger et al., 2010). Manginas (Manginas et al., 2009) has shown that endothelial progenitor cells are also mobilized by VAD use in patients. EPC may be stimulated to home into myocardium supported by VAD and improve myocardial function. As reviewed by Tsiavou (Tsiavou & Manginas, 2010), rescue of myocardial function during cardiac support by VAD may be mediated by CD45+ EPC promoting neovascularization and transdifferentiating into or fusing with cardiomyocytes. However, the possible involvement of CPC fusion with existing myocytes as repair mechanism is not widely accepted. The implications of the above observations are that progenitor cells may at least be participating in, if not be a primary mechanism mediating these physiological changes observed with VAD therapy.

What physiological mechanisms might underlie the expansion of the myocardial cell population during VAD support? Current thinking is that paracrine mechanisms are involved. For example, mechanical stimulation by the VAD may induce the production of cytokines such as growth factors (see section 3.1.3.1), which then stimulate mitotic expansion of CPC. Additionally, the production of chemokines under the influence of the same mechanical stimulation may promote the homing of bone marrow-derived progenitor cells. Indeed, much of the success of cell delivery-based therapies, although still rather modest, are thought to be largely due to paracrine effects mediated through the injected cells, the carrier media or in some cases the physical-mechanical changes induced by injection of liquid boluses into the muscle wall.
3.2.2 Augmenting current therapy with CPC targeting

3.2.2.1 CPC activation as an adjuvant to VAD “resting” of ventricle

It has been reported that pharmacological therapy in conjunction with VAD support may enhance myocyte population expansion. Recent studies by Soppa used therapy with the beta-2 agonist clenbuterol (Soppa et al., 2008) in a murine heterotopic abdominal transplant of failing hearts. Testing the effects of clenbuterol on mechanical unloading, they were able to show that it improves LV function. Bhavsar demonstrated that clenbuterol positively affects cardiac physiology through myocyte hypertrophy, concluding that the effect was mediated by a paracrine action of fibroblast-derived IGF-1 (Bhavsar et al., 2010). At the present time, we can find no reports of an effect of clenbuterol on CPC recruitment/activation. It is conceivable that such combined pharmacological plus mechanical therapy approaches could provide a markedly re-strengthened ventricle capable of many more years of function if not for the rest of the patient’s life. CPC recruitment could be combined with VAD-mediated myocardial unloading to augment myocardial tissue while “resting” the ventricle, whether left or right sided. Another possible use of therapies designed to expand the population of CPC is in the area of “ventricular training” a potential approach to prepare the LV of, e.g., delayed repair TGA patients for greater force production once the arterial switch operation has been performed. If VAD use can augment cardiomyocyte populations in otherwise normal ventricles, this could potentially help prepare the TGA patient for the switch operation by enhancing ventricular adaptation to increased loads.

3.2.2.2 Cardiomyopathy

Is it realistic to expect the manipulation of resident CPC populations to achieve a reversal in the decline in myocardial function in the setting of cardiomyopathy? Given the genetic nature of known lesions in sarcomeric proteins in this disease (Frazier et al., 2011), one may anticipate that the progenitor cell population may also harbor the same mutant alleles and therefore the expansion of that population may provide no benefit. However, for cardiomyopathy induced by chemical injury such as doxorubicin/adriamycin therapy (Shi et al., 2011), strategies to promote expansion of the resident CPC population could be considered an adjuvant or co-therapy used to mitigate cardiotoxicity. It is important to consider that, although the resident CPC may have an advantage in already being present within the muscular wall of the heart, therapies designed to help recruit bone marrow-derived CPC (and EPC) (see section 3.1.3.1) are certainly worthy of exploration while investigators try to understand the possibly different significance of resident versus bone marrow-derived CPC. Indeed, given the mismatch between patients in need of transplantation and the availability of transplantable hearts there would seem to be little reason not to emphasize the exploration of multiple approaches designed to utilize endogenous progenitor cells whether they be resident in the tissue or delivered to the tissue from sites such as the bone marrow.

3.2.2.3 Summary: Potential therapeutic opportunities

At present, investigators have only begun to exploit the potentials of using small molecule (drugs, growth factors) based therapies to expand desirable cell populations. We know of no examples of demonstrated CPC-based therapies for congenital cardiac disease at this time. Since CPC likely undergo senescence and their number as a percentage of total cells declines...
with expansion of the myocardial cell population, conceivably the benefits of such therapy may be far greater for the pediatric population than the adult.

4. Conclusions

The presence of resident CPC in myocardium is well supported through multiple studies. There is still much independent confirmation to be completed to clarify the promise of cardiac progenitor cell-mediated repair. Importantly, the major novel discoveries in the field of CPC biology have been made by only a small group of investigators and interpretation of some data is impaired by the lack of independent corroborating studies. Controversies also continue regarding the origin of CPC: during cardiac development, e.g., Isl1+ CPC, or from bone marrow, e.g., c-Kit+ CPC. Most likely, both sources are important but their therapeutic utilization may need to be approached with different strategies. Methods for activating resident CPC to realize their potential for effecting endogenous cardiac repair are still in the early discovery period. The fundamental question of CPC role in homeostatic maintenance of the myocardium throughout life has yet to be fully clarified, although an understanding of this highly significant role appears to be limited only by a lack of detection. Nonetheless, the potential applications of CPC-focused therapies in congenital heart disease treatments are likely manifold, awaiting only further investigation and implementation.

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6. References


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There are significant advances in the understanding of the molecular mechanisms of cardiac development and the etiology of congenital heart disease (CHD). However, these have not yet evolved to such a degree so as to be useful in preventing CHD at this time. Developments such as early detection of the neonates with serious heart disease and their rapid transport to tertiary care centers, availability of highly sensitive noninvasive diagnostic tools, advances in neonatal care and anesthesia, progress in transcatheter interventional procedures and extension of complicated surgical procedures to the neonate and infant have advanced to such a degree that almost all congenital cardiac defects can be diagnosed and “corrected”. Treatment of the majority of acyanotic and simpler cyanotic heart defects with currently available transcatheter and surgical techniques is feasible, effective and safe. The application of staged total cavo-pulmonary connection (Fontan) has markedly improved the long-term outlook of children who have one functioning ventricle. This book, I hope, will serve as a rich source of information to the physician caring for infants, children and adults with CHD which may help them provide optimal care for their patients.

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