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Review

Pluripotent stem cell derived cardiovascular progenitors – A developmental perspective

Matthew J. Birket, Christine L. Mummery*

Leiden University Medical Center, 2300 RC Leiden, The Netherlands

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ABSTRACT

Human pluripotent stem cells can now be routinely differentiated into cardiac cell types including contractile cardiomyocytes, enabling the study of heart development and disease *in vitro*, and creating opportunities for the development of novel therapeutic interventions for patients. Our grasp of the system, however, remains partial, and a significant reason for this has been our inability to effectively purify and expand the intermediate cardiovascular progenitor cells (CPCs) equivalent to those studied in heart development. Doing so could facilitate the construction of a cardiac lineage cell fate map, boosting our capacity to more finely control stem cell lineage commitment to functionally distinct cardiac identities, as well as providing a model for identifying which genes confer cardiac potential on CPCs. This review offers a perspective on CPC development as understood from model organisms and pluripotent stem cell systems, focusing on issues of identity as well as the signalling implicated in inducing, expanding and patterning these cells.

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Introduction

Progenitor cells have conventionally been distinguished from stem cells by their limited ability to replicate *in vivo* or *in vitro* and their restricted differentiation capacity. Their differentiation state is often considered more advanced, their fate being determined by both their parent cell and the niche in which they are found. For some tissues, like the intestine and stomach, this concept changed with the observation that in adults, there is a progenitor cell population that behaves like a stem cell in that it can divide indefinitely (Barker et al., 2010). Like the hematopoietic niche in the bone marrow to produce blood, these endodermal tissues have high turnover rates to replace cells lost daily so that an active stem cell population is not unexpected. The heart and brain, however, are relatively quiescent organs that were long regarded as "post-mitotic", with no ability to repair. This again, has turned out to be incorrect and both organs show cell turnover and replacement after damage, albeit at low rates (Bergmann et al., 2009; Jessberger and Gage, 2014; Waring et al., 2014). Accordingly, neural progenitors that can be expanded in culture have been described for adult and foetal brain (Gage and Temple, 2013). For the heart, this has been more contentious: cardiovascular progenitors with various identities have been observed *in situ* (Bearzi et al., 2007; Beltrami et al., 2003; Laugwitz et al., 2005; Martin et al., 2004; Messina et al., 2004; Moretti et al., 2006; Oh et al., 2003; Wu et al., 2006), and isolated as proliferative cell cultures that should ordinarily be restricted in differentiation to the three cardiac cell types: cardiomyocytes, smooth muscle cells and endothelial cells. In contrast to the various endodermal and neural progenitor populations, putative progenitor cells from the heart have not shown stem cell features of prolonged proliferation. If expansion of these multipotent cardiovascular progenitor cells (CPCs) were achieved, it would be useful in a wide range of cardiac-related research areas, from basic developmental enquiry through to cardiac disease modelling, tissue engineering and cell therapy (Mercola et al., 2011; Mummery and Lee, 2013; Thavandiran et al., 2013), through either enhancing endogenous CPC numbers *in vivo* or isolating, expanding and transplanting cultured cells in the heart. While efforts continue towards making practical use of primary or endogenous CPC populations in the heart (not covered extensively here, but recently reviewed by Van Berlo and Molkentin (2014)), increasing attention is being directed to using self-renewing human pluripotent stem cells (PSC) for generating cardiac cells. Differentiation protocols have advanced tremendously over the last few years, most particularly those based on defined media using small molecular inhibitors and growth factors identified through developmental biology logic (Kempf et al., 2014; Lian et al., 2013). PSC-derived cardiomyocyte-studies are burgeoning, particularly in the area of cardiac disease modelling and drug safety pharmacology (Doherty et al., 2013; Drawnel et al., 2014; Matsa et al., 2014). Combined advances in induced pluripotent stem cell (iPSC) and genome editing technologies now permit study of large numbers of genetic changes on isogenic backgrounds (Li et al.,

* Corresponding author. Fax: +31 71 526 8289.
E-mail address: c.l.mummery@lumc.nl (C.L. Mummery).

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2014; Wang et al., 2014a; Zhang et al., 2014), where multiple disease mutations can be introduced into a single PSC line. This also presents an opportunity for mutation-specific drug screening and the development of novel treatments for cardiac disease, which is currently a major global cause of morbidity and mortality and for which treatment options are currently inadequate (Adler et al., 2009; Lloyd-Jones et al., 2010).

Yet in terms of developing therapies for the heart, some fundamental challenges remain which are still restraining full exploitation of this powerful PSC technology. These include: 1) maintenance and expansion of PSC-derived CPCs as pure populations in a stable state, 2) efficient direction of PSCs/CPCs to ventricular, atrial and nodal cardiomyocyte subtypes, or vascular cells and 3) maturation of these cardiomyocytes to stages beyond those resembling the early foetal heart.

For several lineages for which the existence of progenitors with stem cell properties has been demonstrated in primary (adult) tissue, the isolation and maintenance of PSC-derived tissue specific progenitors is now achievable (Cheng et al., 2012, 2013; Darabi et al., 2012; Nakamura et al., 2014; Okabe et al., 1996; Ran et al., 2013; Reubinoff et al., 2001; Sneddon et al., 2012), whereas less progress has been made with CPCs. If this could be mastered in much the same way as for PSC-derived neural progenitors, which now serve as a stable and renewable source of multiple neural cell types, it would significantly enhance the options for research and accelerate progress towards new cardiac therapeutics. One of the principal restraints has been the uncertain molecular identity of CPCs; during development; putative populations in the heart; and also those derived from PSCs. This review discusses these issues and highlights some of the existing knowledge which could guide researchers in addressing the challenge of isolating, expanding and differentiating PSC-derived CPCs *in vitro*.

Cardiovascular progenitor cells: an identity crisis?

While CPCs can easily be defined functionally by their tripotency in clonal analysis, their molecular identity during development is only partially understood. The best evidence comes from classical lineage tracing in mice, although detailed examination of protein and gene expression during development has provided surrogate information. These studies have shown that although stable states may exist for certain periods of heart development, the molecular identity of these populations (*i.e.* their chromatin/epigenetic signature and gene and protein expression profiles) may not be static for long, and defining a spatiotemporal map of any changes as they occur during development may be critical for mimicking this *in vitro*. Conversely, defining these stable or metastable states and progression to differentiated cell types at the clonal level using *in vitro* models may help us better understand heart development (Fig. 1). This is particularly relevant in studies of human heart where lineage tracing is not an option.

The earliest markers of the cardiac lineage can be seen in the gastrulating mesoderm and include Mesp1/2 and Fgf8 (Saga et al., 1999; Sun et al., 1999). Mesp1-driven Cre activity can be detected in all cells of the mouse heart of mesoderm origin, and while Mesp1$^+$ cells contribute broadly to a number of mesodermal derivatives, a subset appear to be dedicated cardiac progenitors (Devine et al., 2014). These proteins are expressed transiently at this stage but have an important role in the migration of cells to the lateral plate mesoderm where the population takes on a crescent shape; this is described initially as cardiogenic mesoderm as it is the site of the first cardiac-specific gene expression. The transcription factor *Nkx2-5*, the vertebrate *tinman* homologue of the *Drosophila* fruitfly, is an important early gene in this hierarchy and within the heart field marks definitive cardiac progenitors. Unlike *tinman* mutant flies in which cardiac lineage commitment is completely compromised so that the flies have no hearts, *Nkx2-5* deficient mice do initially form hearts, although expression of many myocardial genes is reduced and heart morphogenesis is abnormal (Lyons et al., 1995). This implies that Nkx2-5 is high in the hierarchy of cardiac transcription factors.

In considering CPC populations during heart development, it is important to be aware that an early lineage segregation takes place into what is termed the first heart field (FHF), which forms the entire left ventricle as well as other parts of the heart, and the second heart field (SHF), which contributes to part of the right ventricle and atria and forms all of the outflow tract (see review by Buckingham et al. (2005)). Mesp1$^+$ cells may already be fixed in their lineage fate, and common precursors may in fact exist only prior to gastrulation (Devine et al., 2014; Lescroart et al., 2014; Meilhac et al., 2004). The FHF differentiates within the cardiac crescent and this field forms the early heart tube. The second field, located medially to the crescent at the point of first differentiation, and then behind the forming heart tube, adds onto the heart tube during its later differentiation. This SHF encompasses the anterior heart field marked by Fgf8/10 and is marked more widely by the LIM homeobox transcription factor Islet 1 (Isl1) (Cai et al., 2003; Watanabe et al., 2010).

Whereas this lineage distinction is important during development, in stem cell models that lack location-dependent diversity, the definition of lineage may be less relevant than that of differentiation potential. At present it is also unclear if and how precisely the progenitors of the two heart fields are different at the molecular level. Support for a more comparable identity comes from a study in mice using a sensitive Cre-activated reporter based on *GATA4*, which was activated by *Isl1*^{Cre} and *Nkx2-5*^{Cre} in very similar domains in all four cardiac chambers (Ma et al., 2008). This suggests that differences among CPCs, at least in terms of *Isl1* and *Nkx2-5* expression, may be quantitative rather than qualitative. The transient and/or limited expression of *Isl*1 in rapidly differentiating FHF progenitors may be due to the fact that on differentiation to cardiomyocytes *Nkx2-5* expression increases and may act to downregulate *Isl*1 as well as other progenitor genes such as *Fgf10* in the first heart field (Prall et al., 2007; Watanabe et al., 2012). In *Nkx2-5* null embryos, expression of these genes can be detected in the cardiac crescent. Yet in a recent molecular analysis of Mesp1-marked derivatives, early regional differences have been suggested to exist (Lescroart et al., 2014).

The knowledge that Nkx2-5 and Isl1 mark multipotent CPCs during development prompted investigations into their possible presence in postnatal hearts. This led to the discovery of Isl1$^+$ cells in mouse and human neonatal heart, which when isolated from mouse based on the *Isl*1-Cre/R26R directed expression of lacZ or YFP, and cultured on cardiac mesenchyme, differentiated to cardiomyocytes or smooth muscle cells (Laugwitz et al., 2005; Moretti et al., 2006). However, their number is few at birth and they are undetectable in the adult. A variety of putative CPCs have been identified in adult hearts based on alternative markers expressed by stem cells in other tissues (Bearzi et al., 2007; Beltrami et al., 2003; Martin et al., 2004; Messina et al., 2004; Oh et al., 2003). Particular interest has focused on a population expressing the stem cell factor (SCF) receptor c-kit, which at least at the neonatal stage encompasses a population with some evidence of cardiomyogenic potential (Beltrami et al., 2003; Jesty et al., 2012; Zaruba et al., 2010). However, using a carefully validated *c-kit* lineage reporter mouse it was later shown that $<0.03\%$ of cardiomyocytes derived from a *c-kit* expressing population during development, and $<0.01\%$ in the first 6 months of postnatal life (Van Berlo et al., 2014). The population in the heart marked by the *c-kit* lineage reporter instead included 18% haematopoietic cells (CD45$^+$) and 77% endothelial cells (CD31$^+$). So while c-kit$^+$ cells do contribute to the developing myocardium of the heart this new evidence suggests they may do so extremely rarely; similarly in the adult. *In vitro* differentiation of heart-derived c-kit$^+$ cells can result in the upregulation of cardiac

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