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REVIEW

The cardiac stem cell compartment is indispensable for myocardial cell homeostasis, repair and regeneration in the adult

Bernardo Nadal-Ginard[a,c,*], Georgina M. Ellison[a,b,c], Daniele Torella[b,**]

[a] Department of Physiology, School of Biomedical Sciences, King's College, London, UK
[b] Molecular and Cellular Cardiology, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro 88100, Italy
[c] Centre for Stem Cells & Regenerative Medicine, King's College, London, UK

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Abstract Resident cardiac stem cells in embryonic, neonatal and adult mammalian heart have been identified by different membrane markers and transcription factors. However, despite a flurry of publications no consensus has been reached on the identity and actual regenerative effects of the adult cardiac stem cells. Intensive research on the adult mammalian heart's capacity for self-renewal of its muscle cell mass has led to a consensus that new cardiomyocytes (CMs) are indeed formed throughout adult mammalian life albeit at a disputed frequency. The physiological significance of this renewal, the origin of the new CMs, and the rate of adult CM turnover are still highly debated. Myocyte replacement, particularly after injury, was originally attributed to differentiation of a stem cell compartment. More recently, it has been reported that CMs are mainly replaced by the division of pre-existing post-mitotic CMs. These latter results, if confirmed, would shift the target of regenerative therapy toward boosting mature CM cell-cycle re-entry. Despite this controversy, it is documented that the adult endogenous c-kit^{pos} cardiac stem cells (c-kit^{pos} eCSCs) participate in adaptations to myocardial stress, and, when transplanted into the myocardium, regenerate most cardiomyocytes and microvasculature lost in an infarct. Nevertheless, the *in situ* myogenic potential of adult c-kit^{pos} cardiac cells has been questioned. To revisit the regenerative potential of c-kit^{pos} eCSCs, we have recently employed experimental protocols of severe diffuse myocardial damage in combination with several genetic murine models and cell transplantation approaches showing that eCSCs are necessary and sufficient for CM regeneration, leading to complete cellular, anatomical, and functional myocardial recovery. Here we will review the available data on adult eCSC biology and their regenerative potential placing it in the context of the different claimed mechanisms of CM replacement. These data are in agreement with and have reinforced our view that most CMs are replaced by *de novo* CM formation through the activation, myogenic commitment and specification of the eCSC cohort.

* Correspondence to: B. Nadal-Ginard, Department of Physiology, School of Biomedical Sciences, King's College London, Shepherd's House, Rm 4.16, Guy's Campus, London SE1 1UL, UK.
** Correspondence to: D. Torella, Molecular and Cellular Cardiology, Dept of Medical and Surgical Sciences, Magna Graecia University, Biosciences Building, Level VIII Rm 09, Campus S. Venuta, Viale Europa, Catanzaro 88100, Italy.
E-mail addresses: bernardo.nadalginard@kcl.ac.uk, bernardo.nadalginard@gmail.com (B. Nadal-Ginard), dtorella@unicz.it (D. Torella).

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Introduction

Despite the remarkable progress made during the past half century in the treatment of cardiovascular disease, which is increasingly effective in dealing with the acute stages of life-threatening pathology, they often extend the life of the patient at the expense of generating a chronic condition. The chronic sequels from an acute myocardial infarction (AMI), such as chronic heart failure (CHF), are frequently without effective treatment or leave organ transplantation as the only alternative to restore function, with all the logistic, economic and biological limitations associated with this intervention (Kahan et al., 2011).

The continuous increase in average human lifespan with progressive aging of the population in all developed countries has generated an increasingly severe epidemic of chronic diseases whose treatment absorbs an ever-larger fraction of human resources and of the healthcare budget. Presently, there are >5 million patients in CHF post-AMI in the USA alone (Roger et al., 2012). More than 550,000 new patients per year are added to this group, which has a similar prevalence in the EU countries. After the first episode, CHF post-AMI has an average annual mortality rate of ~18% and in the USA alone absorbs >$30 billion annually for its care (Roger et al., 2012). The root problem of CHF in general and post-AMI in particular is a deficit of functional myocardial contractile cells (cardiomyocytes) and adequate coronary circulation to nurture them. This combination triggers pathological cardiac remodelling, which, in turn, produces further myocyte death and the late development of cardiac failure in these patients (Jessup et al., 2003). For these reasons, during the past decade a goal of cardiovascular research has been to find methods to replace the cardiomyocytes lost as a consequence of an MI and other insults in order to prevent or reverse the pathological cardiac remodelling. Therefore, stem cell-based therapies have become an attractive experimental treatment for heart disease and failure (Terzic et al., 2010).

Until recently, a paucity of understanding about the cellular homeostasis of most adult solid tissues has been a major factor limiting the expansion to other areas of medicine of the early breakthroughs in adult stem cell research and therapy, such as those applied to the blood and bone marrow diseases. Early in the last decade the prevalent view was that, although tissues like the bone marrow, intestinal epithelium and skin exhibit a robust self-renewal capacity based on the presence of adult (also called "tissue-specific") stem cells (Mercier et al., 2011; Simons et al., 2011; Fuchs, 2009), they were an exception. The established paradigm was that the majority of the remaining solid tissues either renewed very slowly (such as the muscle and the endothelial lining of the vascular system), with renewal being physiologically irrelevant, or not at all. It was firmly believed that starting shortly after birth many tissues did not harbour functional regenerating (stem) cells. A logical consequence of the above paradigm was the belief that for most organs the number and function of their parenchymal cells was in a downward spiral starting in late infancy and continued until death. With the exception of the three main self-renewing tissues mentioned above, it necessarily followed that all therapeutic approaches to disease processes caused by a deficit in the number of functional parenchymal cells could be only directed toward improving and/or preserving the performance of the functional cells remaining in the tissue. Thus, to return the tissue or organ to the *status quo ante* required the transplantation of either identical cells from another individual or transplantation of a cell type capable of differentiating into the cells whose shortage needed to be covered. Because the cells needed for the second option did not exist for the majority of tissues, heterologous/allogeneic organ and cell transplantation became the only possible avenues. In fact, despite the multiple drawbacks of heterologous cell/organ transplantation, its practice has become the cutting edge for several medical specialties (Badylak et al., 2012). However, the extreme shortage of donors, high costs, and the severe side effects of immunosuppression have limited this therapy to a small fraction of candidates in need of treatment. Thus, the positive reception and high expectations that received the successful derivation of multipotent human embryonic stem cells (hESCs) (Evans et al., 1981; Thomson et al., 1998; Murry, 2008) with the capacity to differentiate into most, if not all, known cell types promised an unlimited supply of