Stem Cell Research (2014) 13, 521–522

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Introduction to the Special Issue on Heart Regeneration and Rejuvenation

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Received 26 September 2014; accepted 3 October 2014
Available online 12 October 2014

Abstract Despite therapeutic advances that slow its progression, heart disease remains the world's leading cause of death. Until recently, the "Holy Grail" of cardiac biology, to regenerate the damaged heart, appeared to be a fantastical and quixotic quest. However, recent studies showing that the mammalian heart possesses an innate, albeit limited, regenerative capacity offer hope that effective cardiac regeneration may be an attainable goal. This Special Issue of Stem Cell Research reviews the remarkable progress that has been made in this field in the last few years.

The root cause of most forms of heart disease is the loss of cardiomyocytes. Past decades of cardiovascular research demonstrated that surviving cardiomyocytes are the target of chronic neurohumoral activation that in the long run causes additional cardiomyocyte dysfunction and death. Recognition of this "cardiomyopathy of overload" led to the development of therapies that block chronic neurohumoral activation, protect remaining cardiomyocytes, and thereby improve survival of heart disease patients. This success story is one of the triumphs of modern medicine, and an example of how bidirectional translation between bench and bedside enhanced basic knowledge and at the same time led to improved therapy.

However, this success was a partial victory, as heart disease remains the world's leading cause of death, and its incidence continues to increase. While improved by modern medical management, the long term survival of heart disease patients remains poor. Achieving qualitatively better outcomes will require replacement of lost cardiomyocytes. This goal of cardiac regeneration has been the longstanding "Holy Grail" of cardiac biology, although the dogma that cardiomyocytes are non-replicating, terminally differentiated cells made this quest appear fantastical and quixotic.

This view has changed dramatically over the past decade, as seminal studies using independent approaches have demonstrated ongoing cardiomyocyte replacement in the normal and injured adult heart. This innate regenerative capacity is, however, limited and inadequate to functionally regenerate hearts after acute ischemic injury or heart failure. Nevertheless, these findings offer the hope that cardiac regeneration can be therapeutically augmented, and cardiac regeneration has become a central focus of cardiac biology. This Special Issue of *Stem Cell Research* reviews the remarkable progress made in this field in a short amount of time.

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http://dx.doi.org/10.1016/j.scr.2014.10.003

There are two distinct mechanisms for cardiomyocyte replacement that might underlie innate cardiac regeneration and become the targets of therapeutic regeneration: proliferation of pre-existing cardiomyocytes and differentiation of cardiac stem or progenitor cells. The extent of cardiomyocyte proliferation has been the subject of considerable debate and controversy, in large part because of technical challenges inherent in accurately measuring cardiomyocyte renewal. These challenges and controversies are reviewed in depth in the articles by Bergmann and Jovinge, and Senyo, Lee and Kuhn.

Models systems with effective regeneration have been developed to understand nature's solutions to cardiac regeneration, in the hopes that the lessons learned will be instructive for augmenting the adult mammalian heart's limited regenerative capacity. Zebrafish have emerged as the best developed system to study innate functional cardiac regeneration. Recent work in zebrafish, reviewed in this Special Issue by Kikuchi, has demonstrated that cardiac regeneration occurs through the proliferation of pre-existing cardiomyocytes rather than through deployment and differentiation of cardiac progenitors. Porrello and Olson developed a mammalian model of effective heart regeneration by demonstrating that neonatal mice are able to regenerate amputated or ischemic myocardium. In this system, new cardiomyocytes also arise from proliferation of existing cardiomyocytes. In this Issue, Porrello and Olson review cardiac regeneration through the lens of their neonatal heart regeneration model. Enhancing cardiomyocyte proliferation is a natural therapeutic target to augment cardiac regeneration and several laboratories have investigated manipulation of the Hippo/Yap pathway. These studies, reviewed in this Issue by Lin and Pu, suggest that augmentation of the activity of YAP or its downstream targets is an attractive approach to stimulating cardiac regeneration.

Cardiac strem and progenitor cells are the essential building blocks of heart development and rare cells with similar properties have been proposed to exist within niches in the adult heart. The diversity of such progenitor cell types and the evidence for their developmental origins and lineage contributions to the adult heart have been reviewed by Chong, Forte and Harvey. Among the many adult cardiac stem cell types described, the most studied is the c-Kit positive, blood lineage negative adult heart cell population. In this Issue, Nadal-Ginard, Ellison, and Torella, and Leri et al. review their work on the cardiac regenerative properties of c-Kit$^+$ cardiac progenitor cells and the biology of the niches that harbor them in the adult heart. Various investigators, including these authors, have reported that c-Kit$^+$ cells have cardiomyogenic activity *in vitro* and *in vivo*, providing the rationale for human cardiac stem cell therapy trials. However, recent genetic lineage tracing of c-Kit$^+$ cells suggests that they have only very limited ability to form cardiomyocytes *in vivo* in mouse models. In human trials, adult progenitor cell-based cell therapy has shown modest efficacy, although most studies in animal models using a range of progenitor cell types for cell therapy in the setting of acute myocardial infarction suggest that donor cells survive only briefly after cardiac delivery and that the beneficial effects are paracrine. These emerging data have cast a shadow on the potential of cardiac progenitor cells to heal the injured heart, although much work remains to be done. The ethical issues of pushing potential new therapies into the clinic based on incomplete data are addressed in this Special Issue in the paper by Munsie and Hyun. An alternative form of cell therapy, transplantation of pluripotent stem cell-derived cardiomyocytes, has shown promise in animal models. As reviewed by Chong and Murry, this form of cell therapy was also recently tested in a non-human primate model, with promising results, albeit that improvements in contractile function with such therapy have yet to be demonstrated. Augmentation of cardiomyocyte mass will of course require new vessel formation, and the review by Michelis, Boehm and Kovacic summarizes the history of revascularisatiaon therapy up to the current day.

A number of other strategies to achieve cardiac regeneration have been advanced. Epicardial cells on the surface of the heart are well established to have critical progenitor and paracrine roles in heart development. Heart injury reactivates a subset of these properties which might be therapeutically enhanced to protect the heart from myocardial injury, and to stimulate heart regeneration. Here, Masters and Riley review the function of these cells in development, adult homeostasis, adult heart injury and repair. Paracrine factors are powerful regulators of cell behavior and fate. Recent studies, summarized herein by Li et al., indicate that thyroid hormone stimulates a burst of cardiomyocyte proliferation in the preadolescent murine heart, indicating continued proliferative competence long after the perinatal period and suggesting a potential role for thyroid hormone therapy in cardiac regeneration. Modulation of paracrine factors can redirect progenitor cell behavior for therapeutic benefit. Of interest in this regard is the recent work of Lui et al. supporting the use of modified RNA to deliver pulse-like paracrine signals to improve myocardial outcome after MI, which they consider in their review. Finally, the role of immune cells in tissue regeneration is coming into focus, and Pinto, Godwin and Rosenthal review the role of tissue macrophages in cardiac inflammatory responses and regeneration.

While much remains to be learned, this Special Issue, therefore, summarizes recent progress in discovering and unlocking the latent regenerative capacity of the adult mammalian heart, which offers hope for effecting clinically meaningful myocardial repair after injury.