Cell therapy holds great promise for the treatment of cardiovascular disease. For the past 2 decades, investigators have been developing methods to implant various types of cells to heal the heart and improve the recovery of the heart after ischemia. Although multiple experimental and several clinical studies showed that different subsets of bone marrow–derived cells and other adult progenitor cells improved the recovery of heart function, the mechanism of action and the extent to which adult progenitor cells are able to restore cardiac function in end-stage heart failure is debated extensively. Therefore, this review series will summarize the current status of cell therapy in clinical trials and discuss the potential of different cell types and ways to enhance their functions. Additionally, epigenetic molecular mechanisms that regulate stem cell functions and fate decisions will be summarized.

The first evidence that cell therapy may constitute a therapeutic option for the treatment of ischemic disease was provided by Asahara et al in 1997, who showed that bone marrow–derived CD34<sup>+</sup> cells can give rise to endothelial-like cells and improve neovascularization after ischemia. In attempts to replace cardiomyocytes, initial animal studies used isolated neonatal cardiomyocytes to replace dead muscle tissue. Because of the limited availability of mature human cardiomyocytes, skeletal muscle cells were considered as an alternative approach.
alternative cell source, which indeed improved cardiac function after transplantation of the cells in animal models. Subsequent clinical trials showed some benefit but also raised safety concerns with respect to arrhythmic events induced by nonintegrated skeletal muscle cells.\(^2\) Cultured cardiac stem cells, embryonic stem cells, or induced pluripotent stem cells are currently considered as cellular sources for generating cardiomyocytes.\(^3,4\) Early reports that bone marrow–derived adult stem/progenitor cells have a greater plasticity than expected and can differentiate into cardiomyocytes raised the hope that bone marrow–derived cells may improve both neovascularization and repair of the infarcted heart. Although multiple experimental and several clinical studies showed that different subsets of bone marrow–derived cells and other adult progenitor cells improved the recovery of heart function,\(^5\) the mechanism of action and the extent to which adult progenitor cells are able to restore cardiac function in end-stage heart failure is debated extensively.

Therefore, the current review series will provide an overview of the current experimental and clinical studies, particularly taking into account that different disease entities may need to be treated with different cells and different delivery approaches. Therefore, the achievements in treating both ischemic peripheral and cardiace diseases and heart failure will be separately discussed by pioneers in the field. Drs Birgit Assmus and Andreas Zeiher together with Dr Stefan Janssens will highlight the current status of cell therapy of acute and chronic myocardial infarction. Dr Roberto Bolli will summarize the current achievements in treating heart failure, which is more challenging because of the established scar tissue that needs to be regenerated. Drs Dirk Walter and Douglas Losordo will highlight the recent trials in patients with peripheral vascular disease. Of note, clinical trials must be interpreted cautiously because of differences in patient populations and study design; therefore, an article by Drs Timothy Henry and Thomas Povsic will specifically address methodological issues in cell therapy studies.

As discussed above, various types of adult stem/progenitor cells and proangiogenic cells showed beneficial effects in experimental studies and might have a therapeutic potential. The characterization of the different cell sources, however, is sometimes challenging, and the individual subtypes of adult stem/progenitor cells may have advantages but also limitations when considered for treatment of cardiovascular diseases. Therefore, several review articles will summarize the current understanding of the basic biology and therapeutic potential of selected cells such as mesenchymal stem cells (Drs Joshua Hare and Adam Williams),\(^6\) the proangiogenic “endothelial progenitor cells” (Drs Stefanie Dimmeler, Gian Paolo Fadini, and Douglas Losordo), and side-population cells (Dr Ronglih Liao).

In addition to the use of different cell types, several strategies might be useful to augment homing, integration, and survival of the transplanted cells, which is a requirement for successful cell therapy. Biomaterials have the potential to modulate the environment for the implanted cells, and this field of study will be reviewed by Drs Richard Lee and Vincent Segers.\(^7\) Genetic or pharmacological modulation is an alternative to biomaterials and might be very useful to pretreat the cells before implantation. Dr Mark Sussman will cover these aspects and specifically highlight the role of antiapoptotic strategies to improve cell survival. To find new ways to modulate cell survival and differentiation, chemical screens might provide new structures to develop small molecules for treating cells or the target tissue to activate endogenous repair. Small molecules also have been shown to augment the efficiency of reprogramming and by this means might be useful to replace vectors that have raised safety concerns. Dr Jay Schneider will summarize chemical strategies to regulate stem/progenitor cell functions.

Imaging of applied cells will be of great help to address important principal questions regarding cell homing and long-term incorporation. Therefore, tools to monitor cell homing, survival, and potentially even function or differentiation are not only important in experimental studies but may also help to refine optimal delivery tools in different patient populations. This important aspect will be summarized by Dr Joseph Wu,\(^8\) who is well known for his important studies measuring cell homing by use of luciferase reporter genes in cardiovascular disease models.

Stem/progenitor cell plasticity and function are critically regulated by epigenetic signaling pathways. In particular, the transition from self-renewable stem cells toward differentiated mature cardiovascular cell types requires extensive remodeling of chromatin and changes in DNA and histone modifications. Therefore, Dr Thomas Braun and colleagues will provide an overview of the epigenetic processes underlying decisions about stem cell fate. Downstream of the transcriptional control, microRNAs are epigenetic modulators of mRNA degradation or protein translation that play crucial roles in development and disease states. Recent studies suggest that microRNAs might be sufficient to induce pluripotency, and several microRNAs that are regulated during cellular differentiation might also control cardiovascular cell functions. These aspects will be addressed by Dr Dimmeler’s review.

Finally, the identification of adult progenitor cells in the heart has not only raised hopes for therapy but also challenged our principal view of the heart as a terminally differentiated organ without the capacity to regenerate. Dr Piero Anversa and colleagues will summarize the paradigm shift in myocardial biology in an article on the “Role of Cardiac Stem Cells in Cardiac Pathophysiology.”\(^9\)

Together, we believe that this review series will provide an overview on the experimental and clinical cutting edge science of stem and progenitor cells in the cardiovascular field.

Disclosures

None.

References


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Stem Cells Review Series: An Introduction
Stefanie Dimmeler and Douglas Losordo

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