12 Cardiovascular Regenerative Medicine: Challenges, Perspectives, andFuture Directions

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Cardiovascular regenerative medicine is an interdisciplinary field that utilizes the principles of engineering and life sciences to restore the structure and/or function of damaged or diseased heart. While current cardiovascular tissue and organ transplantation therapies suffer from scarce donor supply and various immune system complications [1], regenerative medicine approaches have enabled bypassing some of these obstacles and heal or replace tissues damaged by acquired or congenital disease [2, 3]. A broad range of regenerative strategies are currently being investigated in preclinical and clinical stages [3]. These methods can be classified to (a) the use of exogenous materials (e.g., scaffolds or cardiac patch systems [4]) and/or cells [5] to replace or salvage the damaged tissue structure and function and (b) leveraging the body's endogenous regenerative mechanisms [6, 7], although adult human heart possesses markedly restricted regenerative capacity. In many cases, a combination of these mechanisms is involved in healing the damaged tissue (e.g., paracrine effects or inducing innate therapeutic responses by implanted patch or cells) [8].

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A variety of conventional and advanced tissue engineering methods are used to create cardiac patch systems including cell sheets [9], decellularized tissues [10], self- or wave-assembly techniques [11], and 3D bioprinting [12]. Although beneficial effects of engineered cardiac patch devices in a variety of in vitro and in vivo animal studies have been demonstrated, there still remain a number of challenges in their clinical applications. These challenges include (1) lack of sufficient vasculature in the patch, (2) precise control on the 3D scaffold structure, and (3) inadequate maturity/functionality of human cardiac muscle cells within engineered constructs [13, 14]. Additive manufacturing (i.e., 3D (bio)printing) technologies have emerged as powerful, versatile tools to manufacture 3D cardiac tissue constructs at remarkably greater precision, consistency, and reproducibility [14–16]. To date, a variety of bioprinted cardiovascular tissues/organs have been investigated including vasculature [17], cardiac patches [18, 19], coronary artery stents [20], and cardiac valves [21]. Despite the significant advances in cardiac tissue bioprinting, significant challenges remain, including but not limited to the need for large quantity of functional cardiac muscle cells and the necessity of incorporating functional vasculature in printed constructs [14]. Further work will be necessary to develop specialized bioink materials with biological and physiochemical properties that are optimized for cardiac tissue bioprinting [16].

While still in its infancy, the cardiovascular regenerative medicine field has made notable advances in recent years to enhance future applications to meaningfully regenerate damaged/diseased adult human heart [22, 23]. Efforts to understand the complexity of adult heart regeneration through basic sciences and translational studies in fields such as genetics, biomaterials and tissue engineering, nanotechnology, imaging, and cardiac cellular and molecular biology will pay dividends in the long run [23]. While the potential therapeutic benefits of many approaches to cardiac regenerative therapies have been examined thus far, their precise mechanisms of action are often unknown. For instance, while application of an epicardial patch, laden with the cardiogenic follistatin-like 1 protein, was recently shown to stimulate cardiomyocyte cell cycle re-entry and division, little is known about the cellular and molecular mechanisms underlying this regenerative effect [24, 25].

Looking ahead, the role for tissue engineering and regenerative therapy to treat patients with heart disease must contend and synergize with the large variety of device therapies that are currently being implemented in patients with cardiovascular diseases. For instance, while patients with sick sinus syndrome may benefit from implantation of biological pacemakers that are made from tissue engineered cells [26], the reliability and efficiency of these cells to maintain pacemaker function must be greater than that of an electronic pacemaker, which is the current standard of care [22]. It is expected that the future of regenerative therapies will focus on a selective number of cardiovascular diseases that are not served well by the current devices and treatments (e.g., genetic cardiomyopathies or acute myocardial infarction) [22]. Thus, economic, practical, and translational considerations must be more carefully taken into account in the future studies aiming at developing next-generation cardiovascular regenerative therapies.

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