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Review

The Role of Tissue Engineering and Biomaterials in Cardiac Regenerative Medicine

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ABSTRACT

In recent years, the development of 3-dimensional engineered heart tissue (EHT) has made large strides forward because of advances in stem cell biology, materials science, prevascularization strategies, and nanotechnology. As a result, the role of tissue engineering in cardiac regenerative medicine has become multifaceted as new applications become feasible. Cardiac tissue engineering has long been established to have the potential to partially or fully restore cardiac function after cardiac injury. However, EHTs may also serve as surrogate human cardiac tissue for drug-related toxicity screening. Cardiotoxicity remains a major cause of drug withdrawal in the pharmaceutical industry. Unsafe drugs reach the market because preclinical evaluation is insufficient to weed out cardiotoxic drugs in all their forms. Bioengineering methods could provide functional and mature human myocardial tissues, ie, physiologically relevant platforms, for screening the cardiotoxic effects of pharmaceutical agents and facilitate the discovery of new therapeutic agents. Finally, advances in induced pluripotent stem cells have made patient-specific EHTs possible, which opens up the possibility of personalized medicine. Herein, we give an overview of the present state of the art in cardiac tissue engineering, the challenges to the field, and future perspectives.

RÉSUMÉ

Ces dernières années, l'élaboration de tissus cardiaques issus de l'ingénierie tissulaire (EHT: *engineered heart tissue*) en 3 dimensions a franchi un grand pas grâce aux avancées de la biologie des cellules souches, de la science des matériaux, des stratégies de la prévascularisation et de la nanotechnologie. Par conséquent, le rôle de l'ingénierie tissulaire en médecine régénérative du cœur devient complexe, alors que les nouvelles applications deviennent réalisables. Il a été établi depuis longtemps que l'ingénierie tissulaire cardiaque a le potentiel de restaurer partiellement ou entièrement la fonction cardiaque après une lésion cardiaque. Toutefois, les EHT peuvent également servir comme substitut de tissu cardiaque humain pour le dépistage des effets toxiques des médicaments. La cardiotoxicité demeure une cause majeure du retrait des médicaments dans l'industrie pharmaceutique. Des médicaments dangereux sont commercialisés puisque l'évaluation préclinique est insuffisante pour éliminer les médicaments cardiotoxiques sous toutes leurs formes. Les méthodes de bio-ingénierie pourraient offrir des tissus myocardiques humains fonctionnels et matures, c'est-à-dire des plateformes physiologiquement pertinentes de dépistage des effets cardiotoxiques des médicaments, et faciliter la découverte de nouveaux agents thérapeutiques. Finalement, les avancées sur les cellules souches pluripotentes induites ont permis l'élaboration de EHT propres au patient, ouvrant ainsi la porte à la médecine personnalisée. Ici, nous donnons un aperçu de l'état actuel de l'art de l'ingénierie tissulaire cardiaque, des défis liés à ce domaine et des perspectives futures.

Cardiovascular disease is responsible for greater mortality than all cancers combined in the Western world.[1] Myocardial infarction (MI) causes irreversible damage to the myocardium because the adult heart has minimal intrinsic ability to regenerate lost cardiomyocytes (CMs). After the initial insult, fibroblasts (FBs) and endothelial cells (ECs) form a dense collagenous scar that maintains wall structure but is inflexible and noncontractile, often leading to heart failure.[2] The most effective current therapy to restore heart function, cardiac transplantation, is limited by insufficient availability of donor organs and the requirement for lifelong immunosuppression. Left ventricular assist devices require invasive surgery and long-term anticoagulation therapy.

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Cardiotoxicity is a major concern for the pharmaceutical industry because differences in the electrophysiological properties of animal and human CMs limit the relevance of preclinical animal studies.[3] Additionally, human clinical trials are limited by small sample pools and, at times, skewed genetic and phenotypic diversity.

Cardiac tissue engineering—based on human CMs, biomimetic scaffolds, and integrated bioengineering concepts—possesses the potential to partially or fully restore cardiac function and serve as a surrogate human cardiac tissue for drug toxicity screening and personalized medicine. However, there are still many challenges to be overcome before these techniques can move toward clinical applications. This article aims to review the present state of the art, challenges to the field, and future perspectives. We focus on tissue engineering methods that provide means of constructing human tissues for *in vitro* modelling of disease and drug discovery as well as functional cardiac patches for restoration of contractile function *in vivo* (Fig 1).

Cell Source Considerations

The objective of cardiac regenerative medicine is to repopulate the injured site with functional cells to replenish the lost cells and regenerate the damaged cardiac tissue. However, adult CMs are terminally differentiated and have a minute capacity for expansion *in vitro* using biopsy samples of a patient's heart tissue. Therefore, alternative cell sources with abundant availability are necessary. The discovery of human induced pluripotent stem cells (hiPSCs) has enabled the generation of potentially unlimited numbers of autologous CMs for cell therapy and for the development of personalized drug therapies,[4,5] without the ethical concerns raised by the use of human embryonic stem cells (hESCs). iPSC-derived CMs (iPSC-CMs) are additionally attractive because they can recapitulate some genetic cardiac disorders in standard monolayer cultures (eg, long Q-T syndrome) and can also potentially be used to assess patient-specific responses to drugs before their use in the body.[6] CM differentiation protocols rely on timed application of growth factors or small molecules that modulate pathways important for cardiogenesis during embryonic development. These molecules are applied to iPSCs or ESCs grown in embryoid body format or in monolayers.[7-9]

In recent years, strong evidence of hESC-CM integration into the recipient heart has been found.[10] Most often, *in vivo* integration of hESC-CMs into recipient hearts has been studied using rodent models,[11-13] which is often criticized as unsuitable because of the large difference in the heart rate between human ventricular CMs (60-120 bpm) and rodent ventricular CMs (350-600 bpm). Studies in a more comparable guinea pig model (heart rate, 200-250 bpm) and recent

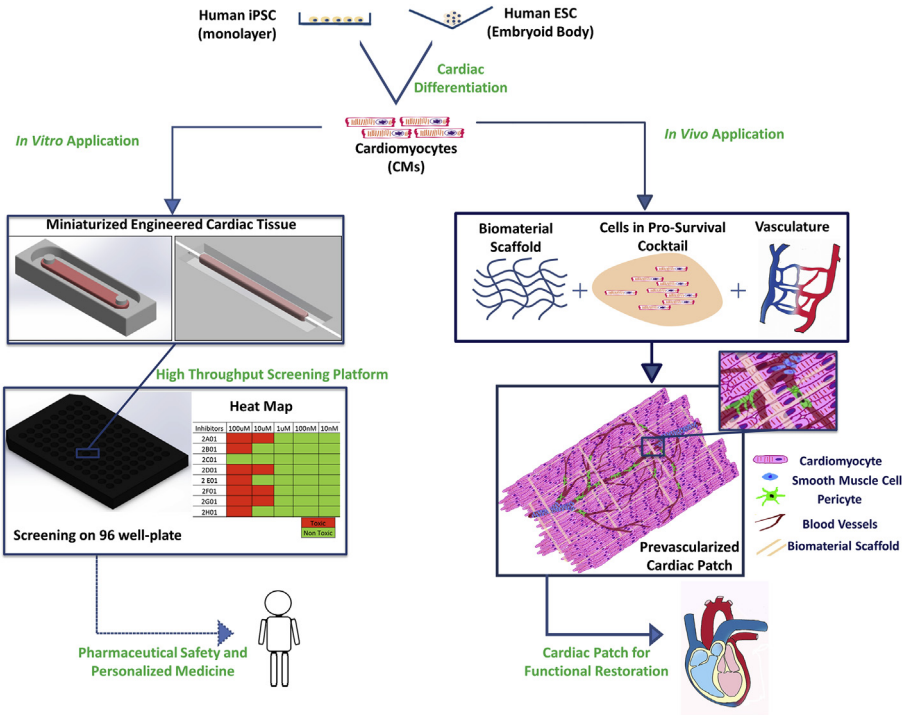

Figure 1. Overview. Human induced pluripotent stem cells and human embryonic stem cells are capable of differentiation to produce cardiomyocytes (CMs), which can be applied to both *in vitro* and *in vivo* applications. *In vitro*, miniaturized cardiac tissues are engineered in large numbers using small numbers of cells and reagents. These microtissues are used in platforms such as customized 96-well plates with topographic cues—eg, wires or posts that guide tissue assembly and enable readout of contractile force. The data are analyzed to evaluate efficacy and safety as part of the pharmaceutical development process. The same strategy can also be used to optimize therapeutics for personalized medicine. *In vivo*, CMs are combined with a prosurvival cocktail, biomaterial scaffold, and pre-established vasculature to generate functional cardiac patches that allow for immediate perfusion and electromechanical coupling between the patch and the host tissue after transplantation for true cardiac functional restoration. ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells.