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Body builder: from synthetic cells to engineered tissues

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It is estimated that 18 Americans die every day waiting for an organ donation. And even if a patient receives the organ that s/he needs, there is still >10% chance that the new organ will not work. The field of tissue engineering and regenerative medicine aims to actively use a patient's own cells, plus biomaterials and factors, to grow specific tissues for replacement or to restore normal functions of that organ, which would eliminate the need for donors and the risk of alloimmune rejection. In this review, we summarized recent advances in fabricating synthetic cells, with a specific focus on their application to cardiac regenerative medicine and tissue engineering. At the end, we pointed to challenges and future directions for the field.

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Introduction: building blocks for regenerative medicine

Our body, built by Mother Nature, is continuously challenged by diseases and common wear and tear. Like a house, after many years, our body needs repair or even a flip. Regenerative medicine is a promising strategy to repair and rebuild our own body, by creating new tissues to restore or replace organ function lost [1]. Regenerative medicine also empowers scientists and bioengineers to manufacture tissues and organs in the laboratory for implantation. Importantly, regenerative medicine holds the potential to alleviate the problem of organ shortages. There is a huge gap between the number of available donor organs and the number of patients on the organ transplantation waiting list. And even worse, unlike other organs and tissues, the heart has very limited regenerative potential [2•]. This limitation is partially due to the lack of resident cardiac stem cells, and genetic/epigenetic roadblocks that limit adult cardiomyocytes from proliferating a short period of time after birth [3].

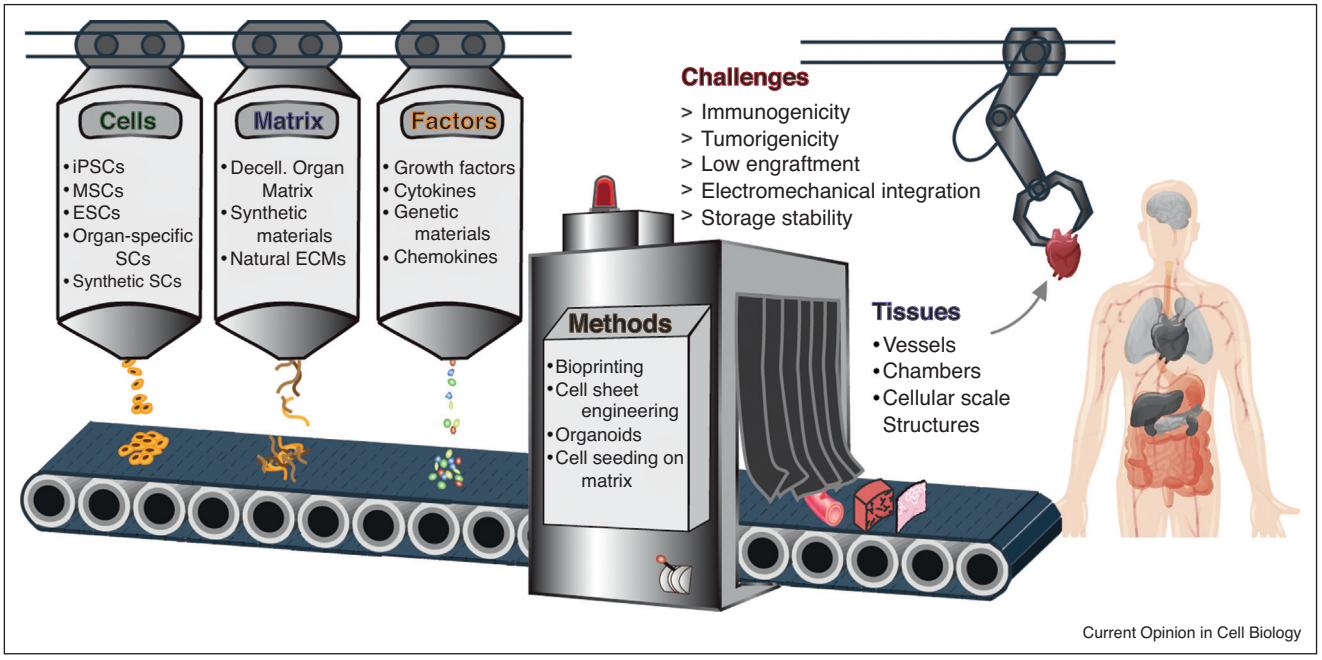
Organs, tissues, cells, and proteins are the main building 'legos' for regenerative medicine. Among them, organs are ready-to-use building blocks. Successful organ transplantation started in 1954 with the first successful kidney transplant [4,5] performed by Dr Joeseph E Murray and his team at Boston. After that, successful transplantation of pancreas, liver, and heart took place. Approximately half million Americans benefit from a transplant each year. Nowadays, in the US more than 120 000 people are waiting to receive a life-saving organ transplant. Many of these individuals will die before a suitable donor organ is available.

Instead of replacing the entire organ, stem cell therapy holds the promise to repair the organ by effectively replacing the lost cells [6]. Generation of transplantable organs *in vitro* using stem cells and scaffolding materials is also a desirable approach for organ regeneration [7••]. While, injected stem cells can promote healing and regeneration *in situ* in the targeted organs [8], however, due to the low cell retention rate, a mass of stem cells need to be injected. This not only raises cost but also represents a safety concern to patients. Typically, a more intentional assembly of raw materials (cells, matrix, factors) and fabrication methods is needed to create functional tissue constructs (Figure 1).

Obtaining cells and tissues from the nature

Cardiac cell therapy using adult stem cells started from the early 2000s. Studies from several groups claimed that transplants of bone-marrow-derived stem cells or c-Kit+ cardiac progenitor cells can regenerate the infarcted rodent heart [9]. About a decade later, this work was translated to the clinic, with phase I clinical trials in patients [10,11]. As the field progressed, a paradigm change occurred as scientists started to realize that the injected cells hardly form any new cardiac tissue but instead promote endogenous repair via paracrine mechanisms [12]. In 2017, Nature Biotechnology expressed a severe concern on the none-to-marginal benefits of cardiac cell therapy trials and argued that cardiac cell therapy is 'far from getting approval' and 'much more preclinical data needs to be performed before any new clinical trials' [13]. Gradually, most scientists in the field now recognize that cardiac stem cells (CSCs) are very rare and the therapeutic benefits of CSCs are mainly from

Figure 1



Assembly of raw materials to tissues for organ regeneration. Functional tissue constructs could be created by cells, matrix, and factors through different methods, including bioprinting, cell sheet engineering, cell seeding in matrix and so on. However, there are still many challenges hindering the clinical application of tissue engineering, like immunogenicity, tumorigenicity, low engraftment, electromechanical integration and storage stability. iPSCs: induced pluripotent stem cells, MSCs: Mesenchymal stem cells, ESCs: embryonic stem cells.

pro-survival, pro-angiogenic, and anti-inflammatory effects rather than direct cardiomyogenic differentiation [14]. As a result, there is a strong movement toward investigating the potential of pluripotent cell types (e.g. ESC and iPSC) to become cardiac cell types necessary for regeneration. Substantial challenges exist in this realm as well including teratoma formation, karyotypic abnormalities, immune rejection, immature phenotypes, cardiomyocyte heterogeneity, etc. [15].

Building synthetic and artificial cells

As a 'live drug', stem cells need to be carefully processed and preserved before clinical application. Studies indicate that the quality of stem cells can directly affect their therapeutic benefits *in vivo*. To switch from the concept of '*obtain from nature*' to '*learn from nature (and build)*', efforts have been made to create synthetic or artificial stem cells. An artificial cell is an engineered entity that mimics one or many functions of a biological (natural) cell. The first artificial cell was developed by Professor Thomas Chang at McGill University in the 1960s [16]. It is important to note that the term 'artificial cell' does not refer to a specific physical or morphological identity. Instead, certain functions or structures of biological cells can be replaced or mimicked with an engineered entity. Often, artificial cells are biological or polymeric blocks that encapsulate biologically active materials. These materials are usually biocompatible and easily modified, including nano-/micro-particles, liposomes, micelles, etc.

We now know that most adult stem cell types exert their beneficial effects through paracrine mechanisms (via secretion of soluble factors). In addition, studies further suggest that cell–cell contact between the injected CSCs and injured cardiomyocytes plays an important role in tissue regeneration [17]. On the basis of these principles, we designed a cell-mimicking microparticle (CMMP) that recapitulates the secretion and bio-interfacing of natural stem cells during tissue repair. Our overall hypothesis is that CMMPs can act as 'synthetic stem cells', harnessing the power of both stem cell membrane and secretome, to induce tissue regeneration, while the genetic materials removed. Poly Lactic-co-Glycolic Acid (PLGA), which is widely used in many FDA approved products, serves as the building material and its degradation results in the slow release of growth factors. Conditioned media from cardiac stem cells (CSC), which contains various regenerative factors secreted by CSCs, is loaded in the PLGA microparticles by a double emulsion process. After that, the microparticles are coated with the cell membranes of CSCs to form the final product, synthetic CSCs (Figure 2). The therapeutic potency of synthetic CSCs was confirmed in a mouse model of myocardial infarction [18••,19]. The scientific premise is that the synthetic CSC technology