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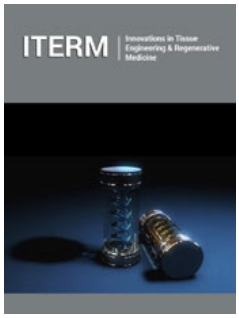
Mini Review

Advances and Innovations and Impediments in Tissue Engineering and Regenerative Medicine

Shivaji Kashte[1] and Sachin Kadam[1,2]*

[1]Center for Interdisciplinary Research, D. Y. Patil University, India

[2]Advancells, India



***[1]Corresponding author:** Sachin Kadam, Advancells: A Unit of Saffron Naturale Product Pvt. Ltd., India

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Abstract

The evolving arena of regenerative medicine requires the use of cells, scaffolds, tissues or genetically edited elements as therapeutic agents for implantable engineered tissues and organs that can regenerate physiological functions. A variety of fabrication techniques like gas foaming, phase separation, salt leaching, and freeze drying have been developed that successfully regenerate complex and functional tissues. Recently developed three-dimensional (3D) printing technology promises to bridge the differences between artificially engineered tissues and native tissues. After 3D printing, 3D bioprinting was introduced as an ultimate solution for vascularized tissue fabrication. The large number of tissues such as bone, cartilage, skin, myocardial, kidney, liver, and lung tissue models were investigated with 3D bioprinting. As there is a need for stimulus-responsive geometry, four-dimensional (4D) printing technology has been developed to fabricate structures that can transform their shape. Tissue engineering and regenerative medicine providing exciting results has brought a new era of medical research and applications with value addition in the field of medicine. It will be important to ensure that appropriate technologies are developed, validated that could result to the betterment of human situation. The positive role of regulatory authorities could enhance the morale of the researchers and scientific communities. This could translate in to the lifesaving new innovations.

Keywords: Tissue engineering and regenerative medicine; Three-dimensional (3D) printing; 3D bio-printing; Four-dimensional (4D) printing

Introduction

The evolving arena of regenerative medicine requires the use of cells, scaffolds, tissues or genetically edited elements as therapeutic agents for implantable engineered tissues and organs that can regenerate physiological functions. An important component in tissue engineering is the functional scaffold. A variety of fabrication techniques like gas foaming, phase separation, salt leaching, and freeze drying have been developed that successfully regenerate complex and functional tissues [1]. Recently developed three-dimensional (3D) printing technology promises to bridge the differences between artificially engineered tissues and native tissues. It constructs complex 3D architectures in a layer by layer manner. It has been applied artificial biological substitutes for the regeneration of tissues [2]. This 3D printing is rapidly emerging as a key scaffold fabrication strategy for mimicking native tissue complexity. It can more precisely deliver different cells or mechanical cures in the designed 3D architecture than cannot be achieved by conventional fabrication method [1]. After3D printing, 3D bioprinting was introduced as an ultimate solution for vascularized tissue fabrication. The large number of tissues such as bone, cartilage, skin, myocardial, kidney, liver, and lung tissue models were investigated with 3D bioprinting [3]. For example, developing bone material capable of substituting the conventional autogenic or allogenic bone transplants have shown a ray of hope. Tissue engineering has shown a full potential of bone repair through the use of osteogenic growth factors like bone morphogenic proteins (BMPs), osteoinductive matrix, gene therapy, use of stem cells etc. [4]. Also, the various materials like polycaprolactone, poly lactic acid, hydroxyapatite, calcium phosphate, Alginate hydrogel, etc. were 3D bio printed to form cartilage and or bone tissues [5].

Similarly, in liver regeneration, due to limited numbers of donor organ donations or living donor liver transplantation (LDLT) across the globe many novel technologies have been proposed which cater to the development of a three dimensional composite constructs, 3D perfused bioreactors for spheroid culture, liver-on-a-chip platforms and bio-printed liver to produce an implantable *in vitro* liver which may reliably predict the *in vivo*–like tissue responses and could also be suitable for drug toxicity testing. The developed 3D biomimetic liver model recapitulates the native liver module architecture and could be used for various applications such as early drug screening and disease modelling. One of the limitations of current approaches to recapitulate the sophisticated liver microenvironment is contributed by the complex micro-architecture and diverse cell combination. Despite the strong potential of 3D printing for tissue regeneration, many challenges still remain, including printing resolution, speed, and processes for bioprinting. By optimizing process parameters such as bio ink concentration, printing mode, nozzle diameter and cell amount, these limitations can be overcome to some extent [1].

As there is a need for stimulus-responsive geometry, four-dimensional (4D) printing technology has been developed to fabricate structures that can transform their shape. The shape-morphing effect is the main feature of the smart material to transform or recover its shape due to its innate properties or in response to external stimuli [2]. The 4D bio printed human bone marrow mesenchymal stem cells and soybean oil epoxidized acrylate structures recovered its original shape when the temperature increases from -18^0 C to 37^0 C [6]. Similarly, 4D bio printed immortalized mouse myoblast cell line and the elastomers (eg. Polycaprolactone –polyurethane) show high shape recovery ability and shape fixity ratio under standard physiological conditions [7].

Discussion

There are various advancements and innovations in the field of tissue engineering. There are positives and limitations for every new technology. Both of this need attention to strengthen the technologies. In the 3D printing, low cost variant of hardware, software, and printing materials could decrease the cost. The time of imaging and data processing decreased to minutes with the development of imaging software. The limitation of model size can be overcome by dividing the models in to small parts, then combining them after printing or by producing a miniature version of large structures via post-processing. The combination of cell biology with micro engineering could produce the goal of recapitulating organ level functionality. The main challenges to achieve these will be reconstituting the appropriate tissue microarchitecture, complex biochemical milieu, and dynamic mechanical microenvironment. However, the strategies of microfabrication and microfluidics are well suited to meet these challenges as they provide dynamic control of structure, mechanics, and chemical delivery at the cellular size scale.

Engineered biomimetic 3D constructs can keep human cells functional for several weeks *in vitro* by providing suitable environment. For example, the newly engineered liver constructs predicting clinical drug outcomes are better than even animal models. Additional challenge lies in integrating these micro-engineered organ mimics with sensors that can detect and measure optical, chemical, electrical, and mechanical signals from cells to analyse their structure and function. Bioengineered 3D microsystems and organ-on-chip technologies are relatively new and still require further validation and characterization, their potential to predict clinical responses in humans could have profound effects on drug and environmental toxicology testing. Though we have developed organ models for various organs, still fully functional, vascularized organs are in the experimental stage. This journey may take several decades to reach its destination [3].

In the future, 4D bioprinting will be useful for advanced *in vivo* experiments where there will be a need for structural developmental of implanted structures after printing driven by environmental changes [2]. 4D bioprinting is now seen as a next generation printing technique allowing fabrication of complex structures with real time shape-morphing features in response to external stimuli by integrating time as the fourth dimension. Although 4D bioprinting has proven potential for fabricating shape transformable tissue like structures, a number of limitations remain to be overcome like viability of printed cells, biocompatibility of smart materials [2]. Tissue engineering has led the health care sector in the past 20 years, however only a handful of cell-based products have made their way to the market. The developments of consensus standards for tissue engineered medical products were initiated in late 19th century. Considerable emphasis was placed on specifications for synthetic origin biomaterial properties and testing methods for obtaining quantitative data about components and constructs of implant devices. Since consensus standards are developed for intended applications, the need for extending research and development towards actual applications of tissue engineered products strongly supports the need for more basic and applied information and interpretation related to the intended benefit to risk ratio. Since this area of medical products was rapidly evolving and many were in a phase of research, terminology and reference materials were considered as a starting point.

Medical innovations provide improved clinical outcomes and generating economic wealth. In concert with the advancement of regenerative medicine technologies, regulatory authorities confront emerging new obstacles in regulating safety of these products for human applications. There are some institutional, regulatory and cultural constraints that hindered these processes. The perceived challenges identified are bureaucratic research governance frameworks and inflexible clinical trial methodologies, a complex and inconsistent regulatory framework, manufacturing and scale up of live tissue production, uncertainties over cost effectiveness and reimbursements and lack of investment from private funders [9]. Bioengineered trachea, autologous chondrocyte implantation

or celution point of care system are some of the techniques impaired in regulatory framework [8,9].

Timely revisions of policies are needed to adequately control the use of regenerative medicinal products. Simplifying and streamlining the regulatory processes from the laboratory to the patient by stratification and characterization of regenerative treatments based on their expected safety profiles have several advantages in terms of making better and more advanced treatments available with the potential benefit of reduced cost [8]. The US FDA introduced the new Regenerative Medicine Advanced Therapy (RMAT) designation thus recognizing the enormous potential of these medicines and the need for efficient regulatory tools to accelerate their development and commercial availability. This move aimed at providing intensive support to companies developing cell-and tissue-based therapies, tissue engineered products, and combination treatments [10]. Such steps are welcome and give the right environment for new innovations and technologies to come to fruition.

Conclusion

Tissue engineering and regenerative medicine providing exciting results has brought a new era of medical research and applications with value addition in the field of medicine. It will be important to ensure that appropriate technologies are developed, validated that could result to the betterment of human situation. The positive role of regulatory authorities could enhance the morale of the researchers and scientific communities. This could translate in to the lifesaving new innovations.

Conflict of Interest

The authors declare no conflict of interest.

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