3D Bio-Printing: A Technological Revolution from Cardiology Therapy to Life Regeneration

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Abstract. In recent years, the continuous breakthroughs in 3D bioprinting technology are expected to revolutionize healthcare and regenerative medicine. This article will comprehensively review the current state-of-the-art organ 3D printing technology, and explore key aspects such as bio-ink materials and bioprinting technology, applications in cardiology treatment, and progress in regenerative medicine. The development and current shortcomings of the technology are summarized through existing literature, which is of great significance for optimizing 3D bioprinting technology for medical development in the future. With the rapid growth of this field, understanding the difficulties and opportunities of organ manufacturing is essential to promote innovation in healthcare and biomedical research.

Keywords: 3D Printing; Cardiology; Bio-ink; Regenerative Medicine; 3D printing technology.

1. Introduction

1.1. Background

With the continuous development of modern medical technology, organ transplantation technology is also constantly improving and developing. However, traditional organ transplantation and repair have many drawbacks, including insufficient donors, immune rejection, and high surgical costs. As a result, many patients lost precious treatment opportunities and thus lost their lives. Therefore, many biologists have begun to work on developing new technical means to replace traditional medical methods, which has led to the technology of biological 3D printing.

In recent years, 3D printing technology has gradually become an important technology in fields such as regenerative medicine and organ transplantation because of its high customization, precision and controllability. By depositing biological materials layer by layer, this technology can generate highly customized 3D structural models. Compared with traditional treatment methods, 3D printing technology has advantages such as reducing surgical risks, improving tissue function and accelerating recovery.

1.2. 3D Printing Technology Overview

3D printing can create physical objects from a geometrical representation by successive addition of material that uses biological materials or biocompatible materials to build 3D tissues and other complex structures [1]. This term is often used to summarize a variety of different bioprinting technologies, all of which can produce biological 3D models.

3D printing is an additive manufacturing technique that builds structures, based on a computer-aided design (CAD), by depositing material in a layer-by-layer manner. There are several methods to accomplish layer-by-layer fabrication depending on the type of material printed [2]. There are a variety of bioprinting technologies to choose from, each designed to process a specific type of biomaterial (commonly known as bio-ink) and build different 3D models. We can divide these technologies into two main types: extrusion-based 3D bioprinting and light-based 3D bioprinting [1].

Conventional printer head systems have also been adapted to selectively print various speciated human cells and special molecules in attempts to construct human organs, beginning with skin and various tissue patches, these technologies have a wide range of applications in the fields of life sciences and biotechnology, including but not limited to cell culture food, drug discovery, personalized medicine, and regenerative medicine[3].

1.3. The significance of 3D printing in organ manufacturing

3D printing can generate personalized organ and tissue scaffolds that are closer to patient needs by precisely controlling the deposition and geometric structure of materials. This method helps reduce immune rejection and improve survival rates after transplantation. In addition, the application of 3D printing in tissue engineering has also made significant progress, especially in the manufacture of scaffolds for complex organs such as the heart and liver. It can implant different types of cells and bioactive factors in the scaffolds to promote cell proliferation and differentiation, thus getting closer to the functionality of natural organs [2]. For example, recent studies have demonstrated the printing of complex structures such as heart valves and blood vessels, which are expected to be used in organ transplantation and regenerative medicine in the future.

1.4. Progress and problems in heart printing

In terms of organ manufacturing, research on cardiac tissue is particularly important. So far, researchers have successfully printed heart tissue containing cardiomyocytes using special bio-inks and high-precision printing technology. However, 3D printing of heart tissue still faces major challenges. First, it is difficult for cells to achieve effective vascularization after printing, resulting in a lack of sufficient oxygen and nutrient supply inside the tissue, thus affecting the long-term survival and functionality of cells [4].

There are two possible routes for manufacturing tissues and organs. Alone or combined with living cells, biocompatible materials, growth factors, and physical factors can be used to create a biomimetic tissue-like microarchitecture scaffold. Known as direct cell assembly, formulates both cells and materials into a composite structure, the mixture of cells and gel is encapsulated into 3D scaffolds that are composed of another kind of gel with good mechanical strength or are printed directly to control the spatial distribution of cells and even realize in situ repair [4].

2. Bio-inks in 3D printing of organs

With the rapid development of 3D bioprinting technology, bio-ink, as a core material, plays an increasingly important role in tissue engineering and regenerative medicine. The design of bio-ink must meet multiple strict standards, including appropriate rheological properties, biocompatibility, mechanical strength, etc., to ensure that a stable structure can be formed during the printing process, while providing an ideal microenvironment for cell proliferation and differentiation.

2.1. Types of bio-inks and their properties

2.1.1. Polymer hydrogel bio-ink

A commonly used material for bio-ink is hydrogels, which are hydrated networks of crosslinked natural or synthetic polymers. The hydrophilic nature of these polymers allows the gel to swell in an environment with a high-water content. Hydrogel materials can be both highly biocompatible and bio-degradable, a necessity for in vivo applications. Furthermore, cells can be encapsulated in 3D when the hydrogel undergoes gelation. The environment created does not affect cell-cell interactions. A disadvantage of hydrogels, however, is their weak mechanical properties. They often do not maintain their designed shape. Whether a hydrogel is suited or not for 3D bioprinting depends mainly on its rheological properties and the crosslinking method employed, which can be both physical and chemical in nature [5]. In contrast, synthetic polymers such as polyethylene glycol (PEG) have controllable mechanical properties and chemical stability and are often used to model more complex structures [6].

2.1.2. Thermo-responsive inks

Thermo-responsive ink is an innovative material that can respond to external stimuli (such as temperature, pH, and light). Almost all bioprinting techniques disperse the bio-ink through a nozzle onto the substrate. To obtain a clear image, the bio-ink should move through the nozzle easily but should become rigid upon dispersion [7]. Thermo-responsive hydrogel inks have the advantageous property of tunability of their sol-gel state by changing the temperature. Thermo-responsive inks solidify when the temperature changes, thus providing structural support during the printing process; photo-responsive inks can quickly cross-link under the irradiation of specific wavelengths of light to form a stable 3D structure [7]. These smart materials are particularly useful in tissue printing where high precision is required, as they offer better process control and structural stability.

2.2. The future of bio-inks

2.2.1. Current Gap

According to current research, existing bio-inks have technical limitations in many aspects, which restrict their widespread application in complex tissue printing. First, although many bio-inks based on natural hydrogels have great advantages in biocompatibility, they perform poorly in mechanical strength and structural stability, and cannot maintain shape and stabilize high-strength tissue structures for a long-time during use [5]. It is important to note that existing bio-inks cannot maintain cell activity for a long time during the printing process. Some physical factors such as temperature will affect the survival rate of cells, which will directly affect the subsequent printing results [8]. The generation of vascularized structures is also one of the key challenges because the ink is difficult to effectively support the generation of small and complex vascular networks, which limits the survival of printed tissues in the body [8]. In addition, the rheological properties of bio-inks have a significant impact on printing accuracy, making it difficult to achieve precise control at the micron level, limiting the complexity of tissue printing [7].

2.2.2. Future Development

In order to solve the shortcomings of existing bio-inks, future bio-ink development can focus on the following aspects. First, composite materials can be developed by introducing nanomaterials into natural polymers to enhance their mechanical strength while maintaining biocompatibility [6]. Secondly, intelligent delivery is also an important solution. By adding controlled-release growth factors or drugs, bio-inks can promote cell proliferation and differentiation at different stages after printing or implantation, thereby improving tissue regeneration [8]. In terms of vascularization, combining microfluidics, microstructure design or cell self-assembly technology is expected to improve the ink's ability to support tiny vascular networks and meet the printing needs of complex organs [7]. These innovations will make bio-inks more adaptable to the needs of complex tissue printing and provide broader application prospects for personalized medicine and regenerative medicine.

3. Bio-printing technology

For the fabrication of 3D bio-printed constructs, the bio-ink and bioprinter are key elements. Important factors such as strength, resolution and shape are dependent on the fabrication method.

3.1. Droplet-based bioprinting

Droplet-based bioprinting (DBB), first introduced in the early 2000s, is a simple and agile technique with which biologics can be deposited in a precise and controlled way. Picolitre droplets are layered on top of a substrate without contact between the nozzle and the substrate [6]. DBB is highly versatile as it is compatible with many biological materials, it can print inks with low viscosities and it enables a high speed and high resolution. However, it faces some challenges. The uniformity of the droplets needs to be improved and encapsulation of cells is inconsistent.

Furthermore, bio-printed constructs have limited mechanical and structural integrity. Cross-contamination of bio-inks when printed simultaneously restricts the size of the constructs as vascularization and porosity are hard to control. DBB can be subdivided into three categories; inkjet**,** acoustic, and micro-valve bioprinting [7].

3.2. Extrusion bioprinting

Extrusion-based bioprinting is one of the most widely used techniques. Extrusion-based bioprinting is one of the most widely used techniques due to its capability to process high-viscosity bio-inks and create large-scale constructs [7]. This method uses pneumatic or mechanical force to extrude high-viscosity bio-inks from a nozzle to form a continuous fibrous structure. Although suitable for printing large-scale tissue scaffolds, its limitation is that the resolution is relatively low compared to other techniques, which restricts its application for fine structures [6].

4. 3D Printing in Cardiology

4.1. Current applications of 3D printing in cardiology

In cardiology, 3D printing technology has gradually been applied in many aspects to provide personalized treatment for patients and significantly improve the treatment effect. The following are several major application directions.

4.1.1. 3D-printed heart scaffolds for myocardial regeneration

The technology of 3D printing heart stents has begun to be applied in the research of myocardial cell regeneration. After a myocardial infarction, myocardial tissue and cells will subsequently be damaged or even necrotic. It is difficult to form new heart tissue in the ischemic area under traditional treatment methods, but 3D bioprinting technology provides a possibility for this research. These scaffolds are printed using biomaterials that provide a microenvironment for cardiomyocytes to attach and grow, promoting the proliferation and reconstruction of new tissue in the injured area [9]. Through the special design of the 3D scaffold, growth factors and other related drugs can be added to further enhance the survival rate of cardiomyocytes, and this technology can be used to improve the functionality of the heart [10].

4.1.2. Preoperative planning and precise surgical design

Another important application of 3D printing technology is preoperative planning, especially for structurally complex heart surgeries. In some complex heart malformations or structural diseases, doctors can use the patient's CT or MRI data to generate a 3D-printed model to accurately replicate the patient's heart anatomy [11]. This personalized heart model enables doctors to perform detailed surgical planning before surgery, identify potential problems during surgery in advance and develop the best path forward. Through this preoperative simulation, the success rate of the operation is significantly improved, while the operation time and intraoperative risks can be reduced. This application is particularly important during heart valve replacement, coronary artery bypass grafting and other complex heart surgeries [10].

4.1.3. Cardiology diagnostic and teaching models

3D printing is also used to make heart anatomical models to help doctors and medical students better understand the structure and disease pathology of the heart. By using 3D-printed models, doctors can explain the condition and surgical plan more clearly to patients and their families, enhancing patients' understanding and trust in the treatment process. In addition, these models are also extremely valuable in medical education, providing medical students and residents with intuitive learning tools, allowing them to become familiar with the structure of the heart and the operation steps before real surgery, thereby improving their technical level and ability to deal with complex cases [11].

4.2. Case studies and research findings

Through the clinical application of 3D printing technology, there have been many studies and case reports showing its positive effects and application prospects in the treatment of heart disease. The following are some typical case studies and research results.

4.2.1. Application of patient-specific coronary artery models

In one study, researchers used CT data to print patient-specific coronary artery models to facilitate evaluation and planning prior to interventional procedures. Through these 3D models, doctors can more accurately assess the morphology and location of coronary artery stenosis, select the appropriate stent size and optimal placement, thereby improving the accuracy and success rate of surgery [12].

4.2.2. 3D models for congenital heart disease surgery in children

When dealing with complex congenital heart surgery in children, 3D printing can model the heart and effectively formulate treatment plans. One case demonstrated the use of 3D bio-printed pediatric heart models to help doctors confirm the complexity and specific structure of heart malformations before surgery. These models allow doctors to better understand the abnormal structure before surgery and develop targeted surgical plans. The results showed that this preoperative planning greatly shortened the operation time and improved the safety and success rate of the operation, especially in complex congenital heart malformation cases [11].

4.2.3. 3D printing for precise guidance in cardiovascular interventional surgery

Another study showed that 3D bioprinting technology can be used for cardiovascular interventional surgery. In this study, doctors used this technology to simulate the catheter path in actual surgery, thereby improving the accuracy and success rate of the surgery. This application is of great significance in complex vascular interventional surgery, and preoperative simulation greatly reduces surgical complications [10].

5. Application of 3D Printing in Regenerative Medicine

3D printing technology has shown great potential for application in regenerative medicine, not only providing new solutions for the treatment of heart disease, but also providing innovative technical support for tissue repair and organ regeneration.

5.1. Bone and cartilage repair

3D printing technology has great potential for bone and cartilage engineering by utilizing printing materials from natural polymers and synthetic materials (polylactic acid). 3D printing technology can produce porous scaffolds with biocompatibility and mechanical stability. These scaffolds can accurately fill bone defect areas while promoting the attachment and differentiation of osteoblasts [13]. In cartilage repair, the printed scaffold provides a suitable growth environment for chondrocytes by mimicking the elasticity and morphological properties of natural cartilage.

5.2. Skin tissue regeneration

In skin tissue regeneration, 3D printing technology simulates the hierarchical structure of natural skin by directly printing cell-containing scaffolds. Among them, the printed scaffolds based on natural materials can effectively support the proliferation of keratinocytes and fibroblasts, and at the same time have antibacterial functions, which helps reduce wound infection [14].

5.3. Liver and kidney tissue repair

The liver and kidney are large organs with complex functions, and the regeneration process requires highly precise cell arrangement and functional zoning. 3D printing technology integrates microfluidics and multi-material printing to achieve a local regeneration model of liver tissue. These printed models can support the long-term functionalization of liver cells while promoting the formation of capillary networks [15]. For kidney regeneration, printed scaffolds are used to create biomimetic structures of the glomerulus, successfully simulating some of the functions of the nephron.

5.4. Soft tissue repair and angiogenesis

In soft tissue repair, 3D printing technology provides stable physical support for cells by manufacturing porous structural scaffolds. These scaffolds can simulate the elasticity and microenvironment of natural soft tissue, thereby promoting the proliferation and migration of fibroblasts and epithelial cells [14]. In addition, vascularization is the key to soft tissue repair. The vascular network generated by 3D printing combined with microfluidic technology significantly improves the survival rate and functionality of transplanted tissues [15]. This approach shows great promise in burn repair and skin transplantation.

6. Conclusion

6.1. Research Gaps

A summary of past 3D printing technology shows that although this technology has made great breakthroughs, there are still many research defects and technical challenges. Although existing research has achieved certain results in bone and soft tissue repair, existing technologies are still insufficient to meet clinical needs in the regeneration of complex organs such as the heart and liver.

In particular, when it comes to generating large volume, vascularized tissues, existing 3D printing technologies and materials make it difficult to simultaneously support long-term survival, metabolism, and functional expression of cells. The balance between biocompatibility, mechanical properties, and degradation characteristics of printed materials has not been fully resolved, especially the lack of smart materials that can dynamically respond to changes in the microenvironment. In addition, the printing process's resolution and multi-material synergy capabilities limit the precise fabrication of complex microstructures and multifunctional tissues.

To address these issues, future research should focus on developing new smart bioinks, optimizing multi-material printing techniques, and exploring efficient methods for generating vascularized tissues. At the same time, it is necessary to strengthen the integration research of biomaterials and cell interfaces to enhance the manufacturing capabilities of functional organs. These efforts will lay the foundation for the comprehensive regeneration and functionalization of complex organs and promote the in depth application of 3D printing technology in regenerative medicine.

6.2. Discussion

Current technology applications still face major challenges, especially in manufacturing and functionalizing complex organs. In the field of regenerative medicine, the future needs to address achieving the coordination and functional zoning of multiple cell types, efficiently generating vascularized tissues and developing high-performance bio-inks.

In the future, 3D printing technology needs to explore further developing new intelligent materials to support cell behavior in dynamic microenvironments; optimize printing equipment to improve accuracy and multi-material synergy; and combine artificial intelligence and microfluidics to develop more functional and stable complex tissues. Through multidisciplinary collaboration and technological innovation, 3D printing is expected to achieve a comprehensive transformation from laboratory to clinic, provide breakthrough solutions for personalized medicine and organ regeneration, and promote the development of regenerative medicine into a new stage.

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