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The application and significance of 3D printing technology in biomedicine

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Abstract. 3D printing technology, also known as rapid prototyping technology, is an emerging production and manufacturing method. Medical researchers can create various medical devices for patients' bodies with greater accuracy by converting 3D digital graphics from computer-aided design into physical entities and printing 3D objects layer by layer. Thriving as medicine is, 3D printing, being a widely used and promising technology, will make significant contributions to the progress of biomedical science in multiple directions. The fundamental principle of this technology is akin to building blocks, where small parts are assembled into a comprehensive structure, utilizing materials such as plastic, metal, ceramics, etc. In the production of medical equipment under traditional manufacturing methods, a significant amount of manual debugging is sometimes necessary, which often results in the waste of considerable time and resources. Nonetheless, the manufacturing technique of 3D printing can rapidly and precisely create intricate instruments, as well as produce implants or tissue models. The main focus of this article is to analyze recent progress, applications and restriction prospects of 3D printing in medical applications. The advancement that 3D technology gains across different domains and levels is poised to significantly influence future medical treatment. The significance is to clarify the application and significance of 3D printing technology in the biomedical field. Through the review and analysis of relevant literature, a comprehensive understanding of the research progress and existing problems on 3D printing in the biomedical domain be gained, providing references and inspiration for future research.

Keywords: 3D-Printing, Biomedicine, Composite.

1. Introduction

As science and technology continue to advance, the usage of 3D printing technology in biomedical field is becoming increasingly widespread. In the field of biomedicine, 3D printing has been widely applied in bio-engineering, medical imaging, surgical simulation and other fields in recent years, resulting in a series of remarkable outcomes. Further research and exploration are still needed to fully understand the application and significance of this technology in the field of biomedicine.

Foresti and his team have developed an innovative technique for creating 5D digital models, which involves utilizing rapid freezing prototyping 3D printers for revival, cutting, rapid freezing gelation, , nano-dry formula, disinfection, and local processing [1]. Using a balloon that elutes drug for percutaneous intervention, they reconstructed fluorescent nanoparticles which elutes free-coating containing 40nm and is also biocompatible with the RFP printers. They then measured the feasibility of

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this coating in vivo. They introduced a 5D device loaded with NPs into the rat cava vein. The method they invented holds the promise of playing a significant role in personalized treatment in the future.

Zhang and his team utilized acellular dermal matrix and polylactic acid as materials to prepare 3D-printed vascular support patches, which they used to repair wall defects which is ventral in animal models [2]. Optimized the proper-designed process conditions to manufacture 3D-printed patches which is implantable. The prepared 3D-printed patches were tested for their surface morphology, mechanical strength, biocompatibility, and cytotoxicity, meanwhile they also contrast it with porcine small intestinal submucosa patches also PLA patches. Further evaluation of the cell phase properties of the 3D printed patch in vitro revealed that the cell viability was both good and non-toxic. An evaluation of biocompatibility and the effect of ventral wall revival in vivo was conducted using rats as animal models. The findings indicated that the , tensive strength, stitch load, hydrophilicity, and degradation rate of the 3D-printed patches were considerably greater than those of PSIS and PLA patches. Simultaneously, the area containing the defect that was repaired using the 3D-printed patch appeared to be effectively healed, without any noticeable signs of infection, seroma, hematoma, etc. In conclusion, the results demonstrate that the prepared 3D patch possesses superior tissue reprocessing capabilities and is capable of achieving tension-free closure of ventral wall defects. This suggests that the 3D patch could potentially be utilized in areas such as ventral wall revival in the future.

Gaetani and his team utilized the printing craft of tissue along with human cardiomyocyte progenitor cells (hCMPCs) for cardiac engineering of tissue (CTE) [3]. It has been proven that the most promising source of cells for post-injury cardiac reprocessing in cardiac reprocessing is cardiac progenitor cells, due to their natural cardiac function and high proliferative capacity. Simultaneously, we can print and culture hCMPCs within scaffolds that is alginate-made, while the conditions of culture remain consistent in terms of cell growth and commitment. The unique porous structure, which is achieved through tissue printing, preserves the vitality of hCMPCs. Their model has the potential to address crucial biological questions, including how cells behave in standard 2D and 3D cultures, and how modifications to different ECM components or growth factors may impact them. This model could potentially serve as the initial step towards establishing fully differentiated cardiac structures in vitro.

Ma and his colleagues proposed a three-dimensional culture model based on hydrogel that incorporates hiPSC-HPCs, whose full name is human umbilical vein endothelial cells, and also adipose-derived stem cells within a micro-scale hexagonal structure [4]. After several weeks of in vitro culture, their 3D three-layer culture model exhibited ameliorated phenotype and function of hiPSC-HPCs, as contrasted to 2D culture with only one layer and 3D HPC models. Their findings showed that the tissue morphology ameliorated, the level of liver-specific genes' expression increased, the metabolites' secretion increased, and the cytochrome P450's induction enhanced. Their experiments demonstrated that the implementation of bioprinting technique in engineering of tissue has the potential to create a 3D bionic liver model, resembling the structure of natural liver modules, which can be utilized for diverse purposes, including early disease modelling also drug screening.

Guo and his team proposed one design for a flexible bio-sensor based on graphene [5]. Liquid phase exfoliation and subsequent exfoliation with bovine serum albumin were used to prepare biocompatible graphene. They used inkjet printing to deposit a single layer of graphene ink onto polyimide, followed by the placement of neuronal cells onto the 3D-printed graphene chip that was thermally annealed. Within 96 hours, the cell survival rate was observed to be approximately 80%. After heat treatment, this design can achieve a print FLG conductivity of 6800 S-m-1. Live cell experiments have further demonstrated that it is biocompatible and does not hinder cell adhesion or neuronal cell proliferation. The original graphene, after heat treatment, will not harmfully affect neuronal cells. Furthermore, graphene does not exert any noticeable negative influence on the proliferation of cells, the morphology of mitochondria, or the level of cell stress. This suggests that the use of 3D-printed graphene annealed on a Kapton PI substrate can enable the burgeon of a biosensor for neuronal cells. It holds immense importance in the treatment of neurological disorders like Alzheimer's disease.

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The robust growth of 3D printing will undoubtedly aid in the rapid progress of various aspects of biomedicine. Then main objective of the article is to introduce the currently prominent applications of 3D printing technology and to detail their corresponding future prospects and limitations.

2. Methods and Discussion

2.1. Bio-scaffolds

The lower extremities' chronic peripheral arterial disease is regarded as one indication of systemic atherosclerosis meanwhile a leading contribution of walking ability loss. Currently, there are two treatment options for lower limb PAD: surgery and endovascular therapy, primarily involving balloon angioplasty. In reality, EVT is currently the most prevalent form of treatment for PAD due to its evident benefits in the short term [6]. Drug-coated balloons consist of balloon catheters that rarely complaint, also anti-proliferative agents and excipients, to enable the transfer of drugs to the vascular wall after balloon expansion. The technology of 3D printing has shown remarkable potential for interactive processes utilized in medicine and associated studies on toxicity and viability. The selected materials for bioprinting stents primarily base on natural polymers, for instance, chitosan, collagen, gelatine, synthetic molecules, hyaluronic acid that enable precise regulation of their chemical and physical properties.

The propose that the burgeon of 5D printing equipment should involve a standardized method with three steps: previous printing, printing, and after printing [1]. To meet the demands of each stage, it is essential to analyse and validate modelling steps as follows: i) requirements, ii) orientation of the model, iii) generating trajectory, iv) analysing process, and v) adherence to the virtual model. They developed a rapid-release therapy through bioprinting immobilization, and then used ethanol for freeze-gelation to create 5D nano-loaded hydrogels. They printed 8 scaffolds 40 nm with fluorescent NPs inside and not inside and dissolved them in DMEM. Unlike typical CaCl2 gel scaffolds, the scaffolds maintained the unchanged structure as 24 hours had passed. Accordingly, SEM images showed that the scaffold that is printed by alginate exhibited a highly porous and fibrous microstructure. This characteristic enables interacting the tissue to a larger extent. The microstructure of the ethanol-gelled scaffold exhibited a more compact and less porous structure, characterized by faster absorption and drug release rates, and a lower surface-to-volume ratio. At the same time, their preparatory analysis in vitro of VSMCs showed that contrasted with the control group, the gelation process and cell viability during lysis were unchanged. To confirm the feasibility of these methods in vivo, they implanted the same structure loaded with NPs into the vena cava of rat and found that after the scaffold rapidly dissolved, NPs internalized into vascular cells also interstitial tissue. Lastly, they evaluated human umbilical vein endothelial cells' cell metabolism and viability, and the results showed that the alginate's proportion used in biological applications did not affect cell viability and metabolism during dissolution.

They employed alginate with EtOH and CaCl2 to gel the scaffold. During the burgeon process of these two biomaterial scaffolds, they discovered that the new material scaffolds exhibited unique micromorphology and functional applications contrasted to traditional materials, and had minimal impact on the normal survival of cells. The results of the tests conducted on HUVECs have demonstrated the unlimited potential of the new material, nano-scaffold, for future application in humans. It will be immensely beneficial for the advancement of 5D (personalized treatment) in both cardiovascular and cerebrovascular treatment if the pertinent processes and technologies can be further enhanced and put through rigorous testing [1].

Because of the boundless potential of customized 3D printing in advanced bio-scaffold burgeon, they are able to conceive and produce 3D-printed 5D personalized medical devices. Select specialized composite biomaterials and manufacturing methods, implant structures, and activate their special functions after implantation to achieve specific physiological functions, based on individual circumstances. For instance, the components of 5D printing can respond correspondingly to external stimuli or chemical reagents. With the gradual amelioration of disease analysis techniques and the digitization of diagnostic methods through medical diagnosis technology, we will eventually receive more accurate treatment plans. This will enable us to prescribe the appropriate medication for future

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illnesses, particularly in the areas of cardiovascular and cerebrovascular diseases, and supply 3D-printed components for related sectors.

2.2. Bioremediation patch

Ventral wall defects, such as incisional hernias, are among the most prevalent issues in surgical procedures, and several approaches exist for managing ventral wall defects. Biomaterials, particularly non-absorbable ones, are frequently employed for the repair of hernias. Polymer materials, including polypropylene, polytetrafluoroethylene, and polylactic acid, possess exceptional mechanical properties [7]. Nonetheless, the use of these polymer materials may increase the risk of complications like infection, intestinal fistula, and intestinal obstruction, thereby leading to wound infection or contamination [8]. Furthermore, because of the absence of tissue reprocessing within the implant, a few patients are necessitated to have a reoperation to tackle the recurrence of the defect. Zhang's team employed ADM-PLA-ADM to prepare a vascular support patch suitable for reconstructing ventral wall defects using 3D printing. They evaluated the mechanical also physical properties of the printed patch, conducted in vitro cell culture experiments, and assessed its tissue reprocessing performance under in vivo conditions [2].

ADM exhibits favourable biocompatibility and has found extensive application in the fabrication of scaffold materials. Furthermore, the scaffolds that were prepared using ADM demonstrate significant biological stability and possess small pores that are observed both in vivo and in vitro. These features facilitate cell proliferation and growth. Complex structures in engineering of tissue scaffolds can be produced using ADM powder and 3D printing technology.

The experimental results indicated that the 3D-printed ADM-PLA-ADM bioprosthetic scaffold did not exhibit cytotoxicity during the preparation process, and the application of Genipin crosslinking agent did not introduce new cytotoxicity. Nonetheless, the present revival of the ADM layer still exhibits imperfections, including a lack of robust mechanical strength.

The mechanical properties hold a significant position in engineering of tissue. If the scaffold possesses adequate mechanical strength to hinder herniation prior to complete degradation, it can considerably diminish the recurrence rate of hernias. Therefore, they also employed PLA patches to enhance the mechanical strength of the bioprosthetic scaffold. PLA patches have found widespread usage in the realm of ventral wall reprocessing. Taking into account the likelihood of adhesion during application, PLA patches can be positioned between two biocompatible ADM layers to create a bio-patch scaffold with intricate channel structures and outstanding mechanical properties, which meet the stitch strength requirements for ventral wall repair patches.

In the experiment, the biological patch scaffold was applied to repair the rat ventral wall defect model, and all rats remained free from recurrence even after 4 weeks. The mechanical properties of the bioactive patch scaffold, which were prepared by Zhang and his team, are clearly indicated by these results to be suitable for tissue reprocessing.

The degradation of stents after implantation is a crucial factor in ensuring successful tissue reprocessing. Although the degradation rate of the ADM-PLA-ADM biologic patch scaffold is relatively fast, experiments conducted on the ventral cavity repair of rats have shown that it exhibits positive biological activity, which facilitates cell reprocessing and reproduction prior to complete degradation. The experimental results with animals showed that the defect area of the ventral wall was effectively repaired, without any noticeable infection, seroma, or hematoma. This demonstrated that the 3D-printed ADM-PLA-ADM bio-patch scaffold used in their experiment was non-toxic and could be safely utilized for ventral wall revival [2].

2.3. Organ manufacturing

Coronary artery disease congestive heart failure and exhibit a significant incidence and mortality rate [9]. Very few ways are available to tackle the core pathologies behind the burgeon of heart failure. Losing cardiomyocytes has the potential to cause permanent harm to the contractile function of the cardiac muscle. After injury happens, the heart repairs itself by forming scarring rather than regenerating cardiomyocytes. The efficiency of the reprocessing endogenous heart is too low to fix the large-area

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human diseases caused myocardial injury [10,11]. Currently, heart transplantation is regarded as the most final solution for patients in a terminal phase; however, this option is impeded by a severe scarcity of donor organs and the risk of rejection reactions. In the past few years, diseased hearts' cell transplantation therapy has performed great potential in animal models of cardiac ischemia. However, there is a serious limitation to direct cell injection for cell therapy: the uncertainty of cell survival and survival as implantation is finished into the diseased myocardium. In vitro cardiac engineering of tissue provides the likelihood of combining cells with the extracellular matrix, providing mechanical support for diseased myocardium, providing suitable conditions for transplanted cells, and improving delivery efficiency. Choosing the right cell source and substrate is one of the important factors in successful CTE cases, while heart progenitor cells seem to be a promising cell source because they have natural differentiating ability for cardiac descent.

Gaetani and his team employed magnetic cell sorting to separate human fetal cardiomyocyte progenitor cells (hCMPC). After conducting three preparatory experiments, they ultimately selected 7. Using a 5% alginate gel as the substrate, the low viscosity of sodium alginate facilitates the observation of sample changes, all while maintaining the longest-lasting cell viability. Cells are cultivated in a matrix using human B integrin, and the resulting mixture serves as the material for 3D printing. Their modelling indicates that every composite structure is made up of six layers of composite gel, wherein each layer is comprised of a linear structure that is printed by the composite gel following a specific distance rule. This results in the creation of a porous structure, which facilitates the growth and attachment of cardiac muscle cells [3].

Specially, the hCMPCs can be made into scaffolds using alginate as the substrate in a complex, and that culture in vitro does not alter cell proliferation and viability, but rather increases the cardiac load-bearing capacity of hCMPCs was demonstrated. In the experiment, they found that the primitive cardiac transcription factors Nkx2. 5, GATA-4, and Mef-2c increased significantly, and the TnT also increased significantly, which was not observed when the cells got cultured under conventional 2D culture conditions. However, the absence of well-organized striped patterns was observed. They can only surmise that the cultural conditions employed did not fully induced the differentiation. In their model, TnT gene expression increased, but there was a lack of functional differentiation, similarity to cardiac progenitor cells reported by others. This suggests that cardiomyocyte progenitor cells are more prone to a cardiac lineage. An essential aspect necessary for the performance of cardiac tissue generated in vitro within the in vivo environment is the capacity of the cells to react to pathological physiological stimuli and migrate away from the matrix. Employing matrix experiments, hCMPCs are encouraged to shift from the structure and develop structures of CD31-positive tubular.

As for the cardiac reprocessing, as the one of most bright sources of cells for cardiac reprocessing after injury, progenitor cells have natural cardiac function and high proliferative capacity. They introduced tissue printing technology and hCMPCs for CTE, demonstrating that hCMPCs can be printed and cultured in alginate scaffolds and that the culture conditions do not alter cell growth and commitment. They also found that the special porous structure which could only be gained through tissue printing preserves the vitality of hCMPCs. Their model also represents the first step towards developing fully differentiated cardiac structures in vitro.

2.4. Biomimetic models for clinical research

The liver acts a crucial role in processing of synthesis of crucial proteins also the metabolism of adventitious agents. The close correlation between the failure of these functions and the burgeon of disease as well as drug-induced toxicity cannot be overstated [12].

Due to these factors, liver models (in vitro) have been developing as platforms for pathophysiological research and as alternative models for animals for drug prediction also screening of liver toxicity. Although primary hepatocytes of human are regarded as the most sophisticated sources of liver cells, their proprietary functions that liver has rapidly diminish when being fed in vitro, primarily because of notable disparities between natural and cultural settings. Additionally, the application of personalized liver models is further impeded by the practical challenge of acquiring liver biopsy samples from

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individual patients. Hepatocytes, which are patient-specific and easily obtainable, are gained from hiPSCs and have been extensively recognized as the most promising cell source for developing proprietary models of human liver [5]. They created two patterns that resembles the anatomical structures of supporting cells also liver cells. Adjust the pattern size to achieve a close match between the lobule size of the printed structure and that of the actual human liver. The pattern is transferred to the GelMA and GMHA hydrogels using 3D bioprinting technology depending on DLP, which uses a digital chip with micromirror device to produce a photomask depending on the input digital pattern. This photomask is then utilized to photopolymerize the hydrogel solution, as previously described. In order to produce a liver model specific to a patient that closely resembles the natural structure and cellular composition, the researchers encapsulated liver cells derived from hiPSC, as well as endothelial and mesenchymal-derived supporting cells, into a complementary pattern through photopolymerization of a hydrogel matrix, thereby mimicking the structure of hepatic lobules. To support the growth of hiPSC-derived liver cells, they synthesized biocompatible and photopolymerizable hydrogel solutions. After photoinduced polymerization, they tested these hydrogel matrices' mechanical stiffness and adjusted it to be similar to that of healthy liver tissue. To create a model that represents non-parenchymal cells derived from the liver and also shows endothelial and interstitial origin 3D printed of hiPSC-derived supporting cells also liver cells, they employed bactericidal methacrylic acid-hyaluronic acid (GMHA). The model size is 3 x 3 mm, and thickness is roundabout 200 μm. It comprises a range of liver lobule structures with physiological sizes. Thus, the proposed two-step bioprinting technique, which is founded on DLP, offers a productive and adaptable approach to developing a 3D in vitro liver model that accurately portrays the anatomy of the liver in vivo.

By combining rapid 3D bioprinting and engineering of tissue, they developed a miniature liver structure consisting of hexagonal cells, which were made up of supporting cells also liver cells. The whole model is produced in a few seconds under the influence of ultra-violet rays with exceptionally low intensity. This model has the latent capacity to enhance the function and structure of pluripotent stem cell-derived liver progenitor cells induced by humanity, making it a useful tool for early proprietary drug screening and liver pathophysiology research in vitro.

3. Conclusion

The investigation of 3D printing in biomedical applications has the potential to bring about profound shifts in clinical treatment strategies and research. This article outlines the crucial role of 3D printing in the creation of novel biological scaffolds, the production of biological patches, the 3D printing of organs, and the burgeon of clinical medical models. 3D printing will advance the production of fresh biomaterials and modelling techniques, enhance clinical treatment options, enable customized and individual medical care, and offer laboratory materials for in vitro experiments that were once challenging to conduct. 3D printing makes the customization of medical devices and patient-specific implants possible. Doctors have the ability to create personalized and exclusive implants quickly and efficiently, by taking into account the patient's personal situation during the modelling process. Nonetheless, the range of materials accessible for 3D printing is restricted. Composite devices, or devices that necessitate unique, non-printable materials or components, may face challenges or even unlikelihood in attempting to 3D print without compromising on quality. New materials are emerging that can be used for 3D printing. For certain manufacturers, developing a suitable material may only take a few months or years; however, for some rare diseases with a limited patient base, manufacturers may not allocate further resources to develop printing materials, thus limiting the reliance on 3D printing for future medical treatment.

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