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Advancement in Regenerative Medicine along with Tissue Engineering: Medical Revolution &Transformation

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ABSTRACT

Congenital abnormalities, trauma, and infections all cause tissue and organ loss in both humans and animals. The human being's body has a lower regenerating capability than urodele amphibians, sometimes known as salamanders. Hundred so thousands of people worldwide would benefit greatly from the ability to replace organs and tissues on demand. Historically, transplanting intact organs and tissues has served as the foundation for replacing damaged and sick body components. Dependence on transplant has resulted in waiting list of persons wanting organs and tissues donated, and supply is often insufficient. To provide risk-free and reputable sources, Scientists together with clinicians attempts to develop medications and procedures for regenerating tissue and, in some circumstances, creating completely new tissue. Tissues engineering, often known as regenerative medicine, is a branch of life sciences that integrates engineering techniques with biological concepts in order to create new organs as well as tissues or to stimulate the regenerative process of injured or diseased tissues. Significant advances are being made not only in regenerative medicine (RM), but also in tissue engineering, which will have a significant influence on natural 3D bioprinting (BP) of organs as well as tissues. 3D BP has tremendous potential not only in tissue BP, but also for artificial organs. This paper examines Recent advancements into regenerative medicine including tissues engineering can assist from 3D BP and conversely. Before 3D bioprinting becomes extensively employed to generate organotypic constructions for RM, several hurdles must be solved.

Index Terms: Tissue Engineering, organ, Biomedical, Biological, Bioprint, Transplant

INTRODUCTION

Tissue as well as organ limits are currently recognized as a major concern to the health of the public, with few people eligible for transplantation [1, 2]. Most organ and tissue waiting lists do not accurately reflect the scale of the crisis, as only patients seek such assistance [3–8]. Scientists and physicians frequently use the phrases RM as well as tissue engineering interchangeably, and they are utilized as synonyms in this review. Regenerative medicine's future prospects are dependent on its capacity to fix and substitute damaged organs as well as tissues [9, 10]. RM has demonstrated encouraging results in regeneration as well as replacement of numerous tissues and organs, including the skin, kidneys, the heart, also liver, which has the potential to heal some congenital abnormalities [11-13]. The customary dependence on volunteers organs and tissue for transplantation is complicated by the shortage of donors and the potential for organ-specific immune rejection [14, 15]. The large number of organ transplants performed in poor countries is an example of transplant tourism in which well-funded and powerful foreigners are prioritized over local residents [1, 16, 17]. Strategies like this are often denounced since they can result in being taken advantage of vulnerable communities [1,18,19]. Regardless of a country's economic status, medical institutions that address issues such as organ shortages and the practical constraints of organ procurement and preservation can assist increase the overall number of persons eligible for organ transplantation [1, 20, 21]. Consequently, there is a need to further develop techniques and technologies to expand access to organs and tissues for transplantation. In most situations, such as when injured in an accident, conflict, or natural disaster, tissues and organs need to be obtained only once for transplantation [22, 23]. The shortage of organs and tissues hampers not only medical care but also scientific research. One possibility is to generate lab-grown tissues, made human tissues from animals, and biosynthetic organ [27-28]. RM has the potential to help solve these problems [29, 30].

For regenerative medicine (RM) approaches to demonstrate effectiveness, the materials employed must possess the capability to serve as replacements for damaged tissue, functioning akin to the original tissue, or facilitate the regeneration of previously compromised tissue [31, 32]. Cells employed in RM and tissue engineering endeavors may be sourced from the patient themselves (autologous) or from a different donor (allogeneic). Moreover, xenogeneic cells sourced from animals are viable options for integration into regenerative medicine protocols [33, 34]. Tailoring the RM strategies to the individual's age enables the exploitation of various techniques to enhance the body's innate recuperative mechanisms [35, 36]. Materials have long been utilized to mimic the extracellular matrix of cells, offering more than mere structural support [37-39]. Biomaterials, in conjunction with biomimetics, possess the inherent capability to stimulate rejuvenation independently, while also serving as carriers for bioactive molecules such as growth factors, crucial for driving cellular proliferation [32, 34, 38-40]. Biomaterials or scaffolds, previously considered essential for supporting physical cells, can now integrate biological signals and cues to improve or enhance tissue and functional regeneration.[41-43]. Different tissues have different regeneration capacity, so certain tissues may not need cells and only need biomaterials and biologicals, while other tissues do not have extensive regeneration capacity and need biomaterials, biological for regeneration. They also need biomoleculesandcells.Organsandtissueswithlittleornegligibleuseof regenerative capacity include cartilage and cornea, while organs and tissues with significant regenerative capacity include liver and lungs [9 , 44 , 45].

Over the past decade, both the FDA and EMA have granted authorization for numerous 3D bioprinted constructs and stem cell therapies [11, 12, 36, 46]. Such therapies along with goods include biologicals, medical equipment, and biopharmaceuticals [36, 47, 48]. This approach uses bone morphogenetic proteins (BMPs) for synthesis of bones and platelet-derived growth factors for healing wounds [49, 50]. Although FDA-approved products often outperform existing treatments, their effectiveness is variable [36 , 51 – 54]. However, most solutions fail to adequately treat intricate injury and disorders [36, 52- 54]. Emerging biologics, including treatments based on stem cells, take longer for them to reach the market due to the stringent rules necessary for FDA clearance and a shortage of funding for these goods. It typically takes over a decade for a product to make it to market, and over a billion dollars is being invested in its development [12, 29, 36, 51, 55-57]. Introducing new medical devices is generally easier and less expensive than introducing drugs or biologicals. This has promoted the research and development of acellular regeneration technologies.

3D printing is one of the most significant technological developments in thelast few decades [58, 59]. Primarily, it is noteworthy that biological materials can be directly deposited onto scaffolds through the process of 3D bioprinting [60]. This innovative technique amalgamates principles from materials science, cell biology, and tissue engineering [59, 61, 62]. To successfully mimic human tissues, 3D bioprinting must demonstrate proficiency in reproducing the intricate architecture of the extracellular matrix (ECM) and the abundant cell populations characteristic of each tissue type [36, 59, 63-65].

1.Augmentationofhumanbodytissueand organs

Bodily tissues,possess both shape and functioning, thus synthetic materials need to be capable of mimicking the morphology and qualities of the desired tissues or organs [66-68].The breakdown of organs along with tissues prior to transplantation holds promise because it removes immune cells while preserving the structure as well as the composition of the original extracellular matrix material. [69, 70]. Decellularization is usually performed on organs that are too old for transplantation. Decellularized ECM offers merit of mimicking Specific to tissue Characteristics and thus provides appropriate signals for cell differentiation and proliferation [69, 71 - 75]. The accumulation of specific decellularization surfactants is an issue that has to be rectified. Decellularization techniques, in conjunction with the advent of biological reactors, have proven to be efficacious in treating a myriad of diseases in laboratoryanimals[44,76,77].Ifthecellularrepopulationstageisskipped,

decellularized organs and tissues can be used as health products [78–80]. The product is considered cell-free, which reduces time to market. There are many methods for decellularization of tissues and organs in general [36, 42]. The majority of breakdown procedures have the potential to alter the physical attributes of tissues or organs; nevertheless, these techniques also entail the removal of messenger molecules typically present within the extracellular matrix (ECM) [36, 42, 69, 71, 74, 77, 81]. Employing chemical agents during the decellularization process may induce changes or degradation in the transplanted tissue or organ over time, thereby posing the risk of additional complications [44, 69, 72, 77, 82].

Fabricated scaffolds often lack the complete fidelity of biological organs and tissues [44, 59, 83, 84]. The overwhelming majority of these scaffolds are composed of a combination of extracellular matrix (ECM) proteins andsynthetic polymers [59, 85-87]. Notably, hydrogels emerge as a compelling option due to their resemblance to native tissue properties and their environmentally sustainable nature [36, 88, 89]. Hydrogels are widelyemployed in diverse fields, with significant applications observed in the treatment of congenital heart defects and the fabrication of vascular grafts [36, 62, 90]. Numerous studies have delved into cell proliferation, encompassing chondrocytes, both in elastin-based hydrogels independently and when combined with polymers such as polyethylene glycol and polycaprolactone [91- 94]. Additionally, researches has explored the impact of combining ceramics with natural biomaterials like type I collagen for the development of mesenchymal stem cells [39]. The role of seeded cells remains a subject of contention, with certain studies proposing that these cells predominantly instigate inflammation, thus promoting the infiltration of host cells to populate the graft and establish distinct blood vessels [36, 62]. Bearing this in mind, numerous vascular grafts, having undergone decellularization following extracellular matrix formation, are presently under scrutiny in clinical trials [78-80, 95]. Several investigations have illustrated that the mechanical characteristics of hydrogels and decellularized extracellular matrices (ECMs) yield therapeutic benefits and impact cellular differentiation [41, 51, 96-98]. Multiple investigations are currently ongoing to assess the impact of blending different scaffolds to enhance or additively improve scaffold performance [99- 101]. Furthermore, advancements in noninvasive imaging technology have made it feasible to tailor replacement tissues specific to a patient's body measurements [102]. Cutting-edge imaging technologies have already been harnessed to produce patient-specific scaffolds. Through the utilization of computed tomography (CT) scans, polymers were employed to fabricate structures such as the trachea and other tissues tailored to individual patients [103, 104].

1. 3DBIOPRINTING

In 2016, TE focused on additive manufacturing technology or 3D bioprinting. This technique involves the deposition of cells and biomaterials (bioinks) into predetermined 3D patterns and shapes through bottom-up assembly [105]. Biofabrication technology has made great advances in replicating the shape, complexity,and durability ofhuman tissue,which could lead to applications in organ engineering and therapy. Combining the use of computer-aided design/manufacturing (CAD/CAM) frameworks and 3D bioprinting has the potential to lead to personalized organ repair for patients.

Several review papers released this year [106-112] provide an up-to-date summary of the rapidly evolving research field.

As3Dbioprintingbecomesmainstream,wehighlightcurrentadvancesin basic and applied research. We use the unique properties of 3D bioprinting to create new bioink biomaterials, combine 3D bioprinting with nanomaterials toaddress unmet needs, and create multifaceted tissue constructs in the clinic. We focus on important technological advances, including advances in the vascular 3D printing process. networks. Relevance and application in regenerative medicine [112].

INK JET BIOPRINTING

Inkjet printing, more commonly known as droplet printers, is suitable for applications that include biological as well as non-biological applications. Commercial inkjet paper printers have effectively become printers of biological materials [31, 114, 115-117]. Biological materials in a liquid state are meticulously applied to specific surfaces with heightened clarity, precision,and swiftness. Conventionally, the liquid is propelled from the printer utilizing either thermal or acoustic pressure, directed onto a scaffold or substrate— integral constituents of the graft that can be implanted into tissue (refer to Figure 1). In thermal inkjet printers, a heated print head dispenses droplets of biological material onto the scaffold [118, 119, 120]. Crucially, the heating process does not compromise the quality or integrity of the biological material. Thermal inkjet printers stand out as the most cost-effective choice and are extensively utilized in numerous bioprinting applications. Inkjet printers can also print on a variety of biological materials. Acoustic printers use piezoelectric crystals to generate sound waves [121]. Adjusting the time interval and the amplitude of the waves generated in the printer head enables the modification of the size of the drops of biological materials. Acoustic inkjet printers provide a convenient means to precisely regulate the size and trajectory of the stream of biological material droplets. Nevertheless, one drawbackofutilizinginkjetprintersisthenecessitytoupholdaspecific

thickness of printed biological materials [59, 122]. Exceeding the specified viscosity may block the printer nozzle. To maintain a liquid-like biological material, the amount of cells that are captured and subsequently printed is generally reduced. A significant concentration of cells reduces droplet production and increases the possibility of printer nozzle clogging [59, 123]. Previously, inkjet bioprinting has been utilized for the regeneration of intact skin and cartilage [92, 113].

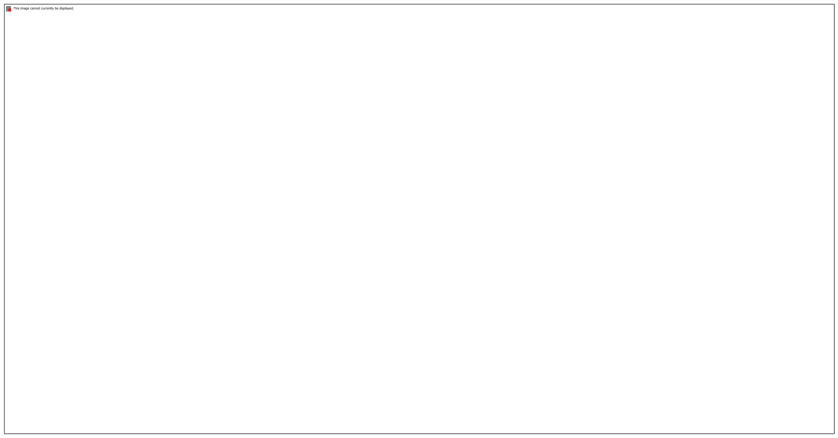

Figure1:Using inkjet technology forbioprinting involves two primary methods. In thermal inkjetprinters,pressurepulses aregenerated by electrically heating the printhead, which directs droplets of biological material through a nozzle. Acoustic inkjet printers, alternatively, utilize piezoelectric pressure pulses to transform liquid into droplets.

“Laser-assistedbioprinting”(LAB)

Numerous biological materials, notably peptides, cells, and DNA, have been successfully printed utilizing laser-assisted bioprinting [124, 125]. While less common than inkjet and micro extrusion bioprinting, this technique employs laser pulses to create pressure bubbles, which are then dispersed onto the scaffold or substrate (refer to Figure 2). This approach does not cause printer head blockage as there is not a nozzle. Furthermore, this approach can be tailored to accommodate various viscosities. This suggests that cell densities akin to those found in natural tissues can be achieved with minimal impacts on cell viability and functionality [127]. Metallic residues are generated during printing and end up in the end product of bioprinted substance; this contamination is a key downside of the technology [59, 126]. Furthermore, this procedure is highly expensive, and it is hoped that these prices would reduce with time. The efficacy of laser-assisted bioprinting has been demonstrated in human tissue as well as in the development of many animals [128,129].

Figure 2 - Laser printers employ a pulsed laser beam directed at an absorbent substrate, creating a pressure bubble facilitates the deposition of biological material onto the substrate.

2. “New perspectives on RM and tissue engineering”

When producing tissues as well as grafts, several parameters must be considered, including the biological material and biological source used [46, 59].Transplanted rejuvenated tissue must align with normal tissue in terms of cell types and function [58, 130, 131, 132, 133].As in healthy organs and tissues, different cells play different roles, including endothelial cells, which provide structural and support functions. Hence, the selection of cells utilized in 3D bioprinting significantly influences the performance of the eventual graft or scaffold [44, 59].

To integrate, implanted graft or scaffold must regenerate itself and continue to maintain homeostasis [29, 134, 135]. Autologous cells are the most preferred cell source because they prevent host immune responses [134, 135]. Autologous cells can undergo in vitro expansion to cultivate into the desired cell types before 3D bioprinting or implantation. Nevertheless, employing autologous cells comes with certain constraints, including the regenerative capacity of primary cells and the technical hurdles associated with in vitro cell culture. Compared to cell-free printing, 3D bioprinting offers greater controllability, as it involves the incorporation of cells during the printing process. Additionally, for successful integration of a graft into the body, proper vascular integration within the patient's blood vessels is essential [136, 137]. Our body cells are strategically positioned near blood vessels to facilitate the transportation of oxygen and nutrients [138]. However, conventionaltechniques like biomimetic scaffolding and tissue and organ engineering often fallshortinmeetingtheneurologicalandvascularrequirementsnecessaryfor tissues and organs. To tackle this challenge, a range of angiogenic growth factors, including VEGF, bFGF, and PDGF, have been integrated into tissue engineering strategies to promote blood vessel formation [138, 139]. These growth factors are administered to the scaffold, prompting the body to initiate angiogenesis. However, the short half-life and potential adverse effects of growth factors raise concerns [96, 140]. Experimental findings indicate that sustained release of growth factors has been successful in preventing necrosis in specific tissues [96, 141]. One strategy to facilitate graft vascularization before transplantation is by promoting angiogenesis within the graft itself. Endothelial cells can be incorporated into suitable substrates during 3D bioprinting prior to implantation. Several approaches, including microfluidics and patterning, have been used to generate or stimulate angiogenesis intissues [59 , 142 , 143]. It has been shown to enhance the engraftment of the implanted graft prior to vascularization of the target site [144 , 145]. Numerous tissues necessitate the presence of additional nerves for optimal functionality. Likewise, analogous tissues require the host to innervate the transplanted tissue for proper integration [59, 146]. Similar to vascularization, growth factors are pivotal in facilitating nerve sprouting within grafted tissues [147]. Hydrogels can be designed with channels containing extracellular matrix (ECM) proteins and growth factors to guide neural growth following implantation [148, 149].

There are various concerns that need to be addressed with cells utilized in 3D bioprinting. Ensuring cell viability throughout the 3D bioprinting process is imperative, staying strong, proliferate, also differentiate, much as stem cells do [59]. When the the scaffold or as graft has been implanted, cells must operate normally. Finally, all cells employed in the 3D bioprinting process ought to be capable of interacting directly or via the release of biomolecules that consist of growth factors & cytokines. Therefore, cells with the ability to self-renew and differentiate into various cell types, such as embryonic and adult stem cells,are highly sought after. Adult stem cells are deemed safer for transplantation compared to other cell types and retain their potency following 3D bioprinting [59, 150]. The introduction of external cells alone stimulates the host tissue to release biological molecules such as growth factors. Transplanted cells,whether accompanied by scaffolds or materials or not, can trigger a host response to repair tissue damage [151, 152]. Moreover, transplanted cells can modify the composition of the host extracellular matrix (ECM) by secreting growth factors, producing new ECM proteins, or releasing ECM-degrading enzymes like matrix metalloproteinases (MMPs) [153, 154]. Transplanted cells do not need to contact host cells to induce these therapeutic responses [59, 150, 155]. Mesenchymal stem cells (MSCs) are the preferred cell type when the priority is the repair of damaged tissue [150, 156, 157]. These cells are consideredsaferthanembryoniccells.Inaddition,cellsderivedfromadult

tissues are widely available. Most commercially available therapies use cells derived from adult tissue [69,158,159]. Induced pluripotentstem cells (iPSCs) and embryonic stem cells (ES cells) serve as abundant cell sources in regenerativemedicineinitiatives[44,160]. Severalstudieshaveshowcased that ES cells have the capacity to differentiate into all cell types present in the human body and can be safely employed in regenerative medicine procedures [161, 162]. iPSCs, derived from a patient's own cells, mitigate the risk of rejection of transplanted cells [163, 164]. However, cells transplanted using scaffolds are rapidly eliminated through the host tissue and their efficiency decreases [165]. To address this, coating the cells with materials such as hydrogels may allow them to remain in the transplanted tissue for a longer period of time, possibly preventing rejection [166,167]. Coating transplanted cells with specific antibodies or peptides facilitates their ability to target particular organs or tissues [168, 169]. Despite its role in graft and new tissue rejection, the immune system may actively stimulate tissue regeneration and improve graft survival [170]. Because of technological advancements, changing scaffold features can reduce graft rejection while increasing graft tolerance [170, 171].

3. BIOPRINTING OF TISSUES

Cartilage Regeneration

Articular cartilage allows humans, along with other animals, to walk without pain. Pathological events and disorders associated with osteoarthritis cancause cartilage loss and pain during movement in humans [172-176]. The presence of cartilage adjacent to joint surfaces serves as a lubricant and absorbs the body's weight during physical activity. Comprised primarily of extracellular matrix (ECM) proteins such as collagen type II and aggrecan, cartilage collaborates with synovial fluid to provide lubrication and withstand loads [177]. Successful regeneration necessitates replicating the surface layer orinterstitialtissue ofcartilage.However,synthetic derivatives ofpolymersand metals pose challenges; for instance, plastic and metal cartilage implants have limited lifespans and can provoke a foreign body response due to wear. Recently,a combination ofchondrocytesand mesenchymalstemcells has been employed to address cartilage abnormalities through regeneration [173, 178]. However, the utilization of cells has yielded relatively satisfactory outcomes, partly due to a limited understanding of the mechanisms underlying cartilage growth. Our research indicates that the extracellular matrix derived from the surrounding cells can direct the differentiation of adipose-derivedmesenchymal stem cells (MSCs) toward the chondrogenic lineage [41, 179]. Recently, biomaterials mimicking cartilage stromal tissue have been developed, concurrently promoting cartilage repair. Incorporating hyaluronic acid into biomaterialsalongsidehydrogelsenhanceslubrication[43,180].Crucially, integrating living cells into biomaterials has enhanced the regenerationprocess, yielding superior outcomes compared to using cells and biomaterials separately [41, 176, 181]. Some translational research has focused on the combination of different biomaterials of stem cells. Multiple studies have showcased that robust soft materials can augment the chondrogenic growth of stem cells [41, 182, 183]. Various polyethylene glycol (PEG) hydrogels have been investigated for cartilage repair alongside other polymers [184, 185]. Successful integration and inclusion of alginate, gellan gum, and type II collagen have been accomplished.

4. 3D BPOF ORGANS

3D organ BP presents significantly greater challenges compared to tissue bioprinting, as it demands precise and intricate placement of multiple cell types to replicate complex organic organs [59, 188]. In addition, not only blood vessels, but also nerves are required for organ function. Scientists and doctors must determine whether these complex organs can be mass-produced for in- vivo transplantation. While thin tissue bioprinting has seen advancements, the 3D printing of larger and more intricate organs and tissues poses ongoing challenges. The complexity and size of organs necessitate extended bioprinting times, potentially impacting cell viability [29, 59, 189, 190]. Biomolecules like chemokines and growth factors can enhance cell viability before and after bioprinting. Bioreactors play a crucial role in post-printing processes by providing an optimal microenvironment for long-term storage and culture ofthe final scaffold or implant. These bioreactors simulate healthy organ environments, facilitating nutrient, oxygen, and biomolecule exchange and ensuring a conducive environment for the scaffold or graft [69, 70, 72, 191]. During incubation, cells must communicate and synthesize extracellular matrix (ECM), leading to an equilibrium among cells, ECM components, and cell surface receptors [66, 69, 192, 193-195]. This equilibrium promotes integration of the graft or scaffold with host tissue. Tissue engineering and regenerative medicine enable the development of functional, full-scale organs for transplantation [66, 69, 192, 194, 196]. Despite the feasibility of 3D bioprinting various tissues due to differences in complexity, bioprinting organs remains a formidable challenge.The complexity of organs requires simultaneous bioprinting of many tissues as well as cell lines [1, 66, 69, 192]. To achieve a single function, both cells and tissues must be interconnected. The key is that organizations must be able to interact with each other.

Heart

The heart, one of the earliest functional organs during fetal development, plays a crucial role in sustaining life by facilitating blood circulation throughout the body[100].With its intricate structure, the heart consists primarily of three

celltypes: cardiomyocytes,endothelial cells,and fibroblasts [200].Heartfailure often necessitates organ transplants, but the limited availability of donor organs underscores the urgency for alternative solutions. In this context, 3D bioprinting emerges as a promising avenue to address this challenge. Numerous publications indicate that many cardiac designs and implants have been evaluated [90, 201-204]. The heart needs proper blood vessels and innervation for effective functioning. Consequently, cardiac structures and grafts require adequate vascularization, which presents a significant problem. The extracellular matrix of the heart plays an important role in cell differentiation, including protein expression. The extracellular matrix (ECM) of the heart is predominantly composed of collagen. Due to its complexity, heart repair has been approached through various techniques such as allografts, xenografts, and even autologous transplants. Tissue engineering and regenerative medicine hold promise in addressing heart repair and cardiovascular diseases, garnering significant attention. Already, 3Dbioprinting has been utilized to create functional heart tissue, including heart valves. Biodegradable materials are commonly employed for bioprinting heart valves, enabling the replication of valve structures. Multiple 3D bioprinting techniques and cell types have been utilized to create living heart tissue [44, 59]. Embryonic stem (ES) cells have shown the capability to form embryoid bodies [98], and direct laser synthetic bioprinting provides precise control over their size and growth [205, 206]. MSCs containing more endothelial cells have been printed on patches to stimulate blood vessel growth [31, 59, 205, 206]. The majority of 3D bioprinted cells demonstrate high cell viability and differentiation towards the cardiac lineage, as indicated by the expression of cardiovascular transcription factor genes. Coronary artery occlusion and myocardial infarction result in significant damage to the heart, prompting exploration of artificial myocardial tissue as an alternative solution [207, 208]. Myocardial infarction primarily leads to heart failure due to cell death caused by necrosis. Notably, bioprinting technology has been utilized to create viable patterned patches that enhance the function of infarcted hearts post- transplantation. For example, alginate hydrogels containing cardiomyocyte progenitor cells sustain cell viability and promote cardiac tissue repair. Additionally, decellularized heart tissue has been employed in microextrusion bioprinting to generate heart tissue [8, 209]. Furthermore, the bioprinting of living prostheses capable of responding to cardiac conditions and integrating moreeffectively with thehumanheartthannon-living prostheseshas improved prosthetic performance.

Liver

Hepatocytes comprise the vast majority of liver tissue [210]. The liver contains severaladditionalcells,includingportalfibroblasts&endothelialcells.The

liver plays a crucial role in several metabolic activities, including plasma synthesis of proteins, hormone production, & xenobiotic detoxification. The liver is divided into four hepatic lobes и contains two types of cells: parenchymal and nonparenchymal. Hepatocytes have a tremendous regenerating ability, rendering the liver among the most regenerative organs. However, once maintained in vitro, hepatocytes degrade rapidly [211]. Adult stem cells are the preferred option for 3D bioprinting of liver tissue because they can be directly harvested from patients, allowing for the bioprinting of personalized tissue [173, 211, 212]. These stem cells also express hepatocyte- like genes. The creation of microlivers has enabled high-throughput screening of numerous promising drugs. Various bioprinting methods have been utilized to create 3D liver tissues [213, 214]. Embryonic stem cells have beenbioprinted to generate liver constructs using valve-based bioprinting techniques, leading to the subsequent differentiation of the cells into hepatocyte-like cells [36, 160, 215]. Adipose-derived stromal cells, Wharton's jelly-based stromal cells, and liver progenitor cells are among the cell sources utilized for liver construction and transplantation. Bioprinted cells have exhibited hepatocyte-like characteristics such as albumin secretion. The incorporation of endothelial cells has enhanced the complexity of these structures. Hydrogels incorporating different combinations of gelatin, polyethylene glycol, and alginate have been employed for the 3D bioprinting of liver-like structures [32, 122, 216, 211-213, 217-221]. In addition to injury responses, many 3D bioprinted tissues exhibit liver-specific functions. Several companies and research institutes have developed liver constructs that mimic the natural structure and function of the liver [52, 211, 212, 214, 222, and 223]. The demand for liver tissue is significant, and producing liver tissue or even whole livers through bioprinting holds the potential to address this demand effectively. Other experiments conducted using liver tissue containing organoids include drug trials, including liver disease research. Stem cell- derived hepatocyte-like cells rapidly degenerate in vitro, similar to adult hepatocytes [211]. The structure of the liver is intricate, characterized by a modular microenvironment, which poses challenges in accurately replicating normal liver tissue [211].

5. Challenges in 3D Bioprinting involving Tissues as well asOrgans

3D bioprinting is a multidisciplinary field, so success requires collaboration between scientists from different disciplines. There are many challenges that must be overcome before the existing limited proof of concept can be translated into real 3D BP of tissues along with organs. Indeed, there is a pressing need for standardized techniques in the design and fabrication of tissues and organs [44, 59, 85]. This is problematic because some cells come from people who are

very different from each other.As a result, the patterns of cell proliferation and final differentiation are different. Many technical issues must also be considered. Indeed, several challenges persist in bioprinting processes, including the slow speed of bioprinting and the biocompatibility of materials utilized [31, 58, 224, 225]. Moreover, many tissues necessitate the incorporation of diverse biomaterials and cells, which must be printed simultaneously and accurately positioned, either as a cohesive unit or within a scaffold. Addressing these requirements may involve employing various bioprinting strategies. Following bioprinting, the scaffold or construct typically undergoes a period of maturation within a bioreactor [69, 71, 159, 194, 226]. This allows the cells to deposit extracellular matrix (ECM) simultaneously with the synthesis of biomolecules such as growth factors, which are essential for the development of viable tissue structures.

Angiogenesis represents one of the most significant challenges in regenerative medicine and tissue engineering, a challenge that 3D bioprinting aims to address [127, 228-232]. Numerous studies have demonstrated successful creation of 3D vascular tissues in both human and animal models [233–238]. For example, Arcudas et al. demonstrated that vascularization of femoral bone defects in rats and sheep resulted in enhanced bone formation [239, 240]. Effective 3D bioprinting holds the promise of customization to meet an individual's specific regenerative needs. In view of the above, superior 3D bioprinting is required to ensure the suitability of the resulting structures and implants for human use. Each step of the process requires strict quality controls comparable to those used in human medicine. Most experiments to date have been conducted on animals. After development, all structures and implants must undergo approval by relevant regulatory authorities such as the FDA or the European Medicines Agency. While challenges persist, the field of tissue engineering, like regenerative medicine, holds immense potential, achievable through collaborative efforts among clinicians and researchers to advance bioprinting strategies and engineering designs. The versatility of 3D bioprinting extends beyond organ and tissue creation to other areas of research, including drug toxicity and oncology.

CONCLUSION

Regenerative medicine is currently used to treat a variety of diseases and conditions. Continuous manipulation of hybrid scaffolds and cells enables precise control of the host response to the presence of cells and scaffolds within organs and 3D bioprinted structures. Technological advances make it possible to colonize cells in specific areas of the scaffold to create customized, patient- specific grafts that resemble natural tissue. Most importantly, as more is learned about the vasculature and innervation of the graft, integration of the graft with the host tissue will improve. Advancements in technology for the

Controlled release of growth factors within 3Dbioprinted structures and organs post-transplantationfacilitateprecisehealingandregeneration.Modulatingthe immune system could potentially minimize the immunogenic response to 3D bioprinted organs and tissues, or at least enable scientists to achieve a more favorable immune reaction. Enhanced understanding of stem cell behavior and controlled cell differentiation may help address safety concerns. Furthermore, modifying the host environment to prevent rejection of 3D bioprinted constructs and organs, as well as creating a conducive niche for transplanted cells to thrive in "natural conditions," can significantly enhance the outcomes of regenerative medicine strategies. Recent research emphasizes the substantial impact of the microbiome on nearly every cellular process within the body. Consequently, comprehending the microbiome's role in graft establishment or integration is vital. The ongoing developmentof3D bioprinted models of human disease and illness must persist to drive significant advancements in regenerative medicine strategies. To propel the field of regenerative medicine and tissue engineering forward, scientists and physicians must embrace a mindset of "mimicking nature" or "collaborating with nature" when designing biomaterials and harnessing advanced technologies such as nanotechnology.

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