Progress in the Application of Biological 3D Printing Technology in Skin Wound Repair

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Abstract. Wound repairs represent a significant area of research within the field of dermatology, and the population affected by skin wounds is increasing year by year globally. Traditional treatment methods often utilize skin substitutes to repair wounds, which may cause issues such as low efficiency, complex operations, and high recurrence rates. Currently, biological 3D printing is applied in skin wound repair due to its unique advantages. This study reviews the basic methods of biological 3D printing, biological inks, and their applications in skin wounds. This study aims to promote the broader application of biological 3D printing technology in skin clinics by analyzing existing research applications to identify the limitations of this technology, also to clarify future development directions, focusing on the innovation of bioprinting technology and the research on biological inks.

Keywords: 3D Bioprinting; biological ink; wound repair; vascularization.

1. Introduction

Wound repair is a major challenge in clinical skin restoration. Globally, the incidence of skin damage has an annual increase. According to statistics from the World Health Organization, approximately 11 million patients with skin injuries require treatment [1]. Explosions, burns, tumors, surgical excisions, skin injuries caused by inflammation, and impaired healing of postoperative incisions all significantly have influence on the physical and mental health of patients. Skin grafting and flap transplantation techniques are traditional repair methods, but they have shortcomings such as the complexity of surgical procedures and a high incidence of morbidity in donors [2]. Bioprinting is based on traditional 3D printing technology, a combination of living cells, biomaterials, and bioactive factors to build biological functions. Due to its ability to flexibly print and create complex bioactive structures, bioprinting is an advantageous technology in the field of constructing artificial skin structures [3]. Common printing methods including inkjet bioprinting, laser-assisted bioprinting, extruder-based bioprinting, and photocuring molding. This article reviews the methods of 3D bioprinting technology, the application of bioinks, and the current status of skin wound repair, in order to discuss the limitations and future development directions. Emphasizing the advanced application and further development potential of 3D bioprinting technology in wound repair of different skin structures.

2. 3D Bioprinting

The key factors affecting the 3D printing effect of biology are technology and bio ink. Extrusion-based bioprinting can accommodate materials or bio-inks with high cell concentrations. The biological structures manufactured through this printing method have appropriate mechanical strength, which helps to transport and circulate nutrients and oxygen, thereby maintaining cell vitality in the skin model. Based on this, it is currently the most widely used bioprinting method [4].

2.1. Biological Ink

For 3D bioprinting, bioink is the most important material, which refers to a mixture of natural or artificially synthesized biomaterials, bioactive molecules, cells, etc. Common biological inks include polyethylene glycol, alginate, and others. Polyethylene glycol (PEG) is a stereocomplex type of bio-ink. As a linear polyether compound, it has good hydrophilicity and water absorption, making it suitable for extrusion-based bioprinting technology and photo-curing molding technology. PEG is commonly used to modify proteins and lipid vesicles, serving as a excipient, support material for scaffolds, and as a drug delivery carrier aided by 3D bioprinting. Sodium alginate, as an ionic bioprinting ink, is suitable for printing technologies such as inkjet printing, laser-assisted printing, and extrusion printing, with rapid gelation and good mechanical properties. It can be prepared as hydrogels under mild pH and temperature conditions, making it suitable for sensitive biomolecules such as proteins and nucleic acids. Therefore, it is used as a scaffold for tissue engineering, a carrier for drug delivery, or a model for basic biological research [5].

2.2. Classification of stem cells

Stem cells, as one of the key components of bioinks, have a significant impact on the printing process. Existing research application scope contains embryonic stem cells, adipose-derived mesenchymal stem cells, etc. Embryonic stem cells (ES cells), are isolated from primordial germ cells or early embryos, which can successfully induced and differentiate into several types of cell both in vivo and in vitro environments, and can build up tissues and organs. ES cells can also result in individuals containing cells of different genotypes, becoming chimeras. Adipose-derived mesenchymal stem cells are mainly found in adipose tissue. It can be obtained through two methods: liposuction or fat removal surgery, which have adequate sources and are easy to acquire.It can secrete a variety of cytokines to promote angiogenesis and has immune regulatory functions. Adipose-derived mesenchymal stem cells can also differentiate into various cell types such as endothelial cells under the induction of different factors [6]. At present, these two types of stem cells are used in bioinks, capable of inducing differentiation into most cell types in the body and promoting vascularization, allowing skin substitutes to better adapt to the native skin microenvironment.

3. The application of bioprinting

3.1. Bioprinting of Vascularized Skin

3D bioprinting of vascularized skin aims to enhance the survival rate of transplants and the integrity of skin functions by simulating the vascular system of the skin. Bioprinting with vascular skin can be divided into two steps, in vitro vascular pre-formation and in vivo induced vascular formation. The most common method for the pre-formation of vascular structures in vitro is to use sacrificial materials, embedding them in the printed structure and then dissolving them to create hollow channels, followed by the infusion of vascular endothelial cells ECs. These ECS can form vascular structures by adhering to the surface of the channels, thereby promoting the vascularization of bioprinted skin substitutes. However, the blood vessels formed directly in vitro usually have certain differences from the microvascular environment of normal skin. Currently, growth factors are commonly used to address this issue by inducing the formation of blood vessels in vivo [7]. Existing research uses endothelial cells (ECs) to perceive mechanical signals and microtopographies of the 3D environment and alter their behavior through inkjet printing technology, employing neonatal dermal fibroblasts (Fb), keratinocytes (KC), and human umbilical vein endothelial cells (HUVECs) as seed cells, and constructing artificial skin using type I collagen and fibrinogen as the matrix. The results indicate that the 3D printed skin graft can accelerate wound healing, with angiogenesis observed in the graft two weeks after the operation. In the above cell types, human umbilical vein endothelial cells play an important role [8].

3.2. Full-thickness Skin Bioprinting

The entire skin is a complete structure including all tissues from the surface to the deep layer, which is the basis for maintaining the normal physiological functions of the skin. The skin play roles in protection, sensation, temperature regulation, metabolism, and so on. Full-thickness skin bioprinting aims to construct a complete skin structure that includes the epidermis, dermis, and subcutaneous tissue using 3D bioprinting technology. Bioprinting of full-thickness skin involves the integration of various cells, including keratinocytes (KCs) and other types of stem cells, which ensure the protective function of the skin [8]. Existing research uses KC and Fbs as seed cells to print skin tissue, and collagen to form the dermal matrix of the skin. There are also applications where Wang et al. used bioprinting to create a bilayer membrane (BLM) scaffold that mimics the epidermis and dermis of the skin, consisting of an outer PLGA membrane and an inner alginate hydrogel layer. In the BLM scaffold, the porous alginate hydrogel promotes cell adhesion and proliferation in vitro, while the PLGA membrane serves an antibacterial role. Applying BLM stents can increase the formation of new blood vessels, thereby achieving a high level of skin regeneration [9] (Figure 1).

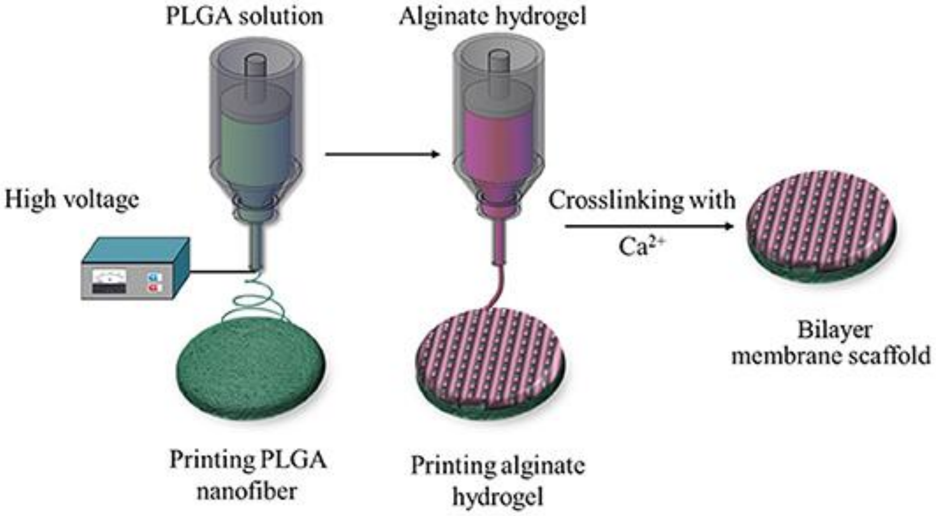

Fig. 1 BLM double-layer membrane schematic diagram [9]

3.3. Bioprinting of genuine leather skin

The dermis is a fibrous connective tissue that contains collagen and elastin fibers, primarily composed of blood vessels, sweat glands, sensory nerve endings, etc., which helps to retain moisture in the skin and prevent microbial invasion. Bioprinting of real leather skin aims to construct the integrity and continuity of dermal tissue structure to aid in the repair of deep wounds and chronic ulcers [10]. Prior studies uses polyelectrolyte gelatin-CS (PGC) hydrogels and laser-assisted bioprinting technology to create dermal substitutes, giving them antibacterial and hemostatic properties while maintaining high shape fidelity [11]. Currently, printing leather alternatives is the mainstream practice for printing real leather skin. Research has combined gelatin methacrylate (GelMA) and chitosan oligosaccharides (COS) to formulate a composite bioink and utilized digital light processing printing technology to print dermal scaffolds. This type of bio-ink has compatible degradation rates and mechanical properties, ensuring the shape fidelity of the scaffold to a certain extent. COS has antibacterial properties and can promote the proliferation of human dermal fibroblasts (HDFs). Dermal scaffolds printed by this method exhibit high cell viability, facilitating the extension of HDFs along the scaffold, which can improve the healing efficiency and quality of wounds [12].

4. Limitations and Future Prospects

In the current research landscape, bioprinting 3D technology has seen innovative development in the repair of skin wounds, which can accelerate wound healing and restore the integrity of skin function, but the choice of bioink and the printing method are critical determinants. The method of biological 3D printed skin substitutes is somewhat limited by compatible bio-inks. The suitable biological ink provides a high-strength structure for printing tissues and maintains cell viability. At the same time, there are certain limitations in replicating the microenvironment of natural wounds, the vascularization of bioprinted skin substitutes, and the adhesion between the dermal and epidermal layers of the skin during the wound healing process [13]. In future research directions, more emphasis should be placed on the selection, development, and combination of bio-inks, allowing multiple bio-inks to work together to achieve better performance, while also focusing on the compatibility between different bio-inks. In addition, strategies for vascularization of skin substitutes need to be explored to investigate whether skin substitutes can meet permanent physiological replacement. Attention should also be paid to the speed, resolution, scalability, and sterilization performance of biological 3D printing. The advancement of technology and the understanding of wound healing will help overcome these limitations, promoting the broader application of bio-printed vascularized skin tissue analogs in clinical settings [14].

5. Conclusion

This study analyzes the fundamental concepts of bio 3D printing, commonly used methods, types and functions of bio-inks, as well as its applications in repairing dermal skin, full-thickness skin wounds, and the vascularization of skin substitutes after repair, ultimately presenting the current limitations of this technology. This review primarily studies the application of this technology in skin wound repair and the vascularization of skin grafts, aiming to derive methods for the application of biological 3D printing in the field of skin.Traditional wound repair methods have many drawbacks, including slow effectiveness, complex processing, and improper treatment operations that can cause secondary damage to the wound, delaying recovery time. Additionally, ordinary skin substitutes do not match the microenvironment of native skin, have a low degree of vascularization, and have defects in both function and aesthetics. Compared with traditional methods, biological 3D printing technology has advantages, higher efficiency, and the performance of the printed skin substitutes is better, which is conducive to the better adaptation of skin substitutes to the original skin and vascularization, thereby shortening the treatment cycle. Bioprinting technology has a promising research and development outlook. In future studies, more attention should be paid to the development and combination of bioinks, innovation in printing methods, as well as printing speed, resolution, and various performance metrics.

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