Research Output Journal of Public Health and Medicine 4(2):6-11, 2024

ROJPHM

ISSN ONLINE: 1115-9715
ISSN PRINT: 1115-6147

https://rojournals.org/roj-public-health-and-medicine/

https://doi.org/10.59298/ROJPHM/2024/42611

Bioengineered Skin for Burn Victims: Advances and Challenges

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ABSTRACT

Burn injuries impact millions worldwide, causing significant physical and psychological burdens due to scarring, limited function, and the risk of infection. Traditional skin grafting techniques have limitations in restoring full skin function and appearance, creating an urgent need for improved treatment methods. Bioengineered skin offers a promising alternative, utilizing tissue engineering, stem cell technology, and advanced scaffold materials to support skin regeneration and healing. This paper discusses the evolution of skin grafting, highlights current bioengineering approaches, including cell and scaffold innovations, and explores clinical applications of bioengineered skin substitutes. Although advances have been promising, challenges remain in material selection, cellular integration, and large-scale clinical application. Future success will hinge on interdisciplinary collaboration, regulatory support, and continuous research to overcome barriers and improve outcomes for burn patients.

Keywords: Bioengineered skin, Burn treatment, Skin regeneration, Tissue engineering, Stem cells.

INTRODUCTION

Burn injuries are prevalent, with over 11 million people seeking medical attention after burns annually. The severity and cause are diverse, yet they equally affect the quality of life, causing extreme injury, cost, scarring, disability, and death. Current treatments of burn wounds and ulcers often do not restore the characteristics or functions of unwounded skin. Modern understandings of the immune response, stem cells, exuberant wound healing, and bioengineered approaches change the questions imperative for reconstructive work such as: What is ideal skin tissue for repair or regeneration? Can skin tissue be repaired, rebuilt, or perhaps engineered to regenerate itself? What does the ideal skin look and behave like? What advances in the lab are making this achievable? Future directions for this rapidly developing field [1, 2]. The skin constitutes an integral interface between our body and the environment. Damage results in substantial physiological deficits, increased microbial entry and infection, heightened chance of morbidity, and a devastating quality of life. Prompt and effective wound healing is paramount to restore the integrity, strength, and protective functions of the skin. Evidence-based research focuses on the regeneration of anatomically, functionally, and aesthetically normal skin with reduced inflammation and hypo-scarification. Reconstructive approaches encompass the transfer of skin tissues or dermal matrices post-debridement, aiding automatic repair by the innate regenerative properties of the skin. Shortcomings such as delayed healing, cost, immune rejection, scar formation, and availability of abundant skin resources indicate the need for skin tissue regeneration research. Developing stem cell-based approaches aids in transitioning to patient-centric and high-throughput methods that have predominantly been investigated for skin pathology. Significant research is aimed at the transplantation of skin substitutes in

induced wounds. Bioengineered dressing materials are also being developed to treat skin pathology. The discovery of bioengineered solutions for pathology and critically burned patients, however, necessitates significant advances in the field. The challenges and future directions are outlined below [3, 4].

Historical Background of Skin Grafting

Humans have been aware of skin and its repair for thousands of years. Skin grafts can be traced back at least as far as ancient India and their related practice of nose repair, although borrowings across other cultures are without proof. A piece of lip skin was used to repair a nose amputated as a punishment. The Indian antecedents of modern-day plastic surgery are further described in a work around AD 530, and similar techniques can be found in the writings of a Buddhist Tantric around AD 630, in an unnamed compilation of later commentaries [5, 6].

Autografting, xenografting, and particularly allografting were known before a definitive monograph on the experimental and clinical use of preserved tissue was published in 1910, while the reunification of knowledge, a potential allograft source from one of the autografts—especially a thin piece of skin—had been known and used for dermatologic repair to some extent for over 50 years. An important book published in Russia in 1919 gave a comprehensive and largely original treatment of contemporary skin surgery mainly employing full-thickness grafts and flaps. Concern was laid on preserving as many appendages as possible, amputating exuberant flaps, and performing delayed synechias. Advances have continued under such pioneers; comprehensive groundwork was laid by others. Pig skin grafting was practiced in the United States in 1910, used it as a temporary skin substitute for burns and as a material for experimental skin transplants, and in France from 1920. The drawbacks of these techniques and the advent of solutions from skin culture banks fostered contraindications to their use, but they continued until salvaged by safer histoincompetent materials in 1981: at one center, full-thickness pig allograft in burn patients was maintained until 2000. Skin biology and skin surgery were advanced by countless contributors, of whom only a few were cited in this historical outline, concerning these traditional full-thickness skin employed in the preface, grafting section, and earlier in this study. As a result, the present generation of surgeons, patients, and researchers has been influenced by many, not least who first opened the door to the management approach of skin for skin, and more skin. At its peak, this was textbook grafting (i.e., rationally using one of the skin's precious components). In extreme cases of burn, e.g., with full-thickness necrosis extending over extensive sites, or in surgically planned ablation of tissue, random pedicle full-time surgical positioning after full-thickness grafts continues to be convenient tools. This surface can also be the result of planar contraction, e.g., due to granulation tissue maturation or beneath an autograft or artificial dermis [7, 8].

Bioengineering Approaches for Skin Regeneration

Because current therapies are limited, bioengineering skin to speed up or mimic the natural healing mechanism and aid in skin regeneration in burn patients has been the subject of many studies. Bioengineering for skin regeneration has been explored through tissue engineering, regenerative medicine, molecular biology, cellular biology, and many other interrelated fields. Tissue engineering is the use of engineering principles and biological sciences to replace normal skin function or heal skin injuries. In skin tissue engineering, a scaffold excludes fibrotic overgrowth, sustains long-term regeneration, and provides a more indistinguishable skin-like structure. Scaffolds can be made of synthetic polymers, natural polymers, decellularized skin matrices, or a combination of those materials [9, 10]. The word “scaffold” is usually employed in tissue engineering, whereas “dressing” is extensively used in the wound healing field, which may refer to a temporary application to a wound or an open incision. Among research fields, there is no clear distinction between a scaffold and a dressing, or whether the two terms are interchangeable. Other new research areas are also required as part of skin tissue regeneration research since improvements in skin functionality are still needed. This is particularly important for wound healing defects, such as those that do not respond to conventional skin therapies or require skin rejuvenation that mimics older, natural skin. To address this specialization, we will begin by discussing the projects involved in recent skin bioengineering construction, starting with important terms in skin regeneration. These include characteristics of skin components, and two major fields: cells and biomaterials [11, 12].

Cell Sources for Bioengineered Skin

Primary Cells. An alternative to searching for wound healing beneficial factors in skin tissue is the use of primary epidermal and dermal cells to build EB/NAB. The use of this type of cell is very appealing due to its natural origin and the ability to functionally mimic fibroblasts and keratinocytes from healthy or pathological tissues. However, primary cells have drawbacks since the availability of keratinocytes is limited, and if they come from healthy skin, it is ethically controversial to take such tissue from a person to build bioengineered skin [13, 14]. Stem Cells. A combination of cells from the mixed human keratinocyte and melanocyte co-culture system and stem cells was used in tissue engineering to form a three-dimensional skin tissue with hair follicles in vitro and in vivo. The co-cultivation of human iPSC-derived keratinocytes with fibroblasts and NHK with this combination of cells, and also with a mixture of these cells with several growth factors and without insulin treatment, was compared. The obtained tissue with the addition of melanocyte-LCs and growth factors has a correct histological structure and high epidermal barrier function [15, 16].

Advantages and Disadvantages of Cell Selection. There are currently no published standard criteria for choosing the sources of cells from the skin or its derivatives of healthy or sick people to apply them for cell-based therapies. At the same time, an analysis showed that guidelines exist for choosing sources of cells for preclinical and clinical use, in particular for the development of systems using mesenchymal stromal cells. Bioengineered skin currently focuses on studying cells from the epidermis and dermis and their use for EB/NAB, since the epidermis-dermis structures are easily reproduced in a lab [17, 18].

Scaffold Materials in Skin Tissue Engineering

Scaffold materials play a crucial role in skin tissue engineering, as they work as the framework for cells while guiding their regrowth into organized replacement tissue. Scaffolds also must be biocompatible, biodegradable, and supply the mechanical strength required for tissue formation. Conventional materials used by burn surgeons are, for example, cadaver skin, amnion, and xenografts. Auxiliary scaffold materials for skin tissue engineering include many natural materials like collagen, fibrin, and elastin, as well as hyaluronic acid, chitosan, and some synthetic polymers, such as gelatin and poly (lactic-co-glycolic acid). For poor-quality burn wounds that do not heal, currently, one exciting area of investigation is the development of bioengineered skin transplants, also known as "artificial" or "living" skin. Over the past few decades, several techniques have been developed to facilitate tissue engineering of scaffolded constructs. While scaffold design and material selection are important for the success of bioengineered skin grafts, such as scaffolds that are well-suited for cell adherence, growth, and differentiation, have been developed and are discussed in this section. To further tune their adhesive growth characteristics, many techniques have been used to modulate both the nanoscale and microscale topography of skin scaffolds. New technologies used in skin scaffold fabrication include extrusion, electrospinning, direct-write, and salt-leaching fabrication techniques. Bioactive factors, such as platelet lysate, VEGF, and hyaluronic acid, can be incorporated into skin scaffolds to allow them to support healing. Overall, many deep dermal materials are currently being used for deep dermal damage repair, but materials research will need to rate the effectiveness of different materials in treating deep dermal wounds clinically before a useful consensus can be developed about the most effective materials for deep dermal repair [19, 20].

Clinical Applications of Bioengineered Skin

Human trials and case reports of burn and non-burn wound treatments have been examined, including a multicenter, open-label study of ten patients receiving autologous fibroblast seeding to split-thickness burns and a prospective, randomized, controlled clinical trial for chronic wounds with the use of a composite graft. Smaller, early-phase clinical trials have also been completed by several companies utilizing fibroblast, keratinocyte, and ECM therapies for dermal and epidermal applications in a variety of therapeutic areas, including both acute and chronic wounds. Skin substitutes have been developed largely as sheets because they are suitable for full or deep wound injury treatment, and recent technologies have enabled the construction of more three-dimensional and stratified structures, with dermal-epidermal junctions being disrupted for improved take of the graft compared to earlier generations of skin substitutes [16, 21]. Burn wounds are currently treated with skin sheets, skin sprays, skin adhesive, spray-on skin, various types of skin cell therapy, burn wound dressings, and new physical treatment modalities, such as fractional laser treatment. Recent advancements have suggested improvements with POCT for burn wound diagnosis, which may provide additional information to inform clinical assessment

and therefore, by extension, wound therapeutic choices. Taken together, these findings and summaries of previous work help to illustrate how wound healing technologies have the potential to play a significant role in pre- and post-burn treatments for victims of total body scald burns. Bioengineered skin could be personalized, as it has in the treatment of other wounds, by tryptic digestion of viable allografts or autografts ahead of adhesive attachment of epidermal organotypic culture on top. This approach is particularly suited for infected wounds or individuals with extensive burn areas for whom autologous advanced therapy is infeasible. Customized skin grafts could play a role in the care of pediatric burn patients or aid chronic burn wound healing, stimulate scar resolution after burn injury removal, or salvage reconstruction, although further research is required to determine the precise role for which engineered skin can most benefit patients. The alloplastic regeneration of human skin should complement existing technologies for the treatment of full-thickness burn wounds, potentially offering a platform to improve patient outcomes. Nevertheless, there remain several challenges preventing certain product progressions, as well as thorough translation of laboratory-based findings into the clinical sector. As a result, there is still currently a scarcity of options for deep tissue burns and a lack of the ability to truly regenerate entirely functional and natural human tissue. The difficulty is in traversing the void between the technologies and tissues currently available and those that remain lost following deep wounds (or wounds to damaged skin). Thus, the integration of plastic reconstructive surgery and burn in the wound care treatment arena focuses on creating continued benefits in healthcare delivery for burns and violence victims, especially with large-scale solar and complex chemical burns, through the use of skin substitutes and cultured cells in the laboratory to improve the understanding and delivery of these treatments [22, 23].

Challenges and Future Directions

There are many things that must still be addressed in order to improve the design, approval, and application of these new skin substitutes. Although the treatment of severely burned patients with new skin substitutes is now well within reach, research must continue. In the future, we cannot afford to be in the same position as we found ourselves in the past, responding too late to advances and opportunities. It is time to look forward to the development of new products planned to be manufactured under Good Manufacturing Practice conditions and administered surgically in anticipation of large-scale clinical application in burn therapy. This can only be achieved by fostering a multidisciplinary approach to research involving extensive collaboration among clinicians, biologists, engineers, biomaterial experts, trading companies, regulatory bodies, and industry and insurance companies. Not only will this type of cooperation help identify the questions that must be addressed, but it will also define the best answers, prioritizing the issues to be resolved in the future [24, 8]. In the Americas, only one product is now approved for clinical application as an acellular dermal matrix. The regrowth in humans of the epidermis into this material shows the great capacity of the dermal compartment for stimulating re-epithelialization. Although such epidermis was formed within the conductive tissues of this material, it is now also evident that the formation of a complete epidermis is a kind of tissue ingrowth that can only occur on a wide scale after tissue allograft is replaced by the patient's autografts. Thus, we believe that, for reconstructive indications, ADM should be implanted in a "tissue-engineering mode," allowing time for both tissue revascularization and tissue regeneration prior to the implantation of autografts [25, 26].

CONCLUSION

Bioengineered skin represents a transformative shift in burn treatment, offering the potential for more functional and aesthetically aligned skin repair than traditional methods. While significant progress has been achieved through tissue engineering, stem cell research, and scaffold material advancements, numerous challenges still prevent widespread clinical adoption. Success in overcoming these challenges will require a concerted interdisciplinary effort, bridging bioengineering with clinical expertise, regulatory considerations, and industry involvement. Looking forward, continued research, along with well-designed clinical trials and adherence to Good Manufacturing Practice (GMP) standards, will be essential in optimizing bioengineered skin substitutes. As these innovations mature, they hold the promise of significantly improving the quality of life for burn victims by enabling more effective, personalized, and accessible treatment options.

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CITE AS: Abaho Areeba Fortunate. (2024). Bioengineered Skin for Burn Victims: Advances and Challenges. Research Output Journal of Public Health and Medicine 4(2):6-11. https://doi.org/10.59298/ROJPHM/2024/42611