Journal of Plastic, Reconstructive & Aesthetic Surgery (2018) 71, 615–623

Review

Skin tissue engineering using 3D bioprinting: An evolving research field

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Received 12 April 2017; accepted 5 December 2017

KEYWORDS
3D bioprinting;
Skin replacement;
Reconstructive surgery;
Tissue engineering

Summary *Background:* Commercially available tissue engineered skin remains elusive despite extensive research because the multi-stratified anisotropic structure is difficult to replicate in vitro using traditional tissue engineering techniques. Bioprinting, involving computer-controlled deposition of cells and scaffolds into spatially controlled patterns, is able to control not only the macro but also micro and nanoarchitecture and could offer the potential to more faithfully replicate native skin.
Methods: We conducted a literature review using PubMed, EMBASE and Web of Science for studies on skin 3D bioprinting between 2009 and 2016, evaluating the bioprinting technique, cell source, scaffold type and in vitro and in vivo outcomes.
Results: We outline the evolution of biological skin replacements, principles of bioprinting and how they apply to the skin tissue engineering field, potential clinical applications as well the current limitations and future avenues for research. Of the studies analysed, the most common types of bioinks consisted of keratinocytes and fibroblasts combined with collagen, although

What's already known about this topic?
- 3D bioprinting of skin is a very novel field, with fewer than 10 original articles published on the topic.
- There are few reviews on this and none apply a clinical perspective.

What does this study add?
- First review on topic that applies research to a clinical setting and summarises the cell types, bioprinters and scaffolds that have been used in this field to date.
- Introduces potential dermatological and reconstructive clinical applications.
- Assesses current limitations and potential future avenues for research.

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https://doi.org/10.1016/j.bjps.2017.12.006

stem cells are gaining increasing recognition. Laser assisted deposition was the most common printing modality, although ink-jet and pneumatic extrusion have also been tested. Bioprinted skin promoted accelerated wound healing, was able to mimic stratified epidermis but not the thick, elastic, vascular dermis.

Conclusions: Although 3D bioprinting shows promise in engineering skin, evidenced by large collective investments from the cosmetic industry, the research is still in its infancy. The resolution, vascularity, optimal cell and scaffold combinations and cost of bioprinted skin are hurdles that need to be overcome before the clinical applicability can be realised. Small scale 3D skin tissue models for cosmetics, drug and toxicity testing as well as tumour modelling are likely to be translated first before we see this technology used in reconstructive surgery patients.

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Introduction

The skin plays a crucial role in protecting the body from the external environment. The structure, comprising of the epidermis, dermis and subcutis is integral to its function – physical barrier for protection, thermoregulation, sensation, homeostasis and immunity. The importance of these functions becomes evident by the physiological disturbances that occur in patients who have toxic epidermal necrolysis (TEN), large chronic ulcers or acute wounds and burns. Any attempt to replace full or partial thickness skin defects needs to accurately recreate skin architecture to reproduce these functions.

Skin replacement has been a long sought goal for modern medicine; from Jacques-Louis Reverdin's[1] pioneering work in 1870 using "fresh skin" allografts, to the biologic materials currently in use in modern operating theatres (Figure 1). Since their inception in 1874, autologous split thickness skin grafts have been unable to restore the full function of skin and to overcome donor site morbidity biological skin substitutes have been developed.[11] Biocomposite dressings have been shown to improve wound healing in partial thickness wounds and their success has made them the most commonly used option for large superficial burns or TEN.[12] For full thickness skin loss, contemporary biological skin substitutes are most commonly based on collagen scaffolds, allowing autologous cell infiltration and the stimulation of further tissue regeneration e.g. Integra.[13] Inert acellular matrices, such Alloderm,[14] as well as cellular matrices with integrated fibroblast and keratinocyte components, such as Apligraf[15] (Figure 1), are also used.

Evolution of biological skin replacement

Contemporary skin tissue engineering involves using keratinocytes, isolated from partial or full-thickness skin by enzymatic digestion, seeded onto bioactive scaffolds.[14,16–18] These porous synthetic or biological scaffolds, allow adequate nutrition via perfusion and promote cellular proliferation and differentiation to produce a tissue that mimics the structural and biological features of skin. The incorporation of a dermal layer or biomimetic scaffold improves the elasticity and structural support for lymphatics, vasculature and nerves and thereby the functionality of skin.[19–21]

Survival of the epidermal component is the main limiting factor of biological skin replacements[22] due to greater diffusion distance between the wound bed and autograft.[14] To overcome this, dermal scaffolds have been seeded with mesenchymal stem cells and growth factors to enhance the vascular supply through angiogenesis. External influences such as topical intermittent negative pressure therapy, can also promote endothelial cell migration and hence vascularisation,[23,24] thereby encouraging dermal regeneration and lowering the risk of infection through increased oxygen and nutrient delivery.[25]

Despite the number of research studies on skin regeneration there are currently no commercially available composite grafts consisting the dermis and epidermis in one grafting stage[26] (Figure 1). This is likely attributed to the fact that the multi-stratified anisotropic structure of the epidermis,[27] containing keratinocytes (at varying differentiation stages), melanocytes and Merkel cells, on top of the thick but elastic vascular dermis, containing nerve endings, sebaceous glands