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Review article

Skin regeneration in three dimensions, current status, challenges and opportunities

Ahmed T. El-Serafi[a,e,*], Ibrahim T. El-Serafi[b,d], Moustafa Elmasry[c,d], Ingrid steinvall[d], Folke Sjöberg[d]

[a] Sharjah Institute for Medical Research and College of Medicine, University of Sharjah, M27-138, P.O. Box 27272, Sharjah, UAE
[b] Division of Experimental Cancer Medicine, Department of Laboratory Medicine, Karolinska Institutet, Sweden and Faculty of Medicine, Port-Said University, Egypt
[c] Plastic Surgery Unit, Surgery Department, Suez Canal University, Egypt
[d] The Burns Centre, Department of Hand Surgery and Plastic Surgery and Burns, Department of Clinical and Experimental Medicine, Linköping University, Sweden
[e] Faculty of Medicine, Suez Canal University, Egypt

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ABSTRACT

Skin regeneration is a life-saving need for many patients, whom list is stretched from burn victims to motor-car accidents. Spraying cells, either keratinocytes or stem cells, were associated with variable results and, in many cases, unfavorable outcomes. As the spatial configuration of the skin is distinctive, many trials investigated the bio-printing or the construction of three dimensional skin models where different layers of the skin were preserved. Although some of these models showed the histological configuration of the skin, their acceptance by the wound was questionable as a consequence of delayed vascularization. In this mini-review, different models for three dimensional regeneration of the skin will be discussed with their main points of strength and challenges as well as their possible opportunities.

1. Introduction

Skin is the largest organ in the human body, which protects all other tissues from the environmental challenges, infections and mechanical stresses. Loss of the skin is associated with the exposure of the underlying tissues to different invaders, such as bacteria, viruses and fungi. The severity of infection is – at least- partially correlated to the depth and surface area of the wound. These invaders will find the ragged edges of the wound as an excellent attachment site, while the blood or serous fluid as a rich nutritious material. Even the normal skin flora can acquire pathological characteristics upon the break of this natural barrier, which is an important reason beyond the mortality associated with skin loss (Church et al., 2006).

In addition, toxemia and septicemia can be the consequence of infection in longstanding diabetic or venous ulcer. Loss of large areas of the skin can be associated with hypothermia as the thermal insulator is defective. The available treatment for this kind of injuries nowadays is skin grafting, however their long-term functional outcome are suboptimal. The urge of immediate protection opened the field for the production of a wide variety of artificial substitutes, which are summarized by Jean et al. (2011). With such background, the existence of many programs for skin regeneration is not surprising. The relative simplicity of the structure of the skin was misleading for tissue engineering programs. The three-dimensional (3D) structure of the multilayers was difficult to achieve even with the use of dermal scaffolds. It is not only the topography, but also the structure of the skin layers which would determine if the regenerated tissue can be considered as skin and used for regenerative purposes. Furthermore, the skin contains many derivative structures, such as the sweat and sebaceous glands and hair follicle and accommodates nerve endings and blood capillaries. Such conformation needs a stringent signaling cascade. Disruption of the latter would lead to the loss of the skin architecture, which is the case during scar formation (Gibran et al., 2007).

The next challenge for the cell based therapy, either stem or differentiated cells, would be the delivery method. Local application, spraying, injection in the wound bare area, edge or underlying muscles as well as systemic administration were tried with inconsistent results regarding the cells survival and engraftment. The formation of three dimensional construct is the most likely method to protect the cells, prevent the single cells from physical stresses and can generate a graft that can cover a wider spaced wound (reviewed in Duscher et al., 2016). In this minireview, we aim to reassess the current situation of three-dimensional regeneration of the skin.

* Corresponding author at: Sharjah Institute for Medical Research and College of Medicine, University of Sharjah, College of Medicine, University of Sharjah, M27-138, P.O. Box 27272, Sharjah, UAE.
E-mail address: aelserafy@sharjah.ac.ae (A.T. El-Serafi).

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2. Historical perspective

The importance of the 3D configuration of the skin, especially for clinical application, was the cornerstone beyond the studies by Howard Green and co-authors in the seventies (Green et al., 1979; Rheinwald and Green, 1975a, 1975b). The authors reported that the colonies made up of keratinocytes would differentiate into multilayers of epithelial cells that resembled the epidermis and they pointed at the possibility of isolating the patient's cells and cultivate them *in vitro* to create skin grafts.

Bell et al. in 1981 took a further step when the authors isolated skin fibroblasts as a biopsy, mixed with collagen lattice and covered with keratinocytes. The graft was implanted in a skin wound and followed up. While the grafts were hairless and thinner than natural skin, some of them contracted and 20% were dislodged with signs of inflammation (Bell et al., 1981).

In 1983, Mackenzie and Fusenig reported that the epithelial-mesenchymal contact and communication was crucial for the organization of the skin in the lab (Mackenzie and Fusenig, 1983). The authors split adult murine skin into epithelial layer and connective tissue and tried different combinations of cells and/or layers from both sources. The 3D architecture of the skin could only be restored when epithelial layer was in direct contact with the connective tissue. Furthermore, the communication between the two layers were essential for the maturation of the skin and the maintenance of the 3D conformation.

3. Why do we need skin tissue engineering programs?

Beside the academic interest of understanding the skin development, the presence of an *in vitro* human model of skin is important for drug and cosmetics testing in the lab. The current direction is to reduce the number of animals in testing, refine their use and find a replacement, which is the 3Rs principal (Liebsch et al., 2011). In addition, there are differences in the effect of various compounds between animals and humans. All these factors direct the current trend towards the synthesis of human cells based tissue/organ models (El-Serafi et al., 2011). For the skin, there is at least a success story for the use of a similar model in testing of cosmetics (Netzlaff et al., 2005).

The cornerstone in the medical field will always be the patient service. There are a wide variety of patients who are desperate for bioengineered skin. The list includes a) burns and explosive victims, whom could lose their lives due to wound infection in the absence of the first line of defense in the body; *i.e.* the skin. b) Patients with scars which can provide serious challenges ranging from disfigurement in exposed areas, such as the face and neck, to limitation of movement and disabilities when the scar crosses over a joint and for all cases, psychosocial impact can be serious. While excision of the scar is possible, the replacement of the lost skin is not usually easy and can be associated with comorbidities and the creation of a secondary wound site. c) Chronic ulcers results as a complication of diabetes or as a consequence of venous insufficiency, which are difficult to heal and can have serious consequences.

Wood (2014) have suggested criteria for the feasibility of any transferable technology for skin regeneration into clinical application. The criteria started with the safety of the procedure, including the selection of the cells and the biomaterials, to reach at the superior outcome quality at affordable costs for the health care system.

4. Different approaches for skin engineering

4.1. Bioprinting

The most recent approach to apply Wood's criteria is the three dimensional bioprinting. This technique customized the combination of the cells with the extracellular proteins which would act as an *in situ*, patient-tailored scaffold. The printed construct showed different characteristics than natural skin when cultured *in vitro* (Lee et al., 2014). Another interesting approach is printing the skin using keratinocytes and fibroblasts, while the binding matrix consisted of collagen, fibrinogen and thrombin. This model resembles the fibrin glue used in earlier studies as a fixative for skin grafts. Based on Green's method, Ronfard et al. (1991) isolated and expanded patients' keratinocytes and used the fibrin glue as a fixative for the cells to cover burn wounds with complete closure and integration with the skin after a year of treatment (Ronfard et al., 1991). In experimental animals, the 'printout' skin was accepted by the animal body and associated with wound closure (Singh et al., 2016). One of the main challenges hindering skin bioprinting is the technical difficulties associated with the nozzle blockage and shearing stresses on the cells. Currently, printing of large areas of the skin is not yet possible. The absence of immediate blood supply as well as the immune rejection are the two main reasons for the failure of the integration of bioengineered skin of allogenic origin (Bi and Jin, 2013; Yoo, 2015). Also, multiscale printing, such as a vascular tree, is another challenge (Ozbolat and Yu, 2013). The emerging technical advances in the bioprinting process is expected to provide solutions for most of the current problems in the near future (Gudapati et al., 2016).

On the other hand, bioprinting may provide an important advantages, in terms of supporting the skin appendages. One of the most important challenges for skin regeneration is the absence of hair, sweat and sebaceous glands as well as the discolouration of the engineered skin. Melanocytes and stem cells can be incorporated within the printed cells for de novo synthesis of the appendages, including hair follicle development with normal cycle and colour of the hair and the skin. Alternatively, intracutaneous hair transplantation could be a following step for the printing (Velasquillo et al., 2013). Sweat glands are another important appendages which keep the skin moist and regulate the body temperature. Liu et al. (2016) concentrated on printing 3D matrix with specific pore size and geometry that would drive the epidermal progenitors differentiation into sweat gland-like structure. Unfortunately, such arrangement was lost when the 3D architecture support was removed. Although many scientists believe that bioprinting can be the future of reconstructive surgery, research is still needed to overcome the previously mentioned obstacles (Sigaux et al., 2017).

4.2. Cells on scaffolds

Apart from bioprinting, it is much easier to print a scaffold that can be seeded by cells later. The scaffold must allow the adherence, migration and differentiation of the cells. Collagen has been used as a natural scaffold that combined the physiological characteristics of skin matrix with appropriate pore size. Lee et al., in 2009, used a robotic arm to print 10 layers of mouse tail derived collagen, with fibroblasts and keratinocytes embedded in layers 2 and 8. The author developed the crosslinking between the multilayers and showed that their technology was able to fill skin defect model *in vitro*. The histological studies showed preliminary evidence for the presence of dermal and epidermal markers (Lee et al., 2009). Unfortunately, the collagen scaffold could be associated with mechanical problem and rapid degradability. Artificial polymers, such as polylactic acid, polyglycolic acid and polylactic glycolic acid provided an artificial alternative which have flexible mechanical properties and require intensive studies before being used in clinical application (Bi and Jin, 2013). By electrospinning, different polymers can be sprayed at the nano-diameter scale, which allow the control of the shape, surface and pore size as well as the penetration of newly formed blood capillaries (Sundaramurthi et al., 2014).

Scaffolds can be used to provide a three dimensional environment, in which the cells can attach, migrate and differentiate along the designated axes in the scaffold. In an interesting approach, the nanofibers of silk were combined with decellularized human amniotic membrane and used as a scaffold. Skin regeneration was more effective

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