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Review

Tissue engineering of skin

Sophie Böttcher-Haberzeth [a,b], Thomas Biedermann [a], Ernst Reichmann [a,*]

[a] Tissue Biology Research Unit, Department of Surgery, University Children's Hospital Zurich, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland

[b] Pediatric Burn Center, Plastic and Reconstructive Surgery, Department of Surgery, University Children's Hospital Zurich, Steinwiesstrasse 75, CH-8032 Zurich, Switzerland

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ABSTRACT

The engineering of skin substitutes and their application on human patients has become a reality. However, cell biologists, biochemists, technical engineers, and surgeons are still struggling with the generation of complex skin substitutes that can readily be transplanted in large quantities, possibly in only one surgical intervention and without significant scarring. Constructing a dermo-epidermal substitute that rapidly vascularizes, optimally supports a stratifying epidermal graft on a biodegradable matrix, and that can be conveniently handled by the surgeon, is now the ambitious goal. After all, this goal has to be reached coping with strict safety requirements and the harsh rules of the economic market.

Contents

1. Introduction

Large full-thickness skin defects resulting from burns, soft tissue trauma, congenital giant nevi, and disease leading to skin necrosis [1–8], represent a significant clinical problem that is far from being solved. The main challenges encountered are the following two.

First, there is donor site shortage for autologous skin transplantation when the defect exceeds 50–60% of the total body surface area (TBSA) [9]. The typical clinical example is a massive deep burn.

Second, most conventional skin grafting techniques to provide autologous defect coverage are based on transplanting split-thickness skin (the today's gold standard).

* *Corresponding author*. Tel.:+41 44 266 7493; fax: +41 44 266 7170.
E-mail address: ernst.reichmann@kispi.uzh.ch (E. Reichmann).
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Split-thickness skin contains all of the epidermis but only part of the dermis, and that frequently leads to scarring. Rarely, scarring is mild and irrelevant. Often, particularly in children, there is hypertrophic scarring or keloid formation that is frequently disabling and disfiguring [10,11]. Interestingly, full-thickness skin transplantation is not usually associated with scarring, however autologous full-thickness skin transfer can only be performed for injured areas <2% TBSA.

Theoretically, both main problems, donor site shortage and scarring, could be reduced if not eliminated if it were possible to grow an autologous full-thickness skin analogue with near normal anatomical and functional properties: a cultured dermo-epidermal skin substitute.

There are still some major challenges concerning the development of such a skin substitute:

1) A dermo-epidermal substitute should exhibit a barrier function immediately or rapidly after transplantation. A central question that remains is what minimum level of differentiation (and barrier function) has to be achieved in a skin substitute during its growth in vitro to result in an optimal structure and function after its transplantation onto the patient.
2) On its way to an optimized and long lasting structure and function, a dermo-epidermal substitute should be efficiently and appropriately vascularized. Attempts to reach this goal have entered a period of significant progress; however, a final breakthrough is still missing.
3) Much is still unknown about the mechanisms by which tissues form and heal, yet insights from developmental biology and other biological disciplines are already guiding the development of ''intelligent materials'' that work with nature's own mechanisms of organogenesis and repair. Biologically active and appropriate matrices and factors in combination with automated (tissue printing) techniques [12], designed to produce a new generation of complex skin substitutes both, in a desired number and with a constant quality, are now the guidelines of modern ''skingineering''.

This article summarizes the progress in the field, reviews some critical aspects of the underlying cell and skin biology, and points out some remaining challenges, key clinical landmarks, commercial considerations and future directions that may foster the progress in the engineering of skin.

2. Principles of skin reconstitution and scarring

Skin is an efficient barrier against external influences such as mechanical disturbances, UV radiation, pathogenic microbial agents; it prevents the substantial loss of body fluid and plays a significant role in thermoregulation and immune defence. Different cell types, such as keratinocytes, melanocytes, fibroblasts and endothelial cells, constituting the epidermis, the dermis and the subcutis, are necessary to guarantee its full function (Fig. 1).

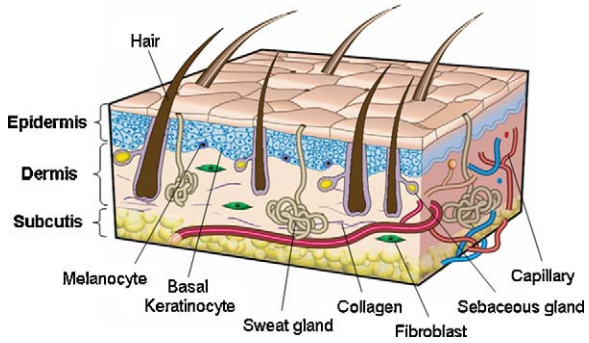

Fig. 1 – The structure of human skin. Human skin consists of three layers. The outermost layer, the *epidermis*, measures about 0.1–0.2 mm. Keratinocytes and melanocytes are prominent cell types of the epidermis. The basement membrane physically separates the epidermis from the underlying *dermis*, however, functionally it connects both tissues. The major cellular components of the dermis are fibroblasts producing extracellular matrix. The rich dermal vascular system provides all cell types with nutrients. Skin appendages like hair follicles, sebaceous and sweat glands are situated throughout the dermis and epidermis. The *subcutis* (*hypodermis*) consists mainly of fat tissue, which functions as insulation and as an energy source [16].

If this barrier is destroyed, different measures need to be taken, depending on the depth of the skin defect. Injuries involving the epidermis alone, and injuries extending into the superficial layer of the dermis, will re-develop an epidermis without surgical intervention, provided there is a sufficient number of keratinocyte stem cells present in the remaining epidermis or in the residual dermis. If epidermal keratinocytes are missing, regeneration may be achieved by epithelial stem cells derived from hair follicles and/or sweat glands.

Patients with defects extending into the deeper dermis or even the hypodermis need a more complex treatment, as the injured surface is depleted of its keratinocyte stem cells. In this case the ''gold standard'' approach is to apply split-thickness skin grafts that contain all the epidermis and marginal parts of the dermis, thereby transferring self-renewing keratinocyte stem cells to the affected area. With full-thickness skin lesions, involvement of surgical excision with closure of the wound is almost always mandatory and scarring a fact [13].

Hence, next to the availability of stem cells, scarring is another crucial hallmark of skin reconstitution. Because scar formation is unique to humans in most aspects, animal model research is only of limited value and has not contributed much to our understanding and the treatment of scars. To mend the damage, the body has to produce new collagen fibers. However, because the body cannot re-build the tissue exactly as it was, the new (scar) tissue will have a distinct collagen pattern and a different skin texture (and quality) than the surrounding normal skin.

The main feature of the phenomenon ''scarring'' is called ''wound contraction''. Wound contraction is caused, at least in

part, by the presence of myofibroblasts which develop characteristics of smooth muscle cells under the influence of TGFβs [14]. In contrast to embryonic wound healing [15,16], which still occurs without scarring, wound contraction is the general mode of wound healing in humans after birth [17,16].

Taken together it can be said that successful reconstitution of skin with skin substitutes depends crucially on two factors: the presence of self-renewing keratinocyte stem cells for re-epithelialization, and a functional dermal substitute consisting of the appropriate cellular and acellular components, that allow no or only limited scarring of the developing skin.

3. Key events in the development of skin substitutes

The first milestones in skin research and skin tissue engineering were the enzymatic separation of the epidermis and dermis [18] and the in vitro culture of keratinocytes [19].

A major breakthrough was made in 1975, when Rheinwald and Green managed to grow human primary epidermal cells in serial culture on a layer of lethally irradiated 3T3 murine fibroblasts (Fig. 2). These researchers showed that limitations observed previously in the cultivation of epidermal cells in surface cultures were not intrinsic, but due to the complex relationship between keratinocytes and fibroblasts [20]. Taking advantage of the 3T3 cell-feeder layer technique, an epidermal graft could be expanded to more than 500 times its size within 3–4 weeks [21]. After the first clinical application [22], cultured epidermal autografts (CEAs) were tested in almost all leading burn centers world wide [23–30]. However, there were disadvantages that included a widely variable CEA take, depending on the wound site and status, age of the patient, and knowledge and experience of the operator [26,31].

In 1981 Bell et al. [32] generated a dermo-epidermal substitute which was tested in an animal model. Subsequently this technique was transformed into the product Apligraf®, which was prepared using human allogeneic fibroblasts and keratinocytes (see also Table 1). On the basis of this development also dermo-epidermal skin substitutes consisting of human autologous keratinocytes and fibroblasts in bovine collagen were applied in severe burn patients [33].

Interestingly, because of the effort to establish dermo-epidermal skin grafts, researchers revealed the importance of epithelial–mesenchymal interactions. They observed that the cross-talk between fibroblasts and keratinocytes was essential for the establishment of a functional basement membrane [34,35].

A further significant progress was the development of a bilayered ''artificial skin'' [36]. This acellular collagen-glycosaminoglycan-based skin substitute is now commercially available as Integra Artificial Skin® (commonly referred to as Integra). Integra® was developed in the 1980s and commercially launched in the United States in 1996. The appealing idea of combining cultured keratinocytes with Integra® has generated a fascinating new field of research and much optimism to finally provide patients with a dermis off the shelf and a laboratory grown epidermis, thus eliminating the need for donor sites. However, reality has shown that simple cultured epidermal autografts do not take well on the neodermis produced by Integra® [37,38].

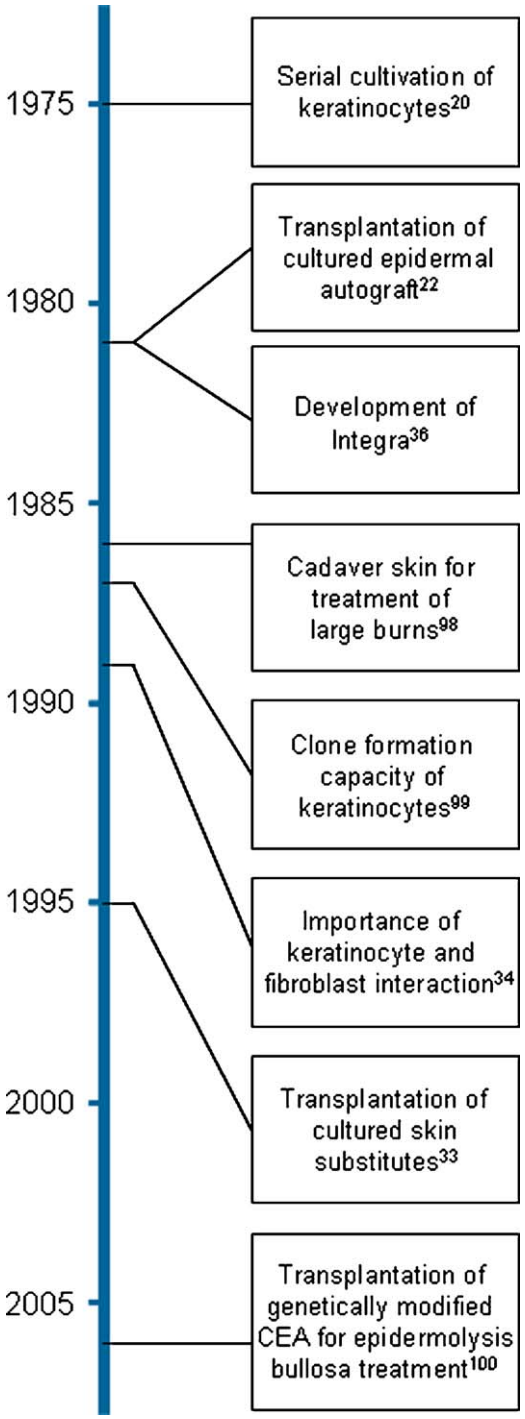

Fig. 2 – Timeline of key developments [100–102].

The invention of Integra Artificial Skin was certainly a major step in tissue engineering of skin. However, the time has come to explore new avenues for the development of a single step clinical application of novel dermo-epidermal skin substitutes. This not only because of increasing hospitalization costs (increasing health insurance costs, budget restrictions) but also, and predominantly, to optimize clinical skin substitution with superior functional and cosmetic results.

Table 1 – Examples of commercially available skin substitutes.

	Commercial product	Company	Layers	References
Cellular epidermal replacement	Epicel®	Genzyme Corp.	Cultured epidermal autograft (autologous keratinocytes grown in the presence of murine fibroblasts)	[26,103]
	Epidex™	Euroderm GmbH	Cultured epidermal autograft (autologous outer root sheet hair follicle cells)	[104–106]
	Myskin™	Celltran Ltd.	Cultured epidermal autograft (autologous keratinocytes grown in the presence of irradiated murine fibroblasts)	[107–109]
	ReCell®	Clinical Cell Culture (C3), Ltd.	Autologous epidermal cell suspension	[55,110,111]
Engineered dermal substitute	AlloDerm®	LifeCell Corp.	Acellular donated allograft human dermis	[112–115]
	Dermagraft®	Advanced BioHealing Inc.	Bioabsorbable polyglactin mesh scaffold seeded with human allogeneic neonatal fibroblasts	[67,68,116]
	Integra®	Integra LifeSciences Corp.	Thin polysiloxane (silicone) layer; cross-linked bovine tendon collagen type I and shark glycosaminoglycan (chondroitin-6-sulfate)	[8,62,65]
	Matriderm®	Dr. Suwelack Skin & Health Care AG	Bovine dermal collagen type I, III, V and elastin	[63,73,117]
Engineered dermo-epidermal substitutes	Apligraf®	Organogenesis Inc.	Human allogeneic neonatal keratinocytes; bovine collagen type I containing human allogeneic neonatal fibroblasts	[74–76,118]
	OrCel®	Forticell Bioscience, Inc.	Human allogeneic neonatal keratinocytes on gel-coated non-porous side of sponge; bovine collagen sponge containing human allogeneic neonatal fibroblasts	[119–122]

4. Improved engineered skin substitutes for clinical applications

Two main groups of patients would profit most from a tissue-engineered skin substitute. The first group includes burn patients, suffering from an acute life-threatening situation (Fig. 3A). Large and deep burn wounds leave little remaining healthy skin to be used for split-thickness skin grafts. The challenge here is to rapidly produce large quantities of autologous, dermo-epidermal substitutes.

The second group denotes the elective or chronic situation. Disabling scars, giant nevi (Fig. 3B) or chronic ulcers are ideally replaced by a skin graft of matching size, texture, and colour. Full- and split-thickness skin grafts may not always be available in a sufficient quantity. The challenge in this respect is the engineering of functionally and cosmetically adjusted skin substitutes, ready for transplantation at a previously scheduled point in time.

There exist several ''commercial'' treatment modalities next to skin grafting. These may or may not help to improve the structure and function of the grafted skin, such as some dermal substitutes or keratinocyte sprays. In any case, various basic problems are still encountered.

For a given skin substitute to attach promptly after transplantation, a well prepared and vascularized wound bed is required. This is not always easy to achieve in deep burn wounds or with chronic wounds. If a dermal substitute reaches a threshold thickness [39], vascularization is too slow to assure nutrition of the overlying epidermis resulting in epidermal necrosis or graft loss. Therefore, most dermal substitutes thicker than 1 mm (Integra®, Matriderm®) are applied using a two-step approach. This avoids epidermal necrosis, as the dermal substitute is given sufficient time to vascularize. However, an additional operation is needed for transplantation of an epidermal component. This procedure is lengthy, gives no guarantee of success and is an additional stress factor for the patient. The transplanted epidermal component produces skin of varying quality and exhibits properties that are distinct from the original. Features of the transplant may be missing elasticity, contraction of the graft, lack of pigmentation, and thereby lack of protection against UV radiation. All these factors let us conclude that there is still

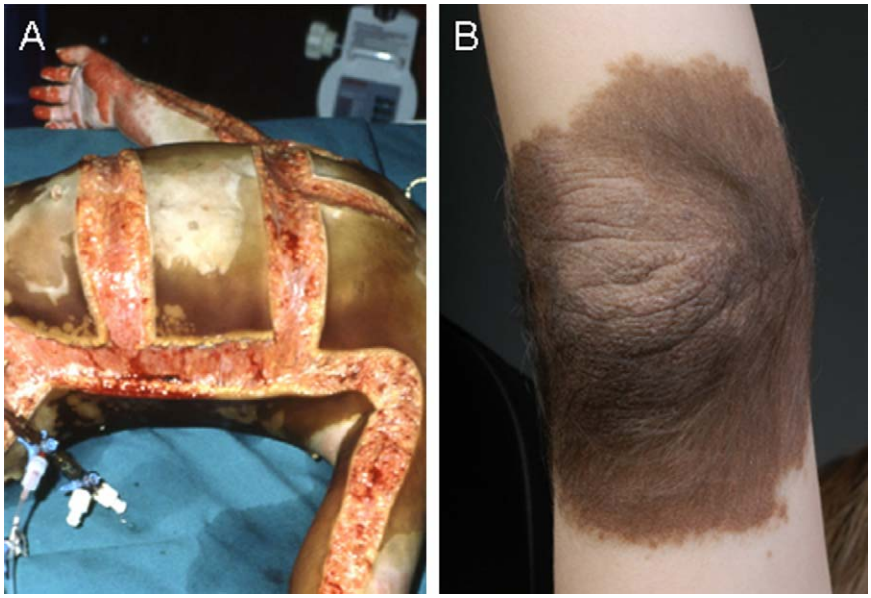

Fig. 3 – The need of tissue-engineered skin. (A) The acute situation. Patient, suffering from large and deep burn injury after escharatomy, necessitating necrectomy and skin coverage. Due to the large total body surface area affected, little healthy skin remains as donor site for a split-thickness skin graft. (B) The elective situation. Patient with a giant congenital melanocytic nevus, expanding over the elbow. After resection, the patient would benefit of the application of a tissue-engineered skin substitute of matching colour and texture to the adjacent skin.

a high potential for the development of novel, significantly improved skin substitutes.

5. Tissue homeostasis, keratinocyte stem cells, and rapid vascularization as indicators of skin quality

To reconstruct skin in the laboratory, a skin biopsy from the patient is required to isolate the different cell types (Fig. 4). Mainly, keratinocytes, melanocytes, dermal fibroblasts and vascular endothelial cells can be obtained. Each cell type is expanded in its appropriate culture medium, in close contact with appropriate extracellular matrix components, and if required in the presence of supportive (mesenchymal) cells. As a result a complex skin substitute may develop. However, the quality of such a skin graft is frequently not determined prior to transplantation. How can the quality of a given engineered skin substitute be monitored? To date only a very limited number of indicators or markers has proven useful in this respect. Cytokeratin 19 (K19) expressed in basal keratinocytes (Fig. 5A) has recently been described as a marker for epidermal homeostasis, and as an indicator of young, possibly laterally expanding skin [40]. Furthermore, K19 is expressed in the stratum basale of engineered skin substitutes, indicating a potentially thriving and functional epidermis that is very likely to be taken after its transplantation. However, as K19-positive keratinocytes are frequently described as keratinocyte stem cells [41,40] and as they are no longer detectable in human individuals older than 2 years, it remains to be determined whether K19-positive basal keratinocytes are a subtype of keratinocyte stem cells, exclusively expressed in very young skin. Other keratinocyte stem cell markers may be the integrin α6 chain (highly expressed) in combination with the transferrin receptor, CD71 (low expression) [42,43]. The problem with any of these markers is that their usefulness has to be confirmed by a reliable bioassay. The only reliable bioassay, however, appears to us is the formation of a stratified epidermis that remains fully functional for at least 12 weeks after transplantation.

An additional criterion significantly influencing the quality of a given skin substitute is its rapid and appropriate vascularization after transplantation. The thickness of a (non-pre-vascularized) skin graft that can easily become vascularized is about 0.7–1.0 mm. In grafts thicker than 1.0 mm, new blood vessels cannot grow quickly enough to nourish the overlaying epidermal layer [44]. Vascularization is particularly problematic if the respective skin substitute is based on a dense or highly cross-linked extracellular matrix, or if it is placed over fatty tissue or poorly vascularized wound beds. One promising line of research investigates the pre-vascularization of engineered tissues in vitro [44–49].

In this context adult human dermal microvascular endothelial cells (HuMECs) are submerged within fibrin or collagen hydrogels in which they develop into true 3D capillaries (Fig. 5B) displaying a real lumen (Fig. 5C) [50]. Subsequently these pre-vascularized substitutes are transplanted to have the engineered capillaries stabilized by mural cells (pericytes, smooth muscle cells) derived from the wound bed. Finally the engineered capillaries are thought to connect to the microvessels of the wound ground (inosculation). So far only very few laboratories managed to convincingly show the proof of this principle.

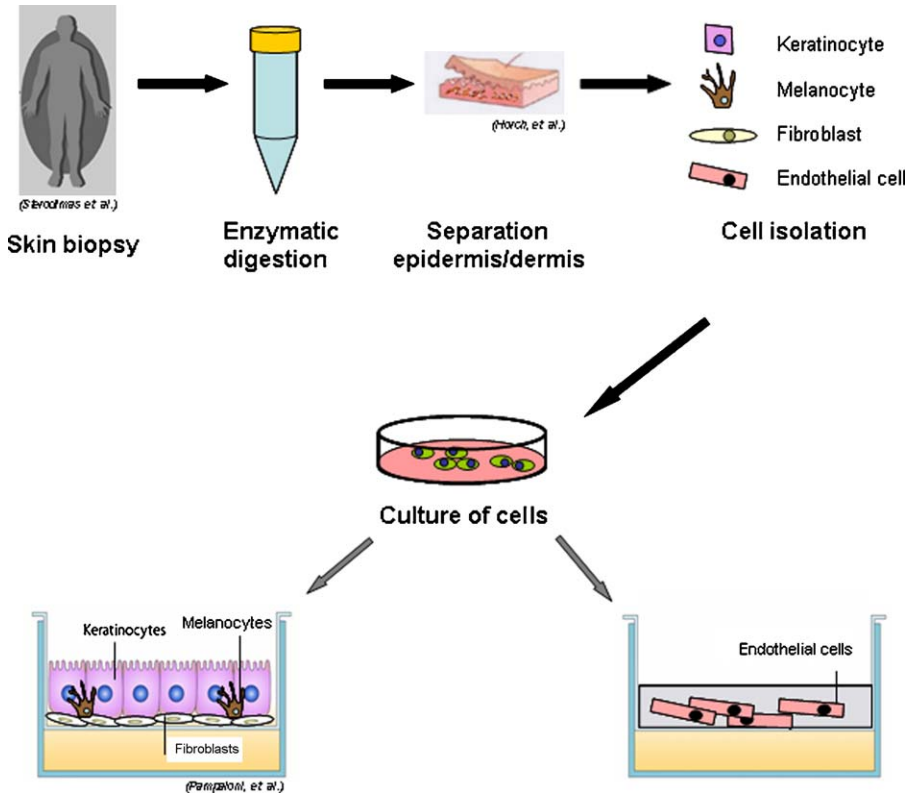

Fig. 4 – Tissue engineering of the skin. Reconstruction of tissue-engineered skin. A patient's skin biopsy is treated enzymatically to digest the basement membrane. Epidermis and dermis are separated, followed by isolation of epidermal keratinocytes and melanocytes, dermal fibroblasts and vascular endothelial cells. The cells are cultured in culture dishes in the appropriate medium for each cell type. Dermo-epidermal substitutes, consisting of fibroblasts in a collagen hydrogel and keratinocytes/melanocytes seeded on top of the hydrogel. Cultured vascular endothelial cells are seeded in hydrogels to form a network of lumenized capillaries [50,54,123,124].

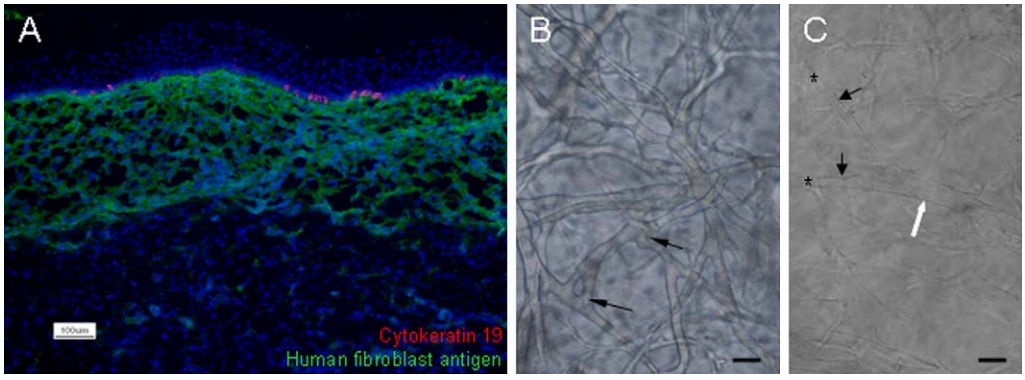

Fig. 5 – Epidermal homeostasis in transplanted dermo-epidermal substitutes and pre-vascularized hydrogels. (A) Cytokeratin 19-positive (K-19) human keratinocytes are indicative of an intact epidermal homeostasis in a grafted dermo-epidermal skin substitute. The dermo-epidermal skin substitute consisting of human keratinocytes as epidermal equivalent and a collagen type-I hydrogel containing human dermal fibroblasts was transplanted onto the back of immuno-incompetent rats. Cytokeratin 19-positive cells (red) are organized in clusters. Note that Cytokeratin 19-positive cells are restricted to the well-defined stratum basale. Human dermal fibroblasts (green) are recognized by the human CD90 (Thy-1)-specific antibody, whereas the rat tissue underneath stains negatively (cell nuclei: blue) [40]. (B and C) Phase contrast micrograph of capillary formation *in vitro*. Human microvascular endothelial cells (HuMECs) were isolated from a skin biopsy, cultured and seeded in a hydrogel. (B) HuMECs develop into dense networks of branching solid cords after 1 week. Anastomoses are indicated by black arrows. (C) Branching, completely lumenized capillaries developing in hydrogels (white arrow). Regularly alternating nuclei (black arrows) and the cytoplasm are retracted towards the plasma membrane. The two branches of a capillary are indicated by asterisks [50]. Scale bars: (A) 100 μm; (B and C) 50 μm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

6. What has been achieved so far: currently available skin replacements

Several commercial products were developed during the last 30 years. Most of them were designed for permanent use, some of them as temporary substitutes. They contain cells of differing origin (autologous, allogenic or xenogeneic) and biodegradable materials (naturally occurring or synthetic polymers) as scaffolds for cell attachment and facilitated handling. To give an overview, we have classified them into epidermal, dermal and dermo-epidermal substitutes (Table 1).

Epidermal substitutes contain autologous keratinocytes, often grown in the presence of murine fibroblasts. Most products belong to the category of ''cultured epidermal autografts'', also called CEAs (Epicel®, Epidex™, Myskin™), for which keratinocytes are grown to stratified cell sheets. Starting off from a skin biopsy, the production of the final substitute takes about 3 weeks [51,52]. This is why burn wounds initially need to be treated with temporary wound dressings. Once applied to the pre-treated dermal wound bed, CEAs can be applied directly or in combination with other methods (e.g. the sandwich technique). Several studies and multi-centre trials over the past years [52,53] show a wide range of take rates with an average value of 50% or less [54] and statements about qualitative outcomes are inconclusive due to the diversity of application methods. Disadvantages are mainly their slow preparation time, variable engraftment rates, difficult handling due to the thin, fragile cellular layers and their high production costs [30].

Another approach for epidermal cellular replacement is the use of cultured autologous keratinocytes in suspension (ReCell®) [55–57]. With this method, keratinocytes can be sprayed onto the wound bed directly after having been prepared from a biopsy in the operation room. Although this method has shown a somewhat faster epithelialization and epidermal maturation in wound models [58], this method is not suited to treat 3rd degree burn wounds. The quality and patient's benefit of this method in clinical settings is still debated.

As with these methods a dermal component is missing, the degree of epidermal attachment and scarring is highly dependant on the quality and condition of the underlying dermal wound bed [39]. The additional unsatisfying results in regard to mechanical stability and scarring led to another approach in skin substitute development.

Engineered *dermal* substitutes restore dermal tissue by promoting new tissue growth and optimising healing conditions [59]. They need to be covered by a permanent epidermal surface or substitute. Some of them consist of acellular matrices and are permanently incorporated into the patient's wound bed (AlloDerm®, Integra®, Matriderm®) [60–65]. After application to a prepared dermis, these substitutes are colonized and vascularized by the underlying cells [66]. Finally an autologous neodermis is formed. As soon as vascularization has advanced sufficiently (usually 3–4 weeks after application), a split-thickness skin graft can be placed on the neodermis [67]. Others include human allogeneic cells and are applied as transient wound dressings that stimulate wound healing (Dermagraft®). Dermagraft® consists of allogeneic fibroblasts seeded in a polyglactin mesh [68]. They secrete growth factors and deposit dermal matrix proteins and are thought to facilitate the healing process [59,67,69]. Histologic evaluation of biopsies did not show any evidence of immunologic response [70], however, the product is mostly used for chronic venous or diabetic foot ulcers [69].

The application of dermal substitutes using the two-step surgical procedure has shown improved scarring [62], but more recent approaches are utilizing thinner dermal layers, with the aim of transplanting the dermal substitute together with the epidermal graft in a single step [56,63,64,71,72]. Clinical studies have so far shown promising results with a thin (1 mm) dermal matrix (Matriderm®) limited to the hand and wrist region. Further clinical applications and studies will show if this method can be applied more broadly.

Few engineered, ''off-the-shelf'' *dermo-epidermal* substitutes have been produced. Human allogeneic neonatal keratinocytes and fibroblasts are combined with a scaffold to form a temporary covering (Apligraf®, Orcel®) and are used mostly for chronic wounds [39,59,66,69]. Studies have mostly reported about its use for chronic wounds and ulcers and have shown a higher incidence of wound closure [74,75]. One study reports improved clinical outcome [76] for burn patients. For autologous cultured dermo-epidermal substitutes [59], keratinocytes and fibroblasts are collected from a burned patient's biopsy and added to a collagen-glycosaminoglycan substrate [77]. Cultivation time after biopsy needs about 4 weeks before the substitute can be transplanted. Few clinical trials have been conducted so far. In terms of graft take and scar appearance, results appear superior to conventional techniques [59], but further clinical studies need to confirm these results.

7. Commercial considerations

Tissue engineering of skin was thought to have such obvious clinical benefits that it led to unrealistic clinical and commercial expectations. The initial objective with the aim to rapidly come up with perfect skin grafts for patient treatment soon turned out to be unrealistic. Delivering a customized product shows a high complexity from its fabrication with autologous cells until delivery at its destination. In addition to slow progress for graft development, even slower progress for administrative demands like quality and safety controls and regulations (GMP production, FDA approval, microbiologic and immunologic safety required) might lead to a delayed market launch. Needless to say that a relatively small number of customized products, with already high production costs, raises costs even more and reduces the chance for health care institutions to approve of upcoming costs. All in all, development and production of tissue-engineered skin substitutes seems unattractive so that companies deviate towards more broadly applicable products, such as acellular materials or temporary dressings, which can be sold as ''off-the-shelf'' products [78,79].

It should, however, be taken into consideration that the application of an engineered substitute made of autologous cells in a fitting size and of matching colour and texture, would also simplify medical treatment. Multiple operations could be avoided by applying the substitute in a one-step procedure.

Some corrective operations would become unnecessary, and therapy for chronic diseases could find an easier solution. With fewer operations and interventions, medical risks for patients could be reduced, recovery time decreased and costs thereby be diminished. In addition to making treatment methods easier and optimizing the biology and function of skin substitutes, hopes for a satisfactory cosmetic outcome are high.

8. Concluding remarks and perspectives

Tissue engineering of skin is based on 25 years of research and rests on a strong background of material technologies and cell and molecular biology. The challenge that still remains is the generation of a complex dermo-epidermal substitute that can be securely and conveniently transplanted with minimal scarring in one single surgical intervention. Means to significantly speed up vascularization in these complex skin grafts, such as controlled release of angiogenic and/or vasculogenic factors from matrices [80–85], seeding endothelial cells directly into the matrix, and engineering the vasculature directly into the tissue [86–88] will largely contribute to reach this goal.

Furthermore the development of novel ECM matrices and scaffolds will still be central in engineering optimized skin grafts. Numerous attempts to develop novel skin substitutes are still (and will be in the future) based on purified ECM components such as collagens, fibrin and hyaluronic acid (see also Table 1). These represent a relative basic ECM environment, which is conductive to the activities of determined, non-stem keratinocytes. Imposing a tissue-specific identity on the epidermal keratinocyte stem cell fraction is likely to require more specific influences during their 3D organotypic culture and after transplantation on the organism, if not already during their expansion in 2D cultures. It is promising that the outcome of growth factor administration can be improved enormously with the employment of technically relatively simple slow release schemes [89]. However, it also needs to be taken into account that an epithelium and its mesenchyme support each other in an equilibrated and complete manner. Thus, the growth factors and matrix components released by different, but interacting cell types may be even more ''instructive'' than slowly released ''instructive'' factors and matrices. It remains to be investigated whether purified factors alone or distinct cell types in concert, or combinations thereof, will provide the ''skingineering'' concept of the future [39,89,90].

The field of stem cell biology also has to be integrated in this future concept. There is a huge potential for using human originated adult stem cells as a source of in vitro generation of skin [91–93]. Human keratinocytes derived from the epidermal stratum basale [20–22,42,43], from hair follicles [94–97] and as recently suggested, also from eccrine sweat glands [98,99], are sources that allow scaling up the self-renewing keratinocyte fraction in engineered human skin grafts.

The experience of the past 25 years has identified that in the production of tissue-engineered materials the focus must move more quickly from laboratory to clinical use. Yet safety precautions have to be met. Production costs must be carefully considered, so that reimbursement gives a sufficient income. New products have to be more rapidly adapted to a rapidly changing regulatory environment. Despite initial unrealistic commercial and clinical expectations, tissue-engineered skin has already now delivered considerable benefits to patients with burns, accidents, infections and chronic wounds. ''Skingineering'' has enormous potential that has just begun to be realized.

Conflict of interest

The authors have declared that no conflict of interest exists.

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