Commentary

Developments toward an Ideal Skin Substitute: A Commentary

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Abstract

Skin grafting always has been considered a challenging task for the researchers and tissue engineers from its first introduction in 1871 by Reverdin. Skin substitutes, composed of degradable synthetic or biological components, are being considered as emergency replacements/grafts to the damaged skin. A number of technical developments in this filed have led to development of several skin substitutes, such as Biobrane®, Integra®, OrCel®, Suprathel® etc which are available for clinical utilization. From these, some characteristics, including infection resistance, water loss prevention, long shelf life, easy to store are set as criteria for assessment of the products. Post grafting problems associated with available skin substitutes questioned their reliability and reject them as an ideal skin substitute. Innovative tissue engineering approaches based on biological scaffolds and clinical grade stem cells could be an attractive alternative for available skin substitutes.

***Keywords*:** Tissue engineering, allografts, xenografts, epidermis, keratinocyte cultures, Skin Substitutes

Introduction

Skin is the largest protective organ of the human body, making up to 15% of the body weight. It acts as a functional barrier against the invasion of germs, body fluid loss, etc. (Lai-Cheong and McGrath, 2013). Skin is composed of three basic layers of epidermis, dermis and hypodermis. Epidermis is the outermost layer which is mainly composed of proliferating and non-proliferating keratinocytes (Arda et al., 2014). Accidental damaging of the skin, cutaneous wounds and burnings result in the severe and life threatening complications to the patients (Blais et al., 2013). Immediate replacement of the skin remained a clinical practice since the 19th century in the form of epithelial cell grafts (Reverdin, 1871). The limited amount of epithelial cells and donor sites are the major challenges in advantageous skin grafts. Conceptual approaches in the development of an ideal skin substitute for immediate replacement of damaged or wounded skin have remained as clinical interests for researchers, globally (Boyce, 2001; Balasubramani et al., 2001). Investigations in this area have resulted in introduction of the first skin substitute in 1981 by Burke and his colleagues (Burke et al., 1981). To date, a number of biological and synthetic skin substitutes are commercially available i.e. Biobrane®, Integra®, OrCel®, Suprathel® etc. Synthetic components are mostly organic polymers which are degradable and provide a regenerative environment for tissue regeneration. Biological skin substitutes are cellular products containing proliferative keratinocytes (Whitaker et al., 2008; Heimbach et al., 1988; Eisenberg and Llewelyn, 1998; Uhlig et al., 2007). Combinatory approaches using skin substitutes and dermal components i.e. fibroblasts have been applied for better wound healing (Eisenberg et al., 1998; Still et al., 2003; Veen et al., 2010). Better understanding of cellular and molecular mechanisms in skin regeneration is needed for the development of an ideal skin substitute (Bielefeld et al., 2013).

Classification of Skin Substitutes

Several skin substitutes are currently available for a variety of clinical applications. They can be classified into different categories, based on different criteria (Atiyeh et al., 2005; Horch et al., 2005). Almost all commercially available skin substitutes have been classified under the following three main headings (Ferreira et al., 2011).

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1. The first category has been classified based on their origin from skin layers. It is subdivided into epidermal (ESS), dermal (DSS) and dermal-epidermal skin substitutes (DESS). Orcel®, and Apligaft® are examples of this group (Hensen et al., 2001). ESSmembers, for example Epidex®, are derived from epidermal, keratinocytes, components of the skin, whereas DSS members are derived from the dermal components like fibroblasts and mesenchymal stem cells. OASIS wound matrix® is an example of the dermal skin substitutes (Ortega-Zilic et al., 2010; Hafner et al., 2006; Demling et al., 2004). Epidermal-Dermal composites are the third category of these skin substitutes to make them more effective for clinical purposes. OrCel® is an example of the epidermal-dermal skin substitutes (Veen et al., 2010).

2. Durability is the second factor in the classification of skin commercially available substitutes. These are further divided into temporary (TSS) and permanent skin substitutes (PSS). Temporary skin substitutes (TSS) provide transient physiologic wound closure, physical barrier to bacteria and creation of a suitable wound environment (Sheridan et al., 2001). Here are some currently available Temporary skin substitutes: Opsite®, Hydrofilm®, and Tegaderm® (Halim et al., 2010; Fikry and Bittner, 2013). Permanent skin substitutes (PSS) cover the wound permanently and replace the skin components in order to provide a more competent skin substitute than the thin autogolous skin grafts, e.g. Suprathel® (Uhlig et al., 2007).

3. Compatibility of the skin substitute is also an important factor in the classification of skin substitutes. Considering this, skin substitutes are classified into biological (BSS), synthetic (SSS) and bio-synthetic skin substitutes (BSSS) as shown in figure 1 (Ferreira et al., 2011). Biological skin substitutes, which act temporarily as replacement to skin, have the advantages of being relatively abundant in supply and not expensive. The biological skin substitutes have a more intact and native ECM structure which may allow the construction of a more natural new dermis. Having a basement membrane also allows excellent re-epithelialization. However, natural constructs can exhibit problems with slow vascularization of the material. The most widely used biological substitutes worldwide are cadaveric skin allograft, porcine skin xenograft, and CellSrpay® (Halim et al., 2010; Gerlach et al., 2011). Synthetic skin substitutes are constructed from non-biological molecules and polymers which are not present in normal skin (Veen et al., 2010). Due to their structures, these substitutes have their own advantages and disadvantages. For example the artificial composition and properties of these products can be much more precisely controlled. Various additives such as growth factors and matrix components can be added to facilitate the wound healing process. However, these synthetic skin substitutes generally lack basement membrane and their architecture does not resemble the native skin. Amongst the synthetic skin substitutes, available in the market, are Biobrane®, Dermagraft®, Integra®, Apligraft®, Matriderm®, Hyalomatrix® and Renoskin® (Halim et al., 2010; Demling, 1985). Biosynthetic materials are a combination of synthetic components with biological derived elements. Hyalomatrix® is the most favorable example of Biosynthetic skin substitutes (Myers et al., 2007).

Composition and Clinical Applications

EpiDex® is an example of epidermal skin substitute composed of autologous hair follicles. In technology, keratinocytes are grown in 1 cm-discs, with a silicone membrane, which are then grafted

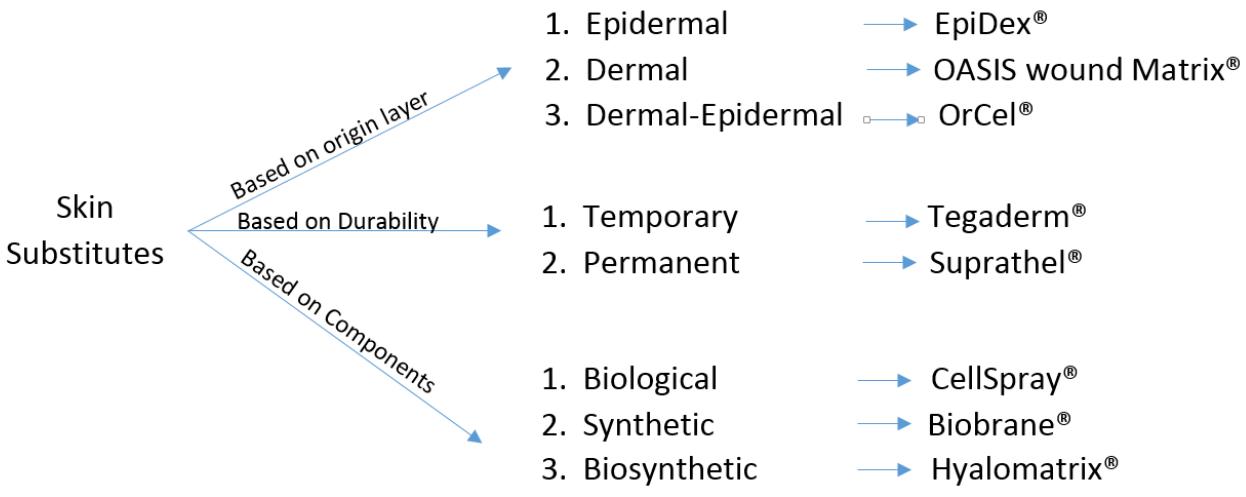

Figure 1: Classification of Skin Substitutes (S.S.)

onto the wound site (Ortega-Zilic et al., 2010; Hafner et al., 2006).

OASIS Wound Matrix® is an acellular dermal regeneration matrix, derived from swine jejunum submucosa (Demling et al., 2004; Brown-Estris et al., 2002), which leaves a structure composed of glycosaminoglycans, fibronectin, proteoglycans, and growth factors. It is commonly used in lower limb wound treatment and can be stored at room temperature (Niezgoda et al., 2005).

OrCel® is a bilayered cellular matrix which consist normal human allogeneic skin cells (epidermal keratinocytes and dermal fibroblasts) within a type I bovine collagen sponge. It is used in the treatment of chronic wounds and skin graft donor sites (Eisenberg et al., 1998; Still et al., 2003; Veen et al., 2010).

Tegaderm® is a temporary skin substitute for a temporary and small wound covering which is composed of Chlorhexidine Gluconate (CHG) IV gel (Fikry and Bittner, 2013). It has been proposed as an alternative approach to deliver autologous cells for chronic wounds (Chua et al., 2008).

Suprathel® is a purely synthetic skin substitute, composed of co-polymers of Lacto-capromer and polylactic acid (Uhlig et al., 2007). Clinically, it has been applied for the superficial partial-thickness burn wounds. As a synthetic substitute, it acts just as a protective barrier against the microbial invasion and relied on the patient's cells to improve their regeneration (Rahmanian-Schwarz et al., 2011).

CellSpray® is a cultured epithelial autograft suspension containing Ringer lactate solution, introduced in 1995 which is applied to the deep wound and stimulate the cells to regenerate the surface area (Gerlach et al., 2011). Its dependence on the culturing of autologous basal keratinocytes is a major challenge in clinical applications as an emergency skin replacement.

Biobrane® is a synthetic skin substitute containing an inner layer of nylon mesh and an outer layer of silastic. In clinics, it is applied on clean superficial burns (Demling, 1985).

Hyalomatrix® is a scaffold based bilayer skin substitute containing hyaluronan with autologous fibroblast and an outer silicone membrane which may limit colonization of cells in wound bed when applied clinically (Myers et al., 2007).

Conclusion and Perspectives

Cutaneous biology from the early use of its first autologous cell grafts, is experiencing a number of challenges for covering or replacement of injured or damaged skin. In spite of detailed understanding of physiological process in skin regeneration, researchers are still facing problems in the development of an ideal skin substitute. Stem cell based therapeutic and tissue engineering approaches are also gaining good deal of attentions. Reliable and xenobiotic-free keratinocyte culture techniques, (MacNeil, 2007), better understanding of the molecular mechanisms in the regulation of epidermal stem cells (Irfan-Maqsood, 2013), techniques to accelerate basement membrane formation and vascularization, solution to post grafting problems associated in skin engineering, such as graft contraction, loss of pigmentation and scars formation (Shah et al., 1989; O'Kane and Ferguson, 1997; Ferguson and O'Kane, 2004) are suggested as main priorities in the field. Graft necrosis, extensive inflammatory reaction, marked foreign-body reaction (FBR), rapid scaffold degradation, abnormal collagen deposition and remodeling still remained the major issues in skin bioengineering (Sriwiriyanont et al., 2013; Haifei et al., 2014). Associated problems with chemical scaffolds, perceives the ideas of biological membranes as alternatives (Hilmi et al., 2013). Application of stem cells, especially mesenchymal stem cells, along with keratinocytes, and identification of specific antigens for keratinocyte grafts would serve as promising elements in skin bioengineering.

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