INTRODUCTION: ARTIFICIAL SKIN AND ITS MEDICAL RELEVANCE

When I was in my 9th grade biology class, my teacher showed us a video about artificial organ development because we had been talking about stem cell research. The part of the video that intrigued me most was how life-like the organs were. Since watching the video, I have been interested in artificial organ creation, more specifically artificial skin development. I am interested in artificial skin development because it plays an important role in our society by allowing us to more effectively treat skin trauma, such as severe burns, along with providing a new research medium.

SKIN: THE LARGEST ORGAN

Skin is the largest organ in our bodies and provides many important functions necessary for life. According to the Wound Care Centers’ website, the skin provides protection from the external environment, regulates body temperature, allows for sensations of touch and pain, and aids in endocrine function [1]. The skin is composed of 3 layers: the epidermis, dermis, and hypodermis. The two layers that are relevant to the discussion of artificial skin grafting are the epidermis and the dermis. The structure of the skin was outlined by the 2011 article, “Artificial skin and in Perspective: Concepts and Applications,” by members of the Department of Clinical Chemistry & Toxicology at the University of São Paulo. In the article the epidermis was described as the outer layer of skin that protects the inside of the body from the environment and contains pigment producing melanocytes, proliferating keratinocytes, sensory Merkel cells, and skin immune system cells called Langerhans cells [2]. The dermis is composed of collagen rich connective tissues that allow the skin to be flexible. In between the dermis and the epidermis are the basement membrane and the extracellular matrix (ECM). The ECM, also called the basal lamina, provides energy, nutrition, and strength to the epidermis, and also houses hair follicles, immune system cells, sweat and oil glands [2]. Understanding the basic structures of the natural skin is necessary in order to create and develop more realistic and more functional skin tissue substitutes and replacement.

CURRENT TYPES OF ARTIFICIAL SKIN BIOCONSTRUCTS

There are several different types of artificial skin bioconstructs that are available, but none of them can perfectly mirror the aforementioned structures and functions of skin. Each category mimics specific basic structures of natural skin. Based on the article by Rostislav Shevchenko, Stuart James, and S. Elizabeth James of the School of Pharmacy and Biomolecular Sciences at the University of Brighton, the types of current categories of artificial skin grafts include: dermo-epidermal (composite) substitutes, epidermal substitutes, dermal substitutes [3]. Dermo-epidermal (Composite) Substitutes are more advanced than other types of substitutes due to the fact that they contain both an epidermal and dermal component, which directly mirrors the structure of the skin [3]. Most brands within this category are temporary and relatively expensive to produce. Available dermo-epidermal substitutes are: allograft, Karoskin, Apligraf, OrCel, PolyActive, and TissueTech Autograft System. These types are formed from either native human cells or from cultured keratinocytes and fibroblast [3].

Epidermal substitutes are composed of keratinocytes that are obtained from a two-five square centimeter donor site. These types of substitutes can be formed rapidly from a small biopsy, but have a variable “take”, or attachment to the wound bed. Commercial epidermal substitutes include: Epicel, EpiDex, EPIBASE, MySkin, Laserskin/Vivoderm, Bioseed, and CellSpray. All of these substitutes are permanent when applied as a skin graft [3]. Due to the fact that they are epidermal substitutes these materials cannot be used alone in deep partial-thickness and full-thickness burns do the lack of sufficient dermal cells to adhere to.

Dermal substitutes play a major role in the treatment of full-thickness burns due to the fact that they mirror the dermal layer of the natural skin and provide the epidermal cells with nutrients and a secure basement membrane. Dermal substitutes are the easiest to manufacture with low cost [3]. This has allowed for numerous products to become commercially available for clinical use. These include: AlloDerm, Karoderm, SureDerm, GraftJacket, Matriderm, Permacol Surgical Implant, OASIS Wound Matrix, and EZ Derm [3].

ARTIFICIAL SKIN IN BURN TREATMENTS

Most all of the discussed skin substitutes are used in the treatment of severely burned patients. However, the most effective treatment of burns does not involve artificial skin grafts and is called split-thickness autologous skin grafting. In this procedure, the epidermis
and the superficial section of the dermis are harvested from a donor site somewhere else on the body and are placed onto the wound bed [3]. This leads to a major problem if there are not enough donor sites available. For example, if fifty percent of the total body surface area (TBSA) is burned then the remaining fifty-percent would be donor sites leading to a wound bed covering one-hundred percent of the body [3]. The aforementioned products are used as supplements when there is not enough tissue from the patient’s own body to act as donor sites.

**Types of Burns**

There are four classifications given to burns depending on which layers of skin are damaged. The first classification is an epidermal burn where damage only occurs in the epidermis and does not require skin grafting. These burns heal by themselves fairly quickly and do not result in scar tissue [3]. Superficial partial-thickness burns occur when the epidermis and the outer part of the dermis are damaged. Superficial partial-thickness burns often heal by themselves through epithelialization, which is the process when basal keratinocytes change into migratory cells that cover the damaged area [3]. More severe burns include deep partial-thickness burns and full-thickness burns. Deep partial-thickness occurs when the epidermis and most of the dermis are damaged and very few regenerative cells remain. Full-thickness burns occur when both the epidermis and dermis are completely destroyed. Full-thickness burns heal by contraction (the wound heals from the edges inward). Any full-thickness burn larger than one centimeter in diameter requires skin grafting [3].

**How Artificial Skin Materials are used in Treatment**

The type of burn that a patient has will determine the necessary type of artificial skin tissues for treatment. If there are not enough donor sites available, the artificial tissues are then used as permanent grafts or as temporary wound dressings [3]. The grafts are applied following either a two-step (full-thickness burns) or single-step (deep partial-thickness and superficial partial thickness burns) process. The single step process involves placement of a single type of substitute graft, whereas the two-step process involves a dermal substitute and an epidermal substitute.

**Clinical Studies Involving Artificial Skin Materials**

The effectiveness of two types of procedures is explained through the results of two clinical studies. The first was a study conducted by members of Burn Units within the Departments of Burns, Plastic and Reconstructive Surgery of various hospitals throughout Spain demonstrated the effectiveness of autologous bioengineered composite skin (dermo-epidermal substitutes) (ABCS). The results of their study are as follows: “Mean area initially engrafted with ABCS was 24% of TBSA, with a final take of 49%. ABCS achieved permanence coverage of a mean of 11% of TBSA [4].” This suggests that the ABCS is likely to be rejected by the patient’s immune system and is more likely to be a temporary wound dressing. However, the cosmetic appeal of the ABCS in the study was evaluated to be satisfactory of very satisfactory in 72% of the patients within the study [4]. This suggests that ABCS is able to mimic the skin’s ability to regenerate without much scarring.

The second study was conducted in Japan by members of the Department of Plastic and Reconstructive Surgery at Nihon University. The study looked to see if a one-step grafting process for full-thickness burns could be created. In their study, the patients were treated with artificial dermal tissue and traditional split-thickness skin graft on top of the artificial tissue. The take of the graph was very successful: in the one patient the graph take was at 80% by the 14th day after the procedure, and epithelialization had been completed by the 30th day after surgery [5]. This study only focused on two patients, not on a large scale; therefore, more research must be done in order to give more credibility to the one-step process that they developed.

Both research studies show that the current methods of artificial skin grafting in burn patients have been successful, but still need to be improved and tested in order to substantiate the procedures and improve their effectiveness.

**ADDITIONAL MEDICAL APPLICATIONS OF BIOENGINEERED TISSUES**

Burn treatment is the most prevalent use of artificial skin materials, but the need for further development of artificial tissues branches out even further. Other research areas that utilize the varying types of artificial skin materials currently available are skin cancer research and ultraviolet (UV) photoaging research.

Artificial skin materials that mimic the natural regenerative abilities of skin cells help researchers better understand the mechanisms associated with skin cancer and UV photoaging. Furthermore, as more bioengineered tissues contain melanocytes (pigment producers), researchers can better understand the stages and interactions of melanoma with surrounding skin cells. Additionally, the artificial tissues allow researchers to test the effects of extreme amounts of UV radiation on skin without breaking any ethical standards [2]. If better artificial skin materials are further developed, then the accuracy of this research will increase.
CURRENT LIMITATIONS OF ARTIFICIAL SKIN MATERIALS

Even though artificial skin materials are useful and helpful in the medical field and research they do have significant limitations that need to addressed and modified. These limitations are mainly the immune-response/rejection of the graft and the cost-effectiveness of the grafts.

Immune rejection of the graft is the biggest problem. The immune response was described by members of the Department of Surgery at the Massachusetts General Hospital. The immune response starts out when donor dendritic cells (Dcs) migrate from the graft and into the lymph nodes of the patient. Here T-cells become activated and reproduce to secrete inflammatory cytokines, which then leave the lymphoid organs and travel back to the graft. Once back at the graft, they attack and kill the donor skin cells [6].

Furthermore, the cost effectiveness of treating burns with artificial skin tissues is not very high. In Spain, the cost of ABCS is about $1.70 per cm², resulting in an average cost of $670 per patient with 1% TBSA burned. Other authors have stated that the cost of Epicel on the same type of patient to be around $5000 [4]. These are relatively high prices to pay for a treatment that is either temporary or may not have a 100% take. The cost-effectiveness can only be reduced if more efficient means of production are researched and if ways to increase take are developed.

POSSIBLE SOLUTIONS AND DEVELOPMENTS

In order to solve the limitations and problems with the current artificial skin tissues, more research must be done in order to understand the reasons behind graft rejection.

A proposed solution to solve the rejection of skin grafts involves the elimination or inactivation of specific T-cells during to grafting process to help eliminate the T-cell immune response on the donor cells [6]. This ultimately blockades the donor Dcs from traveling to the lymph nodes, thus preventing the immune response. By researching how to decrease the rejection rate of the artificial skin tissues the cost-effectiveness will increase. This is caused by the decreased need for subsequent surgeries needed with the grafts that serve as temporary wound dressings along with a higher take rate of the permanent artificial skin tissues.

CONCLUSION: CONTINUATION OF ARTIFICIAL SKIN RESEARCH

Artificial skin materials not only provide a more effective grafting substance for severely burn patients, but have additional medical research applications. These materials still need to be developed and researched in order to provide a skin substitute that is almost identical to natural skin in function and is not rejected by the immune system. Additionally, the research areas of skin cancer and UV photoaging associated with artificial skin materials will help increase the knowledge on how these diseases affect the body. Overall, artificial skin materials are an important area of engineering that needs to be further developed because they are becoming a valuable resource within the medical community, thus benefiting the society as a whole.

REFERENCES


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