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Review Article

Cultured Epidermal Autograft in Wound coverage

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ABSTRACT

Cultured epidermal autograft (CEA) was performed in 1975 and developed the technique in result of large sheets of multi-layer keratinocytes. Limitations are need of dermal layer support, take time of culture process and high expense. Consider cost-benefit compared to skin graft harvest disadvantage, cultured human epidermal keratinocytes should be gold standard treatment in skin loss wound closure in the future.

Keywords: Cultured epidermal autograft; CEA; Wound coverage

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Introduction

Gold standard for deep burns wound coverage is using autologous skin grafts that harvested as split-thickness skin grafts (STSG) or full-thickness skin grafts (FTSG). However, the limited of donor sites in severely burned patients and substantial donor site morbidity. In otherwise in open wound that need wound coverage, skin grafts also are commonly used. Disadvantage of skin graft harvest are painful donor site and unacceptable donor site scar commonly occurred. The objective of this article was to provide a review on the application of cultured keratinocytes, covering the development and culturing technique, the advantages and the limitations of the clinical application as well as its future perspectives.

History of the development and the initial use of keratinocytes

Rheinwald and Green in 1975, first published to describe serial cultivation of strains of human epithelial cells.[1] Differentiation of confluent cells resulted in the formation of cultured epidermal autograft (CEA).[2,3] Now the process can be divided in three phases: phase A - cell isolation, phase B - cell expansion and phase C - sheet formation (Figure 1).

Phase A - cell isolation, starting from taking autologous skin then use enzymatic process for isolation of keratinocytes. Estimate a 4 cm^2 skin biopsy can produce sheets covering 1 m^2 of TBSA.

Phase B - cell expansion, in this step culture medium is importance and precaution to avoid the risks associated with xenogeneic and allogeneic cell co-cultures.

Phase C - sheet formation, keratinocyte sheet formation is initiated by plating the cells then serial adding the appropriate differentiation medium. Keratinization process is triggered, for the keratin layer is import layer, it protects the graft from drying.

The technology of CEA sheet creation has relied on the methodology first described by J. Rheinwald and H. Green in the 1970s.[4,5] With culture medium development, 3D reconstruction of the epidermis and keratinization process triggered by the Air-Liquid Interface technique6 produced large sheets of multi-layer keratinocytes known as EpiSkin models. During the 90s Martin Rosdy produced and distributed reconstructed human epidermis (RHE)[7] through a company he had created and named SkinEthic. L'Oréal cosmetic company used SkinEthic RHE with characteristics close to the normal human epidermis for chemical toxicology skin test.

Clinical application in a burn patient was applied for the first time in 1981.[8] After that, several studies on the use of CEA grafts in the treatment of burns were done and extended to difficultly healing skin ulcer.[9]

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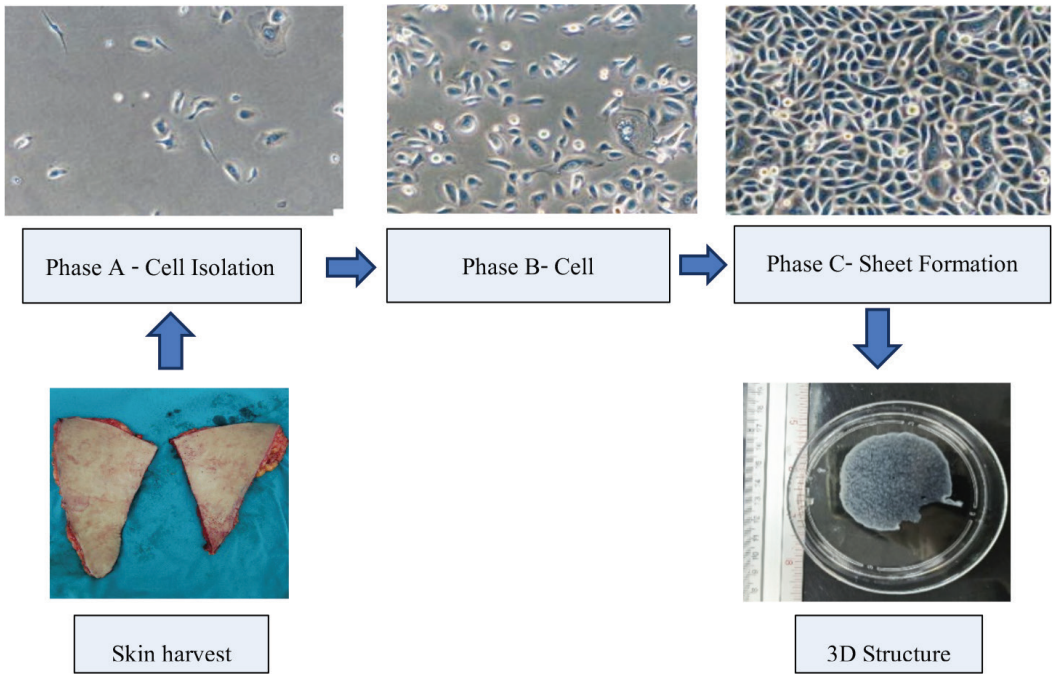

Figure 1 Process of Cultured Human Epidermal Keratinocytes (Picture courtesy of Dr Pawinee Chetprayoon. PhD)

Whereas human skin samples collect from newborn foreskins, adult cells are most often isolated from female donors (breast reduction, abdominoplasty), creating some gender bias between available newborn and adult human keratinocytes. For antigenic, in clinical treatment use cultured epidermal autograft (CEA) so need for patient skin sample.

Clinical application

CEA compared to conventional split skin graft, skin graft contains blood vessels within the dermal elements and is fully keratinized. The capillaries will connect with vessels of recipient bed within a matter of 48 to 72 hours, serving both to secure the graft and to supply nutrients. The keratin layer protects the graft from drying. Although the cultured keratinocyte sheet is multilayered and terminally differentiated, it still lacks of vascular system and support bed that very vulnerable in the first 48-72 hours following grafting.

However, CEA in wound coverage can be used in three applications. First, apply on wound that remaining of dermal layer. Second, apply on wound company with autologous skin graft. Third, apply on full thickness skin loss wound.

Use of CEA in wound coverage is replaced of using autologous skin grafts. But disadvantages of

CEA are need of dermal layer support, take time for complicated culture process and high expenses. Dermal layer of skin roles as functional layer, it supports epidermal layer for endurable to force and induce epidermal growth. Without the dermis, it will not be robust. So direct use of CEA is limit in partial thickness skin loss wounds that remaining of adequate support of dermal layer or full thickness skin loss wounds that already dermal layer was built. Therefore, skin substitutes are produced with acellular dermal matrix (ADM) to be transplanted to form neo-dermis before using cultured keratinocytes to cover it. Commercial dermal skin substitute such as Integra™, bovine ADM well know using in deep burn wound.

Alternatively, there are double-layered options available with both dermis and epidermis, human fibroblast and cultured autologous keratinocytes known as Apligraf™. But they are not preferred due to their difficult application and high cost.

Although culture process of CEA now is advance development but remain complicated, need of special medium and technique for large sheets of keratinocytes was built such as SkinEthic RHE take time at least 21-28 days.[10]

For CEA sheet production take long time, CEA cell suspension in fluid, that less than 21 days in culture process, use on burn wound. The technique is using of CEA suspension in fluid and spray on burn wound compare the duration of hospital stay between patients who were treated with autologous skin grafts and cultured autologous keratinocytes and those who were treated with autologous skin grafting without cultured autologous keratinocytes.[11] The experiment report good result of scar and shortened the duration of hospital stay.

In other hand, trial of direct CEA application on full thickness skin loss wound was reported.[12] They claimed epidermal layer can develop but the incidence of contractures and reconstructive procedures was significantly higher. In addition, the implementation of an active and aggressive rehabilitation program is subjectively troublesome and delayed because of the nature of the CEA graft and the tendency to blister under minimal mechanical trauma.[13]

Conclusions

Although high expense, depend on supply and demand principle, need of dermal or neo-dermal layer but CEA is the challenge treatment when consider of cost-benefit compare to skin graft harvest disadvantage. Successful long-term result really is limited in the wound that has enough dermal layer support. But in the future with autologous dermal culture development human epidermal keratinocytes should be gold standard treatment in skin loss wound closure.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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