EPIDERMAL AND FIBROBLAST GROWTH FACTOR INCORPORATED POLYVINYL ALCOHOL ELECTROSPUN NANOFIBERS AS BURN WOUND DRESSING SCAFFOLD

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ABSTRACT

The primary concern of wound burn is a failure in wound healing and the transition to a chronic wound. Specifically, in full-thickness burn wound, even though skin autograft is the treatment of choice, it has several drawbacks in the donor site, including repeated transplanting; therefore, a robust wound dressing is still needed. Polyvinyl alcohol (PVA) is a synthetic biodegradable polymer which has been widely employed as an artificial substitute for wound dressing. Epidermal growth factor (EGF) and fibroblast growth factor (FGF) are two prominent growth factors (GFs) that mainly assist wound healing. Therefore, in this study, the incorporation of biomolecules, such as GF, into PVA matrix is deemed necessary to enhance the biological properties of the polymer. Thus, PVA-GFs biologically active scaffold for burn tissue is developed and tested on *in vitro* human dermal fibroblast cells (HDFs) and *in vivo* burn models. The scaffold design was fabricated as single, mix and multiple layers of PVA loaded with EGF and FGF by electrospinning technique. The chemical composition, morphological, surface roughness, wettability and mechanical properties of the electrospun nanofibers were characterized. The biocompatibility of different nanofiber scaffolds was assessed through *in vitro* cell culture with HDFs. The cell viability and attachment were analyzed by MTT assay and FESEM. The fabricated GFs incorporated PVA nanofibers were also evaluated through *in vivo* studies on a burn wound rat model. Sixty-three male Sprague-Dawley rats were divided into seven groups, control, burn, PVA/EGF (single), PVA/FGF (single), PVA/EGF/FGF (mix), and PVA/EGF-FGF (layers) nanofibers groups which all nanofibers set the ratio at PVA:EGF:FGF, 9.5:0.5:0.5 v/v respectively. On days 7, 14, 21, the wound closure was measured, and tissue samples were obtained, then stained with hematoxylin and eosin (H&E) stain to study the process of burn wound healing histologically. The chemical functionalities of both PVA/EGF/FGF and PVA/EGF-FGF nanofiber membranes were mainly attributed to O–H and N–H bonds. In this study, the morphology of the scaffold showed long protrusion and smooth nanofibers without beads and spray with an average range of 198 - 286 nm fiber diameter. Both PVA/EGF/FGF and PVA/EGF-FGF nanofibers manifested decrement in fiber diameter, improved wettability and surface roughness. The Young's modulus of the electrospun PVA nanofibers incorporated GFs were also observed in between 18 and 20 MPa which were in the range of preferable properties of human skin. The *in vitro* studies showed no cytotoxic effect of all GFs incorporated PVA nanofibers against HDFs cells and showed the highest HDFs viability and adhesion compared to the PVA control sample. Results from the *in vivo* studies showed that on the 21st post-burn wound day, the closure rate of the PVA/EGF/FGF and PVA/EGF-FGF nanofibers groups were visualized at 88%-89%, respectively. The neovascular structure, sebaceous gland, and hair follicles were observed in PVA/EGF/FGF and PVA/EGF-FGF nanofibers groups and appeared more healthy skin at day 21. In conclusion, the PVA/EGF/FGF and PVA/EGF-FGF nanofibers display convergently results with superior PVA/EGF/FGF, which could be projected as a suitable biological burn wound dressing scaffold.

ABSTRAK

Kebimbangan utama terhadap luka akibat kebakaran adalah kegagalan penyembuhan luka dan peralihan kepada luka kronik. Khususnya, dalam luka terbakar dengan ketebalan penuh, walaupun autograft kulit adalah rawatan pilihan, ia mempunyai beberapa kelemahan pada pihak penderma, termasuk pemindahan berulang; oleh itu, pembalut luka yang teguh masih diperlukan. Polivinil alkohol (PVA) adalah polimer biodegradasi sintetik yang digunakan secara meluas sebagai pengganti tiruan kepada pembalut luka. Faktor pertumbuhan epidermis (EGF) dan faktor pertumbuhan fibroblas (FGF) adalah dua faktor pertumbuhan (GF) yang menonjol dalam membantu penyembuhan luka. Oleh itu, dalam kajian ini, penggabungan biomolekul, seperti GF, ke dalam matriks PVA dianggap perlu untuk meningkatkan sifat biologi polimer. Oleh yang demikian, perancah faktor pertumbuhan-PVA aktif biologi untuk tisu yang terbakar telah dibangunkan dan diuji secara *in vitro* terhadap sel-sel fibroblas dermal manusia (HDFs) dan model terbakar secara *in vivo*. Rekabentuk perancah telah dibangunkan sebagai satu lapisan, lapisan campuran dan pelbagai lapisan PVA yang dimuatkan dengan EGF dan FGF dengan teknik elektroputaran. Komposisi kimia, morfologi, kekasaran permukaan, kebolehbasahan dan sifat mekanikal elektrospun nanofiber telah dicirikan. Keserasianbio perancah nanofiber yang berbeza dinilai melalui kultur sel *in vitro* dengan HDF. Daya maju sel, pertumbuhan dan lekatan dianalisis dengan ujian MTT dan FESEM. Nanofiber PVA yang digabung dengan GF yang direka diuji melalui kajian *in vivo* pada model tikus. Enam puluh tiga tikus jantan Sprague-Dawley dibahagikan kepada tujuh kumpulan; kawalan, terbakar, PVA/EGF (tunggal), PVA/FGF (tunggal), PVA/EGF/FGF (campuran), dan PVA/EGF-FGF (lapisan) kumpulan nanofiber yang mana semua nanofiber masing-masing ditetapkan pada nisbah PVA:EGF:FGF, 9.5:0.5:0.5 v/v. Pada hari ke-7, 14, 21, penutupan luka diukur, dan sampel tisu diambil, kemudian diwarnai dengan pewarna hematoxylin dan eosin (H&E) untuk mengkaji proses penyembuhan luka kebakaran secara histologi. Fungsi kimia kedua-dua membran nanofiber PVA/EGF/FGF dan PVA/EGF-FGF adalah disebabkan oleh ikatan O–H dan N–H. Dalam kajian ini, morfologi perancah menunjukkan unjuran panjang dan nanofiber yang licin tanpa manik dan semburan dengan julat purata diameter serat pada 198 - 286 nm. Kedua-dua nanofiber PVA/EGF/FGF dan PVA/EGF-FGF menunjukkan penurunan diameter, kebolehbasahan yang lebih baik dan kekasaran permukaan. Menurut modulus Young, nanofiber PVA elektrospun yang digabungkan GF juga diperhatikan antara 18 dan 20 MPa yang berada dalam julat sifat yang lebih baik dari kulit manusia. Kajian *in vitro* menunjukkan tiada kesan sitotoksik pada semua nanofiber yang digabungkan GF terhadap sel HDF dan lekatan tertinggi berbanding dengan sampel kawalan PVA. Dalam kajian *in vivo*, kadar penutupan kumpulan nanofiber PVA/EGF/FGF dan PVA/EGF-FGF masing-masing dilihat pada 88%-89%, pada hari ke 21 selepas luka terbakar. Struktur neovaskular, kelenjar sebum, dan folikel rambut diperhatikan dalam kumpulan nanofiber PVA/EGF/FGF dan PVA/EGF-FGF dan menunjukkan kulit yang lebih sihat pada hari 21. Kesimpulannya, PVA/EGF/FGF dan PVA/EGF-FGF nanofiber menunjukkan hasil yang berbeza dengan PVA/EGF/FGF yang unggul, yang mana sesuai dimajukan sebagai perancah biologi untuk pengubatan cedera luka terbakar.

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LIST OF ABBREVIATIONS

3D	-	Three-Dimensional
ATR	-	Attenuated total reflectance
AFM	-	Atomic Force Microscopy
BAS	-	Bovine Albumin Serum
CAD	-	Computer-aided design
CO_2	-	Carbon dioxide
DMEM	-	Dulbecco's modified Eagle's medium
DMSO	-	Dimethylsulfoxide
ECM	-	Extracellular matrix
EDTA	-	Ethylenediaminetetraacetic acid
EGF	-	Epidermal Growth Factor
EGFR	-	Epidermal Growth Factor Receptor
ERKs	-	Extracellular signal regulated kinase
FBS	-	Foetal bovine serum
FDA	-	Food and Drug Administration
FDM	-	Fused deposition modelling
FESEM	-	Field emission scanning electron microscope
FGF	-	Fibroblast Growth Factor
FGFR	-	Fibroblast Growth Factor Receptor
FTIR	-	Fourier transform infrared spectroscopy
GFs	-	Growth Factors
Grb2	-	Protein 2
HDFs	-	Human Dermal Fibroblast cells
H&E	-	Hematoxylin and Eosin
HGF	-	Hepatocyte Growth Factor
Ig	-	Immunoglobulin
IGF	-	Insulin-like Growth Factor
IL	-	Interleukins
MEK	-	Mitogen-activated protein kinase
MAK	-	Mitogen-activated protein kinase

MAPK	-	Mitogen-activated protein kinase
MTT	-	3-(4,5-Dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium
PBS	-	Phosphate buffered saline
PCL	-	Poly ε-caprolactone
PDGF	-	Platelet-derived Growth Factor
PGA	-	Polyglycolic acid
PLA	-	Polylactic acid
PLGA	-	Polylactic-co-glycolic acid
PU	-	Polyurethane
PVA	-	Polyvinyl alcohol
PVP	-	Polyvinyl pyrrolidone
RP	-	Rapid prototyping
SEM	-	Scanning Electron Microscopy
SLS	-	Selective laser sintering
SOS	-	Son of sevenless
TEM	-	Transmission Electron Microscopes
TGF-a	-	Transforming Growth Factor-a
TGF-b	-	Transforming Growth Factor-b
TIPS	-	Thermally Induced Phase Separation
TNG	-	Tumor necrosis factor
UV	-	Ultraviolet rays
HUVEC	-	Human Umbilical Vein Endothelial Cells
VEGF	-	Vascular Endothelial Cell Growth Factor
WHO	-	World Health Organization

LIST OF SYMBOLS

%	-	Percentage
°	-	Degree
×	-	Times
°C	-	Degree celcius
=	-	Equal
ug	-	Microgram
h	-	Hour
v/v	-	Volume/Volume
min	-	Minutes
kV	-	Kilovolt
ml	-	Mililiter
mL/h	-	Mililiter/Hour
cm	-	Centimetre
um	-	Micrometer
uL	-	Microliter
mm	-	Milimeter
MPa	-	Megapascal
mg	-	Miligram
nm	-	Nanometer
g	-	Gram
s	-	Second
Ra	-	Average Roughness
mm^2	-	Square Milimeter

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CHAPTER 1

INTRODUCTION

1.1 Research Background

Wound is known as damage the integrity of biological tissue, involving skin, mucous membranes, and organ tissues [1]. The skin integrity can be compromised, because of genetic disorders, acute trauma, chronic wounds or even surgical interventions that accompanies wound [2,3]. Burns and scalds are widely common reasons for losing skin and could be resulted in deep wounds thereby, affecting the immunity and the natural form of the body, and may result in fluids loss, scarrings, disability or even death [3,4]. According to WHO (2018), the global death rate from burns is about 180,000 deaths /year, and about 3.6/100,000 population [5]. Furthermore, burns have been classified to first, second, third and fourth degree. Severe or major burn injury may cause uncontrolled inflammatory process which leads to delay healing, organ failure, infections and even death [6].

Clinically, wound healing is a challenging issue that focuses on wound care management and emphasizes scavenging new treatment approaches [7]. In particular, burn wound care is increasingly becoming an issue of concern in clinical practices, with available treatments including skin substitutes, wound dressings, and skin grafting [8]. Many factors are known to delay healing, such as comorbidities in patients who suffer from diabetes mellitus, ischemia, pressure, or venous stasis disease. Consequently, delayed wound healing could result in infections and pains, and consequently increase the financial burden on the patients and the healthcare system [8].

Wound dressing is a repair approach which is essential to keep the wound site from factors that affect healing [9] and create an environment that minimizes infection, promotes the correct moisture balance, and facilitates re-epithelialization of the

wound. Presently, several types of dressings are obtainable in the market that are more than 3000 types, which are making numerous options to address all aspects of wound care such as cotton wool, natural or synthetic bandages, and gauzes [10]. According to Borda *et al.,* the dressing materials include semipermeable silicone foams, hydrocolloids, hydrogels, and hydro-fibres, which protect burn wounds while they could not assist dermal and epidermal tissues to recover [11].

Fabricated biological scaffold are increasingly used in novel regenerative therapies for wound repair in cases of significant soft tissue loss. A scaffold serves as an artificial extracellular matrix (ECM) and a microenvironment that has been increasingly recognized for the development of wound healing products. It is biologic and derived from animal or human tissues or they could be composites containing a combination of biologic and synthetic products [12]. The scaffold evolvement for skin regeneration is becoming necessary in the tissue engineering field especially those that involve use of polymers [13]. Scaffolds could be polymeric three dimensional (3D) structures that have the prospect to address the limitation of traditional wound dressing materials. The unique synthetic scaffold properties allow cell attachment, cell migration, modifying the diffusion of vital cell nutrients and controlling the behaviour of cell phases which exert certain mechanical and biological influences [14]. Various techniques have been utilized to fabricate scaffolds such as solvent casting, freeze-drying, phase separation, gas foaming, and electrospinning [15,16]. Electrospinning is a simple and versatile technique that produces scaffolds formed by nano- and microfibers, which offers a favourable micro- environment for cellular development by mimicking the native extracellular matrix [17].

Electrospun nanofibers have attracted considerable interest for use in several applications including tissue engineering application and could be synthesized from natural and synthetic polymers. Several studies have used natural and synthetic polymers to synthesize a dressing, showing a good relationship between clinical efficacy and manufacturing cost [8,17,18]. The natural polymers being clinically used for tissue engineering purposes due to the good interaction with various cell types and lack of an immune response. Similarly, synthetic materials have gained great attention due to high versatility, tenability, and easy functionalization for better biocompatibility

[19]. Recently, the biomaterials used in scaffold fabrication are based on natural or synthetic polymers or a combination, while the synthetic polymers are widely utilized as cell supporting matrices in tissue regeneration. In addition, polymers have been considered as attractive approaches due to the similarities of chemical, biological and extracellular matrices (ECM) [20]. The incorporated biomolecules such as a protein are commonly used as to enhance the wound microenvironment using growth factors or cytokines, and growth factor encoding genes [21].

Polyvinyl alcohol is one of the materials used in the scaffolds fabrications and categorized as a polyhydroxy polymer, which has been studied intensively due to its excellent film-forming and physical properties. It also has high processability, biocompatibility, hydrophilicity and excellent chemical resistance [22–24]. This polymer has been utilized in several areas, such as food chemistry, pharmaceuticals, medicine, and biotechnology [25]. PVA has high usefulness in diverse pharmaceutical and biomedical applications [26], where it has been approved by Food and Drug Administration (FDA) [25,26]. Additionally, polyvinyl alcohol has been used as PVA hydrogels to fabricate contact lenses, wound dressings, coatings for sutures and catheters. It is also prominent to be modified as a water-soluble and biodegradable carrier and thus beneficial in drug delivery systems [25,27].

Growth factors are one of the biomolecules (proteins) that have the characteristic of binding to the receptors on the surface of cells and regulating cellular activities involved in new tissue regeneration [28]. The most prominent growth factors are the epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF). The EGF is mitogenic to form various epithelial cells, hepatocytes and fibroblasts [29]. It possesses high-affinity receptors that are expressed by both fibroblasts and keratinocytes. EGF utilization is aimed at improving the epidermal and mesenchymal regenerations, cell mobility, proliferation and ECM synthesis, which consequently facilitates wound healing [30,31], while FGF is associated with heparan sulfate in ECM, which serves as a reservoir for storing inactive factors [32–34]. It is recognized by a family of cell surface receptors that has intrinsic tyrosine kinase activity. Many functions are attributed to FGF, including developing new blood vessels, wound repair and hematopoiesis [32,33].

In this study, incorporation of polyvinyl alcohol (PVA) electrospun nanofibers loaded with epidermal growth factor (EGF) and fibroblast growth factor (FGF) was fabricated as a wound dressing scaffold. The competency of the scaffolds was emphasized by the promoted proliferation and cell adhesion with in repairing skin tissue.

1.2 Problem Statement

Burn wound is a significant issue in the health care system global [5] especially as it relate to reduced immune response in elderly and diabetic patient. Although, there are many dressing methods for treating the burn wounds in clinical practice, less efficient wound care may end with complicated implications that cause prolonged morbidity or mortality [35–38].

Significantly, the full-thickness burn is a life-threatening one, the time factor is not only improving the healing process, but playing an important role in saving a life. The healing rate has a range of time in 8-12 weeks in full thickness burn wound to avoid the transition to chronic wound and progressive, irreversible tissue damage that can results in necrosis, vascular damage, or even amputation. Clinically, skin autograft has been used as treatment of choice for full thickness burn, however, it has several drawbacks as a deficit of donor sites with repeated transplants [3,6,39–42].

The conventional wound dressing used in burn wounds still has some drawbacks that do not allow the typical physiological environment to facilitate the wound healing process due to the lack of some biological activities and responses to used materials. While, it is essential to have an optimal wound environment and maintain the wound under a moist wound dressing and certain conditions, the severe tissue loss in full-thickness burn may inhibit tissue regeneration [40,41,43–45].

Recently, the tissue engineered polymeric scaffold has been enormously applied for wound dressings and they ideally mimic the natural ECM in structure and function, including the synthetic polymers as polyvinyl alcohol. There are some

properties that favor the use of PVA for nanofibers fabrications, including the excellent physical, and mechanical properties with high biocompatibility, hydrophilicity and premium chemical resistance. Many studies showed the PVA dressing to be successful in wound healing such as PVA/collagen/curcumin, PVA/alginate, and PVA/chitosan. However, they still show variation in the biocompatibilities moreso, some studies found that pure PVA has poor as affinity for cell attachment [14,23,24,39,46–48].

Growth factors such as EGF and FGF has been used for full thickness burn care and improved wound healing by stimulating proliferation, migration, and angiogenesis. However, GF has limited clinical application because GFs bioactive is still challenging due to low stability and sensitivity to environmental conditions that lowers bioactivity. Some techniques of production may has negatively affect growth factor bioactivity due to the influence of high temperature applied during the fabrication process. Thus, growth factor bioactivity is one of limitation in the current fabrication scaffold technique [49–51].

In view of the properties of PVA and GFs as a beneficial solution to wound healing issues, they are foreseen in this study to be potentially effective wound dressing. Therefore, the aim of this study was to develop PVA-GFs scaffold that provides the function of repairing tissues, effective in directing cell growth, migration, and differentiation in vitro and improve skin regeneration in vivo.

1.3 Research Questions

The main research question of this study is “How can wound dressing scaffold be improved with EGF and FGF to enhance burn wound healing?" This can be further divide in to three research questions as follow:

Question (1): What are the characteristics of EGF and FGF incorporated PVA nanofibers.

Question (2): What are the cell biocompatibilities of EGF and FGF incorporated PVA nanofibers.

Question (3): What are the bioactivities of EGF and FGF incorporated PVA nanofibers on in vivo burn model

1.4 Hypothesis

Use EGF and FGF incorporated PVA nanofibers for wound dressing will enhance healing of full thickness burn wound.

1.5 Research Objectives

This research aims to synthesize a beneficial scaffold that can act as a dressing and carry the growth factors with a safe and effective burn wound healing process. The following specific objectives were accomplished:

1. To synthesis epidermal growth factors (EGF) and fibroblast (FGF), incorporated polyvinyl alcohol (PVA) nanofibers and characterize the chemical composition, morphology, wettability, and mechanical properties.
2. To assess the cell biocompatibility of EGF and FGF incorporated PVA nanofibers in *vitro*.
3. To evaluate the bioactivities of EGF and FGF incorporated PVA nanofibers on *in vivo* burn model as a biological scaffold.

1.6 Scope of study

The scope of this study is based on the fabrication of PVA- GFs scaffolds, which are composed of PVA, EGF, and FGF for full thickness (third degree) burn wound healing. Five membranes were fabricated by using electrospinning, which consisted of pure PVA (control), single layer PVA/EGF, single layer PVA/FGF, mix layer PVA/EGF-FGF and multiple layers PVA/EGF/FGF. The characteristics of the nanofibers including chemical composition, morphology, surface roughness, wettability, and mechanical properties of the electrospun nanofibers were determined principally through an attenuated total reflectance-fourier transform infrared spectroscopy (ATR-FTIR), scanning electron microscopy (SEM), atomic force microscopy (AFM), water contact angle and tensile test analyses, respectively.

Furthermore, the biocompatibility of nanofibers was evaluated through in vitro cell studies with human dermal fibroblast cells, in which the cell viability, proliferation and cell attachment were evaluated by using MTT assay and FESEM.

Subsequently, a burn wound model was studied in vivo. Rats were burned (full thickness) by using a hot circular steel billet then treated with nanofibers. Macroscopic and microscopic measurements were taken. The technique of studying the sample was through wound closure and histological examination using Hematoxylin and Eosin stain (H&E). All results were statistically analysed. The collected data of MTT assay and wound closer were performed by using one-way ANOVA of variance followed by Tukey's test for multiple comparisons by using GraphPad Prism 6.01 software (GraphPad Prism, La Jolla, CA, USA).

1.7 Significant of Study

The tissue of the skin is able to regenerate, repair, and remodel, however, the skin integrity could be lost due to genetic disorders, acute trauma, chronic wounds, or even surgical interventions. Full thickness burn wounds may contribute to the risk of healing failure and associated complications. Thousands of wound dressings still lack

ideal environment that can assist wound healing, thus alternative solution such as tissue engineering is highly needed. Tissue engineering aims to promote wound healing itself while avoiding the drawback of autografting. This field could contribute to providing the novel biological dressing that can help in the regeneration of human skin tissue, because the scaffold distinguishes the unique structure of nanofibrous which is similar to native ECM.

The finding of this study could be beneficial for full thickness burn wounds. The EGF and FGF incorporated PVA nanofibers could contribute to reducing the time for healing, as GFs could stimulate various cellular functions, including proliferation, migration, deposition of extracellular matrix molecules, and remodelling of collagen synthesis. This may reduce the tissue damage and complication of severe burns. In addition, this study could be advantageous in enhancing burn care in undeveloped countries. GFs incorporated PVA nanofibers could also improve cell proliferation and attachment with GFs activity. Furthermore, this can aid in the introduction of selective, tolerable, and safe wound dressing constituents in the treatment protocols of burn wounds, which can improve the healing capacity of epidermal and derma cells in an efficient and safe way with reduced costs.

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