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RESEARCH ARTICLE

Recent prospective of nanofiber scaffolds fabrication approaches for skin regeneration

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ABSTRACT

The largest organ of human body is skin, which acting as a barrier with immunologic, sensorial and protective functions. It is always in exposure to the external environment, which can result many different types of damage and injury with loss of variable volumes of extracellular matrix (ECM). For the treatment of skin lesions and damages, several approaches are now accessible, such as the application of allografts, autografts, and tissue-engineered substitutes, wound dressings and nanofiber scaffolds approaches. Even though proven clinically effective, these methods are still characterized by main drawbacks such as patient inadequate vascularization, morbidity, the inability to reproduce skin appendages, low adherence to the wound bed and high manufacturing costs. Advanced approaches based on nanofiber scaffolds approaches offer a permanent, viable and effective substitute to explain the drawbacks of skin regeneration and repair by combining growth factors, cells, and biomaterials and advanced biomanufacturing methods. This review details recent advances of nanofiber scaffolds in skin regeneration and repair strategies, and describes a synthesis method of nanofiber scaffolds.

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Introduction

Skin regeneration and repair has made significant progress over recent years, but there are still many factors that obstruct its further improvement; these include the serious select of drug-based skin products. Many researchers eager to develop new drug-based skin products have focused on the use of nanofiber scaffolds, which have exhibited many prospects for being put into clinical and lab application.

Natural and synthetic fibers and scaffolds are applied widely for skin regeneration and repair and these fibrous scaffolds are mechanically constant and proficient of having biologically function in the embed site (Gosiewska et al. 2001). Primarily, mechanical stability is reliant on the architectural design of the scaffold, the biomaterial, and the cell–material (drugs or other beneficial materials) interactions (Li et al. 2002). Biological function is managed by biological signals from extracellular matrix (ECM), the surrounding cells and growth factors (Reddi 2000). The cells surrounded by ECM molecules to regulate cellular activities and make available the mechanical support. The final and main goal of the nanofiber scaffold design is the fabrication of an ideal structure, which can substitute the natural ECM until host cells can regenerate and refabricate a new natural matrix (Alberts et al. 2002). Another application of nanofiber scaffolds is loading and delivering of drugs, which are promising and possible for skin regeneration and repair. As scaffolds make available mechanical support, the scaffold-loaded drug has a lot time for drug delivery, which always has been a hug problem. In this paper, we review the recent studies investigating the use of different drug-based skin scaffolds as load drug for skin regeneration and repair.

Skin damage, wound healing and treatment of skin lesions

Skin is the largest a multilayer organ of the body, serving primarily as a protective barrier against the environment (Ravichandran et al. 2012, Supp and Boyce 2005) and helps to inhibit body dehydration and organizes a physical barrier, avoiding the penetration of potentially dangerous agents to internal organs of body. The WHO estimates six million patients

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worldwide annually suffer from burns every year, while 300,000 deaths are related to burn injuries (Yildirimer et al. 2012).

Skin has a normal facility to stimulate regeneration after injury, which is a complex cascade of highly five integrated and overlapping phases of hemostasis, inflammation, migration, proliferation and maturation (Zahedi et al. 2010). The healing dynamic and continuous process, involving the interaction between growth factors, cellular components and cytokines, is highly dependent on the extension of the lesion and the number of affected layers and acting in concert to repair the damaged tissue (Boateng et al. 2008).

The treatment of skin lesions wound healing is an important problem in healthcare services and systems and need the critical consider in several parameters, which impact on the healing process, such as the wound depth (e.g., superficial partial-thickness, epidermal, full-thickness and wounds deep partial-thickness), the wound type (e.g., ulcer, burn, chronic and acute wound), the level of the exudate and the patient's health (e.g., diabetes and other persistent infections) (Guo and DiPietro 2010).

Currently, a great variety of strategies are available for the treatment of different types of skin lesions such as autografts or allografts strategies, creams, solutions and ointments products, tissue-engineered skin substitutes and *in situ* biofabrication of skin substitutes (Boateng et al. 2008, Groeber et al. 2011).

Currently, the use of autografts and allografts remains the 'gold standard' for skin regeneration. Autografts approaches have good adhesion to the wound bed, provide pain relief and reduce rejection rates. The main limitation of autografts approaches is limited availability of donor sites, induction of scar formation, patient morbidity and lengthy hospital stays.

In allografts approaches, main advantages are the possible incorporation into deep wounds and temporary prevention of wound dehydration and contamination with important limitations such as limited availability, possible leading to immune rejection and transmission of diseases.

Creams, solutions and ointments are widely used due to ease of use, low cost, their ability to provide disinfection, cleaning and debridement but using of these products may limit by some disadvantages such as limitation in skin regeneration and short residence time on the wound, which require frequent administrations.

Another approach for the treatment of different types of skin lesions is wound dressings, which mainly are used as a substitute to the autografts and allografts (Boateng et al. 2008, Groeber et al. 2011). However, demonstrated clinically effective, these types of products have some main disadvantages such as low adherence to the wound bed, an inability to regenerate skin attachments and promote regeneration of the lost tissue. Despite latest advances in biomaterials and manufacturing methods, both wound dressings and autografts/allografts have important limitations for skin regeneration and repair, which were earlier discussed and for overcome this limitation has been introduced another advanced approaches.

Tissue-engineered skin substitutes

In order to overcome limitations and solve the problem of discussed above approaches were developed tissue-engineered skin substitutes in both cellular (e.g., Apligraf™, MA; Organogenesis, MA) and acellular (e.g., Alloderm™; Biohorizons, AL) forms. Cellular constructs comprise both biomaterials and cells, which obtained from different origins including allogenic, autologous or xenogeneic (Böttcher-Haberzeth et al. 2010). However, cellular constructs are prepared of natural or synthetic biomaterials only, and can be applied in blend with autografts (Groeber et al. 2011).

The main advantages of tissue-engineered skin substitutes are promotion the regeneration of dermis and epidermis, prevention fluid loss and provide protection from contamination as well as delivery of ECM components, cytokines, growth factors and drugs to the wound bed and site and enhancing the healing process. However, available skin substitutes often suffer from a range of problems including inadequate vascularization which leading to poor integration, scarring at graft margins or the difficulty of reproducing skin appendages, inefficient adhesion to the wound bed and the inability to regenerate full-thickness wounds (Metcalfe and Ferguson 2007). Clinically available and novel skin regenerator and substitutes can be generally divided into epidermal, dermal and dermoepidermal tissue-engineered agents (Yildirimer et al. 2012). Table I provides characteristics of the ideal skin substitute, which has been used for skin regeneration and repair and is commercially available.

The main disadvantage of tissue-engineered skin substitutes and other drug for skin regeneration and repair is the remaining time in favorite site. This problem can be overcome with scaffolds. Scaffold has been used mainly to deliver the drug/cell/gene into the body.

Nanofiber scaffolds, synthesis methods and types of used polymer electrospinning technology and methods of scaffolds synthesis

Electrospinning or electrostatic spinning is a popular method capable of make ultrafine and non-woven nanoscale fibers (Figure 1). The electrospinning method has the important features such as affordability, simplicity, very high surface-to-volume ratio, wide range of materials selection, flexibility to adopt over a broad range of sizes and shapes and tunable porosity (Daraee et al. 2014a,b, Eatemadi et al. 2014c). Nanofibrous materials have been widely used because they have important promise for wide range of applications. Nanofibrous scaffolds materials can be fabricated of biodegradable and biocompatible polymers. Because of the significant potential of applying biomaterials in wide spectrum applications, the field of nanofibers has achieved extensive interest in biotechnology, tissue engineering and medicine.

Several fabrication techniques have been used to produce suitable polymer nanofiber scafold (NFS) for skin regeneration and repair and tissue engineering applications such as phase separation, self-assembly and electrospinning. Table II compares the key aspects and properties of these three fabrication methods.

Types of most used polymer in scaffolds fabrication

Many biodegradable polymers can be applied to fabricate nanofiber scaffolds such as natural, synthetic and composite of

Table I. Examples of current commercialized tissue-engineered skin substitutes which have been used for skin regeneration and repair

		Patient safety	Scaffold degradability	Duration of cover	Neodermis formation
Dermoepidermal substitute (composite)	Cadaveric skin	Potential for viral transmission immune rejection	Rejection rather than degradation	Temporary	Dermis revascularises and integrates into the wound bed. The epidermis is rejected 3–4 weeks post-transplantation
	Karoskin	Potential for viral transmission immune rejection	Rejection rather than degradation	Temporary	Dermis revascularises and integrates into the wound bed. The epidermis is rejected 3–4 weeks post-transplantation
	Apligraf	Potential for viral transmission	1–2 months	Temporary	Delivers ECM components, cytokines and GF to the wound
Dermal substitute	Alloderm	Potential for viral transmission	Incorporates into wound bed	Permanent	Repopulated by host cells, i.e., incorporates into host tissue
	SureDerm	Potential for viral transmission	Incorporates into wound bed	Permanent	Repopulated by host cells, i.e., incorporates into host tissue
	Integra	Not applicable	Half-life, 30 days	Semi-Permanent	Neodermis formation complete in 15–20 days
	Derma graft	Potential for viral transmission	Degrades by hydrolysis	Temporary	Scaffolds degrade over 20–30 days. Fibroblasts simultaneously produce ECM components and GF
Epidermal substitute	MySkin	Autologous keratinocytes are co-cultured with irradiated murine cells	<29 days	Permanent	Only applicable in partial-thickness and graft donor side wounds, but not in full thickness wounds
	CellSpray	Not applicable	Not found	Permanent	Only applicable in partial thickness and graft donor side wounds, but not in full-thickness wounds

Data were extracted from references.

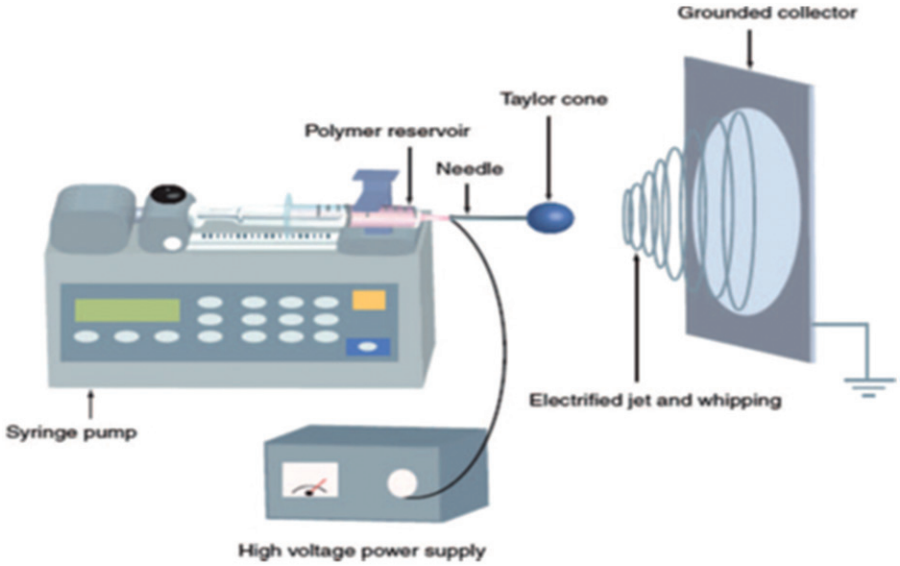

Figure 1. This diagram shows the structure of electrospinning device for the fabrication of nanofiber scaffolds. Scaffolds collect on a collector, which is different based on application.

the both. Biodegradable polymers have been applied to improve nanofiber scaffolds with diverse applications based on the requirement. Some scaffolds can be applied to provide temporary function such as cell carrier, agent and drug delivery, and short-time scaffolds, which are used until new tissue become mature and independent. In this class, polymer will substituted by native tissue or can easily deliver drug to favorable sites for improvement of regeneration and repair of skins. However, some scaffolds have been used for long-term applications such as use in surgery implants.

There are many different synthetic polymers for synthesis of scaffolds (Table III) such as PLGA (Badami et al. 2006, Chew et al. 2005), PCL (Luong-Van et al. 2006, Zare et al. 2014), PLLA (Badami et al. 2006), PLDLA (Cui et al. 2006) and copolymers, for example PCL-PLLA (Nikkola et al. 2005), PCL-PEG, PLLA-PEG (Mellatyar et al. 2014), PLGA-PEG (Daraee et al. 2014b, Mellatyar et al. 2014) and the main advantages of natural polymer are similarity and identically to some molecular biomaterials that exist in the human body. However, the main disadvantage of natural polymer is their decreased mechanical characteristics when isolated, thus this natural polymer requires further processing for handling.

Studied natural polymer has been applied to fabricate nanofiber scaffolds that have achieved increasingly research interests, including collagen (Venugopal et al. 2005), elastin (Boland et al. 2004), silk protein (Jin et al. 2004), fibrin, tropoelastin (Abbasi et al. 2014), elastin-mimetic peptide (Huang et al. 2005), oxidized cellulose (Son et al. 2004), hyaluronic acid (Um et al. 2004) and fibrinogen (Sindelar et al. 2006). Two main widely used types of ECM of human skin are

Table II. Comparison of various nanofiber scaffold processing methods

Scaffold processing method	General descriptions	General descriptions	Advantages	Disadvantages
Electrospinning	A process that essentially employs electrostatic forces for the production of polymer nanofibrous scaffolds, typically involves top-down approach	Relatively easy, lab and industrial scales	Simple and cost-effective, capable to produce long and continuous fibers with control over fiber orientation, mechanical properties, size and shape, versatile to many polymers	Using apparatus by high voltage
Self-assembly	A process in which atoms, molecules, and supramolecular aggregates organize and arrange themselves into an ordered structure through weak and non-covalent bonds; typically involves a bottom-up approach	Difficult and lab scale	Mimic the biological process in certain circumstances	Complex process, limited to a few polymers. Unable to produce long and continuous fibers with control over fiber orientation
Phase separation	A process that involves various steps, typically raw material dissolution, gelation, solvent extraction, freezing and drying, leading to the formation of nanofibrous foam-like structure	Easy and lab scale	Simple process, tailorable mechanical properties	Limited to a few polymers, longer processing time, unable to produce long and continuous fibers with control over fiber orientation

Table III. Different forms of electrospun polymeric scaffolds used in skin regeneration and tissue engineering

Biomaterial	Cells seeded on the scaffold	References
PCL	MSCs derived from the bone marrow of neonatal rats	Yoshimoto et al. (2003), Shin et al. (2004)
PCL	hMSCs	Binulal et al. (2010)
PCL	MSCs were isolated from male Wistar rats	Ruckh et al. (2010)
Collagen type I	Bone marrow hMSCs	Shih et al. (2006)
Silk fibroin	Human mesenchymal stem cells (hMSCs)	Daraee et al. (2014c)
Silk fibroin	Human bone marrow stromal cells (BMSCs)	Jin et al. (2004)
Chitosan	Human osteosarcoma cell line MG63	Jin et al. (2004)
PCL/collagen	Pig bone marrow mesenchymal cells (pBMMCs)	Ekaputra et al. (2009)
PLA/DBP	Human mandible-derived mesenchymal stem cells (hMSCs)	Ko et al. (2008)
PLGA/MWNTs/HA	Rat bone mesenchymal stem cells (BMSCs)	Zhang and Chen (2010)
Gelatin-siloxane (3-glycidoxypropyl trimethoxysilane)	Bone marrow-derived mesenchymal stem cells (BMSCs)	Ren et al. (2010)
Silk/PEO/BMP-2, Silk/PEO/nHAP, Silk/PEO/nHAP/BMP-2 (control: silk/PEO)	Human bone marrow derived mesenchymal stem cells (hMSCs)	Li et al. (2006)

including of proteoglycans and fibrous proteins. In the human skin fibrous proteins, depending on types of tissue possesses fiber diameter with limited spectrum between 50 and 150 nm (Eatemadi et al. 2014d).

Natural polymers used as biomaterials or scaffolds for tissue engineering and skin regeneration and repair are gelatin, cellulose, fibrinogen, fibrin, chitin, chitosan, hyaluronic acid, elastin, silk and collagen. Fabrication of this material into scaffolds for skin regeneration and repair and tissue engineering may possibly give new possessions to biomaterials. Biomaterials fabricated with this natural polymer are physically lighter and more porous, optically more tunable optical emission, mechanically stronger, electrically more conductive, magnetically more paramagnetic and chemically more reactive or less corrosive (Huang et al. 2003).

Blends of synthetic polymer and natural polymer were also applied for encompass properties of both. Studied merging polymer involved collagen-loaded PLLA-PCL (Huang et al. 2003), gelatin-loaded PCL (Ma et al. 2005), composites of PLLA-PCL and collagen (He et al. 2005), blends of PEO and silk (Li et al. 2002), composites of hyaluronic acid and PCL, composites of PCL and starch, composites of PLGA, elastin and collagen and composites of PLGA with PHBV (Ebrahimi et al. 2014a).

Two most approaches in skin regeneration and repair

The two important principles in skin regeneration and repair are based on two approaches: potential of the cells surrounding the damaged tissue for regeneration and delivery of skin drug to interest sites. The cells that are involved in the spontaneous repair of the damaged tissue or the cells surrounding the damaged tissue have the potential to regenerate into molecular structures that similar the original tissue. Living cells in native ECM have a 3D network molecular structure composed of two most multifibrils at nanoscale such as mainly proteins and proteoglycans. Thus, this hierarchical organization and structures presents a defined cell surroundings and environment with intermolecular binding interactions at nanoscale that will impact on the functional and morphological improvement of the cells. Studies have shown the importance of nanofiber scaffolds for skin regeneration and repair and tissue engineering applications. Nanofiber scaffolds with nanoscale molecular architectures and a larger surface area to adsorb proteins and skin drugs and offer many binding sites to receptors of cell membrane would be more biomimetic to support better cell–matrix interactions. Because of all reasons discussed above, thus the fabrication of a suitable nanofiber scaffolds is an important aspect to consider when designing scaffolds for skin regeneration and repair.

Nanofiber scaffolds as a tool for loading of drug and skin delivery

Another important principle in skin regeneration and repair is successfully delivery of skin drug to interest sites. Electrospinning methods are applied for skin regeneration and repair and tissue engineering and imitating of the morphology and size of natural ECM and fabricate of collagen nanofibrous scaffolds. As mentioned in Table II, many different types of scaffolds were fabricated for tissue engineering and skin regeneration and repair.

These scaffolds are applied to regenerate, replace and repair the skin and therefore need to be well fabricated and must have dimensional equality. By this way, fabrication of types I and III collagen scaffolds can mimic properties of natural collagen structure (Matthews et al. 2002). Electrospinning has been used for the fabrication of nanofibrous scaffolds, which imitate the structure of human body natural fibrous and regeneration of dermis (Aval et al. 2014, Venugopal et al. 2005), bones (Fujihara et al. 2005), nerve (Yang et al. 2004) and blood vessel (Venugopal et al. 2005). Blend of collagen scaffolds with polycaprolactone was fabricated as the aim of elasticity, flexibility and subsequently promising method for the production of smooth muscle tissues for engineered blood vessel (Venugopal et al. 2005). Wnek et al. fabricate a nanofiber scaffolds using fibrinogen for wound dressing, hemostatic products and skin repair (Wnek et al. 2003). Compositions of chitosan and gelatin nanofiber have improved the cellular and biological activities and skin regeneration and this blend was evaluated in regeneration of various tissues including skin and bone (Bhattarai et al. 2005).

Hydrogel scaffolds for skin regeneration and repair

Hydrogel matrices are scaffolds that chemically or physically cross-linked, water-soluble polymers, which can easily swell to form a gel-like scaffolds on exposure to water (Drury and Mooney 2003), because of their high water content and biocompatibility hydrogels are attracting for biological applications and skin regeneration and repair (Hoffman 2012) and can be fabricated from naturally occurring polymers such as chitosan, gelatine and collagen or synthetic polymers such as polyvinyl alcohol and poly(ethylene glycolide). Drug and growth factors are released from hydrogels scaffolds through diffusion of the drug and growth factor through mechanical stimulation, hydrolytic degradation of the scaffold or the highly hydrophilic scaffold (Drury and Mooney 2003). For example, dextran and gelatin can be synthesized as a scaffold polymer hydrogel for drug and cell delivery and can be used for skin regeneration and repair. An injectable physical hydrogels scaffold of poly(*N*-isopropylacrylamide) encapsulating cells have been fabricated for cartilage and nerve regeneration (Rahimzadeh et al. 2014) and as had improved effect this can be applied for skin regeneration and repair. Heparin/pluronic composite hydrogel scaffolds delivering drug and growth factor have also been prepared to encourage angiogenesis (Yoon et al. 2007).

Bilayer-structured membrane scaffolds for skin regeneration and repair

Recent approaches for wound dressings and skin regeneration have been focused at the improvement of the bilayer-structured membrane scaffolds, with composition of growth factors into nanofibers scaffolds for improved healing and skin regeneration. For example microspheres loaded by gelatin hydrogel containing epidermal growth factor (EGF) scaffolds have been an improved effect on skin regeneration and repair as well as re-epithelialization, improving the healing of the wound area. As aim prevention of infections antibiotics should be incorporated into the membranes since remaining a necessary drug concentration at the site of infection is essential for the treatment of an infected wound and repair of skin. For example, a bilayered-structured membrane scaffold combines a laminin-modified collagen membrane and silver sulfadiazine has been shown facilitation of the skin regeneration and dermal wound healing process (Lee et al. 2002).

Growth factor functionalized skin-regeneration scaffolds

EGF is associated in fibroblast proliferation, keratinocyte migration and differentiation, as well as granulation tissue formation. EGF highly improves skin regeneration and wound healing (Boateng et al. 2008) as well as the tensile strength of the consequential ECM (Baldwin and Saltzman 1998). Recent challenges concerning the delivery of EGF at favorite concentrations and duration's times still conquer because of its rapid failure within the wound environment, boosting research and studies into effective delivery and immobilization methods. For example, biodegradable micro- and nanospheres that comprise EGF make available remained EGF delivery and hence more effective skin regeneration and wound healing in a rabbit dorsal skin wound model (Ein and Langer 2012).

Fibroblast growth factor (FGF) is including of a large family of mitogens that actively involved in the processes of skin regeneration and repair, wound healing, angiogenesis, tumor progression and embryonic development (Süntar et al. 2011). Both acidic FGF and basic FGF are detected within the wound fluid at the primary stages of regeneration and healing (Kumbar et al. 2008). Both of them are effective mitogen and chemo-attractant for dermal fibroblasts, epidermal keratinocytes and vascular endothelial cells.

During skin regeneration and wound healing, vascular endothelial growth factor is highly expressed by keratinocytes within the wound bed to trigger new blood vessel construction vital for tissue and skin regeneration (Liu et al. 2012) and re-epithelialization and reformation of wounds (Ebrahimi et al. 2014b). Another GFs have been studied and proved their potential in skin regeneration and repair such as insulin-like growth factor-1 (Renner et al. 2009), Platelet-derived growth factor and transforming growth factor-b (Bartolo et al. 2012).

The outcomes achieved with the use of GFs to accelerate and improvement of skin regeneration and wound healing process in experimental and clinical levels must be applied carefully, because such factors are often implicated in tumor growth and exuberant tissue. Such abstruse conditions mandate cautious assessment for two mainly reasons. First, the

determination of beneficial effects on skin regeneration and wound healing is constant. Selective GF treatment results in accelerated rates of regeneration and healing both in preclinical and experimental trials.

Second, inappropriate amounts of GFs are prevented because of potentially carcinogenic affinities *in vivo*. Any such longstanding adverse effects must be accepted before starting clinical trials. GFs are quickly destroyed into natural metabolites by the wound fluid, thus removing any downstream effects. Such fast removal from the body is preventable via encapsulation techniques and scaffold technology, supporting GFs to remain within the wound for longer prolonging their trophic effects.

Conclusion

The burden of cutaneous in personal and financial terms and the increasing need for more suitable skin regenerator and wound dressing's agents has promoted the search for alternative skin substitutes and regenerator that actively induce wound regeneration. But clinically available and promising treatment approaches are still requiring despite various skin regenerator and substitutes being under full investigation.

There are a multitude of choices and potential alternatives for tissue engineering skin constructs and numerous regenerator and substitutes are being investigated for skin regeneration and repair in human usage in which some of them are already commercialized (Table I). The current absence of more complex and superior skin alternatives needs a focus on regeneration rather than replacement and for this reason the advanced researches and studies are progressively integrating the engineering skin nanofiber scaffolds that actively encourage regeneration by incorporating external drug and GFs and SCs to regenerate and recreate an advantageous cellular microenvironment and normal skin.

The ultimate purpose of tissue-engineered skin scaffolds is to empower natural, complete and accelerated wound regeneration. In this review focused on the multitude of different scaffold materials, fabrication techniques and delivery of drugs with scaffolds. The skin regeneration using stem cell is beyond the scope of this article but has been extensively reviewed elsewhere (Wang et al. 2006). The suitable skin regeneration scaffold should actively assist skin regeneration and formation and avoid scarring. Thus, much attention has been focused on generating appropriate nanofiber scaffolds that can performance as delivery tools for drugs and GFs.

Declaration of interest

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