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Biomaterials for Promoting Wound Healing in Diabetes

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Abstract

Impaired wound healing is the leading cause of non-traumatic lower limb amputation in people with diabetes mellitus. Skin substitutes engineered from biomaterials currently play an important role in the healing process of diabetic wounds, especially those wounds that fail to show progress after standard wound care. This article summarizes current developments of biomaterials used for promoting the wound healing process in either diabetic animal models or patients with diabetes mellitus. Those biomaterials can be categories into tissue-derived scaffolds, hydrogel-based biomaterials and biomaterials with controlled-release of signaling molecules. Tissue-derived scaffolds maintain perfect extracellular matrix architectures for three-dimensional cell growth and rebuilding of multi-layer tissue structures within scaffolds after implantation. Hydrogel-based biomaterials are engineered to resemble the natural extracellular matrix for cell invasion and capillary growth. Biomaterials processed with cells or controlled-release of signaling molecules (growth factors, cytokines) can induce angiogenesis, re-epithelialization, cell recruitment and migration as well as inhibit consistent inflammation, thereby accelerating the wound healing process. Better understanding of the mechanism of diabetic wound healing will lead to the development of even better biomaterials possibly with inclusion of engineered patient derived cells or factors which will aid *in vivo* vascularization and consistent release of tissue-inductive signals. By reviewing the recent literature, we draw future perspectives on new strategies for further improvement of the individualized therapy of diabetic wounds.

Keywords: Wound healing; Biomaterials; Scaffolds

Introduction

Impaired wound healing is the leading cause of amputation in people with diabetes mellitus [1]. It produces a high risk of recurrent hospitalization and has a long-term negative effect on quality of life, morbidity and mortality as well as on social economy [2,3]. Despite a relatively high standard in the treatment of chronic wounds, there still exists a high amputation rate. In diabetic wounds, due to infection and inflammation which lead to imbalance of protease and reactive oxygen species, essential growth factors are degraded, the ability of angiogenesis is impaired and cell recruitment to the wound sites is inhibited [4]. To facilitate wound healing and tissue regeneration in this situation, biomaterial-based scaffolds are currently widely used to provide extracellular matrix for cell proliferation and migration. In the recent years additional optimization of the cellular response by delivery of angiogenic factors for vascularization to the affected tissue was a focus of research in this area. This article reviews the literature on biomaterials used for diabetic wound healing and draws some future perspectives for further development.

Type of Biomaterials Applied for Diabetic Wound Healing

According to the components of biomaterials, they can be categorized into three types: tissue-derived biomaterials, hydrogel-based biomaterials and biomaterials with controlled-release of signaling molecules (Figure 1 and Table 1).

Tissue-derived scaffolds

Scaffolds derived from tissues mimic the natural extracellular matrix substrates and provide three-dimensional natural structures as extracellular microenvironment for the cells. These valuable properties are frequently exploited for tissue engineering applications as well as for improvement of diabetic wound healing [5-7].

Those scaffolds can be processed from either cadaveric allografts of skin tissue, placenta tissue, porcine small intestinal submucosa (SIS) or from microalgae [8]. Cadaveric allograft is made from cadaveric human skin, in which the epidermis and cells are removed to avoid immunologic rejection [8]. Dehydrated Human Amnion/Chorion Membrane (DHACM) is composed of human amnion/chorion membrane, with a single layer of epithelial cells, a layer of basement membrane and an avascular connective tissue matrix to promote wound healing [9,10]. It has been reported to achieve wound closure faster than standard wound care. Cryopreserved micronized amnion (CPM) is a human wound matrix. It is able to provide fetal cells like MSCs, neonatal fibroblasts and epithelial cells as well as growth and angiogenic factors to the wound [11], however their respective contribution to the wound healing is still a matter of debate. Zheng et al. [12] applied cryopreserved living micronized amnion onto the wounds of db/db mice. They reported that the wound healing process was greatly promoted. They attribute this effect to secretion of growth factors, inflammation-related, and chemotaxis-related factors, which regulated migration of macrophages, recruitment of CD34+ progenitor cells, and neovascularization [12]. Porcine SIS is an acellular matrix derived from small intestinal submucosa of porcine, which showed positive effects on promoting diabetic wound healing [13]. Those tissue-derived scaffolds provide nearly perfect extracellular matrix architectures for three-

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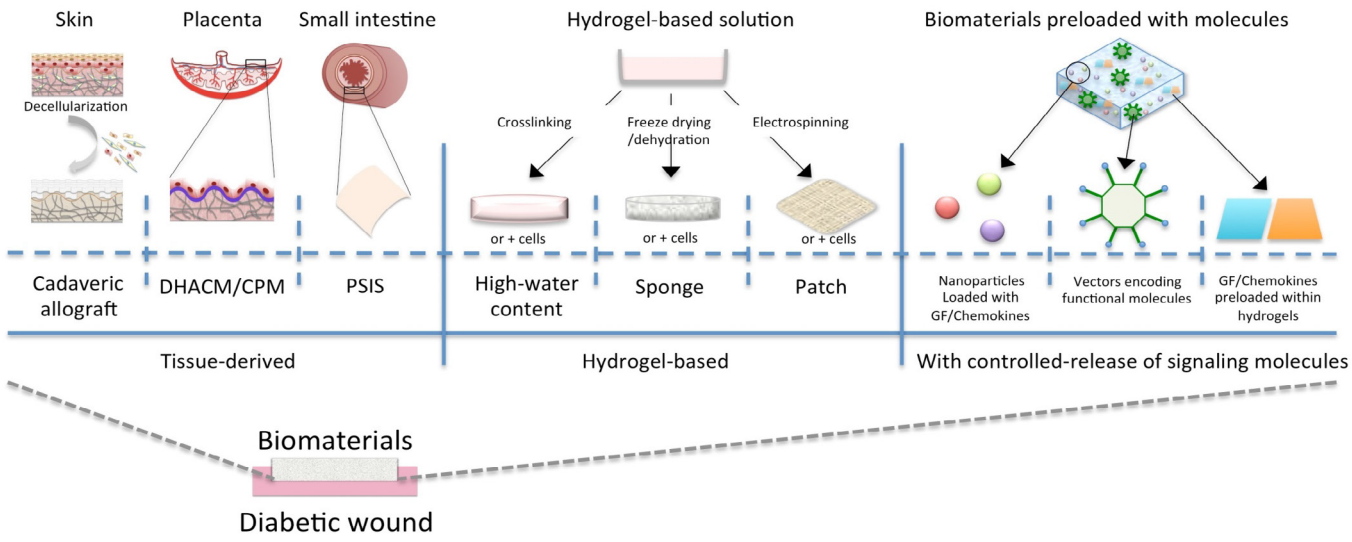

Figure 1: Schematic illustration of the categories of biomaterials used on diabetic wounds.

Categories	Source	Biomaterials reported in literature
Tissue-derived biomaterials	Skin tissue from cadaver	CAM(cadaveric acellular matrix) [8]
	Placenta	DHACM [9,10] CPM [11,12]
	Small intestine	Porcine small intestinal submucosa [13]
Hydrogel-based biomaterials	High-water content hydrogels	Fibrin [19]
		Collagen-GAG [20]
		Gelatin microcryogels [23] GAG [28] BLCC [29]
	Freeze-drying sponges	pGlcNAc [18] Collagen sponge [27]
	Electrospun patches	Collagen/PLGA [21] Silk fibroin [24]
Biomaterials with controlled-release of signaling molecules	Nanoparticles loaded with GF/chemokines	VEGF, bFGF nanoparticles in PEtU-PDMS/ fibrin [33] Curcumin loaded chitosan nanoparticles into collagen-alginate [36]
	With vectors encoding functional molecules	AdeNOS in fibrin scaffold [37] Hyaluronic acid-MMP hydrogels with VEGF plasmids [34]
	GF/Chemokines preloadedd within Hydrogels	Glucophage-loaded collagen/PLGA [21] Gelatin-PGA-based scaffold payload MCP-1 [35]

Table 1: Categories of biomaterials used on diabetic wounds.

dimensional cell growth and rebuilding of multi-layer tissue structures within scaffolds after implantation, promoting tissue regeneration in diabetic wound healing processes.

Hydrogel-based biomaterials

Engineered hydrogels have the advantage over tissue derived matrices, that their properties can be changed more or less at will and that the ingredients are better defined. Usually they are engineered to resemble the extracellular matrix of natural soft tissues [14]. These biomaterials can be prepared as high-water-content hydrogels, sponge and patch structures or other architectures, processed by crosslinking, dehydration or freeze drying and electrospinning technique, respectively [15-17].

Poly-N-acetyl Glucosamine (pGlcNAc) is a matrix derived from microalgae, which is FDA approved for treating diabetic foot ulcers [18].

Fibrin is a common hydrogel used to fabricate scaffolds in the treatment of diabetic wounds [19]. It is able to enhance angiogenesis and modulate inflammation in the wound, which will accellerate the healing process. Integra is a collagen-glycosaminoglycan scaffold, which has been already applied in clinic for fibroblast and endothelial invasion and capillary growth [20]. It could also support epithelialization in the absence of vascularization. Lee et al. developed a nano-fibrous collagen/poly-D-L-lactide–glycolide (PLGA) scaffold membrane by electrospinning technique. This scaffold could be applied onto diabetic wounds and loaded with drugs, providing sustained release of glucophage and promoting wound closure [21].

In addition to biocompatible hydrogel scaffolds, cells play an important role in the process of wound healing by producing essential growth factors and inducing neovascularization. Therefore, cellularized scaffolds based on above biomaterials were developed for diabetic wound healing [22,23]. Navone et al. demonstrated electrospun nano-fibrous Silk fibroin patches cellularized with human adipose-derived mesenchymal stem cells (ADMSCs) as an effective treatment for wound healing, which improved skin regeneration in diabetic mice [24]. ADMSCs were reported to confer benefits as tissue restorative agents *in vivo*. This is ascribed to their own multi-linear differentiation properties as well as their ability to produce trophic factors for tissue regeneration [25,26]. O'Loughlin et al. seeded autologous early endothelial progenitor cells onto collagen scaffolds. They observed that cells exposed to osteopontin accelerated the speed of wound closure along with increased angiogenesis [27]. It was noted that the wound

healing benefit was associated with a more efficient vascular network. Breitbart et al. seeded mouse dermal fibroblasts onto polyglycolic acid scaffold matrices, on which the cells were retrovirally transduced with the human platelet-derived growth factor B (PDGF-B) gene [28]. Results showed accelerated wound healing in the group with PDGF-B transduced cells. Bilayered Living Cellular Construct (BLCC) is a FDA-approved product, which is engineered as bilayered collagen matrix with a dermal equivalent made of human neonatal foreskin fibroblasts and an epidermal equivalent made with human neonatal keratinocytes [29]. In randomized controlled trials, BLCC achieved closure in 56% of patients by 12 weeks compared with 38% of patients with standard wound care. Those hydrogel-based biomaterials provide a defined extracellular matrix for cell invasion, proliferation and vascularization, facilitating skin regeneration and angiogenesis in diabetic wounds.

Biomaterials with controlled-release of signaling molecules

In addition to the extracellular matrix support and biological effect provided by the biomaterial scaffolds, tissue-inductive signals for the cells that rebuild the skin are also essential. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) have been shown to promote would healing by inducing angiogenesis and inhibiting prolonged inflammation [24]. However, these molecules are degraded quite fast by enzymes existing in the protease-rich wound environment [30]. Therefore, researchers have developed controlled-release systems which are able to provide an efficient concentration of those functional molecules at the wound site during the healing process as well as protect the growth factors and cytokines from degradation and inactivation [31,32]. The release of the molecules was maintained by encapsulating nanoparticles, vectors (virus, plasmid, DNA, etc.) as well as preloading molecules within hydrogels during preparation [33-35].

Losi et al. developed a poly (ether)urethane–polydimethylsiloxane/fibrin-based scaffold containing nanoparticles loaded with VEGF and bFGF. This scaffold induced complete re-epithelialization of the wound of diabetic mice, along with enhanced granulation tissue formation and collagen deposition [33]. Karri et al. impregnated curcumin loaded chitosan nanoparticles into collagen-alginate scaffolds for treating diabetic wounds [36]. Breen et al. developed a fibrin scaffold for delivery of adenovirus encoding endothelial nitric oxide synthase (AdeNOS) to the wound of diabetic rabbits [37]. The combined material enhanced eNOS expression, inflammatory response and lead to a faster rate of re-epithelialisation, resulting in augmented production of nitric oxide and thereby acceleration of wound healing. Tokatlian et al. created porous hyaluronic acid-MMP hydrogels with VEGF plasmids for local gene therapy in a diabetic mouse wound [34]. Yin et al. engineered a gelatin-polyglycolicacid (PGA)-based scaffold with a payload of monocyte chemoattractant protein-1 (MCP-1) by electrospinning technique. *In vivo* experiments confirmed an increased recruitment of F4/80+macrophages into the wound bed by MCP-1, accelerating wound healing in a diabetic mouse model [35]. The biomaterials releasing tissue-inducing signals can promote angiogenesis, re-epithelialization, cell recruitment and migration as well as inhibit consistent inflammation in the wound area, which accelerates wound healing processes.

Conclusion and Future Perspectives

Chronic wounds in patients with diabetes mellitus are a major drain on the social economy, and are projected to play an even bigger role in the future. They result in a high risk of amputation, morbidity and mortality. According to the mechanism of impaired diabetic wound formation, tissue repair process and regeneration, biomaterials based on tissue-derived scaffolds, hydrogels as well as controlled-release growth factors and cytokines have been applied on diabetic wounds in research and clinical settings. Results showed positive effects on accelerating wound healing processes, by promoting angiogenesis, cell migration, re-epithelialization and tissue regeneration. However, the speed of vascularization of scaffolds, which occurred *in vivo* after implantation, might be insufficient to supply embedded cells within the first critical week. The level of tissue-induced molecular signals released from biomaterials is mainly dependent on the initial concentration and drops after implantation [36,37]. New strategies for *in vivo* vascularization before implantation and devices or systems for consistent releasing of tissue-inductive signals should be considered for future investigation. Antibacterial ability of biomaterials could also be created with a consistent releasing system. Developing new biomaterials on the basis of a better understanding of the underlying mechanisms will further promote diabetic wound healing. Advances in autologous cell therapy like iPSC (Induced pluripotent stem cell) technology and use of blood derived cells for autologous factor production may overcome the need of non-autologous cells/factors in the future, leading to optimized individualized therapy for diabetic wounds [38,39].

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