Pyrex Journal of Medicine and Medical Sciences

Vol 4 (5) pp. 44-49 October, 2017
Author(s) retain the copyright of this article
http://www.pyrexjournals.org/pjmms
ISSN: 2579-1230
Copyright © 2017 Pyrex Journals

Review paper

Nano Biomaterials: A promising therapeutic strategy for skin wound healing in diabetic populations?

Juan Du[1] and Xuelai Liu[2*]

[1]Department of Endocrinology, The People's Hospital of Jilin Province, Chang Chun, China.
[2]Department of Surgery, Li Ka Shing Faculty of Medicine, the University of Hong Kong, Hong Kong.

Accepted 3rd, October 2017

Abstract

The diabetic wound healing is a common problem faced by both physicians and surgeons. The applications of nano biomaterials opened a new way to heal diabetic wounds. There were four parts in this review. First, we introduced the concept of the nano biomaterials. Second, we summarized systematically the mechanism of the nano biomaterials used for promoting wound healing. Thirdly, the application of nano biomaterials in clinical practice was introduced. At last, we mentioned the features of diabetic wound and presented the basic and clinical researches of the nano biomaterials in diabetic wound healing.

Keywords: Nano biomaterial, diabetes mellitus, wound healing.

INTRODUCTION

Skin wound healing is a complicated biological process, which is characterized by coagulation and hemostasis, inflammation, proliferation and remodelling. The coagulation and hemostasis usually last several seconds post-wounding in normal. The activated platelet activation during the coagulation process will induce inflammatory responses and potential vascularization. The exposed extracellular matrix (ECM) released in the wound site and microorganisms accessing into the wound bed. The function cells including keratinocytes in the epidermal layer and fibroblasts in the dermal layer will start to proliferate and migrate towards wound bed. Then the granulation tissue forms and re-epithelialization processes are activated, (Du and Liu, 2017). The various cellular responses and different molecular regulate in normal inflammatory and proliferation processes. With the minimized wound bed and following complete wound healing, the remodelling process is further activated. It consists of decreased ECM content and optimized histological structures.

But the diabetic wound healing is more complex. The high blood glucose level can affect almost every step of the healing process. Thus, diabetic wound healing is a problem faced by both physicians and surgeons. Many new theories and technologies have been used in medicine in recent years. Especially the nanotechnology and nano biomaterials have been emerging rapidly in numerous applications of diagnosis and therapy in the last three decades.

When a new method is applied in basic or clinical medicine, medical researchers often ask whether it can be used in their interested studies. As a result, doctors have a novel therapeutic direction with nanomedicine on diabetic wound healing. Some doctors have focused on this exciting technique. This review article provides a systematic evaluation of nano biomaterials in diabetic wound healing.

Corresponding author email: liuxuelai_steven@163.com

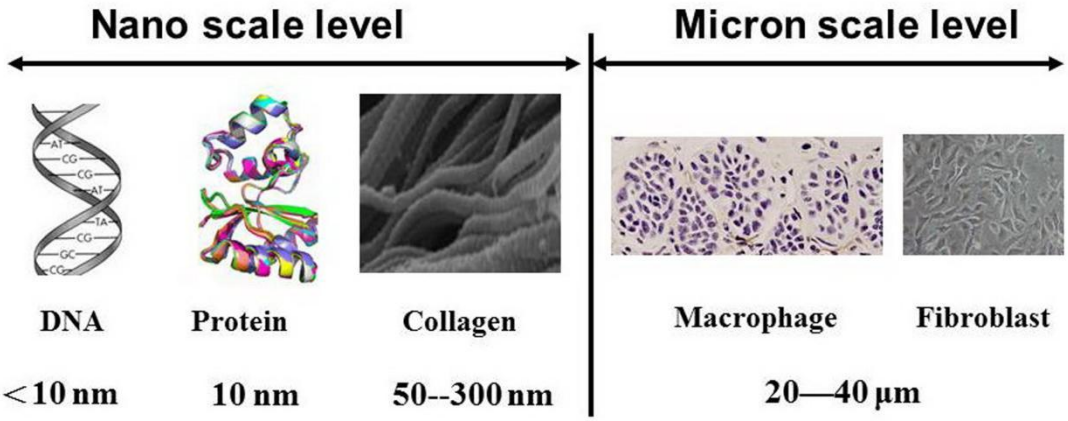

Fig 1: Nano particles have greater surface area-to-volume ratios

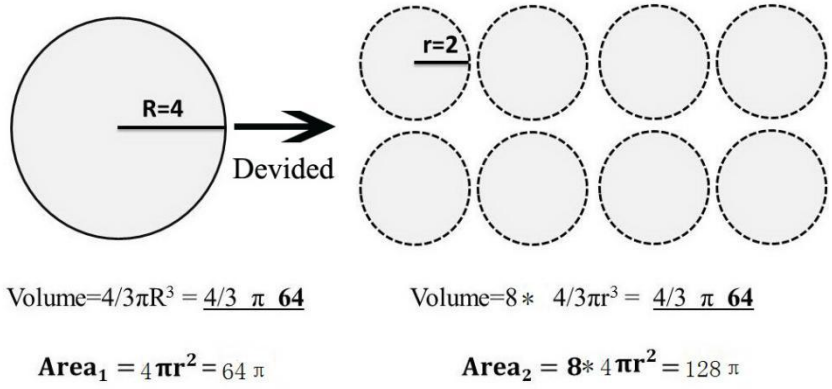

Fig 2: Comparison between nano scale and micro scale

WHAT ARE NANO BIOMATERIALS?

A nanometer (nm) is a scale that equal to one billionth of a meter 10^{-9}m. The size of nano biomaterial is usually controlled at 1 to 100 nm level, which is very important to biological properties and functions. The smaller the particle, the larger surface area-to-volume ratio it is. That can increase the particle dissolution rate. The large surface areas of nano particles can load more surface functional ligands. So the nano particles have good solubility and bioavailability, (Du and Liu, 2014; Liu and Wong, 2013; Liu, 2012) (Fig 1). The sizes and surface characteristics of nano particles can be controlled. The width of the DNA is approximately 2.5 nm and the measure of protein molecules is 1-20 nm, (Wong and Liu, 2012) (Fig.2). The nano particles have been used in therapeutic applications because of the same size of domain equal to proteins. Currently the useful nano biomaterial includes Ag nano-particles (nano-Ag), Au nano-particles (nano-Au), SiO2 nanoparticles and TiO2 nanoparticles, (Zhukova *et al.,* 2012; Hassan *et al.,* 2012). Nano-Ag and Nano-Au are main biomaterials in medical research.

MECHANISM OF NANO BIOMATERIALS IN WOUND HEALING

Silver nitrate was used as a classic and effective antibacterial drug in clinical therapy, as well as silver sulfadiazine has been used in burn treatment until now. With the progression of nanotechnology, the nano-Ag antibiotic efficiency has absorbed the researchers' eyeball. Nano-Ag is more efficient than other silver compounds because of their significantly stronger antibiotic activity and larger surface area to volume ratio, (Gravante *et al.,* 2009). The mechanisms of nano-Ag biological action included:

1). Nano-Ag provides a larger surface area for attaching

bacteria cell membrane and entering the cell inside. It is important for the antimicrobial activity, (Liu and Wong, 2013; (Wong *et al.,* 2009).
2). Nano-Ag can damage the respiratory chain of bacterial mitochondria. The bacterial cell will die without respiration, (Wong *et al.,* 2009).
3). Nano-Ag had anti-inflammatory properties. The nano-Ag can modulate various cytokines expression, including IL-6, TNF-α, IFN-γ, (*Wong et al.,* 2009; Wong and Liu, 2010) and so on.
4). Nano-Ag can release continuously Ag+ inside the bacterial cells at lower pH. The further anti bacterial activity includes free radicals and oxidative stress, (Wong and Liu, 2010).

Nano biomaterials can promote wound healing directly

Our group focused on the cellular response and events including epidermal re-epithelialization and dermal contraction during wound healing treated with nano-Ag. We found that nano-Ag could drive fibroblast differentiation into myofibroblasts to promote wound contraction. So it could increase the rate of wound healing. Our findings further extend the current knowledge of nano-Ag in cellular level, (Liu et al., 2010).

As we know, the collagen is produced mainly by fibroblasts in the dermal layer. Especially Type I collagen and III collagen are the most abundant. Thus, we further explored the tensile properties of healing skin after nano-Ag treatment. The results revealed that nano-Ag improved tensile properties and promoted better fibril alignment in skin wound healing. So we concluded that nano-Ag could regulate collagen deposition and promote excellent wound healing, (Kwan *et al.,* 2011). These events have significant implications for wound treatment in clinical practice.

Furthermore, a Nano-fibrous membrane (NFM) was obtained with nano-Ag and surface-grafted collagen. After modification, the NFM inhibited bacteria's growth with a concomitant increase of membrane water absorption. The NFM was better than the commercial collagen sponge wound dressing in animal wound models, (Chen and Chiang, 2010). Recently a series of novel chitosan-bentonite nano-composite films were reported in wound healing application, (Archana *et al.,* 2013; Devi and Dutta, 2017). Similarly the TiO2 nanoparticles dressing could accelerate healing of open excision type wounds in vivo and in vitro, (Archana *et al.,* 2013; Archana *et al.,* 2015). The synergistic effects of nano compound dressing made it a suitable candidate for wound healing applications.

ECM regulation for tissue regeneration

It is well known that ECM is very important for cell proliferation both in vivo and in vitro. The main content of native ECM is collagen as a scaffold. The electrospun nanofibrous structures affect the efficiency of the novel scaffold for regenerating biological tissues, (Wang *et al.,* 2017). The electrospun nanofiber matrices demonstrated morphological near to natural ECM and could modulate cell behaviour. It was found that electrospun nanofibrous scaffolds could support attachment, spreading, and proliferation of mesenchymal stem cells, (Perumcherry *et al.,* 2011). The nanofiber could provide models of environment to support stem cell differentiation and proliferation. Thus, nanofiber matrices can be used as scaffolds for the soft tissues regeneration just like skin and skeletal muscle, (Kumbar *et al.,* 2008).

American scientists also reported the formation of multilayered three-dimensional (3D) tissues using nanofibers. The cells proliferated continuously in 3D constructs and deposited new ECM. Both fibroblast and keratinocyte being cultured within layers constructs the bilayer skin tissues including epidermal and dermal layers were consequently produced at least. This method has large potential to form functional skin tissues composing of multiple cell types and scaffold, (Yang *et al.,* 2009). The similar result was reported by other innovators, (Chong *et al.,* 2007).

Romano NH *et al.,* described how to synthesize protein use multiple repeats of nanoscale peptide together and design full-length engineered ECM mimics. These were the ultimate goal for biological studies of cell-matrix interactions, both in physiological processes and in regenerative medicine. That was a similar idea but different method was reported by others. M Skotak and his group prepared the nanofibrous scaffolds and without micrometer-sized polyethylene glycol (PEG) fibers that served as sacrificial templates, (Skotak *et al.,* 2011). So the nano fibrous scaffolds lead to artificial skin feasibility.

Nano biomaterials can support skin regeneration by promoting stem cell growth

Nanofibrous scaffolds coupled with stem cells are emerging as a key technique in the development of tissue engineering, (Prakash *et al.,* 2010). Researchers have improved human cell growth on titanium (Ti) used for dental implants through the formation of a nano-network surface oxide layer. They found the formation of a TiO2 nano-network on Ti surfaces can promote human mesenchymal stem cell growth both in vitro and in vivo, (Chiang *et al.,* 2009).

The other group evaluated the activation of wound dressing based on anionic polymers and magnetic nano-particles loaded with usnic acid (Fe3O4@UA). They determined that the nano wound dressings could increase normal human fetal stem cell and antimicrobial properties, (Grumezescu *et al.,* 2014). But it is not clear on the mechanism of nano materials to promote stem cell differentiation yet.

THE CLINICAL APPLICATION OF NANO BIOMATERIALS IN WOUND HEALING

Commercial application of Nano-Ag dressing has been used widely in clinic. This innovation promotes the healing process of residual wounds, (Huang *et al.,* 2007; Yin *et al.,* 1999). Because of the reduced number of dressing changes, nano-Ag dressings are less expensive, (Silver *et al.,* 2007; Cox *et al.,* 2011). It was reported that a case of large body surface toxic epidermal necrolysis treated successfully with a nanocrystalline silver dressing, (Asz *et al.,* 2006). Another case was nanocrystalline silver in an acute surgical wound to prevent localized skin necrosis due to infection and avoid skin grafting as a secondary procedure, (Bhattacharyya and Bradley, 2008). Because of reducing evaporative water loss, increasing oxygen permeability, promoting fluid drainage and inhibiting Gram-positive and Gram-negative bacteria (Unnithan *et al.,* 2012), the electrospun nanofibrous membranes has potential applications for wound dressing based upon its unique properties, (Khil *et al*., 2003).

NANO BIOMATERIALS AND DIABETIC WOUND HEALING

Wound healing is an important branch of diabetes research. Higher blood glucose levels can affect so many tissues and organs in the body. So the diabetic wound had its special characteristics. First, skin thickness, microvascular density, collagen fibers and collagen content in diabetics are significantly reduced compared with normal controls (Elsharawy *et al.,* 2012). Epidermal stem cell content also decreased in the skin of diabetic subjects, (Liu *et al.,* 2005). High glucose levels could affect epidermal keratinocytes and dermal fibroblasts directly, (Yu *et al.,* 2011; Deveci *et al.,* 2005). These cells usually play important roles in skin wound healing. Second, diabetic subjects tolerated infection poorly, on the contrary the infection status affected blood glucose control. This repetitive cycle leads to uncontrolled hyperglycemia, which further affects the host's response to infection, (Hobizal and Wukich, 2012).

Inflammatory mediators and cytokines can also be changed in a hyperglycemic environment, (Tiaka and Papanas, 2011; Rajangam and An, 2013). These factors can affect the diabetic wound proliferation phase. Third, endothelial progenitor cell dysfunction induced by diabetes could impair wound healing, (Kanitkar *et al.,* 2013). Impaired neovascularization in diabetes often causes the malnutrition of the local wound skin. Particularly high glucose-related neopathologies often induce sensory nerve defects. This can lead to secondary damage to the lower limbs. Fourth, the high blood glucose and the open wound can affect the catabolic state. This metabolic dysfunction of negative nitrogen balance impairs protein, fibroblast and collagen synthesis, and further systemic deficiencies are propagated, which cause nutritional compromise, (Hobizal and Wukich, 2012; Du and Liu, 2016). All of these reasons lead to non healing diabetic wound.

There is another reason that diabetic animals are very weak and usually cannot tolerate a second injury. It is difficult to establish a trauma model on diabetic animals. Thus, data regarding the application of nano biomaterials on diabetic wounds in animal are limited. Researchers have reported on nanofiber treatment of diabetic wounds. Their results suggested that a good provisional matrix may provide the missing cues to cells and response toward improved healing directly in situ, (Balaji *et al.,* 2012). Xu Jun *et al.,* observed that human epidermal growth factor nano-particles could promote ulcer healing in diabetes animals, (Xu *et al.,* 2009).

An Indian research group developed a wound dressing for diabetic foot ulcers composed of chitosan, hyaluronic acid and nano-Ag. Their results suggested that the compound dressing could be used in diabetic foot ulcers with antibiotic resistant bacteria. They also optimized the best antibacterial with the lowest toxicity concentration of nano-Ag towards mammalian cells, (Anisha *et al.,* 2013). Kumar PT *et al.,* reported the results of the compound of chitosan hydrogel and nano zinc oxide on the wound. They found the compound could active platelet, enhance blood clotting and control degradation in the wound. The new nano composting bandage can be used for chronic diabetic wound, (Kumar *et al.,* 2012).

Our laboratory group observed db/db mice wound healing treated with nano-Ag. The nano-Ag could promote diabetic wound healing with less healing time. Even in diabetic littermates, nano-Ag still accelerated wound healing compared with the control group, (Tian *et al.,* 2007). Nano-Ag has been reported as the mechanism of non-contractile refractory wound in type 2 diabetic animals, (Elsharawy *et al.,* 2012). Our group determined that nano-Ag could regulate differential responses in both keratinocytes and fibroblasts during skin wound healing. Fibroblasts can further differentiate into myofibroblasts. The latter can promote effective wound contractility. So our hypothesis is that nano-Ag may heal diabetic wounds. The data will be published in the future.

In clinical applications, Fu Xiangyang observed 250 cases of diabetes with body surface abscess drainage that were treated with antibiotic nano-Ag dressings. They observed the infectious time, healing time, and dressing change time between the experimental group and the control group. At last they concluded that medical antibiotic nano-Ag dressings could promote diabetic wound healing, (Fu and Guo, 2011).

A new dressing based on lipidocolloid technology (TLC) impregnated with nano-oligosaccharide factor (NOSF) has been developed. TLC-NOSF was made of carboxymethylcellulose particles spread in a petroleum gel network. The TLC-NOSF clinical random trial,

including 14 French hospital departments was reported that were involved in diabetic foot ulcer management. The results suggested that TLC-NOSF matrices could be a beneficial therapeutic strategy for diabetic wounds, (Richard *et al.,* 2012).

Furthermore, a number of randomized controlled trials with TLC-NOSF dressings on chronic wounds were observed. Their aim was to determine whether the clinical trials' results translate into routine management of diabetic and chronic wounds. All the results indicate that using TLC-NOSF dressings in routine wound management can reduce the healing time. In addition, their data also suggest that the earlier the decision to use this dressing, the shorter the time to closure, whatever the severity and the nature of these chronic wounds, (Münter *et al.,* 2017; Sanahan, 2013).

OUTLOOK

Nano biomaterials opened a new way to treat diabetic wounds. However, there are many questions that are not clear yet, such as the exact signaling pathway in the diabetic wound healing treated by nano bio-particle. We also need cell culture results from different glucose levels and nano biomaterial interventions. Additionally, we need to understand how to decrease the nano scaffold. Another side effect is that the appearance of skin wound would have a slate-gray because of the silver diposition. This is not only a surgical problem, but also a cosmetic problem. These will be directions for future studies on the application of nano biomaterials on diabetic wounds. Meanwhile, some novo approach including 3D bio-printing technique (Du and Liu, 2014) and stem cell research will make nano medicine more mature and eventually serve as a more effective treatment for our health care.

REFERENCES

Anisha BS, Biswas R, Chennazhi KP, Jayakumar R. Chitosan-hyaluronic acid/nano silver composite sponges for drug resistant bacteria infected diabetic wounds. Int J Biol macromol 2013;62:310-320.

Archana D, Dutta J, Dutta K.Evaluation of chitosan nano dressing for wound healing: characterization, in vitro and in vivo studies.Int J Biol Macromol. 2013 ,57:193-203.

Archana D, Singh BK, Dutta J. Chitosan-PVP-nano silver oxide wound dressing: in vitro and in vivo evaluation. Int J Biol Macromol. 2015, 73:49-57.

Archana D, Singh BK, Dutta J. In vivo evaluation of chitosan-PVP-titanium dioxide nanocomposite as wound dressing material. Carbohydr Polym. 2013 ,95(1):530-539.

Asz J, Asz D, Moushey R, Seigel J, Mallory SB, Foglia RP. Treatment of toxic epidermal necrolysis in a pediatric patient with a nanocrystalline silver dressing. J Pediatr Surg 2006 ; 41:e9-12.

Bhattacharyya M, Bradley H. A case report of the use of nanocrystalline silver dressing in the management of acute surgical site wound infected with MRSA to prevent cutaneous necrosis following revision surgery. Int J Low Extrem Wounds 2008 ; 7:45-48.

Chen JP, Chiang Y. Bioactive electrospun silver nanoparticles-containing polyurethane nanofibers as wound dressings. J Nanosci Nanotechnol 2010;10:7560-7564.

Chiang CY, Chiou SH, Yang WE, Hsu ML, Yung MC, Tsai ML. Formation of TiO(2) nano-network on titanium surface increases the human cell growth. Dent Mater 2009; 25:1022-1029.

Chong EJ, Phan TT, Lim IJ, Zhang YZ, Bay BH, Ramakrishna S. Evaluation of electrospun PCL/gelatin nanofibrous scaffold for wound healing and layered dermal reconstitution. Acta Biomater 2007;3:321-330.

Cox SG, Cullingworth L, Rode H. Treatment of pediatric burns with a nanocrystalline silver dressing compared with standard wound care in a burns unit: a cost analysis. S Afr Med J 2011 ; 101:728-731.

Devi N, Dutta J. Preparation and characterization of chitosan-bentonite nanocomposite films for wound healing application.Int J Biol Macromol. 2017, 27. pii: S0141-8130(16)32687-3.

Deveci M, Gilmont RR, Dunham WR, Mudge BP, Smith DJ,Marcelo CL. Glutathione enhances fibroblast collagen contraction and protects keratinocytes from apoptosis in hyperglycaemic culture. Br J Dermatol 2005 ; 152:217-224.

Du Juan and Liu Xuelai. 3D-bioprinting, a promising technique to fabricate dermal equivalent for wound healing. PYREX Journal of medicine and Medical Sciences, 2017, 4(3):11-17.

Du Juan and Liu XL. The application of nano biomaterials in diabetic wounds（in Chinese) Chin J Endocri Surg, 2014;8(6):463-466.

Du Juan, Liu Xuelai. The promising research of 3D bio-printing in skin wound healing. (in Chinese) Chinese Journal of Trauma. 2014, 30(10): 1063-1066.

Du Juan and Liu XL. The application of Epidermal stem cell in diabetic wounds (in Chinese). Chin J Endocri Surg, 2016, 10（3）: 246-248

Elisavet K Tiaka, Nikolaos Papanas, Anastassios C Manolakis, Maltezos E. The role of nerve growth factor in the prophylaxis and treatment of diabetic foot ulcers. Int J Burn Trauma 2011 ; 1:68-76.

Elsharawy MA, Naim M, Greih S. Human CD34+ stem cells promote healing of diabetic foot ulcers in rats. Interact Cardiovasc Thorac Surg 2012 ; 14:288-293.

Fu XY ,Guo CL. Medical antibiotic nanosilver applied in wound covering by diabetes mellitus covering abscess with body (in Chinese). Chinese Journal of Nosocomiology. 2011;21:1818-1819.

Gravante G, Caruso R, Sorge R, Nicoli F, Gentile P, Cervelli V . Nanocrystalline silver: a systematic review of randomized trials conducted on burned patients and an evidence-based assessment of potential advantages over older silver formulations. Ann Plast Surg 2009;63:201-205.

Grumezescu AM, Holban AM, Andronescu E, Mogosanu GD, Vasile BS , Chifiriuc MC. Anionic polymers and 10nm Fe3O4@UA wound dressings support human foetal stem cells normal development and exhibit great antimicrobial properties. Int J Pharm 2014 ; 463 : 146-154.

Hassan MS, Amna T, Mishra A, Yun SI,Kim HC, Kim HY. Fabrication, characterization and antibacterial effect of novel electrospun TiO2 nanorods on a panel of pathogenic bacteria. J Biomed Nanotechnol 2012;8:394-404.

Hobizal KB, Wukich DK. Diabetic foot infections: current concept review. Diabet Foot Ankle 2012 ; 3:18409-18416.

Huang Y, Li X, Liao Z, Zhang G, Liu Q, Tang J. A randeomized comparative trial between Acticoat and SD-Ag in the treatment of residual burn wounds, including safety analysis. Burns 2007 ; 33:161-166.

Kumar PT, Lakshmanan VK, Anilkumar TV, Ramya C, Reshmi P, Unnikrishnan AG. Flexible and Microporous Chitosan Hydrogel/Nano ZnO Compodite Bandages for Wound Dressing: In Vitro and in Vivo Evaluation. ACS Appl Mater Interfaces 2012 ; 4,2618-2629.

Kumar PT,Lakshmanan VK, Biswas R, Nair SV, Jayakumar R. Synthesis and biological evaluation of chitin hydrogelnano ZnO composite bandage as antibacterial wound dressing. J Biomed nanotechnol 2012;8:891-900.

Kumbar SG, James R, Nukavarapu SP. Electrospun nanofiber scaffolds: engineering soft tissues. Biomed Mater 2008;3:034002.

Kwan KH, Liu X, To MK, Yeung KW, HO CM, Wong KK. Modulation of collagen alignment by silver nanoparticles results in better mechanical properties in wound healing. Nanomedicine 2011;7:497–504.

Khil MS, Cha DI, Kim HY, Kim IS, Bhattarai N. Electrospun nanofibrous polyurethane membrane as wound dressing. J Biomed Mater Res B Appl Biomater. 2003 ; 67(2):675-679.

Kanitkar M, Jaiswal A, Deshpande R, Bellare J, Kale VP. Enhanced growth of endothelial precursor cells on PCG-matrix facilitates accelerated, fibrosis-free, wound healing: a diabetic mouse model. PLoS One 2013;8:e69960.

Liu XL, Wong KKY. The research and application of Nano biomaterials in wound healing （in Chinese）. Chinese Journal of Surgery 2013;51:748-752.

Liu XL. The research and application of nano biocarrier in niopasmas （in Chinese）. Chinese Journal of Pediatric Surgery 2012; 33: 705-709.

Liu X, Lee PY, Ho CM, Lui VC, Chen Y, Che CM. Silver nanoparticles mediate differential responses in keratinocytes and fibroblasts during skin wound healing. Chem Med Chem 2010;5:468–475.

Liu YJ, Lai XN, Guo WZ, Huang H. Distribution regularity of epidermal stem cells of diabetic rats in different periods (in Chinese). Chinese Journal of Clinical Rehabilitation, 2005 ; 9 : 125-127.

Münter KC, Meaume S, Augustin M. The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSFwound dressings.J Wound Care. 2017 ,26(Sup2):S4-S15.

Perumcherry SR, Chennazhi KP, Nair SV, Menon D, Afeesh R. A novel method for the fabrication of fibrin-based electrospun nanofibrous scaffold for tissue-engineering applications. Tissue Eng Part C Methods 2011; 17:1121-1130.

Prakash S, Khan A and Paul A. Nanoscaffold based stem cell regeneration therapy: recent advancement and future potential. Expert Opin Biol Ther 2010; 10:1649-1661.

Rajangam T, An SS. Fibrinogen and fibrin based micro and nano scaffolds incorporated with drugs, proteins, cells and genes for therapeutic biomedical applications. Int J Nanomedicine 2013; 8:3641-3662.

Richard JL, Martini J, Bonello Faraill M.M. , Bemba JM,Lepeut M, Truchetet F,et al. Management of diabetic foot ulcers with a TLC-NOSF wound dressing. J Wound Care 2012; 21:142-147.

Romano NH, Sengupta D, Chung C, Heilshorn SC. Protein-engineered biomaterials: nanoscale mimics of the extracellular matrix. Biochim Biophys Acta 201;1810:339-349.

Sanahan DR. The explorer study:the first double-blind RCT to assess the efficacy of TLC-NOSF on DFUs. J Wound Care 2013;22:78-82.

Skotak M, Ragusa J, Gonzalez D, Subramanian A. Improved cellular infiltration into nanofibrous electrospun cross-linked gelatin scaffolds templated with micrometer-sized polyethylene glycol fibers. Biomed Mater 2011;6:055012.

Silver GM, Robertson SW, Halerz MM, Conrad P, Supple KG, Gamelli RL. A silver-coated antimicrobial barrier dressing used postoperatively on meshed autografts: a dressing comparison study. J Burn Care Res 2007 ; 28:715-719.

Swathi Balaji, Sachin S. Vaikunth, Stephanie A. Lang, Sheikh AQ, Lim FY, Crombleholme TM. Tissue-engineered provisional matrix as a novel approach to enhance diabetic wound healing. Wound Repair Regen 2012 ; 20:15-27.

Tian J, Wong KK, Ho CM, Chun-Nam Lok,Wing-Yiu Yu, Chi-Ming Che. Topical delivery of silver nanoparticles promotes wound healing. Chem Med Chem 2007;2:129-136.

Unnithan AR, Barakat NA, Pichiah PB, Gnanasekaran G, Nirmala R ,Cha YS. Wound-dressing materials with antibacterial activity from electrospun polyurethane-dextran nanofiber mats containing ciprofloxacin HCl. Carbohydr Polym 2012 ; 90:1786-1793.

Wang S, Hu F, Li J. Design of electrospun nanofibrous mats for osteogenic differentiation of mesenchymal stem cells, Nanomedicine. 2017,26: S1549-9634.

Wong KKY, Liu XL. Nanomedicine: a primer for surgeons. Pediatr Surg Int 2012; 28: 943-951.

Wong KK, Cheung SO, Huang L,Niiu J, Tao C, Ho CM. Further evidence of the anti-inflammatory effects of silver nanoparticles. Chem Med Chem, 2009;4:1129–1135.

Wong KKY and Liu XL. Silver nanoparticles—the real “silver bullet” in clinical medicine? Med Chem Commun 2010;1:125–131.

Yang X, Shah JD, Wang H. Nanofiber enabled layer-by-layer approach toward three-dimensional tissue formation. Tissue Eng Part A 2009;15:945-956.

Yin HQ, Langford R, Burrell RE. Comparative evaluation of the antimicrobial activity of ACTICOAT antimicrobial barrier dressing. J Burn Care Rehabil 1999 ; 20:195-200.

Yu P, Wang Z, Sun X, Chen X, Zeng S, Chen L. Hydrogen-rich medium protects human skin fibroblasts from high glucose or mannitol induced oxidative damage. Biochem Biophys Res Commun 2011 ; 409:350-355.

Zhukova LV, Kiwi J, Nikandrov VV. TiO2 nanoparticles suppress Escherichia coli cell division in the absence of UV irradiation in acidic conditions. Colloids Surf B Biointerfaces 2012; 97:240-247.