Review Article

A review on Nano-therapeutic drug delivery carriers for effective wound treatment strategies

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Abstract

Background: Wound healing is an intricate process that requires complex coordination between many cell types and an appropriate extracellular microenvironment. Chronic wounds often suffer from high protease activity, persistent infection, excess inflammation, and hypoxia. While there has been intense investigation to find new methods to improve cutaneous wound care, the management of chronic wounds, burns, and skin wound infection remain challenging clinical problems. **Objectives:** In this review paper we discuss recent advances in the development of biomaterials and nanocarrier therapeutics to enhance wound healing. In particular, this review focuses on the novel cutaneous wound treatments that have undergone significant preclinical development or are currently used in clinical practice. **Conclusion:** Ideally, advanced wound dressings can provide enhanced healing and bridge the gaps in the healing processes that prevent chronic wounds from healing. These nanotechnologies have great potential for improving out-comes in patients with poorly healing wounds but face significant barriers in addressing the heterogeneity and clinical complexity of chronic or severe wounds. Active wound dressings aim to enhance the natural healing process and work to counter many aspect that plague poorly healing wounds, including excessive inflammation, ischemia, scarring, and wound infection.

Keywords: Nanotherapeutics, biomaterials, nanoparticles, wound care, wound healing, microsphere, liposome, hydrogel

Introduction

Nano-particles have play as important role to treat skin wounds, as Silver, gold, and copper nanoparticles, as well as titanium and zinc oxide nanoparticles, have revealed potential therapeutic property on wound healing or transdermal treatment (Pandey et al., 2012). Due to their precise characteristics, nanoparticles such as nanocapsules, polymersomes or herbosomes (Shukla et al., 2012), solid lipid nanoparticles, Microsponge (Shukla et al., 2016) and polymeric herbal nano complexes are ideal vehicles to develop the effect of drugs (antibiotics, growth factors, etc.) designed for wound healing and protect the skin against microbial infection (Pandey et al., 2016). The skin is the largest organ of the body and serves as the first line of defense against pathogens, toxins, and trauma. It also has a critical role in fluid homeostasis and provides sensory functions and thermal regulation. Damage or loss of skin integrity resulting from an injury or disease may cause to significant morbidity and even death. Wound healing is defined as a complex, regulated process in which regulated collagen deposition, in response to tissue injury, results in scar formation. Its principles include inflammation, fibroplasia, and scar maturation. Sometimes cutaneous wound does not progress to normal healing with formation of a final mature scar formation but to a continuing inflammatory process, which may lead to a more aggressive carcinogenic transformation in long time of evolution (Marjolin's Ulcer). Many chronic wounds are resulted into chronic inflammation. In contrast to adult wound healing and early gestation fetus offer a significant ability to heal wounds without scarring. Fetal wounds heal rapidly and can be characterized by a relative lack of inflammation (Moore et al., 2006). The starting of inflammation into normally scarless wounds produces scarring (Frantz et al., 1993). Conversely, reduction of inflammation in postnatal wounds may reduce scarring (Ashcroft et al., 1999).

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Postnatal Wound Healing Process and different healing phases

An initial inflammatory phase, and then a

proliferative/repair phase and it outcome with a remodeling phase, which converts into scar formation in postnatal mammals. In response to tissue injury, inflammatory cells can be recruited to wounded tissue. The acute inflammatory responses are followed by proliferation of fibroblast, which is responsible for synthesizing collagen and extracellular matrix. Fibroblasts differentiate into myofibroblasts, which may be responsible for collagen deposition and wound contraction. Ultimately, scar outcomes from accumulation of extracellular matrix. Despite scar remodeling during maturation, normal architecture can never be completely restored (Colwell et al., 2005); only 70 percent of the tensile strength of normal skin is found to be recovered (Madden and Peacock, 1971). The early stage of inflammation may be regarded as a critical period of the wound healing process, essential for clearing contaminating bacteria and providing an environment favorable to the succeeding results of tissue repair and regeneration (Mercado et al., 2002). The injury reasons a gap, which is without delay filled by clots in the presence of platelet aggregates. Then, during the inflammatory phase, leukocytes, such as neutrophils, monocytes, and macrophages, penetrate the site, remove the breakdown products of the injured cells and clots, and release various growth factors and cytokines (Singer and Clark, 1999). In response to growth factors and cytokines, the proliferative phase starts. In this phase, epidermal cells migrate, proliferate to fill up the wound gap, and relocate remnants of the original clots. Thus, it may generally be accepted that leukocyte and macrophage infiltration is essential step to wound healing. Cytokines have been widely considered because they are significant to wound healing; they control the activity of the cells that produce the healing response to tissue injury (Molloy et al., 2003). Several cytokines, including interleukin- (IL-) 1β and tumor necrosis factor- (TNF-) α, have been revealed to regulate the recruitment and function of neutrophils. In irradiated mice, an investigation of the capability of exogenous IL-1β or transforming growth factor-β to reverse radiation-induced defective wound healing found that IL-1β improved wound tensile strength (Vegesna et al., 1995). TNF-α is a most important cytokine secreted by macrophages and neutrophils during the inflammation phase of wound healing; it is prominent in early wound healing (Goel et al., 2010). In all phases of wound repair, extracellular matrix (ECM) proteins take part in a key role in directing the fate and activities of progenitor and reparative cells. Immediately after injury, the ECM orchestrates the recruitment of platelets and expresses the inflammatory cell response that initiates the hemostatic and the cellular debridement phases (Schultz et al., 2011). These cells, move around into the wound bed of the ECM of the initial haemostatic plug and then migrate into the provisional matrix, respond to individual ECM components and growth factors (which can be bound to this matrix). These cells, in turn, draft and direct stem/progenitor and reparative cells from both distant and local sites to mediate the proliferative/repair phase of healing. Particularly, in this rebuilding phase of healing, adult stem cells participate critically in replenishing cells that were damaged or lost after injury. In addition to their role after trauma, adult stem cells participate in the maintenance of the skin as well as wound healing (Volk et al., 2013). Cutaneous injury is a universal aspect of medical care, with approximately 300 million chronic and 100 million traumatic wound patients worldwide. Wounds include an enormous financial burden on health-care systems worldwide, accounting for over $25 billion every year in the US alone (Sen et al., 2009). In addition, the occurrence of chronic wounds has rapidly increased due to the growing prevalence of type 2 diabetes, peripheral vascular disease, and metabolic syndrome. Although treatments for acute and small area traumatic wounds are efficient, problems arise in the long-term care for patients with large area burns, infected wounds, and chronic wounds. However, many mechanistic aspects of wound repair stay behind poorly understood, we undeviating the reader to other reviews for further information about detailed mechanisms of wound healing (Martin, 1997; Gurtner et al., 2008; Eming et al., 2014 Branski et al., 2009; Heublein et al., 2015). Role of mechanical forces in wound healing (Agha et al., 2011; Wong et al., 2011a, 2012), and immune response to biomaterial implants.

Fundamental aspects of wound healing

There are about four relatively differentphases in wound healing process that contain hemostasis, inflammation, proliferation, and remodeling (Figure 1). To understand the process better, let us illustrate analogy with a kingdom at war. The first footstep during war is to seal the gates of the castle that is alike to the hemostasis phase of wound healing, which demands clotting of blood mediated by platelets. The subsequent step is to accumulate a massive attack against the enemy, which is parallel to the inflammation phase of wound healing, mediated by macrophages and neutrophils. Then a huge number of repair people like plumbers, roofers, framers, and laborers are to be recruited to fix the damage done to the castle, which may be similar to the proliferation phase of wound healing, mediated by macrophages, lymphocytes, fibroblasts, and keratinocytes. Finally, the restorations of the castle are handled by interior designers for the final redecoration similar to the remodeling phase of wound healing mediated primarily by fibroblasts. Wound healing phases are found in delicate balance with each other, especially the inflammation and proliferation phases. If

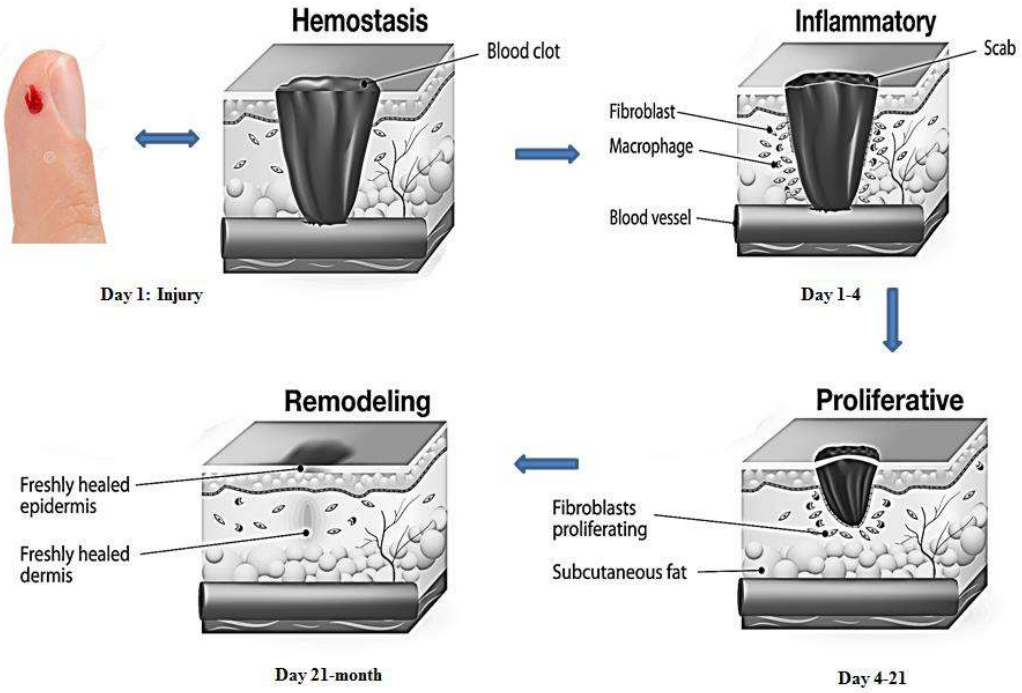

Figure 1. Wound healing phases. Schematic diagram elucidating the four distinct stages of normal wound healing, including hemostasis, inflammation, proliferation, and remodeling, along with the time scale of each phase.

there are chances of too much inflammation during healing, it leads to chronic non-healing wounds that are likely to common in many peripheral vascular diseases and type 2 diabetes patients. On the contrary, too much prolifera-tion during healing directs to scar formation that may not esthetically be pleasing and lessens the quality of life. In addition, if there is harm to the underlying muscle tissue, the satellite cells can be activated to form myoblasts to initiate the muscle healing process, which generally acquires even longer than skin wound healing.

Hemostasis Phase

Following the primary wounding, there may be the potential for bleeding and requiring hemostasis (Figure 1). On the combat zone, blood loss or hemorrhage from acute injury is found to be the leading cause of fatalities for soldiers (Clifford, 2004). Even though tourniquets are still used in the ground to stop blood flow momentarily in large wounds, it may cause to ischemia and reperfusion injury in the tissue (Percival and Rasmussen, 2012). Thus, products to develop hemostasis are of paramount significance in preventing exsanguination and hemorrhagic shock in people with extensive wounds. The most commonly preferred methods to make possible hemostasis is direct pressure on the wound and application of hemostatic materials. Hemostatics may be of three different types including clotting facilitators (e.g., kaolin) and mucoadhesive agents (e.g., chitosan) (Kozen et al., 2008).

Inflammation Phase

The natural response of the immune system to any physicalinjury is to monitor the condition and illicit inflammatory reaction to undertake the foreign particles (Figure 1). The classic signs of inflammation have been explained since first century AD in Rome and are referred to as dolor (pain), calor (heat), rubor (redness), and tumor (swelling) (Karimbux, 2014). The inflammatory response is arbitrated by the neutrophils and monocytes (that differentiate into macrophages) (Broughton et al., 2006). The neutrophils are involved in infection control, and macrophages take away cellular debris and provide soluble signals that make active fibroblasts and myofibroblasts in the proliferation phase of wound healing, releasing various kinds of cytokines, proteases, and growth factors. For patients with chronic conditions, the wounds often obtain a highly inflammatory state, necessitating the make use of non-steroidal anti-inflammatory drugs (salicylates, arylalkanoic acids, 2-arylpropionic acids, *N*-arylanthranilic acids, pyrazolidines, oxicams, and COX-2 inhibitors) (Su et al., 2010) and antibiotics (polymyxins, macrolides, tetracyclines, aminoglycosides, lincosamides, streptogramins, and pleuromu-tilins) (Martin, 1997).

Proliferation Phase

This is defined as the rejuvenation phase of the wound healing process (Figure 1). During the inflammatory phase, the macrophages and neutrophils discharge various cytokines and chemokines that be a magnet for cells into the wound microenvironment, including other lymphocytes, endothelial cells, fibroblasts, myofibroblasts, and keratinocytes (DiPietro, 1995). The keratinocytes migrate

from the wound edge, cover the wound bed, and restore barrier func-tion in the skin. The fibroblasts propagate and exude various extracellular matrix (ECM) proteins including fibrin, fibronectin, collagen and other ECM proteins that offer a provisional matrix for tissue remodeling and angiogenesis. This forms the granulation tissue of the wound, which may be*imperative* for the proper wound healing (Mayet et al., 2014). Lymphocytes and other immune cells offer additional responses to infectious agents, continuing the processes initiated by the early influx of neutrophils. The endothelial cells underneath the stimulation of soluble factors released by platelets, macrophages, and other cells initiate neovascularization in the wound bed to get better nutrient and oxygen exchange. The new vessels also assist in the transport of other cells into the affected area facilitating the wound healing process. This step can be last anywhere from 4 days to 3 weeks.

Remodeling Phase

The concluding phase of the wound healing course is the remodeling of the wound and surrounding tissue by the fibroblasts, which start in about three weeks after injury and maycontinue until as long as two years (Figure 1). The fibroblasts and myofibroblasts place down a network of collagen fibers and other ECM proteins in an orderly manner while using proteases to humiliate existing disordered tissue. The granulation tissue formed during proliferation phase is made up of immature type III collagen and is relatively feeble. During remodeling, the fibroblasts gradually put back the type III collagen with mature type I collagen (Hantash et al., 2008). The final goal is to reinstate the tissue to pre-injury conditions during which the wound becomes gradually fewer vascularized.

Animal Models for wound Healing

To learn wound healing efficiently by mimicking the human wound healing process, a number of wound healing animal models (Kim et al., 2015) have been urbanized in mouse (Wong et al., 2011b), rat (Dorsett-Martin and Wysocki, 2008), rabbit (Chien, 2007; Aksoy et al., 2009; Pelizzo et al., 2015), and pig (Sullivan et al., 2001). Small mammals such as rats, mice, and rabbits are relatively reasonably priced, need fewer resources, contain multiple mutant models for delayed wound healing, and thus are with no troubleavailable. Furthermore, the wound healing process in tiny mammals is accomplished in 1–2 weeks instead of weeks or months in human clinical studies. Though, a major restriction of these models is the differences in the mechanisms of wound healing in contrast to human wound healing and, in particular, the complexities of a chronic non-healing wound (Ansell et al., 2012). The human skin anatomy is considerably different from that of rats, mice, or rabbits (Ansell et al., 2012). Consequently, the wound healing process may be very much different and hence hard to evaluate. In addition, rodents primarily employ wound contraction using the underlying thin muscle layer, panniculuscarnosus to cure wound, while humans repair wounds by granulation tissue formation (Dunn et al., 2013). Among large animal models, porcine skin has a close structural similarity to human skin in terms of epidermal thickness and dermal-to-epidermal thickness ratio (Sullivan et al., 2001). They also contribute to similar patterns of hair follicles and vasculature in the skin. Moreover, the dermal collagen and dermal elastic content in porcine skin is seen more similar to humans than other commonly used mammals (Sullivan et al., 2001). However, a major restriction of wound healing models in pigs is the major costs of housing and care of the animals; variable wound contraction in pigs depending on the site, and the high rate of growth of pigs that may skew the wound healing process.

Nanocarrier system used in the delivery of biomaterials and treatment of wound

Nanoparticulate systems

El-Feky with his coworkers prepared chitosan nanoparticles used as drug carriers for the development of a silver sulfadiazine wound dressing. The dressing was characterized for its physical properties, in addition, FTIR, X-ray, SEM and in vitro release were used for characterization and found that the dressing was proven effective for the inhibition of the growth of Gram positive and Gram negative bacteria as well as candida on an infected wound (El-Feky et al., 2017). Meanwhile the strategy presented here has strong implications for developing complex drug delivery systems for wound healing applications or for the sustained release of pharmaceuticals from a drug-loaded gel and will lower the need for multiple drug administration's by controlled nanoparticle release from a hydrogel by DNA-mediated particle disaggregation (Nowald et al., 2017). Silver nanoparticles (AgNPs) were synthesized via biological reduction of silver nitrate using extract of the fungus *Fusariumverticillioides and*evaluated in vitro and in vivo and found superior antibacterial activity and wound-healing capability, with normal skin appearance and hair growth (Mekkawy et al., 2017). Hussainet et al. (2017), reviewed a new trends and state of nanoencapsulation, with efficient and promising approach to maximize wound healing efficacy of curcumin and concluded the offer better wound healing activities, nanoencapsulation of the curcumin were attributed to its target-specific delivery, longer retention at the target site, avoiding premature degradation of the encapsulated cargo and the therapeutic superiority of the advanced delivery systems over the conventional delivery (Hussainet et al., 2017; Zheng et al.,

2017), synthesized copper-containing bioactive glass nanoparticles using a modified Stöber method for biomedical applications. They suggested that Cu-containing bioactive glass nanoparticles (Cu-BGNs) were promising nanoparticulate fillers to develop nanocomposites for biomedical applications especially in bone regeneration and wound healing (Turner et al., 2017). The use of porous silicon nanoparticles (pSi NPs) was demonstrated for the controlled release of Flightless I (Flii) neutralizing antibodies (FnAbs) to diabetic wounds and a significant improvement in healing is observed for Delivery of Flightless I Neutralizing Antibody from Porous Silicon Nanoparticles Improves Wound Healing in Diabetic Mice. Peng with his coworker demonstrated that low molecular weight chitosan-coated silver nanoparticles (LMWC-AgNPs) were effective against methicillin-resistant *Staphylococcus aureus* (MRSA)-infected wounds, had better biocompatibility, and had lower body absorption characteristics in a dorsal MRSA wound infection mouse model (Peng et al., 2017). Raguvaran et al., 2017) synthesized sodium alginate and gum acacia hydrogels of ZnO nanoparticles and showed wound healing effect on fibroblast cells and suggested that high concentrations of Zinc oxide nanoparticles (ZnONPs) were toxic to cells but SAGA-ZnONPs (sodium alginate-gum acacia) hydrogels significantly reduced the toxicity and preserved the beneficial antibacterial and healing effect. Lau et al. (2016) investigated the effect of gold nanoparticles (AuNPs) in photobiomodulation therapy (PBMT) on wound healing process and found the application of gold nanoparticles in PBMT (photobiomodulation therapy) has potential to accelerate wound healing due to enhanced epithelialization, collagen deposition and fast vascularization. SDF1 α–elastin–like-peptide nanoparticles for wound healing and comprised of SDF1 (stromal cell-derived growth factor-1) and an elastin-like peptide that confered the ability to self-assemble into nanoparticles and resulted that SDF1-ELP fusion protein nanoparticles were promising agents for the treatment of chronic skin wounds (Yeboah et al., 2016). Tang et al. (2015), developed a new method of wound treatment that was targeted therapy of skin wounds with reactive oxygen species-responsive nanoparticles containing SDF-1α.And encapsulated SDF-1 α (stromal cell-derived growth factor-1) could exist for a long time in blood. In mice with full-thickness skin defects, SDF-1α was effectively released and targeted to the wounds, thus promoting the chemotaxis of bone marrow mesenchymal stem cells toward the wound and its periphery, inducing wound vascularization, and accelerating wound healing. Meanwhile Rath with his coworkers formulated collagen nanofiber containing silver nanoparticles for improved wound-healing applications.In vitro results confirmed the potential antimicrobial efficacy provided by AgNPs and AgNPs composite nanofibers, essential to provide an aseptic environment at the wound site. In vivo study revealed that the rate of wound healing of the composite nanofiber mats was found to be accelerated compared with plain collagen nanofibers Rath et al. (2016), developed and characterized of cefazolin loaded zinc oxide nanoparticles composite gelatin nanofiber mats for postoperative surgical wounds. Composite medicated nanofiber mats showed an accelerated wound healing as compared to plain cefazolin and ZnONP loaded mats. Macroscopical and histological evaluations demonstrated that ZnONP hybrid cefazolinnanofiber showed enhanced cell adhesion, epithelial migration, leading to faster and more efficient collagen synthesis.

Hydrogel system for drug delivery for wound treatment

Antibacterial anti-oxidant electroactive injectable hydrogel were developed as self-healing wound dressing with hemostasis and adhesiveness for cutaneous wound healing. It was based on quaternized chitosan-g-polyaniline (QCSP) and benzaldehyde group functionalized poly(ethylene glycol)-co-poly(glycerol sebacate) (PEGS-FA) as antibacterial, anti-oxidant and electroactive dressing for cutaneous wound healing and found that the antibacterial and electroactive injectable hydrogel dressing prolonged the lifespan of dressing relying on self-healing ability and significantly promoted the in vivo wound healing process attributed to its multifunctional properties, meaning that they were excellent candidates for full-thickness skin wound healing (Zhao et al., 2017). Morgado et al. (2017), formulated Ibuprofen (IBP)- β-cyclodextrins carriers were designed to customise the release profile of IBP from poly(vinyl alcohol)/chitosan (PVA/CS) dressings in order to promote a faster skin regeneration. The dressings were produced using supercritical carbon dioxide ($scCO_2$)-assisted technique. In vitro IBP release studies showed that β-cyclodextrins allowed a controlled drug release from the hydrogels which was crucial for their application in wound management. Moreover, the in vivo assays revealed that the presence of PVA/CS membranes containing IBP- β-cyclodextrins carriers avoided scab formation and an excessive inflammation, enabling an earlier skin healing. Yasasvini et al. (2017) developed a prolonged release drug delivery system was developed by loading Simvastatin-chitosan microparticles into poly vinyl alcohol (PVA) hydrogels for enhanced wound healing efficiency.Hence, the incorporation of Simvastatin-chitosan microparticles in PVA hydrogels has demonstrated significant wound healing efficiency at optimum dose. Gupta et al. (2016), studied biosynthetic bacterial cellulose hydrogels synthesised by gluconacetobacterxylinus and subsequently loaded with silver were characterized and investigated for their antimicrobial activity against two representative wound infecting pathogens, namely *S. aureus* and *P. aeruginosa* and the results indicated that both $AgNO_3$ and AgZ loaded

biosynthetic hydrogels possess antimicrobial activity ($p < .05$) against both *S. aureus* and *P. aeruginosa* and may therefore be suitable for wound management applications. Chen et al. (2017) prepared antibacterial and biodegradable composite hydrogel dressing integrated with microspheres were developed for drug delivery and wound healing. To enhance antibacterial and mechanical properties, tetracycline hydrochloride (TH) loaded gelatin microspheres (GMs) were fabricated by an emulsion cross-linking method, followed by integrating into the OAlg-CMCS (oxidized alginate- carboxymethylchitosan) hydrogel to produce a composite gel dressing. Ninan et al. (2016), developed an anti-bacterial and anti-inflammatory pH-responsive tannic acid-carboxylatedagarose composite hydrogels for wound healing. The resulting hydrogels exhibited negligible release of tannic acid at neutral and alkaline pH and sustained release at acidic pH, where they also displayed maximum swelling. Taken together, the cytocompatibility, anti-bacterial and anti-inflammatory characteristics of these novel pH-sensitive hydrogels made them promising candidates for wound dressings. Xiao et al. (2016) used peptide-modified hydrogels to target re-epithelialization for diabetic wound regeneration and found that it was a promising candidate for wound-healing interventions that enhance re-epithelialization and the formation of granulation tissue. Verma et al. (2017) formulated sericin and chitosan-capped silver nanoparticle (S/C-SNP)-loaded hydrogel for accelerated wound healing and antimicrobial properties and concluded that hydrogel containing capped SNPs has application in wound healing treatment. Wu et al. (2016), developed a thermos-sensitive heparin-poloxamer (HP) hydrogel to load and deliver different (GFs) growth factors (aFGF and bFGF) for wound healing in vivo and the resulting GFs-based hydrogels with and without HP hydrogels were systematically evaluated and compared for their wound. More importantly, HP-aFGF dressings exhibited the higher healing efficacy than HP-bFGF dressings, indicating that different a/bFGF surface properties lead to different binding and release behaviors in HP hydrogels.Momin with his coworkersdeveloped and evaluated a biodegradable superporous hydrogel based wound healing composite of chitosan and alginate incorporated with curcumin and honey as novel biodegradable hydrogel sponge and chitosan and honey contributed to effective faster wound healing (Momin et al., 2016). Jahani-Javanmardi et al. (2016) developed nanocomposite hydrogels on the basis of egg white and poly (vinyl alcohol) (PVA) containing 0, 5, and 10 wt. % of montmorillonite (MMT) nanoclay were prepared by a facile cyclic freezing-thawing technique and their properties investigated for wound dressing application and they finally concluded that the prepared egg white/PVA/MMT nanocomposite hydrogels were capable materials to be used as novel wound dressings in wound and burn care.

Micro-spherical system

A microfluidic process was developed by Yu et al. (2016), to produce hollow BC microspheres with desirable internal structures and morphology. Microfluidics was used to produce a core-shell structured microparticle through an alginate core and agarose shell as a template to encapsulate Gluconacetobacterxylinus for long-term static culture. In vitro, a highly porous scaffold was created to enable effective 3D cell culture with a high cell proliferation rate and better depth distribution. In vivo, that injectable scaffold facilitated tissue regeneration, resulting in rapid wound-healing in a Sprague Dawley rat skin model. Aramwit et al. (2016), developed wound dressing materials which are easier to apply and to provide extended release of sericin. Different amounts of chitosan and sericin (CH/S microspheres were implanted into various compositions of polyvinyl alcohol/gelatin (PVA/G) scaffolds and fabricated using freeze-drying and glutaraldehyde cross linking techniques and found to be a promising candidate for wound dressing application. Wang with his coworkers, developed vasoactive intestinal peptide loaded microspheres in mussel-inspired polycaprolactonenanosheets creating spatiotemporal releasing microenvironment to promote wound healing and angiogenesis and the result showed that the wound healing was significantly promoted via favoring the growth of granulation tissue and angiogenesis (Wang et al., 2016). Gao et al. (2017) developed microspheres containing levofloxacin and evaluated its efficacy of wound dressing on burns treatment and found that microspheres had minimal skin irritation, effectively promote wound healing of burn. Perumal et al. (2014) developed a bio-composite using synergistic combination of mupirocin as an antimicrobial drug, sol-gel processed silica microsphere as drug transporter for sustained delivery of drug and collagen, an established wound healer as scaffold. Consequently, the synergistic strategy of combining mupirocin-loaded silica microspheres and collagen as a Mu-SM loaded collagen dressing material would be an ideal biomaterial for the treatment of surface wounds, burns and foot ulcers. Charged polystyrene microspheres for the treatment of wounds following breast reduction and mastopexy with subsequent wound dehiscence prepared by (Weissman et al., 2014). Machado et al. (2014), formulate PLGA microspheres in a thermo sensitive gel that was to develop a topical microsphere delivery system in a thermo responsive 20% poloxamer 407 gel (Pluronic F127) to control release of KSL-W, a cationic antimicrobial decapeptide, for a period of 4-7 days for potential application in combat related injuries and found to provide effective antimicrobial activity and release of a wound-healing agent. A serratiopeptidase and metronidazole based alginate

microspheres developed by (Rath et al., 2011), for wound healing and obtained that alginate microspheres showed good loading efficiency with spherical in shape and suggested wound healing was improved by using serratiopeptidase and metronidazole in full thickness wounds in rabbits. Adhirajan et al. (2009) developed a novel wound dressing to attenuate the proteases and bacterial growth by functionally modified gelatin microsphere andthe modified microspheres were loaded with doxycycline and impregnated in a reconstituted collagen scaffold as novel wound dressing. Thus the system developed provides wider scope to control the pathogens involved in infection and also the excess matrix degradation. Pedraza et al. (2008) formulated hydroxyapatite-coated microspheres for bone wound healing and found that Osteopontin (OPN) is an effective opsonin able to facilitate particle uptake (including mineralized particles) by macrophages.

Liposome system

Li with his coworkers prepared and optimized a biodegradable liposomes containing madecassoside and also performed in vitro dermal permeation, and in vivo bioevaluation and concluded that double-emulsion liposome formulation was an applicable and promising pharmaceutical preparation for enhancing Madecassoside (MA) delivery toward wound healing effect and improving wound-healing progress and increased cutaneous wound healing effect (Li et al., 2016). Wardlow et al. (2016) developed low temperature-sensitive liposomes (LTSLs) containing an antimicrobial agent (ciprofloxacin) for induced release at mild hyperthermia (~42 °C), and characterised in vitro ciprofloxacin release, and efficacy against Staphylococcus aureus plankton and biofilms, and also determined the feasibility of localized ciprofloxacin delivery in combination with magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) hyperthermia in a rat model and found that technique had potential as a method to deliver high concentration antimicrobials to chronic wounds. Mancaet al. (2015) developed acurcumin loaded sodium hyaluronate immobilized vesicles (hyalurosomes) and in vitro and in vivo performances, and evaluated that the hyalurosomes appeared as promising nanocarriers for skin inflammation and wound restoring. Olekson et al. (2016) developed nanosized Stromal cell-derived factor-1 (SDF-1) liposomes, which were then incorporated into decellularized dermis scaffolds used for skin wound healing applications and found that SDF-1 liposomes promote sustained cell proliferation in mouse diabetic wounds. Jangde et al. (2016) prepared aquercetin-loaded liposomes for wound healing, using response surface methodology and concluded that quercetin-loaded liposomal formulations achieve sustained release of drug in wound areas. Ambrosone et al. (2014) formulated verbascoside-based liposomal eyedrops and indicate a latency time of only three hours and furthermore the corneal epithelium heals in 48 hours. Consequently, the topical administration of verbascoside appeared to reduce the action time of cells, thus promoted corneal epithelial wound healing. Kawaguchi et al. (2014) prepared liposome-encapsulated hemoglobin and found their effects on gastric wound healing in the rat and concluded that liposome-encapsulated hemoglobin (LEH) might improve microcirculation and oxygen metabolism at a surgical wound to accelerate its healing. Değim et al. (2011) formulated and evaluated a chitosan gel containing liposome-loaded epidermal growth factor and found there were significant increases in cell proliferation observed in the EGF-containing liposome in chitosan gel (ELJ) formulation on burn wound healing. Xiang et al. (2011), prepared and characterisedthe basic fibroblast growth factor (bFGF)-encapsulated liposomes and found to improve the stability of bFGF and to prolong its effects in vivo thus enhanced wound-healing activities in the rat. Kurilko et al. (2009), developed liposomes and ceftriaxone-entrapped liposomes and found their performed impact on skin wound healing in rats and concluded that the use of the PhCh "empty" liposomes promoted more rapid healing of the wound vs. the control or the treatment with CT aqueous solution and found thatthe treatment of the wound with the ceftriaxone (CT)-entrapped phosphatidyl choline (PhCh) liposomes provided 2 times more rapid healing vs. the control or the use of the CT aqueous solution. Beukelman, et al. (2008) developed a liposomal hydrogel with povidone-iodine (Repithel) were developed and found that a liposomal hydrogel with 3% povidone-iodine (PVP-ILH, Repithel) had shown clinical advantage in settings where inflammation and/or reactive oxygen species are thought to impede wound healing (e.g., burns, chronic wounds and in smokers. Liposome formulations containing epidermal growth factor (EGF) and investigated the healing effects of these formulations on second-degree burn wounds in rats and indicated thatthe EGF-liposome formulation was effective and can be used for the treatment of burn wounds (Alemdaroğlu et al., 2008). Pereira et al. (2007) determined the interaction between keratinocyte growth factor (KGF) administered as liposomal cDNA with other dermal and epidermal growth factors and collagen synthesis in an acute wound and found that KGF cDNA increased re-epithelialization, improved dermal regeneration, and increased neovascularization thus improves wound healing.

Conclusion

Biomaterials have been used to treat wound purpose since the rise of Egyptian civilization, but NPs have become tremendously important in engineering an effective treatment strategy, only in the last two decades. Biomaterials

have been successfully used in manufacturing clinically approved products for aiding wound healing like films, foams, wafers, hydrogels, hemostatics, sealants, and composite dressings. However, there are no biomaterials currently approved that release bioactive components (like growth factors, cytokines, chemokines, plasmids, recombinant proteins, small molecules, cellular therapy, etc.) that directly influence the wound healing cascade. Here, we reviewed biomaterials used in the clinic and those under preclinical development. We are excited about the potential of the biomaterials undergoing development, specifically those that encapsulate bioactive compounds or cell therapies. Nanocarrier therapies on the other hand have not been used widely in clinic barring silver NPs. However, there is a lot of compelling nanocarrier therapies that have shown great potential in animal models as we discussed in the paper. With the advent of CRISPR-Cas9 technology, it would be interesting to see how scientists apply this remarkable gene editing technology to engineer the wound microenvironment. There are many genes that are involved in the regulation of the wound healing process, and wound healing models have been tested only on a few mutant mouse models. CRISPR-Cas9 technology reduces the time to create a knockout mouse from several months too few weeks, thus enabling researchers to ask various questions. The overall goal would be to achieve fetal wound healing properties in adult wound healing with complete regeneration of hairs and glands, without delay and scarring. Wound care is a significant economic and social burden on both the patient population and the health-care system at large. In this review, we have discussed the different biomaterial and NP-based wound therapies, which are either in current clinical usage or in preclinical development. Since there is significant variability of presentation of symptoms in the patients, effective wound care therapies need to have a multipronged approach to tackle the complex problems of pain, inflammation, infection caused by resistant bacteria, delayed healing, and associated costs to health systems and populations worldwide. The precipitous rise in multidrug-resistant bacteria is going to be the biggest challenge for wound care professionals all over the world in this decade. Emerging treatments using biomaterials or NPs to target multiple aspects have great promise for enhancing wound care and will add to the clinical armamentarium to address poorly healing wounds.

A lot of remarkable approaches have been developed for the therapy of inflammatory diseases. Almost all systems exhibit a higher specificity in terms of delivering the drug load to the site of action. Nanocarriers show great potential for selective drug delivery to inflamed barriers. Since the exact target cells are still unknown, further investigations are necessary in order to develop specific and disease-related adhesion mechanisms. Until now the therapeutic options appearing closest to clinical use are based on passive targeting approaches. Other remaining problems are release control and industrial scale-up.

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