Nanoparticles in Wound Healing-A Review

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Abstract

Impaired Wound Healing is a battle that millions fight every day. Thus, novel and innovative strategies are of utmost need. Nanotechnology has revolutionized the way we treat wounds. This review discusses about the various nanomaterials used for treating wounds, also talks about the development of a novel and potent nanomaterial made of melatonin with special interest as to why it would prove superior to the other materials when it comes to oral tissues.

Key words: *Nanomaterials, wound healing, melatonin, nano particle, silver*

Introduction

The healing of wounds is one of the most complex biological processes that occur during human life. After an injury, there is a synchronized activation of multiple biological pathways. In our everyday life we encounter all kinds of injury from a paper cut to an ulcer to a much severe organ damage. Unlike earthworms that are capable of re-growing lost body parts, we humans are incapable of any such miraculous feats. Hence, it is only natural to possess carefully orchestrated ways to heal our damaged tissues. Wound healing is the process by which the integrity of a damaged tissue is restored. It consists of four phases: Hemostasis, inflammatory phase, proliferative phase and remodeling. These phases involve a series of physiological events that are driven by bioactive mediators that are specific for each phase of healing. [1] Hemostasis phase involves vasoconstriction and activation of the complement cascade; inflammatory phase involves vasodilation and activation of macrophages. In the proliferative phase epithelialization, neo-angiogenesis and granulation tissue formation begins. [2] The principal feature of the remodeling phase is the deposition of Extracellular matrix in an organized manner, formation of myo-fibroblasts and wound contraction.[3] The same holds good when it comes to wounds of the oral cavity. Periodontal tissue destruction is in a sense, a wound as well, since there is ulceration and destruction of tissues within the gingival sulcus leading to further tissue destruction of the periodontium. An alteration or hindrance in any of the phases lead to inadequate or an improper wound healing. Many factors such as lifestyle of the patient, systemic health etc plays a major role in wound healing. [4] When it comes to periodontal tissue destruction, materials that have potent antimicrobial activity in addition to those that are capable of stimulating growth factors and angiogenesis are of utmost need.

Nanomaterials in Wound Healing:

At present wide range of therapy either conventional dressings or modern approaches like usage of biomaterials, synthetic polymers with excellent mechanical properties and biocompatibility are available. Wound healing potentiated by nanomaterials have proved to be promising. The size, biocompatibility, colloidal stability, surface charge, surface functionalization and higher surface area offered by the nanomaterials have an additional advantage and could play a critical role in wound healing. [2]

Polymer Based Nano materials:

The most versatile polymers that are used to manufacture biomaterials specially for wound healing and care are poly (lactide- co-glycolide) (PLGA), polycaprolactone (PCL) and PEG (Polyethylene glycol. PLGA-curcumin nanoparticles showed a tremendous improvement in wound-healing capability compared to that of macromolecules of PLGA or curcumin.[5] Durga Prasad et al[6] , Mau[7] et al in their studies found that PLGA nanoparticles loaded with Curcumin which are known for their anti-inflammatory and antioxidant properties were capable of Quenching Reactive oxygen

species and also had the potential to inhibit the enzyme Myeloperoxidase. A study by Chen Yu et al tested the usage of PLGA nanoparticles to deliver recombinant human EGF (rhEGF) to enhance Full-thickness wound closure in Diabetics rats. [8] The rhECF delivered through PLGA nanoparticles showed sustained release for 24 hours. Park et el in their study proved that Sonic hedgehog intradermal gene therapy using a biodegradable poly (beta-amino esters) nanoparticle facilitated angiogenesis and tissue regeneration by activating angiogenic signaling pathways, thereby enhanced the wound healing.[9] Another study by Archana D et al investigated chitosan nano-dressing to potentiate wound healing and found an excellent antimicrobial and anti inflammatory response.[10]

Carbon Based Nano materials:

Fullerenes and Carbon Nanotubes showed promise in wound healing and angiogenesis. They are powerful Anti-oxidants that are capable of scavenging Reactive Oxygen Species and nitrogen substances. Fullerenes can also be functionalized, thereby reducing their aggregation, altering their solubility as well as reducing their toxicity. [11] Functionalization is done by using hexa-dicarboxyl, tris-dicarboxyl and gamma (γ)-cyclodextrin (CD). Modified Fullerenes are said to have better properties compared to the unmodified ones.[12] Gao et al in their study postulated that tris-C60 significantly reduced the production of proinflammatory cytokines in dermal keratinocytes in a dose/time-dependent manner. [13]

Lipid based Nano materials:

Liposomes loaded with curcumin and quercetin were studied to treat full thickness skin defects in in-vitro and in-vivo models in a study by Castangia et al.[14] They used phytodrugs that possessed antioxidant and anti-inflammatory properties which were able to prevent skin ulceration and enhance early regeneration of wounds. In another study by Fukui et al [15], Liposome-encapsulated hemoglobin accelerated skin wound healing in mice. Study by Plock J et al showed that hemoglobin-loaded phospholipid bilayer vesicles coated with polyethylene glycol (HbVs) improved wound healing and tissue survival in critically ischemic cutaneous wounds in mice. [16]

Metal Based Nano materials:

The most investigated nanoparticle so far is Silver. Silver nanoparticles (AgNPs) have proven to exhibit antimicrobial activity, anti inflammatory as well as anti oxidant potential. [17] Kwan et al, in their study stated that Silver nanoparticles were capable of improving tensile properties of repaired skin by influencing the alignment of collagen. [18] Silver nanoparticles modified with chondroitin sulfate and acharan sulfate were demonstrated to be capable of wound healing and accelerating collagen deposition in the wound area.[19] Dhapte et al in their study found that Green synthesis of silver nanoparticles using Bryonia laciniosa leaf extract improved the cytocompatibility of the particles and had a better effect on wound healing compared to that of a commercially available cream of silver sulfadiazine[20] . A very interesting finding was that, the authors found a scar-less healing which they attributed to the potential of silver to modulate the Pro-inflammatory cytokines (IL-6 and IL-10). Trickler et al [21] and Dykman et al [22] in their studies on Copper and Gold nanoparticles respectively, found that they were capable of enhancing wound healing as well. Potential of Iron oxide in improvement of wound healing was also studied by Ziv-Polat et al, who found that Thrombin-conjugated Iron oxide nanoparticles accelerated the healing of incisional wounds significantly by improving the tensile strength of skin and also reducing scarring.[23]

Ceramic Based Nano materials:

Several materials like Silicates and its derivatives, bioactive glass nanoparticles fall under this category. Krausz AE et al used a Curcumin-TMSO(Tetramethyl orthosilicate) nano material for Wound closure and observed a well organized Granulation tissue,enhanced and organized collagen deposition, improved neovascularization in the wound site.[24] Meddahi-Pelle A et al used Silica nanoparticles for suturing as an alternative to Dermabond (2-octyl cyano-acrylate) and Ethicon sutures in wistar albino rat model and found that they were much more efficient than the compared two. [25]

Melatonin in Wound Healing:

While various nanomaterials such as silver, gold, carbon, zinc oxide, iron oxide, polymers such as PLGA, PCL, chitosan polysaccharides have a successful place as wound healing materials, there is still a need for much effective and potent wound healing stimulators. Once such compound is Melatonin. Melatonin is an indoleamine synthesized and secreted by the pineal

gland, retina, bone marrow and intestines in a circadian rhythm. [26]

Melatonin is of special interest especially in the oral cavity since it is a potent anti oxidant and anti-inflammatory agent. It plays a role in bone remodeling as well. [27] Melatonin is said to promote Osteoblast differentiation, increase the synthesis of type I collagen, Bone matrix proteins such as osteopontin and osteocalcin. [28]-[30] A study by Castrovejo et al showed that melatonin influences bone cell precursors in the bone marrow of rats. [31] Ramirez et al in their animal study proved that melatonin was capable of promoting angiogenesis. [32] Study by Pugazhenthi et al investigated the effect of melatonin on the expression of one of the most potent angiogenic protein, VEGF (Vascular endothelial growth factor) and found a significant increase in VEGF expression. [33] Another study by Soybir et al showed similar results. [34] Several studies have provided evidence that melatonin has significant inhibitory effect on different types of tumors like Breast,Ovary, endometrium, prostrate, intestine, liver and Bone.[35],[36] In addition to this, studies have also shown that melatonin was able to counteract the side effects of chemotherapeutic drugs.[37]

However, melatonin has a short half-life. Thus,encapsulation of melatonin with PLGA particles have had benefits in numerous studies. Zhang et al in their study showed the effectiveness of melatonin encapsulated into PLGA micro and nano particles on osteogenesis of human mesenchymal cells in vitro. [38] Similarly melatonin releasing PLGA nanoparticles seemed to have a good effect on osteosarcoma cells. In addition to these beneficial properties, melatonin loaded on nanohydroxyapatite was capable of regenerating bone in infrabony defects. Thus, formulation and usage of melatonin nanoparticles would have further additional benefits by improving their bioavailability and efficiency. [39]

Conclusion

Beneficial aspects of different nano-materials for wound-healing applications have been reported; however, the underlying molecular mechanisms and signaling pathways are not clearly elucidated or understood. Better understanding of such mechanisms and studies aiming to formulate novel nano-materials such as melatonin will redefine the face of Nanotechnology based wound healing. Further studies involving the development of a nanomaterial using melatonin would have the potential to change the way we look at wounds of the oral cavity.

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