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Surface charge engineering of nitric oxide-releasing polymeric nanoparticles: Adhesion and anti-biofilm efficacy against wound infection associated MRSA biofilm in db/db mice

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Biofilm-associated wound infections have been considered a life-threatening infection that affects millions of people each year and are among the major cause of infectious disease-related mortality and morbidity worldwide. Bacterial biofilms protect bacteria from host immune responses and promote strong resistance to antibiotic treatment which leads to impaired wound healing, hospitalization and amputation particularly in chronic wound such as diabetic foot ulcer. Recently, nitric oxide (NO) has emerged as novel agent in biofilm dispersal and accelerates wound healing. In this study, we investigated the potency of positively charge NO-releasing PLGA/PEI nanoparticles (NO/PPNPs) for adhesion on biofilm surface that elevate biofilm dispersal and wound healing efficacy. Poly (lactic-co-glycolic acid) (PLGA) were used to incorporate polyethyleneimine (PEI)/NO adduct (PEI/NONOate) by an oil-in-water (O/W) emulsion evaporation method to form NO/PPNPs. Adhesion of NO/PPNPs on bacterial biofilm and the progress of *in vivo* biofilm dispersal were performed in biofilm wound and characterized by 3D confocal microscopy. *In vivo* biofilm was prepared by inoculating Methicillin-Resistant Staphylococcus aureus (MRSA) suspension on the surface of wound in db/db mouse (type-2 diabetic). Photographs of the wounds were taken to observe the gross visual wound healing. Furthermore, histological analysis was performed with H&E and Masson trichrome stain to observe the skin morphological and collagen deposition, respectively. Positively charged of NO/PPNPs facilitated the electrostatic binding to the negatively charged biofilm matrix, thereby increasing the biofilm dispersal by NO released from NO/PPNPs. NO/PPNPs treatment a biofilm-challenged diabetic mouse accelerated wound healing as compared to untreated and blank nanoparticles. In addition, histological examination revealed that wounds treated with NO/PPNPs showed increased numbers of fibroblast-like and collagen deposition with healed skin structures close to the normal healthy epidermis. Thus, the NO-releasing polymeric nanoparticles investigated in this study could be a promising approach for the treatment of biofilm-challenged chronic wounds and various skin infections.

Recent Publications:

1. H Nurhasni, J Cao, M Choi, I Kim, B L Lee, Y Jung, J W Yoo (2015) Nitric oxide-releasing poly (lactic-co-glycolic acid)-polyethylenimine nanoparticles for prolonged nitric oxide release, antibacterial efficacy, and *in vivo* wound healing activity, International journal of nanomedicine. 10: 3065.
2. J S Choi, J Cao, M Naeem, J Noh, N Hasan, H K Choi, J W Yoo (2014) Size-controlled biodegradable nanoparticles: Preparation and size-dependent cellular uptake and tumor cell growth inhibition, Colloids and Surfaces B: Biointerfaces.122: 545-551.
3. J O Kim, J K Noh, R K Thapa, N Hasan, M Choi, J H Kim, J H Lee, S K Ku and J W Yoo (2015) Nitric oxide-releasing chitosan film for enhanced antibacterial and *in vivo* wound-healing efficacy, International journal of biological macromolecules. 79: 217-225.
4. J W Yoo, J S Lee, C H Lee (2010) Characterization of nitric oxide-releasing microparticles for the mucosal delivery, Journal of Biomedical Materials Research Part A. 92: 1233-1243.
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