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# Wound healing and silver nanoparticles

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Burn injury induces global changes to the entire immune system resulting in suppressed immune function and increased susceptibility to infection. Patients with severe burns are more likely to die from sepsis due to the massive release of inflammatory mediators from the burn wounds [1]. The repair process of skin wound starts immediately during which various growth factors such as transforming growth factor beta (TGF-β) will release [2]. TGF-β is the growth factor affecting all cell types that are involved in all stages of wound healing [3]. TGF-β released by macrophages and platelets. It acts as a potent chemo-attractant for macrophages, neutrophils, lymphocytes, and fibroblasts. TGF-β stimulates release of other growth factors and induces its own auto expression. In addition, TGF-β plays an important role in tissue fibrosis and post- injury scarring [4]. Abnormal levels of pro inflammatory mediators, such as tumor necrosis factor alpha (TNFα) interleukin-1b (IL-1b), interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-10 (IL-10), have reported both systemically and locally in burn patient. A recent and interesting study indicates that genetically determined individual differences in IL-10 production might influence the susceptibility to septic complications in burned patients [5]. [6] showed that the circulating levels of the pro inflammatory cytokines, IL-6 and interferon-gamma (IFN-γ) were higher in rats with full thickness burns as compared to rats with only partial thickness burns, one hour after burn injury. The authors suggested that early elevation of IL-6 and IFN-γ) can prolong inflammation in full-thickness burns. Interleukin 10 (IL-10) is a potent anti-inflammatory cytokine that plays a crucial, and often essential, role in preventing inflammatory and autoimmune pathologies [7,8]. Deficiency or aberrant expression of IL-10 can enhance inflammatory response to microbial challenge but also lead to development of inflammatory bowel disease and a number of autoimmune diseases [9,10]. For centuries, silver compounds and ions have extensively used for both hygienic and healing purposes, due to their strong bactericidal effects, as well as a broad-spectrum antimicrobial activity [11,12]. It seems that silver shows a multilevel antibacterial effect, due to blockage of respiratory enzyme pathways, alteration of microbial DNA and the cell wall [13]. Silver is applied to burns, either in the form of impregnated bandages or as a cream containing silver sulfadiazine as the active agent, considered the benchmark silver product [14]. The antimicrobial mechanism of AgNPs is generally considered as a multi-factor, multi-way, and multi-target process [15,16,17]. AgNPs can attach to the cell membranes and interact with the molecules on the membranes, which will damage the integrity and permeability of the membranes and thereby leading to the cytomorphosis and the leakage of intracellular contents [18,19]. And the reactive oxygen species (ROS) produced by AgNPs and silver ions released from AgNPs not only damage the cell membranes but also react with the molecules in the functional proteins and DNA, which will interfere the metabolism and DNA duplication [20,21]. AgNPs with more reactive facets had enhanced affinity with the cell membranes and increased dissolution rate of silver ions, which resulted in the enhanced antimicrobial activity [22,23,24]. The antimicrobial spectrum of AgNPs is broader than that of common antibiotics. Most researchers normally select *Escherichia coli* and *Staphylococcus aureus* to study the inhibition of bacteria by AgNPs [25,26]. The antibiotic ability of AgNPs against *E. coli*, *Staphylococcus aurous*, *B. subtilis*, and *K. mobilis* enhanced with increasing the silver content [27]. [28] studied the biocide activity of the AgNPs on *Pseudomonas aeruginosa* (a gram-negative bacterium), is an opportunistic microorganism that can cause severe, life-threatening infections. The bactericidal effect of AgNPs depends on different parameters including size, shape, and the surface charge of the particles. In this respect, smaller particles have greater antibacterial activity and shown to have two benefits. Firstly, they can easily reach the nuclear content of bacteria due to the structure of the bacterial cell wall, especially in gram-negative ones [29]. Secondly, they provide a greater surface area and therefore stronger bactericidal interactions [30,31]. NPs greater than 10nm accumulate on the cellular surface and compromise cellular permeability; however, NPs smaller than 10 nm penetrate into the bacteria, affecting DNA and the enzymes leading to cellular death [32,33]. Furthermore, the electrostatic attraction between positively charged nanoparticles and negatively charged bacterial cells is shown to be another important aspect with regard to the antimicrobial activity of the AgNPs [19]. Although gram-positive and gram-negative bacteria have differences in their membrane structure, most of them have a negative charge. The gram-negative bacteria have a layer of lipopolysaccharide at the external surface followed by a thin layer of peptidoglycan. On the other hand, the cell wall in gram-positive bacteria is mainly composed of a thick layer of peptidoglycan [34]. Macrophages will infiltrate the wound tissue at approximately 3 days after neutrophils infiltration post-wounding, and be involved in the ongoing inflammatory process by performing phagocytosis of pathogens and necrotic cells or debris. They will release cytokines, chemokine and growth factors, such as IL-4, IL-1β and TNF-α to induce cell regeneration and tissue repair, as well as synthesis of collagen by fibroblasts and macrophages in healing tissue [35].

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