Bioactive Materials xxx (2017) 1–11

Contents lists available at ScienceDirect

Bioactive Materials

journal homepage: http://www.keaipublishing.com/en/journals/bioactive-materials/

Chitosan based metallic nanocomposite scaffolds as antimicrobial wound dressings

Annapoorna Mohandas, S. Deepthi, Raja Biswas, R. Jayakumar*

Centre for Nanosciences and Molecular Medicine, Amrita Institute of Medical Sciences and Research Center, Amrita Vishwa Vidyapeetham, Kochi, 682 041, India

ARTICLE INFO

Article history:
Received 10 June 2017
Received in revised form
17 November 2017
Accepted 17 November 2017
Available online xxx

Keywords:
Antimicrobial Chitosan nanocomposities
Silver
Zinc oxide
Gold
Copper
Wound healing

ABSTRACT

Chitosan based nanocomposite scaffolds have attracted wider applications in medicine, in the area of drug delivery, tissue engineering and wound healing. Chitosan matrix incorporated with nanometallic components has immense potential in the area of wound dressings due to its antimicrobial properties. This review focuses on the different combinations of Chitosan metal nanocomposites such as Chitosan/nAg, Chitosan/nAu, Chitosan/nCu, Chitosan/nZnO and Chitosan/nTiO_2 towards enhancement of healing or infection control with special reference to the antimicrobial mechanism of action and toxicity.

1. Introduction

The wound is any type of injury occurring on the skin either due to cut or damages. Wound healing is a process by which any loss in the tissue integrity is being repaired by a series of phases [1]. Healing is dependent on several factors, including medical condition of the person. The phases are yet complex and are regulated by cellular and molecular mediators. The different stages include haemostasis, inflammation, proliferation and remodeling (Fig. 1). In an acute wound, haemostasis, which is the initial phase, is a mechanism that helps in the prevention of excess blood loss in the wound site. There is initiation of coagulation cascade, via extrinsic or intrinsic pathways leading to platelet accumulation and formation of a fibrin clot. The platelets would release several growth factors that would recruit and enable migration of cells, such as polymorphonuclear leucocytes (PMN), endothelial cells etc. Haemostasis occurs within minutes and is accompanied by the formation of a blood clot, which prevents further bleeding. Inflammation is marked by the activation of immune cells to defend the foreign substances at the wound site. Inflammatory phase is marked by the infiltration of neutrophils and macrophages for subsequent destruction of microbial flora. The stage is followed by proliferation, where fibroblast cells undergo rapid division, secrete collagen and a new extracellular matrix is built up. The inflammatory cells secrete many mediators required for the granulation tissue formation. Transforming growth factor-β (TGF-β) is an inflammatory cytokine that regulates cellular proliferation and apoptosis. Various other growth factors such as platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), etc. are secreted to the site. All these pro-angiogenic factors initiate cell proliferation and differentiation. In remodeling, the collagen fibers mature and the wound heals with scar formation. When the healing phase is halted at any of the above mentioned stages, wounds become chronic. As a result, the wounds become more prone to secondary infections. Infected wounds are characterized by an increase in microbial burden, large volume of exudates, and an increase in the number of pus cells causing necrosis of tissues [2,3]. Hence, the necrotized areas are debrided to allow the growth of new granulation tissue. The chance that diabetic patients get limb amputation is nearly 15% [4]. Therefore, special care has to be taken in dressing the wound to decrease the microbial burden and control infection. Hence, wound dressing materials are important in maintaining different phases of

* Corresponding author.
E-mail addresses: rjayakumar@aims.amrita.edu, jayakumar77@yahoo.com (R. Jayakumar).
Peer review under responsibility of KeAi Communications Co., Ltd.

https://doi.org/10.1016/j.bioactmat.2017.11.003

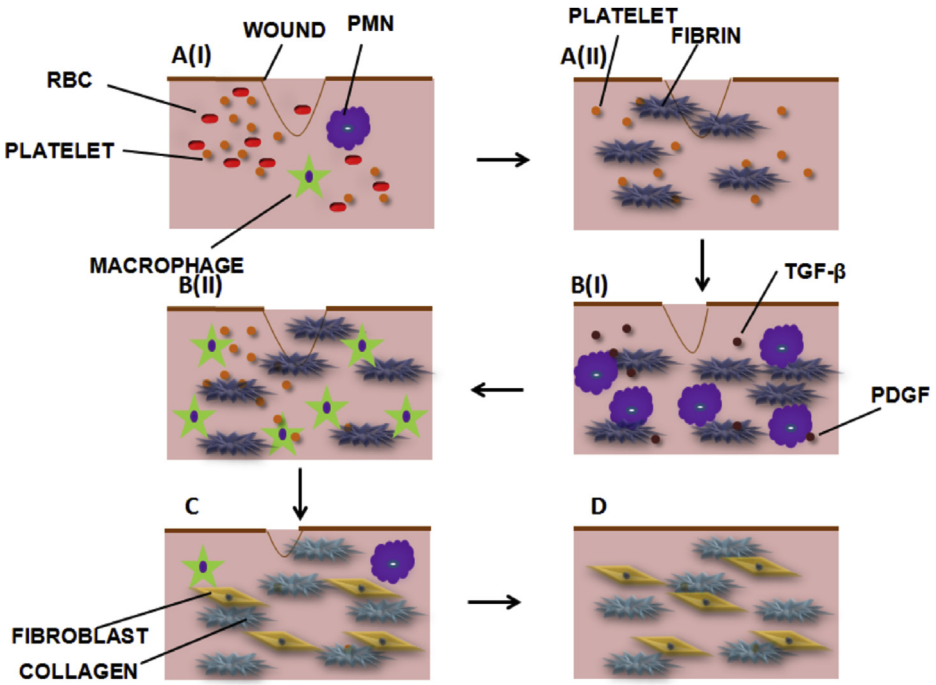

Fig. 1. Wound healing process (A) Haemostasis (I) Platelet activation (II) Fibrin clot (B) Inflammatory phase(I) Early Inflammation (24 h) (II) Late Inflammation (48 h) (C) Proliferation (72 h) and (D) Remodeling (Weeks to months).

healing [5]. To assure a complete clinical solution, special emphasis is being laid to identify the types of wound and the design of dressing material. Ideally a dressing material, should cover the wound from foreign infection, allow gaseous exchange and maintain a moisture balance, which ultimately destines the fate of the wound [5].

Traditionally, people used cotton gauze as dressings which served only as a structural framework to cover the wounds. Such dressings are mentioned as passive dressings. However, modern dressings are either interactive or bioactive. Interactive dressings include films, sponges, hydrogels etc., which provide an antibacterial efficacy in addition to the structural framework [5]. Bioactive dressings play a role beyond the interactive dressings in the process of healing.

Currently, dressings are developed using different types of polymers whose origin is either synthetic or natural. There are synthetic dressings made from poly (Methacrylates), polyvinyl pyrrolidine, etc. These dressings render a low mechanical strength, making it difficult for patients to handle [5]. Though synthetic dressings impart good anti infectious property, their degradation products should not cause any harm to the skin [5]. This condition could not be met by synthetic polymers. Infected wounds are characterized by the presence of excess exudate formation with improper healing [6]. The infection spreads rapidly to other parts of tissue leading to surgical removal of affected parts. Management of such wounds is a major difficulty in the field of wound care. Therefore, much research has been focused to bring forward dressings developed from natural polymers. Need of the hour is an effective bandage that not only eliminates the microbial burden, but also assists in other healing activities such as control of scar formation, ECM remodeling, mediating inflammatory activities, etc. Often these are met by more than one active agent or a multitude of changes that happens within the dressing material.

Metal based active agents have received much interest in the clinical scenario. Extensive studies have been done on silver (Ag) nanoparticles or zinc oxide (ZnO) nanoparticles incorporated into Chitosan scaffolds/bandages. Certain redox-active transition metals, especially copper (Cu) can participate in the Fenton reaction resulting in the production of reactive oxygen species. Soft and borderline acids such as Ag^{+}, Au^{+}, Cu^{+}, Cu^{++} and Zn^{++} respectively form covalent bonds with thiols or protein containing sulphur group [6]. This causes oxidation and subsequent depletion of microbial antioxidant reservoirs. Amino acids such as histidine, arginine, lysine and proline are susceptible to metal based oxidations leading to carbonyl products. Ag, gold (Au) and Cu attacks Iron-Sulphur- (Fe-S-) containing dehydratases. Ag has a high affinity with the highly electronegative polymeric membranes of bacteria. In addition to factors such as size, shape, surface charge, etc., the toxicity initiated by metallic nanoparticles is dependent on the mode of release of metallic ions from the material [6].

However, concerns regarding the possible environmental and health impacts prevail in the use of metallic nanoparticles, which calls for a detailed evaluation of cytotoxicity [7]. Toxicity of nanoparticles increases with lowering of the size of nanoparticles solely due to the enhancement in surface area to volume ratio, which amplifies the interaction of surface atoms or molecules with the outside environment. The type of interaction further depends on the surface moieties whether it is hydrophobic, hydrophilic, lipophilic, lipophobic, active or passive [8,9]. Shape dependent toxicity adjoins aggregation of particles, surface coating or solubility resulting in the changes in transport properties whose accumulation may cause dose dependant toxicity in tissues. The major attribute to cytotoxicity of metallic nanoparticles include the reactive oxygen species (ROS) generated by the disruption of the electronic and ionic flux, permeability of transition pores and reduction of the intracellular glutathione level [9]. The overall cytotoxicity of metal based nanocomposites can be reduced by incorporating into suitable biodegradable matrices. Moreover, healing of wounds with larger tissue defects requires a biomaterial support for the regeneration of cells and matrix. Therefore, a bioactive dressing is largely encouraged and is extensively studied.

Dressings made out of marine based polymer, i.e. Chitosan, is the

Please cite this article in press as: A. Mohandas, et al., Chitosan based metallic nanocomposite scaffolds as antimicrobial wound dressings, Bioactive Materials (2017), https://doi.org/10.1016/j.bioactmat.2017.11.003