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Review

Functionalization of electrospun polymeric wound dressings with antimicrobial peptides

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ABSTRACT

Wound dressings have evolved considerably since ancient times. Modern dressings are now important systems that combine the physical and biochemical properties of natural and synthetic polymers with active compounds that are beneficial to wound healing. Antimicrobial peptides (AMPs) are the most recent addition to these systems. These aim to control the microbial proliferation and colonization of pathogens and to modulate the host's immune response. In the last decade, electrospun wound dressings have been extensively studied and the electrospinning technique recognized as an efficient approach for the production of nanoscale fibrous mats. The control of the electrospinning processing parameters, the selection of the polymer and AMPs, and the definition of the most appropriate AMPs' functionalization method contribute to the successful treatment of acute and chronic wounds. Although the use of electrospinning in wound dressings' production has been previously reviewed, the increased development of AMPs and the establishment of functionalization methods for wound dressings over recent years has increased the need for such research. In the present review, we approach all these subjects and reveal the promising therapeutic potential of wound dressings functionalized with AMPs.

Contents

1. Introduction

During wound healing, dressings are used to protect dermal and epidermal tissues. Wound dressing design and fabrication are important segments of the medical and pharmaceutical wound care market worldwide. In the past, traditional dressings with natural and/or synthetic bandages were used to simply manage the wound, to provide moisture balance and keep fomites out [1,2]. Nowadays, the fabrication of wound dressings has achieved higher standards and are now based on the concept of creating an optimal environment, in which accelerating wound healing, skin regeneration, oxygen exchange, and preventing microbial colonization are the main goals [3–5].

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Research on fabrication methods of polymeric nanofibers remains one of the most important topics in wound dressings. Several techniques such as electrospinning, melt-blown, phase separation, self-assembly, and template synthesis have been employed to produce suitable polymer nanofibers for wound dressings [6]. Between those, electrospinning has become the most popular. Electrospinning is a simple and effective method to produce nanoscale fibrous mats with controlled pore structure, from both natural and synthetic origin polymers. This technique has gained much attention because of its versatility, reproducibility, volume-to-surface ratio and submicron range [5,7–10].

More recently, a major advance in the manufacture of wound dressings by electrospinning has been uncovered: the incorporation or functionalization of electrospun mats with antimicrobial peptides (AMPs) [11–13]. The rise of antibiotic-resistant infection agents has increased the need for such therapies. While antibiotics act selectively against bacteria, AMPs act at multiple sites within microbial cells, thus reducing the likelihood of bacteria to develop resistance [14,15]. The functionalization of electrospun dressings has become a hot topic as it defines not only the applicability of the dressing but as well its therapeutic abilities. Indeed, the antimicrobial performance of a dressing will depend on the stability and activity displayed by the AMPs while functionalized. Therefore, selecting between co-spinning, adsorption, layer-by-layer or covalent binding strategies to immobilize the AMP on electrospun dressings requires meticulous study and comprehensive analyses [16]. In this paper, we review the basic concepts associated with electrospinning technique and explore the use of AMPs in the treatment of acute and chronic wounds. Specific AMPs and their mechanisms of action are highlighted, and the methods available to functionalize electrospun mats with these molecules are described. In addition, we reveal the promising therapeutic potential of these systems and infer about their significance in the near future.

2. Antimicrobial peptides (AMPs) in wound healing

From a microbiological perspective, the primary function of normal, intact skin is to prevent invasion of the underlying tissue. Exposure of subcutaneous tissue, following loss of skin integrity, provides a moist, warm, and nutritious environment for microorganisms to colonize and proliferate. Colonization is most frequently polymicrobial, involving multiple microorganisms that are potentially pathogenic and may lead to biofilm formation, like *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Escherichia coli*, *Escherichia hermanii*, *Peptostreptococcus* spp., *Bacteroides* spp., *Candida*, *Klebsiella*, etc. [17–19]. Wound infections have become an increasing cause of death in severely ill hospitalized patients and an important economic burden to the healthcare system [20]. To fight these infections and control microbial proliferation, multicellular organisms developed an arsenal of host-defense molecules, also known as AMPs [21].

AMPs form an integral part of the innate immune system, working as a defense mechanism in most organisms including plants, insects, bacteria, vertebrates and humans. Despite being known for many years, their role in the human immunology was initially neglected or underappreciated and, only recently, have been recognized as essential to the mammalian immune response [22]. These natural and synthetic peptides provide a non-specific defense against a broad spectrum of invaders; gram-positive and gram-negative bacteria, fungi, and certain viruses, acting like a component of innate immunity [23].

AMPs are low molecular weight molecules, with less than 10 kDa, and are composed of 5–100 amino acid residues [22–24]. AMPs are often cationic due to the excess of lysine, arginine and histidine amino acids. Most AMPs are also amphipathic, a trait by which peptides contain hydrophilic amino acid residues aligned along one side and hydrophobic amino acid residues aligned along the opposite side of a helical molecule. Amphipathic helical structure is most effective interacting with biomembranes, since it endows the AMPs with the capacity to bind to lipid components (hydrophobic regions) and phospholipid groups (hydrophilic regions) [25,26]. There are several types of AMPs but it is possible to group them in four main classes, according to their structural diversity: α-helix, β-sheet, extended and loop. The most common types are α-helix and β-sheet; the first is formed only when the peptide contacts with a membrane, and the second is stabilized by 2–4 disulfide bonds. The less common, extended and loop, display a curved form in response to a simple disulfide bond or the presence of proline residues in its structure [27,28]. AMPs can also be classified based on their target microorganism: antibacterial peptides (most common), which target bacterial cell membranes and cause disintegration of the lipid bilayer structure; antiviral peptides, which neutralize the viruses by integrating in either the viral envelope or the host cell membrane; antifungal peptides, which kill by targeting either the cell wall or the intracellular components; and antiparasitic peptides, which form a smaller group compared with the other classes, and kill through direct interaction with the cell membrane [28]. So far, over 2500 AMPs of different origins have been identified [29]. The most common sources are plants or animals but they can also be produced by prokaryotes, as bacteria, and by fungi or protozoa. Synthetic or synthesized AMPs are nowadays also available to fight infections. These are produced artificially through chemical synthesis or recombinant expression systems. Because they are composed of amino acids it is relatively easy to immobilize or modify their structure, being possible to obtain new AMPs with improved stability and greater targets range. In addition, AMPs may also display synergistic effects with antibiotics to increase antibiotic activity above the antibiotic individual effect [28,30].

2.1. Mechanisms of action

AMPs kill cells by disrupting their membrane integrity, interfering with the synthesis or normal function of proteins, DNA and RNA, or by interacting with certain intracellular targets. AMP-mediated killing is a very quick process that, depending on the AMP specificity, can be completed in few seconds after contact with the cell membrane [28,30]. Yet, regardless of the time required or the specific antimicrobial mechanism, specific steps must be taken to induce microbial killing: first, electrostatic attraction between the cationic AMP and the anionic cell membrane takes places, then, and upon binding, the AMP adopts an amphipathic structure, if not yet displayed, adapting to the specific conditions at the membrane-water interface. After this point, it is unclear how the disruption of the membrane occurs; however, some hypotheses have been proposed, for instance creation of physical holes from which leakage of cellular content occurs, activation of hydrolases to degrade the cell membrane, alteration of lipids distribution and, consequent, disruption of the membrane functions, etc [25,31,32]. From here, five models have been proposed to explain the AMPs mechanisms of action [28,32]:

(1) (Carpet-like: AMPs coat the microbial membrane up to saturation, after which point wormholes are formed causing the abrupt lysis of the microbial cell;
(2) Toroidal pore: after binding to the phospholipid head groups, the AMPs align and insert into the membrane and cluster into unstructured bundles that span the membrane. These bundles interact with water molecules to create channels within the membrane, responsible for ions and molecules leakage;