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Feature article

Controlling macromolecular structures towards effective antimicrobial polymers

Mitra S. Ganewatta, Chuanbing Tang*

Department of Chemistry and Biochemistry, University of South Carolina, Columbia, SC 29208, USA

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ABSTRACT

Drug resistance of pathogenic bacteria is a major global problem leading humanity towards a pre-antibiotic era. Decline in the discovery of novel antibiotics and the lack of a resilient platform to develop novel antimicrobial agents worsens the situation. Amphiphilic antimicrobial polymers, which have roots coming from antimicrobial peptides, show promise as potent antimicrobials having low susceptibility for developing resistance, unlike small molecular antibiotics. This feature article highlights recent advances in the fabrication of membrane-active antimicrobial polymers. The design of various types of macromolecular architectures with control of structural parameters such as hydrophobicity/hydrophilicity balance, molecular weight, and ionic groups will be emphasized in order to achieve strong antimicrobial activities while minimizing toxicity to mammalian cells. Advanced polymeric assemblies with well-defined nanostructures including core/shell shaped nano-objects and polymeric vesicles are also discussed. Lastly, current challenges and future directions in the field of antimicrobial polymers for ensuing practical biomedical applications are presented.

1. Introduction

Antimicrobial chemotherapy has revolutionized modern medicine in many aspects and has significantly reduced ailments and death from infectious diseases. Many classes of antibiotics that are clinically used today were discovered during the golden era of antibiotic discovery from 1940s to 1960s [1,2]. Molecular targets of pathogens, which are absent or significantly different from human cells such as cell wall, 60S ribosomes, cell membranes, genetic materials and biosynthetic pathways, are utilized to design antimicrobial agents (Fig. 1A). Environmental pressure from the action of antibiotics combined with short life cycles and lateral gene transfer mechanisms have resulted in rapid appearance of resistant pathogenic populations of microorganisms [3]. For example, widespread outbreaks of penicillin-resistant *Staphylococcus aureus* and methicillin-resistant *S. aureus* (MRSA) infections occurred just a few years after the introduction of β-lactam antibiotics, penicillin and methicillin.

Resistance mechanisms include efflux pumps, chemical modifications such as phosphorylation, acetylation or hydrolysis, altering target and reprogramming biosynthesis, most of which are against small molecule antimicrobials (Fig. 1B) [1,6]. The most prominent issue is the expeditious growth of acquired resistance in bacteria that cause major healthcare crisis. For example, since the introduction of the first β-lactam antibiotics, the number of unique β-lactamase enzymes has grown from zero to over 1000 [6]. Decades of use and misuse of antibiotics, combined with a forty year lull in the pipe line of novel antimicrobial agents, have consequences of a global superbug threat that could lead human civilization to a pre-antibiotic era. The devastating nature of the increasing resistance to available antibiotics is a global concern at high priority. Antibiotic resistance seems inevitable. Therefore, it is essential to continuously develop antibiotics with novel modes of action to face the evolving resistance [7].

Antimicrobial polymers are a class of novel antimicrobial agents that is fueled by the combined knowledge on antimicrobial peptides (AMPs) [8] and polymer disinfectants that have emerged as two distinct fields since the 1980s [9]. There are several books, a variety of reviews and highlights on antimicrobial polymers published over the past few years that give broader and diverse perspectives [5,9–25]. However, there has been a rapid expansion of novel antimicrobial polymers and related research in the last decade (Fig. 2), which has not been reviewed frequently.

* Corresponding author.
E-mail address: tang4@mailbox.sc.edu (C. Tang).

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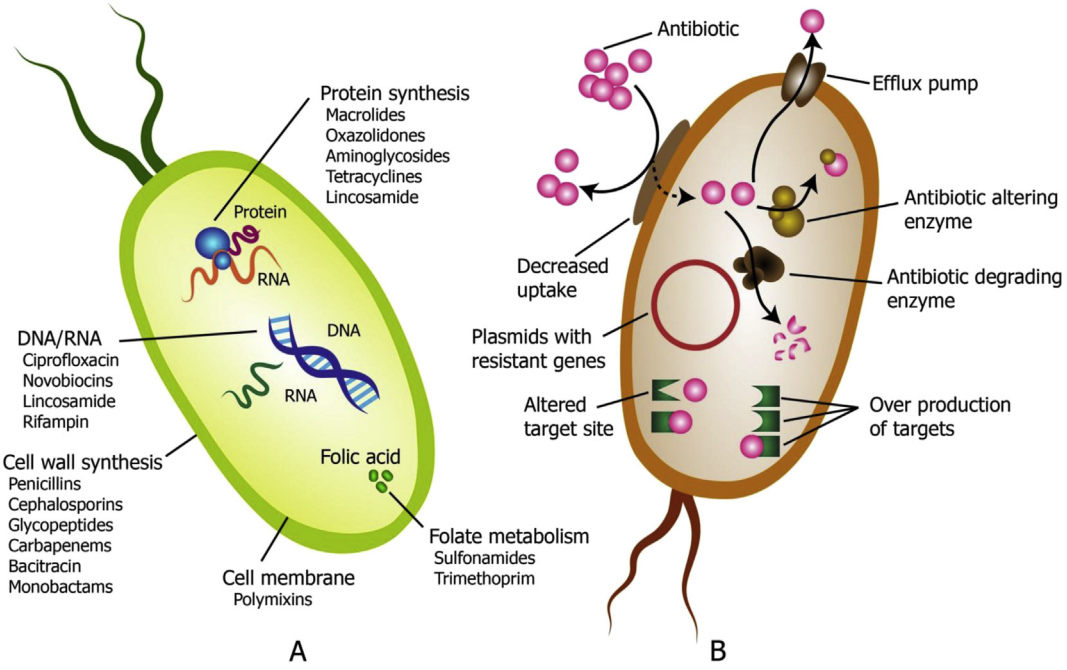

Fig. 1. (A) Typical antibiotic target sites present in bacterial cells and; (B) mechanisms of antibiotic resistance. Adapted with permission from Refs. [4,5].

Hence this feature article focuses on the most recent advances in membrane-active cationic polymeric antimicrobials and our perception about modulating the structural features of these materials to optimize their potential as clinically relevant materials. However, we do not intend to provide an exhaustive review of all aspects of antimicrobial polymers. The emphasis will be placed on research related to antimicrobial polymers and assemblies in solution. The discussion will start by looking at the feasibility of antimicrobial polymeric macromolecules as an innovative platform to address the current healthcare crisis pertaining to infectious diseases. Then the emphasis will be moved to the current understandings and most recent experimental explorations about polymer architectures and macromolecular structural determinants to improve the properties of antimicrobial polymers with regard to antimicrobial activities and biocompatibilities. We will discuss research on nano assemblies of antimicrobial polymers. Synthetic strategies, including polymerization techniques, post-polymerization modifications and self-assembling procedures, will be briefly mentioned in prominent case studies. Lastly, the current challenges in the field and future directions will be deliberated with the hope for further expansion of antimicrobial polymer research.

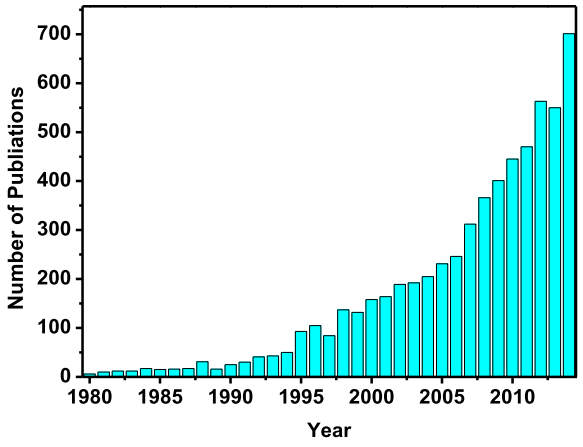

Fig. 2. Number of publications containing "antimicrobial polymer" from 1980 to 2014, searched via SciFinder.

2. Tailoring next-generation antibiotics

It is increasingly recognized that microbial membranes provide an effective target for the development of de novo designed antimicrobial agents. Recent understanding of the innate immunity mediated by macromolecules highlights the importance of short amphiphilic peptides that modulate host defenses against microbial pathogens [26]. Also known as antimicrobial peptides, these molecules are produced by almost all forms of life [27]. AMPs are potent, broad-spectrum antimicrobials that act as the first line of defense against a wide range of invading pathogens including bacteria, protozoa, yeast, fungi and viruses by rapid and direct killing as well as several other means of modulating host immune systems [28,29]. Several decades of studies have revealed more than two thousand AMPs with diverse sequences of amino acids and a range of structures. (Readers are directed to the comprehensive AMP database curated by Wang and co-workers (http://aps.unmc.edu/AP/main.php) [30].) However, all AMPs show a common characteristic: the presence of an amphiphilic structure (in some literature, "amphipathic" is often used). The optimal amphiphilicity, which comes from cationic amino acids (e.g. lysine, arginine) and hydrophobic residues (e.g. isoleucine, valine), enables AMPs to fold into cationic and facially amphiphilic secondary structures. This feature permits AMPs to strongly interact with biological membranes. Interestingly, receptor-mediated antimicrobial activity is generally absent in AMPs. For instance, it was shown that all-D synthetic enantiomer homologous of magainins and cecropins have similar potency to all-L natural peptides [31]. This non-specific property has shown to be a class of promising anti-infective agents that are assumed to defer long-term resistance development compared to small molecule antibiotics.