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Review

Antimicrobial resistance challenged with metal-based antimicrobial macromolecules

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ABSTRACT

Antimicrobial resistance threatens the achievements of science and medicine, as it deactivates conventional antimicrobial therapeutics. Scientists respond to the threat by developing new antimicrobial platforms to prevent and treat infections from these resistant strains. Metal-based antimicrobial macromolecules are emerging as an alternative to conventional platforms because they combine multiple mechanisms of action into one platform due to the distinctive properties of metals. For example, metals interact with intracellular proteins and enzymes, and catalyse various intracellular processes. The macromolecular architecture offers a means to enhance antimicrobial activity since several antimicrobial moieties can be conjugated to the scaffold. Further, these macromolecules can be fabricated into antimicrobial materials for contact-killing medical implants, fabrics, and devices. As volatilization or leaching out of the antimicrobial moieties from the macromolecular scaffold is reduced, these medical implants, fabrics, and devices can retain their antimicrobial activity over an extended period. Recent advances demonstrate the potential of metal-based antimicrobial macromolecules as effective platforms that prevent and treat infections from resistant strains. In this review these advances are thoroughly discussed within the context of examples of metal-based antimicrobial macromolecules, their mechanisms of action and biocompatibility.

1. Introduction

In 1940, the antibiotic, penicillin, was introduced [1], heralding a new era in the treatment of infectious diseases. The introduction of these antibiotics resulted in a landslide victory in the clinical setting as, for instance, mortality from infectious diseases dropped from 283 to 75 per 100,000 individuals between 1937 and 1952 in the United States [2]. By the early 1940s, however, it was apparent that bacteria evolve resistance, deactivating antibiotics. Indeed, in 1941, Abraham and coworkers observed that cultures of staphylococci develop resistance by continuous subculture in the presence of penicillin [3], and in 1942, Rammelkamp and Maxon isolated four strains of penicillin-resistant staphylococci during treatment of local infections with penicillin [4]. Within two decades of penicillin's introduction, most strains of *Staphylococcus aureus* isolated in large hospitals were resistant to penicillin and to other antibiotics including streptomycin, tetracycline and erythromycin [5]. To overcome penicillin resistance, methicillin was introduced in 1959; regrettably, within two years, 18 strains of *S. aureus* showed resistance to methicillin [6]. Scientists responded to the threat of resistance, developing new antibiotics including vancomycin, which seems the last resort for treating methicillin-resistant *S. aureus* infections. Unfortunately, in 2002, physicians in the United States reported vancomycin-resistant strains of *S. aureus* [7].

Clearly, microorganisms have challenged modern science and medicine, evolving resistance that threaten the effective and sustainable treatment of infectious diseases, which eventually protract illnesses and increase mortality. Global annual mortality is projected at 10 million by 2050 if action is not taken to combat resistance [8]. To combat resistance, a strategy aims at mitigating healthcare-acquired infections in clinical settings. Indeed, infections acquired from medical devices and implants is a major clinical issue, therefore, reducing microbial adhesion on, and colonization of these devices and implants is an attractive strategy to combat resistance. Under this strategy, scientists are designing antimicrobial materials that include antimicrobial macromolecules as precursors for fabricating medical devices and implants [9–16].

Antimicrobial macromolecules are attractive since they are less volatile, more chemically robust, and therefore, possess longer

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lifetimes, and better environmental compatibility compared with antimicrobial small molecules. Again, from the application perspective, these macromolecules can be extruded into fibers for sterile bandages and surgical gowns, or fabricated into medical devices and implants or used as surface coatings in medical devices, hospital furniture, and shower walls to minimize microbial colonization. Consequently, antimicrobial macromolecules have been intensively researched since the 1960s [17–24]. These early antimicrobial macromolecules were mostly organic, and derived their activities from conjugated antimicrobial moieties [21,22,24]. Organic antimicrobial macromolecules continue to attract attention; nonetheless, metal-based antimicrobial macromolecules are being explored as an alternative.

Metal-based antimicrobial macromolecules have been known since 1969 [25], and have been shown to be effective against various microorganisms. Recent interest in this class of macromolecules is inspired by the anticancer property of cisplatin, a clinically approved platinum-containing molecule as well as the antimalarial property of ferroquine, an iron-containing molecule currently undergoing clinical trials. Mechanistically, metal-based macromolecules can function via multiple mechanisms; for instance, it is possible for metals to simultaneously interact with intracellular ligands such as proteins and enzymes, and catalyse intracellular biochemical processes, posing a greater challenge to resistant strains. Precise insertion of the metals into the macromolecular scaffold has been possible through advances in organic chemistry, inorganic chemistry, along with macromolecular chemistry. These advances also allow excellent control over the architecture of the macromolecule, which in turn tunes the properties. Further, advances in biochemistry have provided insights into the mechanisms of action of these macromolecules. Overall, remarkable achievements have been made in the design of metal-based antimicrobial macromolecules with precise and tunable antimicrobial activity, and importantly, with activity against resistant strains.

As microorganisms will evolve resistance for self-preservation, it is therefore, logical to assume that no antimicrobial agent will be efficacious forever. However, provided there is a continuous supply of new antimicrobial agents with mechanisms of action that bypass resistant pathways, it will be possible to effectively check the virulence of new resistant strains. In this Review, we focus only on metal-based antimicrobial macromolecules without limiting the discussion to a particular metal or microorganism or discussing other biomedical applications unlike other published excellent reviews [9,14–16,26–32]. First, we will discuss mechanisms of action of metal-based antimicrobial agents including small organometallic molecules as a thorough understanding of these mechanisms informs rational design of these macromolecules. Then, a discussion of several metal-based antimicrobial macromolecules, in which the metal functions as the antimicrobial moiety, is given. Last, an emerging class of antimicrobial agents, organometallic bioconjugates, where an organometallic molecule is conjugated to known antimicrobial macromolecules, is discussed.

2. Mechanisms of action of metal-based antimicrobial agents

The mechanism of action of metal-based antimicrobial agents is mostly independent of osmotic shock, relying on selective interference in cellular processes, and depending on the physicochemical properties of the metal and its associated ligands. Many discoveries in this area suggest that metal-based antimicrobial agents damage and kill microbial cells by inducing oxidative stress, causing protein dysfunction, or damaging cell membrane [33–36]. Evidently, metal-based antimicrobial can combine multiple mechanisms of action [36], which act in synergy to pose potent challenge to drug-resistant microorganisms. As an example, the organometallic compounds designed from cyclopentadienyl manganese tricarbonyl, dipicolyl rhenium tricarbonyl, and ferrocene (**1**) or ruthenocene (**2**) (Fig. 1a) is potently active against Gram-positive methicillin-resistant *Staphylococcus aureus* (MRSA) and simultaneously interferes with cell wall biosynthesis, targets cytoplasmic membrane, depolarizes membrane potential, and induces oxidative stress [36]. As the cytoplasmic membrane was the target structure (Fig. 1b), the authors postulated that compound **1** disrupts the phospholipid bilayer of the membrane, changing the structure and ultimately affecting the function of some membrane proteins [36]. Unarguably, membrane-targeting antimicrobial agents more potently act against resistant strains and effectively mitigate the evolution of resistance [36], it is still logical to presume that the multiple mechanisms of action contribute to the effectiveness of these metal-based antimicrobial agents against the drug-resistant strain.

Further, compound **1** is more active against the drug-resistant strain, MRSA, than compound **2**, and the difference in activity was speculated to result from ROS-induced oxidative stress. Indeed, oxidative stress assays using CellROX, a ROS-sensitive fluorescent probe, indicated that **1** generates ROS, fluorescing red in contrast to **2** and negative control (Fig. 2). The authors attributed the formation of ROS to redox activity of iron in ferrocene, which as part of its electron transfer processes may generate ROS, inducing oxidative stress. It is important to note that the reversible one-electron redox behaviour of ferrocene [37] differs from that of the experimental conditioned redox behaviour of ruthenocene [37–39], and this may contribute to difference in the antimicrobial activity of **1** and **2**.

A fundamental property of redox active species is reduction potential, which affects the ability of the species to acquire electrons. If the electron transfer process is essential to the antimicrobial activity of metal-based antimicrobial agents, then, differences in reduction potential should influence activity. Indeed,

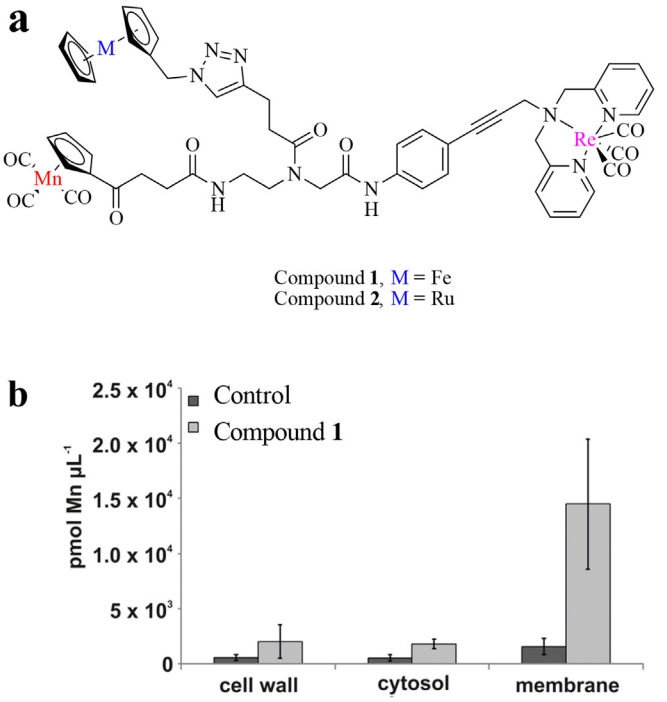

Fig. 1. (a) Structures of compounds **1** and **2**. (b) Compound **1** targets and localizes in cytoplasmic membrane as evidenced by measurement of manganese content of different cell fractions by atomic absorption spectroscopy. Adapted with permission from ACS Chem. Biol. 8 (2013) 1442–1450. Copyright©2013 American Chemical Society.