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Review

Antimicrobial peptides as an alternative to anti-tuberculosis drugs

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ABSTRACT

Tuberculosis (TB) presently accounts for high global mortality and morbidity rates, despite the introduction four decades ago of the affordable and efficient four-drugs (isoniazid, rifampicin, pyrazinamide and ethambutol). Thus, a strong need exists for new drugs with special structures and uncommon modes of action to effectively overcome *M. tuberculosis*. Within this scope, antimicrobial peptides (AMPs), which are small, cationic and amphipathic peptides that comprise a section of the innate immune system, are currently the leading potential agents for the treatment of TB. Many studies have recently illustrated the capability of anti-mycobacterial peptides to disrupt the normal mycobacterial cell wall function through various modes, thereby interacting with the intracellular targets, as well as encompassing nucleic acids, enzymes and organelles. This review presents a wide array of antimicrobial activities, alongside the associated properties of the AMPs that could be utilized as potential agents in therapeutic tactics for TB treatment.

Contents

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1. Introduction

Human tuberculosis (TB) is the manifestation of the infection of humans by members of the *Mycobacterium tuberculosis* complex, comprising *Mycobacterium tuberculosis*, *Mycobacterium africanum*, *Mycobacterium bovis*, *Mycobacterium microti*, *Mycobacterium leprae* and *Mycobacterium canetti* [1]. The patients suffering from active pulmonary TB are considered as the main source of infection, while most people carrying the *M. tuberculosis* infection remain asymptomatic (latent TB infection (LTBI)). Globally, there are about two billion LTBI cases, who are in danger of the disease being reactivated [2,3]. Despite the introduction of the aforementioned four affordable and efficient drug treatment regimens four decades ago, TB has continued to spread to all corners of the world [4].

The World Health Organization's (WHO) 17th report on the global occurrence of TB signifies that it maintains the status of a global emergency. It was estimated that in 2015, there were about 10.4 million new cases and 1.8 million deaths from TB, including 0.4 million deaths among people co-infected with HIV. The greatest rates per capita of TB are found in sub-Saharan Africa, which is mainly challenged by the HIV epidemic in the region. Nearly 60% of global TB cases are found in South Africa, China, India and the Russian Federation [5]. In the United States and Western Europe, the majority of TB cases are found among residents from other nations where TB is highly endemic [6,7]. Currently, multidrug-resistant TB (MDR-TB) is widespread, with around 580,000 documented cases for 2015. Extensively drug-resistant TB (XDR-TB) has currently been reported in about 84 countries of the world. Owing to the financial limitations and laboratory infrastructural inadequacy, only about 19% of the globally approximated numbers of MDR-TB cases were reported to the WHO in 2011, while less than 4% of MDR-TB cases are presently diagnosed at a global level. The treatment of TB is challenging, requiring a precise diagnosis, screening for resistance to drugs and the administration of effective treatment regimens for a minimum of six months through directly observed therapy (DOT). Therefore, there is a need for the development of novel TB agents for shorter TB treatment regimens [8].

The study of AMPs commenced during World War II when gramicidin, an antimicrobial agent from the soil bacterium *Bacillus brevis,* was discovered by Rene J. Dubois. This antimicrobial agent was found to be effective against Gram-positive bacteria and used for the treatment of soldiers' wounds and ulcers [9]. Nonetheless, AMP as a term was not broadly used before the 1960s when a number of proteins with selective antimicrobial actions in polymorphonuclear (PMN) leukocytes were discovered [10–12]. During the 1980s, cecropins were isolated from larva, followed by the unveiling of magainins from the skin of frogs, indicating that AMPs are made in the higher vertebrates [13]. Two mammalian AMPs were identified in the 1980s, comprising cathelicidins and defensins, albeit with several scrutinies. Defensins can be categorized into α-defensins, β-defensins and θ-defensins [14]. Described as cationic peptides, cathelicidins have a common N-terminal cathelin-like domain, but possess a variable C-terminal region.

The defensins, as well as the cathelicidins, have a wide and varied antimicrobial spectrum against both Gram-positive and Gram-negative bacteria, mycobacteria, viruses and fungi [15,16]. Nonetheless, there is currently little information on the manner in which antimicrobial agents influence pathogens, resulting in the disruption of the normal cell membrane, growth inhibition and even cell death. Specifically, the significant activity of AMPs against *M. tuberculosis* has viewed them as prototype molecules in the planning of novel anti-TB agents [17]. In this review, several natural AMPs from varying organism sources with a wide range of *in vitro* and *in vivo* cidal activity against *M. Tuberculosis* are detailed, even while their overall mechanism of action is debated.

2. Need for new anti-tuberculosis drugs and schemes

Even though the presently available treatment regimens for the drug-sensitive tuberculosis are greatly efficient subject to patients' adherence under ideal conditions, the results are not perfect when the actual life realities of tuberculosis programmatic conditions are considered [18]. The WHO's suggested treatment regimens for drug-susceptible and drug-resistant tuberculosis are saddled with several inherent challenges, rendering novel antituberculosis drug discovery a priority for clinical and public health [19–24].

The first challenge is the protracted nature of the treatment regimen for the drug-susceptible disease, which extends over a minimum period of six months [25]. Additionally, the first-line oral drugs (isoniazid, ethambutol, pyrazinamide, and rifampicin) have to be taken simultaneously in the first two months of treatment, while isoniazid and rifampicin are taken over a consecutive period of four months during the continuation stage, resulting in the challenges linked to patients' adherence to the regimens. These regimens are associated with high mortality rates and patients' non-adherence. They can lead to the development of chronic drug-resistant tuberculosis [23,26]. Therefore, a key concern for drug development has been for novel tuberculosis agents, which will reduce the treatment regimen. Strong sterilizing agents, which may reduce the treatment period to two months and below, could enhance adherence and decrease the cost of distribution and programme supervision [27]. In addition, the drugs that could decrease the total duration of the treatment and regularity of drug intake are always preferable. Studies on the life cycle of *M. tuberculosis* have illustrated that mycobacteria generates a dormancy phenotype under anaerobic conditions and nutrient deprivation [28–31]. The bacterial population of the persisters may endure for a maximum of 100 days following the commencement of anti-tuberculosis treatment, while a reviving element is needed for duplication in order to encourage a swift reproduction of the inactive bacilli. Such dormant bacteria are not susceptible to numerous anti-tuberculosis agents and can lead to an extension of anti-tuberculosis treatment. Therefore, novel drugs and regimens are required for a complete denaturing of all the persisters, regardless of the developmental stage attained by the *M. tuberculosis* [29,32–34].

Secondly, novel drugs are required to deal with the increasing global challenge of MDR-TB and XDR-TB [35]. MDR-TB, which results from the resistance of the *M. tuberculosis* to rifampicin and isoniazid, is currently widespread at a global level, with around 500,000 cases documented in 2015 [36]. XDR-TB (as a result of *M. tuberculosis* resistance to isoniazid, rifampicin and any fluoroquinolone, as well as at least one of the three injectable second-line medications: kanamycin, amikacin, or capreomycin) has been documented in many countries. Patients with MDR-TB require a combination of second-line and third-line anti-tuberculosis agents [37], which are considerably costlier, noxious and less efficient than regular treatment. The WHO's recommendations for addressing MDR-TB and XDR-TB refer to second-line drugs and a treatment period covering more than 18–24 months [23]. These directions are based on low-grade evidence, experts' viewpoint and little observational information, and do not have the rigour of evidences according to the data from randomized trials. The implementation of such directions comes with a broad array of treatment regimens, which rely on the availability of drug-susceptibility assessments, expenses, doctors' preference and the availability of drugs in developing countries. Therefore, there is a need for novel regimens for MDR-TB and XDR-TB, which are less protracted, more bearable, more efficient and have been assessed under programmatic conditions [38,39].

Thirdly, anti-tuberculosis agents may interact with antiretroviral therapy (ART), thereby presenting a great control challenge in sub-Saharan Africa, where the cases of TB are mostly driven by