



Which Antimicrobial Peptides Have An Inhibitory Effect On Tuberculosis?

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Abstract

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (MTB) which is one of the top 10 causes of death worldwide. The emergence of multi-drug and extensively-drug resistant *Mycobacterium tuberculosis* strains has become as a global crisis. It's necessary to introduce the novel generation of bactericidal agents for treatment and control of drug-resistant strain. Nowadays, Antimicrobial peptides (AMPs), which are short-length, cationic and amphipathic peptides have a remarkable strategy for replacement with antibiotics in the treatment of drug-resistant infections. In this study, we discuss about numerous AMPs which have anti-tuberculosis activities against both of susceptible and drug-resistant TB strains.

Keywords: *Mycobacterium Tuberculosis*; Antimicrobial Peptide; Tuberculosis; Antibiotics; Treatment

Introduction

Tuberculosis (TB) remains as one of the important infectious diseases which is considered as the ten top of cause of people dying by WHO; According to WHO reports, there are approximately 10.7 million new TB cases in 2018, about two billion of people were contaminated by *Mycobacterium tuberculosis* which not clinical symptoms but 5-10% of there are developed to reactivation of tuberculosis [1,2]. In recent years, the advent and distribution of drug-resistant TB (DR-TB) are converted to the major concern of public health services throughout the world [2]. There are 558,000 Rifampin-resistant TB cases which 80% of these cases have MDR-TB (Multi-drug resistant which is resistant to rifampin and isoniazid) [1].

Antimicrobial peptides (AMPs) are oligopeptides which expressed in eukaryotic cells particularly human and play a key role as part of the innate immune response to infectious agents [3]. This class of macromolecules has broad-spectrum antibiotics effects which approved as novel therapeutic agents which inhibits Gram-positive, Gram-negative, fungi and enveloped virus [4]. According to the review of literature, AMPs have antimycobacterial activities which could be efficient in susceptible and MDR strains of *M. tuberculosis* [5]. In this report, we

discussed about several antimicrobial peptides which approved as a potent antibiotic for the treatment of tuberculosis.

Discussion

The current tuberculosis treatment and anti-TB resistance

The conventional therapy of tuberculosis is consisting two stages including the initial phase of rifampicin (RIF), isoniazid (INH), pyrazinamide (PYZ), and ethambutol (ETB) which are recommended daily for 2 months; followed preservative phase of RIF and INH for additional 4 months [6]. Unfortunately, the emergence and spread of Drug-resistant TB (DR-TB) particularly, Multidrug-resistant TB (MDR-TB) which is resistant to both isoniazid and rifampicin, and extensively drug-resistant TB (XDR-TB) that is MDR strains which are resistant to fluoroquinolone and one of the second-line injectable are considered as a major treat [7]. According to the review of literature, DR-TB is commonly associated with high mortality rates; it estimated that 50% of MDR-TB cases and lower than 30% of patients with XDR-TB are survived [8]. MDR-TB and XDR-TB strains are mediated by spontaneously point mutation in KatG (INH), rpoB (RIF), gyrB (fluoroquinolones) and rrs (aminoglycosides) [9]. In addition, side effect and limitation of anti-tuberculosis drugs have forced to investing in a novel generation of ant-TB drugs; nowadays, it is suggested that anti-microbial peptides are considered as potential anti-tuberculosis drugs [10,11].

Defensins

Defensins are classified as Human neutrophil peptide (HNP) and β -defencin; Human neutrophil peptide 1 (HNP-1) (peptide sequence: ACYCRIPACIAGERRYGTCTIYQGRWAFCC) is a β -sheeted cationic AMP which has antibacterial activity because of three intramolecular disulfide bonds (Figure 1) [12]. Kalita et al., have shown that MIC value of HNP1 against *M. tuberculosis* H37Rv was 2.5 μ g/ml which was higher than isoniazid (0.3 μ g/ml) and rifampicin (0.2 μ g/ml) [13]. Also, there are four types

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of β -defensin (HBD1-4); Corrales-Garcia et al., were found that HBD2 revealed sufficient bactericidal activity against *M. tuberculosis* H37Rv (1.5 M) [14].

Cathelicidins

Cathelicidins are known as one of the great AMPs which was purified from myeloid cell lines (bone marrow) for the first time; LL-37 (peptide sequence: LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLPVPTES) peptide is derived from human cationic antimicrobial protein which expressed by macrophages during entry of pathogens which significantly reduces the intracellular survival of *M. tuberculosis* [15]. Murine cathelicidin known as CRAMP (peptide sequence: GLLRKGGEKIGEKLLKIGQKIKNFFQKLVPPQEQ) has similar activity like to the human cathelicidin (Figure 1) [16]. Rivas-Santiago et al., have shown the bactericidal activity of LL-37 and mouse CRAMP against a susceptible strain of *Mtb* H37Rv and MDR strain during in vitro and in vivo studies [17].

Hepcidin

Hepcidin is a natural AMP (peptide sequence: DTHFPICIFCGCCHRSKCGMCKKT) compounds, which is expressed by the liver cells during the inflammatory process (Figure 1) [18]. Sow et al., have suggested that hepcidin could be reduced the CFUs of *Mtb*H37Rv with a concentration of 200 μ g/ml [19].

NK-lysin and granulysin

NK-lysin and granulysin are homologous cationic antimicrobial peptides which are expressed by pig and human cytotoxic lymphocytes respectively (Figure 1) [20]. NK-lysin (peptide sequence: GYFCESCRKIIQKLEDMVGPQPNEDTQTQAASQVCDK-LKILRGLCKKIMRSFLRRISWILTGKKAICVDIKICKE) has destroyed *Mtb* H37Rv during 8 days at 30 μ M [21]. Granulysin (peptide sequence: GRDYRTSLTIVQKLKMMVDKPTQRSVSNAAATRVSR) has cytolytic effects against both drug-susceptible *M. tuberculosis* and MDR-TB [22]. Also, it suggested that Granulysin has a candidate as a biomarker for diagnosis of TB [23].

Ubiquitin

Ubiquitin is naturally stored in secretory chromaffin granules and released in response to different pathogens during Pro-inflammatory process from chromaffin cells (Figure 1) [24]. Kieffer et al., identified Ub2 in lysosome which plays a key role in autophagy for *Mtb* lysis in phagolysosome [25]. Also, studies were showed that synthesized peptide Ub2 (peptide sequence: STLH-LVLRRLGG) were antibacterial activity against tubercle bacillus [21].

There are numerous class of AMPs which show bactericidal activity against both drug-susceptible strains and MDR-TB strains which classified in different class including 1) Animal AMPs (PR-39), 2) Human Immune cell-derived (LL37, mCRAMP, E2, E6, Human neutrophil peptide 1 (HNP-1), Human B-defensin (hBD2), Granulysin, granF2, G13, Lactoferrin, IDR) Human Non immune cell-derived (Ub2 (ubiquitin-derived), Hepcidin), 4) Human host defense (RNase 3, RNase 7, HCL2) , 5) Microbial AMPs (Lactacin 3147, E50-52, Lassomycin, Bacteriocins (Bcn1-Bcn5),

AS-48, NZX), 6) Synthetic AMPs (LLKKK-18, (LLKK)2, D5 (Synthetic 26-residue, amphipathic α -helical peptide), D-LAK analogs, ATRA-1A, IDR-1018), 7) Mycobacteriophage AMPs (PK34, CHAP, PlyG), lactacin 3147, E50-52 and human host defense ribonucleases (RNase) [21,26-28].

In recent years, these studies are continuously performed and novel AMPs are introduced with anti-mycobacterial effects against TB such as CXCL1/CXCL2, NZX, and AS-48 which are novel potential option for treatment of tuberculosis (Figure 1) [29-31].

CXCL1 / CXCL2

Boro et al., showed that chemokines of CXCL1 and CXCL2 were expressed during *Mtb* infection and recruit neutrophils to the site of tubercle bacillus [29].

NZX as a novel derivative of Plectasin NZX (peptide sequence: GFGCNGPWSEDDLRCRHRHCKSIKGYRGGYCAKGGFVCKCY) is derived from Plectasin in fungi which has bactericidal effects on *M. tuberculosis* both in vitro and in murine model studies [30]. Tenland et al., was found that the plectasin derivatives NZ2114 and NZX have antibacterial activities against *Mtb* (MIC concentrations were 6.3 μ M for H37Rv, 6.3 μ M and 3.2 μ M for two clinical *M. tuberculosis* isolates and 6.3 μ M for the clinical MDR isolate, respectively); they found that NZX was less toxic to human cells than LL37 [32].

AS-48

AS-48 is 70-aminoacid, an α -helical membrane-interacting peptide which is extracted from *Enterococcus faecalis* and is active against Gram-positive bacteria [31]. Aguilar-Pérez et al., have shown that the combination of AS-48 plus either lysozyme or ethambutol has anti-TB activities [33].

During present decades it is suggested that numerous cyclic peptides have antimycobacterial activities, for example, griselmycins, depsidomycin, hytramycin, brunsvicamides, pyridomycin, hirsutellide A and wollamides particularly, Wollamide B which is evaluated in several studies [34].

Wollamide B

Wollamide B is cationic cyclohexapeptide which is extracted from *Streptomyces nov.* strain MST-115088 by Khalil et al., in 2014 [35]. This compound has two uncommon residues such as D-Orn, D-Leu or four L-amino acids in the structure [35-36]. For the first time, Khalil et al., have shown that Wollamide B had IC50 of 3.1 μ M against *M. bovis*. In recent years, Asfaw et al., suggested that this compound has anti-TB effects during in vitro studies (MICs \leq 3.1 μ M against *Mtb* H37 Rv) [34,35].

The cathelicidin-like antimicrobial protein of *D. melanogaster* (dCAMP)

Jin et al., was reported the cathelicidin-like antimicrobial protein which is induced by *Drosophila* cg6568 gene during infection with *M. marinum* infection in *D. melanogaster*; this compound is cathelicidin like the activity that inhibits intracellular growth of mycobacterial species [37].

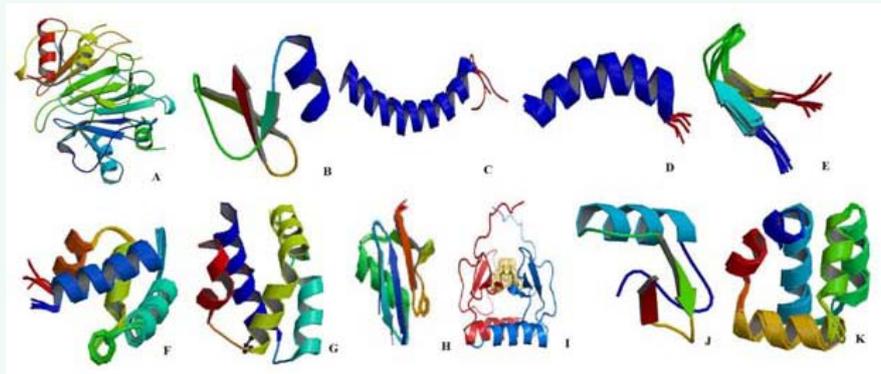


Figure 1 AMPs have ant-tuberculosis activity from A-L; A: Human neutrophil peptide, B: β -defencin, C: LL-37, D: CRAMP, E: Hepcidin, F: NK-lysin, G: granulysin, H: Ubiquitin 2, I: CXCL1, J: Plectasin, K: AS-48; respectively..

Conclusion

Antimicrobial peptides are natural oligopeptides which have the best candidate for the development of a novel natural generation of antibiotics; According to the review of the literature, there are 10 AMPs which entered clinical trials. In addition; there are several AMPs with anti-tuberculosis activity (both of susceptible and drug-resistant TB) provide the hypothesis that AMPs have the best candidates for the treatment of tuberculosis.

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