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Mini Review

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 anti-mycobacterial 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.

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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: ACYCRIPACIAGERRYGTCIYQGRLWAFCC) 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 μg/ml which was higher than isoniazid (0.3 μg/ml) and rifampicin (0.2 μg/ml) [13]. Also, there are four types

of β-defencin (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 form myeloid cell lines (bone marrow) for the first time; LL-37(peptide sequence: LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES) 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: GLLRKGGEKIGEKLKKIGQKIKNFFQKLVPQPEQ) 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: DTHFPICIFCCGCCHRSKCGMCCKT) 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 MtbH37Rv with a concentration of 200 μg/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: GYFCESCRKIIQKLEDMVGPQPNEDTVTQAASQVCDKLKILRGLCKKIMRSFLRRISWILTGKKAICVDIKICKE) has destroyed Mtb H37Rv during 8 days at 30 μM [21]. Granulysin (peptide sequence: GRDYRTSLTIVQKLKKMVDKPTQRSVSNAATRVSR) 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: STLHLVLRLRGG) 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 (ubiquitndrived), Hepcidin), 4) Human host defense (RNase 3, RNase 7, HCL2) , 5) Microbial AMPs (Lacticin 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), lacticin 3147, E50-52 and human host defense ribonucleases (RNase) [21,26-28].

In recent years, these studies are continuously performed and noel 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: GFGCNGPWSEDDLRCHRHCKSIKGYRGGYCAKGGFVCKCY) is derivate 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 μM for H37Rv, 6.3 μM and 3.2 μM for two clinical M. tuberculosis isolates and 6.3 μM 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 alpha-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 μM against M. bovis. In recent years, Asfaw et al., suggested that this compound has ani-TB effects during in vitro studies (MICs ≤ 3.1 μM 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].

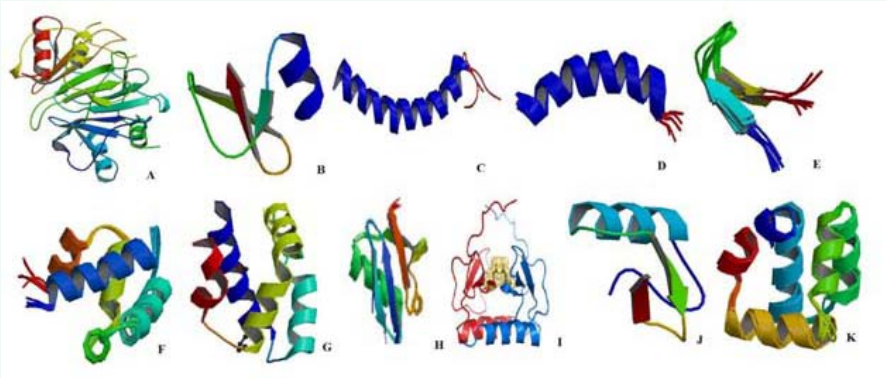

Figure 1 AMPs have ant-tuberculosis activity from A-L; A: Human neutrophil peptide, B: β-defencin, C: LL-37, D: CRAMP, E: Hepcidin, F: NK-lysin, G: granulysin, H: Ubiquitin 2, I: CXCL1, J: Plectasin, K: AS-48; respectively..

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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