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Natural antimicrobial peptides against *Mycobacterium tuberculosis*

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TB, caused by *Mycobacterium tuberculosis*, is one the leading infectious diseases worldwide. There is an urgent need to discover new drugs with unique structures and uncommon mechanisms of action to treat *M. tuberculosis* and combat antimycobacterial resistance. Naturally occurring compounds contain a wide diversity of chemical structures, displaying a wide range of *in vitro* potency towards *M. tuberculosis*. A number of recent studies have shown that natural antimycobacterial peptides can disrupt the function of the mycobacterial cell wall through different modes of action and thereafter interact with intracellular targets, including nucleic acids, enzymes and even organelles. More importantly, the probability of antimycobacterial resistance is low. This review presents several natural antimicrobial peptides isolated from different organism sources, including bacteria, fungi, plants and animals. In addition, the molecular features of these molecules are the subject of much attention. Such peptides have common traits among their chemical features, which may be correlated with their biological activities; hence, different parts of the molecular structures can be modified in order to increase penetration into the target cells. This review also summarizes the available information on the properties of antimycobacterial peptides associated with their biological activities.

Keywords: tuberculosis, drug-resistant tuberculosis, antimycobacterial agents, toxicity, TB

Introduction

Mycobacterium tuberculosis, the causative agent of TB, was discovered by Robert Koch at the end of the nineteenth century.[1] This infectious killer agent currently is one of the most common diseases, infecting approximately one-third of the world's population.[2,3] According to the WHO survey,[4] it is estimated that there were 8.6 million people infected with TB in 2012. In addition, there are an estimated 450 000 MDR-TB cases and 170 000 fatalities occur as a result. The development of new cases, adverse events in response to anti-TB drugs, co-morbidity with HIV and the lack of an effective vaccine pose great problems in the search for new anti-TB drugs.[2,5,6]

TB can be cured with multidrug chemotherapy, but the lengthy therapy (at least 6 months) has led to poor patient compliance.[5] Currently, the treatment for TB includes a cocktail of first-line drugs, isoniazid and rifampicin, supplemented with pyrazinamide and ethambutol in the first 2 months.[5] If the early 6–9 month treatment protocol using four drugs, namely isoniazid, rifampicin, ethambutol and pyrazinamide, fails due to the emergence of first-line drug resistance, an alternative treatment programme is started of a further 4 months of drug administration with a combination of second-line drugs, including aminoglycosides, cycloserine, terizidone, ethionamide, protionamide, capreomycin, aminosalicylic acid and fluoroquinolones. These second-line drugs are generally more toxic, less effective and less tolerable.[6]

MDR-TB (resistant to at least rifampicin and isoniazid) and XDR-TB (MDR-TB plus resistant to fluoroquinolones and one of the second-line treatments), which occur through spontaneous chromosomal mutation at low frequency, are posing a threat to the control of TB.[7] Therefore, due to the emergence of drug resistance in *M. tuberculosis* against currently available antimycobacterial therapies, there is an urgent need for the development of new drugs.

This scenario has attracted attention to achieving effective prevention, durable cure and treatment of the expanding problems of TB.[3] For this purpose, research focused on naturally occurring compounds or their derivatives has shown the potential of this field for taking a leading role in the investigation and development of new drug candidates. Such molecules are essential for the pharmaceutical industry due to their wide structural diversity and potential biological activities. The acquisition of resistance to naturally occurring molecules is also a rare phenomenon.[8] Among them, peptides have been found to be more effective due to their unique molecular features and antimicrobial mechanisms.

Several studies have shown that peptides could have many applications in medicine. An important reason for interest in peptides is that they bind to a broad range of biological targets, including *in vivo* targets, resulting in remarkably high potencies of action and potentially lower toxicity than small molecules.[9] In addition, many studies have indicated that some peptides may use multiple mechanisms of action, which can be effective in increasing antimicrobial efficiency and evading potential

resistance mechanisms.[10] Thus, many research efforts have dealt with the identification and characterization of naturally occurring peptides to provide novel structures for drug discovery.

With the recent addition of new methodologies, antimicrobial peptides (AMPs) may represent a valuable therapeutic source in medical care and treatment. Various studies have demonstrated that the main advantages of AMPs are their broad-spectrum antimicrobial activity against Gram-negative and -positive bacteria, fungi, viruses and parasites, and their low probability of induced resistance in pathogens.[11] However, there is still little information about how antimicrobial agents affect the pathogen to cause cell membrane disruption, growth inhibition or cell death. In particular, the remarkable activities of natural AMPs against *M. tuberculosis* have been considered as prototype molecules in the design of new anti-TB agents.[3]

It is appropriate to review the literature covering AMPs with antimycobacterial activity, published until 2013. In this review, natural compounds isolated from a wide range of species, including bacteria, fungi, plants and animals, with a broad spectrum of *in vitro* killing activity against *M. tuberculosis* are described and their general mode of action with their biophysical and biochemical properties is discussed.

Antimicrobial features of AMPs

Structural features of AMPs

AMPs are naturally synthesized antibiotics, characterized as an important part of the innate immune response in all living organisms from bacteria to plants and animals.[12] AMPs are endogenous polypeptides synthesized by ribosomes. However, some AMPs are produced by non-ribosomal peptide synthetases (NPRSs) or polyketide synthetases (PKSs). For instance, bassianolide,[12] beauvericines and enniatins are antimycobacterial cyclodepsipeptides synthesized by NPRSs,[13] and pitipeptolides[14] are biosynthesized by a mixed PKS/NPRS pathway. The overall structure of ribosomal and non-ribosomal peptides can be linear, cyclic or branched cyclic, and might be modified by methylation, acylation or glycosylation.

Basically, AMPs are relatively short (<100 amino acid residues) and positively charged (generally +2 to +9) with an amphipathicity structure (having both hydrophobic and hydrophilic sides).[15] They are considered promising in the prevention and management of TB due to their broad-spectrum antimicrobial activity, rapid efficiency and low possibilities of resistance. AMPs from different sources have been reported to exhibit antimicrobial activity with MICs, as shown in Table S1 (available as Supplementary data at *JAC* Online).

Molecular mechanisms of action

Recent developments in antimicrobial agents have heightened the need for understanding how peptides target the membranes by different modes of action. It is generally accepted that most of the cationic AMPs initially interact with the anionic surface of microbial membrane, which causes the peptide molecules to be accumulated on the membrane surface. Afterwards, the hydrophobic interaction between amphipathic AMPs and the cell membrane makes a specific peptide–lipid complex, which might produce possible alteration in bacterial membrane, such as thinning, pore formation, altered curvature, modified electrostatics and localized perturbations.[16] At this point, the peptides may translocate across the membrane and diffuse into the cytoplasm, possibly interacting with intracellular targets including nucleic acids, enzymes and even organelles.[16,17]

A number of studies have reported that AMPs exhibit strong bactericidal activities through an increased permeability of mycobacterial cell wall.[18] Extensive research has been carried out on the various mechanisms of actions of anti-TB agents; however, their targets and the resistant mechanism are still under study.[17,19] It is mainly considered that the distinctive cell wall of *M. tuberculosis*, which functions as a primary permeability barrier to the entry of anti-TB drugs, contributes to the pathogenicity and resistance.[20] In fact, the unique structure of the mycobacterial cell wall contains a very high concentration of lipid, which makes the cell surface hydrophobic. More specifically, mycolic acids with long hydrocarbon chains characterized as the major constituents of the outer layer play an important role in the lipid-rich cell wall structure.[19,21] This tightly packed array with extremely low fluidity[22] induces aggregation of the cells and consequently reduces the permeability of the cell wall.[23]

The interaction of each of the AMPs and bacterial membrane cannot be explained due to the variety of structural motifs as well as the size, residue composition, overall net positive charge, degree of structuring, hydrophobicity and amphipathicity character.[16] However, there is evidence that AMPs could increase the permeability of the cell membrane by creating pores as well as disrupting the organization of cell wall synthesis, unlike conventional antibiotics, which require transportation across the cellular membrane before they can be effective. Several parts of the molecule could be modified with the aim of altering the physicochemical properties in order to increase the cell wall penetration.

Some authors have reported that a number of AMPs have more than one mode of action. A study by Carroll *et al.*[24] showed that lantibiotics nisin and lacticin 3147 possess different modes of actions in that they bind to the peptidoglycan precursor and thereafter inhibit the biosynthesis of peptidoglycan as well as forming pores in the membrane of target cells. It has been also shown that uridyl-peptide antibiotics might inhibit bacterial translocase MraY, involved in bacterial cell membrane, and exhibit activity against *M. tuberculosis*, e.g. rifampicin and isoniazid. Interestingly, antimycobacterial agents working through this mode of action inhibit the replication of drug-susceptible TB as well as MDR-TB. For instance, sansanmycin A is a class of novel uridyl-peptide antibiotics, as reported by Li *et al.*[25]

Structure–activity relationships (SARs)

SAR studies investigate the relationship between the structure of an AMP and its biological activities. However, these molecules are diverse compounds differing in several parameters, such as sequence, charge, size, hydrophobicity, amphipathicity and degree of three-dimensional formation, although they have common features contributed to their activities. In fact, SAR studies are a useful tool in the design of novel antimicrobial agents with improved properties. In this review, a number of factors suggested to be important for antimycobacterial activity have been mentioned. Many authors have demonstrated that increased antimicrobial potency might be due to the modification of structures and functional groups during the synthesis of effective

compounds. It is well known that amphipathicity of AMP is a crucial parameter required for antimicrobial action, particularly for initial interaction with the membrane surface. Increasing evidence is showing that the amphipathic α-helix is the most common conformation characterized as an important antimicrobial domain. Moreover, several studies have indicated that antimycobacterial peptides often contain disulphide bonds in their structure, such as VGF-1,[26] HNP-1,[27] lariatin A,[28] NK-lysin and protegrin.[29] In fact, formation of disulphide bridges by cysteine residues commonly stabilizes and enhances the antimicrobial activity.[29] It has also highlighted that the disulphide-constrained-loop structure may be important for biological activities.[30] Furthermore, some studies showed that small natural antibacterial peptides (chain length of C_{20}) containing a disulphide bond possess loop structures. N22 peptide derived from an active fragment of NK-lysin is the best example, as reported by Gu *et al.*[31] The amphipathic structure of N22 contained an α-helix and a turn formed into a loop by an internal disulphide bond. This super-secondary peptide structure has been shown to exhibit strong antimycobacterial activity.

Another important feature is the hydrophobicity of AMPs. The evidence collected so far proves that the balance between the hydrophobicity of a peptide and its polar regions promotes efficient antimycobacterial activity.[32] This feature was demonstrated by Bourel-Bonnet *et al.*[33] in a study comparing activities between kahalalide A and its related analogues. The authors reported that increasing the hydrophobicity by changing the methyl butyrat side chain to achiral hexatoate led to a 2-fold increase in potency compared with its natural analogue (MIC = 32 and 64 mg/L, respectively). In another study, the relationship between the activity of AMP and hydrophobicity was examined by Montaser *et al.*[14] for pitipeptolides. In this case, the hydrophobicity of certain units was decreased by replacing Hmpa with a Hiva unit, and changing Ile to Val residue. Such modifications resulted in increased anticancer activity, while also increasing the antibacterial activity. The hydrophobic helical domain will drive the AMP insertion into the hydrophobic core of the membrane, but overall data have provided evidence that the hydrophobicity of α-helical amphipathic peptides exhibits more potent toxicity than the antimicrobial activity.[32] The best example is N22, which has been shown to exhibit low toxicity to human erythrocytes.[31]

Moreover, restricting the conformational freedom of peptide by converting a linear structure into a cyclic skeleton may lead to increased biological activity. The best example was also addressed by Bourel-Bonnet *et al.*[33] in a study comparing activities between kahalalide A and its related analogues that showed that a constrained depsipeptide framework plays an important role in biological activity. Furthermore, a comparison between the analogues at the positions of the Ser and Thr side chains highlighted the importance of a free alcohol functional group. In another study, Li *et al.*[25] reported that the introduction of alkyl groups could increase the activity. In this work, the introduction of an isopropyl group at the amino terminal of sansanmycin A resulted in high antimycobacterial activity.

Some studies have provided evidence of the biological activity of lasso peptides. Iwatsuki *et al.*[28] reported that lariatin A possesses a lasso structure in which the C-terminal tail of the peptide passes through the ring structure formed by the N-terminal segment.

Another important structural aspect is N-methylation, which is the most common post-translational modification in NPRS. Peptides having N-methylated amino acid residues have displayed potent biological activities. Pitipeptodides were modified by N-methylated phenylalanine, as reported by Montaser *et al.*,[14] showing both cytotoxic and antimycobacterial activities. In fact, this modification involves protecting peptide bonds against proteolytic cleavage, resulting in biological activity. In another study, Suksamrarn *et al.*[34] showed that methoxyl and the *N*,*N*-dimethyl amino groups in ziziphine N and Q play an important role in their activity. Furthermore, it has been shown that replacing the leucine unit in ziziphine N with valine moiety in ziziphine Q showed a similar trend of biological activity. In addition, cyclopeptide alkaloids containing a hydroxyl proline unit in the terminal N-methylated or N,N-dimethylated amino acid residues possess potent biological activities. Such a feature was observed by Panseeta *et al.*[35] in a study on mauritine M.

Andreu *et al.*[29] suggested that a short version of a relatively large antibacterial peptide can be synthesized and designed on the basis of the native three-dimensional structures, which means the antibacterial domain in the parenteral molecule, preserving significant conformational properties and even improving some of the parental molecular features. In particular, this segment seems to define the structural elements essential for antimicrobial activity, and hence the selectivity of the antimicrobial compounds could be increased through structural modifications. Therefore, the SARs demonstrate that the side chains, entire peptide chain length and structural skeleton are important for antimicrobial activity.

Toxicity

It is important to find out if a candidate molecule is toxic for host cells. The structural features required for antimycobacterial activity cannot be applied for cytotoxicity activity, which means that the cytotoxic activity in eukaryotic cells could be separate from the antimycobacterial activity.[14] There are literature reports describing the *in vitro* cytotoxicity of antimycobacterial peptides presented in this review. A number of studies have shown that naturally occurring enniatins evoked toxicity in *in vitro* assays. The enniatins have been isolated from strains of some species of the fungal genera *Alternaria*, *Fusarium*, *Halosarpheia* and *Verticillium*.[36] Their molecular structures are composed of three D-α-hydroxy isovaleric linked to an alternating sequence of three *N*-methyl-L-amino acids residues. Ivanova *et al.*[36] reported that individual or combinations of enniatins exhibited substantial cytotoxicity. Nilanota *et al.*[37] examined the cytotoxicity of enniatins B-I, isolated from *Verticillium hemipterigenum*, towards two cancer cells (KB and BC-1) and Vero cells. They observed that EN I showed higher cytotoxic activities with IC_{50} values of >20, 18 and 38 mg/L for KB cells, BC-1 cells and Vero cells, respectively.

In another study, beauvericin and beauvericin A was also represented by Nilanota *et al.*,[38] exhibiting cytotoxicity against tumour cell lines with IC_{50} values of 4.9 and 2.5 mg/L, respectively. Luesch *et al.*[39] demonstrated that pitipeptolides A and B exhibit weak cytotoxicity to LoVo cells with IC_{50} values of 2.25 and 1.95 mg/L, respectively. In an analysis of pitipeptolides, Montaser *et al.*[14] found that the π system in the fatty acid unit plays an important role in the cytotoxicity activity in mammalian cells.

Davis *et al.*[40] reported that microcionamides A and B possess a high level of cytotoxicity against human breast tumour cell lines.

The activity of microcionamide A to MCF-7 and SKBR-3 cells showed IC_{50} values of 125 and 98 nM, respectively. Microcionamide B also showed similar activity towards MCF-7 and SKBR-3 cells with IC_{50} values of 177 and 172 nM, respectively.

Cathelicidin AMPs exhibit cytotoxicity towards human erythrocytes and polymorphonuclear cells. It has been also reported that HNP-1 displays significant cytotoxicity to various types of cells, including human lymphocytes, polymorphonuclear neutrophils (PMNs), endothelial cells and murine cells at high concentrations.[41] Sharma *et al.*[27] observed low cytotoxicity of HNP-1 towards the macrophage cell line at a concentration bactericidal to mycobacteria. It was suggested that this low cytotoxicity is probably due to the presence of FBS in the culture media.

A number of studies have reported that kahalalides F (KF) has rapid and potent *in vitro* cytotoxic activity against selected cell lines, including breast, prostate, non-small cell lung and colon carcinomas, neuroblastoma and osteosarcoma.[42] Shilabin and collaborators showed that KF exhibits higher cytotoxic activities against most of the human cell lines and in particular colon.[42] In another study, Hartiakun *et al.*[43] examined a new cyclodepsipeptide compound, cordycommunin, for cytotoxicity activity against cancer cell lines and Vero cell lines. From the data, cordycommunin displayed weak cytotoxicity against KB cells (IC_{50} = 45 μM); however, there was no activity against MCF-7, NIC-H187 and non-cancerous Vero cell lines at 50 mg/L. Jirakkakul *et al.*[12] observed that bassianolide had biological activities against KB, BC, NCI-H187 and Vero cells with IC_{50} values of 3.64, 2.49, 1.10 and 4.8 mg/L, respectively.

It is highly desirable to find antimycobacterial peptides with minimum or no human cell toxicity. In general, many AMPs are considered to be less toxic to eukaryotes, but the potential toxicity of AMPs for oral application has not been evaluated. In order to overcome such barriers, many solutions have been suggested. For instance, unusual amino acids (mainly D-form amino acids) or modification of the terminal regions (acetylation or amidation) may improve the stability of peptides to protect them from proteolytic degradation.[17]

Conclusions

The evolution of drug-resistant pathogens has triggered the need to develop novel therapeutic agents. Many studies have provided consistent evidence that antimicrobial host defence peptides display a broad spectrum of activity against bacteria, fungi, plants and viruses. As described in this literature review, natural peptides with their unique structural architectures are remarkable scaffolds for future drug discoveries. Studying the relationship between peptide structure and function as well as the molecular mechanism of action will lead to a more comprehensive understanding that may be used to design novel compounds with desired activities. Among the AMPs indicated in Table S1, cyclomarin A,[10] mycobactin S,[22] HNP-1,[27] lariatin A,[28] nocathiacine[44] and DHMP A[45] show the greatest antimycobacterial activity with MIC values ≤4 mg/L. It is noteworthy that the bacterium has been the most common source of antimycobacterial peptides.

The presented natural compounds have been evaluated for *in vitro* antimicrobial activity against non-resistant and drug-resistant strains of *M. tuberculosis*, but they are not yet widely used as therapeutic agents due to a number of limitations, including proteolytic degradation, low bioavailability, sensitivity to salt, pH or serum, high cost of production and potential toxicity. Hence, the clinical optimization of anti-TB agents needs to be progressed under *in vivo* conditions. For instance, hydroxylamine hydrocarbon and 1,10-phenanthroline showed *in vitro* antimycobacterial activity at 17.5 and 0.8 mg/L, respectively, but they were inactive under *in vivo* conditions due to their lack of ability to reach the intracellular compartment of macrophages within the lungs or other unknown mechanisms.[46] Further work is needed to overcome these drawbacks in order to design next-generation antibiotics with a high degree of efficacy in animal models and clinical outcome.

Transparency declarations

None to declare.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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