Molecular modeling of natural antimicrobial peptides to artificially design and synthesize new peptides with antibiotic activity.

Antimicrobial peptides are small peptides made of few (12-45) amino-acids developed and conserved during evolution by eukaryotes in response to their innate immune system to combat microbial infections. These peptides have been found to be potent, broad spectrum antibiotics and can be tentatively classified as amphipathic $\alpha$-helices, disulfide bond stabilized $\beta$-sheet structures, peptides with predominant amino acids or peptides with loop structures. Hundreds of peptide antibiotics have been reported during the last decade (Hancock, 1997; Robert et. al., 1999; Koczulla and Bals, 2003).

It has been shown that these peptides are less susceptible to bacterial resistance than traditional antibiotics and could form the basis for a new class of therapeutic agents. They have been demonstrated to kill Gram negative and Gram positive bacteria (including those strains that are resistant to conventional antibiotics), mycobacteria (including *Mycobacterium tuberculosis*), enveloped viruses and fungi. They have even been found to transform cancerous cells in many cases. Unlike the conventional antibiotics, a number of antimicrobial peptides have shown the ability to enhance immunity by functioning as immunomodulators (Zasloff, 2002). All these unique features and novelty of these peptides is interestingly exemplified by their small size with a patterned arrangement of specific amino acids i.e. their design.

Antimicrobial peptides have been reported to act directly, and non-specifically, on biological membranes except on those containing cholesterol as a component as in higher animals. Bacteria fail to develop resistance against these peptides seemingly due to the inability of their plasma membrane to resist their tear-off effect.

These peptides are understood to interact with the membranes in two stages. First, cationic amino acids are attracted by negative charges (e.g. phospholipid headgroups) on the surface. Second, hydrophobic and positively charged patches of the peptide interact with the aliphatic fatty acids and the anionic components respectively. This induces membrane destabilization, and, bacteria are thought to be killed by the leakage of cytoplasmic contents, loss of membrane potential, change in membrane
permeability, disorientation in lipid distribution followed by the entry of the peptide and blocking of anionic cell components. The whole sequence of events may also trigger the activity of autolytic enzymes.

Most of the peptides without disulfide bridges have random structures in water, and it is only when they bind to a membrane or other hydrophobic environment, or self-aggregate, that these peptides form a structure (Falla et al., 1996), as for example, the antibiotic peptide cecropin folds into amphipathic alpha-helices when comes in contact with membranes. It is known that the dual cationic and hydrophobic nature of the peptides is important for the initial interaction between the peptide and bacterial membrane. Cationicity promotes interaction with bacterial outer and cytoplasmic membranes (Wu and Hancock, 1999). Hydrophobicity of the peptide is also significant as it causes increased binding of the peptide to the membrane due to increased hydrophobic interactions between lipid acyl chains and the hydrophobic helix core (Wieprecht et al., 1997).

Though, few investigations have been taken up by workers at various places globally in the area of antimicrobial peptides especially those with broad spectrum antibiotic effects with an aim to obtain new and more potent structures, it is imperative to approach the problem from various angles. One approach would involve deciphering the structural design pattern of the known peptides through chemical modeling with bioinformatics tools and software’s based on pattern reading algorithms, suggest some new possible structures with potency on higher side and applicability, their design and parameter test, and, synthesis. Exercise in synthesis may take the route of gene cloning and expression in a laboratory bacterium. The present project aims to take up the project with the above approach to obtain few antibiotic peptides of significance.

The project would involve following steps in study and investigation -

1. Attempt to develop algorithm for pattern analysis of the known antimicrobial peptide structures on the basis of significant parameters to suggest few new structures followed by writing a suitable software (in C++ or Perl),

2. Analysis and modeling of the known major antimicrobial peptides,

3. Analysis of 3D structure of peptides with standard visualization/modeling software’s,
4. Designing suggested structures,
5. Parameter test and similarity blast to other known structures at AMP Database,
6. Study of interaction of the suggested antibiotic peptides with the target bacterial membrane components through molecular docking and other approaches, and
7. Gene design, cloning and expression in E. coli.

The above mentioned work would hopefully result into some new peptides with antibiotic activities and obtain new information and protocols that may form the basis of future works.

References


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