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Antimicrobial Peptide Lexicon: A Comprehensive List of Arginine and Tryptophan Sequences

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Commentary Article

The activity of cationic Antimicrobial Peptides (AMPs) has been restricted to well-studied natural sequences or small sets of synthetic peptides created from scratch. We've investigated the underlying main structural elements that lead to the formation of activity in AMPs in great detail. We investigate a complete collection of all potential peptides, up to 7 residues long, that are made up of positively charged Arginine (R) and/or hydrophobic Tryptophan (W), the two most generally related properties with activity. The shortest active peptides were discovered to be 4 or 5 residues long, and the overall landscapes of activity against gram-positive and gram-negative bacteria were found to be similar. We discovered a single activity peak for all three organisms, corresponding to sequences with roughly 40% R; the presence of contiguous W duplets and triplets also imparted increased activity. The mechanisms behind these activities include lipid binding, particularly to negatively charged membranes, as well as peptide aggregation, a previously unknown method of action for such peptides. When considering activity per peptide residue, the maximal specific antibacterial activity appears to occur in peptides of roughly 10 residues, implying 'diminishing returns' for producing larger peptides. Antimicrobial peptides (AMPs) are short amino acid sequences with various and wide modes of action that kill or limit the growth of bacteria. They are produced broadly by many different organisms and occur naturally as a component of innate immunity, but they can also be synthesised de novo from natural or non-natural amino acids. Two characteristics often related with AMP activity are the presence of a high number of cationic and hydrophobic residues. Cationic residues (such as Arginine, R, Lysine, K, or Histidine, H) are thought to mediate interactions with negatively charged bacterial lipids, whereas hydrophobic residues (such as Tryptophan, W, Phenylalanine, F, or Leucine, L) are thought to mediate interactions with positively charged bacterial lipids. Although active synthetic peptides with fewer than ten residues have been found, naturally occurring AMPs are typically >15 amino acids long. Although shorter peptides have lower antibacterial efficacies than longer AMPs, they have the advantage of being less expensive if utilised pharmaceutically. W and R are the most hydrophobic and cationic residues found in shorter AMPs. Antimicrobial action has been linked to the aromatic and hydrophobic residue W in particular. The most prevalent route of action for AMPs, especially short cationic peptides, is to disrupt the bacterial cytoplasmic membrane. The barrel stave and toroidal pore models, in which peptide monomers insert into the membrane and form structured pores, resulting in increased lysis, or the carpet model, in which peptides accumulate on the bacterial surface, causing stress on the membrane, which tears, causing lipid removal, are two proposed mechanisms. Some AMPs may also require peptide aggregation prior to membrane contact for activation, albeit this is currently unknown. The self-aggregating amyloid (A) peptide associated with senile plaques in Alzheimer's Disease (AD) has previously been shown to be increased in response to infection, and others have suggested that it may serve as a typical AMP. Although most hydrophobic AMPs in aqueous solution are anticipated to undergo some peptide aggregation, the significance of aggregation in giving or suppressing antimicrobial activity has remained largely unstudied, the effect of replacing all eight hydrophobic L residues in apoE-derived cationic AMPs with any

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other single natural amino acid in a systematic and thorough manner. The W change produced the most efficient and broadly active peptide, indicating that the W version caused most membrane disruption. Other AMPs have been found to associate W and R residues via delocalized -electrons, with the side-chains of both residues lining up, permitting hydrogen bonding between the R residues and the solvent. By hiding R's charge within W's benzene ring, R (but not the other strongly cationic natural amino acid K) can insert into a lipid membrane. Because W and R are the most hydrophobic and cationic residues, they are the two natural residues most closely connected with AMP activity. Although there is indirect evidence that W and R is important in conferring antimicrobial action, their involvement has not been directly addressed to far. The antibacterial activity of natural W or R amino acids, as well as the development of efficacy as these residues are systematically combined in peptides of increasing size and in most or all conceivable permutations, have never been investigated before. Furthermore, it is unknown which method of action will predominate in this new peptide family.