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Machine learning antimicrobial peptide sequences: Some surprising variations on the theme of amphiphilic assembly

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Abstract

Antimicrobial peptides (AMPs) collectively constitute a key component of the host innate immune system. They span a diverse space of sequences and can be α-helical, β-sheet, or unfolded in structure. Despite a wealth of knowledge about them from decades of experiments, it remains difficult to articulate general principles governing such peptides. How are they different from other molecules that are also cationic and amphiphilic? What other functions, in immunity and otherwise, are enabled by these simple sequences? In this short review, we present some recent work that engages these questions using methods not usually applied to AMP studies, such as machine learning. We find that not only do AMP-like sequences confer membrane remodeling activity to an unexpectedly broad range of protein classes, their cationic and amphiphilic signature also allows them to act as meta-antigens and self-assemble with immune ligands into nanocrystalline complexes for multivalent presentation to Toll-like receptors.

Keywords

Antimicrobial peptides; Membrane curvature; Machine learning; Toll-like receptors; Innate immunity

Introduction

Antimicrobial peptides (AMPs, or host defense peptides or innate immune peptides) have been systematically investigated for four decades. AMPs are generally characterized by their short amino acid sequences (<50 amino acids), net cationic charge (2 to 9), and amphiphilicity [1–6]. These seemingly simple molecules also span an enormous diversity of sequences and secondary structures and can be α-helical [7], β-sheet [8], or extended linear peptides [9,10]. Well over 2000 natural and artificial AMPs have been characterized and information about them are organized into well-maintained databases [11–13]. However, given this knowledge, how do we think about them as a class of molecules? They are known

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to be cationic amphiphilic molecules but how are they different from other amphiphilic cationic molecules? They are known to be important components of innate host defense [1–6] since they preferentially permeate bacterial membranes over eukaryotic membranes. However, are there other functions in innate immunity besides membrane activity that are enabled by their cationic charge and amphiphilicity? What do the answers of these questions imply about undiscovered functions of AMPs and how we ultimately define AMPs? We and others have done some recent work that suggests such questions may be answerable and offer a biased perspective on some emerging directions of inquiry by incorporating machine learning methods. By way of passing, we provide an early critical assessment of machine learning in the context of AMPs by giving examples of what machine learning discovered unexpectedly and what it failed to anticipate, at least with the currently available data and data structures.

Amphiphilicity and membrane activity

It is thought that AMPs generally function by preferentially permeating microbial membranes, which leads to cell death due to the loss of electrochemical gradients, vulnerability to osmotic stress, loss of cellular contents, and disruption of metabolic processes [2,6]. This type of antimicrobial activity has be ascribed to interactions between amphiphilic AMPs and membranes [14]. Such interactions have been studied using experimental techniques such as X-ray scattering, nuclear magnetic resonance (NMR), fluorescence microscopy, and electron microscopy [6], and historically different models of membrane permeation have been proposed [15–18]. One of the canonical features of AMPs is their selectivity for bacterial membranes over eukaryotic membranes, which is a result of their differential activity on membranes of different compositions [1,2,6]. Early work has identified one necessary condition: bacteria membranes contain large amounts of exposed anionic lipids (e.g. phosphatidylglycerol) on the outer leaflet, while eukaryotic membranes contain mostly zwitterionic lipids (e.g. phosphatidylcholine and sphingomyelin) [19–21]. However, bacterial membranes also contain large amounts of negative intrinsic curvature lipids, such as phosphatidylethanolamine, which makes such membranes vulnerable to permeation [22–27]. The majority of early experimental studies agree that membrane permeation underlies the primary mechanism of action of AMPs, and that such action is a natural consequence of AMP amphiphilicity.

Machine learning of AMP sequences

In this age of “big data”, it is not surprising that molecular data science has been applied to AMPs. Machine learning studies of AMPs are typically based on the development of quantitative structure-active relationship (QSAR) models, which seek to use physicochemical descriptors to predict levels of biological activity. Such studies have employed a broad range of machine-learning approaches including artificial neural networks (ANN), support vector machines (SVM), quantitative matrices (QM), hidden Markov models (HMM), random forests (RF), knearest neighbors (k-NN), and self-organized maps (SOM) [28–38]. The preponderance of this work has employed data-driven learning with the primary goal of the discovery and design AMPs with enhanced microbial potency. In 2016, we employed machine learning with an additional goal: We built an SVM classifier trained

on ahelical AMP sequences with the dual intents of achieving high predictive accuracy and teaching us something about what physicochemical and sequence-level properties make a peptide antimicrobial [39–41]. To achieve this aim, we combined a linear SVM as a relatively "white box" machine-learning technique together with principled feature selection to establish a 12-descriptor QSAR model that identified the key properties governing AMP activity and exposed the learned classification procedure in a human-comprehensible manner. Despite the simplicity of our approach, we nevertheless achieved high classification accuracy and thus established an accurate and interpretable model of α-helical AMP activity. The trained model also allowed us to probe how increasing degrees of "antimicrobial-ness" in a peptide e as defined by the machine learning classifier e ultimately correlate to that peptide's increasing ability to mediate specific physical processes, and how those processes might in turn correlate to antimicrobial activity.

We constructed and trained an SVM classifier on a dataset of 286 α-helical antimicrobial peptides and 286 "decoy" α-helical non-antimicrobial peptides. We began with a panel of 1588 physicochemical descriptors [42–46], which included simple peptide metrics of length, charge, hydrophobicity, as well as more complicated metrics based on autocorrelation and sequence order. From these descriptors, we identified the 12 most predictive descriptors using the L1 feature selection approach of Bi et al. [47]. The linear SVM constructed in this way possessed a 91.9% classification accuracy on an 86-peptide hold-out test set, demonstrating as good or better performance than more complex models employing the entire descriptor ensemble and/or nonlinear SVMs. Each peptide sequence occupies a point in the 12-dimensional space spanned by these descriptors, and the linear SVM classifier draws the optimal 11-dimensional hyperplane dividing the antimicrobial sequences from the non-antimicrobial. From an arbitrary peptide sequence as input, the SVM outputs a single parameter s, the distance between that peptide sequence to separating hyperplane. Intuitively, a larger positive value of σ denotes higher confidence of antimicrobial activity, and a large negative value denotes a higher confidence of lack of antimicrobial activity.

Although the "antimicrobial-ness" of the peptide sequence is described by the metric s, calibrating experiments exposed the initially puzzling finding that σ did not correlate with traditional metrics of antimicrobial activity such as minimum inhibitory concentrations (MIC) [39]. We reasoned that this lack of correlation was due to the multiple modalities by which AMPs in the training data mediated their antimicrobial activity, including disruption of DNA synthesis, inhibition of protein production, and modulation of immune and defense responses. In other words, the trained classifier learned not to distinguish these diverse modes of antimicrobial-ness directly, but rather identified a unifying characteristic underpinning these various mechanisms. This led us to hypothesize that membrane activity may have been learned as the discriminant between AMPs and decoys as a prerequisite to antimicrobial activity by numerous pathways. We tested this hypothesis using synthesized peptides with diverse σ scores assigned by the classifier, and characterized their activity using antimicrobial assays and small-angle X-ray scattering (SAXS) with artificial membranes. The SVM σ score was found to correlate strongly with a peptide's ability to generate negative Gaussian membrane curvature (NGC) [39], the type of curvature topologically required for membrane restructuring processes, such as pore formation, blebbing, budding, vesicularization. Indeed, AMPs were found to induce NGC preferentially

in membranes with bacterial lipid compositions [48,49]. The ability to generate NGC has also been observed for both natural and synthetic AMPs [50,51], cytokines [52], cell-penetrating peptides [53], and viral fusion proteins [54,55]. Taken together, these results suggest that the generation of NGC is not only a feature of AMPs, but a far more general and common root mechanism for membrane restructuring processes in general.

Using the SVM classifier as a screening tool, we then proceeded to explore peptide sequence space with the intention of finding new AMP-like sequences in two specific regions of unknown sequence space: peptides close in homology to known AMP sequences, and those far in homology e and therefore far in evolutionary distance e to known AMPs. Using a Monte Carlo approach, we screened peptides with lengths of 20e25 amino acids, the most common lengths of AMPs, and focused our search on AMP-like candidates with large positive values of s. To identify optimal candidates, we applied multi-objective optimization to identify sequences lying on a “Pareto frontier” that compromises between s, homology criteria, and peptide helicity. This analysis led us to discover interesting surprises in peptides very dissimilar to known AMPs. One might intuitively expect that peptide sequences far in homology from known AMPs, membrane permeating peptides par excellence, should have lower or negative values of s. Surprisingly, not just new peptides but a number of peptide families and domains within proteins were predicted by our classifier to be membrane active at the same level as AMPs [39]. That these peptides with AMP-like membrane activity have little sequence homology with known AMPs highlights an interesting and important difference between our methods and traditional bioinformatics methods based on sequence comparison such as BLAST. The sequences with AMP-like activity include neuropeptides, amyloids, and viral fusion proteins. In other words, the SVM classifier enabled us to efficiently identify and discover sequences in both peptides and diverse proteins families that generate NGC to remodel membranes for permeation or transduction. We describe a few of these examples below.

Neuropeptides

Neuropeptides are used by neurons to communicate [56] and mediate functions ranging from endocrine signaling and homeostatic regulation to immune signaling, pain modulation, and circadian rhythm maintenance. At present, over 100 neuropeptides are known to be released from neurons in mammals and are not only present in the central nervous system (CNS) [57], but also are found in the enteric nervous system, peripheral nervous system, and within immune organs. Neuropeptides are known to primarily exert their biological function by binding to their cognate receptor (usually a G-coupled protein receptor), triggering a signal transduction pathway that leads to a functional change in the target cell [56]. Neuropeptides are typically thought of as neurotransmitters or endocrine/ paracrine hormones, but recent work has illuminated their potential role as integral components of the innate immune system. In fact, neuropeptides are central to modulation of neuroinflammation [58] and triggering of the innate [59,60] and adaptive [61] immune responses, and facilitating communication between the immune system and nervous system [62].

A significant number of positive hits predicted to have membrane remodeling activity were found to be members of the neuropeptide family. These included vasoactive intestinal peptide (VIP), neuropeptide Y (NPY), α-melanocyte stimulating hormone (α-MSH), and pituitary adenylate cyclase activating peptide (PACAP). Another peptide, substance P, not included in the initial search, was also found to have predicted antimicrobial activity. Interestingly, previous work has preliminarily shown that substance P, VIP, and NPY possess moderate to substantial antimicrobial activity against a range of organisms [63–65]. Moreover, consistent with our predictions, the neuropeptide PACAP was very recently found to possess potent *in vitro* antimicrobial activity [66]. A small number of neuropeptides possess similar amino acid content and secondary structure to AMPs cathelicidins and defensins [67], but our results suggest that antimicrobial activity and membrane activity may be far more common than previously thought, even in sequences without obvious sequence homology. These findings lead to many questions that may attract and reward attention: Why do neuropeptides possess direct antimicrobial activity? Are neuropeptides induced at sites of infection? Is this observed activity relevant to how the CNS defends itself? Additional studies are needed to show biological relevance.

Viral membrane fusion and fission machinery

Enveloped viruses, such as human immunodeficiency virus (HIV) and influenza, enter host cells to initiate infection via virusecell fusion. This process involves viral membrane fusion proteins, which mediate the fusion between the viral lipid envelope and the host cell plasma membrane. These proteins typically feature an N-terminal fusion peptide (FP) and a C-terminal transmembrane domain (TMD) [68]. While previous studies have demonstrated that the FPs of HIV, influenza, and paramyxovirus adopt a partially inserted topology in the membrane to induce nonlamellar structures [69–73] the structure and role of the TMD in viral membrane fusion are less not well understood. In fact, the TMD has been traditionally regarded as a passive anchor to the virus envelope. Recent work using solid-state NMR and SAXS on the parainfluenza virus 5 (PIV5) fusion protein has found that the TMD changes its conformation in response to the membrane lipid composition to play an active role in viralecell fusion by mediating the necessary membrane topological changes [55]. More specifically, in membranes that have high concentrations of phosphatidylethanolamine, the TMD adopts a β-strand-rich conformation and generates NGC, the type of curvature required for the formation of hemifusion intermediates and fusion pores. Aside from the key role of proteins, this finding additionally underscores the influence of constituent lipids of membranes in viralecell fusion. Lipid-dependent conformational changes, which have been found to occur for both the FP [73,74] and TMD [55], suggest that the intact fusion protein can adapt to the different lipid environments of the virus envelope and host cell membrane [75].

To spread infection, many enveloped viruses complete their replication cycle by budding progeny virions from infected host cells. As viruses engage membrane fusion to enter a cell, viruses exiting a cell undergo the reciprocal process in which viral particles assemble, bud, and pinch off from the host membrane. This budding process involves membrane deformation and fission, which require membrane curvature generation. A large number of enveloped viruses recruit the host endosomal sorting complex required for transport

(ESCRT) machinery to assist in budding and virion release [76–78], however, influenza has been implicated to utilize an ESCRTindependent mechanism [77,79]. M2 from the influenza A virus is a multifunctional protein that assembles into a homotetramer to function as a proton channel in the membrane [80,81]. The protein has also been recognized for other roles during the viral life cycle, including mediating budding and virion release from cells [82–86]. Interestingly, not only is M2 predominantly localized at the necks of budding virions, but experiments using electron microscopy and SAXS have found the protein capable of generating NGC in model membranes and that this membrane activity is primarily attributed to its cytoplasmic C-terminal α-helix [54]. Indeed, this region of the protein received a high σ score from the SVM classifier [87].

Mitochondrial remodeling machinery

The morphology and intracellular distribution of mitochondria are crucial in maintaining normal cell function and are governed by a balance between the antagonistic processes of mitochondrial fission and fusion [88–91]. Excessive fusion leads to elongated mitochondria that form highly interconnective networks, while uninhibited fission leads to increased mitochondrial fragmentation [89,92–94]. The proteins that control mitochondrial fission and fusion play important roles in health and disease, as the dysregulation of these dynamic processes is associated with a variety of developmental disorders and neurodegenerative diseases [94–96]. The major essential protein involved in mitochondrial fission, Dnm1 in yeast [88,91,93,97] and Drp1 in humans [92,98], is a highly conserved cytosolic dynamin-related GTPase. One prominent model describes Dnm1/Drp1 as a molecular motor that selfassembles into ring-like oligomeric structures that encircle the outer mitochondrial membrane at sites of fission. GTP hydrolysis then leads to conformational changes in Dnm1/Drp1 that cause constriction and pinching of the membrane to drive membrane scission [99–103]. Our recent work using machine learning predicted a conserved α-helical domain in Dnm1 and Drp1 (and protein relatives with fission activity) to be capable of remodeling membranes by generating NGC. SAXS measurements revealed that the full Dnm1 protein restructures model mitochondrial membranes into phases rich in NGC and can induce a membrane fission neck diameter of 12.6 nm, which is smaller than the observed diameters achieved from mechanical constriction. These findings together suggest that Dnm1-induced membrane curvature and molecular motor driven mechanochemical forces function synergistically to efficiently drive mitochondrial fission. In fact, when members of the dynamin superfamily are individually examined using the SVM classifier, it is found that their machine learning σ scores decreased as phylogenetic distances from classical dynamin Dyn1 increased, which suggests that the dynamin superfamily GTPases likely evolved the ability to generate membrane curvature to optimize their membrane remodeling roles [104].

New architectures of cell penetrating peptides

Cell-penetrating peptides (CPPs) are recognized for their ability to efficiently translocate across cell membranes, and therefore, often utilized for mediating the uptake of conjugated cargos [105–107]. Similar to AMPs, CPPs are generally short, cationic peptides that can also be amphiphilic. In fact, there are marked similarities in the amino acid content of AMPs and CPPs in the form of a correlation between the lysine/arginine ratio and the hydrophobicity,

which has been rationalized in terms of patterns of H-bonding required to induce NGC in target membranes [49,108]. Naturally derived CPPs, which typically exist as linear amino acid sequences, have since inspired numerous research groups to explore synthetic mimetics with often more complex architectures but still feature the key characteristics of cationic charge, hydrophobicity, and amphiphilicity. The diversity of these synthetic designs has ranged from circular peptides to side-chain-rich comb, brush, and dendrimer structures [109–113]. More recently, unique architectures composed of long flexible side chains surrounding a core have introduced the new attributes of radial amphiphilicity and metaphilic surfaces [51,114], which can lead to greater membrane activity than that of natural AMPs and CPPs.

Beyond membrane activity: AMPs as selfassembling amphiphilic meta-antigens that organize innate immune ligands for presentation

Here we describe an aspect of AMP activity that has not been predicted by machine learning, that of immune modulation. There have been many examples of AMPinduced immune in the last 15 years (especially with human cathelicidin LL37 and defensins [115]), but we focus on cases where the cationic charge and amphiphilicity of AMPs, the very characteristics that drive membrane activity according to both machine learning and traditional forms of scientific inquiry, may form the basis of unanticipated immune activity. Cationic AMPs can structurally organize and scaffold anionic immune ligands into spatially periodic complexes, and that the crystallinity of such complexes can determine the degree of immune amplification via multivalent presentation [116–118].

AMP–dsDNA complexes

Toll-like receptor 9 (TLR9) is an innate immune sensor for viral and bacterial CpG DNA [119]. In 2007, Lande et al. demonstrated that human cathelicidin LL37 could form complexes with human genomic dsDNA and potently activate plasmacytoid dendritic cells (pDCs) by binding to TLR9 [120,121]. In fact, overexpression of LL37 in autoimmune diseases like lupus [122] and psoriasis [123] has been linked to TLR9-mediated inflammation in both pDCs and keratinocytes [124]. Moreover, the ability to enable immune recognition of DNA and induce TLR9 activation in immune cells is not limited to LL37. Subsequent studies have shown that the AMPs human β-defensin 2 (hbD2) and human β-defensin 3 (hbD3) also co-assemble with dsDNA to activate pDCs [125]. It is clear that certain natural AMPs can induce TLR9 signaling through dsDNA binding, but many other molecules that also bind to dsDNA cannot. To delineate the necessary and sufficient criteria for immune activation by dsDNA complexes, high-resolution synchrotron SAXS was used to correlate the structures of complexes formed between dsDNA and AMPs and measurements of pDC IFN-a production induced by these complexes [116]. Cationic AMP molecules such as LL37 can form columnar nanocrystalline complexes with dsDNA, and present the DNA at an optimum range of inter-DNA spacing (dw3.5 nm) that can promote multivalent binding with clusters of TLR9 [126,127].

AMP–dsRNA complexes

The textbook role of Toll-like receptor 3 (TLR3) is to sense viral dsRNAs in infections [128]. Recently, it was shown that TLR3, which is expressed at high levels in human keratinocytes [129], also plays a critical role in sensing skin injury by binding to non-coding self-dsRNA [130,131]. Similarly, keratinocytes also produce large amounts of AMPs which are important for microbial defense in the skin. Interestingly, LL37 and other cationic peptides have been shown to enhance or inhibit TLR3 signaling by viral dsRNAs [132–134]. In addition, in autoimmune diseases like psoriasis, IL-6 production by keratinocytes, which is downstream from TLR3, play a role in aberrant cytokine production in response to LL37 [131,135,136]. We showed that the structural ordering of dsRNAs by AMPs can influence TLR3 activation, similar to how scaffolding of dsDNA by AMPs modulates TLR9 activation. Again, AMPe dsRNA complexes with inter-dsRNA spacings commensurate with the steric size of TLR3 lead to a w5e10-fold amplification in IL-6 production from keratinocytes [117,137], but complexes with interdsRNA spacings much smaller or larger than the steric size of TLR3 lead to low levels of activation.

In both LL37edsDNA complexes and LL37edsRNA complexes, the inter-nucleic acid spacing is significantly larger than the diameter of the nucleic acid and too large to be spanned by the diameter of a single α-helical LL37 mol. There has been a recent surge of interest in understanding the assembly of amphiphilic or chemically “patchy”, anisotropic objects. These systems can assemble into structures considerably more complex than micelles [138]. Indeed, systems such as colloids with directional bonding [139] and programmed assembly of “Janus” particles into a Kagome lattice [140] have been realized. Moreover, shape and chemical heterogeneity can exert different demands on the assembly process and lead to counterintuitive results [141]. It is interesting to see how these types of organizing principles influence immune modulation. Although AMPs are known to aggregate under special conditions [142], it is not clear how curved cationic amphiphiles such as AMPs electrostatically assemble with anionic DNA, much less how the resultant self-assembled structures connect to their immunomodulatory behavior.

Outlook

In this review, we discussed two different aspects of AMP activity mediated by their amphiphilicity and cationic charge: their well-known membrane remodeling activity, and their ability to assemble with and present immune ligands: AMPs can kill microbes through direct action, including membrane permeation, disruption of electrochemical gradients, and inhibition of metabolic processes. However, AMPs can also orchestrate host immune responses by communicating with the innate and adaptive immune systems, leading to downstream responses such as chemotaxis, differentiation/maturation, and cytokine production. We have shown that the application of machine learning methods can lead to a powerful forms of sequence analysis beyond algorithms for sequence comparison such as BLAST. (The SVM classifier can identify AMP-like behavior in sequences that have little homology with natural AMP sequences [87].) On the other hand, we have also highlighted some limitations of machine learning: Whereas membrane activity can be successfully “predicted” by machine learning in arbitrary sequences, the immunological activity is

completely unanticipated, even though both types of activity are related to amphiphilicity and cationic charge. Finally, the picture of AMPs presented above represents a generalization of the central paradigm in immunology: AMPs are not just effector molecules but can also act as meta-antigens that activate innate immunity by organizing immune ligands. Moreover, innate immune receptors such as Toll-like receptors (TLRs) recognize not just pathogenassociated molecular patterns of single ligand molecules, but also recognize nanocrystalline arrangements of AMPs and ligands.

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