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Tailored Design of Antimicrobial Peptides through Artificial Intelligence

The escalating threat of antibiotic resistance underscores the urgent need for innovative therapeutics, with antimicrobial peptides (AMPs) emerging as viable alternatives due to their diverse mechanisms of action (Fjell et al., 2011). This study introduces a systematic strategy to design two classes of AMPs with distinct bactericidal mechanisms: proline-rich peptides, which disrupt intracellular protein synthesis, and arginine-rich peptides, which destabilize bacterial membranes. Machine learning (ML) models trained on sequence-function data revealed critical physicochemical determinants for each class. For proline-rich AMPs, charge distribution and hydrophobicity patterns were identified as pivotal features, aligning with their role in intracellular targeting (Krizsan et al., 2015). In contrast, arginine-rich AMPs were governed by high charge density and membrane interaction motifs, consistent with their membrane-disruptive activity (Melo et al., 2009). Leveraging these insights, we utilized the generative AI model ESM-2 (Lin et al., 2023), fine-tuned on ML-classified sequences, to design 50 novel AMPs. Generated sequences were optimized for class-specific properties: proline-rich peptides prioritized structural motifs linked to protein synthesis inhibition, while arginine-rich variants emphasized cationic and amphipathic traits for membrane targeting. This integrative approach—combining ML-driven feature analysis with AI-powered sequence generation—advances the rational design of mechanism-specific AMPs. By elucidating sequence-function relationships and enabling tailored peptide engineering, our framework provides a scalable blueprint for developing next-generation antimicrobials (Porto et al., 2018).

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