Optimization of pH-Responsive Cationic AMP-Inspired Polymers

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Antimicrobial peptides (AMPs) are promising alternatives to conventional antibiotics due to their membrane-disruptive activity, but clinical translation is hindered by host cytotoxicity, poor selectivity, and instability. This project investigated whether minimal-motif, pH-responsive AMP-inspired polymers could be engineered to retain selective bacterial membrane binding while reducing large aggregation typical in current AMPs and mimics. AMP sequences active against Gram-positive and Gram-negative bacteria were curated and analyzed using a pattern-coding approach, classifying residues as cationic, hydrophobic, or neutral. Overlapping 12-residue motifs were extracted and clustered, revealing three dominant interaction architectures: helical amphipathic, aromatic-anchored, and cationic-dominant motifs. These were translated into four synthetic polymer designs (P1–P4) by mapping residue classes to pH-responsive tertiary amines, aliphatic hydrophobes, and aromatic anchoring groups. Short oligomer surrogates were modeled in neutral and protonated states and evaluated via molecular docking and dynamics against bacterial membrane domains, in both normal physiological pH and acidic infection pH. Docking showed that higher cationic density increased binding strength, while amphipathic and aromatic-anchored designs achieved comparable affinity with lower charge. The cationic-dominant polymer (P4) reached a binding affinity of -8.455 kcal/mol, comparable to PHMB, a clinically used antimicrobial polymer during infection ($p<0.05$). The findings indicate that AMP motif architecture can be systematically encoded into smaller, pH-responsive polymer designs, offering a scalable route to selective antimicrobial materials with reduced cytotoxicity potential.

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