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ARTICLE

Antimicrobial PEGtides: A Modular Poly(ethylene glycol)-Based Peptidomimetic Approach to Combat Bacteria

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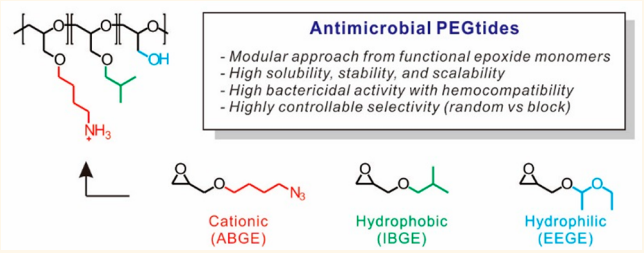
ABSTRACT: **Despite their high potency, the widespread implementation of natural antimicrobial peptides is still challenging due to their low scalability and high hemolytic activities. Herein, we address these issues by employing a modular approach to mimic the key amino acid residues present in antimicrobial peptides, such as lysine, leucine, and serine, but on the highly biocompatible poly(ethylene glycol) (PEG) backbone. A series of these PEG-based peptides (PEGtides) were developed using functional epoxide monomers, corresponding to each key amino acid, with several possessing highly potent bactericidal activities and controlled selectivities, with respect to their hemolytic behavior. The critical role of the composition and the structure of the PEGtides in their selectivities was further supported by coarse-grained molecular dynamic simulations. This modular approach is anticipated to provide the design principles necessary for the future development of antimicrobial polymers.**



KEYWORDS: *polymeric antimicrobials, polyethers, functional epoxide monomer, peptidomimetics, molecular dynamic simulation*

INTRODUCTION

The increasing threat of multi-drug-resistant bacteria is a public health concern worldwide.[1] Thus, there is a long-standing interest in the development of antibiotics. Antimicrobial peptides (AMPs), a natural part of the autoimmune system of most organisms, have been recognized as a promising solution to address the emergence of this global challenge.[2] AMPs are amphiphilic oligopeptides generally composed of 30−50 amino acids,[2−4] majorly cationic amino acids, which promote their interaction with the negatively charged bacterial membrane.[5] Subsequently, the hydrophobic amino acids present in the AMPs allow them to slide into the phospholipid bilayer and destabilize the membrane.[2,5] In addition, the rigid polypeptide backbone of the AMP provides a regular arrangement of functional groups, increasing its bactericidal effect. Despite their potent antimicrobial activities, widespread use of natural AMPs is still challenging due to low scalability, which contributes to their high cost of production,[2,6] their inactivation by proteases,[7,8] and their high hemolytic activities.[9]

To address these issues, various synthetic antimicrobial polymers possessing diverse functional moieties have been suggested,[10−22] including polymers constructed with different backbones, such as polyoxazoline, polyacrylate, poly(2-hydroxyethyl methacrylate), and polyacrylamide.[14,23−26] However, polymers with an all-carbon backbone are structurally rigid but suffer from poor aqueous solubilities. Alternatively, an antimicrobial polymer platform that has not been explored in the literature is PEG, which can offer several benefits, including flexibility, solubility, high biocompatibility, and nonimmunogenicity.[27,28]

Therefore, we suggest here a peptidomimetic approach that combines the advantages of a PEG backbone with the amino acid residues commonly found in natural AMPs, *i.e.*, lysine, leucine, and serine, leading to PEG-based peptides (PEGtides). It is of note that the term "PEGtide" is more relevant to functionalized linear polyglycerols; however, to highlight the structural features of the polyether backbone developed in this study, we have opted to use this term.[29] Specifically, we

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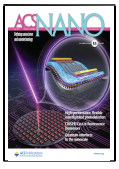

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