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Alpha-beta chimeric polypeptide molecular brushes display potent activity against superbugs-methicillin resistant *Staphylococcus aureus*

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Staphylococcus aureus (*S. aureus*) are frequently encountered for both nosocomial infections and community acquired infections, with special concerns on the quick emergence of methicillin resistant *S. aureus* (MRSA) [1,2]. Antibiotics are used extensively to treat these infections [2]. However, antimicrobial resistance has been a tremendous challenge against current antibiotic and calls for urgent actions to explore novel antimicrobial agents that are active against MRSA and are less susceptible to antimicrobial resistance than do conventional antibiotics [3–13]. Encouraged by the low propensity for microbes to develop antimicrobial resistance, host defense peptides (HDPs) and their synthetic mimics were actively studied [3,4,14–34]. Although peptidyl mimics of HDP have variable structures, many of them involved multiple copies of α-L-lysine to introduce into the molecules positive charges that were critical for the antimicrobial activity [35,36].

Polymer brushes have been explored not only for their interesting morphology [37–49], but also for their unique functions compared to linear polymers [50–64]. In this study, we designed alpha-beta chimeric polypeptide molecular brush (α/β CPMB) with β-polypeptide or poly-β-amino acid (PβAA) as the backbone and poly-α-L-lysine (PαLL) grafting from the backbone for antimicrobial studies. We chose β-polypeptide as the backbone for the antimicrobial molecular brush because β-polypeptides are biocompatible and can be easily prepared *via* anionic ring opening polymerization to provide diverse structures and functions [22–25,65–67]. In addition, the β-polypeptide backbone can easily introduce amine groups as desired activation sites for graft from polymerization of α-L-Lys-NCA (α-L-lysine *N*-carboxyanhydride) to incorporate multiple poly-α-L-lysine sidechains with adjustable density [68]. We hypothesized that above α/β CPMB have highly packed poly-α-L-lysine sidechains to exert multivalent interactions with bacteria and achieve strong antimicrobial activity, which was supported by our recent study on end tethered β-polypeptides [69]. This design also implies that the α/β CPMBs may not be biodegradable very easily due to the steric hindrance of sidechain polylysine, a result we pursue to prolong the antimicrobial activity of these polymer brushes. To the best of our knowledge, this is the first demonstration of coupling two ring-opening polymerization (ROP) systems, the β-lactam ROP and the NCA ROP, in generating alpha-beta chimeric polypeptide molecular brushes and evaluating on their antimicrobial activities.

The backbone of the α/β CPMB, a β-polypeptide or poly-β-amino acid (PβAA), was synthesized from a base catalyzed anionic ROP of 1:1 mixture of two β-lactams by following a previously reported method, with one β-lactam having a hydrophobic sidechain and the other β-lactam having an amine-containing sidechain [25,66]. The pendent amine groups of the β-polypeptide backbone then serve as activation sites for the ROP of α-L-Lys-NCA to provide the α/β CPMB as described in Fig. 1. The β-polypeptide backbone was synthesized with narrow polydispersity index (PDI) of 1.20 as summarized in Table 1. The average degree of polymerization (DP) of this β-polypeptide backbone was found to be 18 using gel permeation chromatography (GPC) characterization. In

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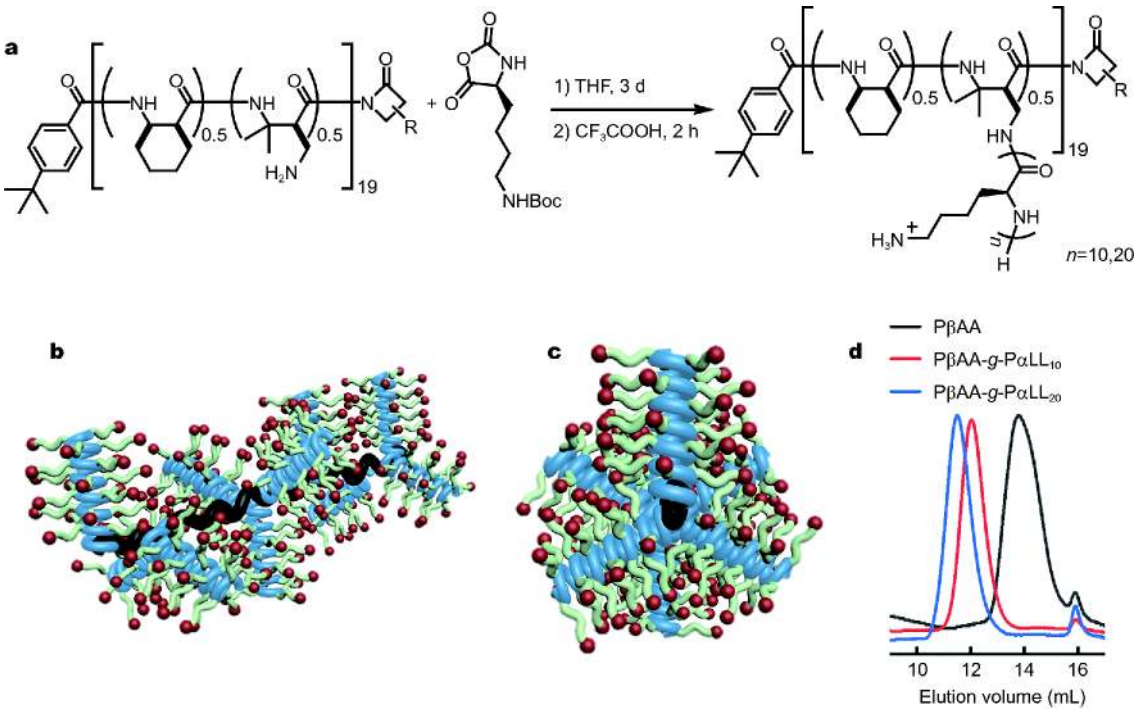

Figure 1 Synthesis of α/β CPMBs. (a) Synthetic route of α/β CPMBs; (b) sideview of α/β CPMBs carton; (c) 3D view of the α/β CPMBs carton; (d) GPC traces of PβAA backbone and α/β CPMB at the amine protected stage.

Table 1 NMR and GPC characterizations of α/β CPMBs

Polymer	NMR	GPC characterization[a]		
	DP	M_n (kDa)	PDI	DP
PβAA	19	3.3	1.20	18
PβAA-*g*-PαLL$_{10}$	17	33.4	1.28	13
PβAA-*g*-PαLL$_{20}$	25	48.1	1.24	20
PαLL$_{20}$	22	8.9	1.24	35

a) GPC characterization on polypeptide at the amine protected stage using DMF as the mobile phase at a flow rate of 1 mL min^{-1}.

order to further attach poly-α-L-lysine onto to the β-polypeptide backbone and generate the α/β CPMBs, we choose the extensively used NCA polymerization. By using the backbone pendent amine groups as the initiation points, the poly-α-L-lysine chains were grafted from the backbone. Two α/β CPMBs, PβAA-*g*-PαLL$_{10}$ and PβAA-*g*-PαLL$_{20}$, were synthesized to have different length of sidechain poly-α-L-lysine, with DP designed to be 10 and 20 respectively. The GPC characterization clearly indicated increase of M_n from the β-polypeptide backbone (PβAA) at 3.3 kDa to the final α/β CPMBs (PβAA-*g*-PαLL$_{10}$ and PβAA-*g*-PαLL$_{20}$) at about 33.4 and 48.1 kDa and a narrow PDI at 1.28 and 1.24, respectively. DP of the β-polypeptide backbone and final α/β CPMBs were also confirmed using nuclear magnetic resonance (NMR) spectra and the results were comparable to those obtained from GPC characterization. The diameters of α/β CPMBs were measured by dynamic light scattering (DLS) to get an average particle size of 8.35±2.02 nm for PβAA-*g*-PαLL$_{10}$ and 17.22±4.14 nm for PβAA-*g*-PαLL$_{20}$ in a solution of phosphate buffered saline (PBS) at 0.5 mg mL^{-1} of polymer (Fig. S1).

The prepared α/β CPMBs were compared with antibiotic vancomycin and a representative HDP magainin II, and their antibacterial activities were evaluated against five strains of MRSA as summarized in Table 2. The antimicrobial activities of PβAA against *S. aureus* were already reported in precedent literature, and this data was not included here because PβAA was used as the backbone in the polymer brushes without showing antimicrobial activities [70,71]. Both α/β CPMBs displayed potent antibacterial activity against all tested strains of MRSA. The sidechain poly-α-L-lysine grafted α/β CPMBs are not only bacterial static but indeed bactericidal with minimum bactericidal concentration (MBC) equal to minimum inhibitory concentration (MIC) value at 0.38 and 0.26 μmol L^{-1} respectively for PβAA-*g*-PαLL$_{10}$ and PβAA-*g*-PαLL$_{20}$. Both α/β CPMBs performed even better than the antibiotic vancomycin that displayed a MBC at

Table 2 Antibacterial activity of α/β CPMBs against multiple strains of MRSA

Antimicrobial compound	MIC (MBC)[a] μmol L^{-1}				
	USA300	USA300 Lac	Newman	Mu50	USA400
PβAA-*g*-PαLL_{10}	0.38 (0.38)	0.38 (0.38)	0.38 (0.38)	0.38 (0.38)	0.38 (0.38)
PβAA-*g*-PαLL_{20}	0.26 (0.26)	0.26 (0.26)	0.26 (0.26)	0.26 (0.26)	0.26 (0.26)
PαLL_{20}	1.44(1.44)	1.44(1.44)	1.44(1.44)	1.44(1.44)	1.44(1.44)
Vancomycin	0.26 (0.52)	0.52 (0.52)	0.52 (0.52)	0.26 (0.52)	0.26 (0.52)
Magainin II	ND[b]	ND[b]	ND[b]	ND[b]	ND[b]

a) MIC (minimum inhibitory concentration) is the minimum compound concentration to inhibit bacteria growth; MBC (minimum bactericidal concentration) is the minimum compound concentration to kill bacteria; b) ND means activity is not detected even under the highest compound concentration at 77.8 μmol L^{-1}.

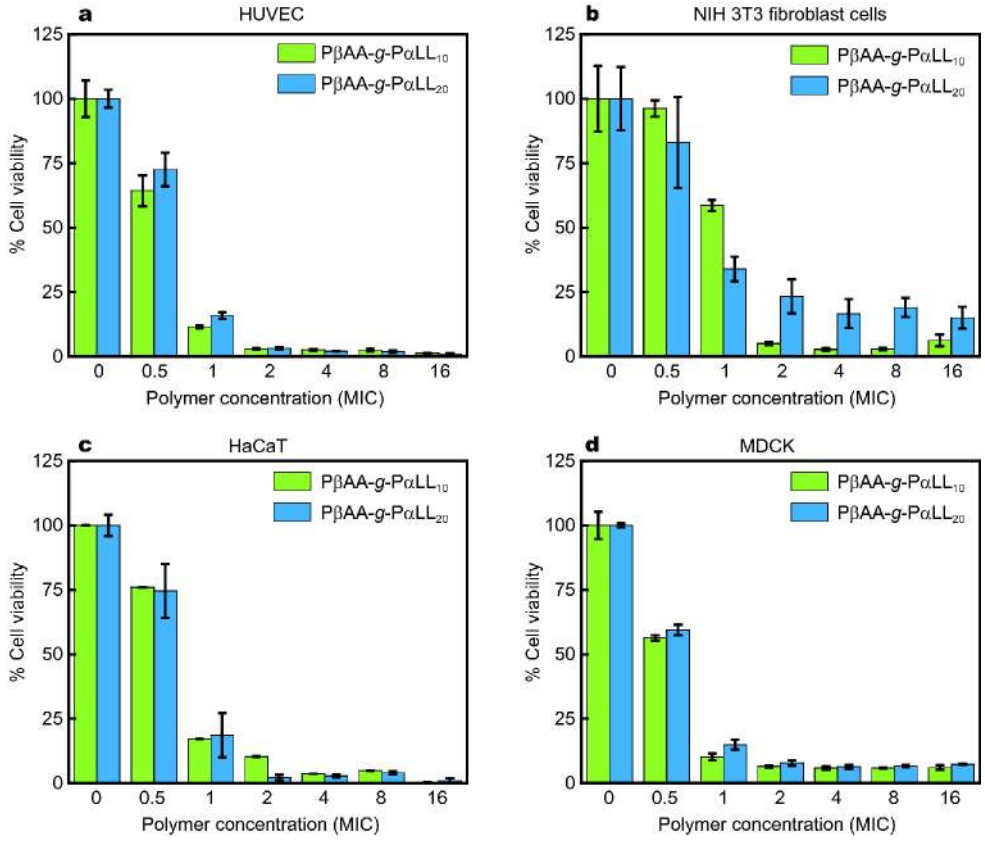

Figure 2 Cytotoxicity of α/β CPMBs toward (a) HUVEC (ATCC PCS-100-010), (b) NIH 3T3 fibroblast cells (ATCC CRL-1658), (c) HaCaT (BNCC342026) and (d) MDCK (NBL-2, ATCC CCL-34). The concentrations of PβAA-*g*-PαLL_{10} and PβAA-*g*-PαLL_{20} used for cytotoxicity experiments are related to their MIC value against *S. aureus* USA300 as shown in Table 2. The value of MIC is 0.38 μmol L^{-1} for PβAA-*g*-PαLL_{10} and 0.26 μmol L^{-1} for PβAA-*g*-PαLL_{20}

0.52 μmol L^{-1} against all strains of MRSA. We also compared the polymer brushes with single chain poly-α-L-lysine (PαLL_{20}) and found the polymer brush PβAA-*g*-PαLL_{20} was 5.5 fold more active than the PαLL_{20} and has similar cytotoxicity compared to corresponding PαLL_{20} (Fig. S2). All these results imply that the potent antibacterial activity of α/β CPMBs (PβAA-*g*-PαLL_{10} and PβAA-*g*-PαLL_{20}) derived from the molecular design of multiple sidechain grafted poly-α-L-lysine that possess multivalent interactions with bacteria. The representative HDP magainin II, as another control within this study, has no activity at all even at the highest concentration (77.8 μmol L^{-1}) within the test. We also did cytotoxicity study on these polymers using four different mammalian

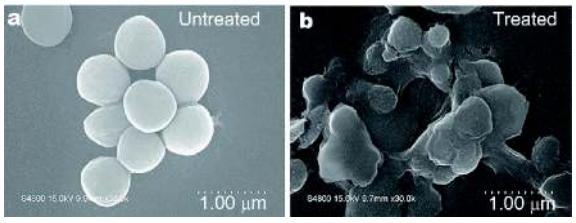

Figure 3 SEM characterization of MRSA cell morphology change after bacteria incubation with the α/β CPMB. (a) MRSA cells without antimicrobial treatment as control and (b) MRSA cells incubated with α/β CPMB for 20 min.

cells and found that these two polymer brushes have similar toxicity for most of the cell types (Fig. 2). As is well known, polylysine itself is generally toxic to mammalian cells due to the high intensity of positive charges along the polymer chain; therefore, the cytotoxicity of these polymer brushes likely comes from the polylysine sidechains.

In order to understand how these α/β CPMBs interact with bacteria, the polymer molecular brush was incubated with MRSA cells for 20 min and then the bacteria cells were characterized by scanning electron microscopy (SEM). As shown in Fig. 3, bacteria from the polymer-free control sample have intact and smooth cell membrane. However, the bacteria after incubation with α/β CPMBs have obviously irregular cell morphology and defects of cell membrane. These results imply that the α/β CPMB kill *S. aureus* quickly by disrupting bacteria cell membrane using its multiple sidechain poly-α-L-lysine that is generally considered as HDP mimics. Similar observations have been reported for HDP and their mimics because these types of antimicrobial agents target cell membrane to have antibacterial activity [72].

In conclusion, we demonstrated a perfect match of two ROP systems, the β-lactam ROP and the NCA ROP, in generating alpha-beta chimeric poly-peptide molecular brushes (α/β CPMBs) using β-polypeptide as the backbone and grafted poly-α-L-lysine as the sidechains. These α/β CPMBs demonstrated potent *in vitro* bactericidal activities, even better than vancomycin, against multiple strains of MRSA superbugs. The easily tunable polymerization of two ROP systems, the diversified structure of both β-lactam and NCA, and the potent superbug killing activity altogether imply great potential of the α/β CPMBs in antimicrobial applications.

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Author contributions Liu R designed and directed the project; Zhang D, Ma P synthesized the samples; Zhang D, Zhang Q and Qiao Z did the characterization of samples; Zhang D, Zhang S, Shao N, Qian Y, Xie J, Dai C, Qi F, Zhang W and Cheng S and Zhou R performed the biological experiments; Liu R, Zhang D analyzed the data; Liu R, Zhang D and Zhang S wrote the paper. All authors reviewed the manuscript.

Conflict of interest The authors declare that they have no conflict of interest.

Supplementary information Experimental details and supporting data are available in the online version of the paper.

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具有高效抗MRSA活性的Alpha-Beta杂化多肽聚合物分子刷

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摘要 近年来, 以耐甲氧西林金黄色葡萄球菌(MRSA)为代表的"超级细菌"不断被发现和扩散, 已经严重威胁人类健康, 因此, 研制新型、高效的抗菌剂迫在眉睫. 以宿主防御肽及其模拟物为代表的多肽和聚合物近年来得到广泛关注. 而分子刷作为一类独特的聚合物也显示了很多特殊的性能. 我们结合前期研究, 首次将两种开环聚合体系即β-内酰胺开环聚合和N-羧基环内酸酐(NCA)开环聚合体系相结合, 以β多肽为骨架结构进而通过其氨基功能基团进一步引发NCA开环聚合, 合成了侧链具有多个聚赖氨酸的α/β杂化多肽聚合物分子刷. 这种新型分子刷对多种MRSA菌株均展现出高效的抗菌活性, 甚至优于万古霉素. 通过扫描电子显微镜(SEM)表征, 揭示了α/β杂化多肽聚合物分子刷的抗菌机理与宿主防御肽类似, 是通过破坏细菌细胞膜的完整性杀菌. α/β杂化多肽聚合物分子刷高度可调的结构特点和高效的抗菌活性, 显示了其在抗菌研究和应用中的潜力.

