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Dual functional β-peptide polymer-modified resin beads for bacterial killing and endotoxin adsorption

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Abstract

Background: Bacterial infections and endotoxin contaminations are serious problems in the production/manufacture of food, water, drinks, and injections. The development of effective materials to kill bacteria and adsorb endotoxins, particularly those caused by gram-negative bacteria, represents a major step toward improved safety. As synthetic mimic of host defense peptides, β-peptide polymers are not susceptible to bacterial resistance and exhibit potent bacteria-killing abilities upon antibiotic-resistant bacteria. This study investigated the potential of synthetic β-peptide polymer-modified polyacrylate (PA) beads to kill bacteria and remove endotoxin, i.e. lipopolysaccharide (LPS), produced by these bacteria.

Results: Synthetic β-peptide polymer-modified PA beads displayed strong antimicrobial activity against *Escherichia coli* and methicillin-resistant *Staphylococcus aureus*, as well as excellent biocompatibility. In addition, these β-peptide polymer-modified beads removed around 90% of the endotoxins, even at 200 EU/mL of LPS, a very high concentration of LPS.

Conclusions: β-peptide polymer-modified PA beads are efficient in bacterial killing and endotoxin adsorption. Hence, these modified beads demonstrate the potential application in the production/manufacture of food, water, drinks, and injections.

Background

Bacterial contamination of food packages, water treatment membranes, industrial pipes, and drug injection and medical devices is a serious problem globally and poses a threat to their biosafety and effectiveness [1–5]. To reduce or prevent bacterial contamination, antimicrobial drugs and antimicrobial coatings are widely used [6–9]. Unfortunately, indiscriminate use of antimicrobials has led to the emergence and spread of drug-resistant bacteria, which poses a challenge to human health [10–13]. In addition, biosafety-related factors such as immunomodulation are also very important.

Endotoxins, lipopolysaccharide (LPS) that function as major pathogenic immune factor, are released from the outer cell membrane of Gram-negative bacteria in response to an attack by antimicrobial agents. Endotoxins can activate complex immune effectors to generate a hyperinflammatory response and even provoke severe endotoxic shock and multiorgan dysfunction [14–18]. Therefore, multifunctional antibacterial materials are highly desirable for both efficient bacterial killing and biosafety considerations [19–25].

In contrast to conventional antibiotics, host-defense peptides (HDPs) have low susceptibility to antimicrobial resistance. Given this advantage, HDPs have received much research attention [26–30]. The versatile biological functions, such as antimicrobial activity combined with

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anti-inflammatory properties, of HDPs have made them promising candidates in relieving acute inflammation via inactivating or neutralizing endotoxins, in addition to killing bacteria [31–34]. The amphipathic structure of HDPs plays an important role in the process of endotoxin removal as well as in bacterial killing through hydrophobic and electrostatic interaction with toxic lipid A. This interaction occurs when the positively charged fragments within HDPs attract negatively charged phosphates of lipids A, and the hydrophobic fragments of HDPs bind with lipid A fatty acid moieties. However, HDPs derived from diverse sources have similar shortcomings: low stability upon proteolysis and a high cost. To address these problems, a series of synthetic mimics of HDPs have been developed. Several studies showed that these synthetic mimics of HDPs exhibited high endotoxin neutralization and killing efficacy against bacteria, thereby showing strong potential in antibacterial applications [35–37].

As synthetic mimics of HDPs, amphipathic β-peptide polymers display broad-spectrum and potent antimicrobial activities, in addition to favorable solution [38–42] and surface biocompatibility [43, 44]. In previous study, a thiol-terminated β-peptide polymer (50:50 DM-CH) was successfully modified to the flat surfaces of gold [43] and variable biomedical materials [44] and displayed excellent antimicrobial activity. In this study, we modified 50:50 DM-CH to the spherical surface of amino-functionalized polyacrylate (PA) resin beads and demonstrated their function in efficient bacterial killing and endotoxin adsorption.

Results and discussion

Preliminary work indicated that 50:50 DM-CH had potential antimicrobial activity. To test whether this β-peptide polymer could endow the surface of resin beads with antimicrobial activity and endotoxin adsorption, we prepared β-peptide polymer-immobilized PA resin beads (Fig. 1a) by shaking the beads at the presence of reacting agents in a tube for solid phase synthesis (Fig. 1c). The amine functionalized PA beads were first modified using a dual functional linker, 3-maleimidopropionic acid *N*-hydroxysuccinimide (MalOSu), to

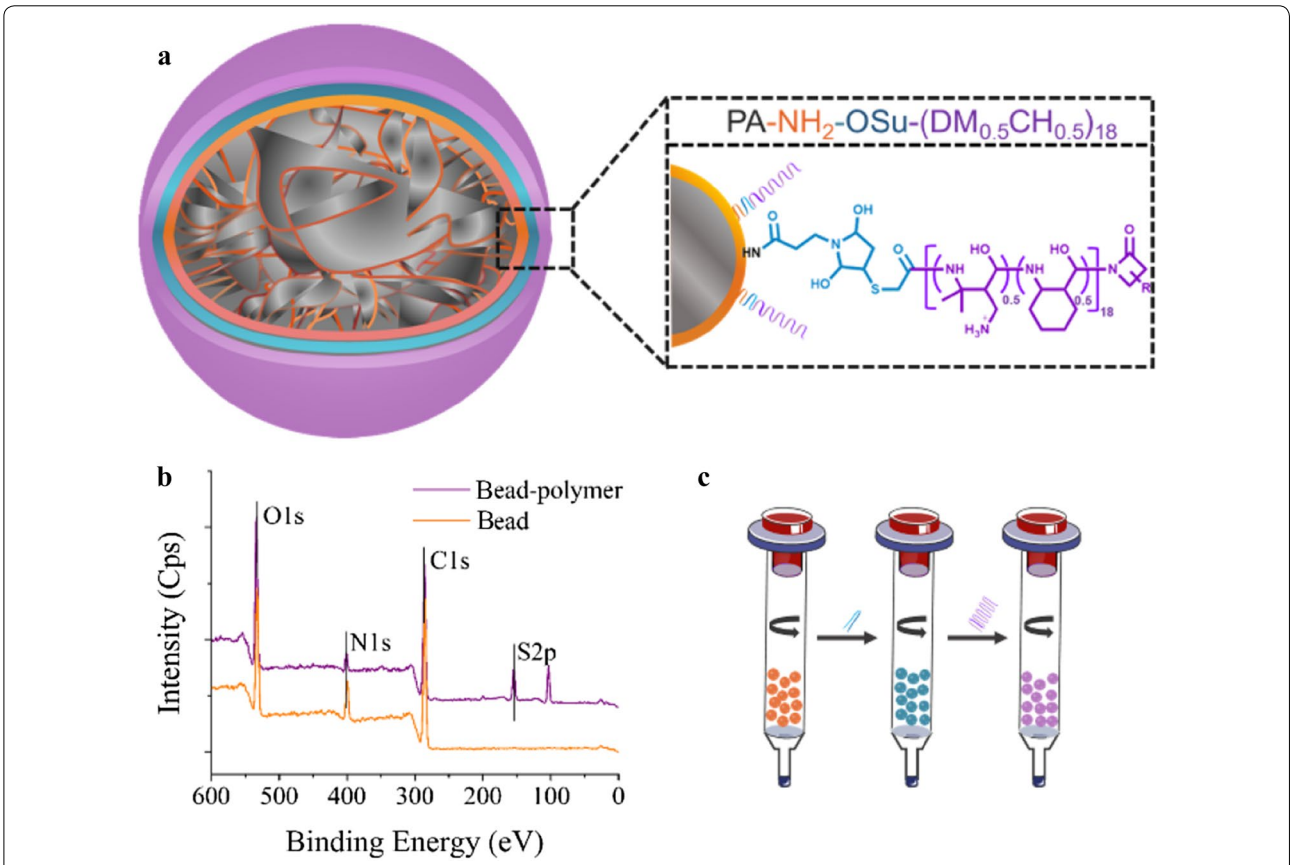


Fig. 1 Synthesis of β-peptide polymer-modified PA beads. **a** The 20-mer 50:50 DM-CH was attached to the amino layer surface of the beads through the link with MalOSu. **b** XPS spectra of β-peptide polymer-modified PA beads. **c** Preparation process of β-peptide polymer-modified PA beads using the apparatus of solid-phase synthesis

afford surface maleimide groups that reacted further with the thiol-terminated β-peptide polymer 50:50 DM-CH to produce antimicrobial polymer-modified beads. The presence of an S2p peak in the XPS spectra (Fig. 1b) of the β-peptide polymer modified beads confirmed successful antimicrobial polymer modification on the surface of the PA resin beads.

We examined the antimicrobial activity of the β-peptide polymer modified PA resin beads in phosphate buffered saline (PBS). The β-peptide polymer-modified beads killed MRSA completely within 2.5 h. When an aliquot of this suspension was added to fresh MH medium, no growth of MRSA was detected after 6 h, as indicated by the optical density (OD) that was identical to that of blank medium (Fig. 2a). The potent bacterial killing of the β-peptide polymer-modified PA resin beads was confirmed by zero colony forming unit (CFU) on the LB agar plate, which was incubated with an aliquot of suspension culture 24 h after OD reading (Fig. 2a). In sharp contrast, rapid growth of MRSA cells was observed on controls of PBS, after incubation with fresh MH medium for 6 h, as clearly indicated by both an increased OD value and a large number of bacterial colonies in the CFU counting test.

Encouraged by these results, we investigated the antimicrobial ability of polymer-modified beads against *E. coli* and MRSA in the presence of serum, using 50% fetal bovine serum (FBS) in the assay medium. We observed 99.9% bacterial killing of both *E. coli* and MRSA by ≥ 50 mg beads per sample were used (Fig. 2b). We used scanning electron microscope (SEM) to assess morphological changes of *E. coli* and MRSA, incubated with the β-peptide polymer modified PA resin beads for 2.5 h. As compared to the intact membrane of bacteria incubated with bare beads, conspicuous shrinkage and damage of the bacterial membrane were observed among bacteria incubated with the β-peptide polymer-modified beads (Fig. 2c). This observation appointed to a membrane-active antimicrobial mechanism similar to that observed in our previous studies on the antimicrobial abilities of gold and polyurethane surfaces coated with β-peptide polymers [43, 44].

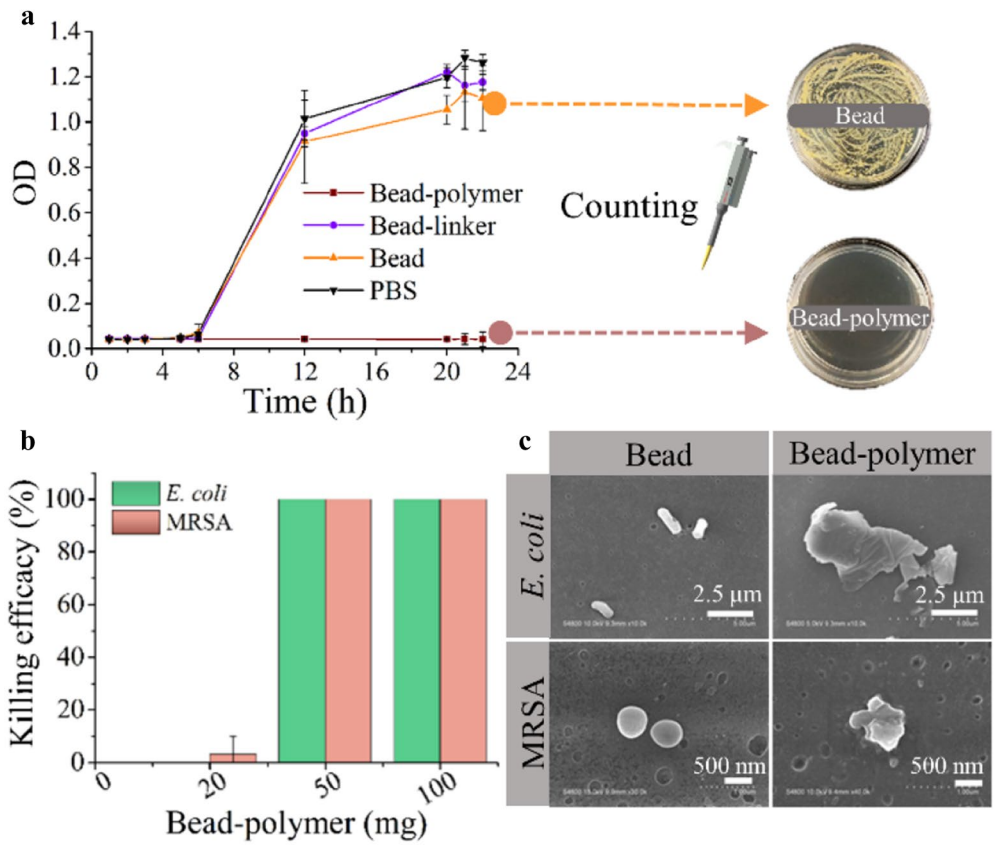


Fig. 2 Antibacterial activity of β-peptide polymer-modified PA beads. **a** Illustration of antibacterial activity against MRSA at initial bacterial density of 1×10^5 CFU/mL with OD and CFU on a counting plate in PBS. **b** Antibacterial activity with different amounts of beads in 50% FBS at initial bacterial density of 1×10^4 CFU/mL. **c** SEM characterization of bacteria before and after 2.5 h of incubation

We then investigated endotoxins adsorption capacity of the modified beads using a FITC-LPS binding assay in PBS and a Tachypleus Amebocyte Lysate (TAL) kit assay in serum (Fig. 3a). The β-peptide polymer-modified beads adsorbed half of FITC-LPS at an initial LPS concentration of 1 μg/mL in PBS, whereas the bare beads and linker-modified beads showed almost no LPS adsorption (Fig. 3b). It is worth mentioning that the LPS concentration at 1 μg/mL in the above test was very high. We used this high LPS concentration on purpose to check the LPS adsorption upper limit of our peptide polymer-modified beads. The ability of LPS adsorption for β-peptide polymer-modified beads was evaluated in the presence of 50% FBS using a TAL assay at a reasonable LPS concentration, which was lower than that used in the FITC-LPS adsorption assay. Using 20 mg of beads per assay sample efficiently adsorbed around 90% of LPS at variable initial LPS concentration from 50 to 200 EU/mL.

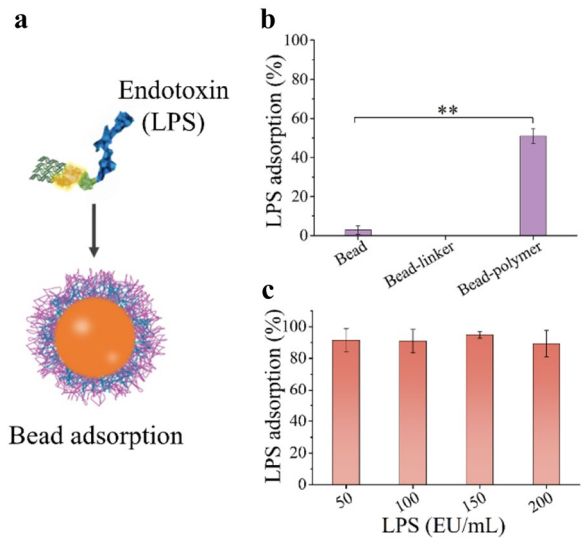


Fig. 3 Effects of β-peptide polymer modified PA beads on the binding of LPS. **a** Illustration of the interaction between LPS and beads. **b** Beads were incubated with FITC-LPS (1 μg/mL) in PBS. **c** Beads cultivated with different concentrations of LPS in serum using the TAL assay, no significant differences among tests using 50–200 EU/mL of LPS. **$p < 0.01$

The results of the LPS adsorption assay in the presence of serum pointed to the potential application of these β-peptide polymer-modified beads in biomedical practice, where the biocompatibility of materials is a major concern. Therefore, we investigated the hemolysis and cytotoxicity of the polymer-modified beads using a static hemolysis assay and MTT assay. Beads with or without modification all showed less than 2% hemolysis (Fig. 4a). Interestingly, the cytotoxicity of bare beads against fibroblast cells was exhibited approximately 42%, whereas the cytotoxicity of the β-peptide polymer-modified beads was substantially lower and at a cell-compatible level (Fig. 4b).

Conclusion

We successfully modified PA beads with a synthetic β-peptide polymer, thiol-terminated 50:50 DM-CH. The resulting resin beads exhibited potent antibacterial activity against both Gram-negative *E. coli* and Gram-positive MRSA. Additionally, the modified beads demonstrated the ability for endotoxin adsorption. The biocompatibility and ease of synthesis of these polymer-modified beads point to their potential application as dual-functional materials for antibacterial and endotoxin adsorption.

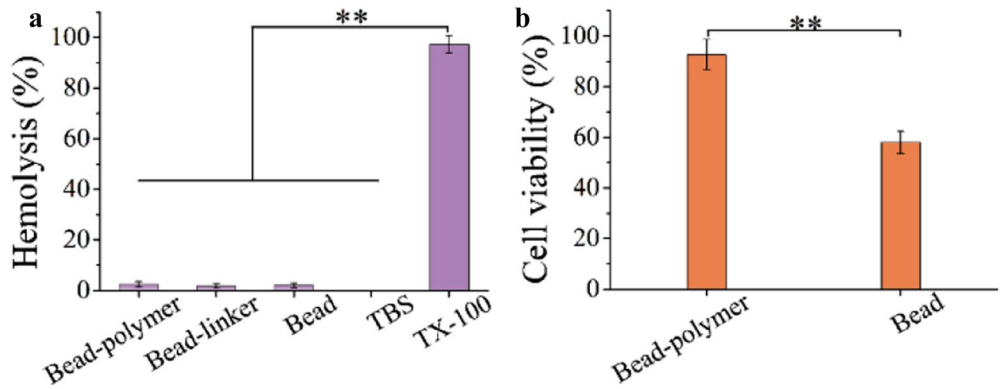


Fig. 4 Biocompatibility studies on PA resin beads. **a** Hemolysis rate of bare beads, linker-modified beads, and polymer-modified beads. TBS and TX-100 were used as negative and positive controls, respectively. **b** Cytotoxicity of NIH-3T3 fibroblast cells after incubation with the extracts of bare beads and polymer-modified beads using MTT assay. **$p < 0.01$

Materials and methods

General

PA resin beads were purchased from Tianjin Nankai HECHENG S&T Co.,Ltd; bromoform, chlorosulfonyl isocyanate, trifluoroacetic anhydride, di-tert-butyl pyrocarbonate were purchased from Adamas-beta; Triphenylmethyl chloride and *N*-hydroxy succinimide (NHS) were obtained from Meryer Technologies in China; PBS was purchased from Thermo Fisher Scientific; LPS from *Escherichia coli* O111:B4, FITC-conjugates was purchased from Sigma-Aldrich; all others reagents and solvents were purchased from General-Reagent. In this study, two types of bacteria were used for in vitro antimicrobial test including *Escherichia coli* (*E. coli* ATCC 25922) and *Staphylococcus aureus* (*S. aureus* USA 300, methicillin-resistant strain, MRSA); NIH-3T3 fibroblast cells (3T3 ATCC CRL-1658) were obtained from the Cell Bank of Typical Culture Collection of Chinese Academy of Sciences (Shanghai, China) and were used for cytotoxicity study. Synthesized chemicals were purified using a SepaBean machine equipped with Sepaflash columns produced by Santai Technologies Inc. in China. $CDCl_3$ or D_2O were used as the solvent to collect the 1H NMR spectra on a Bruker spectrometer at 400 MHz. 1H NMR chemical shifts were referenced to the resonance for TMS internal standard for $CDCl_3$ and residual protonated solvent for D_2O; The mass spectrum data of compounds were collected using an Agilent HPLC 1100/MS G1956B mass spectrometer. Element analysis of the β-peptide polymer-modified PA resin beads was acquired using Thermo Fisher ESCALAB 250XI X-ray photoelectron spectroscopy (XPS). Morphology of bacteria on the modified resin beads was observed on a Hitachi S-4800 Field Emission Scanning Electron Microscope (FESEM). The TAL assay was provided by Xiamen Bioendo Technology. Co., Ltd. (Xiamen, China).

Synthesis of β-lactam monomers and poly-β-peptides

β-lactam monomers and poly-β-peptides were prepared by following the procedure in the literature [43, 45, 46]. The details are given in the Additional file 1, Synthesis S1. Synthesis of racemic β-lactam monomer (±) DMβ; Synthesis S2. Synthesis of β-Lactam monomers (±)-CHβ; Synthesis S3. Synthesis of polymerization co-Initiator; Synthesis S4. Synthesis of β-peptide polymers; Figure S1. ^{1}H NMR spectrum of monomer (±) DMβ; Figure S2. ^{1}H NMR spectrum of monomer (±) CHβ; Figure S3. ^{1}H NMR spectrum of co-initiator; Figure S4. ^{1}H NMR spectrum of β-peptide polymer 50:50 DM-CH.

Synthesis of the surface linker

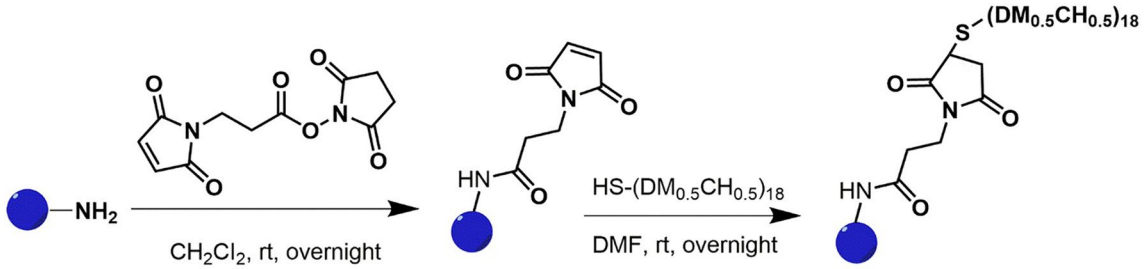
3-Maleimidopropionic acid *N*-hydroxysuccinimide ester (MalOSu) was prepared according to the literature [47]. The details are given in the Additional file 1, Synthesis S4. Synthesis of the surface linker; Figure S5. ^{1}H NMR spectrum of surface linker MalOSu.

Synthesis and characterization of poly-β-peptide immobilized on the surface of PA resin beads

Poly-β-peptide modified PA resin beads were synthesized from 400 to 600 μm diameter PA beads with an amino layer, of which the density was 0.8 mmol/g (Synthesis 1). Initially, 20 mg of beads were treated with MalOSu (26.5 mg, 0.1 mmol) in anhydrous CH_2Cl_2 overnight at rt, washed consecutively with CH_2Cl_2 and methanol, and dried. MalOSu-modified beads were reacted with a solution of Poly-β-peptide (SH-$(DM_{0.5}CH_{0.5})_{18}$) (30.8 mg, 0.008 mmol) in anhydrous DMF overnight at rt. After the synthesis, Poly-β-peptide modified PA resin beads were washed with DMF, CH_2Cl_2, and methanol, and dried in vacuo. The dried samples were then characterized by XPS analysis (the raw data of figures in Additional file 2).

Examination on bactericidal efficacy of polymer modified surface in PBS and serum

Bacteria cells were inoculated in LB medium and cultured overnight at 37 °C with shaking at 150 rpm. An aliquot of 7.5 mL the bacterial suspension was centrifuged at 4000 rpm for 5 min to harvest bacteria cells as a pellet as the bottom of the tube and then the collected cells



Synthesis 1 Synthesis of poly-β-peptide modified PA resin beads

were suspended in PBS. After repeating above operation for 3 cycles, the bacteria cell suspension was adjusted to a cell density of 2×10^5 CFU/mL for antimicrobial assay. MRSA was used in the PBS system. The polymer modified PA beads (20 mg) were placed in each well containing 100 μL PBS to obtain the working suspension of 10^5 CFU/mL. After gently shaking at 37 °C for 2.5 h, an aliquot of 80 μL bacterial suspension after diluted 100 × from each well was added into the 96 well plate containing 100 μL LB medium, the plate was then incubated at 37 °C and observed OD value at 600 nm at regular intervals (the raw data of figures in Additional file 3). Above bacterial suspension finally extracted 10 μL after 24 h was spread onto agar plates and overnight cultured at 37 °C for colony counting to evaluate the viability of bacteria with the colony number. Additionally, MRSA and *E. coli* were used in the medium of 50% (FBS). Polymer-modified beads with different weight of 20 mg, 50 mg, 100 mg were added in the bacterial suspension at the final centration is 10^4 CFU/mL. An aliquot of 35 μL bacterial suspension with the dilution of 5X after incubating 2.5 h was enumerated on the LB agar plate to acquire the killing efficacy of the beads. Bacterial suspension without any beads was used as the negative control to give the colony number C_{control}, and incubation with polymer-modified beads was marked as C_{sample}. The killing efficacy of the polymer-tethered surface was calculated using the equation:

$$\text{Killing efficacy}\,(\%) = \frac{C_{\text{control}} - C_{\text{sample}}}{C_{\text{control}}} \times 100.$$

SEM characterization of bacterial morphology

Bacterial cell suspension at the end of the above antimicrobial assay was collected and was fixed with 4% glutaraldehyde in phosphate buffer (PB) at 4 °C overnight. Then the fixed cells were rinsed with PBS three times and were dehydrated using a graded ethanol series of (30–100% ethanol). The sample was dried under N_2 and was used directly for FESEM characterization.

FITC-LPS binding assay on polymer modified surface

200 μL of 1 μg/mL FITC-LPS in PBS was treated with 20 mg polymer-modified beads in each well of the 48-well plate [36]. After gently shaking away from the light, 100 μL solution was transferred from transparent 48-well plate to 96-well black plate. Adsorption of the FITC-conjugated LPS by modified beads was studied through exciting the FITC-LPS at 480 nm and monitoring the emission of FITC at 516 nm using a microplate reader (SpectraMax M2, USA) after 30 min. 200 μL of PBS without any beads and with modified beads was marked as F_{control} and F_{sample} respectively. The fluorescence intensity was calculated as follows:

$$\text{LPS adsorption}\,(\%) = \frac{F_{\text{control}} - F_{\text{sample}}}{F_{\text{control}}} \times 100.$$

Adsorption of endotoxin (LPS) in serum

20 mg of polymer-modified beads were incubated in 50% FBS with 0–200 EU/mL endotoxin at 100 rpm for 3 h. The Chromogenic Tachypleus Amebocyte Lysate kit (Xiamen Bioendo Technology company, China) was used to measure endotoxin. Samples were heated at 70 °C to precipitate proteins followed by testing endotoxin concentration according to the manufacture's introduction (the raw data of figures in Additional file 3).

Hemolysis assay on polymer modified surface

Fresh human blood was washed with Tris-buffered saline (TBS) for three times and the collected human red blood cell (hRBC) was diluted to 5% (v/v) with TBS. An aliquot of 100 μL HRBCs was added into the 48-well plate containing 20 mg of bead first immersed in the 100 μL TBS. Beads were incubated at 37 °C for 1 h with the gentle shake and then the collected cell suspension centrifuged at 3700 rpm for 5 min. An aliquot of 80 μL supernatant was transferred to each individual well of a 96-well plate to read the OD values at 405 nm (the raw data of figures in Additional file 3). The OD value for polymer modified surface, the OD value for negative control using TBS, and the OD value for positive control using TX-100 at 3.2 mg/mL were marked as A_{test}, A_{negative} A_{positive}, respectively. The percentage of hemolysis was calculated from the equation:

$$\text{Hemolysis}\,(\%) = \frac{A_{\text{sample}} - A_{\text{negative}}}{A_{\text{positive}} - A_{\text{negative}}} \times 100.$$

Cytotoxicity evaluation

The cytotoxicity of beads was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay using NIH-3T3 cells [21]. Beads were first immersed in the DMEM culture medium at 37 °C for 24 h. extracts were then obtained and added into the wells of 96-well plate overnight containing the fibroblast solutions ($\sim 1 \times 10^4$ cell/well). After incubation, 100 μL of MTT (5 mg/mL, in PBS) was added into each well for another 4 h. Then 10 μL of MTT solution (5 mg/mL) was added to each well and the plate was incubated at 37 °C for 4 h. After removing the supernatant from each well, 150 μL/well of DMSO was added to dissolve the purple MTT-formazan crystals under shaking for 15 min. The absorbance of the solution in each

well at 570 nm was measured using a microplate reader. The A_{test} represents the OD value corresponding to the β-peptide polymer modified beads and the bare beads, the $A_{control}$ means the OD value corresponding to the control, the A_{blank} means the OD value corresponding to DMSO blank control. Cell viability was calculated from the equation:

$$\text{Cell viability (\%)} = \frac{A_{test} - A_{blank}}{A_{control} - A_{blank}} \times 100.$$

Statistic analysis

Statistic analysis of the data was conducted using ANOVA and Tukey's HSD posthoc test. A p value ≤ 0.05 is considered as statistically significant.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s42833-019-0005-3.

Additional file 1. Experimental data for the characterization of monomer, polymer and surface linker, including **Synthesis S1.** Synthesis of racemic β-lactam monomer (±) DMβ; **Synthesis S2.** Synthesis of β-Lactam monomers (±)-CHβ; **Synthesis S3.** Synthesis of polymerization co-Initiator; **Synthesis S4.** Synthesis of β-peptide polymers; **Synthesis S4.** Synthesis of the surface linker; **Figure S1.** ^{1}H NMR spectrum of monomer (±) DMβ; **Figure S2.** ^{1}H NMR spectrum of monomer (±) CHβ; **Figure S3.** ^{1}H NMR spectrum of co-initiator; **Figure S4.** ^{1}H NMR spectrum of β-peptide polymer 50:50 DM-CH; **Figure S5.** ^{1}H NMR spectrum of surface linker MalOSu.

Additional file 2. Raw data of Fig. 1. **b** XPS spectrum of polymer-modified beads displayed in the manuscript.

Additional file 3. Raw data of other figures in the manuscript, including Fig. 2. **a** OD (optical density) of initial bacterial density of 1×10^5 CFU/mL MRSA; Fig. 2. **b** Antibacterial activity with different amounts of beads in 50% FBS at initial bacterial density of 1×10^4 CFU/mL; Fig. 3. **b** LPS adsorption of beads with FITC-LPS (1 μg/mL) in PBS; Fig. 3. **c** LPS adsorption of beads in different concentration of serum; Fig. 4. **a** Hemolysis rate of bare beads, linker-modified beads, and polymer-modified beads; Fig. 4. **b** Cytotoxicity of NIH-3T3 fibroblast cells after incubation with the extracts of bare beads and polymer-modified beads using MTT assay.

Abbreviations

PA: polyacrylate; MRSA: methicillin-resistant *Staphylococcus aureus*; LPS: lipopolysaccharide; HDPs: host defense peptides; MalOSu: *N*-hydroxysuccinimide; OD: optical density; CFU: colony forming unit; SEM: scanning electron microscope.

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Not applicable.

Authors' contributions

RHL and FD proposed the research. YXQ, YS, RHL, and FD designed the experiments. YXQ, DS, QF, LZY carried out the preparation of monomer and polymer, synthesis of modified beads, XPS analysis, antimicrobial assay, hemolysis assay and then interpreted the data and drafted the manuscript. YS and TYL did antimicrobial assay in serum and TAL assay. LQL conducted the synthesis of the surface linker. NS performed cytotoxicity test, JYX made SEM characterization. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

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References

1. Guo LY, Yuan WY, Lu ZS, Li CM. Polymer/nanosilver composite coatings for antibacterial applications. Colloid Surf A. 2013;439:69–83.
2. Coad BR, Kidd SE, Ellis DH, Griesser HJ. Biomaterials surfaces capable of resisting fungal attachment and biofilm formation. Biotechnol Adv. 2014;32(2):296–307.
3. Valdes A, Ramos M, Beltran A, Jimenez A, Garrigos MC. State of the art of antimicrobial edible coatings for food packaging applications. Coatings. 2017;7(4):56/51–56/23.
4. He C, Ji HF, Qian YF, Wang Q, Liu XL, Zhao WF, Zhao CS. Heparin-based and heparin-inspired hydrogels: size-effect, gelation and biomedical applications. J Mater Chem B. 2019;7(8):1186–208.
5. Neoh KG, Li M, Kang ET, Chiong E, Tambyah PA. Surface modification strategies for combating catheter-related complications: recent advances and challenges. J Mater Chem B. 2017;5(11):2045–67.
6. Wei T, Tang Z, Yu Q, Chen H. Smart antibacterial surfaces with switchable bacteria-killing and bacteria-releasing capabilities. ACS Appl Mater Interfaces. 2017;9(43):37511–23.
7. Tu Q, Shen X, Liu Y, Zhang Q, Zhao X, Maitz MF, Liu T, Qiu H, Wang J, Huang N, et al. A facile metal–phenolic–amine strategy for dual-functionalization of blood-contacting devices with antibacterial and anticoagulant properties. Mater Chem Front. 2019;3(2):265–75.
8. Qu Y, Wei T, Zhao J, Jiang S, Yang P, Yu Q, Chen H. Regenerable smart antibacterial surfaces: full removal of killed bacteria via a sequential degradable layer. J Mate Chem B. 2018;6(23):3946–55.
9. Zhao X, Olsen I, Pratten J, Knowles JC, Young AM. Reactive calcium-phosphate-containing poly(ester-co-ether) methacrylate bone adhesives: setting, degradation and drug release considerations. J Mater Sci Mater Med. 2011;22(9):1993–2004.
10. Stearns-Kurosawa DJ, Osuchowski MF, Valentine C, Kurosawa S, Remick DG. The pathogenesis of sepsis. In: Annu Rev Pathol. Edited by Abbas AK, Galli SJ, Howley PM, 6;2011:19–48.
11. Martin GS. Sepsis, severe sepsis and septic shock: changes in incidence, pathogens and outcomes. Expert Rev Anti Infect Ther. 2012;10(6):701–6.
12. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5(1):4–11.
13. Ghosh C, Sarkar P, Issa R, Haldar J. Alternatives to conventional antibiotics in the era of antimicrobial resistance. Trends Microbiol. 2019;27(4):323–38.
14. David SA. Towards a rational development of anti-endotoxin agents: novel approaches to sequestration of bacterial endotoxins with small molecules. J Mol Recognit. 2001;14(6):370–87.
15. Shi JJ, Zhao Y, Wang YP, Gao WQ, Ding JJ, Li P, Hu LY, Shao F. Inflammatory caspases are innate immune receptors for intracellular LPS. Nature. 2014;514:187–92.
16. Koziel J, Bryzek D, Sroka A, Maresz K, Glowczyk I, Bielecka E, Kantyka T, Pyrc K, Svoboda P, Pohl J, et al. Citrullination alters immunomodulatory function of LL-37 essential for prevention of endotoxin-induced sepsis. J Immunol. 2014;192(11):5363–72.
17. Navas A, Ferrer R, Martinez ML, Goma G, Gili G, Masip J, Suarez D, Artigas A. Impact of hemoperfusion with polymyxin B added to hemofiltration in

patients with endotoxic shock: a case-control study. Ann Intensive Care. 2018;8(1):1–9.
18. Lelubre C, Vincent JL. Mechanisms and treatment of organ failure in sepsis. Nat Rev Nephrol. 2018;14(7):417–27.
19. Zhao J, Song LJ, Shi Q, Luan SF, Yin JH. Antibacterial and hemocompatibility switchable polypropylene nonwoven fabric membrane surface. ACS Appl Mater Interfaces. 2013;5(11):5260–8.
20. Ding XK, Duan S, Ding XJ, Liu RH, Xu FJ. Versatile antibacterial at materials: an emerging arsenal for combatting bacterial pathogens. Adv Funct Mater. 2018;28(40):1802140.
21. Ding YY, Sun Z, Shi RW, Cui HQ, Liu YY, Mao HL, Wang B, Zhu DM, Yan F. Integrated endotoxin adsorption and antibacterial properties of cationic polyurethane foams for wound healing. ACS Appl Mater Interfaces. 2019;11(3):2860–9.
22. Chen H, Cheng RY, Zhao X, Zhang YH, Tam A, Yan YF, Shen HK, Zhang YS, Qi J, Feng YH, et al. An injectable self-healing coordinative hydrogel with antibacterial and angiogenic properties for diabetic skin wound repair. NPG Asia Mater. 2019;11(1):1–12.
23. Wu SM, Li AH, Zhao XY, Zhang CL, Yu BR, Zhao NN, Xu FJ. Silica-coated gold-silver nanocages as photothermal antibacterial agents for combined anti-infective therapy. ACS Appl Mater Interfaces. 2019;11(19):17177–83.
24. Wei T, Yu Q, Chen H. Responsive and synergistic antibacterial coatings: fighting against bacteria in a smart and effective way. Adv Healthc Mater. 2019;8:e1801381.
25. Wu J, Hu C, Tang Z, Yu Q, Liu X, Chen H. Tissue-engineered vascular grafts: balance of the four major requirements. Colloid Interface Sci Commun. 2018;23:34–44.
26. Zasloff M. Antimicrobial peptides of multicellular organisms. Nature. 2002;415(6870):389–95.
27. Boman HG. Antibacterial peptides: basic facts and emerging concepts. J Intern Med. 2003;254(3):197–215.
28. Hancock RE, Sahl HG. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat Biotechnol. 2006;24(12):1551–7.
29. Wiesner J, Vilcinskas A. Antimicrobial peptides: the ancient arm of the human immune system. Virulence. 2010;1(5):440–64.
30. Chowdhury R, Ilyas H, Ghosh A, Ali H, Ghorai A, Midya A, Jana NR, Das S, Bhunia A. Multivalent gold nanoparticle-peptide conjugates for targeting intracellular bacterial infections. Nanoscale. 2017;9(37):14074–93.
31. Hancock RE. Cationic peptides: effectors in innate immunity and novel antimicrobials. Lancet Infect Dis. 2001;1(3):156–64.
32. Guani-Guerra E, Santos-Mendoza T, Lugo-Reyes SO, Teran LM. Antimicrobial peptides: general overview and clinical implications in human health and disease. Clin Immunol. 2010;135(1):1–11.
33. Brandenburg K, Andra J, Garidel P, Gutsmann T. Peptide-based treatment of sepsis. Appl Microbiol Biotechnol. 2011;90(3):799–808.
34. Martin L, van Meegern A, Doemming S, Schuerholz T. Antimicrobial peptides in human sepsis. Front Immunol. 2015;6:1–7.
35. De Bhattacharjya S. novo designed lipopolysaccharide binding peptides: structure based development of antiendotoxic and antimicrobial drugs. Curr Med Chem. 2010;17(27):3080–93.
36. Ong ZY, Gao SJ, Yang YY. Short synthetic β-Sheet forming peptide amphiphiles as broad spectrum antimicrobials with antibiofilm and endotoxin neutralizing capabilities. Adv Funct Mater. 2013;23(29):3682–92.
37. Lam SJ, O'Brien-Simpson NM, Pantarat N, Sulistio A, Wong EH, Chen YY, Lenzo JC, Holden JA, Blencowe A, Reynolds EC, et al. Combating multidrug-resistant gram-negative bacteria with structurally nanoengineered antimicrobial peptide polymers. Nat Microbiol. 2016;1(11):16162.
38. Gelman MA, Weisblum B, Lynn DM, Gellman SH. Biocidal activity of polystyrenes that are cationic by virtue of protonation. Org Lett. 2004;6(4):557–60.
39. Mowery BP, Lee SE, Kissounko DA, Epand RF, Epand RM, Weisblum B, Stahl SS, Gellman SH. Mimicry of antimicrobial host-defense peptides by random copolymers. J Am Chem Soc. 2007;129(50):15474–6.
40. Liu RH, Chen XY, Hayouka Z, Chakraborty S, Falk SP, Weisblum B, Masters KS, Gellman SH. Nylon-3 polymers with selective antifungal activity. J Am Chem Soc. 2013;135(14):5270–3.
41. Qian YX, Zhang DF, Wu YM, Chen Q, Liu RH. The design, synthesis and biological activity study of Nylon-3 polymers as mimics of host defense peptides. Acta Polym Sin. 2016;10:1300–11.
42. Zhang Q, Ma PC, Xie JY, Zhang S, Xiao XM, Qiao ZQ, Shao N, Zhou M, Zhang WJ, Dai CZ, et al. Host defense peptide mimicking poly-beta-peptides with fast, potent and broad spectrum antibacterial activities. Biomater Sci. 2019;7(5):2144–51.
43. Qian YX, Qi F, Chen Q, Zhang Q, Qiao ZQ, Zhang S, Wei T, Yu Q, Yu S, Mao ZW, et al. Surface modified with a host defense peptide-mimicking β-peptide polymer kills bacteria on contact with high efficacy. ACS Appl Mater Interfaces. 2018;10(18):15395–400.
44. Qi F, Qian YX, Shao N, Zhou RY, Zhang S, Lu ZY, Zhou M, Xie J, Wei T, Yu Q, et al. Practical preparation of infection-resistant biomedical surfaces from antimicrobial β-peptide polymers. ACS Appl Mater Interfaces. 2019;11(21):18907–13.
45. Liu RH, Chen XY, Gellman SH, Masters KS. Nylon-3 polymers that enable selective culture of endothelial cells. J Am Chem Soc. 2013;135(44):16296–9.
46. Zhang JH, Kissounko DA, Lee SE, Gellman SH, Stahl SS. Access to poly-beta-peptides with functionalized side chains and end groups via controlled ring-opening polymerization of beta-lactams. J Am Chem Soc. 2009;131(4):1589–97.
47. Vigier-Carriere C, Garnier T, Wagner D, Lavalle P, Rabineau M, Hemmerle J, Senger B, Schaaf P, Boulmedais F, Jierry L. Bioactive seed layer for surface-confined self-assembly of peptides. Angew Chem Int Ed Engl. 2015;54(35):10198–201.

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