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RESEARCH ARTICLE

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Silk-inspired β-peptide Materials Resist Fouling and the Foreign-body Response

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Abstract: The functions of implants like medical devices are often compromised by the host's foreign-body response (FBR). Here, we developed low FBR materials inspired by serine-rich sericin from silk; our poly-β-homoserine (β-HS) materials comprise the hydrophilic unnatural amino acid β-homoserine. Self-assembled monolayers (SAMs) of β-HS resist adsorption by diverse proteins, as well as adhesion by cells, platelets, and diverse microbes. Experiments lasting up to 3 months revealed that, whereas implantation with control PEG hydrogels induced obvious inflammatory responses, collagen encapsulation, and macrophage accumulation, these responses were minimal with β-HS. Strikingly, the β-HS hydrogels demonstrate angiogenesis in implant-adjacent tissues. Molecular simulations indicated that the low FBR performance of β-HS results from what we term "dual hydrogen bonding hydration", wherein both the backbone amide groups and the side chain hydroxyl groups of β-HS undergo hydration. We anticipate that our low fouling and low FBR β-HS materials can outperform PEG for many biomedical applications.

Introduction

Implanted biomaterials and biomedical devices are extensively used in clinical applications, including tissue engineering scaffolds, prostheses, catheters, and glucose detectors.[1] Nevertheless, failures of implanted biomaterials and biomedical devices are encountered frequently due to the host's foreign-body response (FBR), which involves initial non-specific protein adsorption on the implants and bacterial adhesion to the implants in infection-related cases, followed by inflammatory and wound-healing processes which can cause encapsulation of the implant by a dense layer of collagen, leading to painful tissue distortion, cutting-off nutrient transportation and increasing the risk of reoperation.[2] To overcome FBR, passive anti-biofouling materials have been explored, among which poly(ethylene glycol) (PEG) is presently considered as the gold standard antifouling and biologically inert material,[2f, 3] and early studies reported that PEG exerts no immunogenicity. However, more recent studies have revealed both immunogenicity and antigenicity for PEG and PEG-modified objects including PEGylated proteins, PEG-modified nanoparticles, liposomes, and micelles.[4] Moreover, PEG can decompose in the presence of oxygen in physiological conditions.[5] Therefore, the long-term in vivo application of PEG is limited in biomedical applications. Other materials such as polyglycidols, poly(2-oxazoline)s, polyzwitterions, peptides, and peptoids, have been reported to resist non-specific protein adsorption,[2f, 3b, 6] yet few materials demonstrate promising anti-FBR property and the development of materials with anti-FBR properties which are suitable for implanted biomaterial applications remains a formidable challenge.[2j-l, 7]

Inspired by nature, the silk fibers of *Bombyx mori* have been studied as a candidate of biocompatible and low immunogenic biomaterial.[8] Silk sericin, which extends around the exterior of silk fibers (Figure 1a, b), has been reported to have low immunological response,[9] and has inspired detailed analysis of its chemical composition. These efforts have revealed that sericin is highly enriched for hydrophilic amino acids such as serine, its most abundant amino acid (accounting for 34% of total)[10] (Figure 1c). This led us to hypothesize that this high serine content may contribute to sericin's low immunogenicity.

Here, leveraging peptides comprising unnatural β-amino acids which are naturally resistant to proteolysis,[11] we designed and synthesized heterochiral poly-β-homoserine (β-HS) from a racemic β-lactam aiming to achieve a low fouling and low FBR materials with enhanced in vivo stability (Figure 1d, e). Surface plasmon resonance (SPR) examination on the self-assembled monolayers of β-HS showed that they can strongly resist adsorption from a single protein or serum. Moreover, β-HS can resist adhesion of cells, platelets, bacteria, and fungi, all of which are widely encountered in implanted biomaterials and

devices, and may lead to FBR. Implanted hydrogels of β-HS into mice displayed low FBR, including low inflammatory response and macrophage density, and substantially reduced collagen wrapping compared to PEG controls after the hydrogels were implanted for 1 week. We also observed angiogenesis and negligible collagen capsulation near β-HS hydrogels, compared to dense avascular collagen around PEG hydrogels upon implantation for 4 weeks. The β-HS hydrogels resisted both FBR and collagen encapsulation for at least 3 months. Mechanistically, molecular simulations indicated that the low fouling and FBR of β-HS result from strong "dual hydrogen bonding hydration"; i.e., strong hydrogen bonding hydration of both the amide groups of the peptide backbone and the hydroxyl groups of the side chain. β-HS thus has great potential for use as an anti-FBR material for implants and other biomedical applications.

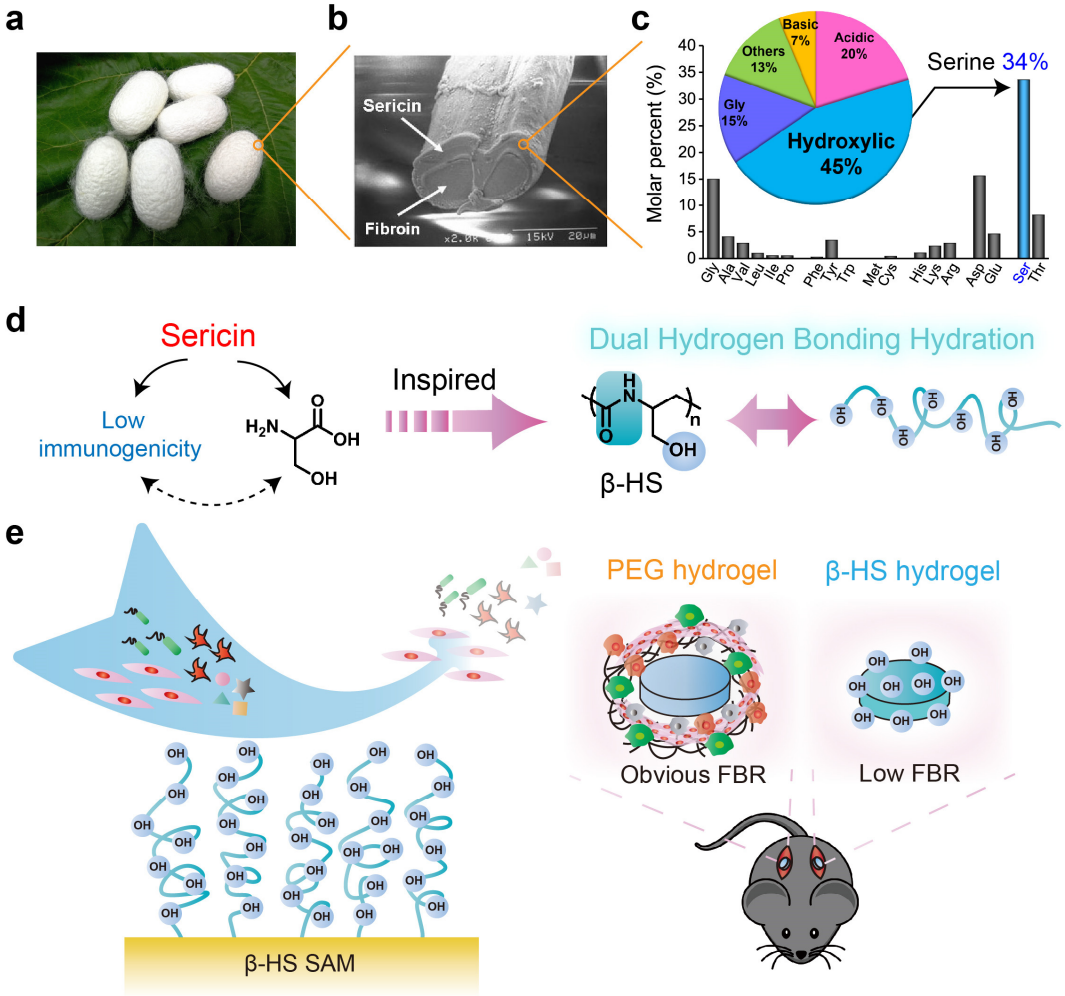

Figure 1. Design of silk sericin inspired β-HS with low fouling and low foreign-body response. (a) Silkworm cocoons of *Bombyx mori*. (b) SEM image of natural silk that contains sericin outside and fibroin inside (Image adapted with permission by Professor Norihisa Kato, Hiroshima University). (c) Amino acid component of sericin contains 45% hydroxylic amino acid including 34% serine, which is the most abundant amino acid in sericin. (d) The design of low fouling and low FBR β-HS composed of racemic β-homoserine that is inspired by the abundant serine within sericin. (e) β-HS materials effectively resist biofouling and foreign-body response.

Results and Discussion

Antifouling performance. Considering that FBR can be triggered by protein adsorption on material surfaces, we modified a gold surface by applying β-HS, which self-assembled into monolayers (β-HS SAMs) via the terminal thiol group. In our initial analyses, we used OEG6, with a terminal thiol group, as the negative control which have strong repulsive force and are considered one of the best material to resist biofouling,[12] and the known fouling dodecanethiol (C12-SH) as the positive control[13] (Figure S1). We synthesized heterochiral homopolymer β-HS with variable lengths (25, 40, 60, 95, and 145 repeating units) and with narrow dispersity (Đ = 1.03-1.18) (Figure S2 and Table S1). The O1s and N1s peaks and the element content increase in X-ray photoelectron spectroscopy (XPS) confirmed successful gold surface modification by β-HS (Figure S3 and Table S1). The film thickness of the β-HS SAM increased incrementally from 3.19 to 5.22 nm for β-HS comprising 25 to 145 repeating units (Figure S4). Whereas the surfaces modified with C12-SH and OEG6 had water contact angles of 111.2° and 26.6°, respectively, all of the β-HS-modified surfaces had water contact angles below 9°, reaching as low as 6° for the β-HS40 and β-HS60 (Figure S5 and Table S2).

Prescreening evaluation of protein adsorption on β-HS modified surfaces using a horseradish peroxidase-conjugated anti-IgG antibody as the test protein, indicated that all five of the tested β-HS SAMs efficiently resisted fouling, exhibiting less than 7% protein adsorption, with the best-performing β-HS40 and β-HS60 having only 2.2% protein adsorption, levels comparable to the excellent antifouling material OEG6 (2.2%

protein adsorption) (Figure S6). We continued to evaluate the antifouling properties of β-HS using SPR, a highly sensitive method for measuring surface protein adsorption.[2f] Specifically, we used β-HS40 modified sensor chips and three proteins: fibrinogen (Fg), lysozyme (Lyz), and bovine serum albumin (BSA) (Figure 2a-e and Table S3). We found Fg adsorption of ~487.6, ~0.8, and ~0.3 ng/cm^2 on control, OEG6, and β-HS surfaces respectively; Lyz adsorption of ~112.4, ~0.2, and ~0.2 ng/cm^2 on control, OEG6, and β-HS surfaces respectively; and BSA adsorption of ~78.4, ~0.5, and ~0.7 ng/cm^2 on control, OEG6, and β-HS surfaces respectively (Figure 2a-c). These results show that β-HS is a low protein fouling material offering comparable performance over OEG6 for the tested proteins.

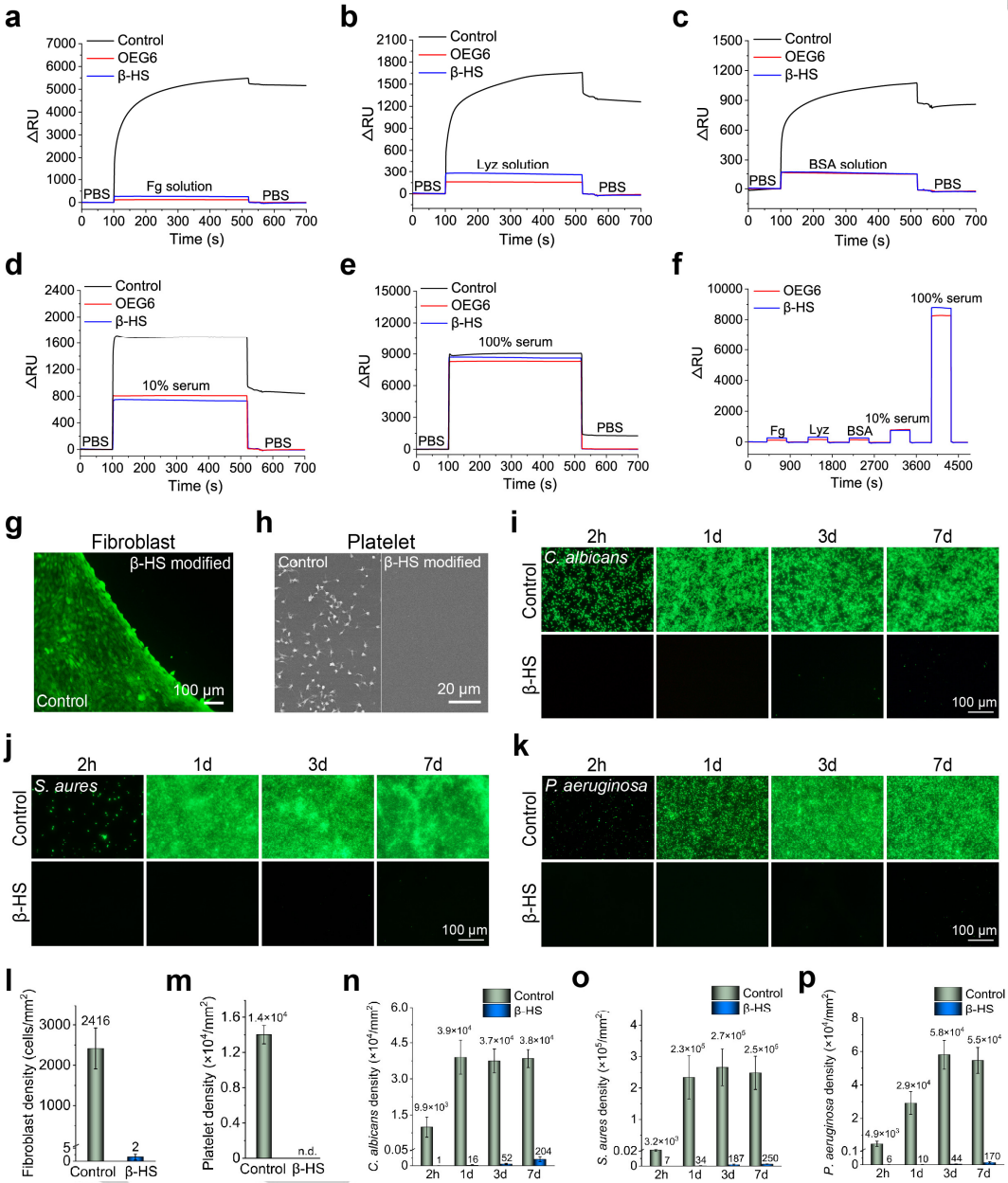

Figure 2. β-HS SAMs resist protein adsorption as well as cell, platelet, and microbe adhesion. SPR sensorgrams of protein solutions and serum flowing over the SAMs: (a) Fibrinogen (Fg, 340 kDa, pI 5.5) is a large, blood plasma protein that strongly adsorbs to hydrophobic surfaces that is commonly used as a model for sticky serum proteins. (b) Lysozyme (Lyz, 14 kDa, pI 11.0) is a small, positively charged protein often used as a model for electrostatic interactions of proteins with surfaces. (c) Bovine serum albumin (BSA, 66.4 kDa, pI 4.7) is the negatively charged and most abundant protein in the bovine plasma (~65%). (d) 10% serum. (e) 100% serum, which comprises a large diversity of proteins and other biomolecules. (f) Challenge of the antifouling surfaces with Fg, Lyz, BSA, 10% serum, and serum sequentially. Fluorescence micrographs and SEM images of surface biofouling from cell and microbes: (g) Fibroblast cell. (h) Platelet. (i) *C. albicans*. (j) *S. aureus*. (k) *P. aeruginosa*. Quantitative analysis on surface attachment of: (l) Fibroblast cell. (m) Platelet, n.d. represents not detected. (n) *C. albicans*. (o) *S. aureus*. (p) *P. aeruginosa*.

We subsequently increase the complexity of the challenge by exposing the surfaces to serum, which comprises a large diversity of proteins and other biomolecules. For 10% serum and 100% serum fluid treatments, the β-HS SAMs had protein adsorption of only ~1.4 and ~1.6 ng/cm^2, respectively, comparable to OEG6 (~0.5 and ~2.5 ng/cm^2) (Figure 2d, e and Table S2). Even upon sequentially challenge with Fg, Lyz, BSA, 10% serum, and 100% serum, the β-HS SAM had a total protein adsorption of only ~3.3 ng/cm^2 comparable to OEG6 (~2.5 ng/cm^2) (Figure 2f and Table S2). These protein adsorption results highlight the low fouling performance of the β-HS materials.

Cell, platelet, and microbe adhesion are also major types of biofouling known to trigger inflammation and FBR,[2h, 4e, 6e, 6g, 14] so we continued to examine the performance of β-HS to resist these challenges. The β-HS SAM efficiently resisted adhesion of fibroblast cells and platelets (Figure 2g-h, m), and also effectively resisted adhesion of fungi (*C. albicans*), Gram positive bacteria (*S. aureus*), and Gram negative bacteria (*P. aeruginosa*) for at least 7 days (Figure 2i-k, 2n-p). It's noteworthy that we observed no platelet adhesion on β-HS surface, which is comparable to the performance of two types of important antifouling materials, PEG and zwitterionic materials.[15]

Analysis of foreign-body response. To examine the FBR of β-HS, we prepared β-HS hydrogels for implantation into mice. We synthesized the gelation precursor polymer, β-HSDA, via an anionic ring-opening polymerization of trityl-protected β-lactam monomer HSβ, using acryloyl chloride and acrylamide pendent β-lactam (AAβ) as the co-initiator and C-terminal functional reagent respectively, followed by treatment with trifluoroacetic acid (TFA) in the presence of triethyl silane (Et_3SiH) to remove the trityl protection (Figure 3a). As characterized by GPC and ^1H NMR, β-HSDA has a polymer length of 11 repeating units and a dispersity of 1.27 (Figure S7). Hydrogels of β-HS and PEG were prepared via UV-initiated gelation of 25% (w/w) β-HSDA and PEGDA solutions respectively, using Irgacure 2959 as the photoinitiator. The water content of PEG and β-HS hydrogels was 74.5 ± 0.8% and 77.4 ± 1.1%, respectively.

The β-HS and PEG hydrogels were implanted subcutaneously in C57BL/6 mice, a genotype known to produce a strong fibrotic response similar to the FBR observed in human patients.[16] We evaluated the mice for inflammatory responses, acrophage density, and collagen density in tissues around the hydrogels at 1 week after implantation (Figure 3b). Hematoxylin and eosin (H&E) staining showed obvious inflammation around the PEG hydrogel, consistent with previous reports,[2j] yet observed a surprisingly low inflammatory response around the β-HS hydrogel. F4/80 staining revealed a mass of macrophage cells in tissues surrounding the PEG hydrogel, while a substantially lower density of macrophage cells was observed in tissues surrounding the β-HS hydrogel. Masson's trichrome staining showed a thick collagen layer surrounding the PEG hydrogel but no obvious collagen encapsulation surrounding the β-HS hydrogel.

After implantation over 4 weeks, the PEG hydrogels were encapsulated by a high density layer of avascular collagen; the surrounding tissue of the β-HS hydrogels had a very low density of collagen (Figure 3c, d). It is notable that a large amount of new blood vessels exhibiting red blood cells were found in tissues surrounding the β-HS but not PEG hydrogels, as shown in Masson's trichrome stained histology sections; this angiogenesis was also confirmed via CD31 staining of endothelial cells (Figure 3e). Specifically, the blood vessel densities in tissues surrounding the PEG and β-HS hydrogels were 22 and 148 vessels/mm^2, respectively (Figure 3f). The significant appearance of the blood vessel surrounding β-HS hydrogels is indicative of active mass transport between the host and the implanted material. We also evaluated the implanted hydrogels for their long-term performance at 3 months after implantation using Masson's trichrome stain and found that whereas the PEG hydrogels were encapsulated by a dense layer of collagen, the β-HS hydrogels still efficiently resisted FBR, showing no collagen encapsulation and open collagen structure, which facilitates the exchange of oxygen, nutrients and metabolites between the implant and the body (Figure 3g).

Antifouling and anti-FBR mechanism. We hypothesized that the low fouling and low FBR performance of β-HS results from strong hydration, so we performed molecular simulations to calculate the hydration free energy, radial distribution functions (RDFs), the number of hydrogen bonds, and the distance between proteins and the β-HS SAM surface; we also performed simulations for OEG6. Our study showed that the chirality has little effect on the simulation result and therefore we chose β-HS with the same chirality in each repeating unit for the simulation. The hydration free energies were −192 and −777 KJ/mol, respectively, for OEG6 and β-HS, indicating much stronger hydration of β-HS than OEG6 (Figure 4a). The RDFs result indicated that the OH-O_{water}, C=O-O_{water}, and N-O_{water} RDF profiles of β-HS all had peaks at r < 0.3 (Figure 4b), indicating the existence of hydrogen bonding interactions with water for both the hydroxyl groups of the β-HS side chains as well as for the amide groups of the backbone along the β-HS polymer chains. We termed the combination of these distinct hydrogen bonding interactions as "dual hydrogen bonding hydration". The sharp RDF peaks for OH-O_{water} and C=O-O_{water} indicate that the O atoms from both the multi-amide bondsin the backbone and from the hydroxyl groups in the side chain contribute significantly to the hydration. A snapshot of β-HS in aqueous solution indicates that the β-HS is surrounded by a hydration shell, and the hydrogen-bonding waters are located near both the backbone amide groups and the hydroxyl groups in the side chain (Figure 4c).

We also examined interfacial hydration by assessing the number of hydrogen bonds between the SAMs (β-HS or OEG6) and the water molecules (Figure 4d). Only the top layer OH groups of the OEG6 SAM form hydrogen bonds with water, and each of these has an average of only 0.56 hydrogen bonds. For β-HS SAM, we simulated the five closest units to the interface between SAM and water, and found that both the carbonyl and hydroxyl groups could form hydrogen bonds with water; the average number of the hydrogen bonds for the carbonyl and hydroxyl groups was 1.88 and 3.04, respectively. The total average hydrogen bond number of β-HS is 8.8 times higher than that of OEG6, supporting our proposed "dual hydrogen bonding hydration" as the likely source of β-HS's low fouling and low FBR. Further, the mean distance between lysozyme and the β-HS SAM surface was predicted at 3.57 nm, a value higher than the 2.53 nm for the OEG6 SAM, results again emphasizing the β-HS SAM's superior resistance to protein adsorption (Figure 4e, f). In addition to above simulation, the "dual hydrogen bonding hydration" hypothesis was also supported by the general conclusion from precedent studies in antifouling that antifouling property is strongly related to the surface hydration that is governed by the hydrogen bonding for uncharged hydrophilic polymers.[6f] Poly(N-hydroxyethyl acrylamide), having both an amide group and a hydroxyl group within the same subunit, also showed strong antifouling performance;[17] however, either oligoalanine or polyvinyl alcohol that has only the amide group or the hydroxyl group showed compromised antifouling properties.[6c, 18] All these supported the hypothesis that "dual hydrogen bonding hydration" is the key to the antifouling and anti-FBR performance of β-HS polymers.

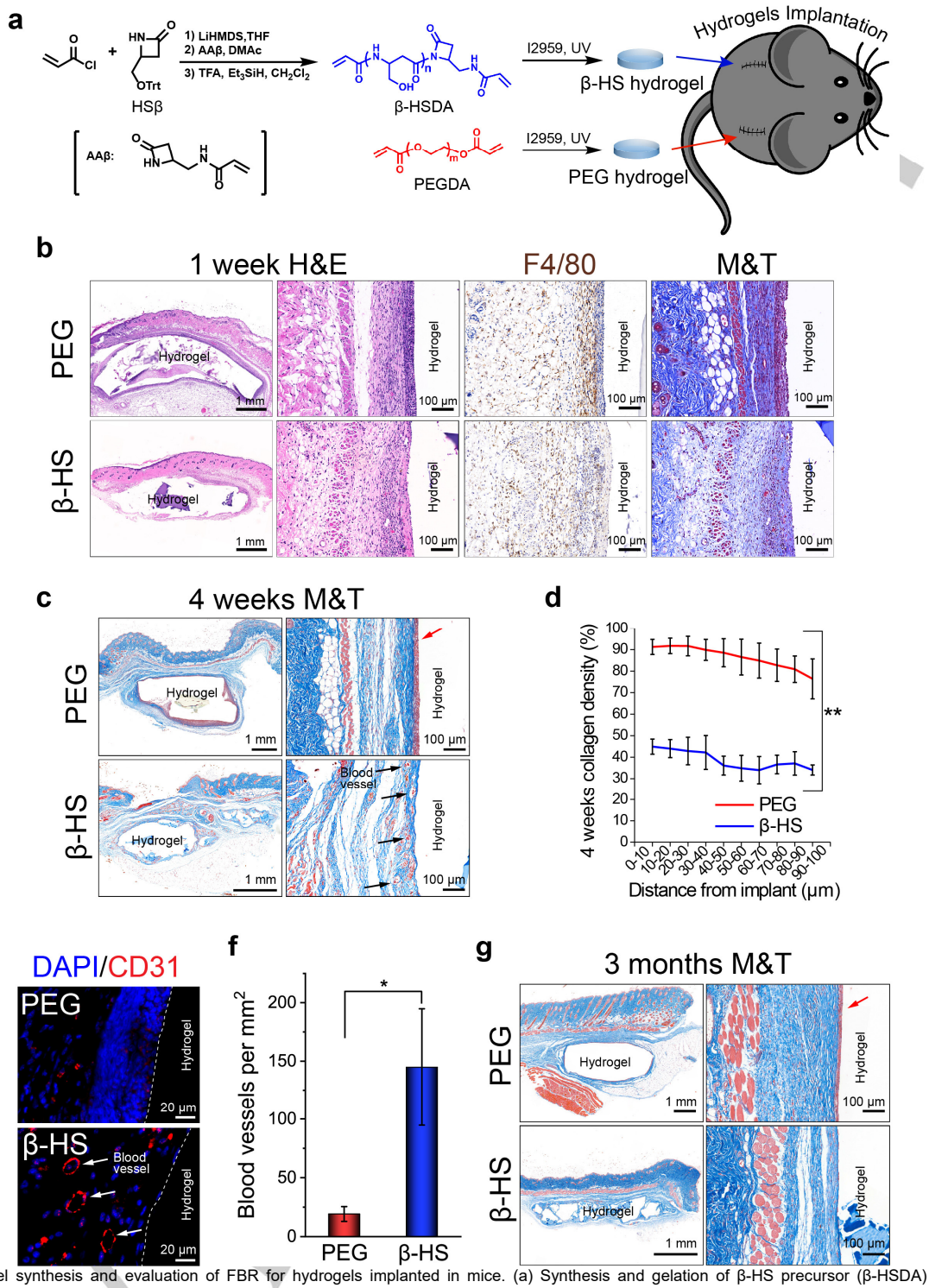

Figure 3. Hydrogel synthesis and evaluation of FBR for hydrogels implanted in mice. (a) Synthesis and gelation of β-HS precursor (β-HSDA) polymers to generate hydrogels, which were implanted subcutaneously into the backs of C57BL/6 mice. (b) Histological analysis after 1 week of implantation: H&E, hematoxylin & eosin, nuclei were stained blue and the cell cytoplasm was stained pink; F4/80, macrophage marker stained in brown; M&T, Masson's trichrome, collagen was stained in blue, nuclei was stained in black, and the cytoplasm was stained in red to evaluate collagen deposition. (c) Masson's trichrome staining to evaluate collagen encapsulation (red arrows) and visualized blood vessels (black arrows) after implantation for 4 weeks. (d) Collagen density within 100 μm (at 10-μm steps) of the hydrogel-tissue interface after implantation for 4 weeks. (e) Visualization of blood vessels (red fluorescence), via immune-staining with the endothelial cells marker CD31, in tissues surrounding hydrogels after 4 weeks of implantation. (f) quantified blood vessel density in tissues surrounding hydrogels after 4 weeks of implantation. (g) Masson's trichrome staining to evaluate collagen encapsulation (red arrows) after implantation for 3 months. *P<0.01; **P<0.001, using one-way ANOVA with Tukey's post-test.

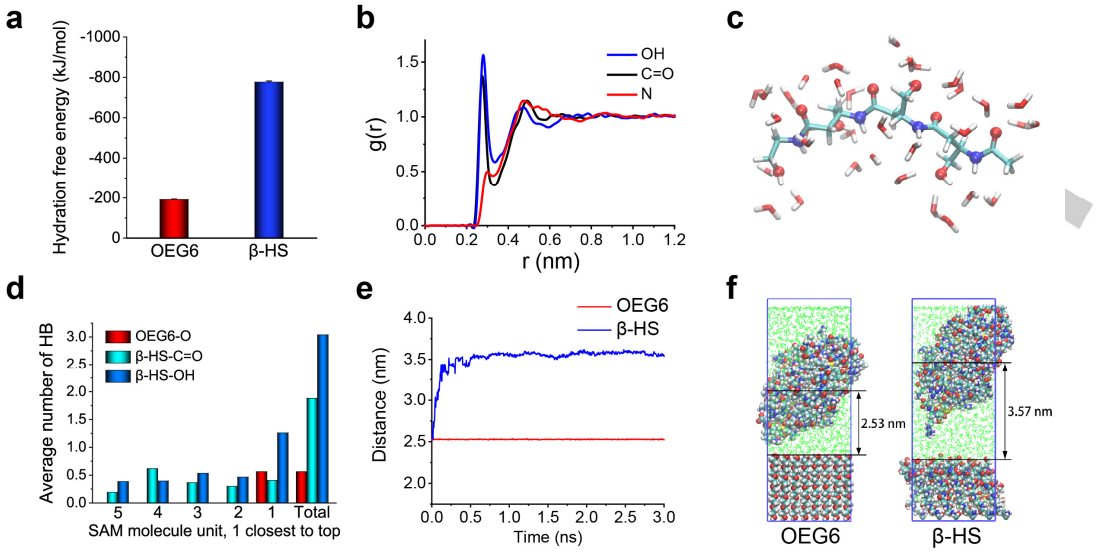

Figure 4. Molecular simulations exploring the mechanisms underlying β-HS's strong antifouling and anti-FBR performance. (a) Hydration free energy of OEG6 and β-HS. (b) Radial distribution functions between water molecules and the atoms of β-HS (the oxygen atoms in the hydroxyl and carbonyl groups, respectively, and the nitrogen atom). (c) Snapshot of β-HS in aqueous solution, the hydrogen bonding waters near both the backbone amide groups and the side chain hydroxyl groups. (d) The average number of hydrogen bonds (HB) between the SAM and water molecules. (e) Distance between the protein (mass center) and the SAM surface of OEG6 and β-HS. (f) Snapshot of lysozyme on the OEG6 and β-HS SAM, with explicit water molecules.

Conclusion

In summary, we designed and synthesized β-HS materials, inspired by silk sericin that has low immunogenicity. β-HS materials can resist adsorption of diverse proteins, as well as adhesion of cells, platelets, bacteria, and fungi, all of which are widely encountered in implantable biomaterials and may trigger FBR. Furthermore, the β-HS hydrogel displays low FBR as shown with negligible inflammatory responses, substantially and significantly reduced collagen encapsulation, and substantially increased density of blood vessels in surrounding tissues compared to control PEG hydrogel after the hydrogels were implanted in the mice. Molecular simulations indicated that 'dual hydrogen bonding hydration' between β-HS and water can account for its low fouling and low FBR. The superior performance of β-HS in antifouling and anti-FBR implies its potential application of β-HS in implanted biomaterials and biomedical devices.

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Keywords: Foreign-body response • silk-inspired • poly-β-homoserine • fouling • dual hydrogen bonding hydration

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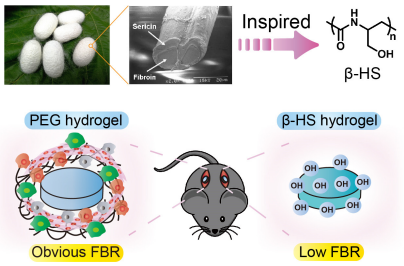
Entry for the Table of Contents



The low immunogenic silk sericin has high content of serine, which inspired us to explore poly-β-homoserine (β-HS) as a new class of low foreign-body response (FBR) material. β-HS showed excellent antifouling property and substantially lower FBR in implanted hydrogels than did PEG, suggesting β-HS as promising materials to address the formidable and long-lasting challenge of FBR that are associated with implants.