Bioinspired Materials

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Mussel-Inspired Dendritic Polymers as Universal Multifunctional Coatings**

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Dedicated to Professor Rolf Mülhaupt on the occasion of his 60th birthday

Abstract: *A rapid and universal approach for multifunctional material coatings was developed based on a mussel-inspired dendritic polymer. This new kind of polymer mimics not only the functional groups of mussel foot proteins (mfps) but also their molecular weight and molecular structure. The large number of catechol and amine groups set the basis for heteromultivalent anchoring and crosslinking. The molecular weight reaches 10 kDa, which is similar to the most adhesive mussel foot protein mfp-5. Also, the dendritic structure exposes its functional groups on the surface like the folded proteins. As a result, a very stable coating can be prepared on virtually any type of material surface within 10 min by a simple dip-coating method, which is as fast as the formation of mussel byssal threads in nature.*

Surface modification of solid materials plays an increasingly important role in modern physical, chemical, biological, and materials science.[1,2] The common methods for surface modification, such as self-assembled monolayer (SAM),[3] irradiation,[4] layer-by-layer assembly,[5] and Langmuir–Blodgett deposition,[6] have worked effectively, but still cannot modify a broad range of material surfaces. Mussel-inspired surface chemistry is one of the most remarkable methods to solve this problem. Dopamine and its derivatives, which mimic the composition of mussel foot proteins (mfps), can form surface-adherent films on virtually any material surface.[7–9] Mussels adhere to solid surfaces with mfp-rich byssus as the holdfast. The formation of mussel byssal threads only needs approximately 3–10 min.[10] Byssus have a set of specialized proteins including mfp-1, which is a key protein to form the byssal cuticle and is usually crosslinked by Fe^{3+} ions.[11] Mfp-5, the most adhesive protein, is localized near the interface between the plaques and the substrates.[12] These proteins contribute greatly to byssus' rapid solidification and adhesion. Both proteins contain a large quantify of 3,4-dihydroxyphenyl-L-alanine (DOPA) 15 mol% and 28 mol%, respectively, as well as a high amount of lysine.[13] The catechol group in DOPA forms strong covalent or non-covalent interactions with substrates for adhesion.[14] In the meantime, they can be coordinatively crosslinked with Fe^{3+} ions or covalently crosslinked by themselves or amine groups in lysines, which leads to solidification of the byssus.[15] However, a dopamine coating takes very long time to form a thick and dense film.[7] Therefore, it is still necessary to identify a better mimic of the mfps and further accelerate the surface coating.

Herein we report on a heteromultivalent catechol- and amine-functionalized dendritic polymer that mimics not only the functional groups of mfp-1 and mfp-5 but also their molecular weight and molecular structure, for a rapid and universal surface coating by both covalent and coordinative crosslinking (Scheme 1). Although many catecholic polymers have already been developed for surface modification, the majority of them are only linear polymers with a low density of catechol groups.[16] Individually catechol and amine groups fail to induce significant oxidative polymerization. Both catechol and amine functional groups must be presented to achieve universal and stable coatings.[17] Furthermore, intra-coating interactions have been less researched and rapid coatings are still elusive. To solve this problem, dendritic polyglycerol (dPG), which has a highly branched architecture, exhibits a relatively distinct "interior", and exposes functional groups on its surface, just like folded proteins do,[18] was used as a scaffold for multivalent anchoring and crosslinking.[19,20] The hydroxy groups present on the dPG scaffold were converted into amine groups, 40% of them were further functionalized by catecholic groups. The large amount of remaining amine groups enhanced the intra-layer interaction of the coatings, and afforded more functional groups for secondary modifications of the coatings. In polydopamine, most amine groups form indole rings or couple with quinone groups by Michael addition and Schiff's base reactions, thus becoming inactive.[21,22] The average molecular weight (M_n) of our mussel-inspired dPG (MI-dPG) is about 10 kDa, which is in the same range as the mfp-5 (ca. 9 kDa).[23] Because of the exposed multivalent functional groups and a suitable initial

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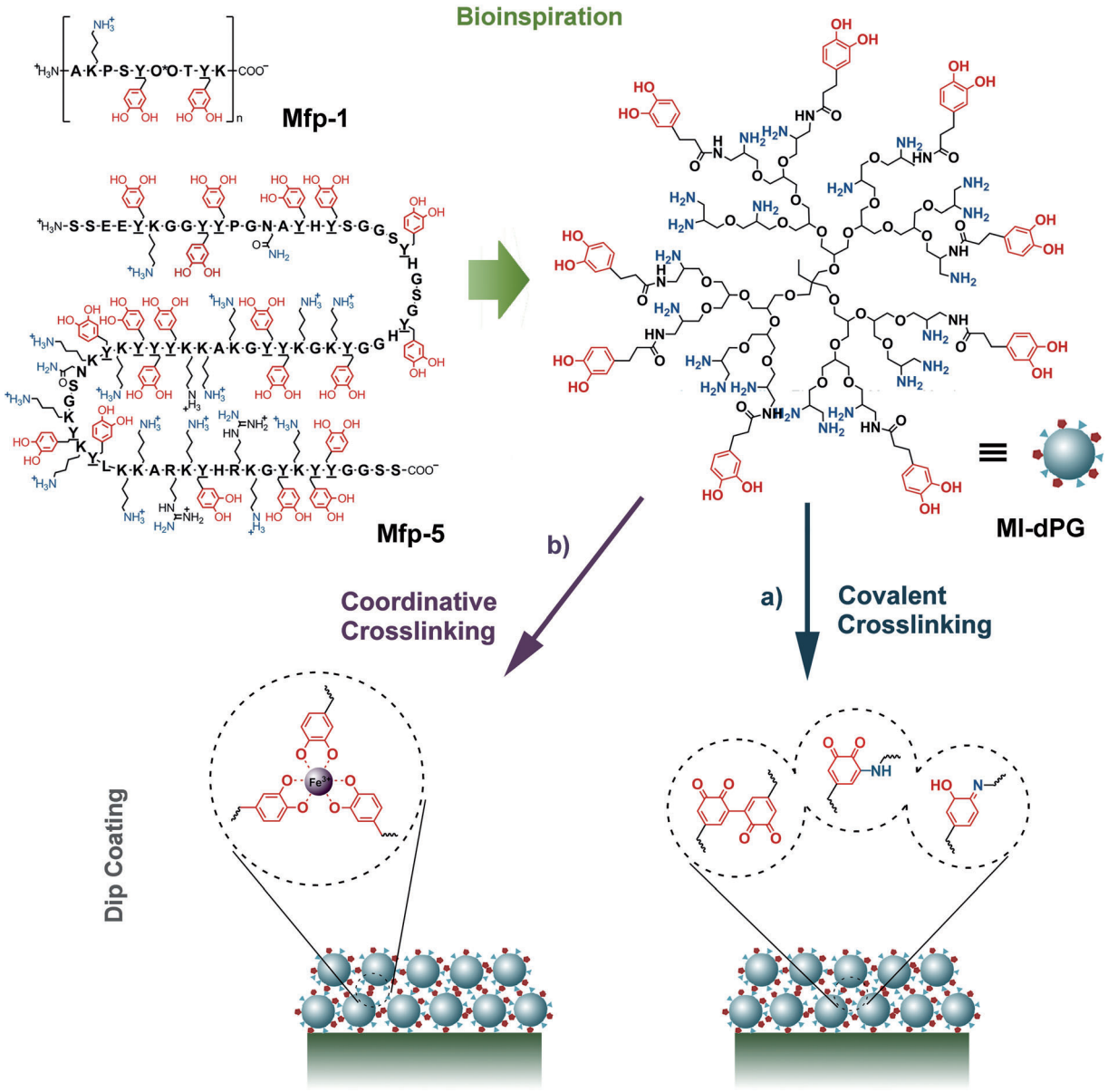

Scheme 1. Top left: Structural formula of the mussel foot proteins mfp-1 and mfp-5 showing the alternating amino acids that contain amine (blue) and catechol (red) units in their side chains.[12] Top right: the chemical mimicry of synthesized mussel-inspired dendritic polyglycerol (MI-dPG). Bottom: the covalent (postulated structure) and coordinative crosslinking for universal surface coatings. a) 0.1 mM MI-dPG in MeOH solution with 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer (4v/1v) at pH 8.5; b) 0.1 mM MI-dPG in MeOH solution with 0.54 mg mL^{-1} $FeCl_3$ aqueous solution (4v/1v, catechol:Fe^{3+} ≈ 6:1)

molecular weight, the MI-dPG can form a highly stable coating on virtually all types of material surfaces within 10 min or a micrometer scale coating in just hours by polydopamine-type covalent crosslinking. Furthermore, a colorless mfp-1 type Fe^{3+} coordinatively crosslinked coating has been developed based on MI-dPG (Scheme 1).

Covalently crosslinked coatings were prepared by oxidizing catechols to quinones in a weak basic buffer near pH 8.5. Though the mechanism of this crosslinking is still debated, it is believed that covalent bonding is the main interaction, hydrogen bonding and π-stacking are subsidiary interactions.[21,22,24,25] As analyzed by UV/Vis spectroscopy (Figure S1, Supporting Information), catechol groups can be immediately oxidized to quinones and subsequently crosslinked with each other or amine groups by Michael addition or Schiff's base reactions[15,23] under weak basic conditions. The crosslinking process was monitored by IR spectroscopy (Figure S2). The band for the deformational vibration of O–H at about 1360 cm^{-1} dramatically decreased in intensity after the covalent crosslinking of MI-dPG, indicating that the catechols may be oxidized to quinones. This assumption is supported by the strengthened signal at 1645 cm^{-1} and weakened signal at 1602 cm^{-1}. The 1645 cm^{-1} peak is a characteristic signal for quinines. The 1602 cm^{-1} peak can be explained by the valence vibration (C=C) of the phenyl of the catechol groups. The weakened bands of the isolated H

atom on the aryl ring at 912 cm^{-1} and the *ortho*-H atom on the aryl ring at 845 cm^{-1} further indicate the crosslinking of the catechol moieties. Additionally, the change of the substitution pattern of the aromatic systems was also shown by the signal between 729 and 814 cm^{-1}. Owing to the strong crosslinking, MI-dPG molecules rapidly aggregated in the solution (Figure S3) and spontaneously deposited on the solid surfaces, including complex surface shapes (Figure S4). The MI-dPG molecules can directly anchor to the substrate surface, then other molecules can be immobilized to the first layer of anchored molecules by crosslinking as a 'grafting from' approach. Meanwhile, the crosslinked aggregates can also anchor to the surface via a 'grafting to' approach. The thickness of the MI-dPG films rapidly increased during incubation and reached 60 nm after 10 min and a maximum value of 3.4 μm after 4 h on silica surfaces (Figure 1a). This growth is much faster than the crosslinking of dopamine coatings under basic and even oxidative conditions.[7,26] It took 24 h to obtain a 50 nm dopamine coating under similar basic conditions,[7] and 2 h for a 70 nm dopamine coating in the more rigorous oxidative condition.[26]

In the case of coordinatively crosslinked coatings, MI-dPGs can be crosslinked by metal ions, such as Fe^{3+}, which prevents the rapid oxidation of catechols and forms a tris-catechol Fe^{3+} complex at pH 10.[27,28] About 1:6 equivalents of Fe^{3+} to catechol groups in MI-dPG was employed to induce the crosslinking of the coatings. Thus half of the catechol groups can form the complex for crosslinking. The remaining half can still work as anchors. As a result of the fewer crosslinking groups and related weak crosslinking, the thickness of the coordination-based coatings only reached about 10 nm after 12 h of incubation (Figure 1b). Meanwhile, the free catechols inside the coatings could be slowly oxidized to cause the covalent crosslinking. Thus these coordinatively crosslinked coatings were stable in a solution of ethylenediaminetetraacetic acid (EDTA) (Figure S5), which was able to decompose the catechol Fe^{3+} complex in solution.[27]

The static water contact angles of both covalently and coordinatively crosslinked MI-dPG-coated silica wafers decreased with the incubation time, which is relevant for the thickness of the coatings (Figure S6). Similar to the thickness variation, the contact angles also reached the equilibrium value. Various substrates that included metals (Al and TiO_2), inorganic non-metals (SiO_2 and glass), and polymers (polytetrafluoroethene (PTFE), polystyrene (PS)) were tested in the coating experiments (Figure 1c). Under equilibrium conditions, the water contact angles on these substrates reached to 20–30° for covalently crosslinked coatings and were also dramatically altered for the coordinatively crosslinked coatings. This indicates that the original wetting property of these substrates was completely changed by the MI-dPG coatings. Moreover, the contact angles of both covalently and coordinatively crosslinked MI-dPG coated PTFE were hardly affected by incubating in PBS buffer for 1 month (Figure S7). This demonstrated the coatings' high stability under physiological conditions.

X-ray photoelectron spectroscopy (XPS) analysis of four kinds of surfaces (PS, PTFE, glass, and TiO_2), which were treated with covalently crosslinked coatings for 10 min,

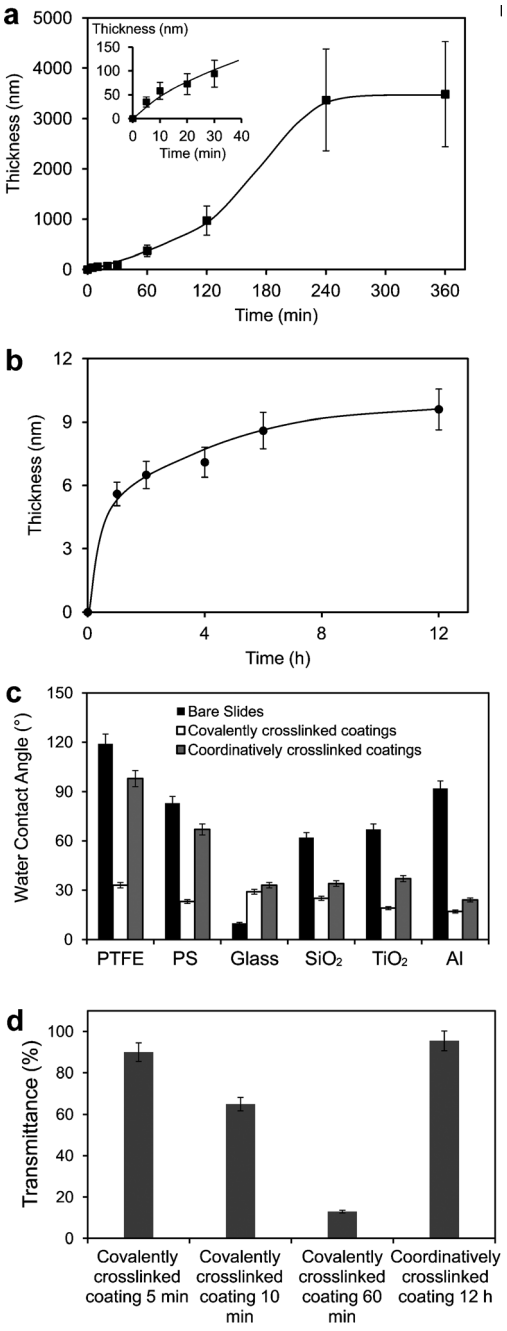

Figure 1. Time-dependent thickness of the a) covalently and b) coordinatively crosslinked MI-dPG coatings on silica surfaces. c) Average static water-contact angle of the covalently (4 h) and coordinatively (12 h) crosslinked MI-dPG coated surfaces. d) Optical transmittance (wavelength 350–1000 nm) of the covalently and coordinatively crosslinked coating.

indicated a dramatic change of signals for the respective substrates compared to the bare surfaces (Table S1). The C, N, and O compositions of the coated surfaces changed to the values of the bulk MI-dPGs. This change suggests that the composition of the MI-dPG coatings is independent of the substrate. The coordinatively crosslinked coatings on PS surfaces exhibited nearby the same signal changes for C, N, and O as the covalently crosslinked coatings, but the additional Fe signal was detected.

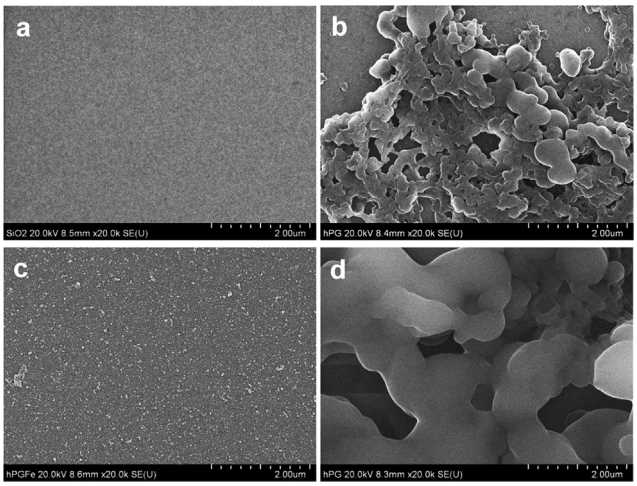

Figure 2. Scanning electron microscopy (SEM) images of a) the bare silica surface and the silica coated by covalently crosslinked MI-dPG for b) 10 min, d) 60 min, and c) coordinatively crosslinked MI-dPG for 12 h (magnification 20000×).

The surface morphology for the two types of coatings was observed by scanning electron microscopy (SEM). As shown in Figure 2, the morphology of the silica surface was completely altered to a rough structure by the MI-dPG coatings, which confirms the hypothesis that the mussel-inspired coatings were formed by crosslinked aggregates. Large aggregates could be observed on the covalently crosslinked coatings, and their size increased to the micrometer scale over time. Much smaller aggregates were observed on the coordinatively crosslinked coatings (The high-resolution atomic force microscopy (AFM) images are shown in Figure S8). Their size was still observed in the nanometer range after 12 h' coating time. Note that a colorless coating was achieved by coordinative crosslinking (Figure 1 d), owing to weak aggregation and low thickness. Only a very few material-independent colorless coatings (for example, polyphenols and a mixture of 2-bromoisobutyryl-substituted dopamine and dopamine) have been reported.[29,30] The transmittance of the coordinatively crosslinked coatings reached about 97% after 12 h of coating time. For comparison, the transmittance of the covalent crosslinked coatings already decreased to 90% after 5 min of coating and quickly decreased to 68% after 10 min. After 60 min coating time the transmittance reached only 12%.

MI-dPG coatings can be used as a universal modifiable platform for various purposes. Functional molecules can be added to the surface of the coatings or to the MI-dPG molecules for a one-step coating (Figure S9). Besides coupling thiol- or amine-containing molecules to catechol groups,[7,31] other functional groups can be coupled to the plenty of remaining amine groups in the coatings. Furthermore, the physical characteristics of the coatings can be adjusted by the surface morphology which is controllable by the size of the covalently crosslinked aggregates.

A hierarchical surface structure with two-tier (micro and nano) roughness such as the micromorphology of a lotus leaf shows superhydrophilic or superhydrophobic properties depending on their surface functionality.[32] Polydopamine coatings must be combined with micro- and nano-metal particles to achieve these properties,[33] whereas the covalent crosslinked MI-dPGs can directly construct the lotus-like coatings with hierarchical roughness. Therefore, bare glass surfaces were alternately incubated in fresh MI-dPG solution for 60 then 10 min. Initially, several micrometer-sized aggregated clusters (Figure 2 d) were formed on the substrates. In the 10 min step, many nanometer-sized aggregated particles (Figure 2 b) were formed on top of the micrometer-scale aggregates which resulted in a hierarchically rough surface (Figure 3). The apparent water contact angle decreased to

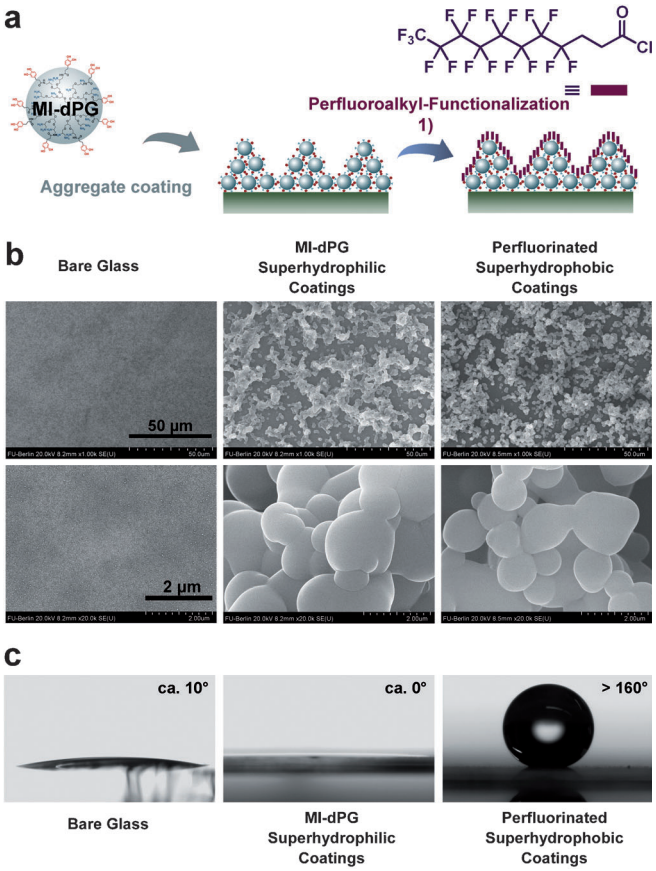

Figure 3. a) Scheme of the MI-dPG constructed superhydrophilic or perfluoroalkyl-functionalized superhydrophobic coatings. 1) 1 mg mL^{-1} heptadecafluoroundecanoyl chloride with 10 equiv of triethylamine dissolved in diethyl ether. b) The surface morphology of the bare glass and the superhydrophilic and superhydrophobic coatings on glass, upper: magnification 1000×, lower: 20000×. c) The related static water contact angle of the surfaces that shown above.

near 0° for a superhydrophilic surface. After perfluoroalkyl-functionalization, the surface morphology was not changed, however, the water contact angle increased to about 166.5° and the surface energy reached about 0.5 mN m^{-1}, which is in the range of a superhydrophobic surface (Figure 3 and Table S2).[34] Furthermore, the contact angle hysteresis was only 6.6°. Because of these properties, this coating, which has been inspired by both nature's water-repellent lotus leaf and adhesive mussel foot proteins, can be potentially applied as a new self-cleaning surface.

Collagen A, which improves the adhesion of endothelial cells on surfaces,[35] can be covalently bound to the MI-dPG coatings by both amide and amine-catechol couplings. A quartz crystal microbalance (QCM) with dissipation monitoring was employed to determine the amount of collagen A that immobilized on the MI-dPG coatings. About 6.9 and 7.0 $\mu g\,cm^{-2}$ collagen A was immobilized on the covalent and the coordinative coatings, respectively, after washing by sodium dodecyl sulfate (SDS) 1% (w/w) aqueous solution (Figure S10). The coupling reagents *N*-hydroxysuccinimide (NHS) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) may cause slight crosslinking of the proteins, but as the experimental results show the effectivity of the proteins was not hindered. For comparison, quite a small amount of collagen A (0.1 $\mu g\,cm^{-2}$) was adsorbed on the bare polystyrene surfaces, after washing by SDS 1% (w/w) solution.

After culturing human umbilical-vein endothelial cells (HUVECs) for 3 days (Figure 4 and Figure S11), only a few cells could be observed on bare-tissue culture polystyrene (TCPS) surfaces (11.2 ± 4.8 cells mm^{-2}). In contrast, a large number of cells had been attached to both the collagen A immobilized covalently crosslinked and coordinatively crosslinked MI-dPG coated TCPS surfaces (101.2 ± 22.8 and 62.0 ± 17.2 cells mm^{-2}, respectively) with a regularly spreading. Standard HUVEC culture dishes, that is, collagen A coated TCPS dishes, were used for comparison. After three days of culturing, there were fewer cells observed (45.6 ± 13.2 mm^2), because the adsorbed collagen A was not stable on the TCPS in cell culture media and therefore could be washed away by rinsing with buffer. Only 12.0 ± 6.4 mm^2 of cells could be counted from the rinsed dishes, which was similar for the cells on the bare TCPS. MI-dPG coatings without immobilization of collagen A also improved the attachment of HUVEC (33.2 ± 7.2 and 30.0 ± 9.6 mm^2 of cells on covalently and coordinatively crosslinked coatings, respectively) but not so significant. This demonstrates that MI-dPG coating has as good cytocompatibility as already shown for polydopamine coatings.[36]

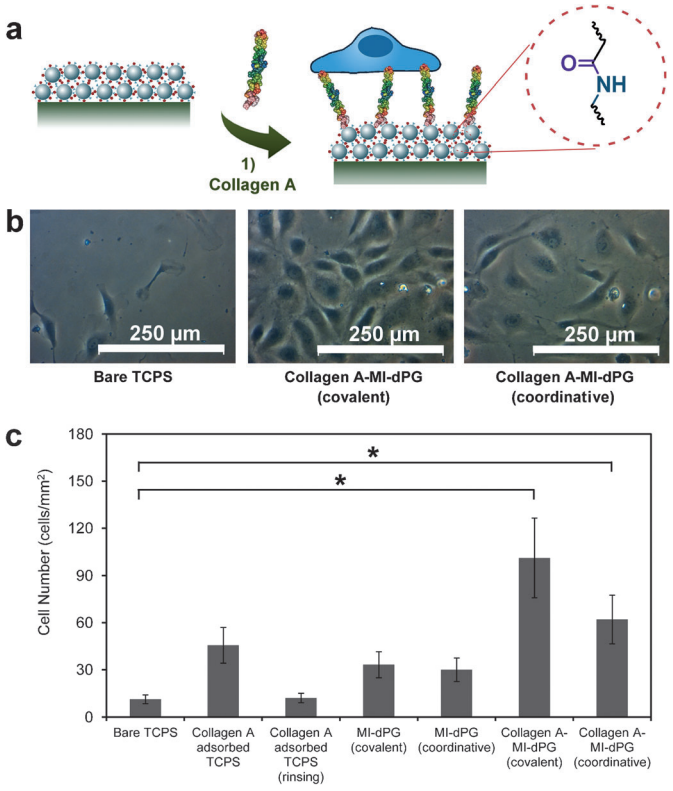

Figure 4. a) Scheme of post-functionalization with collagen Abny amide bonding to MI-dPG coatings. 1) 0.1 $mg\,mL^{-1}$ collagen A, 0.01 $mg\,mL^{-1}$ *N*-hydroxysuccinimide (NHS), and 0.01 $mg\,mL^{-1}$ 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in PBS buffer for 4 h. b) Human umbilical-vein endothelial cell (HUVEC) adhesion on bare and collagen A modified tissue-culture polystyrene (TCPS) surfaces after 3 days culturing. c) HUVEC numbers on bare and different functionalized TCPS surfaces after 3 days culturing (*: $p < 0.0001$).

In summary, we developed a new mussel-inspired dendritic polyglycerol (MI-dPG) that effectively mimics mussel foot proteins with regard to their functional groups, molecular weight, and molecular structure. Compared to the first generation of mussel-inspired coating material, polydopamine, this new MI-dPG benefits from its heteromultivalent character and molecular weight, which provide a strong adhesive power. It can rapidly adhere on virtually all kinds of material surfaces and form a thick film by covalent crosslinking within 10 min, which is close to the time of byssal thread formation in nature. Meanwhile, ion-based coordinative crosslinking of MI-dPG generated thin and colorless coatings. Until now only polyphenol tannic acid achieved similar coatings.[37] Furthermore, the multiple active groups in the coatings and the controllable surface morphology could induce many kinds of secondary modification for diverse functional applications.

Besides catecholic surface chemistry, mussels employ Mfp-6 to reduce quinones back to catechols to adjust the binding and crosslinking,[38] and Mfp-3 "slow" (Mfp-3s) to enhance the hydrophobic interaction because of the facile autoxidation of catechols.[39] The adhesion of mussel byssus, however, is more complicated than a simple catechol-mediated recipe. Therefore, the biomimicry of mussels will continue to be a source of inspiration.

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