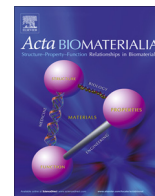




Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actabiomat

Full length article

Hydrolysis-controlled protein adsorption and antifouling behaviors of mixed charged self-assembled monolayer: A molecular simulation study [☆]

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ARTICLE INFO

Article history:

Received 20 November 2015
 Received in revised form 20 March 2016
 Accepted 28 April 2016
 Available online xxx

Keywords:

Molecular simulation
 Protein adsorption
 Self-assembled monolayer
 Antifouling
 Antimicrobial

ABSTRACT

Understanding the mechanism of the antimicrobial and antifouling properties of mixed charged materials is of great significance. The interactions between human gamma fibrinogen (γ Fg) and mixed carboxylic methyl ether-terminated (COOCH_3^-) and trimethylamino-terminated ($\text{N}(\text{CH}_3)_3^+$) SAMs and the influence of hydrolysis were studied by molecular simulations. After hydrolysis, the mixed SAMs exhibit behaviors from antimicrobial to antifouling, since the COOCH_3 -thiols were translated into carboxylic acid (COO^-) terminated thiols, which carried a net charge of -1 e. Simulation results showed that the main differences between $\text{COOCH}_3^-/\text{N}(\text{CH}_3)_3^+$ -SAM and $\text{COO}^-/\text{N}(\text{CH}_3)_3^+$ -SAM are the charged property and the hydration layer above the surface. γ Fg could stably adsorb on the positively-charged $\text{COOCH}_3^-/\text{N}(\text{CH}_3)_3^+$ -SAM. The adsorption behavior is mainly induced by the strong electrostatic attraction. There is a single hydration layer bound to the surface, which is related to the $\text{N}(\text{CH}_3)_3^+$ groups. The van der Waals repulsion between γ Fg and the single hydration layer are not strong enough to compensate the strong electrostatic attraction. After hydrolysis, the positively-charged SAM was transferred to a neutral mixed charged surface, the electrostatic attraction between γ Fg and the surface disappears. Meanwhile, the SAM surface is covered by double hydration layers, which is induced by the $\text{N}(\text{CH}_3)_3^+$ and COO^- groups; water molecules around COO^- groups are obviously denser than that around $\text{N}(\text{CH}_3)_3^+$ groups. With the combined contribution from double hydration layers and the vanishment of electrostatic attraction, γ Fg is forced to desorb from the surface. After hydrolysis, the internal structure of mixed SAM appears more ordered due to the electrostatic interactions between charged groups on the top of SAMs.

Statement of Significance

The antimicrobial and antifouling materials are of great importance in many biological applications. The strong hydration property of surfaces and the interactions between proteins and surfaces play a key role in resisting protein adsorption. The mixed SAMs, constructed from a 1:1 combination of COOCH_3^- and $\text{N}(\text{CH}_3)_3^+$ -terminated thiols, can induce protein adsorption mainly through the electrostatic interaction. When the COOCH_3^- -terminated thiols were hydrolyzed to negatively charged COO^- -terminated thiols, the mixed-charged SAMs switched from antimicrobial to antifouling. Due to the strong hydration property of the mixed charged SAMs, the adsorbed γ Fg moved away from the surface. Understanding the interactions between protein and mixed-charged SAMs in the atomistic level is important for the practical design and development of new antimicrobial and antifouling materials.

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1. Introduction

Bacterial cells adhesion and biofilms formed by the nonspecific protein adsorption on implanted biomaterials or wound dressing materials usually cause infections, which is a major problem in clinical surgeries and implantation operations [1]. Therefore, inte-

[☆] Part of the Special Issue on Zwitterionic Materials, organized by Professors Shaoyi Jiang, Kazuhiko Ishihara, and Jian Ji

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grating the antifouling and antibacterial properties into one material is of great practical significance in biological applications.

Recently, it is realized that the zwitterionic materials [1–7] (e.g., carboxylic betaine, sulfonic betaine etc.) can well prevent the surface from nonspecific protein adsorption. A distinct characteristic of zwitterionic molecule is that it contains two counter-charged groups and maintains overall charge neutrality. A series of charged groups (e.g., carboxylate, sulfonate, or phosphate as anionic groups, and quaternary ammonium, phosphonium, pyridinium, or imidazolium as cationic groups) can be used to assemble zwitterionic molecules [1]. In addition, combination of oppositely charged groups into one single molecule or different polymer side-chains (called mixed-charge) is another way to design antifouling materials [8–11]. It is shown in previous works that an antifouling surface can be achieved when the surface contains a nanometer-scale homogenous mixture of balanced charged groups not only from zwitterionic but also mixed positively and negatively charged moieties from different groups, such as mixed charged self-assembled monolayers (SAMs) [12,13], polymer coatings, or hydrogels [7]. Mixed charged polymer brushes or hydrogels with uniform charge distribution have been applied to a broad range of biomaterials, such as antifouling materials [8,14–16], platelet compatible materials [10,17–20], wound dressing materials [21] and responsive antibacterial materials [22]. Chen et al. [23] studied the ultra-low-fouling natural peptides composed of certain negatively and positively charged residues such as glutamic acid or aspartic acid and lysine, in the form of either alternatively or randomly mixed-charge. They found that natural peptides developed by uniformly mixed charges exhibited high resistance to nonspecific protein adsorption comparable with what is achieved by poly(ethylene glycol) (PEG)-based materials. Liu et al. [20] found that gold nanoparticles, modified by mixed charged zwitterionic SAMs, can be stable at the pH of blood and normal tissues but aggregate instantly in response to the acidic extracellular pH of solid tumors. Jhong et al. [21] suggested that the mixed charged copolymers with a perfect balance of positive and negative moieties represent the latest generation of biomaterials for wound dressing.

Poly(carboxybetaine), which is different from other betaines, has a unique aspect that it can be prepared in hydrolyzable form, such as poly(carboxybetaine) esters. These poly(carboxybetaine) esters, which carry positive charges, can easily interact with negatively charged protein, DNA and bacteria. Upon hydrolysis, the properties of polymer converted to nontoxic and ultralow-fouling [7,24]. Cheng et al. [24] reported a new switchable polymer surface coating, which combined the advantages of both antifouling and cationic antimicrobial materials. They illustrated that poly-(N,N-dimethyl-N-(ethoxycarbonylmethyl)-N-[2'-(methacryloyloxy)ethyl]-ammonium bromide) on a surface could kill greater than 99.9% of *Escherichia coli* K12 in one hour and 98% of the dead bacterial cells could be released when the cationic derivatives were hydrolyzed to antifouling zwitterionic polymers. Upon hydrolysis, the antimicrobial cationic poly-carboxy betaine ester switched to ultralow-fouling zwitterionic poly-carboxy betaine. Then 98% of the killed bacteria cells were released [7,25]. Inspired by these works, we chose the mixed carboxylic methyl ether-terminated and trimethylamino-terminated SAMs as a model surface to investigate the interactions between proteins and mixed charged SAMs. We also would like to check the influence of hydrolysis reaction.

Although some experimental studies [8,10,18–21] were focused on the zwitterionic materials, the inside mechanism was not thoroughly understood yet. Molecular simulation, as a tool to investigate the atom-level information, was widely used in the protein-surface interaction study [26–34]. Ishihara et al. [35] indicated that when the free water fraction on the phospholipid polymer surface was kept at a higher level, proteins could contact the surface reversibly, without significant conformational change. Feng

et al. [36] pointed out that the main determinant of the protein resistance of surface was the 'water barrier layer' resulting from their hydrophilic character. Zheng et al. [37,38] reported in their works that the protein resistant property of oligo(ethylene glycol) (OEG) SAM was mainly induced by the tightly bound water molecules around OEG chains. He et al. [39] studied the interaction between lysozyme and phosphorylcholine-terminated SAMs by molecular simulations. They found that the interfacial water molecules above the surface played an important role in the protein repulsion. Chen et al. [13] combined molecular simulations and experiments to study the mixed SAMs with various counter-charged terminal groups of different valence and protonation/deprotonation states to nonspecific protein adsorption. They demonstrated that the antifouling surfaces can be readily constructed from mixed positively and negatively charged components of equal valence. White et al. [40] proposed that people should consider several important factors in order to determine if a molecule was a candidate to form antifouling surface. The molecule should lack any specific interactions among themselves and with proteins. When such interactions did not exist, strong hydration played a key role. Those molecules which could form a uniform hydration shell were preferred. In some protein adsorption studies, human gamma fibrinogen (γ Fg) was usually used as a model protein [41,42]. Agashe et al. [43] studied the conformational changes of γ Fg on implant surfaces by molecular simulation to explain phagocyte accumulation at implant surfaces. Köhler et al. [44] performed atomistic simulations to investigate the initial stages of the adsorption process of Fg on mica and graphite surfaces.

When the mixed SAMs switched from antimicrobial surface to antifouling surface, the changes inside and above the mixed SAMs was crucial for understanding. To the best of our knowledge, recently, there was few simulation studies pay attention to the interactions between proteins and mixed charged SAMs. The objective of this simulation work was to found out the mechanism of the adsorption behavior of γ Fg on positively charged SAM and the desorption behavior of γ Fg from mixed charged SAM. In this work, we focused on the interaction between γ Fg and two states of mixed SAMs before and after hydrolysis. The parallel tempering Monte Carlo (PTMC) and all-atom molecular dynamics (AAMD) were combined [31,32,34,26] to study the interaction between γ Fg and mixed SAMs and the influence of hydrolysis were studied by MD simulations. The two different thiols were mixed with the ratio of 1:1.

2. Materials and methods

2.1. Mixed SAM and protein

2.1.1. Mixed SAM

In Chen et al's work [13], they mentioned that the lattice structure of the mixed SAM system (consisted of 11-mercapto-N,N,N-trimethylammonium chloride thiols and 11-mercaptoundecylsulfonic acid thiols with the ratio of 1:1) was $(0.52 \pm 0.02 \times 0.52 \pm 0.02 \text{ nm})^2 60^\circ$. This lattice structure was used as the SAM structure in this work (shown in Fig. 1). Before hydrolysis, the mixed SAM contained COOCH_3 -terminated thiols (i.e., $\text{HS}(\text{CH}_2)_{11}\text{COOCH}_3$) and $\text{N}(\text{CH}_3)_3^+$ -terminated thiols (i.e., $\text{HS}(\text{CH}_2)_{11}\text{N}(\text{CH}_3)_3^+$) with the ratio of 1:1; the surface charge density of COOCH_3 -/ $\text{N}(\text{CH}_3)_3^+$ -SAM was $+0.36 \text{ C/m}^2$. After hydrolysis, the mixed SAM was composed of COO^- -terminated thiols (i.e., $\text{HS}(\text{CH}_2)_{11}\text{COO}^-$) and $\text{N}(\text{CH}_3)_3^+$ -terminated thiols (i.e., $\text{HS}(\text{CH}_2)_{11}\text{N}(\text{CH}_3)_3^+$) with the ratio of 1:1; the charge property of the COO^- -/ $\text{N}(\text{CH}_3)_3^+$ -SAM was neutral. The purpose of this work was to compare the differences between γ Fg adsorbed on mixed SAMs before and

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