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Early adsorption of collagen on the reduced rutile (110) surface mediated by water: A molecular dynamics study

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ABSTRACT

The adsorption of collagen on the reduced rutile (110) surface with monatomic step defects in aqueous solution was modeled by classical molecular dynamics simulation. The step defects on the rutile surface were mainly parallel to the <1$\bar{1}$1> crystal orientation. Possible binding modes including direct and indirect binding modes, that were the peptide interacted with substrate surface directly or via the first layer water molecules, and the structural properties of collagen were discussed in order to analyze the adsorption dynamics of collagen on the reduced rutile surface. The simulation results suggested that the initial poses of collagen on the rutile surface could influence the adsorption conformation of collagen. The reduced rutile surface, which could increase the density of water molecules in the first layer, would provide active sites for collagen adsorption. The direct binding mode was responsible for the stable adsorption of collagen. The indirect binding mode may play an important part at the initial adsorption stage, but itself alone could not 'trap' the collagen on the surface stably unless the direct binding mode had already been formed. In addition, the triple helical structure of collagen was sustained by the inner-chain hydrogen bonds among different chains.

1. Introduction

Metallic biomaterials have been widely used in clinical field such as orthopedics [1] where titanium has very promising applications accounting for its good corrosion resistance and excellent biocompatibility, due to the adherent dioxide layer with a thickness of 0.5–10 nm [2,3]. The applications of Ti materials in biomedical field have been widely investigated both in vivo and in vitro, but the interface reaction mechanism between titanium dioxide and cells or tissues still remains unclear. It is well known that the surface of biomaterials will be immediately covered by proteins from blood or interstitial fluids after implanted into human body, thus it is the adsorbed proteins, rather than the surface itself contact with the tissue and human cells, such as osteoblast [4]. Therefore, biochemical surface modification [5] via binding specific extracellular matrix (ECM) proteins on the biomaterial surfaces to mimic the natural environment [6] in vivo is a very promising approach. Many researches utilized the ECM proteins, such as fibronectin [7], collagen [8,9] or short peptides (RGD [10]), to fabricate the surface of implants, and these bioadhesive motifs have been proven to be capable of exerting positive influence on cell adhesion, cell proliferation, differentiation or matrix mineralization. Simultaneously, it is confirmed that the surface non-uniformly distributed proteins [11] would affect cell behaviors. On the other hand, surface topographies [12] with micro-/nano-structures on the biomaterials obtained via ultra-precision machining methods such as lithography [13], laser processing [14], mechanical machining [15], sand blasting [16], acidic etching, and thermal oxidation [17,19], have been turned out to affect cell behavior, e.g., cell adhesion or cell migration. Manwaring et al. [19] found that the secreted matrix proteins became more organized as the surface roughness increased, which in turn accounted for cell adhesion or migration. There are various explanations about how surface topography affects protein adsorption or its organization. Many researchers found that the geometric features of the surface nanostructures may have positive effect on protein adsorption, while others thought that the surface chemistry, surface energy or roughness may also play a part in protein adsorption. However, the mechanism of peptide adsorption on the reduced TiO_2 surface is still not fully understood.

Since the contribution of surface nano-topographies to the peptide adsorption has attracted tremendous attention, classical molecular dynamics (MD) simulation has been applied to investigate the adsorption process at an atomic level. The adsorption of Arg–Gly–Asp sequence (RGD) on the grooved TiO_2 surface was studied by Song et al. [20,20], and the RGD could adsorb rapidly on the grooved surface with higher surface energy and form a more stable conformation, compared with the perfect flat surface. Claudio Melis [22] found that the geometric size of the hemisphere structure on the rutile surface was responsible for the adsorption of Poly (3-hexylthiophene) (P3HT), and the adhesion was favored when the curvature radius of spherical rutile cap was smaller than the average chain length of P3HT. However, the simulation research conducted by Friedrichs et al. [23] suggested that the rutile surface roughness had little effect on the adsorption of collagen, since the long and rod-like structure

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was too big to be inserted into the microgrooves. The present work was designed to investigate the influence of surface defects on protein adsorption. As a main component part of the extracellular matrix especially in bone, collagen plays an important and irreplaceable role in biomineralization [24]. In many researched, collagen was used to modify biomaterial surfaces, and it has been confirmed that the pre-adsorbed collagen on titanium could improve adhesion [8] and differentiation of osteoblasts. Collagen stimulates cell behaviors mainly through the amino acid sequence Arg–Gly–Asp interacting with the integrin at the cell membrane in cell adhesion, while the carboxyl groups in collagen play a key role in hydroxyapatite nucleation [24][25].

The present work was designed to study the early adsorption process of collagen segment on TiO_2 surface with defects using MD simulations. The binding mode of collagen–rutile complex and the distribution and dynamics of hydration layers at the interface were analyzed, as well as the conformational stability of collagen.

2. Materials and methods

2.1. Model building

The most stable and frequently observed surface on rutile has a (110) orientation. The repeat of rutile (110) surface was built by cleaving the unit of rutile crystal perpendicular to the [110] crystal orientation, with a lattice dimension of $\sqrt{2}a \times c$, that is, 6.497 Å and 2.958 Å along $[\bar{1}10]$ and [001] crystal orientation respectively.

In general, the metal oxide surface is heterogeneous and complicated. Many physical and chemical properties of the metal oxides surfaces are believed to be related to the defects on the surface. Scanning tunneling microscopy (STM) has been employed to investigate the surface defects such as step edges or oxygen vacancies [26,27], and the step edges on the reduced rutile TiO_2 (110) surface were observed to run predominantly parallel to $<1\bar{1}1>$ and <001> directions [27,29,30]. In present work, two kinds of surface with different monatomic step edge were built as shown in Fig. 1. The surface with step edge parallel to $<1\bar{1}1>$ direction shown in Fig. 1a), hereafter named S1, exposed more unsaturated atoms along the step edge compared with the upper terrace. It is well known that a decrease in coordination number of surface atoms often results in an enhancement in chemical reactivity [28]. The O atoms along the $<1\bar{1}1>$ edge are two-fold and three-fold coordinated. The formation of the step edges creates four-fold and five-fold coordinated Ti atoms, which terminate the Ti rows and the bridging oxygen (O_b) rows along the [001] crystal orientation on the upper terrace, respectively. The rutile surface with a kink structure with more unsaturated Ti atoms on the upper terrace (hereafter named S2 and shown in Fig. 1b)), which was observed by STM [27], was formed when a $[1\bar{1}1]$ type step edge turned into a $[1\,\bar{1}\,\bar{1}]$ type one. The atoms along the $[1\bar{1}1]$ and $[1\,\bar{1}\,\bar{1}]$ crystal orientation were nearly the same and the two type edges were converged to a five-fold coordinated Ti atom as shown in Fig. 1b).

Seven TiO_2 layers with a simulation box of $140.5 \times 50.7 \times 22.0$ Å^3 comprised the entire substrate. Since periodic boundary conditions were applied in both x- and y- directions during the present MD simulations, the step parallel to $<1\bar{1}1>$ orientation was truncated by the steps parallel to [001] orientation to eliminate the non-periodic effect, which was also shown in Fig. 1a).

Collagen has a long but rod-like structure about 1.5 nm wide and over 300 nm long, which consists of three right-hand helical chains. Each helical chain presents a periodic successions of Gly–X–Y sequences, where X or Y site is often replaced by proline (Pro) or hydroxyproline (Hyp) residue [31,32]. The inter-chain hydrogen bonds between carbonyl oxygen (O_{CO}) of Pro (or Asp) and amino hydrogen (H_{NH}) of Gly account for the high stability of the triple helical structure [32,33]. A short segment of the collagen with an ID of 2KLW in the Protein Data Bank [34,35] (shown in Fig. 2) was selected as the adsorbate in the following MD simulations. The 2KLW segment presents a triple helical structure, which is formed by three different helices consisting of 90 amino acid residues including charged amino acids like aspartic acid (Asp, negatively charged) and lysine (Lys, positively charged). The inner-chain hydrogen bond interaction and the amino sequences were shown in Fig. 2b) and c). To avoid spurious end effects, peptide sequences were blocked by adding a $-NHCH_3$ group (Nme) to the C-terminus and a $-COCH_3$ group (Ace) to the N-terminus. The net charge of the 2KLW segment was 0.

2.2. Molecular dynamics simulation protocol

Classical MD simulation of collagen segment (2KLW) adsorbing on the reduced the rutile (110) surface with monatomic step was performed in this work. The AMBER force field [36] was employed to describe the structure of 2KLW segment, which was immersed in aqueous solution with SPC/E [37] water model. TiO_2 was calculated using the Buckingham potential [38], and the interaction potentials between TiO_2 and collagen segment were described elaborately in Ref. [39]. The parameters which described the rutile–water interface were derived from the results by A. V. Bandura [48]. Periodic boundary condition in the x-, y- and z- directions and canonical ensemble (NVT) using Nose–Hoover thermostat [40] was adopted in the simulation. Meanwhile, the SHAKE algorithm [41] was used to restrain the geometric structure of SPC/E water molecules. The long-range electrostatic interactions were treated with the particle–particle particle-mesh (PPPM) solver [49], while the short-range interactions were truncated at 12 Å.

The collagen segment was initially solvated in pure aqueous solution. Since each of the three different chains in the collagen segment

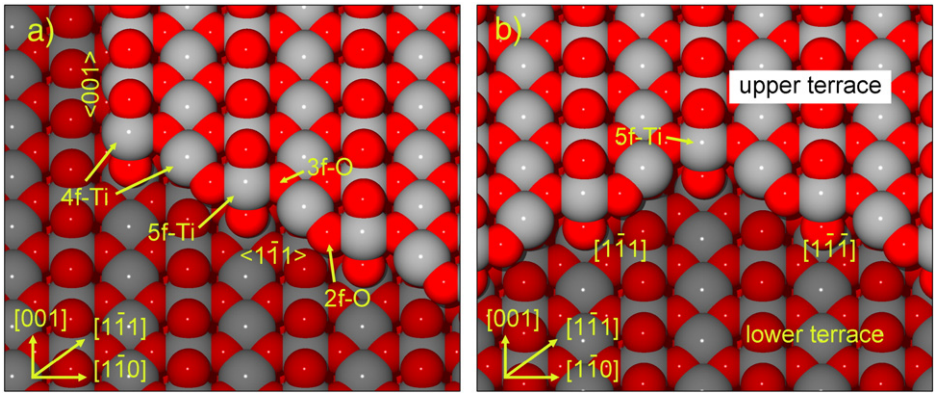

Fig. 1. Step defects on the rutile (110) surface: a) step edge parallel to the $[1\bar{1}1]$ crystal orientation and b) kink defect.