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Molecular Modeling of Cell Adhesion Peptides on Hydroxyapatite and TiO_2 Surfaces: Implication in Biomedical Implant Devices

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ABSTRACT

Molecular modeling as a tool in studying peptide-substrate interactions provides insight on peptide adsorption conformation, adsorption energy, and stability of the peptide-inorganic interface. This work investigates the hydration and interaction of cell-adhesion peptides, specifically RGD and YIGSR, with the hydroxyapatite surface and TiO_2 surface in cluster and periodic boundary condition approaches. The comparison of adsorption energies of RGD and YIGSR on both Hydroxyapatite (HA**)** and TiO_2 surfaces reveals the similarities in adsorption energy and orientation pattern of peptides on both surfaces. The models demonstrate that initial peptide orientation affects adsorption energy for both. YIGSR is consistently more strongly adsorbed to HA-(001) surfaces and steps than RGD for both the surfaces. In addition, RGD maintained its "hairpin"-like structure during adsorption on a flat HA-(001) surface, and a slightly "relaxed hairpin" structure on TiO_2 (110) surface. Adsorption energies of RGD on TiO_2 (110) surface are significantly more favorable compared to HA-(001) surface, suggesting potential role of TiO_2 as biomedical implants when tissue regeneration occurs via cell signaling.

Keywords: Hydroxyapatite; Nanobiomaterial; Bone-Tissue Engineering; RGD; TiO_2

1. Introduction

The structure-function properties in bone and teeth are based on organic-inorganic interactions at the surface, and these properties are used to design developing functional tissue engineered bone substitutes. Specifically, the organic-inorganic microenvironment of a biomaterial surface can influence cellular behavior positively by enhancing cell adhesion, spreading, and growth or negatively by promoting cell death, or apoptosis [1]. Bioactive surfaces can incorporate extracellular proteins, cell-mediated synthetic proteins, or bio-engineered motifs, all of which interact with the substrate material. This biological molecule-inorganic mineral interaction can dictate a series of cellular events, including cell-adhesion. The main goal of bone tissue engineering is to restore functionality of the damaged tissue. Interactions of organic molecules such as proteins with inorganic biomaterials such as apatite have already been studied extensively. The major challenge is to design a biocompatible medical device to be inserted inside the damaged tissue whose growth pattern will be similar to that of protein-hydroxyapatite interactions.

It is well known that Ti shows a mechanically stable interface towards bone. The good biological properties are due to the beneficial properties of the native oxide (TiO_2) that forms on Ti when exposed to oxygen. The native titanium oxide on Ti is usually amorphous and very thin, 2 - 7 nm. In addition to being stable in the physiological environment, titanium oxides increase calcium ion interactions, which are important for protein and subsequent osteoblast adhesion (osseointegration). It is therefore essential to know the interaction of protein molecules with TiO_2 which is the starting point of cell adhesion mechanism that finally leads to bone tissue engineering. In the previous works, interaction of RGD and YIGSR with hydroxyapatite (001) surface and surface steps has been studied extensively. It was determined that initial orientation of the peptide is important regarding final adsorption energies on the mineral surface. For example, orientation of the peptides can dictate the sur-

face charge of material surfaces, influencing whether cells will begin to form focal adhesions. The cell-adhesion peptides used in this study were YIGSR (Tyr-Ile-Gly-Ser-Arg), derived from laminin [2-4], and RGD (Arg-Gly-Asp), a ubiquitous adhesion peptide [5,6]. The RGD portion of the hydrated fusion peptide can change orientation on the hydroxyapatite surface as the fusion peptide itself binds strongly to the hydroxyapatite surface during the cell adhesion process. However, the orientation of the peptide and interaction with surface ions when adsorbed on the TiO_2 surface are unknown. Thus it is important to calculate the adsorption energies of RGD and YIGSR with TiO_2 surface and compare the results with the interactions of the same peptides with hydroxyapatite surface.

As we know, Computational molecular modeling provides an alternative to the experimental limitations, and can provide alternative views of organic-inorganic interactions. Molecular modeling has proven useful for investigating protein-substrate and peptide-substrate interactions in calcite, calcium oxalate, and apatite systems [7-12]. Various parameters regarding the interactions of oligopeptides with biominerals can be deduced from this type of modeling, such as adsorption conformation, adsorption energies, and stability of the organic-inorganic interface. Molecular modeling is employed to study interactions between cell adhesion peptides and the hydroxyapatite and TiO_2 system. The introduction of surface steps can also be included to simulate imperfections in natural or man-made hydroxyapatite/TiO_2 materials.

The goal of this work was to utilize molecular modeling methods to investigate the influence of peptide orientation on adsorption of peptides to a hydroxyapatite mineral surface and TiO_2 surface, with the intent to compare the adsorption energies for the interaction of cell-adhesion peptides with the hydroxyapatite (001) surface and surface steps along with TiO_2 (110) surface. This was investigated using both a cluster approach and a periodic boundary condition approach. Specifically, the aims of this work are to determine the orientation of RGD and YIGSR when adsorbed to the (110) TiO_2 surface and then compare the results with (001) hydroxyapatite surface with a [010] step. Empirical methods were used to study the adsorption of these peptides on hydroxyapatite surfaces and TiO_2 surface using clusters and periodic surfaces, in addition to studying the hydration energies of the peptides on hydroxyapatite and TiO_2.

2. Computational Modeling Procedures

2.1. Molecular Modeling Set-Up

Using the Cerius^2 software, hydroxyapatite (001) surfaces and surface steps parallel to [010] were created. The HYDROXYAPATITE force field was developed and used to investigate the interactions within the organic molecules and interactions between each organic molecule and the substrate. This HYDROXYAPATITE force field is derived from the UNIVERSAL1.02 force field [13] for the interactions within the peptides, but was altered to accommodate interactions relevant to hydroxyapatite surfaces and organic molecules. Suitable parameters for three bond intra-atomic potentials, Morse intra bond potentials and Buckingham interatomic potentials were obtained by fitting potential parameters to the experimental structure and physical properties of HA using GULP [14].

The HYDROXYAPATITE force-field parameters control the interaction between P and O atoms in the phosphate group and the O-P-O angle in the tetrahedral phosphate group. These parameters also account for the bond stretching action between the P and O atoms and interatomic van-der-Waals interaction. The UNIVERSAL1.02 force field does not contain off-diagonal van der Waals force terms that are necessary to represent the interactions between non-bonded atoms in both the inorganic and organic layer. Ca^{2+} ions, P and O atoms in PO_4^{3-}, O and H atoms in OH^- have non-bonded van der Waals interactions between them. In order to represent these interactions correctly, non-bonded van der Waals terms are generated by fitting Lenard-Jones potentials to experimental constants for these respective atoms. The above measures are similar to the previous work done in [15], where adsorption energies of RGD and YIGSR on hydroxyapatite surface and surface steps are calculated. Here in this study, interactions of the same peptides on TiO_2 is calculated with TITANIA force field. The nature of TITANIA and HYDROXYAPATITE force-fields are almost identical except for few terms that did not require presence of Ca and P. The Buckingham potential involving Ca-O, Morse potential involving O-P and the Three-body potential involving O-P-O is not included in TITANIA force-field, as the interaction of RGD with TiO_2 does not require any interactions involving the above-mentioned atom pairs.

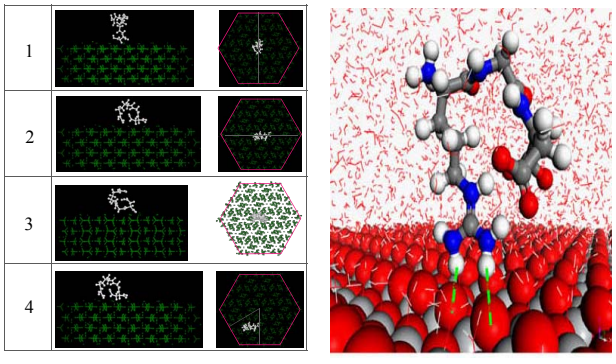
The charge distribution within the peptide molecules, RGD and YIGSR, was calculated using the QEq charge equilibration scheme for the neutral peptide molecule [16]. Molecular dynamics simulations at 300 K were performed to avoid trapping the adsorbate in a local energy minimum before and during optimization. These dynamics simulations were performed using a constant NVE ensemble. The dynamic time step was 0.001 ps, and for each molecular dynamics simulation 50,000 steps were run. These parameters are also similar to the previous work of RGD-YIGSR interaction with HA, to maintain similarity between HA and TiO_2 interactions with

the peptides. Two different set-ups were used in calculations involving peptide-HA interactions; a slab with periodic boundary conditions parallel to the slab and a cluster that is an atomic equivalent of a hexagonal apatite prism. For peptide-TiO_2 interactions, also both cluster and periodic boundary conditions are used, but no surface step is created. Four initial peptide start orientations were used in both set-ups (**Figure 1**).

2.2. Hydroxyapatite and TiO_2 Surface Set-Up for Simulation

The cluster for hydroxyapatite is chosen in such a way that there are 76 formula units of $Ca_5(PO_4)_3(OH)$ in the cluster. Different initial positions of the peptides were applied 3 - 4 Å away from the flat terrace of the hexagonal cluster of the hydroxyapatite. Then, the peptide geometry was optimized on the cluster with all atom positions within the cluster being fixed. Finally, the calcium ions at the top of the hexagonal cluster were allowed to move during the energy minimization process. This allows the relaxation and movement of calcium ions during the adsorption of peptides on the mineral surface, better mimicking the dynamic aqueous environment in *in vitro* or *in vivo* experiments.

Subsequently, a surface step parallel to [010] on the hydroxyapatite (001) surface was introduced. This step direction was chosen to keep the cluster stoichiometric and charge neutral. A small dipole moment perpendicular to the step was unavoidable in this setup. Peptide adsorption energies can vary with the starting position and orientation of the peptide along the surface steps. This variation in adsorption energy occurs because each peptide has different functional groups at the side chain (of the amino acids present in them). These side-chain functional groups interact with the mineral surface atoms differently depending on the orientation of the peptide with respect to the mineral surface, because different atoms of the functional groups are in contact with the hydroxyapatite surface atoms in different peptide orientations. Thus, variable adsorption energies are obtained depending upon orientation of the peptide. Four different starting positions (**Figure 1**) for the peptide were observed for their final orientation on the hydroxyapatite surface after energy minimization.



(a) (b)

Figure 1. Orientation of RGD on (a) Hydroxyapatite and (b) TiO_2 (1 1 0) surface.

In case of TiO_2 (110), the Ti_4O_8 formulae unit is taken and the surface has been made with 53 × 53 × 19 $Å^3$ dimension with the units separated by 40 Å, which means there were about 72 formulae units of TiO_2.

Calculation of hydration energies was necessary to estimate the effective adsorption energy of these peptides at different orientations on the TiO_2 surface. Hydration energies were calculated for RGD and YIGSR adsorption on Hydroxyapatite surface in the previous work using Materials Studio Modeling 4.1 DMol[3]. It was used to calculate the extent of hydration on different fragments of both RGD and YIGSR, as all side chains are not equally hydrated. For hydration of peptides on TiO_2 surface, similar approach has been taken. Here in the hydration energies calculation, like the previous work, water was used as a homogeneous solvent with a dielectric constant of 78.54, and the contribution of the "Cosmo" hydration energy to the total energy is calculated. "Cosmo" approximates the free energy between water molecules and functional groups in peptides. The hydration energy of the part of the peptides that are hydrated and those that are on the mineral surface are treated separately to correct the calculated *in-vacuo* adsorption energy into aqueous hydration energy. This is required for yielding the effective hydration energy change during the adsorption of the peptide. Extent of hydration for the peptide molecules are slightly more in case of TiO_2 compared to hydroxyapatite. When adsorption energy of a peptide is calculated, it is performed according to the following equation.

$$E_{\text{ads HA}} = E_{(\text{peptide+HA})} - \left[E_{\text{peptide in vacuum}} + E_{\text{HA}} + E_{\text{hydration of specific functional groups of peptide}}\right]$$

$$E_{\text{adsTiO}_2} = E_{(\text{peptide+TiO}_2)} - \left[E_{\text{peptide in vacuum}} + E_{\text{TiO}_2} + E_{\text{hydration of specific functional groups of peptide}}\right]$$

3. Results

The adsorption energies for the four different initial orientations of both peptides, RGD and YIGSR, on hydroxyapatite and TiO_2 (110) surface, are calculated for cluster and periodic calculations, and the data for cluster calculations are shown in **Table 1** when the surface is relaxed. For hexagonal cluster calculations, RGD adsorption energies were low negative values with orientation 4

Table 1. Adsorption energies of peptides on Hydroxyapatite and TiO_2.

Peptide orientation along hydroxyapatite and TiO_2 surfaces	Adsorption energy on hydroxyapatite surface $E_{ads\ HA}$ (eV)	Adsorption energy on hydroxyapatite surface $E_{ads\ TiO_2}$ (eV)
RGD parallel to Y-axis **(Orientation 1)**	−4.62	−5.03
RGD perpendicular to Y-axis **(Orientation 2)**	−4.20	−6.63
RGD with open end of "hairpin" on the surface **(Orientation 3)**	−3.53	−6.74
RGD at the edge of the cluster **(Orientation 4)**	−9.45	−9.83
YIGSR parallel to Y-axis **(Orientation 1)**	−1.04	−3.67
YIGSR perpendicular to Y-axis **(Orientation 2)**	−5.52	−8.23
YIGSR with open end of "hairpin" on the surface **(Orientation 3)**	−5.26	−7.23
YIGSR at the edge of the cluster **(Orientation 4)**	−1.52	−5.02

(RGD at the edge and parallel to [010]) being the most favorable at −3.69 eV. For YIGSR, the hexagonal flat cluster was the least favorable set-up. Overall, RGD had lower standard deviations compared to YIGSR when adsorbed on hydroxyapatite surface. On TiO_2 surface, RGD interacts with the surface atoms mainly via electrostatic interactions along with VDW interaction. YIGSR's initial position changes vigorously when brought close to the surface as initial position on TiO_2. The static condition decreased this fluctuation, whereas when the Ca^{2+} ions on the top layer of the HA was allowed to move, this variation increased which is indicative for the different degree of apatite relaxation during adsorption. For TiO_2, no such variation has occurred.

When the Ca^{2+} ions were allowed to move during the simulations on HA surface, a general increase for both RGD and YIGSR was observed in the adsorption energy values when compared with appropriate static adsorption energies. The adsorption of RGD on the terrace of a hexagonal cluster of the hydroxyapatite (001) face (orientation 1) was −2.64 eV when the atoms in the cluster are fixed, but this value increased to −4.62 eV when the Ca^{2+} ions were allowed to move. In the latter case, the Ca^{2+} ions interact with the aspartic acid residue of RGD. The calcium ions are electrostatically attracted to the $-COO^-$ group in aspartate, which causes the RGD to move closer to the apatite surface during energy minimization. The Ca^{2+} ions relax parallel to the [010] direction and do not distort the lateral symmetry of the cluster during relaxation. When RGD was adsorbed on to TiO_2 surface when fixed, adsorption energy is −2.95 eV. The surface energy is increased by many folds when surface is relaxed, and the RGD retains its near hairpin shape on the TiO_2 surface after simulation.

The hydration energy for relevant functional groups for both RGD and YIGSR on HA and TiO_2 surface are calculated, respectively, for all set-ups run. Variations in calculated hydration energies are caused by different functional groups being adsorbed and the remaining ones still hydrated after adsorption of the molecule. The results show that the hydration energy calculated depends on the peptide orientation with respect to the apatite surface.

4. Discussions

Nanomaterials will replace traditional implants in near future in the process of tissue-regeneration, where the cell adhesion peptides with nanomaterial surfaces are the stepping stone of regeneration process [17,18]. The adsorption of cell adhesion peptides on hydroxyapatite surfaces depends on the orientation of the peptide with respect to the hydroxyapatite surface. The dependence of adsorption energies of the peptides on initial orientation is a little less on TiO_2-surface compared to the HA surface. The adsorption energies vary with the starting orientation of the peptide and are more negative, or more favorable, when the Ca^{2+} ions of the top-layer of the hexagonal hydroxyapatite cluster are allowed to move during energy minimization. When the cluster is kept fixed during the simulation, adsorption energies have low negative values when the RGD is at the step or near the step edge. Interestingly, RGD maintains its "hairpin"-like structure when adsorbed to the flat apatite surface. However, adsorption energies become highly negative and more favorable for RGD near the step-edge (orientation 4) when the Ca^{2+} ions at the top-layer of the cluster are allowed to move (−9.45eV) (**Table 1**). When a step parallel to the [010] direction on the hydroxyapatite (001) surface was introduced, adsorption was most favorable for static conditions when the open end of the RGD "hairpin" loop is in contact with the surface. When the peptides are adsorbed onto TiO_2 surface, the adsorption energies are more negative compared to hydroxyapatite surface for similar initial orientations, which shows that RGD and YIGSR are more favorable adsorbed on to a TiO_2 surface that RGD surface. The nanomaterial like behavior of TiO_2 surface provides larger surface area for the peptides compared to HA surface, thus, the adsorption energies for TiO_2-peptide adsorption becomes more favorable. This also enables on to come to a conclusion that TiO_2 nanomaterial like surface will be more suited for designing biomedical implant devices where peptides

can be adsorbed directly toinitiate the cell-adhesion process during bone tissue regeneration process.

The water molecules occupy the adsorption sites on the hydrophilic TiO_2 surfaces, *i.e*. the water oxygen atoms bond to the surface titanium atoms to form the stable first hydration layer and interact with the surface oxygen atoms to form the second hydration layer. Besides being in competition with RGD for the adsorption sites, the adsorbed water layers also play an intermediary role, forming HB interactions with the hydrophilic groups of RGD. The guanido (NH_2), amino (NH_3) and carboxyl groups (COO-) of tripeptide RGD are the main groups bonding to TiO_2 surface by electrostatic and VDW interactions.

The extent of hydration of different functional groups on each peptide was also considered. Some of the functional groups in the peptide are still hydrated after adsorption and the others are bonded to the mineral surface. The final adsorbate structure on the mineral surface evaluates which functional groups were bonded to the mineral surface, and hydration energies of these functional groups were subtracted from the peptide vacuum adsorption energy to obtain the effective adsorption energies. The NH_2- with peptide bond elements are more strongly hydrated than other functional groups (−1.465 eV hydration energy), followed by the amide functional group (C(NH)=NH-NH_2) of arginine (R) (−1.106 eV). The COO- groups have hydration energies of ∼−0.2 eV to −0.5 eV. When the peptide is kept parallel or perpendicular to the [010] direction (orientations 1 and 2), the amide and carboxylic groups interact with the mineral surface, allowing the peptide to maintain its "hairpin" position.

The above hydration strategies were used in exactly same way when adsorption of peptide is calculated only on HA surface. Adsorption of peptides on TiO_2 surface followed similar course and the hydration energies for responsible functional groups on TiO_2 surface has been deducted accordingly to calculate the effective adsorption energy of RGD, YIGSR on TiO_2. The retention of hairpin like structure of RGD on TiO_2 surface is of great importance in showing similarity of behaviour of RGD on both HA and TiO_2-surface in aqueous environment.

5. Conclusion

The adsorption energies of RGD and YIGSR on Hydroxyapatite surface and TiO_2 surface reveal similar trends. Comparing the adsorption energies for both the surfaces, we can conclude that RGD behaves similarly on both the surfaces, with positioning of the peptide near the edge of the cluster (Orientation 4) yielding most favorable adsorption energy. This gives us a clear idea about the peptide orientation during the tissue-engineering process. When artificial inclusion of Titania-based nanoparticles is required inside the tissue, it is important to know how the peptides are going to interact with TiO_2 surface. The adsorption energies and favorable conformations of peptides on TiO_2 assist researches to design biomedical implants making them appropriately keep in mind that the most favorable surface for peptide adsorption on TiO_2 is (1 1 0). Future studies will concentrate on more TiO_2 surfaces and more peptides to develop a more general approach for designing of biomedical implants to facilitate bone-tissue engineering.

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