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Introducing Novel Titanium Binding Peptides; Effect of the Sequence of Amino Acids on Their Adsorption Energy to TiO_2

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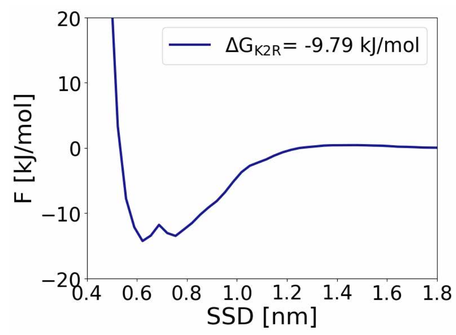
Abstract

Standard inert materials used in the production of orthopedic and dental implants include titanium (Ti) and titanium alloys due to their mechanical qualities, biocompatibility and corrosion resistance. A layer of titanium dioxide (TiO_2) forms when the Ti is in contact with oxygen or water, which is intact and stable at physiological pH and improves the biocompatibility of titanium used as implants. However, the absence of recognizable moieties on the implant prevents cell activities from being regulated and may induce a foreign body reaction to the implant causing infections due to biofilm formation and bacterial adhesion. Solid-binding peptides are short amino acid sequences that can specifically recognize and bind by one end to solid surfaces like titanium while the other end can be used to link with various bioactive molecules. No specific binders have evolved in nature for TiO_2. Therefore, it is important to design novel peptides that specifically bind to TiO_2. An established titanium-binding peptide (TBP), RKLPDA (min TBP-1), introduced by Sano and Shiba using the phage display method, has shown significant antimicrobial effect and enhanced bone formation activities in osteoblasts-like (bone synthesizing) cells [1].

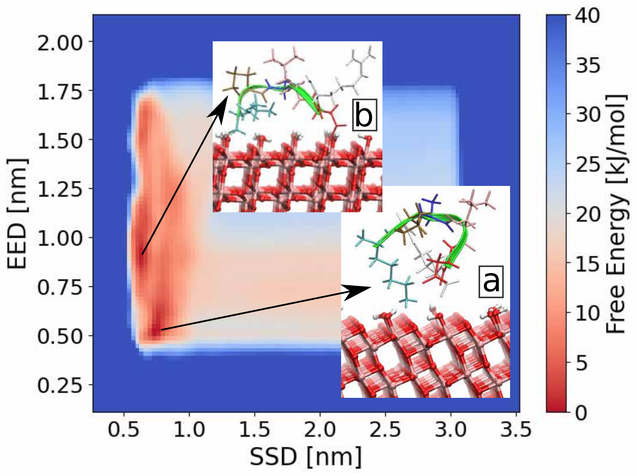
Achieving binding and selectivity at the interface of peptide-TiO_2 is vital for constructing well-organized hybrid materials. One of the important determinants in the binding process is the composition of peptides, encompassing the sequence of amino acids, structural conformation, and charge. The aim of this work is to find new TBPs which bind to TiO_2 stronger than the min TBP-1 using computational methods. We mainly focused on two aspects: one is the selection of potential titanium binding peptides by reordering the amino acid sequences in min TBP-1 using atomistic molecular dynamics (MD) simulations, and the other is to quantify the functionality of these potential peptides by calculating their adsorption free energy to TiO_2 using enhanced sampling MD simulations. We discovered several peptides which show much stronger affinity to titanium than the established min TBP-1. We also investigated the conformation of these peptides on the surface of TiO_2 which is crucial for their functionality in the vicinity of bioactive molecules on cells.

Results

- 20 peptides showed potential adsorption affinity to TiO_2 in unbiased atomistic MD simulations.
- By employing the enhanced sampling multiple-walker metadynamics method, we calculated the adsorption free energy of these 20 potential peptides to TiO_2. After 10-16 microseconds of simulations, 13 peptides showed adsorption energies higher than min TBP-1 (see table on the right) implying better affinities toward TiO_2 than the min TBP-1.
- **K2R**, **R1D**, **A1D**, **L1D**, **K1L** peptides adsorb 2-6 times stronger than min TBP-1.

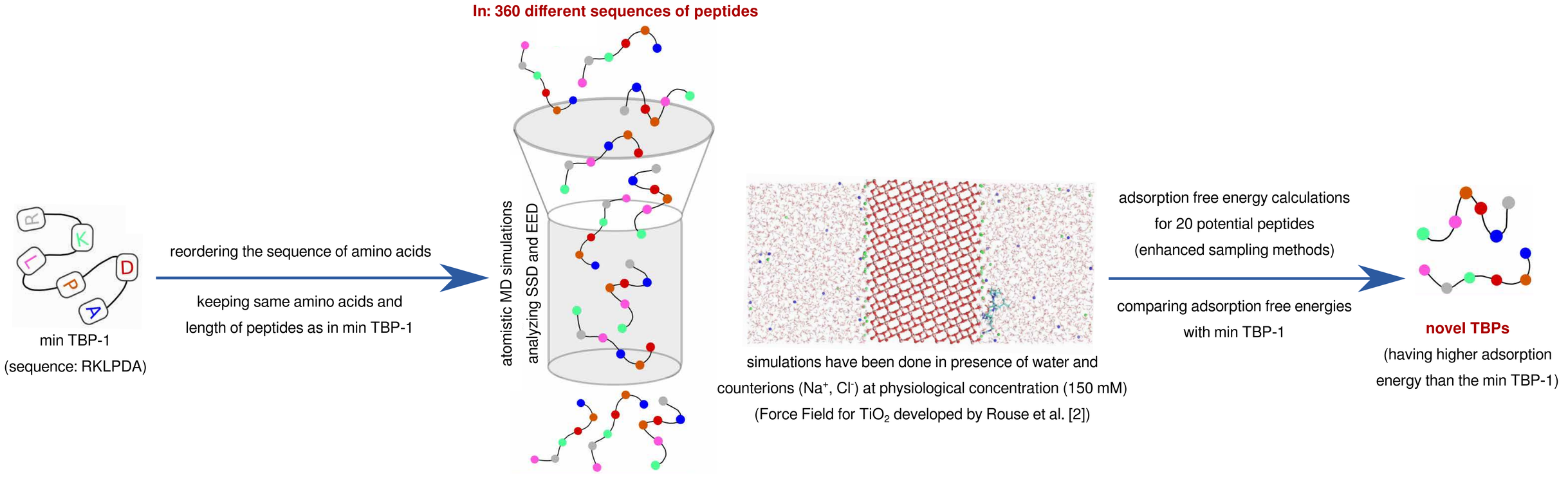


Peptides	ΔG (kJ/mol)
K1L	-29.31
L1D	-18.84
A1D	-14.32
R1D	-12.81
K2R	-9.79
K3D	-8.92
R2D	-8.91
L2P	-8.77
P1D	-8.31
L3D	-7.87
K4P	-7.74
A2R	-6.50
L4R	-5.47
min TBP-1	-5.08



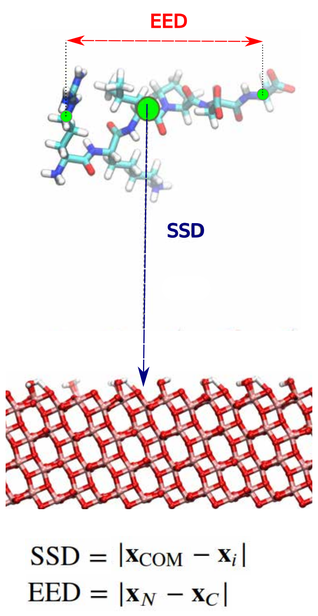
- We have done cluster analysis to extract the bound state conformations of these 13 peptides. Some peptides have several favorable conformations when they are adsorbed on the surface.
- We show a 1D free energy profile of K2R peptide along SSD (see plot above) and its 2D free energy surface along the SSD and EED (to the left), together with the compact (a) and stretched (b) bound states of K2R on TiO_2 (inner pictures).

Can we introduce new peptides having higher affinity to titanium by reordering the sequence of amino acids in min TBP-1?



Methods

We started from 360 peptides each possesses six amino acids (Arg, Lys, Leu, Pro, Asp, Ala) in its structure and is distinctive in its sequence. Given the computational cost associated with calculating the free energy of adsorption directly, we implemented a two-step approach to narrow down our choices of potential TBPs efficiently. First, we used unbiased atomistic MD simulations to select peptides that might potentially have affinities to TiO_2 by analyzing the separation distance of each peptide from the surface of TiO_2 (SSD) and end-to-end distance of the peptides (EED). In the second step, to quantify their adsorption strength, we employed the multiple-walker well-tempered metadynamics (MW WT-MetaD) method to calculate the adsorption free energies of these potential peptides [3]. We used the GROMACS and PLUMED softwares for the simulations [4, 5].



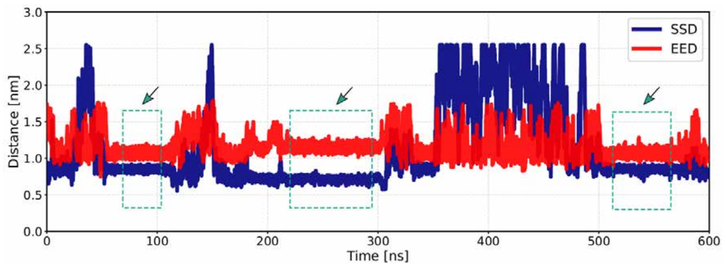


figure above is an example of 20 potential peptides shown (green arrows) low separation distance from surface (SSD) and stable end-to-end distance (EED)

$$\mathrm{SSD} = |\mathbf{x}_{\mathrm{COM}} - \mathbf{x}_i|$$
$$\mathrm{EED} = |\mathbf{x}_N - \mathbf{x}_C|$$

$$C_{ads} = \frac{1}{z_0 - z_{min}} \int_{z_{min}}^{z_0} \exp(-\beta G(z))\, dz$$

$$C_{bulk} = \frac{1}{z_{max} - z_0} \int_{z_0}^{z_{max}} \exp(-\beta G(z))\, dz$$

$$\Delta G = -k_B T \ln \frac{C_{ads}}{C_{bulk}}$$

Summary

- This work aimed to introduce novel titanium-binding peptide (TBP)s which have higher affinity to titanium dioxide (TiO_2) than the already reported TBP called min TBP-1 by reordering the sequences of the min TBP-1 and calculating the adsorption free energy of new sequences to TiO_2 using computational methods.

- We found 13 novel sequences having higher affinities to TiO_2 than the intial sequences in min TBP-1. Some of these novel sequences adsorb to 2-6 times stronger than min TBP-1. Further investigations showed several bound state conformations for peptides when they are adsorbed on the TiO_2.

- These novel sequences promise much better specificity toward TiO_2 than min TBP-1 and their performance and selectivity could be explored experimentally.

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