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Molecular modeling the adsorption behavior of bone morphogenetic protein-2 on hydrophobic and hydrophilic substrates

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ABSTRACT

Adsorption of BMP-2 on hydrophobic gold and hydrophilic silicon nitride is studied using molecular dynamics simulations. The wetting behavior of the dissolution media directly guided the protein-substrate interaction, impacting the protein adsorption. The saline solution restricted the movement of the protein on gold, limiting adsorption to hydrophobic and charged residues while preserving the secondary structure. Stronger adsorption occurred on silicon nitride where the protein had more flexibility to interact with the surface leading to the disruption of β-sheet structures in two orientations. This research contributes to the understanding of BMP-2 adsorption behavior in four orthogonal orientations with medically relevant materials.

1. Introduction

Protein adsorption onto substrates is an important phenomenon in biotechnology due to its influence in the biocompatibility of implants and the effectiveness of engineered tissue scaffolds for cellular differentiation and proliferation [1,2]. The protein-substrate interactions are vital in preserving the biological response of the proteins [3]. The properties of the substrate surface, including wetting properties, crystal orientation, and topology, regulate the final conformation and bioactivity of the adsorbed protein [4]. Protein structure can change from its native state to an unfolded configuration depending on the surface characteristics, which can lead to partial denaturation of the protein [3,5].

Bone morphogenetic protein-2 (BMP-2) is an essential protein for bone formation and restoration because of its potential to promote differentiation and proliferation of osteoblasts [6]. BMP-2 combined with standard methods for bone repair can reduce the healing time and risk of rejection, allowing savings in the treatment cost. However, its use for clinical procedures requires the protein to be incorporated in a carrier agent without significant conformational changes to maintain its bioactivity [7]. For the effective bone development, BMP-2 adsorption on the implant surface must be stable and occur exclusively on the implant site. Also, the protein must interact with its receptors to activate signaling cascades, inducing osteoblasts proliferation [3]. Partial denaturation of the protein can occur if the binding to the surface is too strong which directly affects the protein bioactivity. Therefore, a balance between steady adsorption on the substrate and conservation of protein activity must be achieved [3]. BMP delivery at the affected site relies on media pH, substrate porosity, temperature, the salt concentration of the solute, and the interaction between substrate and protein [8]. Therefore, its retention depends if the growth factor is immobilized on the substrate during manufacturing or absorbed into the substrate [8].

The interaction between protein and substrate at the nanoscale depends on different surface parameters, including chemical composition, charge, topography, and hydrophilicity, which influence protein conformation, adsorption, and bioactivity [9]. Proteins interact with a substrate through intramolecular bonds, including hydrophobic interactions, ionic bonds, and charge transfer. Hydrophilicity of substrates is a critical parameter for the adsorption of proteins. Usually, hydrophilic surfaces adsorb fewer proteins than hydrophobic [10]. However, protein adsorption also depends on the properties of the amino acids that form a protein. Amino acids are classified as charged, polar and hydrophobic. Charged residues are highly exposed to solvents, often forming salt bridges which influence the stability of proteins [11]. Hydrophobic amino acids residues tend to adsorb on hydrophobic substrates, whereas polar residues on hydrophilic substrates [10].

Different substrate materials with medical relevance, such as gold [12], graphite [3,13], and hydroxyapatite [9,14] have been

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studied to understand their interaction with proteins. In recent years, a new class of materials which include silicon nitride [15] and silicon dioxide [16] have been used for orthopedic applications due to their improved biocompatibility. Gold has been widely used as a substrate material because of its optical, magnetic, and chemical properties, with applications in biological imaging, drug delivery system and biosensors [12]. Silicon nitride has been used in spinal surgery for bone fusion and to extend the durability of prosthetic hip and knee joints [15]. However, the interaction of proteins with these materials needs further exploration for their effective implementation in clinical settings.

Molecular modeling can be used to visualize better, understand and predict the interaction between proteins and material surfaces to control cellular function [1,2]. Studies of 3D protein structures are essential to understanding the BMP-2 release kinetics for orthopedic applications [17]. The benefits of BMPs in the regeneration of bone tissue are well-known and studied in the medical field [18–20]. However, the effective release of this protein at tissue-implant interface needs further investigation. Understanding how ambient conditions affect the release kinetics of BMP-2 on different substrate materials and morphologies will progress the field of orthopedics. Successful coatings of BMP-2 on implants might reduce the cases of rejection and avoid infections, significantly reducing the recovery time of bone and cartilage injuries [6]. Current clinical practices employ BMP-2 growth factors at implant site with mixed results [21]. Growth factors are typically sensitive to ambient *in vivo* environments and susceptible to denaturation [22]. Also, prolonged retention is required to maintain the properties of growth factors in the cells, artificial scaffolds, or extracellular matrix [23]. Thus, it is critical that the molecular mechanisms for the adsorption kinetics and bioactivity of BMP-2 be studied to direct cell-specific differentiation and proliferation. Our research group implements MD simulations to investigate BMP-2 growth factor in four initial orientations concerning substrate materials based on their varying wetting behaviors. The hydrophobic and hydrophilic characteristics are represented by gold and silicon nitride (Si_3N_4) substrate materials, respectively.

2. Methods

The MD simulations were performed on a 64-bit Linux platform (Fedora 21) with two graphical processing units (GPUs) from NVIDIA® Corporation (K40 and K20, with 2880 and 2496 cores, respectively). Nanoscale Molecular Dynamics (NAMD) source code version 2.11 was implemented to execute the simulations with CHARMM27 force field [24]. Visual Molecular Dynamics (VMD) platform was used to create the molecular models and analyze the results [25]. The Theoretical and Computational Biophysics Group at Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign developed both NAMD and visual MDs [25].

A BMP-2 protein representation (PDB: 3BMP) was obtained from the RCSB Protein Data Bank [26]. The BMP-2 molecule consisted of 1641 atoms, with 1664 bonds, at 2.7 Å resolution. An explicit TIP3P water model was used to solvate the protein in a minimum water sphere [27], and then, sodium chloride (NaCl) ions were added using VMD plugin at a concentration of 0.15 mol/L. This solvated aqueous protein model consisted of a 6.5 nm droplet with 13,863 atoms. Non-bulk models have been successfully used to study protein conformation [3,5,28].

For modeling the interaction of the substrate with the droplets, the solvated protein was placed tangent on the center of a flat

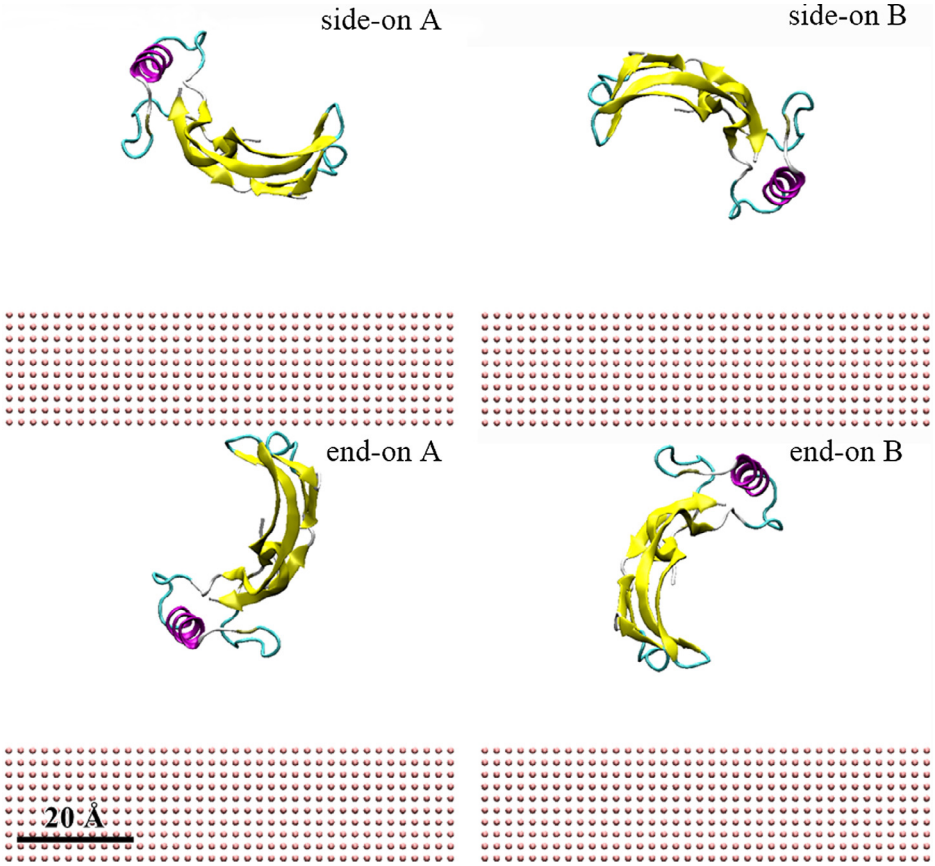

Fig. 1. Initial orientations of BMP-2 on hydrophobic gold (same orientations considered for silicon nitride). Protein is represented using secondary structure, α-helix is represented in pink and β-sheets in yellow. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)