Amino acid polymorphisms in the fibronectin-binding repeats affect the fibronectin bond strength

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\textbf{Abstract:} The envelope of Staphylococcus aureus contains cell wall proteins like fibronectin binding protein A (FnBPA) that bind to host ligands (e.g., fibronectin; Fn) present in the extracellular matrix of tissue or coatings on implants. Molecular simulations was used to investigate interactions between Fn and eight, 20-mer peptide variants synthesized to mimic fibronectin-binding repeat 9 (FnBR-9) of FnBPA from S. aureus, with particularly interested in double “mutations” at residues equivalent to positions 782 and 786 in FnBPA. Simulations reveal that the bond strength depends on whether a peptide dissociates through the lowest-energy pathway or is forced to unbind along a determined pathway. Additionally, data show anomalous unbinding behavior for H\textsubscript{782}Q\textsuperscript{+}K\textsubscript{786}I compared to the wild- and H\textsubscript{782}Q\textsuperscript{+}K\textsubscript{786}N-polymorphs, suggesting structural unfolding of Fn domains distant from the binding site. Together, these data demonstrate that cooperative amino acid substitutions in FnBR-9 may affect adhesion by altering bond strength at the site of binding, and may also influence cell invasion reactions by causing the extension of more distant regions within Fn, particularly under the influence of an external stress [1]. This provides a mechanistic explanation for clinical, endovascular infections caused by S. aureus that have nonsynonymous single nucleotide polymorphisms in the region of fnbA that codes for FnBRs in FnBPA.

\textbf{Key-words:} Bacterial Adhesion; Staphylococcus Aureus; Fibronectin; Metadynamics

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\textbf{References:}