Describing the dynamics behind extension/retraction of Enterohemorrhagic Escherichia coli Type 4 Pilus

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Type IV pilus (T4P) are distinctive dynamic filaments at the surface of many bacteria. They can rapidly extend and retract with the rate of ~1000 subunits per second [1]. Such behavior enables T4P to play different and crucial roles: adhesion to cell host, twitching motility, DNA uptake and microcolony formation. One of the important human pathogens belongs to the Enterohemorrhagic Escherichia coli (EHEC), in which T4Ps are shown to be among the virulence factors [2]. The structure of the periplasmic domain of EHEC PpdD has been recently determined by Nuclear agnetic Resonance (NMR) spectroscopy. This structure has been used in combination with cryo-EM data of the EHEC pilus to determine an atomistic model of the T4P filament with the resolution of 8 angstrom [2]. However, the mechanism behind the extension and retraction of the pilus are not fully described yet .

We have performed all-atom molecular dynamics (MD) simulations to better characterize the dynamical behavior of the Pilus. Our simulations revealed the network of interactions between the subunits and highlighted key regions and residues that play role in modulating the flexibility of the filament. We have further analyzed the effects of the key residues by performing MD simulations of several mutants. Previous mutagenesis experiments revealed a set of important residues for the assembly and stability of the pilus [2]. Here we show that our results are in agreement with the experiments and we are able to better describe the role of those residues. Finally, we have investigated the effects of calcium ions on the overall stability of the pilus by performing MD simulations of PpdD in the calcium-bound and free forms.

Our results revealed at atomistic detail, the network of dynamic interactions between subunits and the role of different regions in modulating the filament flexibility. This characterization of the conformational dynamics can also explain the physico-chemical basis of the molecular mechanisms behind the extension and retraction of the pilus. In addition, the analysis of mutants enabled us to better describe the role of key residues for the function of T4P. Consequently, our study will shed light on the physico-chemical interactions that drive the behavior of large and dynamic molecular assemblies. Finally, the obtained knowledge enables us to design strategies modulating the behaviour of the filaments, which in turn can pave the way toward the development of vaccines and therapeutics.

Bibliography :

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