Unfolding the Mysteries of vWF: Experimental vs. Computation Studies of vWF's A2 Domain

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vonWillebrand Disease debilitates 4+ million people in the US with most subtypes induced by mutations of the von Willebrand Factor (vWF) multimeric glycoprotein responsible for hemostasis. In homeostatic regulation, vWF's mechanosensitive A2 domain unfolds under shear stress induced via vasculature rupture stenosis. This mechanism's dual-functionality initiates coagulation and ADAMTS13 proteolysis of vWF multimers. The studied 1541 mutation induces hemophilia via unknown mechanisms. The research question was whether in-vitro optical tweezer experiments (OT) and molecular dynamics (MD) could characterize the hydrodynamic unfolding forces for wildtype (WT) and 1541. The hypotheses stated that the 1541 mutant would induce altercations to the domain's bending modulus, subjecting it to greater unfolding susceptibility. In addition, a calcium ion's expression in A2 would conversely limit configurational deformations of the protein, thereby increasing resultant force. OT involved implementing lasers traps for A2 pulling to determine work, contour and persistence length. Data was fit using non-linear regression solvers for the Worm-Like Chain model. CHARMM, NAMD, and VMD platforms were programmed for MD modeling of A2 and its variants under shear stress. Key conclusions were that the average linearization force for Calcium and 1541 variants were 237% and 66% when compared to the WT. OT demonstrated significant decrease in the contour/persistence length of 1541 vs WT, validating conformational instabilities. Thus, both OT and MD defined 1541 disease mechanisms and proved calcium's reinforcement of A2, giving both experimentation platforms encouraging applications in preventing vWF dysfunctionality and expanding optimized MD parameters to other mechanosensitive disease studies.

Awards Won:

Third Award of $1,000