No. 2235

Atomic-Level Analysis for Salt Concentration-Dependent Structural Responses of a Plasma Protein von Willebrand Factor

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Summary

Under significant fluid dynamic stress in blood vessels during bleeding, the tertiary structure of the A2 domain of von Willebrand factor (vWF-A2) is unfolded. The unfolded vWF-A2 is cleaved, and the cleaved vWF forms multimers with the appropriate binding capacity for platelets, leading to platelet accumulation at the injury site. This mechanical response of vWF-A2 is crucial in the initial phase of hemostasis but should not be overly sensitive or insensitive. Increased blood sodium concentration due to dehydration or excessive salt intake hinders the cleavage of vWF, resulting in excessive platelet binding and an increased risk of thrombosis. However, the influence of salt on the mechanical response of vWF remains poorly understood. To analyze the mechanical response of vWF-A2 in detail, we employed rheology nuclear magnetic resonance spectroscopy (NMR) to observe vWF-A2 at the atomic level and in real-time under the physiological fluid dynamic stress.

First, we prepared isotope-labeled vWF-A2 in Escherichia coli and examined its structural stability at different salt concentrations using fluorescence spectroscopy. We found that higher salt concentrations stabilized the core structure of vWF-A2. Nonetheless, under fluid dynamic stress, rheology NMR revealed that the core structure of vWF-A2 was more likely to be unfolded at higher salt concentrations. This observation was supported by rheology molecular dynamics (MD) simulations that traced the protein unfolding under fluid dynamic stress.

A recent study has shown that salt addition inhibits the cleavage reaction of vWF-A2. Therefore, while the core structure of vWF-A2 is more prone to unfolding under fluid dynamic stress at high salt concentrations, the inhibitory effect of salt on cleavage surpasses the unfolding effect. Thus, the stability of the core structure of vWF-A2 increased with higher salt concentration, making the mechanical response to fluid dynamic stress more sensitive, as revealed at the atomic level. Further investigation into the influence of salt on the mechanical response of vWF-A2 may contribute to understanding the relationship between elevated blood sodium concentration and thrombosis.