Molecular Modelling of the HSulf-2 protein, one intrinsically disordered protein (IDP)

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A sulfatase is an enzyme responsible for modulating the sulfated state of macromolecules, such as heparan sulfate proteoglycan (HSPG), by cleaving the ester-sulfate or sulfamate bond and thus releasing sulfate. It is involved in cellular metabolism and developmental cell signaling. The cysteine or serine in the active site is converted to formylglycine (FGL) to perform enzymatic activity. Among the 17 known human sulfatases, endosulfatases 1 (HSulf-1) and 2 (HSulf-2) were discovered in 2002 [1]. These two HSulf isoforms are composed of three domains: the catalytic domain (CAT), the hydrophilic domain (HD), and the C-terminal domain (Cter). One of the main differences is that HSulf-1 tends to suppress cancer development, whereas HSulf-2 is overexpressed in numerous cancers, particularly breast cancer, making it a promising therapeutic target. Structural exploration of HSulf-2, especially of the ligand-binding pocket, is essential for the design of inhibitors as potential anticancer drug candidates [2].

However, no experimentally resolved structure of HSulf-2 has yet been uploaded to the Protein Data Bank (PDB). One alternative is to use the state-of-the-art AI-based structure predictors to predict the apo form of HSulf-2, and the holo form with polysaccharide ligands, to especially reveal the binding cleft of the HD. Molecular dynamics simulations are run to study the dynamic profile of the HD and the potential binding pockets. This study sheds light on the IDR-binding mechanism of the HD and contributes to the eventual design of inhibitors targeting it.

Bibliography :

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