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C-terminus of the histone-lysine N-methyltransferase NSD3 characterized by small-angle X-ray scattering

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Nuclear receptor binding SET domain (NSD) proteins, a family of three histon lysine methyl transferases, are considered decisive for suppressing currently lethal cancer diseases.[1] Aside from the well characterized catalytic SET domain, NSD have multiple potential chromatin-binding motifs that are clinically relevant, such as the proline-tryptophan-tryptophan-proline (PWWP), the plant homeodomain (PHD) and the adjacent Cys-His-rich domain (C5HCH) located at the C terminus. The crystal structure of the individual domains is available and has allowed initiating drug-designing of potential inhibitors, but the analysis of the intra-domain features and the characterization of mutual domain conformations has been hindered by the intrinsic flexibility of larger constructs. We have obtained the first structural characterization of the NSD3 C-terminal region comprising PWWP2, SET and PHD4 domains, by using solution small-angle X-ray scattering (SAXS). The challenging task of modelling flexible systems has been faced by complementing SAXS data on two multiple-domain NSD3 constructs with size-exclusion chromatography and advanced computational modelling. Structural models predicted by state-of-the-art homology modelling based on machine learning have been validated in direct space, by comparison with the SAXS-derived molecular envelope, and in reciprocal space, by reproducing the experimental SAXS profile. Selected models have been refined by molecular dynamics simulations, where the ab initio molecular envelope calculated from SAXS data represents an additional potential. The role of S-adenosyl methionine and histone H3 peptide ARTKQTARKSTGGKAPGGC in determining the geometrical features of the interdomain conformation has been also elucidated, finding a dramatic effect of the first ligand in shrinking the SET-PHD4 region. This study shows how SAXS data can be used in synergy with advanced computational modelling technique to achieve a detailed structural characterization that sheds light on how NSD3 domains are interconnected in the C-terminus.

Figure 1. Structural model of the NSD3 C-terminal region comprising PWWP2, SET and PHD4 domains (center), obtained by modelling SAXS data on the constructs PWWP2-SET and SET-PHD4.

[1] M. Morishita, E. di Luccio, Biochim Biophys Acta, 2011, 1816, 158.

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