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Elucidation, functional clustering and structural characterization of β TrCP1 substrates through a molecular dynamics study

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The current interest in the identification and characterization of β TrCP1 substrates necessitates a promising approach with broad structural constraints of WD40 potential binding sites. Here, we employed an in silico integrative approach to identify putative novel substrates of β TrCP1. Through a screened degradation motif (DSGXXS) for the entire human proteome and comparative substrate binding analysis of β TrCP1, we identified 344 substrates, sharing high sequence similarity with the consensus motif. Subsequent filtering on the basis of functional annotation and clustering resulted in of hits having clear roles in various cancer types. These substrates were phosphorylated at the Ser residues (Ser14 and Ser18) of the conserved motif. A comprehensive and thorough analysis of β TrCP1–phosphopeptide association indicated residual contributions located at the upper face of the b-propeller. Evidently, upon binding to phosphopeptides, the channel of β TrCP1 more open conformation to assist substrate binding. To elaborate on the oncogenic function of β TrCP1, the SKP1– β TrCP1–CDH6 ternary complex was docked against CUL1–RBX1 and the acquired model exactly resembled the previously characterized SKP1– β TrCP1– β -catenin model. Overall, a deeper understanding of substrate targeting mechanisms coupled with the structural knowledge of β TrCP1 and associated proteins will be useful for designing novel targets for cancer therapeutics.

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