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Cancer Molecular Medicine: Targeting C-Myc and USP37 Interactions

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Abstract

Background: C-Myc is master transcriptional regulator found to be dysregulated in variety of cancers. One major ubiquitin specific protease that regulate the turnover of C-Myc is USP37. The present work aims to explore molecular interaction points between C-MYC and USP37. Secondarily, a peptide disruptor is designed for this interaction.

Methods: A composite molecular model of USP37 was generated by Modeller v9.17 using atomic coordinates of C19 domain of USP46, pleckstrin domain and atomic coordinates of USP37 generated using iterative threading modeling. After thermodynamic and structural refinement, finally selected model of USP37 was docked against atomic coordinates of C-Myc (PDBid 5l4Z) under static and dynamic state. The disruptor peptide was designed de novo and based on the hotspots of interactions between USP37 and C-Myc. Finally, the potential activity of disruptor peptide was assessed by undertaking molecular docking of peptide with USP37.

Results: Structurally, USP37 molecule resemble with a bowl shape where both C19 and pleckstrin domain were found in the central region. Near N-terminal the un annotated region was found to adopt structure homologous to the Zn finger. This denotes the possibility of USP37 interaction with DNA alone or along with c-Myc. The interaction points of USP37 and c-Myc lies at region which is exterior to both pleckstrin and C-19 domain. This binding interface contains both polar and no polar residues, taken this and sequence permutation into account a peptidyl disruptor is designed and docked against USP37. Most docking simulation results in the congregation of designed peptidyl disruptor to the targeted spatial position on USP37 molecule, suggesting its potential effectiveness.

Conclusion: The findings could be exploited in designing small molecular and peptidyl disruptor that could be used as a chemotherapeutic agent in cancers where C-Myc-USP37 interactions plays an important role in pathogenesis.

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