Synergy and Anti-Cooperativity in Allostery: Molecular Dynamics Study of WT and Oncogenic KRAS-RGL1

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Abstract

This study focuses on investigating the effects of an oncogenic mutation (G12V) on the stability and interactions within the KRAS-RGL1 protein complex. The KRAS-RGL1 complex is of particular interest due to its relevance to KRAS-associated cancers and the potential for developing targeted drugs against the KRAS system. The stability of the complex and the allosteric effects of specific residues are examined to understand their roles as modulators of complex stability and function. Using molecular dynamics simulations, we calculate the mutual information, MI, between two neighboring residues at the interface of the KRAS-RGL1 complex, and employ the concept of interaction information, II, to measure the contribution of a third residue to the interaction between interface residue pairs. Negative II indicates synergy, where the presence of the third residue strengthens the interaction, while positive II suggests anti-cooperativity. Our findings reveal that MI serves as a dominant factor in determining the results, with the G12V mutation increasing the MI between interface residues, indicating enhanced correlations due to the formation of a more compact structure in the complex. Interestingly, although II plays a role in understanding three-body interactions and the impact of distant residues, it is not significant enough to outweigh the influence of MI in determining the overall stability of the complex. Nevertheless, II may nonetheless be a relevant factor to consider in future drug design efforts. This study provides valuable insights into the mechanisms of complex stability and function, highlighting the significance of three-body interactions and the impact of distant residues on the binding stability of the complex. Additionally, our findings demonstrate that constraining the fluctuations of a third residue consistently increases the stability of the G12V variant, making it challenging to weaken complex formation of the mutated species through allosteric manipulation. The novel perspective offered by this approach on protein dynamics, function, and allostery has potential implications for understanding and targeting other protein complexes involved in vital cellular processes. The results contribute to our understanding of the effects of oncogenic mutations on protein-protein interactions and provide a foundation for future therapeutic interventions in the context of KRAS-associated cancers and beyond.

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