

Conformational states of Kras in its active and inactive form

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RAS proteins are in the forefront of cancer research. Despite the intensive efforts of the past decades to date no efficient RAS inhibitor has been discovered yet. It is difficult to target Ras directly as the oncogenic mutants are locked in the active (GTP-bound) conformation. There is a high intracellular concentration of GTP and the protein has a great affinity for it while Ras has only an inherently low GTPase activity. While there is a large amount of experimental data (e.g. more than 100 X-ray structures), our view of RAS structure and mechanism through which it is regulated is mainly based on static structures, and overlooks conformational dynamics and allosteric effects. While an increasing number of simulation data are emerging, there is an acute need for simulation methods that can efficiently map the conformational surface of KRAS. The goal of our research is to map the conformational space of the GDP bound inactive and the GTP bound active states, to detect the interactions between the HVR (hyper variable region) and the catalytic domain and to discover similarities and differences between the two activation states.