Oncogenic K-Ras Proteins: Mechanisms of Activation by Guanine Exchange Factors

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Ras proteins work as GDP–GTP binary switches and regulate cytoplasmic signaling networks that are able to control several cellular processes, playing an essential role in signal transduction pathways which may turn on genes involved in cell growth, differentiation and survival and eventually leading to cancer [1]. Mutations in Ras genes are found in about 25% of human cancers so that identifying anti-Ras therapeutic strategies is very relevant for cancer treatments, but despite intense effort no general therapies have reached full clinical application [2]. One of the hardest challenges to face is that, with more than hundred different missense mutations found in cancer, mutation-selective therapeutic strategies are needed. In the present communication a mutated GDPase "Kirsten Rat Sarcoma" KRas-4B protein at the inactive state bound to the guanine exchange factor (GEF) "Son-of-Sevenless" SOS1 [3] has been simulated in aqueous solution by molecular dynamics at the all-atom level (Figure 1). The Gibbs free-energy landscape reveals stable configurations of the KRas-SOS1-GDP complex at given values of RMSD and gyration radius of the complex (Figure 2). A specific mechanism due to the binding of the SOS1 to KRas has been identified as the key for GDP extraction and consequent protein activation for signaling, so that such mechanism can be targeted by small-molecule drugs designed to block the release of GDP and its eventual substitution by GTP, i.e. to promote the inactive states of KRas.

REFERENCES

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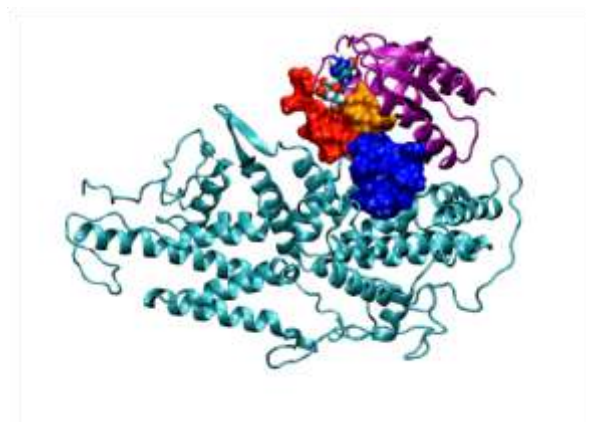
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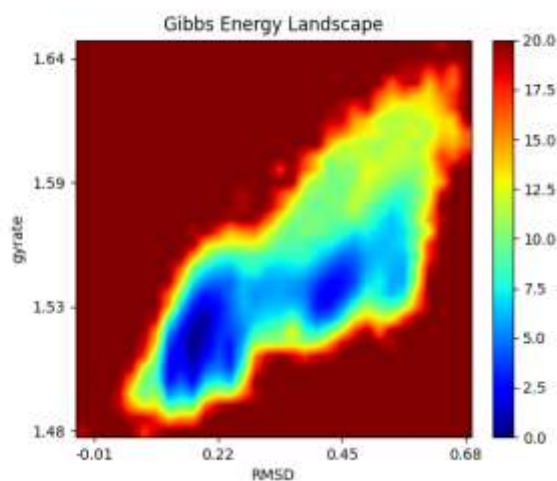

Figure 1: The KRas-SOS-GDP complex

Figure 2: Gibbs free-energy landscape of KRas-SOS-GDP complex (left)