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A structural model of a megadalton Ras-Raf signalosome

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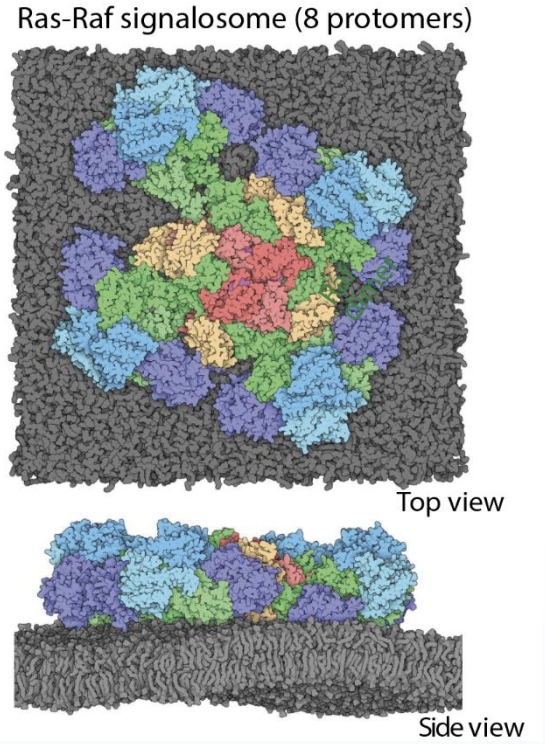
Date	:	29 April 2019 (Mon)
Time	:	11:30 am – 12:30 pm
Venue	:	SCM 013
Language	:	English
Facilitator	:	Prof. Bian Zhao Xiang

Abstract

The protein K-Ras functions as a molecular switch in signaling pathways regulating cell growth. In the MAPK pathway, which is implicated in many cancers, multiple K-Ras proteins are thought to assemble at the cell membrane with Ras-effector proteins from the Raf family. Here we propose an atomistic structural model for such an assembly. Our starting point was an asymmetric, GTP-mediated K-Ras dimer model, which we generated using unbiased molecular dynamics simulations and verified with mutagenesis experiments. Adding further K-Ras monomers in a head-to-tail fashion led to a compact helical assembly.



This assembly stabilizes K-Ras in its active state and presents composite interfaces to facilitate Raf binding. Guided by existing experimental data, we then positioned C-Raf, the downstream kinase MEK1, and accessory proteins (Galectin-3 and 14 3 3σ) on the helical assembly. The resulting Ras-Raf signalosome model illustrates the organization of signaling proteins at the plasma membrane upon MAPK signaling. The construction of this megadalton model based on extensive simulations suggests that molecular dynamic simulations combined with experimental validations have entered into a new phase as a unique platform of structural biology and drug discovery.

~ All are welcome ~