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Allosteric modulation of the Ras active site: from biochemistry to binding specificity

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Ras is found mutated in about 20% of human cancers, associated with poor prognosis due to a lack of drugs able to deter uncontrolled signaling through multiple pathways in the cell. There are three isoforms: H-, K-, and N-Ras. The G-domain, which catalyzes GTP hydrolysis and mediates downstream signaling, is 95% conserved between the Ras proteins. To date, biochemical studies done on H-Ras have been considered representative of all three Ras proteins. We have recently shown, using a combination of X-ray crystallography, NMR spectroscopy, enzyme kinetic assays and molecular dynamics simulations, that the three isoforms are biochemically distinct due to allosteric effects of isoform-specific residues on the population of conformational states. Furthermore, oncogenic mutations also affect conformational states in the particular isoforms. An engineered high-affinity binder shows a modest specificity toward K-RasG12D over the wild type protein and crystal structures of the complexes reveal allosteric effects on conformational states induced by the mutation, providing a view of specificity features that may be further developed to direct targeting of oncogenic mutants of K-Ras.

Biography

Carla Mattos received her PhD at MIT and did Post-doctoral work at Harvard University and at Brandeis University. She is a recipient of the Boroughs Wellcome Fund New Investigator Award in the Pharmacological Sciences, the CAREER award from the NSF and the Presidential Early Career Award for Scientists and Engineers. She uses a combination of biophysical and biochemical approaches to study Ras structure, dynamics and allosteric connections to infer and test hypothesis associated with function. She is actively engaged in the Ras initiative at the NCI through her collaborations at the Frederick National Laboratory for Cancer Research.

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