Crystal Structure of the Small G Protein M-Ras and its Implications

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Ras proteins are involved in a wide variety of cellular responses. They undergo conformational changes in two conserved regions, named “switch I” and “switch II” by cycling between GTP-bound active and GDP-bound inactive states, and thereby function as ‘on/off’ biological switches. In the active state, they bind to their specific effectors to initiate various signaling events.

We have determined the crystal structure of a Ras-family protein, M-Ras (residues 1-178), in complex with GDP and GTP. The overall structure of M-Ras resembles those of other Ras-family proteins excluding its characteristic conformations in switch regions. In the GTP-bound form, Ras proteins, including H-Ras and Rap2A, are known to conserve several intra-molecular interactions essential for conformational stabilization of switch I. In particular, hydrogen bonds between Thr-35 and the ã-phosphate of GTP play important roles to stabilize this effector loop, yielding a preferable conformation for effector recognition. In the case of M-Ras-GTP, the corresponding interaction through Thr-45 is completely lost, and this lack causes a distinctive switch I conformation, where switch I loop is pulled away from the guanine nucleotide and shows an open unstable conformation. In addition, the orientation of the á2-helix in switch II shows a remarkable difference from those of H-Ras and Rap2A. These structural features may provide new information to investigate effector recognition mechanisms by Ras proteins.

Keywords: Ras, switch region, crystal structure