Role of the arginine finger in Ras-RasGAP revealed by QM/MM calculations

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Ras is a key enzyme in cellular signal transduction inducing cell division. The signal is ON when Ras contains the substrate guanosine triphosphate (GTP). The OFF state is taken during hydrolysis of GTP to GDP and P_i. The switch is induced by the activator RasGAP docking to Ras.

In the Ras-RasGAP complex, hydrolysis of GTP is strongly accelerated as compared to Ras alone (10^5 times). This is largely attributed to the arginine finger R789 of RasGAP pointing to the tip of the substrate in the transition state analogue (1). We performed QM/MM simulations where triphosphate was treated using density functional theory while the protein complex and water environment were described classically using MD. IR spectra of triphosphate and various properties were calculated for Ras and Ras-RasGAP. Compared to Ras, charge shift, bond stretching and distortion towards an eclipsed γ-to-β orientation are much more pronounced in the complex. The crucial electron shift is such that GTP approaches the charge distribution of the product state. The explanation is found by detailed analysis of the electrostatic field at the phosphorus atoms. The positive charge of the arginine finger has a negligible or even counterproductive effect. Instead, arginine is shown to act by displacing water (~ 14 molecules) out of the binding niche. The resulting enhanced electrostatic field catalyses the cleavage step (2). Only as a complex do Ras and GAP form the perfect binding pocket for GTP with optimal electrostatic forces. The mechanism provides an explanation for the catalytic effect of similar complexes observed in signalling and elsewhere.

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