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Perturbation of the conformational dynamics of an active-site loop alters enzyme activity

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SUMMARY

The role of internal dynamics in enzyme function is highly debated. Specifically, how small changes in structure far away from the reaction site alter protein dynamics and overall enzyme mechanisms is of wide interest in protein engineering. Using RNase A as a model, we demonstrate that elimination of a single methyl group located >10 Å away from the reaction site significantly alters conformational integrity and binding properties of the enzyme. This A109G mutation does not perturb structure or thermodynamic stability, both in the apo and ligand-bound states. However, significant enhancement in conformational dynamics was observed for the bound variant, as probed over nano- to milli-second time scales, resulting in major ligand repositioning.