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The transient kinetic mechanism of protein arginine methylation

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Protein arginine methyltransferases (PRMTs) catalyze the transfer of the methyl group from S-adenosyl-L-methionine (AdoMet) to the guanidino group of arginine residues in protein substrates, resulting in mono and di-methylarginine residues. Protein arginine methylation is an important posttranslational modification mark regulating epigenetics and many other cellular pathways. We sought to resolve significant kinetic steps of PRMT catalysis by combining steady-state and transient kinetics techniques. We have constructed a novel turnover model which reveals critical information about the ternary complex formation and methyl transfer process. Methyl transfer was found to be the rate limiting step. Significantly, the catalysis is found to follow a unique mechanism in which PRMT1 is able to randomly bind AdoMet or peptide substrate to form binary complex but follows a kinetically preferred (ordered) pathway to form the ternary complex. The delineation of PRMT1 transient kinetic mechanism provides new insights to understand biological function of arginine methylation and to design potent PRMT inhibitors.

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