STRUCTURAL REARRANGEMENTS OF THE PIN1 PROLYL ISOMERASE DURING CATALYSIS

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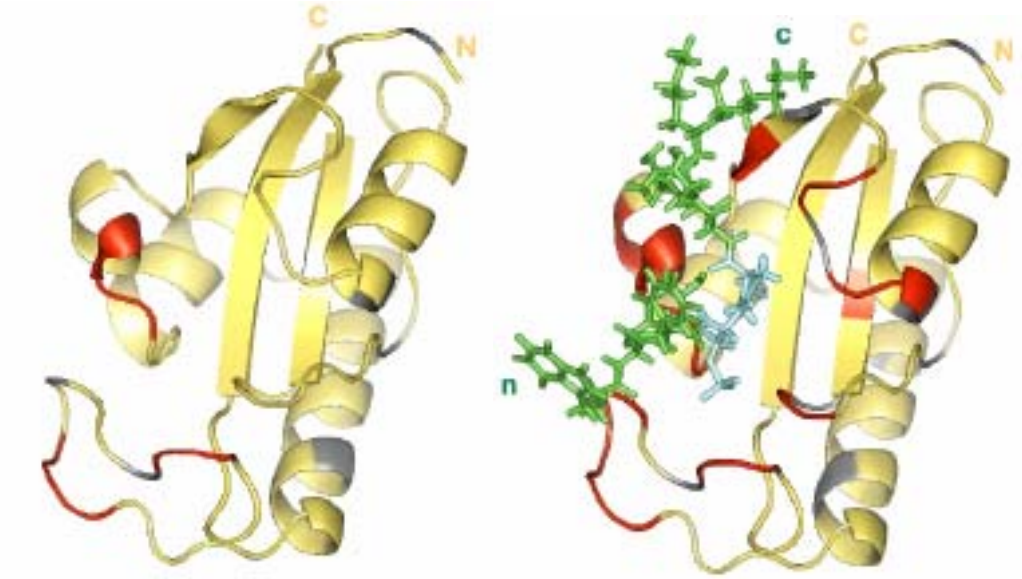
Introduction

Prolyl isomerases (PPIases) catalyze the cis-trans isomerization about the prolyl peptide bonds. Pin1 is unique among prolyl isomerases in that it specifically isomerizes phosphorylated Ser/Thr-Pro (pSer/pThr-Pro) bonds. The acceleration of this isomerization may serve as a second regulatory mechanism in addition to phosphorylation in the form of a kinetic control. Known substrates of Pin1 include a subset of cell cycle proteins (e.g. NIMA, Cdc25, Cyclin D) as well as the Alzheimer protein Tau and the transcriptional activator p53; however, the role of a conformational switch and the mechanism of its regulation by Pin1 is not understood. Here we perform structural and dynamic NMR experiments on Pin1cat during catalysis of a true substrate. Intermolecular NOE data collected during turnover of the peptide substrate together with
backbone dynamics measured during catalysis reveals insight into the reaction trajectory. Conformational exchange in the free enzyme similar to the one observed during turnover suggests the pre-existence
of dynamics.

Experimental

NHMFL Varian 720 and 600 solution magnets were used in this study.

Results and Discussion



Backbone ^{15}N probes exhibiting conformational exchange in the free enzyme (left) and in the saturated, turning-over complex (right) are highlighted in red. Similar conformational exchange suggests preexisting functional protein motions in the free enzyme.

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