DYNAMICS OF Pin1-PPlase MUTANTS IN THE FREE AND SUBSTRATE-SATURATED STATES

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Introduction

The link between internal enzyme motions and catalysis is poorly understood. Correlated motions in the μ-ms timescale may be critical for enzyme function. We have characterized the backbone dynamics of the peptidyl-prolyl isomerase Pin1 catalytic domain in the free state and during catalysis. Pin1 is a prolyl isomerase of the parvulin family; it is essential for cell-cycle progression and therefore an attractive new target for anti-tumour therapies. In addition, it has recently been shown to interact with neuronal tau protein and to inhibit its aggregation into fibrillar tangles as found in Alzheimer's disease.

We are characterizing mutants of the Pin1 catalytic domain that have enhanced activity with respect to wild-type. We would like to determine whether there is a correlation between the mutant activity and mutant backbone flexibility in the active site.

Experimental

^{15}N -CPMG-TROSY relaxation experiments on solution-state 600 MHz magnet, Tallahassee.

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