CONFORMATIONAL DYNAMICS OF THE Na^+/Ca^{2+} EXCHANGER

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Introduction

The Na^+/Ca^{2+} exchanger (NCX) plays a critical role in the contraction of the heart by acting as the major exporter of Ca^{2+} across the plasma membrane. Regulation of the NCX is achieved in large part by two intracellular Ca^{2+} binding domains, CBD1 and CBD2, whose structures were recently solved by NMR spectroscopy and X-ray crystallography.[1,2] The structures revealed that the two domains respond very differently to Ca^{2+}. While the CBD2 structure is affected relatively little by the removal of Ca^{2+}, CBD1 is reported to be intrinsically disordered in the absence of Ca^{2+}. In order to further define the mechanisms by which CBD1 and CBD2 regulate the activity of the NCX, we have initiated a detailed description of the conformational dynamics in these two domains.

Results and Discussion

Longitudinal (R_1) and transverse (R_2) ^{15}N relaxation rates and heteronuclear nuclear Overhauser effects (NOEs) were measured along the protein backbone for both the Ca^{2+}-loaded and the apo state at 800 MHz proton frequency using a cryogenically cooled probe. The relaxation data are currently being analyzed by the Lipari-Szabo model-free method,[3] molecular dynamics simulations and contact models .[4]

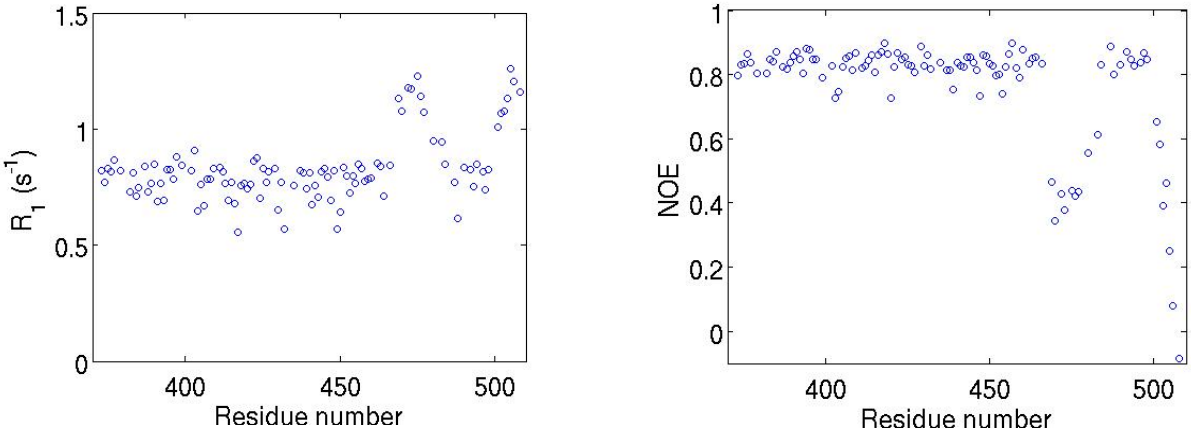

Figure caption: R_1 and NOE profile for Ca^{2+}-loaded CBD1. The NOE values decrease in the FG loop and C-terminus, indicative of larger amplitude motions. Structural models of the NCX suggest that the FG loop may regulate Ca^{2+} binding.

Acknowledgements

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References

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