Probing Molecular Protein Dynamics by NMR Relaxation: Insights from the Transthyretin A97S Mutation

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ABSTRACT

Protein mutants often resemble their wild-type counterparts in structure yet behave very differently. Such differences often come not from their static conformation but from how the molecules move. NMR relaxation allows us to learn these molecular motions and connect them with protein stability. Relaxation data provides insights into which regions of a protein move more or less freely, creating a simple map of motion. This dynamic information complements what can be seen from static structure analysis obtained by methods such as X-ray crystallography or cryo-electron microscopy.

In our ongoing study of transthyretin (TTR), a human transport protein, we use NMR relaxation to investigate how mutations alter its molecular dynamics. Its Ala97Ser (A97S) mutation is the main pathogenic form in Han-Taiwanese patients. Although the mutant and wild type look almost the same in static views, relaxation analysis shows that a short flexible segment on the protein surface in A97S moves more freely, weakening the contacts that hold the four subunits together. This example demonstrates how relaxation analysis connects magnetic measurements with molecular motion and underscores the importance of dynamic information for interpreting mutation-induced changes. The same framework can be extended to other proteins where structural similarity conceals important dynamic differences.

REFERENCES

1. Lipari, G. et al. Model-free approach to the interpretation of nuclear magnetic resonance relaxation in macromolecules. *J. Am. Chem. Soc.* **104**, 4546 (1982).

2. Kovermann, M. et al. Protein dynamics and function from solution state NMR spectroscopy. *Q. Rev. Biophys.* **49**, e6 (2016).

3. Feng, Y.-C. et al. The structural and dynamic insights into the Ala97Ser amyloidogenic mutation in transthyretin. *Chem. Asian J.* **20**, e202401438 (2024).

4. Liu, Y.-T. et al. Clinical and biochemical characterization of the Ala97Ser transthyretin variant in Taiwanese patients with hereditary amyloidosis. *Amyloid* **22**, 45 (2015).