How structurally similar protein domains achieve functional diversity?

Researchers at the Department of Chemistry & Molecular Biology and the Wallenberg Centre for Molecular and Translational Medicine have developed a new compare-&-contrast approach to discern the dynamics of protein domains which are structurally very similar yet display large functional diversity.

In their recent work, Associate Professor Björn M. Burmann and Post-doctoral Fellow Ashish Kawale employed a technique called solution NMR (nuclear magnetic resonance) spectroscopy to probe protein motions at the amino acid level. The investigation of the inherent motions of backbone atoms from five structurally similar protein domains using NMR relaxation method allowed them to extract an interesting correlation between protein dynamics of the protein backbone and their respective functional repertoire.

Lead author Björn Burmann says: “Understanding the intrinsic protein dynamics is nowadays still only done for a small number of proteins, but it presents the most appropriate and insightful way to describe the protein molecule in its entirety and has a tremendous potential for the detailed understanding of the functional roles of proteins in general. Our approach to probe protein dynamics is robust and practically applicable to any small to medium sized proteins of pharmaceutical interest for correlating their structural and dynamical properties to their functions, providing important cues for more effective rational drug design in the future.”

Dynamics are pivotal to protein functionality.

Proteins are important constituents of cells and can be imagined as molecular machines executing a specialized set of tasks. The ‘wiggle-jiggle’ between different conformations i.e., conformational fluctuations allow proteins to modulate their functional efficiency, perform novel tasks or even totally activate or inactivate their functions. Thus, the interplay between protein structure and dynamics is crucial for understanding protein functions.

To discern the dynamics the main challenge is the lack of the suitable techniques. Solution NMR spectroscopy aids to uncover the hidden dynamical motions by in-depth investigation of protein dynamics at an amino acid level under near physiological conditions.

Ashish Kawale says: “A lot of emphasis is placed on understanding the protein structure, predominantly because proteins are easily mistaken as LEGO-type rigid entities. In reality, proteins are inherently dynamic and undergo a series of conformational changes which help them to perform their peculiar function. Using our recently developed compare-&-contrast approach, we can now understand the dynamics of structurally analogous proteins at an unprecedented resolution to comprehend their functional properties in detail”.

The research has been published in the journal Structure in a paper entitled Inherent backbone dynamics fine-tune the functional plasticity of Tudor domains.

The detailed protocol “Characterization of backbone dynamics using solution NMR spectroscopy to discern the functional plasticity of structurally analogous proteins” will appear in STAR Protocols November 4, 2021 (DOI: https://doi.org/10.1016/j.xpro.2021.100919).

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