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Hydrogen exchange method to identify the protein targets of drugs

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Abstract

It is essential to identify a drug's target(s) to better understand the mechanism of action and anticipate possible side effects. Identifying these target(s) is a significant challenge in drug discovery. The most commonly used approach to identify the protein targets of small bioactive molecules is to capture binding proteins by affinity chromatography. Although well established, the affinity-based methods have considerable drawbacks. Small bioactive molecules need to be attached covalently to a solid support, which may result in masking critical recognition site(s) for the target proteins, and extensive washes are required to minimize the contamination of non-specifically bound proteins. This decreases the likelihood of identifying weakly bound proteins that may play significant roles in the pharmacological actions of small bioactive molecules. We propose here a new approach that does not require the immobilization of drugs. Our method measures the thermodynamic stability of proteins in the presence and absence of a small molecule drug by monitoring the changes of hydrogen-deuterium exchange rates of histidine residues in varying concentrations of protein denaturant. Because binding of a small molecule to a protein usually enhances the thermodynamic stability of the protein, the experiment should identify the target proteins. The results from our proof-of-concept study will be presented, and the strategy for the target identification in a proteome-scale sample will be discussed.

Biography

Masaru Miyagi has Ph.D. degree in Protein Chemistry and Mass Spectrometry (Osaka University, Japan). He is Assistant Professor at Case Western Reserve University. Dr. Miyagi's scientific interests are focused on understanding how proteins function in the living cell. He has published more than 75 papers in reputed journals and has been serving as an editorial board member of Journal of the Mass Spectrometry Society of Japan, Journal of Integrated OMICS, and The Open Spectroscopy Journal.