Photoaffinity Labeling for Structural Probing Within Protein

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Editors

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Foreword

Harnessing the Protein

The highly ordered molecular assembly of living systems represents an endless frontier for the application of chemical biology. A useful chemical approach to define specific molecular recognition is covalent cross-linking of a ligand and its receptor in an affinity-based manner. The chemical basis for affinity cross-linking is classified into two categories: ground-state reactions secure the residue-selective nature of affinity labeling and excited-state reactions generate highly reactive species to characterize the powerful feature of photoaffinity labeling. The major advantage for photoaffinity labeling is that the probe is inert before irradiation to prevent ground-state side reactions with surrounding molecules in a non-specific manner. Ideally, the irradiation immediately generates an extremely reactive species to complete specific and stable cross-links which comes in contact with any one of the residues located close by. Since Frank H. Westheimer originally introduced this unique idea of the method in 1962, photoaffinity labeling remains and should continue to be a principal chemical method for the identification of a particular target among the complex mixture of biomolecules.

Photoaffinity labeling has become increasingly important in association with the development of rationally designed powerful probes. Simply stated, probes are prepared by installing a photoactivatable functional group (photophore) on the framework of biological ligands. For target-specific labeling, probes are always needed to satisfy conflicting requirements. The probe structure should be close to the original ligand whereas the introduction of the photophore and detection tag cause an increase in the size of probes resulting in the decrease of affinity. For designing probes, the generated reactive species should react rapidly within the functional domain depending on the affinity between the ligand and the target but should not indiscriminately react with co-existing molecules.

This book is composed of 12 chapters that describe recent topics of photoaffinity labeling mainly by taking advantage of the use of diazirine photophore. Leading experts have written their chapters by focusing on the photophore's application for illuminating the interesting protein world. The first three chapters describe the

rational design of efficient probes, followed by two chapters that consider the rapid and specific approach for the analysis of trace photo-labeled products. Chapters introducing synthetic, chemoselective, and genetic approaches for installing the diazirine photophore suggest new aspects of the methodology for the elucidation of bio-molecular assembly. Successful applications for glucose transporter and peroxisome represent the power of the methodology to analyze their structure and function. The last two chapters introduce the recent topic of photoaffinity labeling in the process of drug discovery and development.

Since the first report of photoaffinity labeling, the probe has been continuously improved through several important innovations to unleash the full power of the methodology. Now, photoaffinity labeling is well defined to ensure its specificity on labeled sites, which reveals the method to be an important approach of chemical biology for entering important areas of life science. An interesting application should be the structural probing of proteins that are difficult to crystallize. Photoaffinity labeling also could be a reliable strategy to reveal the molecular target during the early stage of drug discovery and development.

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