The latest progress of chemical array techniques for chemical biology research

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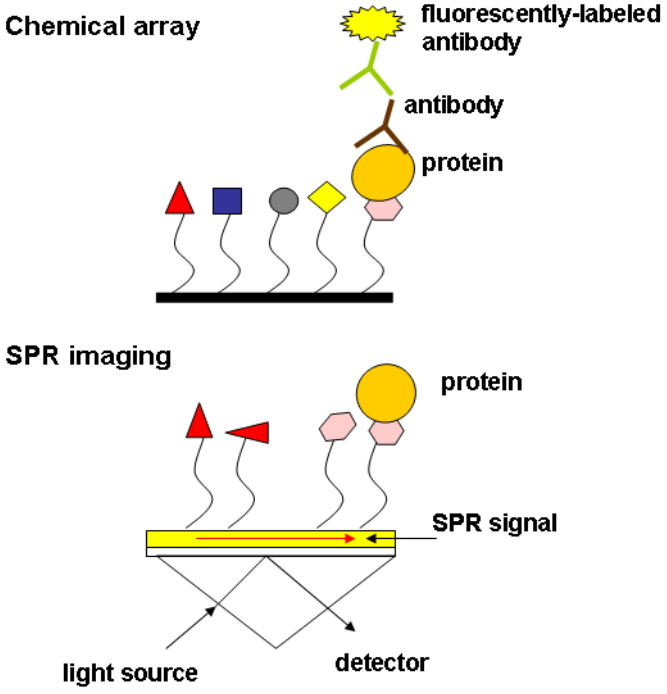
Chemical biology elucidating biological systems with small molecules (as chemical tools), attracts attention of organic chemists and molecular biologists now. Small-molecules which specifically modulate the function of proteins of interest, so called bioprobes, are powerful tools for chemical biology. The high throughput screening system to identify the aimed inhibitors and bioprobes is very important. Chemical array platform is a promising approach to detect ligand molecules for individual proteins. We have developed a photoaffinity chemical array to immobilize structurally diverse small-molecules, natural products, its derivatives and drugs on a solid support in a functional group independent manner. The advantages of photoaffinity cross-linking method are to immobilize a variety of compounds on a single chip easily and to expose the diverse moieties of small molecule toward a protein of interest on a chip. In addition, we have developed photoaffinity SPR imaging platform to observe multiple interactions between non-labeled proteins and surface-bound small-molecules. In this symposium, we report the recent results of chemical biology studies with chemical array and the remaining issues for chemical array.

Tau proteins are microtubule-associated proteins and known to be related with Alzheimer's disease. Tau proteins are abundant in neurons of the central nervous system and are less elsewhere. The aggregation of tau protein is often found in the Alzheimer's disease brain and is thought to contribute to neuronal dysfunction. There is a possibility that the inhibitor of the tau protein aggregation become a potent preventer of Alzheimer's disease. In order to discover small-molecules inhibiting the tau aggregation, we screened 2011 compounds by tau protein binding assay using chemical array. As tau-binding compounds, 202 compounds were identified by chemical array assay. Among them, 53 compounds were confirmed to bind to tau protein directly by our



photoaffinity SPR binding assay. Finally, it was revealed that 42 compounds have inhibitory activity for tau aggregation.

p38 mitogen-activated protein kinase (MAPK) has been identified as anti-inflammatory drug binding protein, a lipopolysaccharide-activated protein kinase, or a stress-responsive protein kinase. We have studied to elucidate the precise molecular mechanism by which p38 can exert various responses to stimuli, and we previously showed that p62/SQSTM1 bound to regulate p38 *in vivo*. Our biological studies revealed that two domains of p62 play an essential role for the interaction with p38, however it was not clear whether both domains interacted with p38 directly. So we attempt to use the photoaffinity SPR imaging platform to determine the binding site of p62/SQSTM1 to p38. SPR imaging experiments using photoaffinity linker to immobilize the peptides derived from p62 on gold substrate indicated that the domain comprising amino acids 164-190 of p62 binds to p38 directly. These SPR analysis data and empirical biologic data revealed that the binding site of p62 to p38 is the domain corresponding to 173-182.

References

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