STRUCTURAL STUDY ON SPECIFIC INTERMOLECULAR INTERACTION AND SELF-AGGREGATION OF BIOMOLECULE AND ITS APPLICATION TO DRUG DESIGN

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Structural study on the specific intermolecular interaction between biomolecules has been carried out using various physicochemical approaches to elucidate the biomolecular recognition mechanism. On the basis of the results of these structural studies, research focused on drug design has also been performed. Among the results obtained so far, three will be presented.

(1) Structural analyses of mRNA cap structure recognition by eukaryotic initiation factor 4E (eIF4E) and its functional regulation by endogenous 4E-binding protein (4EBP)

Model structural studies have shown that tryptophan (Trp) has the ability to bind specifically to 7-methylguanine (m^7G). The structural analyses of mRNA m^7G cap analogue–eIF4E complex proved the importance of Trp for the specific recognition of the cap structure. Furthermore, the mechanism of regulation by 4EBP of the function of eIF4E was also elucidated following the structure determination of the mRNA cap analogue–eIF4E–4EBP ternary complex.

(2) Structural study on self-aggregation mechanism of tau protein and development of aggregation inhibitor

To find a way of blocking the self-aggregation of tau, a causal protein of Alzheimer's disease, the aggregation mechanism of its central region, microtubule-binding domain (MBD), was investigated by various spectroscopy and structural methods. Consequently, the starting region of aggregation and amphiphilic behavior of MBD were elucidated, and an aggregation model was proposed. On the other hand, some aromatic compounds such as cyanidin and methylene blue, which were derived from various foods, can strongly exhibit the self-aggregation of MBD by stabilizing its random structure.

(3) Molecular design of cathepsin B (CB)-specific inhibitor and drug development

To design a CB-specific inhibitor from E64c, which exhibits a broad spectrum of cystein proteases (CPs), its complex structure with papain, which belongs to the CP family of CB, was determined by X-ray analysis, and the tertiary structure of CB was constructed by molecular dynamic simulation, on the basis of the complex structure. On the basis of the specificity of the predicted substrate-binding pocket of CB, a number of E64c analogues were designed, finally leading to the development of a CB-specific inhibitor, CA074. The X-ray structure of the CA074–CB complex provided the basis for the design of a noncovalent-type CB inhibitor.