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Prospects for the Coming Generation of Bioscience, Biotechnology, and Agrochemistry

—From Molecules to Systems and Bioinformation for Future Bioindustries—

Chemistry and Etiology of Marine Toxins

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Fish, bivalve mollusks, other marine animals and algae that are normally consumed safely may become toxic and thereby cause human intoxication. The spotty and unpredictable occurrence of the toxicity lay obstacles to securing enough material needed to elucidate toxin structures and identify the primary origins. Aggravating the problem of tiny sample amounts, toxins are often large and highly complex. A typical example is explained by the ciguatera study

where structural determination was achieved with 0.35 mg of ciguatoxin isolated from 124 kg of moray eel livers collected over 10 years and with 20 mg of maitotoxin accumulated by culturing a slow-growing dinoflagellate over 10 years. The study also opened a door to numerous dinoflagellate toxins that accumulate in fish and shellfish *via* food chain. Additionally, tetrodotoxin in pufferfish was revealed to be of bacterial origin.

Development of Intracellular Signal Transduction Modulators

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We have been working on several projects focusing on the development of novel intracellular signal transduction modulators. Development of selective inhibitors of protein kinases and phosphatases is of particular interest. Selective inhibitors of protein kinases and phosphatases are expected to be useful tools for clarifying biological functions of the specific enzymes themselves, and also candidates for novel therapeutics. Protein kinases and phosphatases are divided into three classes according to the substrate specificity, respec-

tively. In this talk, development of inhibitors of protein Ser/Thr phosphatase 2B (PP2B) and protein kinase C will be presented.

Protein Ser/Thr phosphatase 2B (PP2B), also known as calcineurin is a key enzyme for T-cell signaling, and its inhibitors FK506 and cyclosporine A (CsA) are clinically used as immunosuppressant drugs. Both FK506 and CsA must, however, form complexes with immunophilins to exert their inhibitory action on PP2B. Thus, it is of interest to find a direct and selective inhibitor of

Fig. 1. Protein Phosphorylation and Protein Kinases/Phosphatases.

Fig. 2. General Strategy for Development of Protein Phosphatase Inhibitors.

Fig. 3. Development of PP2B-Selective Inhibitor.

PP2B that does not involve the immunophilins as a biological tool for studies of PP2B, and also as a candidate therapeutic agent. For protein phosphatase, we are focusing on the catalytic site-directed inhibitor. Our basic strategy for creating selective inhibitors of biologically important protein phosphatases is summarized in Fig. 2. The key for this approach is identification of a good "core" structure that discriminates and selectively binds to the highly conserved catalytic site of each family of enzymes. We selected a natural product cantharidin that was known as an inhibitor of PP2A and PP1 but not PP2B. After clarifying basic structure-activity relationship (SAR) of cantharidin derivatives, we identified 7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid as a good selective "core" for Ser/Thr phosphatase family enzymes. According to the rational structure-based approach, we have succeeded to develop a first catalytic site-directed PP2B-selective inhibitor.¹⁾

Protein kinase C (PKC) plays important roles in intracellular signal transduction of a variety of cell events,

such as proliferation, differentiation, and apoptosis. Many catalytic site-directed inhibitors of PKC such as staurosporine have been reported, but selectivity of these inhibitors is generally not sufficient because of the high structural similarity of the ATP-binding site of PKC to those of other kinases. Thus we planned to develop a regulatory site-directed inhibitor. A novel isobenzofuranone (IB) template was designed as a PKC ligand.^{2,3)} Various IB derivatives were synthesized and evaluated. In addition to a powerful activator, a compound showing PKC inhibition was also developed.

References

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