DEVELOPMENT OF MICROBIAL SECONDARY METABOLITES WITH POTENTIAL USEFULNESS

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Discovery of antibiotics and low molecular weight inhibitors of various enzymes has shown that microorganisms produce almost unlimitted number of compounds which are not involved in the growth function of the cells producing them. This has also been supported by the study of their biosynthesis. The intracellular enzyme involved in the last step of the biosynthesis is inhibited by the product which is released extracellularly. If a quantitatively exact screening method is applied, the sought-after compounds can be found with a high probability. The study of enzyme inhibitors has already led to the discovery of hypotensive compounds, the compounds useful in the treatment of cholestremia, etc. This study has also been expanded to immunity-enhancing compounds useful in cancer treatment.

Moreover. as shown by the study of spergualin. oxanosine. etc.. new types of antitumor antibiotics are being discovered by the continuation of the screening. Furthermore, at the present, the derivatives and analogs of useful antibiotics are being studied exhaustively. We have been successful in the structure determination and total synthesis of bleomycin. Useful information on the structure-activity relationships has been obtained by preparing its derivatives and analogs, and new bleomycins with stronger therapeutic effect than the present bleomycin is being developed. Many researchers have studied anthracyclines. We have found aclacinomycin and 4'-tetrahydropyranyladriamycin which may contribute to the increase of the rate of curing leukemia, lymphoma, ovarial tumors, the tumors of head and neck, etc.

As well known, synthetic studies of β-lactams has made great success in the development of many useful antibacterial drugs. We are developing tylosin derivatives which inhibit the growth of macrolide resistant strains. On the basis of mechanism of resistance to aminoglycoside antibiotics, we have been successful in the development of useful derivatives. Recently we found that the amino groups play a predominant role in the antibacterial action of aminoglycosides, but the hydroxyl group do not. Also we found that the deoxy-derivatives of spergualin have strong antitumor action. Nitrogen atoms in bioactive compounds play an important role in the biological actions.

In this paper, I will review my recent studies with my collaborators on antibiotics and their derivatives, enzyme inhibitors, immunity-enhancing compounds and discuss about the future progress.