SUMMARY OF Ph.D. DISSERTATION

School School of Fundamental Science and Technology	Student Identification Number	SURNAME, First name FUTAMURA Yushi

Title

Discovery of a new class of chemical tools to study biological systems from microbial origin

Abstract

The use of small molecules for the study of biological phenomena lies at the heart of medicinal chemistry and chemical biology research. Small molecules allow rapid and conditional modulation of biological function and can also modulate individual functions of multifunctional targets. Furthermore, through the identification of their target proteins, they provide a new insight into the unknown biological processes. Therefore, the author has searched for the natural bioactive substances that modulate cellular responses and found both incednine as a potent modulator of the anti-apoptotic function of Bcl-xL and trierixin as an inhibitor of ER stress-induced XBP1 activation. In this report, the author described the chemistry and biology of these two novel compounds;

(1) Incednine, a potent modulator of the anti-apoptotic function of Bcl-xL

Anti-apoptotic oncoproteins Bcl-2 and Bcl-xL are overexpressed in many cancers and play a crucial role in cancer initiation, progression, and resistance to chemotherapy; however, the exact molecular mechanism of these proteins is still obscure. Therefore, the discovery of a functional inhibitor for these proteins and the improved understanding of the molecular mechanisms of these proteins will be an aid to novel anti-tumor therapies. Using chemical genetic cell-based screening, the author has found a chemically and biologically unique substance, incednine, as a novel functional modulator of Bcl-2/Bcl-xL from the fermentation broth of *Streptomyces* sp. ML693-90F3. Detailed spectroscopic analysis revealed that incednine consists of a novel skeletal structure, enolether-amide, in a macrolactam core, with two aminosugars. Incednine inhibits the anti-apoptotic function of oncoprotein Bcl-2/Bcl-xL without affecting the heterodimerization of Bcl-xL and Bax. Thus, incednine exerts its activity through a distinct mode of action from the other known Bcl-2 inhibitors and could provide a chemical probe to study the underlying mechanisms of Bcl-2/Bcl-xL.

(2) Trierixin, a novel inhibitor of ER stress-induced XBP1 activation

Trierixin, a novel triene-ansamycin group compound, has been isolated from the fermentation broth of *Streptomyces* sp. AC654 as an inhibitor of ER stress-induced XBP1 activation. The author determined the structure of trierixin on the basis of its spectroscopical and chemical properties. Trierixin possessed a 21-membered macrocyclic lactam, which contains a unique methylthio-benzenediol structure, and *N*-hexahydrobenzoylalanine at the C-11 position.