Structure and Biological Activity of Iezoside, a Novel Peptide-Polyketide Hybrid Compound from Marine Cyanobacteria

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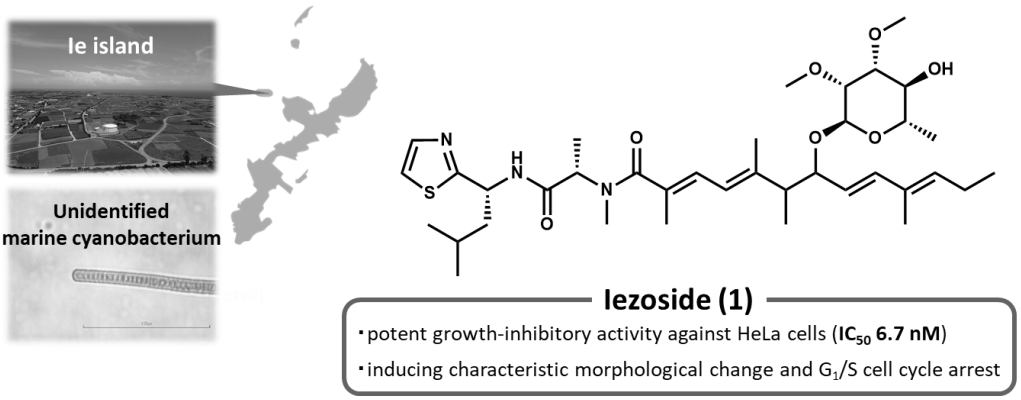
Marine cyanobacteria are prosperous sources of structurally novel secondary metabolites possessing a wide range of biological activities. In a series of investigations, we isolated a novel peptide-polyketide hybrid, iezoside (**1**), from unidentified marine cyanobacterium collected at Ie island.

The gross structure of **1** was determined based on the analyses of several spectral data. As a result, it was clarified that iezoside (**1**) has an unprecedented peptide-polyketide hybrid structure which contains an *O*, *O*-diMe-rhamnose residue between an α, β, γ, δ-unsaturated amide group and a conjugated diene group. The absolute configuration of a peptide moiety of **1** was determined by acid hydrolysis followed by chiral phased HPLC analyses and Marfey's method, revealing the presence of L-leucine and *N*-Me- D-alanine. The stereochemistry of *O*, *O*-diMe-rhamnose was determined to be L-form based on the analyses of proton coupling constants and NOESY correlations, and modified Mosher's method. Now, we are trying to determine the absolute configuration of the fatty acid moiety by comparing the HPLC retention times between a degradation product of **1** and synthetic standards.

Iezoside (**1**) showed a potent growth-inhibitory activity (IC_{50} 6.7 nM) against HeLa cells and induced the characteristic morphological change. In addition, we clarified that **1** arrested cell cycle at the G_1/S stage. In order to analyze the mode of action of **1**, we examined its growth-inhibitory profile against 39 human cancer cell lines (JFCR39)[1)]. The results clarified that compound **1** showed potent and differential growth-inhibitory activities (average GI_{50} 87 nM) against various cancer cell lines. To reveal the potential of **1** as an anticancer drug with a novel mode of action, we are carrying out detailed evaluations of its bioactivity.



1) Yamori, T.; Matsunaga, A.; Sato, S.; Yamazaki, K.; Nakanishi, O.; Kohno, H.; Nakajima, Y.; Komatsu, H.; Andoh, T.; Tsuruo, T. *Cancer Res.* **1999**, 59, 4042–4049.