

学 位 論 文 要 旨	
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題 目	Studies on tumor selective cytotoxicity of plant alkaloid Nitidine (植物アルカロイド Nitidine の腫瘍選択的細胞毒性に関する研究)
<p>Drug resistance has been a major issue in cancer chemotherapy. It is therefore important to screen more potent natural anti-cancer agents against the drug-resistant cancer phenotype. The present study investigated the cytotoxicity of the traditional and natural medicinal agent nitidine (NTD) against the drug-resistant cancer phenotype of A549 human lung adenocarcinoma cells <i>in vitro</i> and <i>in vivo</i>.</p> <p>The capmptothecin (CPT) tolerant phenotype was selected after A549 cells were exposed to CPT for a week. The cytotoxicity of NTD in these CPT-resistant cells (CRC) was studied <i>in vitro</i> in relation to its accumulation and expression of the ATP binding cassette (ABC) transporter gene. CRC expressing higher levels of ABCC1, ABCC2, ABCC3, and ABCA1 were more resistant to CPT compared to normal A549 cells. CRC was, however, more susceptible to NTD compared to normal A549 cells with preferential accumulation of NTD. A statistically significant difference in the protein level was only noted with ABCC1 and ABCC2 between normal A549 and CRC. Furthermore, gene expression of ABCC2 and ABCC3 showed positive correlation with NTD accumulation, and negative correlation with the D₅₀ of this agent in 9 cancer cell panels. CRC was therefore found to be more susceptible to NTD compared with the normal phenotype. The cytotoxicity of NTD was associated with its accumulation and the expression of ABCC2 transporter genes, suggesting that the involvement of this transporter in the selective incorporation of NTD into cancer cells, which results in enhanced cytotoxicity.</p> <p>In the second experiment, we examined the <i>in vivo</i> anti-tumor effects of NTD on CRC-derived tumors and oral treatment on nA549 using a xenograft mouse model. Cancer cells were intradermally inoculated into the back of mice. Then, 100 µg NTD was injected i.p. into the nA549- or CRC-derived tumor-bearing mice. To confirm the anti-tumor effects of oral NTD, the nA549-transplanted mice were fed a diet containing NTD concentrate prepared from <i>Toddalia asiatica</i> Lam. The anti-tumor effect of NTD (i.p.) manifested earlier in CRC-derived tumors than in the A549-derived tumors. Oral NTD concentrate also significantly inhibited the growth of the nA549-derived tumors. NTD was detected in the tumor but not in other tissues in the NTD concentrate-fed mice. CRC-derived tumor was more susceptible to NTD treatment than nA549-derived tumor. Furthermore, the anti-tumor effect of oral NTD and its preferential accumulation in tumor tissues have been demonstrated for the first time. These findings are promisingly useful for the development of safe anti-cancer drugs.</p>	