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제 목	Bufalin as a New Potent Inducer of Differentiation of Human Leukemia Cells -A Story of the Search for Active Substances from Oriental Medicines-
연구자	Takemi Yoshida and Yukio Kuroiwa
소 속	Showa Unive., Japan
내 용	<p>Chan'su, the dried toad venom preparation, has been used for centuries as a cardiotoxic, a local anesthetic and in the treatment of eczema. Bufadienolides are major effective components of Chan'su. Their pharmacological activities have been studied to date. However, their pharmacokinetic and metabolism have not been studied.</p> <p>Considering variously divergent pharmacological actions of bufadienolides, we decided to examine their metabolism and their other biological activities. We isolated and purified various components of bufadienolides. Cinobufagin and bufalin are prominent components. Firstly, we examined metabolism of cinobufagin and found that this compound was extensively metabolized into various metabolites by mixed-function oxidase and deacetylase.</p> <p>Parallel to metabolic study, we also examined their biological activities, and found highly cytotoxic effect on established cell lines. Of interest was that bufalin produced potent cytotoxic effect on human-derived cancer cells than animal-derived cells, suggesting that this compound has rather a specific effect on human cell lines. This finding prompted us to apply bufalin to screening system of differentiation of human leukemia cells. The experimental results obtained from this screening test were fully satisfactory for us. Namely, Bufalin inhibited the growth of human leukemia cells at various phases of cell cycle, and under these conditions it was found to be a potent inducer of differentiation of human leukemia cell lines (HL60, U937, M1 and K562). The effective concentrations of bufalin to differentiate human leukemia cells were approximately 5-10nM, and were comparable to other well-known inducers such as all-trans retinoic acid and 1<math>\alpha</math>, 25-dihydroxyvitamin D<sub>3</sub>. The combination of bufalin with other inducers synergistically induced the differentiation of human leukemia cells. At present, a mechanism for the bufalin-mediated induction of the differentiation of these human leukemia cells remains to be determined.</p> <p>A possible mechanism for a great difference in the ability of bufalin to differentiate leukemia cells between human and animal-derived cells could be attributable, if not all, to the amounts of its binding proteins, either specific or nonspecific proteins. We are now trying to characterize this bufalin-binding proteins in leukemia cells.</p> <p>Bufalin was also able to inhibit melanoma cell growth, with being highly effective on human-derived melanoma than mouse-derived. All of these findings suggest that bufalin could be an active substance on human-derived various cancer cell lines. Therefore, it is of interest to examine further whether bufalin is effective on solid cancer <i>in vivo</i>.</p> <p>Growing extensive efforts have been taken to search for anti-cancer drugs from plants and marine products, and so on. Our study also suggests that we can happen upon an active drug from oriental medicines which have been utilizing by our ancestor and by us to date.</p>