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Radiosensitization for Human Lung Cancer cells of Quinone-methide Triterpenes by Modification of Antioxidant Thiol Molecules

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폐암세포내 퀴논메치드 화합물의 ROS증가에 의한 방사선 치료 증대 효과

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실험목적 (Objectives)

The radiosensitizing effects of natural occurring triterpenes were investigated in a human lung cancer cell system.

재료 및 방법 (Materials and Methods)

○ 실험재료 및 방법

Human lung cancer cells, NCI-H460, were treated with 6 triterpenes (β-hydroxy tingenone, and 6-(2-oxopropyl)-22-β-hydroxytingenol with or without ionizing radiation (IR). Cell proliferations and cytotoxicities were investigated using MTT and clonogenic survival assays, and apoptosis was quantified by flow cytometry. The expressions of proteins related to apoptotic pathway were determined by Western blotting. Finally, nude mouse xenografting experiments were performed to confirm the radiosensitizing effect observed *in vitro*.

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실험결과 (Results)

The quinone methide containing triterpenes (QMT), celastrol, pristimerin, iguesterin, tingenone, and 22-β-hydroxy tingenone enhanced the cytotoxic effect of IR, but 6-(2-oxopropyl)-22-β-hydroxytingenol, which does not contain the quinone methide moiety, did not. Of the QMTs, celastrol had the greatest enhancing effect (SF_2 = 0.22 at 2 μM and SF_2 = 0.08 at 4 μM) and synergistically increased IR induced caspase-dependent apoptosis as compared to celastrol or IR alone treated cells. Furthermore, the quinone methide moiety of celastrol was found to be essential for celastrol-mediated radiosensitization because dihydrocelastrol, which does not contain the quinone methide moiety, did not have a radiosensitizing effect. Radiation induced G_2/M phase arrest was overrode by co-treatment of celastrol, which was coincided with the synergistically decreased expressions of cyclinB_1 and histoneH3 phosphorylation. *In vivo* mouse xenograft data also indicated that celastrol plus IR had a significantly greater effect than IR or celastrol alone in nude mice.