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ORAL

Mechanisms underlying the anticancer activities of the selected phytochemicals and their therapeutic implication in AGS gastric cancer cells

Somi Kim Cho 1,2

1. Faculty of Biotechnology, College of Applied Life Sciences, SARI, Jeju National University, Jeju 690-756, Republic of Korea
2. Subtropical Horticulture Research Institute, Jeju National University, Jeju 690-756, Republic of Korea

Abstract

The cysteine-rich angiogenic inducer 61 (CYR61), an extracellular matrix-associated protein, is involved in survival, tumorigenesis, and drug resistance. There is an increasing demand for developing agents that target CYR61. Hence, we study the effects of flavones against CYR61-overexpressing human gastric adenocarcinoma AGS (AGS-cyr61) cells. Among the various flavones, quercetin had lowest IC50 value and reduced the viability of AGS-cyr61 cells even greater than that of AGS cells. Quercetin (1) down-regulates CYR61 and concomitantly decreases in the levels of MRP1 (multidrug resistance-associated protein 1) and nuclear factor NF-kappa B (κB) p65 subunit, (2) reverses multidrug resistance, and (3) inhibits colony formation in AGS-cyr61 cells. AGS-cyr61 cells treated with quercetin at sub IC50 over a range of 5-FU or ADR concentrations manifested strong synergistic effects with these two drugs. Our results demonstrate that CYR61 is a potential regulator of ABC transporters and quercetin can be the novel agent that improves the efficacy of anticancer drugs by down-regulating CYR61 and ABC transporters.

Histone deacetylase 6 (HDAC6) is a unique cytoplasmic enzyme which contributes to malignant progression in various cancer. Such effect on cancer brings more interest on developing HDAC6 inhibitors. Here, we found that compound D inhibits HDAC6 activity, increases acetylated α-tubulin, reduces the level of β-catenin, and suppresses cell proliferation. Increase of α-tubulin acetylation by compound D resulted in tubulin polymerization, and consequently, induced aberrant mitosis. Moreover, DTBP elicits different effects depending on different concentrations.

Treatment with high concentrations of compound D induces cell death by mitotic catastrophe, whereas low concentration of compound D induces senescence with upregulation of p21 and Rb, and increase in the phosphorylation of mTOR and the β-galactosidase activity. Therefore, compound D can also be considered as a promising new candidate for anti-cancer drug development.

*For correspondence:

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