Selective targeting of glioma-initiating cells by Eckol, a natural phlorotannin

Kyung-Hwan Hyun¹, Rae-Kwon Kim¹, Hyejin Lee¹, Myung-Jin Park², Jin-Won Hyun³, Min-Jung Kim¹, Su-Jae Lee¹

¹Department of Chemistry, Hanyang University, 133-791 Seoul, Korea, Republic of; ²Division of Radiation Cancer Biology, Korea Institute of Radiological and Medical Sciences, 139-706 Seoul, Korea, Republic of; ³College of Medicine and Applied Radiological Science Research Institute, Cheju National University, 690-756 Seoul, Korea, Republic of

A subpopulation of cancer cells with cancer stem cell properties is responsible for tumor formation, maintenance and progression, and also contributes to resistance to anticancer therapies. Thus, compounds that selectively target cancer stem-like cells could be usefully applied to overcome resistance to anticancer treatments in human cancers. In this study, we show that Eckol, a phlorotannin compound found in some brown algae, suppresses maintenance of glioma-initiating cell populations, and synergistically induces cell death of glioma stem-like cells in combination with anticancer therapies. Treatment of sphere-forming glioma stem-like cell populations with Eckol effectively reduced the number and size of spheres as well as the size of the CD133⁺ cell population. Treatment with Eckol suppressed expression of the glioma stem cell markers CD133, Nestin, and Musashi-1. Expression of the known self-renewal-related proteins Sox2, Notch2, β-catenin in sphere-forming cells was also downregulated by Eckol treatment. Moreover, treatment of sphere-forming cells with Eckol significantly suppressed anchorage-independent growth in soft agar and tumor formation in nude mice. Importantly, treatment with Eckol effectively reduced the resistance of sphere-forming glioma stem-like cells to radiation and chemotherapy. Interestingly, treatment of glioma stem-like cells with Eckol markedly blocked both phosphoinositide 3-kinase-Akt and Ras-Raf-1-Erk signaling pathways. Furthermore, in glioma stem-like cell population derived from patients, Eckol treatment effectively reduced stemness, and decreased resistance to anticancer treatments. These results indicate that the natural marine phlorotannin Eckol selectively targets glioma-initiating cells, and synergistically enhances the sensitivity of glioma stem-like cells to anticancer treatments. These results indicate that Eckol treatment may be beneficial in treating brain cancer by suppressing or eliminating brain cancer stem-like cells.