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Activation of Nrf2 signaling pathway by glyceollins is independent of p53 in human colon cancer model**Jong-Sang Kim**

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Glyceollins, soybean-derived phytoalexins are reported to induce antioxidant and phase two detoxifying enzymes through nuclear factor (erythroid-derived 2)-like 2 (Nrf2)-mediated signaling pathway and thus protect normal cells from xenobiotic or cellular stress stimuli. Serendipitously, we observed that low doses of glyceollins promoted the proliferation of colorectal cancer cells carrying normal *p53* gene while the compounds inhibited the growth of *p53*-negative colon cancer cells in a dose-dependent manner. As *p53* is known to activate its downstream gene *p21* that interferes Kelch-like ECH-associated protein 1 (Keap1)/Nrf2 heterodimer formation, we hypothesized that glyceollins at low doses stimulate Nrf2 signaling pathway by up-regulating *p53*-mediated *p21* expression, leading to proliferation of *p53*-positive colon carcinoma cells. When treated with glyceollins, the growth of wild type (wt) *p53* HCT116 cells was increased by glyceollins in the range of 1-20 µg/mL while the growth of HT29 and Caco-2 cells carrying mutated *p53* was unaffected or gradually decreased by glyceollins treatment. Glyceollins led to significantly increased expressions of *p53* and *p21* in wt *p53* HCT116 cells, but did not affect the gene expression in *p53*-knockout HCT116 cells. However, the expression of Nrf2 and its downstream genes was significantly enhanced both in *p53*-mutant cells as well as *p53*-wild type cells, suggesting that glyceollins promote Nrf2 signaling pathway in a *p53*-independent manner. In contrast, sulforaphane and tert-butylhydroquinone, well-known activators of Nrf2 signaling pathway did not activate Nrf2 signaling pathway in *p53* wild type HCT116 cells although they stimulated Nrf2 signaling pathway in *p53*-mutant cells. In conclusion, the activation mechanism of Nrf2 signaling pathway by glyceollins is likely to be different from common phase two enzyme inducers and not suppressed by *p53*.