CDDO-Me Protects Against Heavy Ion-Induced Transformation of Human Colonic Epithelial Cells

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Radiation-induced carcinogenesis is a major concern not only for cancer patients being treated with therapeutic radiation but also for astronauts on long-term space missions. Exposure to radiation induces oxidative stress and chronic inflammation, known critical initiators and promoters of carcinogenesis. Previous studies have demonstrated that non-steroidal anti-inflammatory drugs and anti-oxidants can reduce the risk of radiation-induced cancer development. In this study we found that a synthetic triterpenoid, CDDO-Me, protects human colonic epithelial cells (HCECs) against radiation-induced transformation. HCECs were immortalized via ectopic expression of the catalytic component of telomerase (hTERT) and cyclin dependent kinase-4 (cdk4). Clones that were diploid or trisomy for chromosome 7 (a non-random chromosome change that occurs in 37% of premalignant colon adenomas and 80% of adenocarcinomas) were used in this study. We observed that these human colonic cells can be experimentally transformed with a combined exposure to 2 Gy of proton at 1 GeV followed 24 hours later by 50 cGy of $^{56}$Fe at 1GeV. Irradiation of normal diploid HCEC clones with similar combinations of charged particles, or irradiation of the trisomy 7 cells with protons or $^{56}$Fe alone resulted in a much reduced effect on transformation. Trisomy 7 cells cultured for one month after irradiation with both protons and $^{56}$Fe showed an increase in proliferation rate, and an increase in both anchorage dependent and independent colony formation ability. Post-irradiation a spectrum of chromosome aberrations was observed in transformed cells with 40% showing loss of 17p (e.g. loss of one copy of p53). CDDO-Me, also known as bardoxolone methyl (BARD) or RTA402 (Reata Pharmaceuticals, Inc. Irving, TX), is an oral bioavailable drug in Phase IIb clinical trials as an antioxidant inflammation modulator in patients with diabetic nephropathy. Pre-treatment of trisomy 7 cells with 50nM CDDO-Me prevented heavy-ion induced increases in proliferation rate and anchorage dependent and independent colony formation. These results demonstrate that experimentally immortalized human colonic epithelial cells with a non random chromosome alteration are valuable premalignant cellular reagents that can be used to study radiation-induced colorectal carcinogenesis. In summary, these premalignant human colonic epithelial cells will have utility to test other combinations of radiation ions, doses, and dose rates to help model if there is an increased risk of astronauts developing fatal cancer on long-term space missions. Future experiments will test if CDDO-Me is an effective countermeasure in mouse models that are susceptible to colon cancer.

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