Abstract

Colorectal cancer (CRC) cells harboring KRAS or BRAF mutations show a more-malignant phenotype than cells with wild-type KRAS and BRAF. KRAS/BRAF–wild-type CRCs are sensitive to epidermal growth factor receptor (EGFR)-targeting agents, whereas KRAS/BRAF–mutant CRCs are resistant due to constitutive activation of the EGFR-downstream KRAS/BRAF signaling pathway. Novel therapeutic strategies to treat KRAS/BRAF mutant CRC cells are thus needed. We recently demonstrated that the telomerase-specific replication-competent oncolytic adenoviruses OBP-301 and p53-armed OBP-702 exhibit therapeutic potential against KRAS-mutant human pancreatic cancer cells. In this study, we evaluated the therapeutic potential of OBP-301 and OBP-702 against human CRC cells with differing KRAS/BRAF status. Human CRC cells with wild-type KRAS/BRAF (SW48, Colo320DM, CACO-2), mutant KRAS (DLD-1, SW620, HCT116), and mutant BRAF (RKO, HT29, COLO205) were used in this study. The antitumor effect of OBP-301 and OBP-702 against CRC cells was analyzed using the XTT assay. Virus-mediated modulation of apoptosis, autophagy, and the EGFR-MEK-ERK and AKT-mTOR signaling pathways was analyzed by Western blotting. Wild-type and KRAS-mutant CRC cells were sensitive to OBP-301 and OBP-702, whereas BRAF-mutant CRC cells were sensitive to OBP-702 but resistant to OBP-301. Western blot analysis demonstrated that OBP-301 induced autophagy and that OBP-702 induced autophagy and apoptosis in human CRC cells. In BRAF-mutant CRC cells, OBP-301 and OBP-702 suppressed the expression of EGFR, MEK, ERK, and AKT proteins, whereas mTOR expression was suppressed only by OBP-702. Our results suggest that p53-armed oncolytic virotherapy is a viable therapeutic option for treating KRAS/BRAF-mutant CRC cells via induction of autophagy and apoptosis.