The regulatory mechanisms of carboxylesterases 2 in gastrointestinal cancers

Shun Zhang¹, Momoko Ishimine¹, Yoshinori Kohira¹, Hajime Orita¹, Toshiyuki Kobayashi¹, Okio Hino¹, Takehiko Yokomizo¹, Tetsu Fukunaga¹, Hyeon-Cheol Lee-Okada¹


Carboxylesterases (CES) are members of the serine hydrolase superfamily and catalyze the hydrolysis of a variety of endogenous and exogenous substrates including esters and amides. CES2 is especially important in terms of cancer therapy because it hydrolyzes and activates several anticancer prodrugs including irinotecan (CPT-11), an anticancer drug that is used for the treatment of a wide spectrum of cancers including gastrointestinal cancer. Recent studies have indicated that CES2 can be transcriptionally activated by a tumor suppressor p53. In this study, we first examined whether p53 activation upregulates CES2 expression and leads to the sensitization to irinotecan using several cell lines of human colorectal and gastric cancer. p53 activators nutlin-3a and doxorubicin increased the expression level of CES2 in p53 wild-type cells but not in cells with mutated p53 or p53-null cells. The cells with wild-type p53 but not with non-functional p53 showed enhanced sensitivity to irinotecan when co-treated with those p53 activators. We next investigated the relationship between TP53 gene status and CES2 expression in human colorectal cancer. Unexpectedly, CES2 expression was decreased in human colorectal cancer with both functional and non-functional p53 compared with the adjacent normal tissue. Interestingly, there was a marked positive correlation between p21, a downstream target of p53, and CES2 expression levels, even in tumors containing non-functional p53. It has been shown that p21 expression can be induced by various stress signals in a p53-independent fashion. We found that a p21 inhibitor UC2288 suppressed the upregulation of CES2 expression mediated by p53 activation. We also found that HDAC inhibitor treatment increased CES2 expression through p21 in p53-null cells. These data, taken together, showed that p21 plays an central role in the regulation of CES2 expression.