ABSTRACT

Most cases of colorectal cancers (CRCs) are microsatellite stable (MSS), which frequently demonstrate lower response rates to immune checkpoint inhibitors (ICIs). RNA editing produces neoantigens by altering amino acid sequences. In this study, RNA editing was induced artificially by chemoradiation therapy (CRT) to generate neoantigens in MSS CRCs. Altogether, 543 CRC specimens were systematically analyzed, and the expression pattern of ADAR1 was investigated. *In vitro* and *in vivo* experiments were also performed. The RNA editing enzyme ADAR1 was upregulated in microsatellite instability–high CRCs, leading to their high affinity for ICIs. Although ADAR1 expression was low in MSS CRC, CRT including oxaliplatin (OX) treatment upregulated RNA editing levels by inducing ADAR1. Immunohistochemistry analyses showed the upregulation of ADAR1 in patients with CRC treated with CAPOX (capecitabine + OX) radiation therapy relative to ADAR1 expression in patients with CRC treated only by surgery ($p < 0.001$). Compared with other regimens, CRT with OX effectively induced RNA editing in MSS CRC cell lines (HT29 and Caco2, $p < 0.001$) via the induction of type 1 interferon-triggered ADAR1 expression. CRT with OX promoted the RNA editing of cyclin I, a neoantigen candidate. Neoantigens can be artificially induced by RNA editing via an OX–CRT regimen. CRT can promote proteomic diversity via RNA editing.