ABSTRACT

Rectal cancer is currently the second most common cancer in the large intestine, and these cases represent one-third of the colorectal cancers that are diagnosed. Neoadjuvant chemoradiation is a treatment for rectal cancer and it reduces the risk of local recurrence. However, a pathologic complete response is only achieved in 10–40% of cases. Thus, the response of rectal cancers to neoadjuvant treatment is poorly understood, as well as the mechanisms that are associated with chemoradiation resistance. To identify potential targets for preventing therapy resistance, a proteomic analysis of biopsy specimens collected from stage II and III rectal adenocarcinoma patients before neoadjuvant treatment was performed. These results were then compared with a proteomic analysis of residual rectal adenocarcinoma tissues that were removed by surgery after neoadjuvant therapy. Three proteins, Ku70, Ku80, and Rab5C, exhibited a significant increase in expression after chemoradiation treatment. To better understand the possible role of these proteins in therapy resistance, a rectal adenocarcinoma cell line was irradiated to generate a radiotherapy-resistant lineage. The cells derived from this lineage overexpressed the same three proteins that were identified in the tissue samples. Furthermore, radiotherapy resistance in this *in vitro* model was found to involve modulation of epidermal growth factor receptor (EGFR) internalization by Rab5C in response to irradiation, and this affected expression of the DNA repair proteins, Ku70 and Ku80. Taken together, these findings indicate that

EGFR and Rab5C are potential targets for the sensitization of rectal cancer cells to neoadjuvant treatment and they should be further investigated.