Expression of xCT as a Predictor of Disease Recurrence in Patients with Colorectal Cancer

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Abstract. Background: The function of a cysteine-glutamate exchanger (xCT) transporter is to increase the intracellular concentration of glutathione in order to protect cells from oxidative stress. In several types of cancer, xCT is thought to play a role in the onset of resistance to chemotherapy and radiotherapy. xCT is stabilized on the tumor cell surface after combining with cluster of differentiation 44 variant (CD44v). Materials and Methods: We examined the xCT and CD44v6 expression in 304 primary tumor samples obtained from patients with colorectal cancer using immunohistochemical analysis. Results: Immunoreactivity for xCT was observed in 208 (68.4%) tumors. Among 218 patients with stage I-III disease who underwent curative surgery, the postoperative recurrence rate was 32.9% in those with xCT-positive tumors, which was significantly (p=0.003) higher than in those with xCT-negative tumors (10.7%). Immunoreactivity for CD44v6 was observed in 101 cases (33.2%), although the rate of postoperative recurrence in patients with CD44v6-positive tumors did not exhibit any significant correlation. Multivariate analyses revealed increased xCT expression to be an independent significant predictor of disease recurrence, in addition to depth of tumor invasion, lymph node metastasis and venous invasion.

Colorectal cancer (CRC) is a major cause of morbidity and mortality worldwide. This type of lesion accounts for over 9% of all cancers (1) and is the third most common type of cancer worldwide and the fourth most common cause of cancer-related death (2). Novel useful independent prognosticators for CRC have long been investigated; however, none have yet been integrated into routine practice, and prognosis remains unresolved with respect to CRC management. Consequently, although some improvements in survival of patients with CRC have recently been achieved due to advances in drugs used in chemotherapy, survival rates remain poor. Even after curative resection, tumor recurrence occurs in 17% of patients (3).

Currently, the prognosis of CRC is determined primarily based on tumor stage. According to the National Comprehensive Cancer Network (NCCN) guidelines for CRC, pathological high-risk factors for CRC recurrence include a tumor depth greater than pT4, dissection of fewer than 12 lymph nodes and poorly differentiated tubular adenocarcinoma; however, these factors do not exhibit adequate reliability for predicting recurrence (4).

xCT is the transporter subunit of the Na+-independent heterodimeric amino acid transport system xc. The xc system consists of xCT and a regulatory heavy chain component (4F2hc) and its function is to exchange cystine/glutamate with cystine entering cells in association with the release of glutamate in a 1:1 ratio. Cystine taken into the cell by xCT subsequently mediates the maintenance of the intracellular glutathione (GSH) level, which is essential for protecting cells from oxidative stress (5,6).

In contrast, cluster of differentiation 44 (CD44) is a major adhesion molecule in the extracellular matrix that functions in a wide variety of physiological processes, including leukocyte homing and activation, wound healing and cell migration, as well as tumor cell invasion and metastasis (7-9). CD44 exists in numerous variant isoforms generated through alternative mRNA splicing (10). Among them, variant type 6 (CD44v6) has been reported to be a cancer stem cell marker of CRC and its level is correlated with poor survival (11).

Ishimoto et al. showed that xCT is stabilized by combining with CD44 variants on the tumor cell surface (12). In human cancer cells, cystine uptake is largely mediated by the xc system, and a high expression of xCT has been demonstrated to be associated with a poor prognosis in a variety of human carcinomas, including Kaposi sarcoma, lymphoma, glioma and liver, breast, prostate, ovarian, pancreatic, gastric and esophageal cancer (13-17).
Although some studies have demonstrated a relationship between xCT expression and the prognosis of patients with various types of solid tumors, as far as we are aware, none investigated the prognosis in patients with CRC. Although CD44v6 has been reported to exhibit a relationship with prognosis in patients with CRC, its effects remain unclear (11). The aim of this study was, therefore, to investigate whether xCT and CD44v6 expression is associated with the prognosis of CRC and assess the potential of these variables as risk factors for CRC recurrence.