学 位 論 文 の 要 旨

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学 位 論 文 名	Clinicopathological and Prognostic Relevance of Tumoral Suppression of Tumorigenicity 2 Expression in Patients With Surgically Resected Pancreatic Carcinoma
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論 文 内 容 の 要 旨

INTRODUCTION

Interleukin-33 (IL-33), a member of the IL-1 cytokine family, is expressed in endothelial cells, fibroblasts, and epithelial cells both during homeostasis and inflammation. The human suppression of tumorigenicity 2 (*ST2*) gene encodes for three splice variants; soluble ST2 (sST2), transmembrane ST2 (ST2L), and variant ST2 (ST2V). The IL-33 receptor is a heterodimeric complex consisting of ST2L and IL-1 receptor accessory protein. ST2 is expressed on the membrane of a variety of immune cell types, such as T helper (Th)2 lymphocytes, group 2 innate lymphoid cells, macrophages, mast cells, basophils, eosinophils, dendritic cells, and natural killer (NK) cells. IL-33/ST2 signaling is crucial for tissue repair, type 2 immunity, allergic and non-allergic inflammation, and viral infection.

Recent studies have shown associations between the biological role of the IL-33/ST2 axis and progression of malignant tumors. However, the significance of tumoral ST2 expression remains controversial in some malignancies.(4) In this study, we investigated the clinicopathological and prognostic relevance of tumoral ST2 expression in patients with resected pancreatic carcinoma after neoadjuvant chemoradiotherapy.

MATERIALS AND METHODS

We reviewed records from patients with invasive pancreatic ductal adenocarcinoma who had undergone pancreatic resection after chemoradiotherapy at Kagawa University between 2009 and 2018 (n = 81). After excluding patients with positive surgical margin (n = 3) or ≤ 10% residual tumor after chemoradiotherapy (n = 2), 76 patients were eventually included in our

analysis. Tissue microarrays were constructed and immunohistochemical analysis was performed for ST2. Using an Olympus BX53 upright microscope (Olympus Corporation, Japan) with a standard 22-mm-diameter eyepiece, anti-ST2 stained tumor slides were reviewed by a pathologist, who was blinded to patient outcomes. Immunohistochemistry scoring was based on the distribution and intensity of the staining in the main tumor. Distribution was scored based on a scale of 0 (0–25%), 1 (26–50%), 2 (51–75%), or 3 (76–100%) according to the percentage of positive cells in each core. Staining intensity was scored as 0 (no expression), 1 (mild expression), 2 (intermediate expression), or 3 (strong expression). Distribution and intensity scores were summed in a total score (0–6) for each patient (Figure 1). The score of ST-2 expression was dichotomized as low or high according to the median value (median: 2, range=0–6). When the score was equal or greater than the median, expression was classified as high.Associations between variables were analyzed using chi-square tests. Disease-specific survival (DSS) and disease-free survival (DFS) were analyzed using log-rank tests. The study protocol was approved by the Research Ethics Committee of Shimane University.

RESULTS AND DISCUSSION

The clinicopathological characteristics of all patients who had undergone pancreatic resection after chemoradiotherapy (n = 76) are summarized in Table I. During the study period, 52 patients recurred and 33 died from pancreatic carcinoma-related causes. The median duration of follow-up for patients who were alive at the time of the last follow-up was 27 months (range=5–113 months).

High expression of ST2 was observed in 43 patients (57%). Associations between patient characteristics and ST2 expression are summarized in Table I. High expression of ST2 was more frequent in patients with high pathological T status (T1 *vs.* T2-3; p=0.002), in those with lymphatic invasion (p=0.049), and in those with ≤ 50% of tumor cells destroyed by chemoradiotherapy compared to those with > 50% of tumor cells destroyed (Evans grade I-IIA *vs.* IIB; p=0.043).

ST2 expression was not associated with DSS (p=0.70) (Table II). In all patients, DFS was lower in patients with high ST2 expression (median 11.7 months) than in those with low ST2 expression (median 23.7 months) (Figure 3A), although this difference was not statistically significant (p=0.067). In stage I patients, DFS was significantly lower in patients with high ST2 expression (median 10.6 months) than in those with low ST2 expression (median 43.4 months; p=0.046) (Figure 3B and Table III). In stage II-III patients, ST2 expression was not associated with DFS (p=0.49).

In pancreatic carcinoma, clinicopathological and prognostic associations with IL-33/ST2 axis, based on immunohistochemical analyses in human cancer samples, have not yet been well

investigated. Takenaga *et al.* have demonstrated that the cancer cell-derived interleukin-33 decoy receptor sST2 enhanced orthotopic tumor growth through up-regulation of CXCL3 *via* inhibition of IL-33/ST2L signaling in the tumor microenvironment in a murine pancreatic cancer model; however, they could not find a consistent association between *IL-33* or *ST2* expression and prognosis, based on analysis of public prognosis databases. Induction of IL-33/ST2 signaling results in activation of immune effector cells that leads to recruitment of pro- or anti-oncogenic cells into the tumor microenvironment. IL-33/ST2 signaling is negatively regulated by sST2, which acts as a decoy receptor and sequesters IL-33 to block its interaction with ST2L. Thus, IL-33 bioactivity is controlled by various factors, such as the balance between ST2L and sST2, and heterogeneous expression in various cell types and immunological conditions, indicating that this complexity may account for the inconsistent literature regarding the prognostic value of ST2 expression in carcinomas.

CONCLUSION

We have identified tumoral ST2 expression as a marker of biological aggressiveness, such as disease recurrence, higher T status and lymphatic invasion, and as a possible predictor of recurrence and lower histopathological response grade in invasive pancreatic ductal adenocarcinoma after neoadjuvant chemoradiotherapy. These findings suggest that ST2 may serve as a predictor of response to current neoadjuvant therapy or as a therapeutic target in tumor immunotherapy in pancreatic carcinoma. Our study was limited by the fact that IL-33 immunohistochemistry was not performed in this cohort, and that interactions between IL-33 and ST2 in tumor cells or tumor immune microenvironment were not investigated. Therefore, future in-depth investigation is warranted based on double staining with anti-IL-33 and anti-ST2 antibodies to confirm the role of IL-33/ST2 axis in the tumor microenvironment.