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EDITORIAL – THORACIC ONCOLOGY

Therapeutic Strategy by Neuronal Pentraxin Receptor for Esophageal Squamous Cancer Cells

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Esophageal cancer has the sixth worst prognosis due to its aggressiveness and a poor survival rate from 2018,[1] although a therapeutic strategy including chemotherapy, chemoradiotherapy, and surgery for esophageal cancer has advanced in recent years. Additionally, its prevalence has continued to increase during the past 30 years.[2] Esophageal squamous cell carcinoma (ESCC), accounting for approximately 90% of all esophageal cancer cases worldwide, is the most common histologic subtype.[3] Therefore, new therapeutic targets for ESCC should be developed to improve the prognosis.

The neural pentraxin receptor (NPTXR) protein locates across the cell membrane and anchors complexes of neuronal pentraxin to the cell's plasma membrane. It serves as an organizer for synaptic transmission and is expressed primarily in the brain.[4] For the role of malignancy in gastric cancer, NPTXR is an important factor, and antibodies targeting NPTXR could be therapeutic agents.[5] However, it has been unclear whether therapeutic strategies using NPTXR are effective in ESCC.

Sinozuka et al.[10] evaluated the association between NPTXR and malignancy and the therapeutic potential of an antibody against NPTXR for ESCC. In the KYSE1260 cell line with undifferented ESCC, NPTXR knockdown (siNPTXR) had low ablity of invasion, migration, and proliferation by *in vitro* assay. In addition, KYSE1260 cells transfected with siNPTXR showed high caspase activity and a decrease in adhesion to extracellular matrix (ECM) proteins such as collagen and fibrinogen, and monoclonal antibody (mAb) against NPTXR prevented the proliferation, migration, and invasion.

Based on these results, low NPTXR expression or antibody targeting NPTXR in ESCC may reduce malignant capacity. Also, the clinical significance of NPTXR mRNA expression in ESCC patients was investigated in 194 primary ESCC patinents who underwent radical esophagectomy. The prognosis for ESCC was significantly poorer in high NPTRX expression than in low NPTRX expression. Moreover, a high mRNA NPTRX expression was a significantly independent prognostic factor for overall survival (OS) by multivariate analysis (hazard ratio [HR], 1.59; 95 % confidence interval [CI], 1.00–2.51; $P = 0.048$). Similarly, NPTRX protein expression was analyzed by immunohistochemistory, and positive NPTXR protein expression had an independent prognostic factor for the OS (HR, 1.86; 95 % CI, 1.05–3.29; $P = 0.033$). In summary, NPTXR has influenced the malignant behavior of ESCC cells. As a prognostic marker, NPTXR may be a companion diagnostic method, and NPTXR-targeting treatment such as antibodies may be a valuable novel therapeutic agent.[10].

Neoadjuvant chemotherapy and chemoradiotherapy followed by surgery strategies have been developed and widely performed as effective treatments to improve long-term outcome for advanced ESCC.[6,7] Recently, an immune checkpoint inhibitor has been noted as a new treatment for cancer. The CheckMate 547 trial showed that nivolumab as adjuvant therapy was effective treatment to extend the prognosis for patients with esophageal or gastroesophageal junction cancer who underwent neoadjuvant chemotherapy plus surgery.[8] However, the prognosis for patients with ESCC

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remains poor. Thus, it is necessary to continue to develop new therapeutic targets for ESCC to improve the outcome.[9]

A previous study using *in vitro* and *in vivo* assays showed that NPTXR plays an important role in regulating the malignant behavior of gastric cancer. Therapeutic antibodies that target NPTXR may be useful as novel diagnostic tools or therapies for gastric cancer.[5] This study demonstrated that NPTXR had an impact on the malignant behavior of ESCC cells and gastric cancer cells. Additonally, anti-NPTXR mAb may be a useful therapeutic agent as neoadjuvant chemotherapy and adjuvant chemotherapy for ESCC.

The aforementioned treatment methods and agents may have the potential to represent a paradigm shift in therapeutic strategies for other cancers. This study may provide a unique paradigm for other cancers with unfavorable responses to the standard multimodality treatment. Therefore, we anticipate further studies that assess new treatment focused on NPTXR, including internalization, for various cancers.

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