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EDITORIAL – TRANSLATIONAL RESEARCH AND BIOMARKERS

Is FGFR2 a Suitable Target to Treat Scirrhous-Type Gastric Cancer?

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Gastric cancer (GC) is the third most common cause of cancer-related death worldwide, and approximately 1,000,000 people suffer from GC every year.[1] Despite the advances in diagnosis and treatment, prognosis of advanced GC still remains poor. Scirrhous-type GC, composed mainly of diffuse-type GC cells, forms a Borrmann type 4 lesion and shows diffuse infiltration into the gastric wall with abundant fibrous stroma, resulting in thickening and rigidity of the stomach wall. Scirrhous-type GC shows rapid proliferation, progressive invasion, and a high frequency of metastasis to the peritoneum. Increasing rigidity and interstitial pressure may interfere with drug delivery to cancer cells. Crosstalk between cancer cells and fibroblasts/macrophages has been deeply involved in the progression of scirrhous-type GC. Reflecting such characteristics, scirrhous-type GC has the worst prognosis, with a 5-year survival rate of $< 15\%$; therefore, better knowledge of the biological basis of scirrhous-type GC is necessary to improve its treatment.

Several comprehensive studies, including those by a team at the Department of Surgical Oncology, Osaka City University, as well as our team, have been performed to clarify the molecular pathogenesis of scirrhous-type GC. We utilized serial analysis of gene expression, *Escherichia coli* ampicillin secretion trap, etc., and found that certain molecules and microRNAs have been associated with scirrhous-type GC[2–4]; however, to date, none have been introduced into clinical practice. By high-throughput sequencing analysis, The Cancer Genome Atlas (TCGA) Research Network[5] proposed the molecular classification of GC into four subtypes: (1) Epstein–Barr virus-positive (EBV +); (2) microsatellite instable (MSI); (3) genomically stable (GS); and (4) chromosomal instable (CIN). Among these, scirrhous-type GC may belong to GS GCs that show predominantly diffuse-type histology and are characterized by a substantially lower frequency of genetic aberrations.

In this issue of *Annals of Surgical Oncology*, Okuno et al.[6] report on establishing a new scirrhous-type GC cell line, OCUM-14, with amplification and overexpression of fibroblast growth factor receptor 2 (FGFR2). Nearly 30 years ago, K-sam/FGFR2 was identified as an amplified gene from the GC cell line KATO III, derived from pleural fluid of a scirrhous-type GC.[7] Its product was later found to be identical to the keratinocyte growth factor receptor or FGFR2. Currently, several FGFR2 inhibitors have been used in clinical studies to treat patients with FGFR2-positive cancers. However, reflecting on the difficulty of establishing a cell line from scirrhous-type GC with abundant fibrous stroma and less frequency (approximately 10% of all GCs) of FGFR2 amplification and overexpression, only a few scirrhous-type GC cell lines with FGFR2 abnormalities were available. While OCUM-14 cells grow singly or in clusters in a floating manner, the xenografted tumor forms by subcutaneous inoculation into nude mice. FGFR2 inhibitors surely inhibited the growth of OCUM-14 cells. This cell line could be a good model to understand the detailed mechanism of FGFR2-related malignant behavior of scirrhous-type GC, and also to clarify molecular bases of FGFR2 inhibitors to FGFR2-positive cancer. Gene amplification and overexpression of FGFR2 are found not only in a portion of scirrhous-type GCs but also in the aforementioned CIN subtype proposed by TCGA.[5] Although the findings reported here only relate to the establishment of one scirrhous-type GC cell line, further

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studies using this cell line would be beneficial for many cancer patients with FGFR2 amplification and overexpression who await optimal treatment.

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