Aim: Neuroendocrine cancer (NEC) of the stomach is a rare type of cancer that is often diagnosed at an advanced stage and with poor prognosis. Its molecular characterization associated with its pathogenesis and therapeutic targets are poorly understood, although chemotherapy based on small cell type of lung cancer is recommended. In this study, we aimed to clarify the molecular characterization of gastric NEC and to find NEC-specific alterations in comparison with adenocarcinoma.

Methods: Twenty samples from gastric cancers with advanced stage (11 adenocarcinomas and 9 NECs) and paired non-cancerous mucosa as controls were obtained by endoscopic biopsy. Analysis of sequence variations of 55 cancer-related genes was performed using the Ion AmpliSeq Panel Kit (Life Technologies), and analysis of DNA methylation was performed using the Infinium HumanMethylation 450 BeadChip array, covering 482,421 CpG sites (Illumina). DNA methylation and sequencing variation was confirmed using methylation-specific PCR and dideoxy sequencing.

Results: Extensive mutation analysis revealed mutations of tumor suppressor genes (TP53 and CDKN2A) were frequently detected, whereas any oncogene mutation was not detected in gastric NECs. However, ERBB2 and KRAS were amplified and overexpressed, which were therapeutic targets. Comprehensive methylation analysis revealed 842 gene promoters were methylated, and gene silencing associated with neuronal differentiation (p=7.6E-21) and regulation of transcription (P=1.24E-21) were significantly enriched in gastric NECs. Among these genes, 13 genes were identified as NEC-specific methylations in comparison with adenocarcinoma, and TLE1 and HNF1B were known to be cancer-related genes in blood and ovarian cancers.

Conclusions: To the best of our knowledge, this is the first study in which both genetic and epigenetic alterations were extensively analyzed in gastric NECs. Gene alteration with therapeutic targets was detected in NEC, and cell differentiation defects and cell cycle progression with DNA methylation are suggested to be involved in carcinogenesis of gastric NECs.

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