Comprehensive genomic profiling of neuroendocrine carcinomas of the gastrointestinal system

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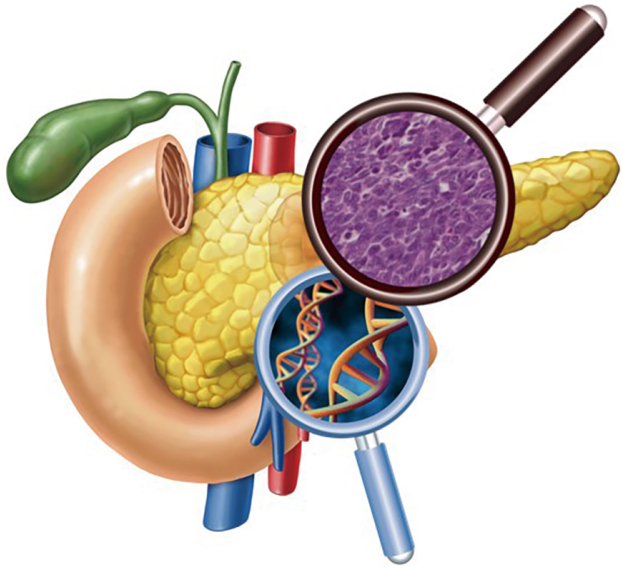
Abstract

The neuroendocrine carcinoma of the gastrointestinal system (GIS-NEC) is a rare but highly malignant neoplasm. We analyzed 115 cases using whole-genome/exome sequencing, transcriptome sequencing, DNA methylation assays, and ATAC-seq and found GIS-NECs to be genetically distinct from neuroendocrine tumors (GIS-NETs) in the same location. Clear genomic differences were also evident between pancreatic NECs (Panc-NECs) and non-pancreatic GIS-NECs (Nonpanc-NECs). Panc-NECs could be classified into two subgroups (i.e., 'Ductal-type' and 'Acinar-type') based on genomic features. Alterations in *TP53* and *RB1* proved common in GIS-NECs, and most Nonpanc-NECs with intact Rb demonstrated mutually exclusive amplification of *CCNE1* or *MYC*. Alterations of the Notch gene family were characteristic of Nonpanc-NECs. Transcription factors for neuroendocrine differentiation, especially the *SOX2* gene, appeared overexpressed in most GIS-NECs due to hypermethylation of the promoter region. This comprehensive study of genomic alterations in GIS-NECs uncovered several key biological processes underlying the genesis of this very lethal form of cancer.

Background & Results

NECs are cancers that originate in most epithelial organs of the body and most often in the digestive system, typically the pancreas. In addition to NEC being rare cancer, patients with NEC do not often undergo surgery, so tissue samples that can be used for research purposes are hard to find.

Structural variants, in which part of a chromosome is inserted, deleted, or inverted, were far more common in Nonpanc-NECs than in Panc-NECs. In addition, Panc-NECs could be classified into two groups ('ductal-type' and 'acinar-type') based on their genomic features. Intriguingly, the researchers also identified unusually high levels of methylation on the promoter of a transcription factor associated with NEC; a previously unknown genetic event where two genes became fused, creating a new hybrid gene (*NET1-AKR1C3/4*) that disrupted cellular function; and deletion of an RNA splicing factor (*SNRNP70*) that has not previously been linked to NEC.



Significance of the research and Future perspective

Our study suggests that different types of NECs arise due to very different sets of driver mutations and genomic changes, which could have important implications for patients' treatment. Given that this is one of the most comprehensive studies of this cancer to date, it is likely that the findings will help develop new, more effective treatments for affected patients. Existing drugs could be used in some of these patients to specifically target the genomic changes leading to disease. The targets defined in this study could even promote new drug discovery.

Patent
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