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OESOPHAGEAL CANCER

Defining tumour subtypes in oesophageal adenocarcinoma

> "...this disease seems to present three major mutational signature-based subgroups..."

A detailed analysis of the genomic alterations associated with oesophageal adenocarcinoma (OAC) has been published in *Nature Genetics*. Using whole-genome sequencing (WGS) of tumour samples, the researchers identified three major mutational subtypes, potentially representing a future approach to stratify patients for tailored treatment.

The sixth most frequent cause of cancer-related mortality worldwide, oesophageal cancer has two main subtypes: adenocarcinoma and squamous cell carcinoma. OAC is the most prevalent form in the West and is associated with a low overall 5-year survival of 15%. "Treatment currently relies on traditional chemotherapy, often combined with radiotherapy followed by an oesophagectomy," explains author Rebecca Fitzgerald, University of Cambridge, UK. Compared with other cancers a lack of targeted therapies currently exist for OAC, owing to limited insight into the molecular mechanisms promoting this disease.

To characterize the genomic landscape of OAC in unprecedented detail, Fitzgerald and colleagues first performed WGS on OAC samples from 129 patients. Compared with exome sequencing, WGS markedly simplifies identification of large-scale genomic alterations, as well as later analysis of mutational signatures.

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In agreement with previous studies, the researchers found abundant point mutations in OAC samples. However, copy number alterations or structural changes represented the most frequent changes in protein-coding genes, and these events were highly heterogeneous between cases. Moreover, structural variations were more recurrent than point mutations.

Next, the investigators assessed whether genomic changes might explain the lack of effect of receptor tyrosine kinase (RTK) inhibitors in OAC compared with other cancers. High-level gene amplification was observed for multiple RTKs, most commonly *ERBB2*, *EGFR*, *MET* and *FGFR*, and many other RTKs showed amplification at a lower level. Tissue expression of amplified genes was also increased. Fitzgerald and colleagues subsequently showed that, in cell line models, combined RTK inhibitor therapy tailored to specific RTK amplifications inhibited cell proliferation.

Using three different statistical approaches, the researchers then defined mutational signatures present across the tumour samples. By considering the context in which a nucleotide substitution occurred, particularly the identity of adjacent bases (the so-called trinucleotide context), the processes acting on the cancer cell (for example, age or acid refluxate exposure) were inferred via comparison to a database of known signatures. "The most significant finding is that this disease seems to present three major mutational-signature-based subgroups," observes Fitzgerald. These subtypes, also validated in a separate cohort ($n = 87$), were: "C>A/T dominant", "mutagenic" and "DNA damage repair impaired".

"Based on the molecular features of these subtypes, we obtained preliminary evidence in cell models that patients could be subdivided into one of the following categories for treatment: targeting the DNA damage repair pathway; combination RTK inhibition or immunotherapy; or WEE1/CHK1 inhibitors," says Fitzgerald. "Importantly, we also showed that this patient classification approach has the benefit of increased accuracy as it seems to be largely independent of the considerable spatial heterogeneity in a tumour."

"It is gratifying to see that WGS was performed in 129 patients," comments Jaffer Ajani (MD Anderson Cancer Centre, USA), who was not involved in the study. "One should strive to inhibit multiple drivers or pathways to derive maximum treatment efficacy, although this approach is not novel and has been played out in melanoma successfully. Some preclinical data is provided, but I am not sure it can pan out in the clinic, and it could take years to figure out."

Fitzgerald and colleagues plan to continue preclinical experiments to demonstrate the utility of patient stratification for a clinical medicine trial in OAC.

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