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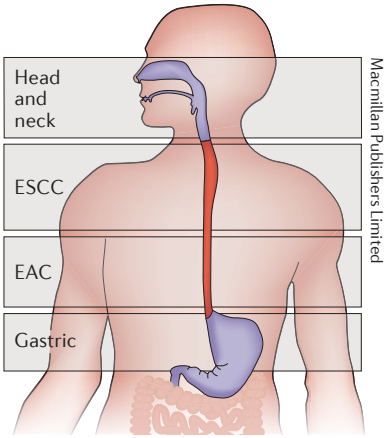
GENETICS

Oesophageal cancer — not all alike



The survival rates of patients with oesophageal cancers are low, and a limited number of targeted therapies are available for these patients. Two major subtypes of oesophageal cancers can be defined according to tumour histology: oesophageal adenocarcinomas (EACs), most frequently occurring in the lower oesophagus near the gastroesophageal junction (GEJ), and oesophageal squamous-cell carcinomas (ESCCs), predominantly ocurring in the upper and mid oesophagus. The histological classification of this cancer type has, however, been the subject of much debate. The results of a genetic characterization of oesophageal cancers, conducted by The Cancer Genome Atlas Research Network, have now been published and indicate that EACs and ESCCs are, in fact, distinct molecular entities.

This study, coordinated by Adam Bass and Vésteinn Thorsson, addressed the demarcation between gastric and oesophageal adenocarcinomas, as well as the classification of adenocarcinomas of the GEJ. The samples used for this purpose were from 164 oesophageal tumours (90 of them histologically classified as ESCCs, 72 as EACs, and 2 as undifferentiated carcinomas), 359 gastric adenocarcinomas (63 of them histologically classified as gastric GEJ carcinomas), and 36 GEJ carcinomas of indeterminate origin.

A comprehensive molecular characterization of the 164 oesophageal carcinomas revealed important differences between EACs and ESCCs. In the former, the expression of genes involved in E-cadherin function (including the E-cadherin gene itself) was upregulated, whereas in the latter, the Wnt, syndecan and p63 pathways were found to be upregulated. In both subtypes, mutations were commonly detected in *TP53*, but subtype-specific recurrent mutations were also identified. The patterns of somatic copy-number alterations (SNCAs) were also subtype-specific. Importantly, many recurrent mutations and SCNAs in different genes were found to affect the same signalling pathways in ESCCs or EACs, indicating that clinical trials of molecularly targeted agents for patients with oesophageal cancers should be carefully designed.

Integrative analysis of ESCC-derived data revealed the existence of three subtypes in this group. The gene-expression patterns of ESCC tumours, especially from the 'ESCC1' subtype, closely ressemble those of head and neck squamous-cell carcinomas (SCCs). Human papilloma virus (HPV) infection strongly contributes to the pathogenesis of head and neck SCCs; however, transcript levels of HPV were similar in ESCCs and HPV-negative head and neck SCCs. Further comparisons of molecular data confirmed that ESCCs are more closely related to head and neck SCCs than to EACs. Moreover, EACs and the chromosomal instability subtype of gastric cancer seem to be the same disease at the molecular level.

These results indicate that the treatment of patients with oesophageal cancer can be optimized with therapeutic decisions made on the basis of molecular subtype rather than according to the organ of origin. Further studies will help to identify the best therapeutic approaches for each subtype.

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