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GENETICS

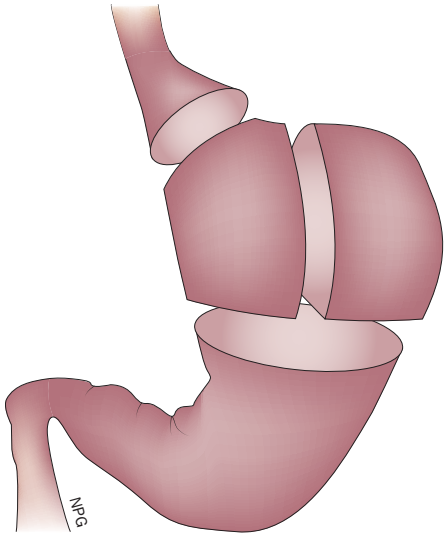
New molecular classification of gastric adenocarcinoma proposed by The Cancer Genome Atlas

Currently, two histological classification systems are available to characterize gastric adenocarcinomas, which represents the majority of gastric tumours. The Lauren classification system comprises two subtypes (intestinal and diffuse) and the WHO classification has four subtypes (papillary, tubular, mucinous and poorly cohesive). Neither system is particularly clinically useful as their prognostic and predictive capabilities cannot adequately guide patient management. Now, The Cancer Genome Atlas research network has proposed a new classification scheme based on tumour molecular biology.

"There's a clear need for a more-refined genomic and molecular understanding of gastric cancer because it is one of the most common and treatment-refractory diseases," explains lead investigator Adam Bass of the Dana–Farber Cancer Institute in Boston, USA. "To date, much of our efforts to develop new therapies have not had the benefit of robust systems to categorize the cancer and to identify key targets for individual patients."

To address this need, the researchers examined tumour tissues from 295 patients prior to treatment (chemotherapy or radiotherapy) using platforms that assessed somatic copy number, whole-exome sequences, DNA methylation patterns, mRNA sequences, microRNA sequences and protein expression. All the samples were also assessed for microsatellite instability.

Clustering the data from these experiments using a variety of methods revealed four major groups, which the researchers propose as the new molecular subtypes of gastric adenocarcinoma. The first group of tumours are Epstein–Barr virus (EBV)-positive, harbour *PIK3CA* mutations, demonstrate DNA hypermethylation and amplification of *JAK2*, *PDL1* and *PDL2*. Although these tumours were distributed throughout the



stomach, EBV-positive tumours were most frequently found in the gastric fundus or body. Comprising approximately 10% of the cancers, the researchers were "quite struck that approximately 70% of EBV-positive tumours had potentially activating mutations in the gene *PIK3CA*, a result that has implications for the possible use of PI3K inhibitors for this subtype," explains Bass. The amplification of the genes encoding the immune checkpoint proteins PD-L1 and PD-L2 could point to a mechanism through which EBV-positive tumours are able to survive in response to a strong immune response. "A number of new inhibitors are being developed against this pathway, which could be tested in patients with this subtype of tumour."

The second subgroup comprised 20% of the samples, and was defined as microsatellite unstable tumours. These tumours had elevated mutation rates, with affected genes that included those commonly observed in other cancers and for which targeted therapies are available—such as *PIK3CA*, *ERBB3*, *ERBB2* (*HER2*) and *EGFR*.

The third subgroup, comprising 50% of the samples, represented chromosomally unstable tumours. *TP53* mutations were frequent in this subtype (71% of tumours), and these tumours exhibited considerable aneuploidy and amplification of receptor tyrosine kinases, VEGFA and cell-cycle mediators (*CCNE1*, *CCND1* and *CDK6*). Chromosomally unstable tumours presented more frequently in the gastro-oesophageal junction/cardia.

The remaining 20% of the samples were classed as genomically stable because they lacked the features of the other three tumour subtypes. These genomically stable tumours were predominantly of the diffuse histological Lauren variant and harboured mutations in *RHO* family genes.

"From these data we have multiple new hypotheses to take forward as we consider how to design trials and how to investigate emerging therapies," expands Bass. For example, future trials of chemotherapy in the metastatic or adjuvant setting might benefit from subgroup analysis to identify if these treatments have distinct effects in different classes of gastric adenocarcinoma, something that is already being done in other cancer types. "By contrast, when the time comes to think about targeted agents, we would want to move beyond just thinking about four distinct groups of gastric cancer and consider the specific molecular and genomic alterations in individual patients," warns Bass. Indeed, these newly described subgroups are not homogeneous entities. "We do not anticipate that all tumours are the same within a given subgroup or that they would be optimally treated by the same therapy."

With these results, the stage is now set for personalized medicine to become a reality for patients with gastric cancer.

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