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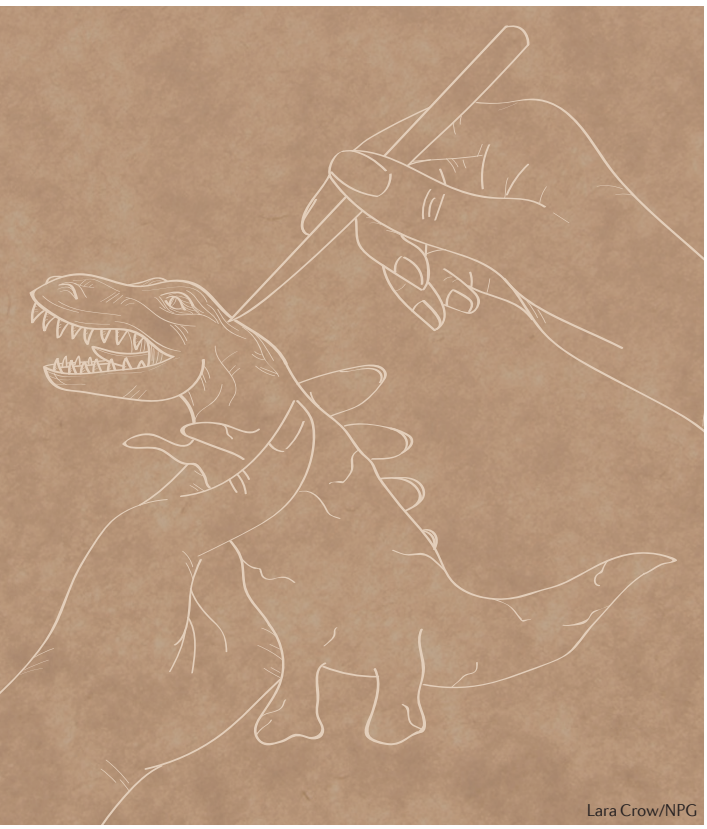
OESOPHAGEAL CANCER

Model refinement

> “Oncogene activation events … probably occur later in tumour progression”

Barrett oesophagus (BE) — a condition in which epithelium of the lower oesophagus acquires features of intestinal epithelium owing to gastroesophageal reflux disease — is the precursor to oesophageal adenocarcinoma (EAC). However, progression from BE to EAC is rare and not well understood; therefore, a better understanding of the molecular relationships between the two conditions should improve strategies for EAC prevention and early diagnosis. Two papers published in *Nature Genetics* now report whole-genome and whole-exome sequencing of paired BE and EAC samples, providing some insights into EAC development.



Lara Crow/NPG

Ross-Innes, Becq *et al.* conducted whole-genome sequencing of 23 paired EAC and adjacent BE samples. BE samples had a high mutation rate, but that of EAC samples was significantly higher. Surprisingly, there was limited overlap between mutations in BE and matched EAC samples, even in genes such as *TP53*, which is known to be frequently mutated in EAC. In addition, BE samples had few copy number changes, whereas EAC samples had significantly more changes, including some regions that were highly amplified. Despite the heterogeneity in genomic alterations between BE and EAC, the mutational signatures were similar in the different lesions, indicating that the same mutagenic process is likely to underlie these mutations.

To determine clonal hierarchy in BE, targeted sequencing of 1,443 loci was conducted on 73 BE samples from a single patient, of which some showed evidence of dysplasia and some did not. In this patient, an initial clonal sweep seemed to be followed by the evolution of two clones with substantial differences, one of which then gave rise to several other clones. The clone with the highest level of copy number changes gave rise to high-grade dysplasia but, interestingly, two other clones did as well. Previous models of BE evolution have suggested either that all clones have a common ancestor or that all clones are distinct, but these data within a single patient provide evidence in support of both models.

Stachler, Taylor-Weiner *et al.* conducted whole-exome sequencing on 25 paired BE (not tumour-adjacent if possible) and EAC samples. These authors also found that BE samples had a high mutation rate, but although they observed a higher rate in dysplastic than in non-dysplastic BE samples, the mutation rate between dysplastic BE and EAC was similar (Ross-Innes, Becq *et al.* also noted this similarity, although it was not statistically significant in their analysis). Like Ross-Innes, Becq *et al.*, these authors observed higher gene amplification in EAC compared with BE, and similar mutational signatures.

Analysis of mutations in *TP53* and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) — the two most commonly inactivated tumour suppressor genes in EAC — indicated that in contrast to the current model, which suggests that *CDKN2A* mutations precede *TP53* mutations, in many tumours *TP53* mutations occurred earlier than, and in some cases without, inactivation of *CDKN2A*. Oncogene activation events (typically via gene amplification) were less prevalent and therefore probably occur later in tumour progression; this is similar to the data reported by Ross-Innes, Becq *et al.* More extensive sampling of BE and EAC in 5 additional patients and a re-analysis of whole-exome sequencing data from 144 EAC cases confirmed these results, and also identified widespread genomic heterogeneity. These authors present a model whereby EAC can progress via two separate paths: *TP53* mutation followed by genome doubling to amplify oncogenes (possibly a crucial event in the transformation of some EACs), or progressive loss of tumour suppressors in those that do not undergo genome doubling.

Overall, these studies provide more detailed information on the progression from BE to EAC, which might improve our ability to predict which patients with BE are most likely to develop cancer.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPERS Ross-Innes, C. S., Becq, J. *et al.* Whole-genome sequencing provides new insights into the clonal architecture of Barrett's esophagus and esophageal adenocarcinoma. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3357 (2015) | Stachler, M. D., Taylor-Weiner, A. *et al.* Paired exome analysis of Barrett's esophagus and adenocarcinoma. *Nat. Genet.* http://dx.doi.org/10.1038/ng.3343 (2015)