CANCER GENETICS

The interloper

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The retrotransposon long interspersed element 1 (LINE-1) is a mobile genetic sequence that can lead to mutagenesis and genetic instability by copying and inserting itself into the genome. LINE-1 insertions have been reported in tumour-suppressor genes in several types of tumour, and now, three studies have revealed LINE-1 activity in tumour progression.

Rodić *et al.* were interested in testing whether somatic retrotransposition events could be found in pancreatic ductal adenocarcinoma (PDAC) genomes. Using samples from autopsies of patients with PDAC, the authors compared LINE-1 insertions in normal tissue, primary tumours and metastases. When comparing transposon insertion profiles of 18 primary tumours with matched normal tissue, the authors found 268 cancer-specific insertions. Similarly, when analysing somatic insertions at 15 metastatic sites, they found 242 insertions that were not present in the corresponding normal tissue samples. In 13 cases in which both primary and metastatic samples were available, they found 45 insertions shared between the two sites. Interestingly, those patients with a higher number of LINE-1 insertions present in the primary tumour had worse survival after diagnosis.

Finally, the authors evaluated the rates of retrotransposition during progression of PDAC, expecting new insertions to be acquired steadily during the course of the disease. However, they found discordant overall rates of retrotransposition in matched primary and metastatic subclones, suggesting that LINE-1 insertions in PDAC occur discontinuously.

By contrast, Ewing *et al.* found that most LINE-1 insertions occur before tumours metastasize. In their study, the authors attempted to determine how early somatic LINE-1 insertions can occur during the development of gastrointestinal cancers. To that end, they compared LINE-1 insertions in 30 tumours of different developmental stages from colon, pancreatic and gastric cancers with those in matched healthy tissue. They found that somatic LINE-1 insertions occurred not only in all cancer types and metastases, but also in precancerous lesions, such as colon polyps, suggesting that these insertions occur early in tumour development, either at the dysplastic stage or even in histologically normal cells. In all cases of colorectal and pancreatic cancer, most insertions were shared between the primary cancer and the metastatic site, indicating that they had occurred before the tumour metastasized.

That LINE-1 insertions occur early in the tumorigenic process was also observed by Doucet-O'Hare *et al.*, who examined LINE-1 insertions in oesophageal adenocarcinoma (EAC) and in Barrett oesophagus (BE), which is often a precursor of this malignancy. The authors wanted to assess whether BE represented a permissive environment for LINE-1 retrotransposition and therefore evaluated the presence of LINE-1 insertions in 5 patients with benign BE, 10 patients with EAC, and 5 patients with BE and concomitant EAC. The authors observed clonal amplification of several insertions that seemed to originate in normal oesophagus or BE and were later clonally expanded in BE or in EAC. Furthermore, 22 of the 25 EAC-specific insertions were found in distinct regions from the same tumour, which suggested that these insertions occurred in the founding clone of these lesions.

Taken together, these studies add to the accumulating evidence that LINE-1 is active during the development of many gastrointestinal cancers. Although they do not assign a definitive function to somatically acquired LINE-1 insertions in cancer, these results open up the possibility that these insertions contribute to tumour phenotypes and might serve as a biomarker for early detection.

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ORIGINAL RESEARCH PAPERS Rodić, N. *et al.* Retrotransposon insertions in the clonal evolution of pancreatic ductal adenocarcinoma. *Nat Med.* **21**, 1060–1064 (2015) | Ewing, A. D. *et al.* Widespread somatic L1 retrotransposition occurs early during gastrointestinal cancer evolution. *Genome Res.* http://dx.doi.org/10.1101/gr.196238.115 (2015) | Doucet-O'Hare, T. T. *et al.* LINE-1 expression and retrotransposition in Barrett's esophagus and esophageal carcinoma. *Proc. Natl Acad. Sci. USA* **112**, E4894– E4900 (2015)