similar mechanical properties to those of thermosets (because they are crosslinked), but remain processable at high temperatures because the dynamic linkages can exchange their positions, allowing the material to be remoulded[3,4].

Using their dynamic crosslinking agents, the authors demonstrated a simple method to convert mixtures of cheap commodity thermoplastics (less than US$5 per kilogram) into multi-component vitrimers. In doing so, the mechanical and high-temperature performance of commodity plastics such as low- and high-density polyethylene can be upgraded. Even more excitingly, stable, reprocessable composites were formed from polyethylene and polyesters. In one particularly compelling example of upcycling, a composite was created using low-density polyethylene from a plastic bag together with polylactic acid from a plastic drinking cup. The presence of dyes and other additives in the two materials was not detrimental to the chemistry, which bodes well for the use of this technology for recycling post-consumer waste.

To understand the potential impact and limitations of this work, it is helpful to consider the scale of worldwide production and use of plastics. Around 460 megatonnes of plastics were used in 2019, 40% of which consisted of polyethylene and polypropylene[5]. Only 9% of manufactured polymers were recycled[6], and the Organisation for Economic Co-operation and Development projects that the amount of plastic waste could almost triple by 2060 if policies are not implemented to address the issue[5]. It is to be hoped that regional and global actions could mitigate this increase, but large-scale recycling will be key to reaching a sustainable, circular plastic economy[7].

The technology developed by Clarke *et al.* has the potential to greatly ease the recycling of post-consumer plastics by lessening the stringency of waste sorting. However, the typical concentration of the crosslinking agent used in the study is still much too high for large-scale application. For example, the compatibilization of 100 megatonnes of mixed-waste plastics (about one-quarter of 2019's global waste) would require the production of 5 megatonnes of dynamic crosslinker — an unrealistic goal, especially given the lengthy synthetic sequences (and expensive reagents) that are used to generate the three prototypical crosslinking reagents. Moreover, the high number of fluorine atoms in the crosslinking agents might be problematic, given concerns about the persistence of highly fluorinated compounds in the environment[8].

Nevertheless, Clarke *et al.* have made an important advance by showing that simple processes for the dynamic compatibilization of mixed plastic are viable. Follow-up work will no doubt improve on the initial discovery and uncover applications for the reported composites — each of which is a fundamentally new material with the potential for use in engineering and manufacturing.

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Tumour biology

Extrachromosomal DNA appears before cancer

David H. Wang

A type of circular DNA called extrachromosomal DNA was thought to be found exclusively in cancer. Its discovery in non-cancerous tissue suggests that it might have an early active role in malignant transformation. **See p.798**

A type of circular DNA not found on chromosomes, termed extrachromosomal DNA, can aid cancer growth by harbouring cancer-promoting genes (oncogenes)[1]. The unique structure of extrachromosomal DNA and its associated protein complex, called chromatin, boosts the efficiency of its transcription, and the inheritance pattern of this DNA, resulting in many copies in a single cell, supports rapid amplification of oncogene content and tumour evolution[2,3]. Although present in many types of human cancer, extrachromosomal DNA was thought to be non-existent in normal tissues. On page 798, Luebeck *et al.*[4] report their finding of extrachromosomal DNA in non-cancerous oesophageal tissue that is predisposed to cancer development, and provide evidence that this DNA might help to drive non-cancerous tissue to become cancerous.

Barrett's oesophagus is a condition in which the cells lining the oesophagus (Fig. 1) change their identity as a complication of the reflux of acidic contents from the stomach and intestinal bile back into the oesophagus (gastro-oesophageal reflux)[5]. A minority of people with Barrett's oesophagus go on to develop cancer after the cells have progressed through low-grade and then high-grade dysplasia — precancerous states in which cells acquire an increasing number of genetic abnormalities and structural changes. Large-scale genetic abnormalities can arise during dysplasia from mutations or loss of genes that function as tumour suppressors, such as *TP53*, and such mutations or loss can lead to whole-genome duplication, genomic instability or catastrophic chromosomal rearrangements called chromothripsis[6,7].

Luebeck and colleagues sought to answer the key question of whether extrachromosomal DNA found in oesophageal cancer is a consequence of genomic instability or a causal event responsible for the transition from dysplasia to cancer. The authors did this through computational analysis of whole-genome sequencing results of oesophageal biopsies from UK and US patients. Oesophageal biopsies from a single time point were examined for 226 individuals who had a diagnosis of one of the following: Barrett's oesophagus; Barrett's oesophagus with low-grade dysplasia; Barrett's oesophagus with high-grade dysplasia; early-stage cancer; or late-stage cancer. Longitudinal biopsies (those taken at different times) from at least two time points and from at least two locations in the oesophagus were analysed for a separate group of 80 people in the United States who had Barrett's oesophagus. This group consisted of 40 individuals who developed oesophageal cancer (67.5% had high-grade dysplasia) and 40 who did not (7.5% had high-grade dysplasia).

For the UK group, none of the people with Barrett's oesophagus or Barrett's oesophagus with low-grade dysplasia had extrachromosomal DNA. However, 4% of individuals with high-grade dysplasia, 25% with early-stage cancer and 43% with late-stage cancer had

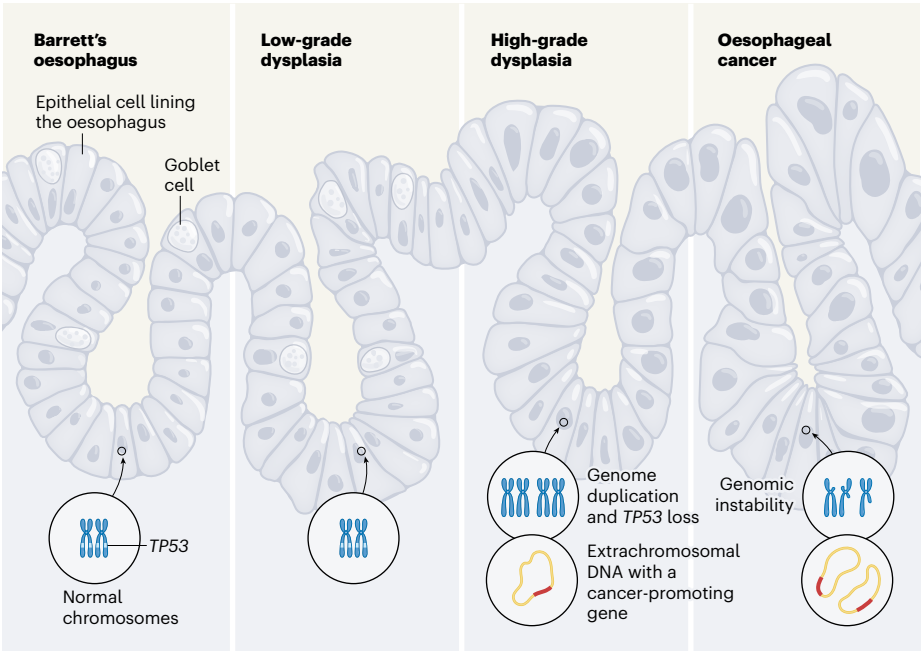

Figure 1 | Changes during the development of oesophageal cancer. The lining of the oesophagus contains epithelial cells. Epithelial cells can undergo cell-shape and DNA changes that might, in some cases, lead to cancer after progressing through states called Barrett's oesophagus (in which goblet cells appear), low-grade dysplasia and high-grade dysplasia. Genetic changes observed can include loss of the gene *TP53* and chromosomal changes such as genome duplication or genomic instability. Another type of abnormal DNA found in this condition is circular DNA called extrachromosomal DNA, which can carry cancer-promoting genes (red). Luebeck *et al.*[4] examined clinical samples to determine when extrachromosomal DNA is first observed, and report that it was present as early as the state of high-grade dysplasia. More copies of extrachromosomal DNA can be found if a cancer develops in the oesophagus. The discovery of extrachromosomal DNA before a tumour forms raises the possibility that it has a role in driving the formation of oesophageal cancer.

extrachromosomal DNA. This finding suggests that extrachromosomal DNA is initially formed during high-grade dysplasia, before cancer develops, and that its frequency increases as cancers become more aggressive.

Among the individuals from the US group, 33% of those who developed oesophageal cancer had extrachromosomal DNA in at least one biopsy before or at the time of cancer diagnosis. In pre-cancer biopsies, extrachromosomal DNA was present in 20% of individuals who developed cancer, but in only 2.5% of those who did not. A long-term clinical follow-up of the single individual with extrachromosomal DNA who did not develop cancer was unavailable, because the person died several years later from an unrelated cause. Ten people without extrachromosomal DNA had long-term follow-ups, and they remained negative for either high-grade dysplasia or oesophageal cancer almost ten years later. These results show a strong correlation between the presence of extrachromosomal DNA and subsequent development of oesophageal cancer.

One US individual underwent biopsies at four time points over a seven-year period. Initially, biopsies revealed high-grade dysplasia, loss of *TP53* and no extrachromosomal DNA. At the second time point, five years later, biopsies showed high-grade dysplasia and the appearance of a single type of extrachromosomal DNA. At the third time point, six months later, the person had developed oesophageal cancer and acquired a second type of extrachromosomal DNA, different from the first. When tumour-removal surgery was performed soon after, the cancer contained both extrachromosomal DNAs, whereas the residual high-grade dysplasia had only the initial extrachromosomal DNA. Luebeck *et al.* concluded that the transformation of dysplasia into cancer was associated with acquisition of the second extrachromosomal DNA.

Further analysis of longitudinal biopsies from the US group showed that extrachromosomal DNA from multiple biopsies at different time points were highly similar in individual patients, consistent with a common origin. Extrachromosomal DNA appeared after *TP53* alterations but could be found independently of whole-genome duplication or chromothripsis. The number of copies of extrachromosomal DNA in individuals was similar if the cellular patterns observed under the microscope (histology) were similar between two biopsies. The copy number became much higher, with increased structural complexity of extrachromosomal DNA, as the number of histological abnormalities present increased. Analyses across all participants found that 31% had more than one extrachromosomal DNA and that one-third of the extrachromosomal DNAs contained more than one oncogene. Together, these data suggest that extrachromosomal DNA has an active role in the transformation of Barrett's oesophagus into cancer.

Although their conclusions are based on associations, a known limitation of observational clinical studies, Luebeck and colleagues examined a large number of individuals representing the entire progression sequence of Barrett's oesophagus to cancer. The authors also analysed two independent groups of patients and carried out longitudinal sampling of Barrett's oesophagus from people with known cancer outcomes. The study is important because it establishes that extrachromosomal DNA can arise in pre-cancerous tissue. In addition, extrachromosomal DNA confers a selection advantage for cells that will progress to cancer and could participate in other processes that promote tumour formation.

A major clinical challenge is being able to identify which cases of Barrett's oesophagus will develop into cancer[8]. Although extrachromosomal DNA seems attractive as a predictive biomarker, it was found in individuals with high-grade dysplasia. The standard clinical care for high-grade dysplasia is to use an endoscopic technique to eradicate Barrett's oesophagus tissue, and intervening at this point removes the need to predict who might progress[9]. Instead, future work should focus on therapeutic interventions relating to extrachromosomal DNA. Barrett's oesophagus can recur after endoscopic eradication[10], so that outcome is a clinical scenario in which inhibiting oncogenic extrachromosomal DNA would be particularly beneficial.

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