OESOPHAGEAL CANCER

Mutation and clonal selection in the ageing oesophagus

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Normal oesophagus epithelium harbours extensive somatic mutations that accumulate with age but do not lead to cancer, according to two new studies published in *Science* and *Nature*.

Somatic mutations that provide a competitive advantage to mutant cells can give rise to cancer. Studies of skin cells, which are exposed to mutagenic ultraviolet light, have revealed that independent precancerous clonal cell populations are present within physiologically normal tissues, suggesting that positively selected mutations accumulate over the life course. Given the difficulty of assessing low-prevalence somatic mutations, the factors influencing the development and evolution of these precancerous clones and how they differ from cancer cells is not well understood.

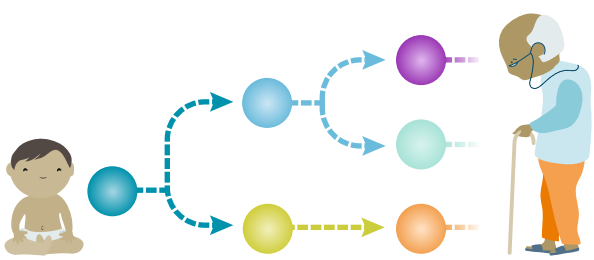
In the first of two new studies, Iñigo Martincorena and colleagues sought to address whether normal oesophageal epithelium, which is exposed to lifestyle-related mutagens such as cigarette smoke and alcohol rather than ultraviolet light, also contained clonal cells possessing numerous mutations. They performed targeted gene sequencing of normal oesophageal epithelium from 9 human donors (20–75 years of age). They found that the number of mutations and the size of mutant clones increased with donor age; on average, individual cells from those in their 20s possessed several hundred mutations, whereas those from the oldest individuals had >2,000 mutations.

Focusing on mutations in cancer-driver genes, the researchers identified positive selection for mutations in 14 genes, including Notch family genes and *TP53*. Mutations in *NOTCH1* were particularly prevalent — on average across the 9 donors, an estimated 25–42% of epithelial cells in the normal oesophagus carried a *NOTCH1* mutation, with more mutations in older individuals. Importantly, this rate of *NOTCH1* mutation is higher than that observed in oesophageal squamous cell carcinomas (ESCCs), suggesting that mutations in *NOTCH1* might not be driving carcinogenesis in these cancers. By contrast, the rate of *TP53* mutation was far less in normal tissue (affecting 5–10% of cells) than in ESCCs (present in 90% of cancers as reported by other studies). Importantly, normal oesophageal tissue did not have the chromosomal instability typical of ESCCs.

In the second study, Seishi Ogawa and colleagues sequenced tissue samples from normal oesophagus, dysplastic oesophagus and ESCC from a total of 139 individuals of varying ages and risk-factor exposures. These investigators also found a high mutation rate in normal oesophageal tissue and clonal expansion of affected cells, suggesting extensive positive selection; oesophaguses from elderly individuals each possessed ~10,000 driver-gene-mutated clones. Moreover, the number of mutations increased markedly with exposure to lifestyle risk factors, and mutation signatures associated with alcohol intake or smoking were more prevalent in ESCC samples and in normal tissue from patients with these risk factors. Further mirroring the findings of Martincorena et al., the most commonly mutated genes in noncancerous and cancerous clones were *NOTCH1* and *TP53*, respectively. Samples from normal oesophageal epithelium also had few chromosomal abnormalities, whereas there was substantial chromosomal instability in ESCC samples.

By calculating the rate of mutation and sequencing clones from densely sampled areas of normal oesophagus as small as 0.2 mm^2, Ogawa and colleagues were able to estimate the temporal sequence of mutations across the oesophageal epithelium. In one 70-year-old individual at high risk of ESCC, a *TP53* mutation was predicted to have occurred in one oesophageal cell at the age of 13. Over the next 57 years, this cell gave rise to a 6.6 mm^2 clonal region without causing a cancer to develop, highlighting the importance of other factors in driving cancer development. "The extensive chromosomal abnormalities in cancers compared with noncancerous clones suggests that these changes might be the critical step of carcinogenesis," ventures Ogawa.

Hugh Thomas



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ORIGINAL ARTICLE Martincorena, I. et al. Somatic mutant clones colonize the human esophagus with age. *Science* **362**, 911–917 (2018) | Yokoyama, A. et al. Age-related remodelling of oesophageal epithelia by mutated cancer drivers. *Nature* **565**, 312–317 (2019)