Mutant cells colonize our tissues over our lifetime

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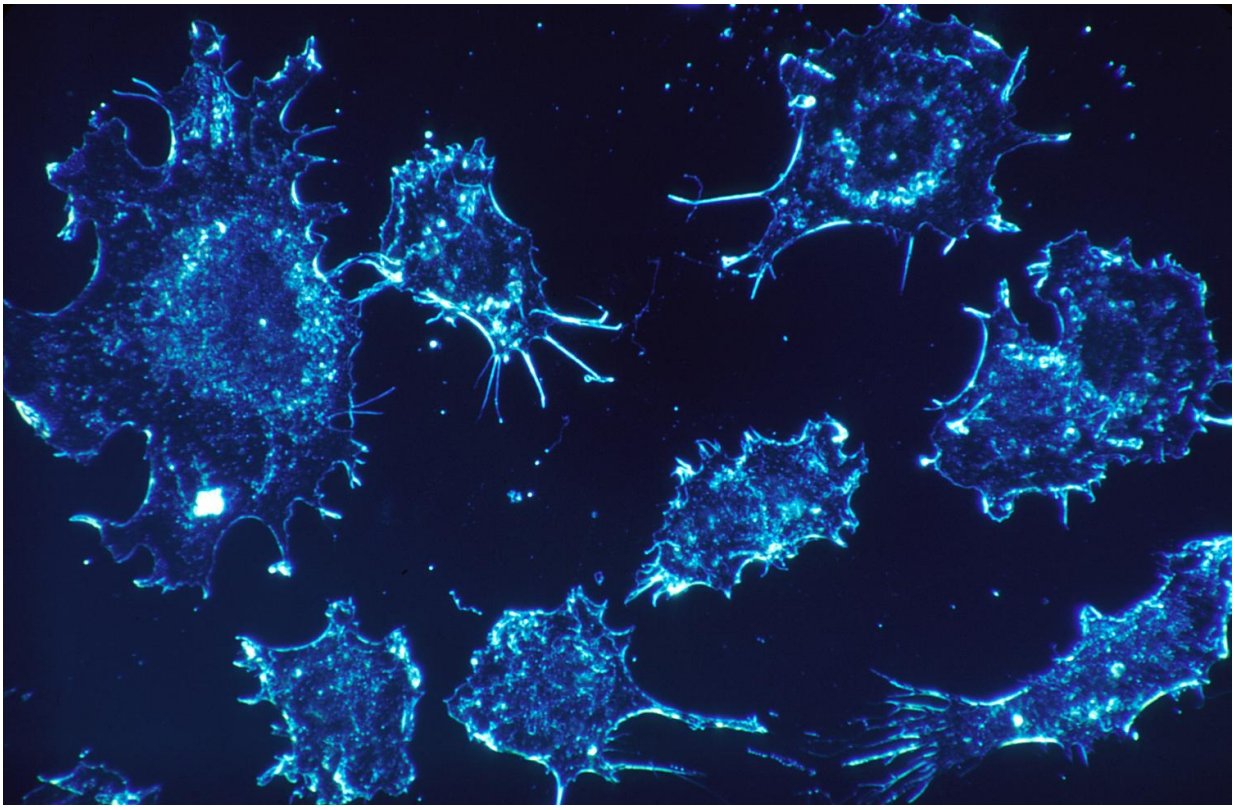

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By the time we reach middle age, more than half of the oesophagus in healthy people has been taken over by cells carrying mutations in cancer genes, scientists have uncovered. By studying normal oesophagus tissue, scientists at the Wellcome Sanger Institute, MRC Cancer Unit,

University of Cambridge and their collaborators uncovered a hidden world of mutations and evolution in our tissues as we age.

The results, published today (18 October) in *Science* show how mutant cells mutate and compete with each other throughout life, and only the fittest mutations survive.

Every person accumulates genetic changes, or mutations, throughout their lifetime. These mutations in normal tissue, called somatic mutations, are key to understanding the first steps to cancer and likely contribute towards ageing, but are unchartered territory due to technical limitations.

For the first time, scientists have uncovered that on average, healthy cells in the oesophagus carry at least several hundred mutations per cell in people in their twenties, rising to over 2,000 mutations per cell later in life. Only mutations in a dozen or so genes seem to matter however, as these give the cells a competitive advantage allowing them to take over the tissue and form a dense patchwork of mutations.

Professor Phil Jones, joint lead author from the Wellcome Sanger Institute and MRC Cancer Unit, University of Cambridge, said: "Under the microscope, the oesophageal tissue looked completely normal—it came from healthy individuals who had no signs of cancer. After studying the genetics we were shocked to see that the healthy oesophagus was riddled with mutations. We discovered that by the time an individual reaches middle age, they probably have more mutant than normal cells."

The team used targeted and whole-genome sequencing to map groups of mutant cells in normal oesophageal tissue from nine individuals aged 20 to 75 years. The individuals' oesophageal tissues were considered healthy as none of the donors had a known history of oesophageal cancer, nor were taking medication for problems relating to the oesophagus.

The study also casts new light on the mutations that are found in the squamous kind of oesophageal cancers. One mutated gene, TP53, which is found in almost all oesophageal cancers is already mutated in 5-10 per cent of normal cells, suggesting that cancer develops from this minority of cells.

In contrast, mutations in the NOTCH1 gene, known to control cell division, were found in nearly half of all cells of normal oesophagus by middle age, being several times more common in normal tissue than cancer. This observation suggests that researchers need to reconsider the role of some genes recurrently mutated in cancer in the light of mutations in normal tissue, and raises the possibility that the NOTCH1 mutation may even protect cells against cancer development.

Dr. Jo Fowler, joint first author from the Wellcome Sanger Institute, said: "For years we have sequenced cancer genomes and looked for genes that are commonly mutated across patients. We assumed that the common mutations are the ones driving the cancer. However, now we have looked at normal tissues we were surprised to find that a gene commonly associated with oesophageal cancer, NOTCH1, was more mutated in normal cells than cancer cells. These results suggest that scientists may need to rethink the role of some cancer genes in the light of sequencing normal tissues."

The discovery that normal aged oesophagus is a dense patchwork of mutant cells carrying mutations previously linked with oesophageal cancer has important implications. It provides insights into key genes that control cell behaviour in normal tissues. It also gives a window into the first steps in the development of some oesophageal cancers, which are believed to arise from these mutant cells, and will be informative for current research efforts on early detection of cancer.

Dr. Inigo Martincorena, joint lead author from the Wellcome Sanger

Institute, said: "We have found that genetic mutations associated with cancer are widespread in normal tissues, revealing how our own cells mutate, compete and evolve to colonise our tissues as we age. Given the importance of these mutations to cancer, it is remarkable that we have been unaware of the extent of this phenomenon until now. While the work sheds light on early cancer development, it also raises many questions about how these mutations may contribute to ageing and other diseases, opening interesting avenues for future research."

Professor Karen Vousden, chief scientist at Cancer Research UK, which part-funded the study, said: "As cancer researchers, we can't underestimate the importance of studying healthy tissue. Our risk of developing cancer increases as we age, and this research brings us closer to uncovering clues within our normal tissues to help us identify individuals at higher risk of the disease.

"This study shows that some genetic changes linked to cancer are present in surprisingly large numbers of normal cells. We still have a long way to go to fully understand the implications of these new findings, but we hope that studies like this will one day help us to develop targeted diagnostic tests. In particular, oesophageal cancer is very hard to treat so detecting signs of the disease at the earliest possible stage could make a huge difference for patients."

More information: I. Martincorena el al., "Somatic mutant clones colonize the human esophagus with age," *Science* (2018). science.sciencemag.org/cgi/doi … 1126/science.aau3879

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