New study shows esophageal cancers driven by 'marginal gain' rather than speed

22 August 2016

Wellcome Trust Sanger Institute scientists have shown that unexpectedly, oesophageal cancer cells do not divide faster than their normal neighbours. But unlike normal cells, the tumour cells produce slightly more dividing daughter cells than non-dividing ones, forming a tumour.

The study, published in *Nature Cell Biology* today, could lead to the development of new treatments for cancers that do not respond to current therapies which target fast-growing cells.

Normal cells produce equal numbers of dividing and non-dividing cells, a balance which sustains the tissue. For every 100 normal cells, 50 of them will divide and 50 of them will not. The researchers found that for 100 pre-cancer cells the balance was slightly skewed in favour of dividing cells, with 52 of those cells dividing and 48 remaining undivided. This is the first time this has been shown. The subtle shift loads the odds in favour of cell division and over time this can lead to tumour growth.

Oesophageal cancer is the sixth most common cause of cancer death in the UK. Each year 8,750 people are diagnosed with the disease, which is hard to treat even with aggressive therapy. Understanding the processes underlying tumour growth could help in the development of new cancer treatments.

Dr Philip Jones, lead researcher from the Wellcome Trust Sanger Institute, said: "We created a new model of human squamous cancer of the oesophagus in mice, and measured the rate of cell division. In these mice all the cells in the body divided once per day, proving that precancerous and cancerous cells can divide at the same speed as surrounding normal cells. But the pre-cancerous cells produced a small excess of dividing over non-dividing cells - it was this marginal gain of cells that led to malignant tumours."

Tissues can naturally change the ratio of dividing versus non-dividing cells in response to certain events. For example, cells divide at the edge of a wound, but this imbalance in cell division stops once the wound has healed.

The scientists saw that in very early tumour tissue development, multiple different cells, each with different alterations in their DNA, came together to form a polyclonal pre-cancerous tumour. However, the researchers showed that as these various pre-tumour cells became cancerous, they evolved differently with some gaining an advantage by producing a greater proportion of dividing daughters. This led to a group of cells in the tumour that dominated and out-competed the other cells in the tumour.

Dr Julia Frede, a lead author from the Sanger Institute, said: "Our research showed that oesophageal carcinoma and possibly other hard-to-treat cancers may behave in a very similar manner to normal cells, rather than dividing more rapidly. This would explain why treatments such as radiation therapy that target fast-dividing cells don't work with all cancers. More research is needed to find the mechanisms that drive the proportion of cells that divide."

Dr Justine Alford, Cancer Research UK's Senior Science Information Officer, said: "This study, carried out in mice, uncovered surprising evidence that unbalanced cell division is important in the development of a certain type of oesophageal cancer. The next important step will be finding out whether the same is true in patients with the disease. If scientists can unpick the biology causing the imbalance, then it may lead to new treatments for this hard to treat type of cancer and boost the number of people surviving."

More information: A single dividing cell population with imbalanced fate drives oesophageal tumour growth, *Nature Cell Biology*,

DOI: 10.1038/ncb3400