Cancer’s genetic tipping point reveals who’d benefit from chemo

Mutar, but not too much. Unstable genomes and genetic variation are crucial for a cancer to evolve into a killer, but go too far, and it can become the cancer’s Achilles heel. The finding could soon refine treatments for messing with a cancer’s genome.

We’ve known for a decade that aggressive cancers that are more likely to spread have unstable chromosomes prone to DNA mutation. This process leads to different cells in the same tumour carrying different genetic combinations or genomes.

Logic would suggest that the more unstable a tumour’s genome, the more chance it has of randomly generating the mutations it needs to develop. But now Carlo Maley from Arizona State University and colleagues have shown that this isn’t the whole story. As a tumour’s genome becomes increasingly unstable, at a certain point, the cancer becomes less aggressive, and a person’s survival starts to improve.

Less aggressive

Maley’s team sequenced the genomes of 1165 tumour samples from 12 different types of cancer stored in The Cancer Genome Atlas. Each cancer has a mix of cells with different genomes, but some cells replicate more than others, meaning that some genomes are more common than others within a tumour.

The team looked at how many genomes were present in 10 per cent or more of a tumour’s cells. They found that the higher the number, the more deadly the tumour – until this number reached four. Once four or more genomes were responsible for more than 10 per cent each of the tumour’s cells, a person tended to survive longer.

The team found a similar trend with larger scale mutations, when a large chunk of chromosome is deleted, moved, or duplicated. They found that the more of these “copy number mutations” a tumour had, the more deadly it was, up until 75 per cent. Once three-quarters of a tumour was affected by these types of mutations, the cancer again became less lethal.

Choosing chemo

These results confirm similar work in breast cancer by Charles Swanton at The Francis Crick Institute in London, showing that a wide range of cancers have this optimum diversity tipping point in common. “We show it is a general phenomenon,” Maley says.

He found that chemotherapy and radiotherapy work best for people whose cancer was at this optimum level of genomic diversity. Both these treatments induce more mutations and genomic instability in a tumour, so are probably pushing them past that optimum level, says Maley.

But to work out who would benefit most from chemotherapy, doctors would need to measure the genetic diversity of a person’s tumour – a process which currently involves large, painful biopsies and costly genetic analysis.

However, Maley’s research suggests you can simply examine cells under a microscope. His team found that the size of a tumour cell’s nucleus...
seems to be a reliable indicator of genomic diversity and the abundance of copy number mutations, suggesting more sophisticated genetic sequencing may be unnecessary.

Nucleus size isn’t ready to be used as a test yet, but should be developed further, says Maley.

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Image information: colon cancer cells *(AMMRF, University of Sydney/SPL)*