Sorting the drivers from the passengers in the cancer genome

February 17 2010

A new study of mutations in cancer genomes shows how researchers can begin to distinguish the 'driver' mutations that push cells towards cancer from the 'passenger' mutations that are a by-product of cancer cell development. The study also shows that at least one in nine genes can be removed without killing human cells.

Many cancer genomes are riddled with mutations. The vast majority of these are likely to be passengers - mutations that don't contribute to the development of cancer but have occurred during the growth of the cancer - while a small minority are the critical drivers. The challenge of efficiently picking out the guilty drivers in the huge identification parade presented by the set of abnormalities found in a cancer genome is yet to be fully answered.

"It is essential that we can distinguish the drivers from the passengers because knowing the driver mutations and hence the critical genes they are in leads to understanding of the cellular processes that have been subverted in cancers and hence to new drugs," explains Professor Mike Stratton, senior author on the study from the Wellcome Trust Sanger Institute. "Our study provides one example of how researchers can sift through the large numbers of a particular type of mutation present in cancer genomes in order to distinguish drivers from passengers."

One class of cancer gene - called a tumour suppressor gene - inhibits tumour formation, acting as a brake on the process. This type of gene has to be inactivated in or deleted from the genome of the cancer cell in

order to release the brake, allowing cancer to develop. The process that inactivates a tumour suppressor gene often involves deletion of both copies of the gene in the cancer (one copy originally inherited from the mother and one from the father). Therefore, in the past finding regions in which both copies of a gene are removed in many cancer cases has proven to be a fruitful way of pinpointing the location of new tumour suppressor genes.

The problem is that both copies of a gene can also be frequently deleted from cancers in regions called fragile sites. The underlying DNA structure of fragile sites appears to make them particularly prone to breakage and hence to being jettisoned from the cancer genome. The deletions at fragile sites are, most often, likely to be passengers. Therefore the challenge is how to distinguish between the passenger deletions over fragile sites and the driver deletions over tumour suppressor genes.

"We analysed almost 750 cancer cell samples for deletions at known tumour suppressor genes and compared them to deletions at known fragile sites," explains Dr Graham Bignell, a lead author on the paper. "We found clear differences between the two which allowed us to construct 'signatures' of deletions that are associated with tumour suppressor genes and signatures associated with fragile sites."

For example, one crucial difference between the tumour suppressors and fragile sites was that both copies of tumour suppressor genes were usually deleted and it was rare to find only one copy deleted. In contrast, it was often the case that only one copy was deleted at fragile sites. This provides a first-pass test to sift through for tumour suppressor genes: if both copies of a gene are usually deleted and one copy deleted only rarely then these deletions may be drivers and the gene may be a tumour suppressor. However, if it is common to find only one copy deleted then the deletions may be passengers and it may well be a fragile site.

The authors then used these signatures to look at the deletions that they found in cancers which were currently unexplained. Three regions had the signature of a tumour suppressor gene, but many looked like fragile sites.

"When it became clear in the 1990s that novel tumour suppressor genes could be discovered by looking at genome deletions, many hands were put to the pump," explains Dr Andy Futreal, co-leader of the Cancer Genome Project. "But it became clear that it wasn't quite that simple. New tumour suppressor genes just weren't that easy to find, despite the presence of many deletions. We now have some insight as to why: many of the regions being studied were actually fragile sites."

Because the researchers were looking in cancer cell lines for genes that have been deleted they also uncovered genes that are simply not required for cells to grow, at least in the artificial environment of the laboratory test tube. In aggregate, over the almost 750 cancer cell lines used in the study, one in nine genes was deleted and therefore not mandatory for the cells to live and grow.

Previous studies showed that one in 100 genes on the X chromosome can be inactivated without apparent effect on the well being of the whole person, while similar work across the genome suggested that one in 50 genes can be inactivated in apparently healthy people. Thus, predictably enough, cancers seem to be more tolerant than healthy people and can lose a much greater proportion of their genes without being impaired.

For cancer research, developing novel methods to discern the driver mutations remains a crucial goal.

"This is one step in building a suite of tools to draw out the important suspects in cancer genetics," continues Professor Stratton, "tools that will make the most of the massive efforts that lie ahead from organizations

such as the International Cancer Genome Consortium, which will sequence as many as 500 samples from each of 50 cancer types over the next few years.

"Our results also illuminate novel findings that emerge from genome wide research, light that is shone on other corners of genome biology. While we mustn't overstate this - these are cancer cells growing in test tubes - it is fascinating to see the catalogue of genes that are not required for basic survival."

More information: Bignell GR Greenman CD et al. (2010) Signatures of mutation and selection in the cancer genome. *Nature* 463 893-898. dx.doi.org/10.1038/nature08768

Provided by Wellcome Trust Sanger Institute