GENETICS

Defining driver mutations in the genomic landscape of breast cancer

The prevailing theory of cancer progression is that ‘driver’ mutations, mostly acquired somatically, confer a growth advantage to the tumour, enabling outgrowth of neoplastic clones. A number of previous studies have examined parts of the genomes of breast cancer, notably the coding exons (or exomes); however, common inherited variants conferring susceptibility to disease are often in non-coding regions of the genome. Thus, by assessing the whole-genome sequences of cancer samples, Michael Stratton and colleagues determined the role of driver mutations in non-coding as well as coding sequences to help elucidate the processes generating somatic mutations that are not fully determined by exome sequence analysis. Stratton explains the basis behind this latest research effort: “it is generally agreed that all cancers arise as a result of mutations that occur in our body throughout life. If a mutation occurs in a particular subset of genes (cancer genes) in a normal cell within the body, that mutated gene will convert that normal cell into a cancer cell.”

The researchers obtained complete catalogues of mutations in both coding and non-coding sequences from 560 breast cancers. “For the first time we sequenced the complete genomes of more than 500 breast cancers and looked for all the different possible types of mutation — such as base substitutions, small insertions/deletions, rearrangements and copy number changes — that occur in all parts of the genome.”

Stratton explains the most significant findings of this study: “we now have an almost comprehensive list of the mutated cancer genes in breast cancer”. The investigators revealed that of the almost 20,000 genes in the human genome, 93 of these showed the features of being cancer genes that carry ‘driver mutations’ for breast cancer. Stratton’s team “found 12 different base substitution mutational signatures and six different mutational rearrangement signatures — hence, a lot of mutational signatures.”

Importantly, a comprehensive and careful assessment of driver mutations in non-coding regions of DNA was undertaken. Although the research team found some

non-coding regions with many mutations, Stratton comments “we think that many of these are regions of hypermutability rather than conferring selection upon neoplastic clones”.

The researchers are quick to point out that more work needs to be done to analyse their data, in order to make absolutely sure that driver non-coding mutations are not obscure. Previous studies have shown five different mutational signatures in breast cancer. Owing to the much greater power conferred by large numbers of whole-genome sequences, this latest study enabled a comprehensive exploration of the mutational signatures and mutational processes that underlie breast cancer. A key deliverable of cancer genomics is the list of cancer genes, which represent targets for new drug discovery. “We are getting towards having a comprehensive list of cancer genes and mutated drug targets for breast cancer as a result of looking at the whole genome in a large number of patients.” The next phase involves exhaustive drug discovery based on these findings to understand the effects of these different genome sequences on responses to drugs.

Stratton summarizes: “there are many different mutational signatures in breast cancer. Currently, we have an incomplete idea of what the mutational processes are behind these. A major direction for future research will be to identify the processes behind these signatures because such altered processes are essentially the causes of cancer.”

Lisa Hutchinson

ORIGINAL ARTICLE Nik-Zainal, S. *et al.* Landscape of somatic mutations in 560 breast cancer whole-genome sequences. *Nature* <http://dx.doi.org/10.1038/nature17676> (2016)
FURTHER READING Morganella, S. *et al.* The topography of mutational processes in breast cancer genomes. *Nat. Commun.* <http://dx.doi.org/10.1038/ncomms11383> (2016)