

EVOLUTION

Cancer drivers everywhere?

Cancer initiation and progression are known to involve positive selection of 'driver' somatic mutations that activate oncogenes or inactivate tumour suppressor genes. A new study now shows that positive selection may be acting on a broader repertoire of genes than currently appreciated.

Various types of selection act during the evolution of an organismal or a cellular population. In addition to the positive selection of beneficial mutations, purifying selection (also known as negative selection) acts to purge detrimental mutations from the population. Ostrow *et al.* used various types of analysis to characterize the signatures of positive and purifying selection that act on somatic mutations in the protein-coding regions of 772 breast cancer genomes in The Cancer Genome Atlas (TCGA) database.

As expected, evolutionary pressures on these cancer-associated mutations were markedly different from those on normal human germline genetic variants in the 1000 Genomes Project data sets. For germline variants, the effects of purifying selection were much more pronounced than those of positive selection. This is mainly due to the fact that organisms tend to be well adapted, so that most functional mutations will harm rather than benefit the organism. By contrast, cancer genomes were less affected by purifying selection and more affected by positive selection. This probably reflects the selection of driver mutations that confer the various adaptive properties that normal cells must acquire to become cancerous.

Interestingly, Ostrow *et al.* found that genes that were ubiquitously expressed across all 16 tissue types examined were under greater levels of positive selection than those with more tissue-specific expression patterns (irrespective of whether expression was specific to breast tissue). This finding of stronger positive selection on globally expressed genes held when analysing somatic mutations in additional tumour tissue types. As globally expressed genes are known to contain a larger proportion of essential and housekeeping genes than tissue-specific genes, this finding implies a potentially broad role in cancer cell evolution for these fundamental genes. Indeed, known cancer genes are enriched for global expression patterns. However, even when such known cancer genes were removed from consideration, a strong signal of increased positive selection on globally expressed genes was maintained. Thus, globally expressed genes are probably enriched for yet undiscovered cancer functions. It may therefore be useful to widen the range of genes that are considered as cancer drivers, the products of which could be putative targets for new anticancer therapies.

Key future steps will be to characterize the functional impact of cancer-associated mutations in these broadly expressed genes and to determine whether therapeutic targeting can provide anticancer benefits without unacceptable toxicity to the many normal tissues in which these genes are expressed.

Darren J. Burgess

ORIGINAL RESEARCH PAPER Ostrow, S. L. *et al.* Cancer evolution is associated with pervasive positive selection on globally expressed genes. *PLoS Genet.* **10**, e1004239 (2014)

