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⮕ GENOMIC INSTABILITY

Close-up on cancer copy number alterations

Somatic copy number alterations (SCNAs) are common drivers of tumorigenesis. Two new computational studies have investigated the genomic features that influence which loci are affected by SCNAs, revealing that shared nuclear localization and replication timing could be key determinants.

The SCNAs that are observed in cancer samples are a result of genomic insertions or deletions, followed by the negative selection of disadvantageous SCNAs and the positive selection of tumour-promoting SCNAs affecting oncogenes or tumour suppressor genes.

De and Michor analysed the chromosomal properties at the boundaries of >300,000 known SCNAs from ~3,000 human cancer samples of various tissue types; these boundaries represent the sites of the initiating genomic rearrangements. By comparing these sites with existing genome-wide Hi-C data of chromosomal regions that are in close three-dimensional proximity to each other and also with data on replication timing, the authors found that most cancer SCNAs involve rearrangements between sites that share long-range chromosomal interactions and have similar replication timing. This is consistent with SCNAs being initiated by sequences at replication-induced DNA breaks that are spatially and temporally coincident.

The authors also found a small but significant enrichment of SCNA boundaries in late versus early replicating regions; this correlates with a known higher point mutation rate in late-replicating regions and may reflect a shortage of repair opportunities prior to mitosis. The predictive value of long-range chromosomal interactions and replication timing was confirmed by their capacity to predict the locations of 47% of SCNAs correctly in an independent ovarian cancer data set.

Fudenberg *et al.* carried out related analyses on ~3,000 cancer samples but focused on a smaller set of ~40,000 intra-arm SCNAs. They tested alternative computational models for their ability to predict the length distribution and locations of SCNAs. The authors found that the length distribution of chromosomal contacts — whether derived from experimental Hi-C data or from a fractal globule model of chromosome organization — resembled the length distribution of SCNAs. This reinforces the view that SCNAs occur through the joining of spatially proximal chromosomal regions. One limitation of both studies is that the Hi-C data was derived from lymphoblastoid cell lines, and hence the predictions may be improved in future by using proximity data from tissues that are matched to the SCNA data sets.

The predictive power of the models of Fudenberg *et al.* was improved by including a negative selection penalty for longer SCNAs, indicating that SCNAs are indeed subjected to negative selection, despite the frequent focus of attention on only tumour-promoting positive selection events.

It will be interesting to see whether functional studies will prove causation from the reported correlations and also to what extent these determinants of cancer-associated SCNAs are applicable to other copy number alterations, such as those that are linked to different diseases or that provide evolutionary diversity.

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ORIGINAL RESEARCH PAPERS De, S. & Michor, F. DNA replication timing and long-range DNA interactions predict mutational landscapes of cancer genomes. *Nature Biotech.* 20 Nov 2011 (doi:10.1038/nbt.2030) | Fudenberg, G. *et al.* High order chromatin architecture shapes the landscape of chromosomal alterations in cancer. *Nature Biotech.* 20 Nov 2011 (doi:10.1038/nbt.2049)