Nature Reviews Clinical Oncology | Published online 15 December 2015; doi:10.1038/nrclinonc.2015.219

GENETICS

Intratumour heterogeneity — a game of snakes and ladders

The Cancer Genome Atlas (TCGA) project has provided a wealth of data on tumour genetics, but generally with only a limited opportunity for assessment of intratumour heterogeneity. The TCGA investigators analysed the 'tumour metagenome', comprising the genomes of all clones present, in only one sample per tumour; thus, 'deconvoluting' the data for individual clones is difficult — but not, as demonstrated by the results of a novel pan-cancer analysis, impossible.

"When Noemi Andor published the EXPANDS package, we realized that we could apply the algorithm to the TCGA data, to test our hypothesis that clonal diversity is a good predictor of survival across cancer types," says Carlo Maley. The EXPANDS algorithm identifies different clones through clustering of mutations and copy-number alterations (CNAs) across the genome that have approximately the same frequency within a single sample. "If a cluster of mutations is detected in ~20% of the reads, and in another set is present in ~30% of the reads, then it is reasonable to infer that there are two clones: one comprising 20% of the sample, and another 30%," Maley explains. This method has caveats, however, as only clones comprising >10% of the sample can be detected — thus capturing 'macroheterogeneity' but not the long tail of low-abundance clones — and only one region of the tumour is represented.

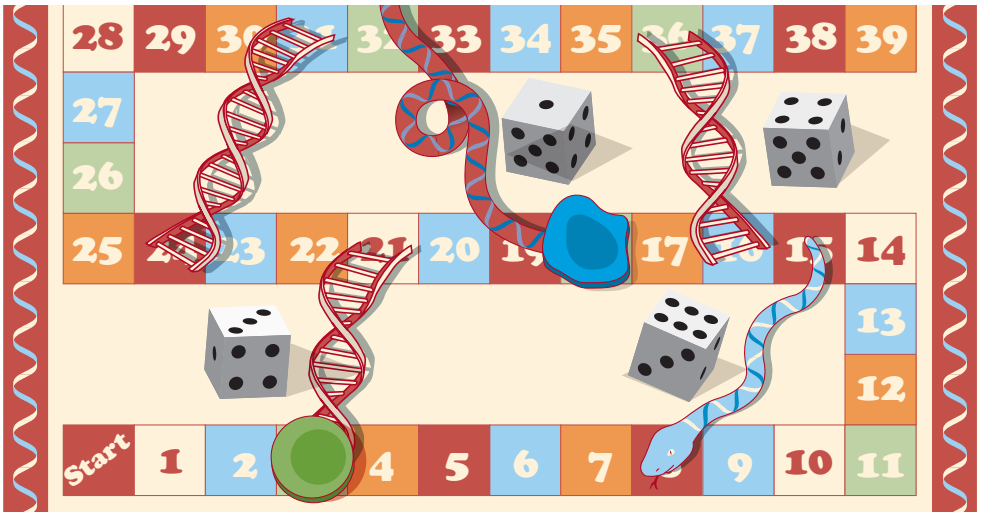
> "...intratumour heterogeneity might present both opportunities and pitfalls..."

Maley, Andor, and colleagues analysed TGCA data from 1,165 samples across 12 different cancer types using EXPANDS and a similar algorithm, PyClone. They found >80% of all the samples harboured at least two subclones, and four on average. Importantly, the researchers found that intratumour genetic heterogeneity was universally associated with prognosis, but in a nonlinear fashion. Maley summarizes: "we showed that, in two independent datasets, patients with either <25% or >75% of the tumour genomes affected by CNAs had improved survival compared with patients with intermediate levels of CNAs. Similarly, patients with moderate levels of macroheterogeneity (3–4 subclones) had a worse prognosis than patients with fewer or more tumour subclones." Interestingly, morphological heterogeneity of tumour-cell nuclei was significantly correlated with genetic heterogeneity, and might, therefore, have clinical utility as a surrogate measure of genetic diversity and/or prognosis.

Thus, intratumour heterogeneity might present both opportunities and pitfalls: intermediate diversity might provide adaptive benefits that allow clones to climb an allegorical ladder leading to more-rapid disease progression or development of therapy resistance, whereas low and high genomic diversity might represent metaphorical 'snakes', that hinder progression — and might ultimately be the downfall of the disease. Notably, intermediate CNA abundance in tumours treated with adjuvant therapies expected to increase mutational frequencies was not significantly associated with patient prognosis. "It might be that DNA-damaging agents can push a tumour over the 'error catastrophe' threshold," Maley suggests, "and the fact that the hazard ratios went down in the 25–75% CNA category if patients had been treated supports this possibility."

Andor concludes, "I would like to see if our findings hold true for individual tumour clones: whether there is a well-defined limit to the extent of CNAs a single clone can tolerate. If so, leveraging a clone's distance to the upper limit of tolerable CNAs may represent a new strategy to optimize therapy intensity. It then remains to be verified to what extent increases in the CNA burden of individual clones can be fine-tuned by chemotherapy or radiotherapy."

David Killock



S.Bradbrook/NPG

ORIGINAL ARTICLE Andor, N. *et al.* Pan-cancer analysis of the extent and consequences of intratumor heterogeneity. *Nat. Med.* doi:10.1038/nm.3984