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GENETICS

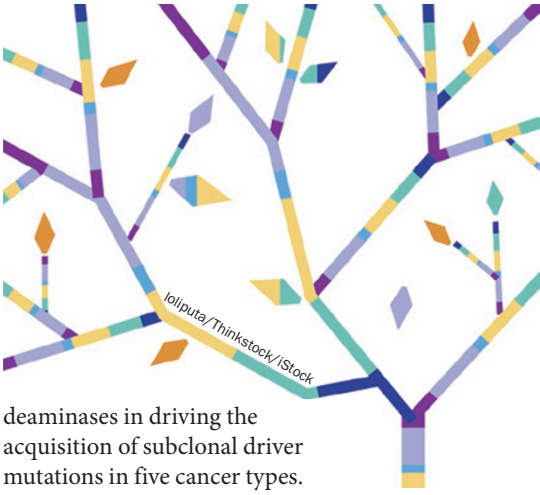
Clonal and subclonal events in cancer evolution—optimizing cancer therapy

Intratumour heterogeneity (ITH) is a prevalent feature in multiple cancer types and constitutes a considerable challenge to the optimization of anticancer therapies. Building on their work on the evolution of lung cancer, Charles Swanton's group has used mutations and copy-number variants from the TCGA dataset to perform a pan-cancer analysis of 2,694 tumours across nine cancer types and explore the extent of ITH, providing a census of clonal and subclonal drivers.

"One of the primary challenges of precision medicine is deciphering which driver mutations are early clonal events and which are later subclonal events—the latter being less robust drug targets due to their heterogeneous nature," explains Nicholas McGranahan, lead author of the study. Furthermore, the identification of the mutational events and processes that drive subclonal expansions might also inform on the selection of both a diagnostic and therapeutic approach.

In this study, the investigators provide a census of driver events, taking into account the fraction of tumour cells in which these events occur—a key element in the management of the disease as targeting a mutation present in only a fraction of cancer cells might only affect that specific subclone and result in a limited clinical benefit.

"Of particular clinical relevance, we find evidence for subclonal mutations occurring in genes that have been linked to targeted therapies in every cancer type, including known hotspot mutations in *BRAF* (V600E), *IDH1* (R132H), and *PIK3CA* (E545K)," highlights McGranahan. Of note, genes of the PI3K–AKT–mTOR signalling axis harbour a significantly higher fraction of subclonal mutations compared to genes associated with the RAS–MEK pathway. In addition, the analysis of the temporal evolution of the cancers revealed a potential role for the APOBEC cytosine deaminases in driving the acquisition of subclonal driver mutations in five cancer types.



"Ultimately, our work highlights that we cannot think of cancer mutations as simply present or absent," concludes Swanton, "it will likely be vital to know what proportion of cancer cells harbour a mutation, in order to optimize therapy".

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Original article McGranahan, N. *et al.* Clonal status of actionable driver events and the timing of mutational processes in cancer evolution. *Sci. Transl. Med.* **283**, 283ra54 (2015)