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CANCER GENOMICS

Indicators for drug response from sequencing

That cancer is a heterogenous disease is well established, but even within cancer types that affect specific tissues or organs, there is a substantial amount of variation that leads to different disease outcomes and response to treatment. Next-generation sequencing has emerged as an excellent tool with which individual cancer types and subtypes can be characterized to understand the underlying heterogeneity better. Reporting in *Nature*, Ellis, Ding and Shen *et al.* have used this tool to explore genetic heterogeneity in the oestrogen receptor (ER)-positive breast cancer subtype. Thanks to sophisticated bioinformatic analyses, they describe mutational signatures that are likely to underlie and predict response to therapy.

ER-positive breast cancer is known to be heterogenous, and this is reflected in variable patient prognosis and response to treatment. To glean insight into this complexity, the authors took advantage of an ongoing clinical trial in which aromatase inhibitors were used before subsequent surgical intervention. In total, over 70 whole genomes and exomes were sequenced, and selected findings were followed up in additional cases. The authors identified 18 frequently mutated genes, including known breast cancer genes and known cancer genes that had not previously been linked to breast cancer, as well as genes that had not previously been implicated in cancer. Intriguingly, they identified many genes that had previously been implicated in haematological cancers; the authors suggest that, similarly to those cancers, breast cancer might be a stem cell disorder. If it is true, this has implications for our understanding of breast cancer evolution and could explain why the prognosis of ER-positive tumours is so variable.

Among the frequently mutated genes was MAP3K1, a serine/threonine kinase that activates the ERK and JNK kinase pathways. Mutations in this locus were found predominantly in the luminal A subtype of ER-positive cancers but also in those that proliferated less aggressively. By contrast, mutations in *TP53* (which encodes p53) were found in luminal B subtype and those that proliferated more aggressively. Aggressive proliferation despite aromatase inhibitor therapy can indicate poor prognosis, and thus MAP3K1 might therefore be a useful marker of sensitivity to aromatase inhibitor treatment, whereas *TP53* mutations might indicate a likely lack of response. The authors also found some evidence that mutations in *GATA3* might also be indicative of a response to aromatase inhibitor.

Because there were many interesting genes found mutated at below-significance level, the authors turned to pathway and network analyses of less frequently mutated loci to look for further insights into the response to treatment. The approach paid off by revealing DNA replication and mismatch repair as being additional processes that are probably involved in aromatase inhibitor resistance. In addition, these analyses identified pathways downstream of MYC, FYN and MAP kinases as being associated with cell-proliferation rates in aromatase-inhibitor-resistant tumours. This result singles them out as possible therapeutic targets in patients with *TP53* mutations.

This work elegantly demonstrates the use of next-generation sequencing in dissecting molecular complexities of cancer. It also shows that this approach can be directly useful in the clinical context. Ultimately, large patient cohorts will need to be analysed in this way before general predictive signatures can be established with confidence.

Magdalena Skipper, Senior Editor, Nature

ORIGINAL RESEARCH PAPER Ellis, M. J. *et al.* Whole-genome analysis informs breast cancer response to aromatase inhibition. *Nature* 10 June 2012 (doi:10.1038/nature11143)
FURTHER READING Meyerson, M., Gabriel, S. & Getz, G. Advances in understanding cancer genomes through second-generation sequencing. *Nature Rev. Genet.* **11**, 685–695 (2010)