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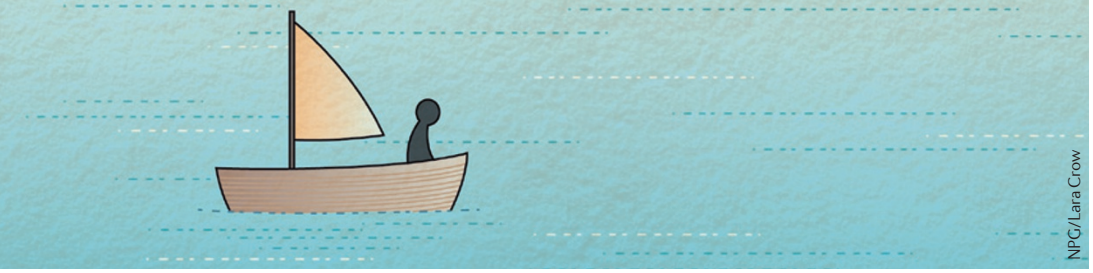
BREAST CANCER

Genes, genes everywhere…



NPG/Lara Crow

> “indicating a link between developmental processes in leukaemia and breast cancer”

Sequencing breast cancer genomes in depth to analyse mutations that potentially contribute to disease aetiology continues apace.

Elaine Mardis and colleagues used whole-genome and whole-exome sequencing to analyse oestrogen receptor-positive (ER^+) luminal A and luminal B breast cancer samples taken before treatment with an aromatase inhibitor. Levels of Ki67 staining (a surrogate marker of cell proliferation) in biopsy samples taken before and after treatment were used as an indicator of sensitivity or resistance to aromatase inhibitors. Having identified a list of 18 significantly mutated genes in these tumours that included *TP53*, *PIK3CA*, *GATA3* and *CDH1*, an additional 240 samples were subject to mutation recurrence screening to look for clinical correlations. *MAP3K1* mutations were clearly associated with the luminal A subtype, low-grade histology and a low level of Ki67 staining. These tumours were sensitive to aromatase treatments, indicating that this is potentially a viable treatment for patients who have tumours with these attributes. By contrast, tumours that had *TP53* mutations, high levels of Ki67 staining, high-grade histology and were of luminal subtype B were mostly resistant to aromatase inhibitors — these patients require other treatment options. Mutation of *PIK3CA* was the most common mutation, in agreement with previous studies, but it did not correlate with either clinical response or Ki67 levels. However, PIK3CA mutations were positively associated with mutation of *MAP3K1* and its target *MAP2K4*. Other mutations identified in this study included histone and chromatin modifiers, such as mixed lineage leukaemia 3 (*MLL3*), and *RUNX1* — genes that are more commonly associated with leukaemia.

Matthew Meyerson and colleagues analysed mutations and translocations in 108 treatment-naive breast cancer samples and matched normal DNA using whole-genome and/or whole-exome sequencing. They also verified that mutations in genes such as *TP53*, *PIK3CA* and *MAP3K1* were relatively common. In addition, they found that mutations in core binding factor-β (*CBFB*), which encodes a partner protein of the RUNX DNA-binding transcription factors, occurred often enough to be of significance. Interestingly, mutations in *CBFB* were also listed as significant by Mardis and colleagues, again indicating a link between developmental processes in leukaemia and breast cancer. Meyerson and colleagues also looked at genomic rearrangements, which occurred with greater frequency in triple-negative breast cancers than in luminal A subtypes, but of the rearrangements confirmed by PCR analyses, none occurred in more than one sample. Detailed analyses of one of these rearrangements from a triple-negative breast cancer, a balanced translocation on chromosome 1 involving membrane-associated guanylate kinase, WW and PDZ domain-containing 3 (*MAGI3*) and the serine/threonine kinase *AKT3*, indicated that this fusion protein resulted in a high level of expression of AKT3. The AKT3 part of the fusion protein has an intact kinase domain and the MAGI3 portion is missing its second PDZ domain, which has been shown to bind PTEN and enable inhibition of PI3K. Expression of this fusion protein in ZR-75 breast cancer cells indicated that AKT3 was phosphorylated and constitutively active and able to phosphorylate downstream targets such as GSK3β. It also induced focus formation and loss of contact inhibition when expressed in RAT1 fibroblasts. Screening of an additional 235 breast cancers identified this fusion in eight of the samples, with five occurring in triple-negative breast cancers. Thus, ATP-competitive AKT inhibitors might be of use in patients with this translocation.

Although these findings are interesting, they need to be considered alongside the complex evolution that occurs in breast and other epithelial cancers. As two papers published in *Cell* indicate, although mutations in genes such as *PIK3CA*, *TP53* and *MLL3* can be present early on in tumour development and are present in most, if not all, of the epithelial cells in the tumour, many thousands of additional chromosomal changes and mutations, influenced by different mutational processes, will have occurred before the outgrowth of a clinically relevant clone. As Mardis and colleagues note regarding their findings, the high levels of genomic heterogeneity identified indicate that if comprehensive sequencing and gene expression analyses are to be used for determining treatment strategies, future prospective studies will need to recruit a substantial number of patients.

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ORIGINAL RESEARCH PAPERS Ellis, M. J. *et al.* Whole genome analysis informs breast cancer response to aromatase inhibition. *Nature* 10 Jun 2012 (doi:10.1038/nature.11143) | Banerji, S. *et al.* Sequence analysis of mutations and translocations across breast cancer subtypes. *Nature* **486**, 405–409 (2012)
FURTHER READING Nik-Zainal, S. *et al.* The life history of 21 breast cancers. *Cell* **149**, 994–107 (2012) | Nik-Zainal, S. *et al.* Mutational processes molding the genomes of 21 breast cancers. *Cell* **149**, 979–993 (2012)