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BREAST CANCER

Divide and conquer?

> “oestrogen receptor (ER)-positive luminal tumours with a *cis* acting 11q13–14 alteration … have a particularly poor prognosis”

Two papers have been published in *Nature* that analyse genomic and transcriptomic changes in breast tumours to further understand the biology of this disease.

Carlos Caldas, Samuel Aparicio and colleagues examined a discovery set of 997 clinically annotated breast tumours (from the Molecular Taxonomy of Breast Cancer International Consortium (METABRIC)) for inherited copy number variations (CNVs), somatic copy number alterations (CNAs), inherited single nucleotide polymorphisms (SNPs) and changes in gene expression. The CNAs, CNVs and SNPs affected approximately 40% of the genes expressed in the tumours, with the majority being CNAs acting in *cis* (at the affected locus) or in *trans* (affecting distal loci). By analysing gene expression outliers affected in *cis* by CNAs, the authors identified known and potentially new breast cancer oncogenes and tumour suppressor genes, including *PPP2R1A* (a gene involved in mitosis), *MTAP* (a gene involved in the salvage of methyladenosine) and *MAP2K4* (a p38 and JUN dual specificity serine/threonine protein kinase). Analyses of the CNAs acting in *trans* indicated that deletions in T cell receptor (TCR) genes, *TRG* and *TRA*, resulted in alterations to a number of mRNAs that encode proteins of the adaptive immune response.

Data from the discovery set were also used to analyse breast cancer subgroups based on joint clustering of CNAs and gene expression data. This identified ten different breast cancer subgroups. A classifier (consisting of 754 features) for these different subtypes was validated in an additional 995 clinically annotated breast tumours from METABRIC. The subgroups identified include oestrogen receptor (ER)-positive luminal tumours with a *cis* acting 11q13–14 alteration that have a particularly poor prognosis, possibly owing to the expression of a number of genes in this region that are associated with cell cycle regulation. Another subgroup contains ER-positive and ER-negative breast cancer of different histological subtypes that have few CNAs. These tumours most often have changes in *TRG* and *TRA* and are associated with increased immune infiltration and a good prognosis. The basal breast cancers were clustered together in a group that had high levels of genomic instability and were associated with regions of chromosomal loss. In particular, deletions on chromosome 5q affected in *trans* many mRNAs encoding transcription factors, signalling molecules and cell division regulators.

Another paper by Aparicio, Caldas and colleagues examined somatic changes at diagnosis in triple-negative breast cancers, which lack expression of ER, the progesterone receptor and ERBB2. Somatic changes in the 104 tumours analysed varied widely, with some tumours having few mutations and others many. Deep re-sequencing of allelic abundance of 2,414 somatic mutations was used to analyse clonal evolution in these tumours. This was also varied, with non-basal triple-negative tumours typically having fewer clonal variants than basal triple-negative tumours. *TP53*, *PIK3CA* and *PTEN* were the most commonly affected genes that showed clonal dominance, but in some tumours the frequency of changes in these genes was incompatible with them being founder mutations. Changes in genes that regulate motility, cell shape and the cytoskeleton occurred less often, indicating that these changes are likely to occur later during tumour progression. Overall, these data indicate that the effective treatment of patients with triple-negative breast cancer might require individual tumour genotyping.

Both papers highlight the heterogeneity of breast cancer and how much work still needs to be done to understand the biology of this disease if we are to improve the outcome for patients with all types of breast cancer, whether biologically or genetically classified.

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ORIGINAL RESEARCH PAPERS Shah, S. P. *et al.* The clonal and mutational evolution spectrum of primary triple-negative breast cancers. *Nature* 4 Apr 2012 (doi:10.1038/nature10933) | Curtis, C. *et al.* The genomic and transcriptomic achitecture of 2,000 breast tumours reveals novel subgroups. *Nature* 18 Apr 2012 (doi:10.1038/nature10983)

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