Breast Cancer RESEARCH

EDITORIAL

Breast cancer genome heterogeneity: a challenge to personalised medicine?

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Abstract

Implementation of high-throughput genomics sequencing approaches into routine laboratory practice has raised the potential for the identification of multiple breast cancer targets suitable for future therapeutic intervention in order to improve cancer outcomes. Results from these studies have revealed bewildering breast cancer genome complexity with very few aberrations occurring in common between breast cancers. In addition, such complexity is compounded by evidence of genomic heterogeneity occurring within individual breast cancers. Such inter-tumoural and intra-tumoural heterogeneity is likely to present a challenge to personalised therapeutic approaches that might be circumvented through the definition of genome instability mechanisms governing such diversity and their exploitation using synthetic lethal approaches.

Next-generation sequencing approaches have enabled the sequencing of the human cancer genome at unprecedented speed, resolution and cost. Several such studies have recently been reported in both oestrogen receptor-positive and oestrogen receptor-negative breast cancer [1-3]. Results of these cancer-genome sequencing studies have highlighted the tremendous complexity and heterogeneity between cancer genomes from different patients with the same breast cancer histopathological phenotype (inter-tumoural heterogeneity). For example, none of the novel fusion genes identified by Stephens and colleagues were present more than once in any of the 24 cancers studied, and three expressed in-frame fusion genes selected for follow-up were not present in an additional 288 breast cancers studied [2]. In a further twist to breast cancer complexity, Navin and colleagues have recently described profound heterogeneity within individual breast tumours (intra-tumoural heterogeneity), where multiple tumour subpopulations have been identified, each with distinct genomic profiles [4].

Both patterns of heterogeneity present challenges from a therapeutic perspective. Heterogeneity within an individual tumour raises the likelihood that if driver mutations can be identified and subsequently targeted, resistance to therapy may develop rapidly due to the genomic variation from one cancer cell clone to the next, as has recently been reported in non-small cell lung cancer [5]. Inter-tumoural heterogeneity implies that potentially different driver mutations may be responsible for cancer cell survival and growth from one patient to the next.

Given the cost (approaching $1 billion [6]) and lead time (10 to 15 years) in drug development, it is economically challenging to develop the next generation of anticancer drugs against each target, suitable for only a small cohort of patients in an individualised approach. Furthermore, the prohibitive costs and challenges imposed by both industry and regulators for combining targeted therapeutics may mitigate against the development of rational drug combinations to target intra-tumoural heterogeneity to limit the acquisition of drug resistance.

Such genomic heterogeneity both between and within individual tumours presents an economically intractable problem requiring a change in drug development strategic approaches. Cancer cell heterogeneity and the continued genomic diversity acquired from one cancer cell division to another may promote cancer cell stress or dependence on alternative cellular pathways that are potentially targetable, as witnessed by success with poly(ADP-ribose) polymerase inhibition in patients who harbour germline BRCA1/2 mutations [7,8].

Recent observations clearly indicate that other patterns of genome instability leading to tumour heterogeneity, initiated by specific defects in the mismatch repair apparatus [9] or chromosome mis-segregation, may also be targetable. Unequal segregation of whole chromosomes at mitosis generates heterogeneity that is

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associated with poor prognosis in solid tumours [10] and early tumour relapse in animal models [11]. Studies in model eukaryotic organisms have identified that aneuploidy is associated with vulnerability to inhibitors of protein folding and synthesis [12]. Finally, evidence is emerging that cancer cell heterogeneity can be a reversible epigenetic event contributing to drug tolerance in cancer cell models that can be attenuated through insulin-like growth factor-1 receptor pathway inhibition [13].

Next-generation sequencing studies have revealed new patterns of genomic instability. Stephens and colleagues identified tandem duplications occurring in large numbers in oestrogen receptor-negative–progesterone receptor-negative breast cancers, and speculate that this pattern of genomic instability may be attributable to an underlying defective DNA maintenance process [2]. Defining the underlying mechanisms responsible for these tandem duplications and potential strategies to exploit them is clearly important.

The identification of common targets upon which tumours rely to sustain and develop heterogeneity is now an experimentally tractable problem in cancer medicine. Inactivation of key cancer cell survival specific to these processes might enhance the efficacy of anticancer drug treatment. Since normal cells may not routinely require such survival pathways due to their genetic identity from cell to cell, the development of anticancer drugs that inactivate genome-instability survival pathways might have an enhanced therapeutic window. Importantly, such an approach may present a more economically viable solution compared with the current strategy of targeting diverse driver mutations in molecularly heterogeneous tumours.

Competing interests
The authors declare that they have no competing interests.

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