Genomic Drivers in Breast Cancers

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Abstract

Significant advances in next-generation sequencing technologies have allowed the identification of genomic alterations in breast cancer. These alterations offer the opportunity to conduct studies with targeted drugs. However, there are still several scientific challenges to be addressed before precision medicine is widely used in the clinic. Nonetheless, different solutions are developed to overcome these obstacles such as the improvement of bioinformatics tools and the use of "liquid biopsy" to assess circulating tumour DNA.

Keywords

Breast cancer, precision medicine, personalised medicine, biomarkers, next-generation sequencing, tumour heterogeneity

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Significant advances in next-generation sequencing (NGS) technologies have allowed the identification of alterations in cancer genomes of different tumour types, providing important insight into the genetic complexity of cancers including breast cancer (BC). Notably, we have learned that primary BC genomes harbour mutations in multiple cancer genes but at a low frequency, less than 5% for the vast majority of the mutations, highlighting the substantial genetic heterogeneity between individual tumours, even at this early stage.[1]

Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient. The genomic alteration in BC offers the opportunity to conduct studies with targeted drugs. However, besides endocrine and anti-human epidermal growth factor (HER2) therapies, there is currently no evidence that it can improve patient outcomes.

There are several potential applications of genomics for precision medicine, including the identification of driver aberrations/mutations, the characterisation of resistant clones, the identification of DNA repair defects and the identification of mechanisms of immune suppression.[2] However, there are still several scientific challenges to be addressed before genomics is used in the clinic.

Potential applications of genomics for precision medicine

Identification of 'driver' mutations

Large-scale genomics studies have allowed the characterisation of the mutational landscape of BC genomes and have provided key insights into BC genomic alterations. First, there is a substantial variation in the number of mutations in cancer genes in primary BC, the maximum number of mutated cancer genes per tumour being six. It is noteworthy that copy number alterations are more frequent than point mutations in BC. Second, 30% of cases only showed a single 'driver' mutation. As a result, 73 different combinations of cancer genes with mutations could be identified.[1] Third, driver mutations are infrequent (the vast majority of mutations are present in less than 5% of the cases), highlighting the diversity and complexity of the disease.[1] Consequently, few driver genes have been identified, namely, *ESR1, ERBB2, PIK3CA* and *AKT1*. Nonetheless, emerging targeted agents against BC cells harbouring these genomic alterations are under clinical development.[3]

Identification of genomic alterations responsible for secondary resistance

Several studies comparing the genomic landscape of early and metastatic BC (mBC) have identified an increased frequency of mutations in already-known but also in new cancer genes in mBC. *ESR1* mutations are increasingly recognised as being acquired mutations in mBC leading to secondary resistance to aromatase inhibitors by a ligand-independent activation of the oestrogen receptor (ER).[4,5] It has been shown that 20–30% of mBC patients progressing under several lines of aromatase inhibitors harbour mutations in *ESR1* gene which are associated with a worse outcome in ER+/HER2- BC subtype. Another example of acquired genomic alteration is the convergent loss of *PTEN* leading to secondary resistance to BYL719, a PI3Kα inhibitor.[6] It is anticipated that, in the near future, the number of acquired alterations identified in patients treated by targeted therapy will increase.

Identification of DNA-repair defects and mutational processes

The use of whole genome sequencing allowed the identification of specific mutation patterns (mutational signatures), which are considered to reflect chronic exposure of exogenous carcinogens such as UV light or tobacco. In BC, five distinct mutational signatures have been reported and have been associated with defective DNA repair progresses such as those found in patients with *BRCA1* and *BRCA2* germline mutations.[7] Tumours from patients harbouring such mutational signatures may be good candidates to be treated with platinum agents or poly(ADP-ribose) polymerase inhibitors.

Identification of mechanisms of immune escape

Another potential application of genomics is the identification of the mechanisms of immune escape. With the advent of immunotherapy, there is a need to predict which patients may benefit from checkpoint inhibitors and/or tumour vaccines. Such biomarkers may include mutational burden, tumour neoantigens, quantification and characterisation of tumoural immune-cell infiltrates and the identification of polymorphisms that are associated with host immune defects.

Precision medicine is facing several challenges in breast cancer

Lack of clinical validation of potential biomarkers

In the Randomised Double-Blind, Placebo-Controlled Study of Everolimus in Combination With Exemestane in the Treatment of Postmenopausal Women With Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer Who Are Refractory to Letrozole or Anastrozole (BOLERO-2) phase III study, progression-free survival benefit with everolimus was maintained regardless of genomic alterations such as *PIK3CA* mutation and/or *FGFR1* and *CCND1* copy number aberrations.[8]

Similarly, in the Open-label, Randomised Study Of The Safety, Efficacy, And Pharmacokinetics Of Letrozole Plus Pd 0332991 (Oral Cdk 4/6 Inhibitor) And Letrozole Single Agent For The First-line Treatment Of Er Positive, Her2 Negative Advanced Breast Cancer In Postmenopausal Women (PALOMA-1) phase II study, the selection of patients on the basis of *CCND1* amplification and/or p16 loss was not associated with improved outcome of palbociclib treatment.[9]

Lack of functional characterisation of the mutations

One of the biggest challenges in precision medicine is to differentiate the real 'driver' mutations from the 'passenger' ones. The importance of conducting functional studies allowing this discrimination is exemplified by the HER2 mutations in BC. These mutations are found in 1–5% of BCs. Interestingly, in preclinical models different HER2 mutations have been shown to have different impacts on the activation of the pathway and on the response to different anti-HER2 therapies.[10]

Several basket trials assessing a single drug on a molecular alteration in different cancer types have been initiated, assuming that the molecular alteration has the same effect in different cancer types. However, we already know that histology may be an important determinant of response in cancer harbouring the same mutations. For instance, single-agent vemurafenib has minimal clinical activity in patients with BRAF V600E mutant colorectal cancer, whereas a huge effect is observed in patients with BRAF V600E-mutant melanoma.[11] Similarly, no benefit of trastuzumab was observed in advanced HER2-amplified endometrial cancer as compared to BC.[12]

Tumour heterogeneity/tumour evolution

The spatial and temporal heterogeneity of BC represents one of the main challenges in precision medicine. Yates et al.[13] showed that the subclonal evolution of BC followed a spatial pattern, but without a clear temporal course. More importantly, they confirmed that tumours evolve over time. These findings emphasise the need to take into account the subclonal structure and temporal evolution in clinical trials in mBC.

Potential solutions

To overcome the obstacles described, different solutions might be proposed. First, the development of novel bioinformatics tools should allow a better prediction of the functional effect of the genomic alterations as well as the possibility to integrate several 'omics' datasets. Second, developing drugs that are more specific of a molecular subclass or isoform, as shown with non-selective vs. selective PI3k inhibitors, should improve drug efficacy. Third, the combination of targeted therapies should delay the development of resistance. Fourth, developing novel preclinical models, such as patient-derived xenografts, should allow individualised testing of drug sensitivity. Finally, the use of 'liquid biopsy' to assess circulating tumour DNA may allow better monitoring of resistance detection.[14,15] ■

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