Breast cancer consists of many diseases. This heterogeneity is visible at the histological, clinical, genetic and genomic level. Genomic studies have identified four intrinsic subtypes of breast cancer: basal-like, luminal A and B, and HER2-enriched. The basal-like subtypes are identified by high expression of ERBB4, HER2, and/or PIK3C2B (basal-like epithelioid cluster). The luminal epithelioid-like cluster is characterized by high expression of ESR1, AKT3, XBP1, and FOXA1. Luminal A tumours have the highest expression of luminal epithelial genes when compared with luminal B tumours; luminal A and B tumours show, respectively, low and high proliferation rates. The HER2-enriched subtype, although expressing the luminal-epithelial phenotype, is defined by amplification of genes on 17q21 including HER2/ESR2B. Recent studies have described the somatic mutations and DNA copy-number landscape of breast cancers, showing a good concordance between these genetic alterations and the genetic intrinsic subtypes. Here, we present an overview of the common genetic and genomic events seen in breast tumours.

Clinical outcomes

The intrinsic subtypes of breast cancer can predict prognosis.1 Luminal A tumours tend to have the most favourable outcomes, while luminal B, HER2-enriched, and basal-like tumours have worse prognosis. At the clinical level, there is correlation between the three established clinical biomarkers—ER, PR, and HER2—and the intrinsic subtypes. Luminal A tumours tend to be ER+, PR+, HER2−, and basal-like tumours tend to be ER−, PR−, and HER2+. The HER2-enriched tumours are usually ER2+/PR−. The basal-like tumours tend to be triple-negative (ER−, PR−, HER2−). Despite this correlation, the intrinsic subtypes cannot be accurately identified using these markers.1 Nonetheless, most luminal A and B tumours are ER+ and/or PR+ and thus candidates for endocrine therapy; most HER2-enriched cancers are HER2+ and thus candidates for HER2 and/or ER antagonists, and most basal-line tumours are ER−, PR−, and HER2− and therefore candidates for chemotherapy regimens.

Luminal A

90% ER+, 89% PR+, 14% HER2−

• Mostly luminal, with very high-level focal amplifications 11q13 (Cyclin D1 56%); 8p11–12 (FGFR1 2%)
• Recurrently mutated genes: PIK3CA, ARID1A, TP53, and PTEN
• The highest level of amplification is found in luminal A relative to luminal B, while HER2 is not expressed in luminal A relative to luminal B, while HER2 is not expressed in luminal A
• Typically responsive to endocrine therapy, possibly less so than luminal B cancers
• Higher pCR rate to neoadjuvant chemotherapy and possibly more sensitive to adjuvant chemotherapy relative to luminal B cancers
• A subset of luminal B tumours have a hypomethylated phenotype (see figure), based on genome-wide DNA methylation patterns

Luminal B

98% ER+, 82% PR+, 24% HER2−

• Mostly amplified, with very high-level focal amplifications 11q13 (Cyclin D1 54%); 8p11–12 (FGFR1 2%)
• Recurrently mutated genes: PIK3CA, ARID1A, TP53, and PTEN
• The highest level of amplification is found in luminal B relative to luminal A, while HER2 is not expressed in luminal B relative to luminal A
• Typically responsive to endocrine therapy, possibly less so than luminal A cancers
• Higher pCR rate to neoadjuvant chemotherapy and possibly more sensitive to adjuvant chemotherapy relative to luminal A cancers

Common genetic alterations

TCA data on breast tumour DNA copy number and somatic mutations were used to identify the frequency of each genetic alteration across TCGA patient (all cancer subtypes).4

Each gene is shaded according to the overall frequency of alteration. Orange indicates a high level of amplification (likely gain-of-function mutations), blue represents homozygous deletions and/or likely loss-of-function mutations.

Three germline mutation rates are shown—taken from a subset of 500 TCGA samples previously published.8

References


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