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GENOMICS ASSOCIATION RESOLUTE THE PROGRESSION OF BREAST CANCER

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ABSTRACT

Breast Cancer (BC) is one of the most prevalent cancer and the second most common cancer of death in women. Among various characteristics of breast cancer, progression, and aggression are currently evaluated using genomic markers. Ki67, TP53, GATA3, PIK3CA, AKT1, ERBB2 large scale genomic analyses have revealed and mutational impact for this diseases. Frequent somatic mutations occur and activating Pi3k – AKT signaling and inactivate the GATA3 JUN kinase pathway. The overexpression of ERBB2 causes by the genomic mutational impact for the development of breast cancer. The over expression of ERBB2 have a clear transcription profile leads to pathogenesis of Breast Cancer. These includes a number of clinically important alterations and mutations are inactivating SWI – SNF and JAK2 – STAT3 pathways. It can provide information on prognosis and predict response to treatment in the adjuvant and neoadjuvant settings (Leung et al., 2016; Urruticoechea et al., 2005; Schwab et al., 1982; Viale et al., 2008). High ki67 score is associated with poor prognosis (Azambuja et al., 2007). Ki67 is a nuclear protein found in a Hodgkin lymphoma cell line (Gerdes et al., 1983). The original aim and scope of TCGA was

to genomically characterize primary, untreated tumors with a basic set of genetic alterations and transcript profiles. As the program is now completed, a future challenge is to expand these analyses to larger sample sets, additional data types, such as metabolite levels, a wider range of epigenetic states, posttranslational modifications of proteins, and to investigate metastatic disease and genomic alterations that arise in post-treatment samples, as well as analysing the role of a wider range of germline alterations and their interplay with somatic events. These new avenues of research will benefit from pathway-level analysis for which the templates and curation pipelines presented here constitute a promising starting point. Similarly, as the catalog of clinically actionable alterations continues to grow, understanding intra- and inter pathway dependencies, such as the ones considered here, will be crucial for the development of effective combination therapies that address or prevent resistance to initially successful single agent therapies.

NOTE

The most important genes are exposed to the mutational effect of TP53, PIK3, AKT1 and ERBB2 leads to the development of Breast Cancer, even though modern technology tool is necessary for analysing the above genes are required, in large scale platform.

INTRODUCTION

Breast cancer incidence 2.4 million with 523,000 Breast cancer, Example: luminal A, Luminal B, HER positive, Triple negative. Worldwide, breast cancer raises concerns to human health, women especially, with continuously increasing incidence and high mortality. 2.1 million new cases diagnosed and 626,679 deaths found in 2021 make 10.5researchers and progressions are seen in early detection, diagnosis, and treatments of breast cancer over the years with a significant extension of breast cancer survival. Nevertheless, early recurrence, distant metastasis and drug resistance are still commonly seen, which hold threads to the prognosis of breast cancer patients and mount challenges for clinicians (Burton et al., 2013; Lin et al., 2013; Arthur et al., 2016). Further researches were urgently needed to unravel the molecular mechanism underlying and discovering valuable prognostic biomarkers for breast cancer survival. Gene expression profiles classify breast cancers into different subtypes, with clinical trials showing that these transcriptional signatures can be used to support therapeutic decisions in primary breast cancer (Harris et al., 2016). Large-scale genomics analyses have now been performed in thousands of primary breast cancers, revealing the complex mutational landscape of the disease (Banerji et al., 2012; Cancer Genome Atlas Network,

2012; Ciriello et al., 2015; Ellis et al., 2012; Nik-Zainal et al., 2016; Shahet al., 2012; Stephens et al., 2012). A number of studies have revealed extensive genomic heterogeneity within primary breast tumors and changes in sub clonal structure during systemic therapy (Balko et al.,2014; Gellert et al., 2016; Miller et al., 2016; Ng et al., 2015; Shah et al., 2012; Wang et al.,2014; Yates et al., 2015). There are two possible explanations for the enrichment of driver mutations in relapse/metastasis samples compared with the cohort of primary breast cancers. It might be that those primary breast cancers with a more disordered genome are more likely to subsequently relapse; or it might be that the relapsing clone continues to acquire new driver mutations after dissemination from the primary lesion. We therefore compared the driver mutation profile of the 51 patients in whom both the primary and a relapse/metastasis sample were sequenced. Mutations in well-known, relatively frequent breast cancer genes, such as TP53, PIK3CA, and GATA3, when present, were typically found in both the primary and the recurrence samples. Interestingly, JAK2 and STAT3 were identified as significantly mutated in the metastasis/relapse screen even though they had not been discovered in the earlier (and larger) exome studies of primary breast cancers (Banerji et al.,2012; Cancer Genome Atlas Network, 2012; Ellis et al.,2012; Shah et al.,2012; Stephens et al.,2012).

Thus, inactivation of JAK-STAT signalling appears to contribute to disease progression and metastasis in some patients with breast cancer. We note that in another study of metastatic breast cancer, a JAK2 nonsense mutation was also discovered (Zehir et al.,2017). Interestingly, homozygous loss of JAK2 has recently been described as a mechanism of resistance to check point inhibitor immunotherapies (Zaretsky et al.,2016). Breast cancer is the most common cancer and the leading cause of cancer death for women worldwide (Fitzmaurice et al., 2017). In 2015, breast cancer incidence was 2.4 million, with 523,000 breast cancer deaths. Invasive breast cancer can be divided in several molecular subgroups (e.g., luminal A, luminal B, HER2-positive and triplenegative) which have different prognoses and different systemictherapeutic options (e.g., chemotherapy, endocrine therapy,anti-HER2 therapy)(Burstein et al.,2021). In a recently published comprehensive genomic analysis of 3831 consecutive breast cancer samples, potential biomarkers (e.g., TMB, microsatellite instability [MSI], BRCA mutations) were assessed to guide the use of ICPIs in these patients (Sivapiragasam et al.,2020). Similarly, JAK/STAT pathways predict response to ICPi therapy (Nishida et al.,2021). In addition, cancer stem cells are a potential biomarker to predict the effectiveness of ICPis (Shi et al.,2021). However, for all of these

potential biomarkers, prospective randomized trials are needed to assess the predictive value in response to genome checkpoint inhibitors.

TP53 was originally identified in the 1970s as a viral SV40 T antigen interacting protein and has been shown to function as a tumor suppressor (Deleo et al.,1979). The tumor suppressor p53 plays an important role in the regulation of cell cycle, apoptosis, DNA repair, cellular senescence and autophagy. ERBB2 is an important factor during the onset and progression of Breast Cancer (Prat et al.,2019;Christgen et al.,2019). It is a preferred dimerization causes autophosphorylation of the tyrosine kinase domains. ERBB2 mediates various downstream carcinogenic signals, such as PI3K/AKT, RAF/MAPK/ERK, Notch, and STAT3 signaling (Mitsuda et al., 2018; Kebenko et al., 2015;Martín- Pérez et al.,2014; Mishra et al.,2012; Shin-Kang et al.,2011).

Figure 1: Oncogenes associate the various mutational effect and physiological activity link with development of cancer.

Description methodology

Cell cycle pathway

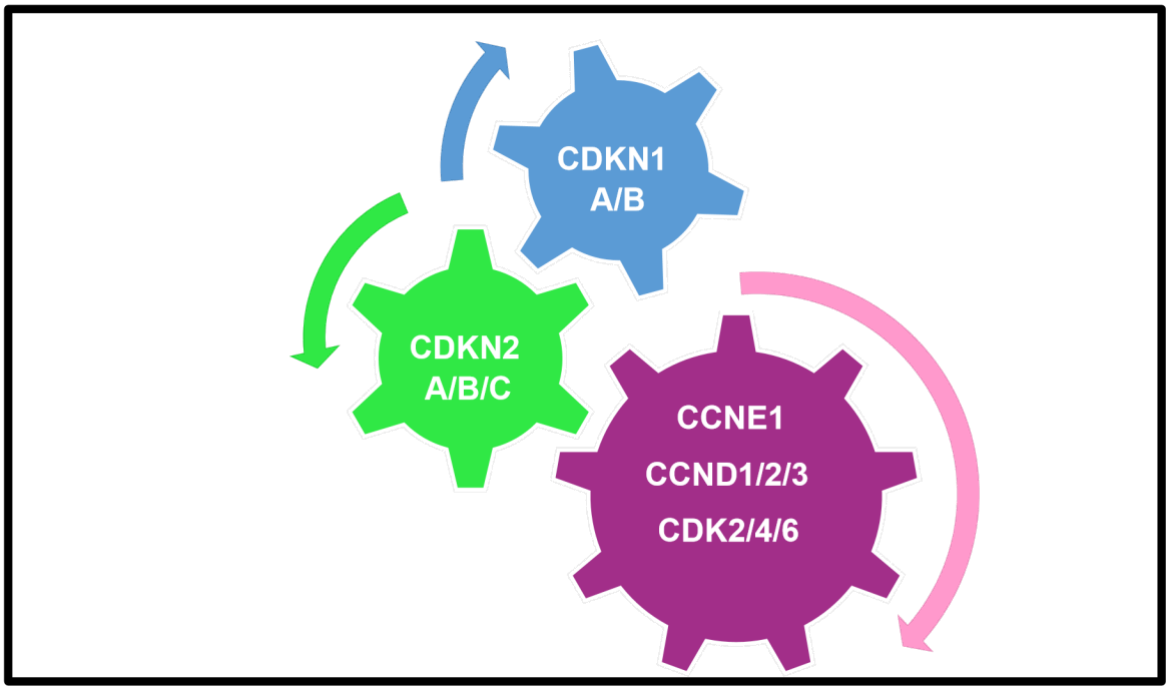

Figure 2: The above figure represent illustration about the cyclic dependent kinase in cell cycle pathway (Chakravarty et al., 2017).

DNA sequencing has been used routinely to inform the choice of targeted therapy in specific cancer types for several years, and some institutions now apply it more broadly to guide clinical trial enrolment for many additional cancer types. A relatively small number of alterations in a subset of tumor types are currently biomarkers for standard care targeted therapies, and a larger number are potential biomarkers for investigational therapies, some with promising clinical results. Using the OncoKB knowledge base of clinically actionable alterations (Chakravarty et al.,2017), we systematically assessed all alterations in each sample of each cancer type, distinguishing between standard care actionability (Levels 1 or 2) and investigational therapies (Levels 3 and 4). Overall, 51% of tumors had at least one potentially actionable alteration in the ten signaling pathways, and 57% had at least one actionable alteration when including genes outside of these pathways, most notably BRCA1/2 and IDH1/2 (all numbers referenced below include these additional genes). Apart from the Her2-enriched breast cancer samples, most of which have a standard care targeted therapy, melanoma was the tumor type with the highest fraction of tumors with a Level 1 or 2A alteration (46%), mainly due to frequent BRAF mutations, followed by esophagogastric cancers (ERBB2 amplifications). Luminal A breast cancer was the tumor type with the

highest frequency of biomarkers with promising investigational data (Level 3A), driven by the high prevalence of PIK3CA, AKT1 and ERBB2 mutations. Several tumor types had frequent mutations that are biomarkers for drugsensitivity in other cancer types (Level 3B), including endometrial cancer, where PIK3CA mutations are common. By a similar consideration linking actionable alterations of targets to their inhibitors, a combination of HER2 and PI3K inhibitors might be beneficial across multiple tumor types, in particular Her2-enriched breast cancer (17%)(Sanchez – vega et al.,2018).

TP53 PATHWAY

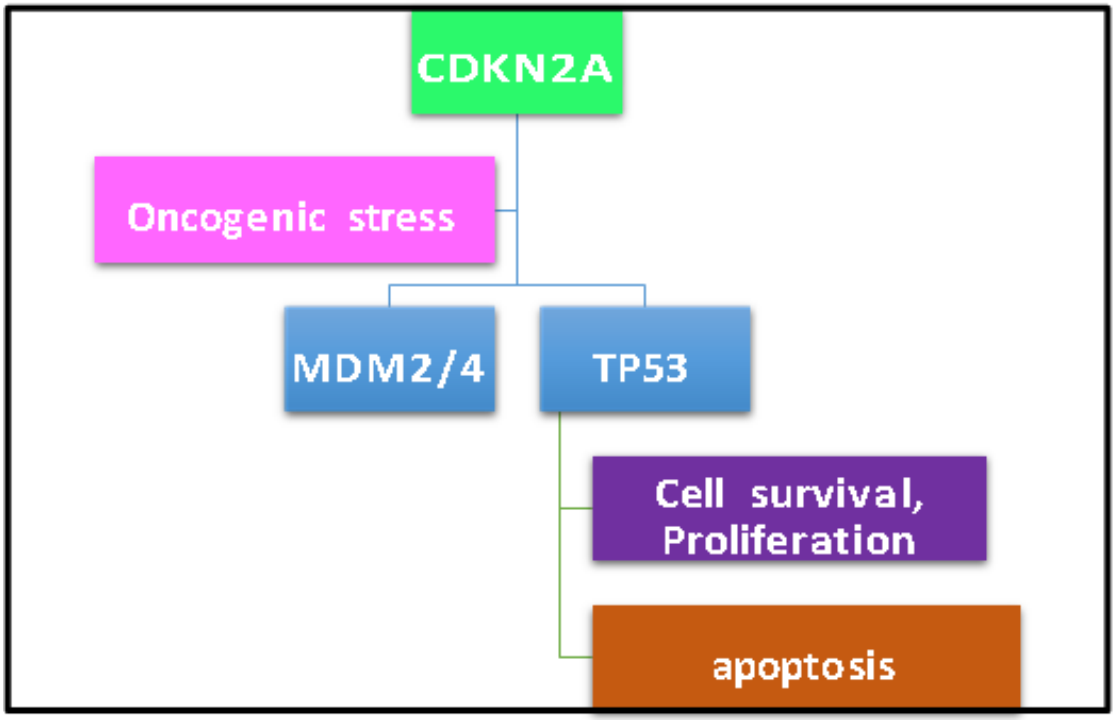

Figure 3: The above figure describe the role of MDM2/4 and TP53 play a major role in apotosis pathway.

Combinatorial application of powerful high-throughput screening techniques with advanced methods and protocols in bioinformatics has greatly facilitated the understanding of molecular mechanisms underlying the carcinogenesis (Banerji et al.,2012). Although multiple studies in which a markedly higher rate of TP53 mutations was detected in young women, as well as medullar carcinoma, suggesting an involvement of TP53 mutations into the hereditary cancer(chappuis et al.,1999;Luo et al.,2018;Kim et al.,2014;Slooten et al.,1999;Castillo-Guardiola et al.,2018). It has been reported that almost all types of cancers harbor somatic TP53 mutations with varied rates ranging from 50% to 5%. (Ara et al.,1990;Olivier et al.,2010).

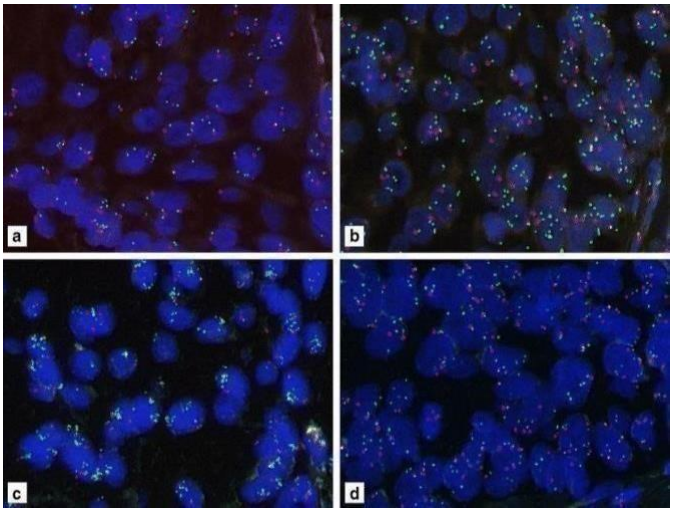

Figure 4: The above phase contrast image of PIK3CA (green) and CEN3 (pink) florescence insitu hybridization. A normal gene status, b, c amplification of PIK3CA gene, and d high polysomy of PIK3CA gene.

HER2 Signalling Pathway

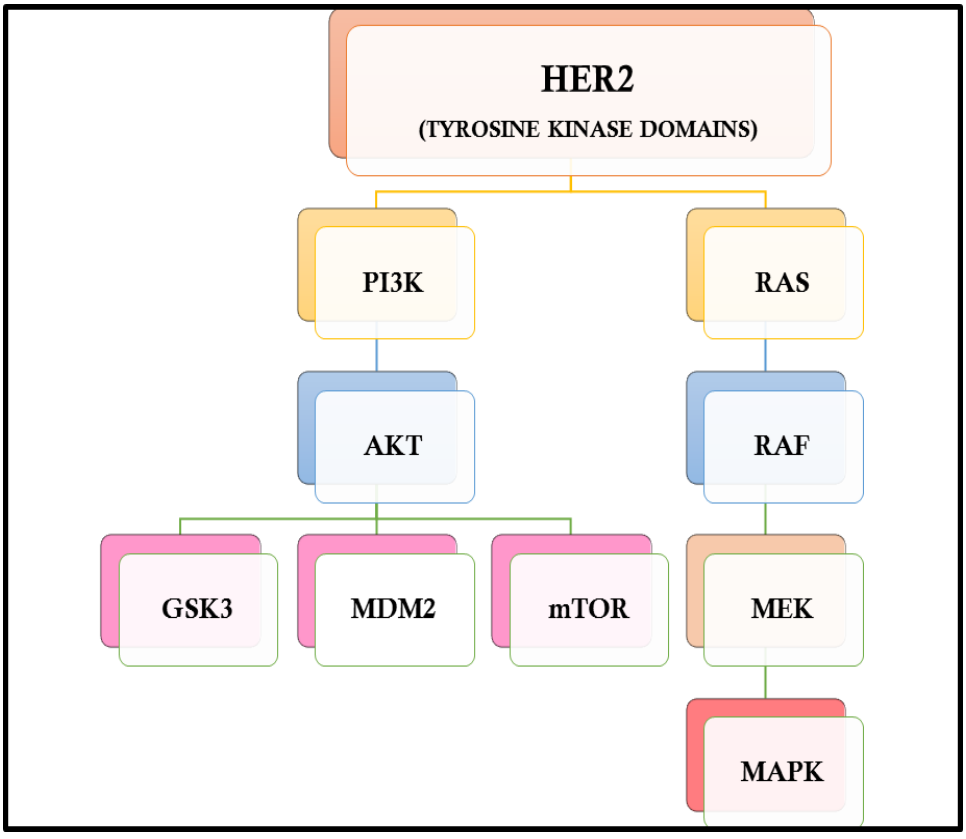

Figure 5: Her2 Signalling Pathway, Phosphorylation of the tyrosine kinase domain in the cytoplasm initiates downstream oncogenic signaling pathway such as PI3K/AKT pathway and RAS/MAPK pathway.

ABBREVIATION

HER– Human Epidermal Growth Factor Receptor

PI3K – Phosphatidylinositol-3- Kinase

AKT – Serine / Theronine-Protein Kinase

GSK3 – Glycogen Synthase Kinase MDM2 – Murine Double Minute 2

mTOR - Mammalian Target Of Rapamycin

RAS – Rat Sarcoma

RAF – Rapidly Accelerated Fibrosarcoma

MAPK - Mitogen Activated Protein Kinase

Different Stages of Molecular Events In Breast Cancer And Therapy.

Table 1: Table represents different level of molecular events in Breast Cancer.

SUBTYPES	***MOLECULAR EVENTS***	***CHARACTERISTICS***	***TREATMENT***
LUMINAL A	ER+,PR ±,HER2- ,Low Ki67	70%, Most common ,best prognosis	Hormonal therapy, Targeted therapy
LUMINAL B	ER+,PR ±,HER2 ±,High Ki67	10% - 20%	Hormonal therapy, Targeted therapy
HER2	ER-,PR -,HER2+	Lower survival than Luminal A 5% - 15%	Targeted therapy
TRIPLE NEGATIVE	ER-,PR-,HER2-	15% - 20%, More common in black women ,worst prognosis	Limited targeted therapy
NORMAL LIKE	ER+,PR ±,HER2- ,Low Ki67	Low proliferation gene cluster expression	Hormonal therapy, Targeted therapy

DISCUSSION

Probably acting through blocking the interferon-gamma pathway. Although none of the patients here received such therapies, it is feasible that these mutations help advanced tumors evade the native immune response mounted against them. Cancers with JAK2 or STAT3 truncating mutations contained a higher number of point mutations on average than other cancers ($p = 3\times10$; F test). Although other explanations are possible, this finding would be consistent with the notion that these cancers may contain more neo antigens, stimulation a more exuberant native immune response, and driving selection of JAK-STAT pathway inactivation. The broadening of the repertoire of cancer genes sampled by late driver mutations likely reflects the diverse selective forces operating during evolution of advanced breast cancer(Yates et al.,2017). Gain of function mutations in TP53 have been associated with metastasis and drug resistance in cell line and xenograft models (Petitjean et al.,2007;

Turner et al.,2017), but in cohort loss-of-function and gain-of-function mutations were equally enriched in patients with progressive disease compared with stable disease (p= 0.5; Fisher'sexact test) and in recurrences compared with primary tumors(p = 0.7; Fisher's exact test)(Yateset al.,2017). Kinesin superfamily (KIFs) were a group of proteins featured to be microtubule based motors and functioned as intracellular transporters that directionally transport various cargos, including organelles, protein complexes and mRNAs, along microtubules in an adenosine triphosphate (ATP) dependent way and played crucial roles in not only cellular morphogenesis and fundamental biology, like mitosis and meiosis, but also various mechanisms for higher life functions, including higher brain functions like memory and learning, left– right asymmetry formation, etc.(Miki et al., 2005; Hirokawa et al., 2008; Hirokawa et al.,2009). There are 45 KIFs discovered and identified in human, among which several family members were demonstrated varied functions in tumor pathobiology(Miki et al.,2002). MSX1 a novel biomarker for primary lung, breast, colon, and prostate cancers(Shames et al.,2006). Cellular experiments validated hypomethylation of CpG sites within the MSX1 gene highly associated with resistant high-grade serous ovarian cancer (HGSOC) disease at presentation and identified expression of MSX1 as conferring platinum drug sensitivity(Bonito et al.,2016).

CONCLUSION

Kinesin superfamily (KIFs) were a group of proteins featured to be microtubule based motors and functioned as intracellular transporters that directionally transport various cargos, including organelles, protein complexes and mRNAs, along microtubules in an adenosine triphosphate (ATP) dependent way and played crucial roles in not only cellular morphogenesis and fundamental biology, like mitosis and meiosis, but also various mechanisms for higher life functions, including higher brain functions like memory and learning, left– right asymmetry formation, etc.(Miki et al.,2005;Hirokawa et al.,2008;Hirokawa et al.,2009). There are 45 KIFs discovered and identified in human, among which several family members were demonstrated varied functions in tumor pathobiology (Miki et al., 2002). MSX1 a novel biomarker for primary lung, breast, colon, and prostate cancers (Shames et al., 2006). Cellular experiments validated hypomethylation of CpG sites within the MSX1 gene highly associated with resistant high-grade serous ovarian cancer (HGSOC) disease at presentation and identified expression of MSX1 as conferring platinum drug sensitivity(Bonito et al.,2016).

Transcripts also associated with improved prognosis, as well as enhanced response to chemotherapy, especially in TNBC. Novel therapies, such as immune checkpoint inhibitors, have improved survival in triplenegative breast cancer(Schmidt et al.,2021). In normal breast tissue, one generally finds low numbers of leukocytes, including T cells. Treatment specifically targeted at HER2 has improved survival during the past decade in patients with HER2positive breast cancer. Nevertheless, resistance remains a challenge, particularly in the metastatic setting. With the deepening fundamental understanding of molecular correlations and characterization of breast cancer, new agents are in clinical development, including those directed at the HER2 receptor itself and those targeting downstream effectors and interacting compensatory signaling pathways such as hsp90, mTOR and IGF-1R inhibitors. Such results are likely to useful in the prognotic effect of HER2positive breast cancer. KIF20A peptidebased immunotherapy for cancer treatment was demonstrated availability and putative efficacy with promiscuous T-H-cell epitopes derived from KIF20A identified in solid tumor tissue and distinguished KIF20Aspecific TH1-cell responses were found in patients with HNMT receiving immunotherapy(Tomita et al.,2013). Microarray data analyses revealed the highly transactivated status of KIF4A in non-small cell lung cancer and targeting KIF4A might hold a promise for the development of anticancer drugs and cancer vaccines as well as a prognostic biomarker in the clinic (Taniwaki et al., 2007). Numerous researches were done highlighting the importance of KIFs in various aspects of breast cancer (Lucanus et al., 2018). KIF2A, KIF14 and KIF26B were found overexpressed in lymph nodes-positive breast cancer patients indicating putative impacts on tumor metastasis (Scanlan et al., 2001; Corson et al., 2006; Wanj et al., 2014). Knocking down of KIF2C, KIF3C, KIF22, KIF18A and KIF24 inhibited proliferation of breast cancer cells via different mechanisms including G2/M phase arrest, delayed exit from mitosis, deregulating cell division and restoring ciliation (Shimo et al.,2008;Suzuki et al.,2008;Takahashi etval.,2008;Zhang etval.,2010;Ahmed et al.,2012;Kim et al.,2015). Recent researches demonstrated implications of KIF1A, KIF5A, KIF12, KIF14, KIFC1 and KIFC3 in resistance to docetaxel by destabilizing microtubule(De et al., 2009; Tan et al., 2012; Singel et al., 2013; Singel et al., 2014), while KIF5A, KIF5B, KIF12, KIF20A and KIFC3 were found to reduce the efficacy of paclitaxel by inducing abnormal breakdown of microtubules in breast cancer treatment(Tan et al.,2012;Klipfel et al., 2011; Ganguly et al., 2011; Khongkow et al., 2016). However, there is a growing corpus of promising preclinical data indicating such combinations can be effective, such as the combination of MDM2 and CDK4 inhibitors (LarocheClary et al.,2017), and the combination of PI3K inhibitors and HER2 inhibitors in HER2positive/PIK3CA mutant breast cancer

patients, even when single gene-therapy approaches (e.g., PI3K monotherapy for PIK3CA mutant tumors) have thus far not had definitive clinical impact. This review article proposed and suggested that the HER2, KIF2c and PIK3CA , MDm2, CDK4,ERBB2 junctures still need to investigate the mutational effect and frame shifting of genes to analysed by modern technology tool and development.

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