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A Study of Genetic Alterations in Triple-Negative Breast Cancer

Bhoomi Vaniya[1], Dr. Nupur Patel[2], Dr. Nidhi Gondaliya[3], Dr. Trupti Trivedi[4], Dr. Hemangini Vora[5]

[1]Ph.D. Scholar at Life Science Department - Gujarat University,
Junior Research Fellow -The Gujarat Cancer and Research Institute
[2]Research Assistant, The Gujarat Cancer and Research Institute
[3]Ph.D. co-guide, Assistant professor at Life Science department, Gujarat University
[4]Ph.D. guide, Assistant professor & Head Molecular Diagnostic and Research Lab 1,
The Gujarat Cancer and Research Institute
[5]Professor & Head of the department - Cancer Biology, The Gujarat Cancer and Research Institute

Corresponding Author: Dr. Trupti Trivedi

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ABSTRACT

Triple-negative breast cancer (TNBC) is an aggressive and heterogeneous subtype of breast cancer lacking estrogen receptor, progesterone receptor, and HER2 expression. This limits the effectiveness of targeted hormonal therapies and contributes to poor clinical outcomes. Recent advances in next-generation sequencing (NGS) have significantly enhanced our understanding of the complex genomic, transcriptomic, epigenomic, and metabolomic landscape of TNBC. This review discusses the molecular subtypes of TNBC, chromosomal abnormalities, copy number variations, transcriptomic signatures, epigenetic modifications and emerging metabolomic markers that offer promise in early detection, prognosis, and treatment resistance. The integration of multi-omics data underscores the biological complexity of TNBC and offers new avenues for precision medicine.

Keywords: *Triple-negative breast cancer, Genetic alterations, Epigenomics, Transcriptomics, Metabolomics, Precision medicine*

INTRODUCTION

Triple-negative breast cancer (TNBC), a subtype of breast cancer distinguished by the lack of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). Targeted medicines that are effective in other subtypes of breast cancer do not work in TNBC, treating this kind of cancer is more difficult. Understanding the genomic landscape of TNBC is critical to identifying potential therapeutic targets and improving treatment outcomes. TNBC tends to be more aggressive and is often associated with poorer prognosis, especially in terms of recurrence and metastasis. In this review we tried to explore genomic landscape of TNBC.

Molecular Subtypes of TNBC:

Molecular subtyping of breast cancer using immunohistochemistry (IHC) based on estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) expression is crucial for predicting prognosis and guiding treatment decisions. Identification of key biomarkers like ER, PR, and HER2 by IHC are used to classify breast cancers into

molecular subtypes like Luminal A (ER+ and/or PR+ Her2-, Ki-67<20%), Luminal B (ER+PR-Her2-, Ki-67>20%), HER2-enriched (ER-PR-Her2+, Ki-67>30%), and triple-negative (TNBC, (ER-PR- Her2-), each with distinct characteristics and treatment responses.

Lehman et al. identified six different TNBC molecular subtypes with distinct biologies using gene expression analysis are two basal-like (BL1 and BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) subtypes [1]. The BL2 subtype involved in growth factor signaling and increased expression of myoepithelial markers, whereas the BL1 subtype is distinguished by increased expression of genes related to the cell cycle and DNA damage response. While the MSL subtype has reduced expression of genes related to proliferation, both M and MSL share increased expression of genes involved in growth factor and epithelial-mesenchymal transition (EMT) pathways. The majority of chondroid and spindle cell carcinomas are of the MSL subtype, which is consistent with the dedifferentiated mesenchymal gene expression pattern [2]. Immunological antigens and genes involved in cytokine and core immunological signal transduction pathways make up the IM subtype. The androgen receptor (AR) drives the LAR subtype, which is distinguished by luminal gene expression. An analysis of the intrinsic subtypes revealed that BL1, BL2, IM, and M are primarily made up of the basal-like subtype, whereas MSL contains a significant proportion of normal-like, and LAR is predominantly comprised of luminal and HER2 subtypes [3]. In addition to these intrinsic subtypes, a novel claudin-low subtype has been identified, which is characterized by a higher presence of EMT markers, immune response, and genes associated with cancer stem cell-like properties [4]. This claudin-low subtype mainly consists of the M and MSL TNBC subtypes [3]. In routine clinical practice, TNBC is diagnosed using immunohistochemical assessment of ER, PR, and HER2, as multi-gene expression profiling via cDNA microarrays is significantly more resource-intensive and not cost-effective for widespread use [5]. The current standard treatment remains chemotherapy, though emerging options such as PARP inhibitors and immunotherapy are being explored and implemented in appropriate subsets of TNBC patients [6].

Comparative Genomic Hybridization (CGH)

Comparative Genomic Hybridization (CGH) widely applied in cancer research to understand the genomic alterations specific to various cancers. CGH is a molecular cytogenetic technique used to analyse copy number variations (CNVs) in the genome. This method allows the detection of chromosomal imbalances (gains or losses of chromosomal material). These genetic changes can include amplifications or deletions of specific oncogenes or tumor suppressor genes providing insights into the genetic alterations involved in cancer. Few studies are available regarding CGH array analysis in TNBC.

Toffoli et al investigated chromosomal aberrations in BRCA1-mutated and non-mutated TNBC. It was observed that general distribution of the genomic aberrations was relatively similar between the two tumor groups and showed a high proportion of gains and losses in both BRCA1-mutated and non-mutated TNBC. The most frequent discriminating genomic alterations in the BRCA1-mutated group as compared to the non-mutated group were gains in 7p22.1, 8q24.3, 11p15.5, 15q22.31, 15q24.1-2, 16p24.3, 17q24.1, 17q24.3, 17q25.1, 17q25.3, 19q13.33, 22q12.3, 22q13.1, and losses in 5q14.3-21.2,5q23.1, 11q24.3, 12q21.33, 18q12.1, 18q12.3, 19q13.2-3. Among all, 17q25.3 gain was the most frequent gain in BRCA1-mutated population which was confirmed by FISH. The prevalence of 17q25.3 gain was 17.2% in BRCA1 non-mutated breast cancers and

more than 90% of the BRCA1-mutated tumors. Eight genes of the 17q25.3 region significantly over-expressed in tumors harboring the 17q25.3 gain compared to negative tumors were C17orf56, CSNK1D, DUS1L, FN3KRP, HGS, SIRT7, SCL25A10, RFNG might represent potential therapeutic targets [7]. A study of Regis et al in African-American (AA) and Caucasian TNBC, a distinct DNA copy number profile was observed between TNBC of AA and Caucasian cases: the cytobands differentially involved in the AA-TNBC cases were 7p22.3-22.1, 12p13.33-p11.1, 17q25.3 and 17p13.3-p11.2. Common cytobands in both groups were 1q21.1-q44, 8q22.1-q24.3, 16p13.33-p11.1 and 20q11.2-q13.12. An average of 30.5 and 16.8 DNA copy alterations were observed between the AA and Caucasian cases respectively [8].

In our study on TNBC, copy number variation region (CNVR) was observed in Chr 1 to Chr 4, Chr 7, Chr 11 and Chr X. Common CNVR associated with amplified regions in Chr 22, Chr 14, Chr 8 and Chr 2 was observed in TNBC, and CNVR associated with Chr 22q11.22–23, Chr 6p21.32–33, Chr11q12.2, Chr14q32.22–23, and Chr 8p11.22–23 was observed in metastatic disease [9]. Our previous institutional study observed frequent involvement of Chr 1 and Chr 2 in breast cancer patients along with Chr B, D, E groups [10]. A study of Pariyar et al. observed CNVR with amplified region in 1q, 8q, 19p and q, 2p and 5p [11] and other studies have found frequent amplification 1q, 3q, 8q, 10p, 12p, 20q and deletion in 3p, 5q, 8p and 17p in TNBC indicating CNVR may have a role in increasing genomic aberrations in TNBC [12-16]. In our study and in other studies common CNVR associated with amplification was observed in only Chr 1 and Chr 3. This discrepancy may be due to disease stage and tumor heterogeneity. These studies collectively showed that no common chromosomal aberration that implied ethnic heterogeneity of TNBC was found. However, CGH offers a glimpse of chromosomal alterations, it might overlook other subtle mutations or epigenetic modifications that also play a role in the development of cancer.

Gene Mutations:

High-throughput sequencing and comprehensive molecular profiling have revealed several recurrent genetic alterations, alterations in DNA damage repair pathways, along with copy number changes and epigenetic modifications.

Germline mutations in triple negative breast Cancer: BRCA1/2 mutations in TNBC

Mutations in the BRCA1 and BRCA2 genes are observed in a significant proportion of TNBC cases, particularly those with hereditary breast cancer. Approximately 10–20% of women with TNBC harbors germline BRCA1 mutations [17]. These genes are critical components of the homologous recombination repair (HRR) pathway. Loss of function in these genes leads to genomic instability and renders cells susceptible to PARP inhibitors, which exploit synthetic lethality [18,19]. BRCA1-mutant TNBCs tend to show a basal-like gene expression profile and may respond better to DNA-damaging agents such as platinum-based chemotherapy.

Studies have shown that up to 15–20% of unselected TNBC cases carry germline mutations in BRCA1 or BRCA2, with BRCA1 mutations being much more prevalent in this subtype compared to hormone receptor-positive cancers [20,21]. In familial TNBC cases or early-onset TNBC, the frequency of BRCA1 mutations may exceed 30–40%. These tumors often exhibit basal-like features, high-grade histology, and aggressive clinical behavior [22].

BRCA1-associated TNBC is characterized by defects in DNA double-strand break repair, leading to genomic instability and reliance on alternative DNA repair pathways. This vulnerability renders these tumors particularly sensitive to DNA-

damaging agents such as platinum-based chemotherapies and poly (ADP-ribose) polymerase (PARP) inhibitors, which induce synthetic lethality in HR-deficient cells [23,24].

BRCA2 mutations are less frequently associated with TNBC compared to BRCA1 but still contribute to HR deficiency. TNBC tumors with BRCA2 mutations may also benefit from PARP inhibitors and platinum agents, although they tend to show less basal-like features.

Clinically, testing for BRCA1/2 mutations—both germline and somatic—is crucial in TNBC patients, particularly those diagnosed before age 60 or with a family history of cancer. Identification of BRCA mutations not only informs prognosis but also determines eligibility for targeted therapies such as PARP inhibitors (e.g., Olaparib, talazoparib), which have demonstrated survival benefit in BRCA-mutant TNBC [25,26].

Other predisposition genes associated with TNBC

PALB2 and FANCM

Genetic attributions of other predisposition genes, excluding BRCA1/2 genes, have been limitedly studied, of which, PALB2 and FANCM were more extensively studied. The PALB2 (Partner and Localizer of BRCA2) gene encodes a protein that plays a pivotal role in the homologous recombination (HR) DNA repair pathway, acting as a molecular bridge between BRCA1 and BRCA2 to recruit RAD51 to sites of double-strand DNA breaks. Pathogenic germline variants in PALB2 confer a substantially elevated lifetime risk of breast cancer, estimated at 35–58% by age 70, with a notable predisposition toward high-grade, triple-negative phenotypes in a subset of cases [27,28]. Germline PALB2 mutations are detected in approximately 1–3% of patients with TNBC, though rates vary across populations [29]. Tumors arising in PALB2 mutation carriers often display basal-like histology, high mitotic indices, and genomic instability, closely mirroring the "BRCAness" phenotype observed in BRCA1/2-mutated cancers [30]. Given their HR deficiency, PALB2-mutated TNBCs demonstrate enhanced sensitivity to DNA-damaging agents such as platinum-based chemotherapies [31]. Moreover, emerging clinical evidence supports the use of poly (ADP-ribose) polymerase (PARP) inhibitors in this subgroup. In the TBCRC 048 trial, germline PALB2 mutation carriers with metastatic breast cancer, including TNBC, achieved objective response rates exceeding 80% with PARP inhibitor therapy [32]. These findings position PALB2 mutation status as a potential biomarker for selecting patients who may benefit from PARP inhibition. In addition, HRD-associated mutational signatures in PALB2-mutated TNBC suggest possible synergy with immune checkpoint inhibitors, an area currently under investigation [33]. Incorporating PALB2 mutation screening into the molecular workup of TNBC can help identify patients eligible for targeted therapeutic strategies, aligning with the broader precision oncology approach to HR-deficient breast cancers.

The FANCM (Fanconi anemia complementation group M) gene encodes a DNA translocase that functions as a critical component of the Fanconi anemia (FA) DNA repair pathway, which cooperates with the homologous recombination (HR) machinery to repair DNA interstrand crosslinks and stalled replication forks [34]. FANCM acts upstream in the FA core complex to recruit DNA repair proteins, including BRCA1 and BRCA2, thereby maintaining genomic stability [35]. Pathogenic variants in FANCM are relatively rare but have been identified in 2–5% of hereditary breast cancer cases, with a higher prevalence among patients with TNBC compared to hormone receptor–positive subtypes [36,37]. FANCM-mutated tumors frequently display basal-like gene expression profiles, high genomic instability, and mutational patterns consistent with homologous recombination deficiency [38]. Biallelic loss-of-function

mutations are associated with a Fanconi anemia phenotype, while heterozygous germline truncating mutations predispose to breast cancer without classical FA symptoms [39]. Loss of FANCM function results in impaired DNA interstrand crosslink repair, rendering tumor cells more sensitive to DNA crosslinking agents such as cisplatin and carboplatin [40]. Additionally, preclinical studies suggest that FANCM-deficient cells exhibit heightened susceptibility to PARP inhibitors, similar to BRCA- and PALB2-deficient TNBC [41]. This HRD-associated vulnerability positions FANCM as a potential biomarker for targeted therapy selection. Although clinical evidence is still emerging, the mechanistic overlap between FANCM loss and other HR pathway deficiencies provides a rationale for including FANCM in multi-gene testing panels for TNBC [42]. Although less common than BRCA1/2 or PALB2 mutations, FANCM pathogenic variants contribute to the HRD phenotype in TNBC and may predict sensitivity to platinum-based chemotherapy and PARP inhibitors. Ongoing translational studies are expected to clarify the prognostic and predictive value of FANCM alterations in this aggressive breast cancer subtype.

Somatic mutations in triple negative breast cancer

TP53 Mutation: The Tp53 gene is a tumor suppressor gene crucial for preventing cancer development. It encodes the p53 protein, which acts as a "guardian of the genome" by regulating cell division and triggering DNA repair or apoptosis when DNA damage is detected. Mutations in p53 are frequently found in various cancers, highlighting its importance in maintaining genomic stability. In TNBC, mutation in the TP53 gene is most frequently observed which accounts for approximately 75–80% of all cases [43,44]. In TNBC, most TP53 mutations are missense mutations that occur in DNA binding domain (exon 5-8), resulting in the loss of normal function and sometimes acquisition of oncogenic gain-of-function properties [45]. These mutated forms of p53 tend to accumulate in the cell nucleus due to increased protein stability, leading to deregulated cell cycle control and enhanced proliferation [46,47]. These mutations are associated with genomic instability and a more aggressive tumor phenotype. Importantly, TP53 mutations are highly prevalent in the basal-like subtype of breast cancer, which overlaps substantially with TNBC. This correlation suggests that p53 dysfunction is a defining feature of the aggressive biology observed in these tumors [48,49]. Moreover, the high mutation burden associated with TP53 alterations contributes to genomic instability, which fuels further tumor evolution and heterogeneity. Clinically, TP53-mutated TNBC is associated with poor prognosis, increased tumor grade, higher proliferation indices, and resistance to conventional chemotherapy. However, the ubiquity of p53 dysfunction in TNBC has spurred interest in targeting this pathway therapeutically. Investigational agents such as APR-246 (eprenetapopt), which aim to restore wild-type p53 function, have shown promise in preclinical and early-phase clinical studies [50]. As TP53 mutation status continues to emerge as a critical biomarker in TNBC, it holds potential not only for stratifying patients by prognosis but also for guiding the development of p53-targeted therapies in this challenging breast cancer subtype.

PIK3CA Mutation: PI3K/AKT/mTOR signalling pathway is a key regulator of cell growth, proliferation, survival, and metabolism. Aberrations in this pathway are commonly implicated in various cancers, including breast cancer. Although PIK3CA mutations—which activate the PI3K pathway—are more frequent in hormone receptor-positive breast cancers, they are also found in approximately 10–15% of TNBC cases, particularly within the luminal androgen receptor (LAR) subtype [49,51]. PIK3CA encodes the p110α catalytic subunit of PI3K, and hotspot mutations

(e.g., E545K, H1047R) lead to constitutive activation of the PI3K/AKT pathway, promoting oncogenic signalling. In TNBC, activation of this pathway can occur not only through PIK3CA mutations, but also via: Loss of PTEN, a tumor suppressor that negatively regulates PI3K signalling—observed in 30–50% of TNBCs [52], also AKT1 or AKT3 amplification or mutation, leading to downstream pathway activation; and Overexpression or activation of receptor tyrosine kinases (e.g., EGFR, FGFR). Importantly, these alterations vary among TNBC molecular subtypes. For example, LAR subtype TNBCs are enriched for PIK3CA mutations and may show relative sensitivity to PI3K or AKT inhibitors, whereas basal-like TNBCs often exhibit PTEN loss and AKT activation without PIK3CA mutation [49, 53]. Targeting the PI3K/AKT pathway has been a focus of therapeutic development in TNBC. Several AKT inhibitors (e.g., capivasertib, ipatasertib) and PI3K inhibitors have been tested in clinical trials. Notably, the LOTUS trial demonstrated improved progression-free survival with the addition of ipatasertib (AKT inhibitor) to paclitaxel in metastatic TNBC, especially in patients with PTEN-low tumors [54]. Furthermore, combinations of PI3K/AKT pathway inhibitors with immune checkpoint inhibitors, chemotherapy, or AR antagonists are being actively explored, particularly in PIK3CA-mutant or AR-positive TNBC.

Other Genetic Alterations

Other recurrent genomic alterations in TNBC include RB1 deletion or mutation, MYC amplification, and overexpression of EGFR [43,45]. Some tumors also exhibit copy number variations and structural rearrangements. Epigenetic alterations, such as promoter methylation of tumor suppressor genes and dysregulation of non-coding RNAs (e.g., miRNAs and lncRNAs), further contribute to the oncogenic phenotype of TNBC [55]. These alterations may also influence immune evasion, metastasis, and resistance to therapy, and are currently being investigated as potential therapeutic targets or biomarkers [56].

Genomic Instability and Tumor Mutation Burden

TNBCs generally show a higher degree of genomic instability and tumor mutation burden (TMB) compared to other breast cancer subtypes [57]. This is partly due to defects in DNA damage repair mechanisms, especially in cases with HRD. Elevated TMB may have implications for immunotherapy response, as tumors with higher neoantigen loads are potentially more immunogenic [58].

Transcriptome Profiling:

Saleh et al led a comparative analysis of triple-negative breast cancer transcriptomics of Kenyan (KE), African American (AA) and Caucasian Women (CA) and reported that genomic profiles of TNBC patients differ for KE, AA and CA ethnic groups. Transcriptome analysis identified racial/ethnic-specific genes that were differentially expressed in TNBCs, showing a higher incidence of basal-like tumors and altered TP53, NFB1, and AKT pathways in AA TNBCs compared to CA TNBCs. The differences were identified not only between KE and CA patients, who often present with lower stage disease, but also with the AA cohort who presented with later stage disease compared to CA patients. Further, 45 KE TNBC-specific genes identified that are involved in the apoptosis (ACTC1, ERCC6 and CD14), cell proliferation (UHRF2, KDM4C, UHMK1, KCNH5, KRT18, CSF1R and S100A13), and Wnt signaling (BCL9L) pathways. Dysregulated genes associated with Wnt/B-catenin signaling pathway observed for KE TNBCs as compared to AA and CA TNBCs, suggest that this pathway contributes to the aggressive phenotypes of TNBCs of KE women. Several of these upregulated factors, identified are functional proteins necessary for cell growth, proliferation, migration, and metastasis may develop new therapeutics, specifically for KE TNBCS

[59]. Another study performed deep whole genome and transcriptome sequencing to uncover somatic mutations occurring in relapse mTNBC. Integrative DNA/RNA analysis provided evidence for deregulation of mutated genes, including the monoallelic expression of TP53 mutations along with LRP1B, HERC1, CDH5, and RB1 mutation in multiple tumors. Largely, it was shown alterations in the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways in mTNBC [60]. A study by Jiang et al performed whole exome sequencing (WES) with copy-number alteration (CNA) and RNA sequencing on primary tumor tissue and paired blood samples of TNBC. The most prominent cancer-related variations observed were TP53 mutations (found in 74% of tumors), followed by PIK3CA (18%), KMT2C (7%), and PTEN (6%) mutations. Interestingly, PIK3CA, PTEN, and PIK3R1 mutations were strongly associated with the luminal androgen receptor (LAR) subtype. They further investigated the differences in genomic features between Chinese and TCGA TNBC cohorts. Chinese TNBCs had a higher PIK3CA mutation rate and frequent somatic copy-number gains on chromosome 22q11 than TCGA TNBCs [61]. R. Sharman et al study aimed to perform multiple comparative transcriptomic analyses on a large number of TNBC versus healthy breast tissue samples using database from the National Center for Biotechnology Information (NCBI) Gene Expression Omnibus (GEO). These analyses focused on predicting differentially expressed genes, pathways, and mechanistic markers relevant to TNBC. This study highlights two novel DEGs in TNBC, FO082814.1 and ELMOD3, as well as established DEGs, including KIF14, ASPM, KIF11, HJURP, ASPM, ZH2, ATAD2, and RGS1. These genes were validated in the cell lines BT-549, HS 578T, and MDA-MB-231 reflect expression trends similar to the mRNA expression trends in their patient cohort. Additionally, identified a novel TNBC mechanistic marker, TNMD, along with other mechanistic markers already known to impact TNBC pathology, including CIDEC, CD300LG, C14orf180, ASPM, RGS1, CFD, CA4, CPA1, CIDEA, CENPF, and CENPE. The presence of both known and novel gene products indicates that the novel highly ranked genes are likely both clinically and biologically relevant [62].

Our study on transcriptome array in TNBC revealed that there were nearly twice as many upregulated genes as downregulated genes. The upregulated genes were involved in Wnt signaling pathway, Integrin signaling pathway and Cadherin signaling pathway and down regulated genes involved in Inflammation mediated by chemokine and cytokine signaling pathways. PPI network analysis revealed that ITGB7, PTPRC, ITGA4, LCK, and CD247 were important down-regulated genes and COL12A1, COL6A3, FN1, MMP3, and WNT5A were important unregulated genes. COL4A1, FN1, COL6A3, COL5A2, and PCDH7 were the five genes that were found to be common genes identified by the CGH array and transcriptome array. Since these genes were not overexpressed in controls, they are implicated in the pathogenesis of TNBC. By examining protein expression using immunohistochemistry, the expression of these genes was confirmed. At diagnosis, FN1 and COL6A3 protein overexpression can be regarded as therapeutic targets to decrease disease metastases, as it predicted worse DFS in TNBC [63]. These transcriptomics results imply that ethnicity may have a significant impact on TNBC's transcriptional landscape.

Epigenomics

Epigenetic modifications, including DNA methylation, histone modifications, and noncoding RNAs, play pivotal roles in regulating gene expression patterns in TNBC cells [64]. Epigenetic alterations critically influence the TME, affecting immune cell composition, cytokine signaling, and the expression of immune checkpoints, which ultimately leads to immune evasion. Hypermethylation of CpG

islands within the promoter regions of tumor suppressor genes leads to their transcriptional silencing contributing to tumor initiation and progression [65]. Further, repeat-rich hypermethylated pericentromeric heterochromatin region in DNA become hypomethylated contributes to genomic instability leading to cancer.

A comprehensive analysis on TNBC methylome classified differentially methylated regions (DMRs) into three methylation clusters as hypomethylated, medium methylated and heavily methylated clusters. It has been observed that patients with hypomethylated cluster exhibited better 5 years' survival than patients with heavily methylated cluster, whereas patients with medium methylated cluster exhibited worst survival [66]. Further, identified 17 DMRs significantly associated with TNBC patient survival. Of 308 genes with promoter methylation, 51 are mutated and 12 (C9orf125, COL14A1, ENPP2, ERG2, PLD5, ROBO3, RUNX1T1, SEMA5A, TBX18, TSHZ3, ZBTB16 and ZNF208) are both mutated and downregulated. Among 12 genes, both ROBO3 and SEMA5A are involved in axon guidance pathway recently implicated in tumor initiation and progression [67,68].

Lin et al identified 3 distinct DNA methylation clusters with specific clinicopathologic and molecular features. Cluster 1 (phosphoinositide 3-kinase/protein kinase B-enriched) patients were significantly older with tumors that were more likely to exhibit apocrine differentiation, a lower grade, a lower proliferation index and lower tumor-infiltrating lymphocyte fractions. Cluster 3 (chromosomal instability) patients were significantly younger, higher tumor grade (grade 3), had a higher proliferation index, and high fraction of tumor-infiltrating lymphocytes. Ninety-one percent of the germline BRCA1/2 mutation carriers were in cluster 3, and these tumors showed the highest level of copy number alterations. Cluster 2 represented cases with intermediate clinicopathologic characteristics and no specific molecular profile [69].

In order to find novel predictive DNA methylation biomarkers of NAC response, Meyer et al. used whole-genome methylation profiling in a TNBC NAC cohort and identified nine DMRs, significantly hypermethylated in non-responder patient samples, with the ability to distinguish both non-responders and partial responders from complete responders (TMEM176A/B, UNC5D, STAC2, SDR42E1, NELL1, GRP, FOXG1, CDH8, GRIA4). Prior research has linked each of the nine response-DMR genes to cancer and pathways linked to it [70]. It also identified 17 individual DMRs capable of stratifying TNBC patients into good and poor prognosis groups. Among the genes included are the *WT1* gene and its antisense counterpart, *WT1-AS*, for which high levels of methylation correlated with elevated levels of expression and poor survival. Hy-permethylation of the bi-directional promoter is associated with decreased *WT1* and *WT1-AS* expression and improved survival; however, these findings remain to be verified on a larger cohort [71]. In the study of Mathe et al determined DNA methylation changes between primary tumors and lymph node metastases. It was observed that expression of 16/38 TNBC-specific genes with altered DNA methylation in primary tumors and novel methylation changes between primary tumors and lymph node metastases, as well as those associated with survival were identified [72]. Another study investigated 5-mC and 5-hmC content in DNA isolated from TNBC pre-treatment biopsy samples in patients undergoing NACT and postoperative tissues in patients without NACT. Further compared relationship of 5-methylcytosine (5-mC) and 5-hydroxymethylcytosine (5-hmC) with clinicopathological features and response of two neoadjuvant chemotherapy in TNBC. In patients who received NACT, those with disease progression had significantly higher pretreatment levels of 5-hmC and a trend

toward higher 5-mC levels compared to those with pathological complete response, partial response, or stable disease. Higher 5-mC and 5-hmC levels were significantly associated with higher tumor grade and showed a positive correlation with Ki-67 proliferation. The study highlights the potential of global DNA methylation and demethylation markers as predictors of tumor aggressiveness and chemotherapy response in TNBC [73].

Histones are highly alkaline proteins of chromatin, acting as spool around which DNA winds. The histone code refers to the pattern of post-translational modifications, such as acetylation, methylation, and phosphorylation, that occur on the N-terminal tails of histone proteins. These modifications play a crucial role in regulating chromatin structure and gene expression. Dysregulated histone modifications, such as histone acetylation and methylation, contribute to the aberrant gene expression profile characteristic influencing tumor aggressiveness and therapeutic resistance.

Non-coding RNAs (ncRNAs) are functional RNA molecules that are transcribed from DNA but are not translated into proteins. Furthermore, non-coding RNAs such as microRNAs (short ncRNAs <30 nts) and long non-coding RNAs (>200 nts) participate in the epigenetic regulation by modulating gene expression at the post-transcriptional level. Long noncoding RNAs (lncRNAs) are a subclass of noncoding RNAs (lncRNAs) that have more than 200 nucleotides and have been implicated in the pathogenesis of various cancers, including TNBC. lncRNAs could act as oncogenic by promoting TNBC, whereas other types of lncRNAs suppressed TNBC pathogenesis and progression [74-76]

In TNBC, various studies have identified a lot of dysregulated lncRNAs that play important roles in the process of tumorigenesis through diverse mechanisms. For instance, lncRNAs can act as miRNA 'sponges' and compete miRNA-targeted mRNAs [77,78], thereby affecting the miRNA-mediated gene regulation. Some lncRNAs were reported to assemble with mRNAs to protect them from miRNA action and increase their stability. Some lncRNAs are named scaffold lncRNAs, which could serve as a central platform to assemble with different molecular components such as proteins and RNAs and promote their intermolecular interactions. Moreover, signal lncRNAs have also been reported to interact with transcription factors (TFs) or histone-modifying enzymes to cis-regulate or trans-regulate the expression of their target genes [79]. Thus, lncRNAs promise potential diagnostic and prognostic biomarkers, therapeutic targets and improve the clinical benefits for TNBC patients. Zhang et al listed 57 lncRNAs identifies in TNBC and of them 40 lncRNAs were upregulated and 17 lncRNAs were downregulated. Upregulated lncRNAs associated with cell proliferation and invasiveness in TNBC and few of them associated with therapy resistance, whereas except one of 17 downregulated lncRNAs associated with inhibition of cell proliferation and invasiveness [80]. ARNILA downregulated lncRNAs involved to promote EMT, invasion and metastasis in TNBC. Liu et al compared the differential lncRNAs expression in the plasma of TNBC patients, non-TNBC patients and healthy controls. At last, they found that the expression levels of three lncRNAs, ANRIL, HIF1A-AS2 and UCA1 were significantly increased in the plasma of TNBC patients, suggesting that those three lncRNAs expression may serve as TNBC-specific diagnostic biomarkers [81].

Small non-coding RNAs called microRNAs (miRNAs) have a role in controlling the expression of some genes [82]. Multiple mechanisms, including as amplification or deletion of miRNA genes, aberrant transcriptional control of miRNAs, dysregulated epigenetic modifications, and deficiencies in the miRNA biogenesis machinery, have been shown to contribute to the dysregulation of miRNA expression in human cancer including TNBC. Under

some circumstances, miRNAs can act as tumor suppressors or oncogenes [83]. There is growing evidence that microRNAs are closely linked to the control of the epithelial–mesenchymal transition in tumor cells [84,85]. In our study, of the 2410 differentially expressed miRNAs found in TNBC, 98% were down-regulated and just 2% were up-regulated. 55 miRNAs that target 16 genes were found to be upregulated. CDNK1A, p53, TGFB1, APC, and HRAS were the top 5 genes found. TGFB1 was found to be the most important hub gene by five out of seven ranking algorithms. Only miR-4532 was shown to be increased in patients who experienced a relapse in their condition when compared to individuals who experienced remission. Moreover, miRNA-4532 upregulation indicated a trend toward lower overall and disease-free survival. 238 genes implicated in the etiology and development of TNBC are targeted by the down-regulated miRNAs. The top five hub genes were VEGFA, MYC, STAT3, PTEN, and CDH1. Out of seven ranking techniques, the fifth one found that STAT3 was the most important hub gene. 32 new miRNAs with a tumor-suppressive function were discovered in this study to be down-regulated in TNBC. Of these two new miRNAs, all TNBC patients expressed miR-1273g-3p and miR-4459. Overall and disease-free survival were considerably lower in patients whose levels of these miRNAs were downregulated. According to the ROC curve study, miRNA-4532 and miRNA-4459 were effective in differentiating between healthy controls and TNBC patients [86]. According to additional traditional cytogenetic research on breast cancer, chromosomal abnormalities that result in a higher gene copy number in chromosome 1q (1q-gain) and/or a lower gene copy number in 16q are common [87]. A study by Sugita et al. in Latin American TNBC patients revealed that the cytobands on chromosomes 1q, 3q, 5q, 6p, 10q, 11p, 14q, 19q, and Xp had differently expressed miRNA and 17 miRNAs were discovered to regulate gene targets linked to the WNT, RAS, ErbB, and RAP1 signalling pathways, while 15 of the 17 miRNAs were shown to affect the HIPPO signalling pathway [88].

Regarding siRNA and piRNA, siRNA, or small interfering RNA, is a tool for silencing specific genes by promoting their degradation or inhibiting their translation. piRNAs, or PIWI-interacting RNAs, are involved in suppressing the activity of transposable elements and may have other functions in gene regulation. In TNBC, both siRNA and piRNA are being investigated for their potential therapeutic applications.

Metabolomics:

Organic acids, lipids, carbohydrates and amino acids are examples of metabolites, which are tiny molecules (less than 1,500 Da) produced during metabolic activities. These metabolites are affected by disease-related metabolic changes, which may lead to the discovery of biomarkers for disease diagnosis, therapy, risk assessment, and recurrence prediction. Two methods are principally used in metabolite analysis: nuclear magnetic resonance (NMR) and mass spectrometry (MS), however, MS provide high sensitivity and selectivity, hundreds of metabolites in biological samples can be analyzed simultaneously.

Several studies have identified metabolic markers as diagnostic, prognostic and predictive markers in all molecular subtypes of breast cancer. It has been proposed that certain amino acid metabolites, such as arginine, proline, histidine, 5-oxoproline, kynurenine, nicotinate, nicotinamide, tryptophan and its related pathway metabolites, could be used as early diagnostic biomarkers for breast cancer. [89-97]. A metabolite indoleamine 2,3-dioxygenase (IDO) depletes Tryptophan causes immunological tolerance, suppress cytotoxic T cell proliferation, increase in regulatory T cells (Tregs) which leads to immunosuppression and treatment resistance [98]. Another metabolite of tryptophan, Kynurenine activates the aryl

hydrocarbon receptor, suppress T and natural killer cells and enhance Treg differentiation. [99,100]. Studies have suggested lower levels of plasma tryptophan is a `biomarker for breast cancer diagnosis [93,95,96]. Similarly, depletion of L-arginine by myeloid-derived suppressor cells and depletion of arginine and proline by altered pathways can serve as biomarkers for breast cancer diagnosis. [89,91,96,97,101-104] Regarding prognosis, low survival rates and unfavorable prognoses are linked to elevated glycine levels in breast cancer tissues [105,106]. Higher glycine metabolism supplies more energy required for cancer cell growth and survival, which are linked to the initiation and spread of cancer [107,108]. Following neoadjuvant chemotherapy (NAC), methionine, valine, alanine, isoleucine, glutamate, and other amino acids were markedly elevated in the feces of the chemotherapy-sensitive group, but not in the chemotherapy-insensitive group, whereas tyrosine levels in the chemotherapy-insensitive group significantly elevated [109]. Serum levels of threonine and glutamine levels significantly decreased in chemotherapy-sensitive group, whereas isoleucine levels significantly increased [110]. On the contrary, leucine and proline levels were increased in the chemotherapy resistance group [111]. With targeted therapy, serum asparagine and sarcosine levels were observed to be elevated in TNBC who were resistant to camrelizumab plus apatinib and eribulin [112].

Alterations in lipid metabolism is also linked to cancer development and progression. L-carnitine, which is necessary for delivering fatty acids into mitochondria for fatty acid oxidation, is markedly reduced in breast cancer patients. Alterations in certain polyunsaturated fatty acid including arachidonic acid pathway are potential target to overcome drug resistance in breast cancer [113,114]. Regarding prognosis, increased levels of sphingomyelin in the breast cancer associated with good prognosis in TNBC [115], whereas elevated levels of sphingosine-1-phosphate have been associated with angiogenesis, migration, and cancer proliferation [116-118].

A carbohydrate metabolic marker Lactate plays a significant role in the development and progression of breast cancer. Glycolysis is a metabolic mechanism that cancer cells frequently use for energy, particularly under hypoxic conditions. The tumor microenvironment (TME) contains high amounts of lactate, which can encourage the proliferation of cancer cells, angiogenesis, metastasis, chemoresistance and poor 5-yr survival rates [105]. Myoinositol involved in cell cycle control and apoptosis and its levels are found decreased in patients with breast cancer [89,96].

A comprehensive metabolomic atlas of TNBC was created by Xiao et al. through profiling the polar metabolome and lipidome in 330 TNBC samples and 149 associated normal breast tissues. This study identified three different metabolomic subgroup by combining transcriptome and genomic data with metabolome data. C1 was distinguished by the enrichment of ceramides and fatty acids; C2 was characterized by the overexpression of metabolites associated with glycosyl transfer and oxidation reactions; and C3 had the least amount of metabolic dysregulation. There was overlap between the metabolomic C1 subtype and the transcriptomic luminal androgen receptor (LAR) subtype. Sphingosine-1-phosphate (S1P), an intermediary of the ceramide pathway, is a possible therapeutic target for LAR tumors, according to experiments conducted on patient-derived organoid and xenograft models. Furthermore, machine-learning techniques were able to differentiate between two prognostic metabolomic subgroups (C2 and C3) within the transcriptome basal-like immune-suppressed (BLIS) subtype. For high-risk BLIS tumors, demonstrate that N-acetyl-aspartyl-glutamate (NAAG) is an important tumor-promoting metabolite and a possible therapeutic target [119].

CONCLUSION

Triple-negative breast cancer represents a biologically and genetically diverse entity marked by high genomic instability and limited therapeutic options. Through this review, we underscore the critical role of next-generation sequencing and integrative multi-omics analysis in unraveling the molecular underpinnings of TNBC. Recurrent genetic alterations such as TP53, BRCA1/2 mutations, PI3K/AKT/mTOR pathway dysregulation, and significant copy number variations highlight key oncogenic drivers and potential therapeutic vulnerabilities. Moreover, transcriptomic and epigenetic profiling have unveiled subtype-specific signatures and novel biomarkers with diagnostic, prognostic, and predictive value. Metabolomic shifts further reflect tumor metabolism and may serve as non-invasive indicators of disease progression and treatment response. Despite ongoing challenges due to intra tumoral and interpatient heterogeneity, multi-dimensional profiling holds promise in guiding targeted therapy and personalized treatment strategies. Future research must focus on clinical validation of identified biomarkers and integration of omics data into routine care to transform the management of TNBC.

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