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REVIEW

Genetic heterogeneity and metabolic reprogramming in breast cancer

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ABSTRACT

Breast cancer is the most prevalent cancer and the leading cause of cancer-related mortality among women. Recent breakthroughs in breast cancer therapeutics have significantly enhanced outcomes for hormone receptor-positive and HER2-negative subtypes. However, the emergence of drug resistance, particularly in triple-negative breast cancer, presents a formidable challenge. The intricate interplay of genetic and metabolic diversity within breast cancer cells is pivotal to its development. By reprogramming metabolic pathways, cancer cells can adapt and thrive, meeting the demands of survival, growth, and invasion. These metabolic shifts also play a key role in the development of resistance to conventional therapies. This review explores the genetic and metabolic complexities of breast cancer, emphasizing the diverse subtypes and their unique profiles. We examine how genetic variations and metabolic alterations contribute to breast cancer development and progression, influencing both treatment efficacy and resistance. By integrating insights into the genetic background and metabolic reprogramming of breast cancer subtypes, this review aims to highlight the genetic variations and metabolic alterations that contribute to the pathogenesis of breast cancer, with a vision of advancing more precise and effective targeted therapies as well as discovering of novel diagnostic and prognostic markers.

Keywords: pathogenesis, breast cancer, genetics, biochemistry, metabolism.

INTRODUCTION

Breast cancer (BC), the most common cancer in women, was the second most common cancer in 2022 and accounted for 22% of all female malignancies. It is the leading cause of cancer-related death in women and is becoming more common [1]. BC is both genetically and molecularly heterogeneous disease with several subgroups that represent a wide variety of tumors with different morphological, biochemical, and clinical characteristics. There are several techniques and criterias to classify BC with different purposes. According to prognostic receptor expressions, BC is currently classified as luminal A, luminal B, HER2-positive, and triple-negative [2]. These BC subtypes show different biological behaviors and responses to therapy, which emphasizes the value of individualized treatments.

Research has shown that there are numerous metabolic and genomic changes in BC and this opens the door for the development of novel treatment approaches. Since current treatments are still insufficient despite the advancements, there is still a need for more effective therapies. The majority of BC cases are sporadic; approximately 5-10% of cases demonstrate hereditary traits [3]. Certain pathogenic variations in genes, such as *TP53, BRCA1, BRCA2, ATM, PALB2, CHEK2, BARD1, RAD51C*, and *RAD51D*, are linked to an increased risk of BC [4]. Furthermore, several low-penetrance

alleles and their various combinations is considered responsible for a significant part of BC susceptibility [5].

The metabolic alterations in BC, including glucose, lipids, and amino acids metabolism, show the adaptability of cancer cells and their ability to survive even in challenging conditions [6]. The Warburg effect highlights the metabolic alterations that, through increased glycolysis and disrupted lipid and amino acid metabolism, support tumor growth and survival [7]. These metabolic shifts are one of the major causes of treatment resistance and being crucial for the growth of tumors [8].

In conclusion, combining metabolic and genetic knowledge is important for developing accurate and effective treatments due to different BC subtypes have distinct metabolic changes [9]. To develop novel and focused treatments, more research is required to elucidate the intricate relationships between genetic alterations and metabolic pathways.

Subtypes of BC

Triple-Negative (TNBC), HER2-enriched, Luminal A, and Luminal B are the commonly identified subtypes of BC [10]. It is necessary to understand these various subtypes in order to create individualized and successful therapies for BC patients.

Luminal A

Luminal A subtype is defined by the presence of estrogen receptor (ER) and/or progesterone receptor (PR) and the lack of human epidermal growth factor receptor 2 (HER2). This subtype has a less than 15% expression of Ki-67. Luminal A carcinomas are low grade, slow growing, and have the best prognosis with less incidence of relapse and a higher survival rate [2, 11, 12]. These cancers show a poor response to chemotherapy and a high response to hormone therapy [13].

Luminal B

Compared to luminal A, luminal B tumors are of a higher grade, grow more quickly, and have a worse prognosis. They are characterized by being ER-positive, can be PR-negative, overexpression or gene amplification of HER2, and have expressions greater than 15% of Ki-67 [14, 15]. Compared to the Luminal A subtype, this group responds better to chemotherapy and benefits from hormone therapy [16].

HER2-positive

The HER2-positive tumors are characterized by high expression of HER2 with or without lack of ER and PR. There are two subgroups of this subtype: HER2-positive (HER2-positive, ER-negative, PR-negative, Ki-67>30%) and luminal HER2 (ER-positive, PR-positive, HER2-positive, and Ki-67:15–30%) [17]. The HER2-positive subtype is usually more aggressive than the luminal subtypes and can be treated with chemotherapy and HER2-targeted treatments such as trastuzumab and pertuzumab [18]. Despite being aggressive high-grade tumors, they respond very well to chemotherapy. Additionally, tyrosine kinase inhibitors such as neratinib and lapatinib can also be used [19].

Triple-negative

TNBC subtype consists of ER-negative, PR-negative, and HER2-negative tumors. TNBC can be divided into additional subgroups including basal-like (BL1 and BL2), mesenchymal, claudin-low, luminal androgen receptor, and immunomodulatory. Within these subgroups, the BL1 and BL2 are the most prevalent [20]. Since the triple-negative subtype is not responsive to hormone therapy or targeted therapies, it is more challenging to treat and generally more aggressive than the other subtypes [21]. However, not all TNBCs respond to chemotherapy, and the main reason for treatment failure in TNBC is drug resistance [22]. Moreover, TNBC tumors have increased cell proliferation, DNA repair gene alterations as well as genomic instability [2]. However, there are some benefits from immune checkpoint inhibitors, and researching the mechanism of chemotherapy resistance is especially crucial in TNBC [23].

Genetic Risk Factors for BC

Several genes are found to be associated with the BC development risk. These genes are divided into three groups: high-penetrance, moderate-penetrance, and low-penetrance mutations. The relative risks for developing BC are ≥ 5, between 1.5 and 5, ≥1.01 and <1.5 for high-penetrance, moderate-penetrance, and low-penetrance mutations, respectively [24].

Germline Genetic Mutations in BC

Most of the BCs are sporadic. Hereditary predisposition is responsible for 5–10% of all BCs [25]. Approximately 50% of all cases of familial BC are hereditary [26]. And hereditary disposition to BC is important for patient treatment and follow-ups. Germline mutations in BC can be classified as high, moderate, and low penetrance mutations. These genes and their effect on metabolism will be discussed in further sections.

High Penetrance Mutations

BRCA1 and BRCA2

BC susceptibility gene 1 *(BRCA1)* and *BRCA2* are the most common tumor suppressor genes mutated in BC, and they play a critical part in DNA repair, cell cycle control, and chromosomal integrity in healthy cells [27]. The coding region of *BRCA1* is located on chromosome 17q12-21. It has been linked to over fifteen distinct transcription-related proteins, either in transcriptional repression or activation, and apoptosis. *BRCA1* helps maintain genomic stability as a tumor suppressor. It interacts with several proteins to generate complexes that are important in DNA repair processes and recognition [28-30]. The *BRCA2* gene is found on chromosome 13q12-13. The gene could play a role in the final differentiation of breast epithelial cells and codes for proteins involved in transcription, cell cycle regulation, and DNA repair [28, 29]. Cells with non-functional BRCA1/BRCA2 proteins experience severe impairment in their capacity to repair DNA double-strand breaks (DSBs) [27].

Accordingly, it is well documented that pathogenic variants in *BRCA1/BRCA2* are correlated with the occurrence of BC in both males and females [31]. About 1 in 400 to 800 women in the total population have a germline pathogenic variant in *BRCA1 or BRCA2* [32, 33]. The risk of BC is increased in *BRCA1* and *BRCA2* carriers with a family history of breast cancer compared to the normal population. Women with a mutation in *BRCA1 or BRCA2* and several affected relatives who were diagnosed at a young age have an 80% to 90% lifetime probability of developing BC [34]. Young women are more likely to develop BRCA-associated BC, and BRCA-positive cancers are generally high-grade and hormone receptor-deficient, compared to sporadic disease [35].

In cases where tumors carry deletions in the *BRCA1/BRCA2* genes, they exhibit higher vulnerability against DNA-damaging substances and Poly (ADP-ribose) polymerase family member (PARP) inhibitors [36]. However, a study has examined the clinical outcome of BC patients with *BRCA1* and *BRCA2* variants according to molecular subtypes. Results suggest that the prognostic utility of *BRCA1/BRCA2* germline mutations in BC patients is determined by the molecular subtypes and additionally, with a survival advantage only shown in women with TNBC [37]. This underscores the importance of comprehending the complex network between genetic background and diverse subtypes of BC for better clinical outcomes.

Tumor Protein 53 Gene (TP53)

The tumor protein 53 gene (*TP53*) serves as a tumor suppressor and is responsible for encoding the p53 protein. This gene is located on chromosome 17p13.1. Found within the cell nuclei, The p53 protein directly binds to DNA and reacts to diverse cellular stressors such as chemicals, radiation, and ultraviolet rays from the sun, thereby managing the expression of target genes. Moreover, p53 plays a role in regulating processes like the cell cycle, apoptosis, senescence, and DNA repair [38, 39]. Approximately 30% of BC tumors exhibit mutations in *TP53*, and from a clinical standpoint, the *TP53* status serves as a significant predictive indicator of the response to chemotherapy. [40]. Considering the different subtypes of BC, interestingly, *TP53* is more frequently mutated in ER-negative subtypes than in ER-positive subtypes, ~50% vs~15% respectively.

The Phosphatase Tensin Homolog Gene (PTEN)

The phosphatase tensin homolog gene (*PTEN*) gene encodes tumor suppressor PTEN protein that controls chromosomal integrity, modulates the activity of inositol 1,4,5-trisphosphate receptors, controls apoptosis, transcription, and cell proliferation [41, 42].

PTEN downregulation in BC is linked to an aggressive tumor type, poor prognosis, and lymph node metastases since it triggers the pro-survival pathway PI3K/AKT, which has been shown to be a significant proliferative pathway [43]. PTEN plays a role in the onset and advancement of BC through various mechanisms, such as germline and somatic

mutations in the *PTEN,* loss of heterozygosity at the *PTEN* locus, silencing by methylation of the *PTEN* promoter, protein interactions which decrease *PTEN* transcription, degradation PTEN protein, and post-translational modifications in PTEN protein [44].

Cadherin 1 (CDH1)

Cadherin 1 (*CDH1*) is a tumor suppressor gene that encodes E-cadherin, and functions as a calcium-dependent adhesion molecule facilitating cell-to-cell interactions in epithelial cells [45].

Mutation in the *CDH1* gene can cause invasive lobular carcinoma of the breast [46]. Female mutation carriers of *CDH1* have a 37% lifetime likelihood of developing BC [47].

RAD51C and RAD51D

The genes *RAD51C (FANCO)* and *RAD51D* encode the proteins RAD51C and RAD51D, both of which are part of the RAD51 protein family taking a role in DNA double-strand repair, are essential for processes like non-homologous end joining (NHEJ) and HR. Individuals with germline mutations in *RAD51C* and *RAD51D* have heightened susceptibility to BC, particularly ER-negative BC [4, 48, 49].

STK11

Human Serine/threonine kinase gene (*STK11*) mutations also increase the BC risk [50].

DNA Mismatch Repair (MMR) pathway genes

The last but not the least, DNA Mismatch Repair (MMR) pathway genes including MutL homolog 1 (*MLH1*), mutS homolog 2 (*MSH2*), (*MSH6*), and postmeiotic segregation increased 2 (*PMS2*) cause genome instability and frequently are seen in the patients with hereditary BC [51].

Moderate Penetrate Mutations

Partner and localizer of BRCA2 (PALB2)

Partner and localizer of BRCA2 *(PALB2)* is encoded on chromosome 16p12.2. *PALB2* interacts with *BRCA2* and participates in HR pathways and *PALB2* also increases *RAD51* strand invasion activity [52-54].

Biallelic mutations in *PALB2* cause Fanconi anemia, while monoallelic *PALB2* mutation carriers have an increased risk of developing multiple cancers, especially BC [55-58].

Ataxia-telangiectasia mutated (ATM)

Ataxia-telangiectasia mutated (*ATM*) gene is located on chromosome 11q23 [59]. C 2 is an effector kinase that mediates the response to double-strand DNA breaks in the ATM/CHK2/p53 pathway [60].

ATM gene mutations can cause Ataxia Telangiectasia (AT), which is an autosomal recessive syndrome. Those AT patients who have several symptoms, such as cerebellar neurodegeneration immunodeficiency, telangiectasias, and ionizing radiation sensitivity have also significantly increased risk of cancer, especially BC. *ATM* variants, including V2424G, have the highest risk of BC incidence while *ATM D1853V*, *L546V*, and *S707P* variants have the least effect on BC incidence [59, 61, 62].

The Checkpoint Kinase 2 (CHEK2)

The Checkpoint Kinase 2 (*CHEK2*) gene encodes a checkpoint kinase that is known to interact with DNA repair proteins and regulate the cell cycle [63]. Mutations in the *CHEK2* gene increase susceptibility to BC [4].

BRCA1-associated RING domain (BARD1)

BRCA1 and *BRCA1*-associated RING domain (*BARD1*) interaction is involved in RNA processing, DNA repair (RAD51-mediated HR), regulation of cell cycle, and apoptosis [64].

Low Penetrant Mutations

Neurofibromin 1 (*NF1*) is a tumor suppressor gene and pathogenic variants of the *NF1* gene can cause Neurofibromatosis Type 1 and BC risk is increased in neurofibromatosis type 1 [65-67]. ADP ribosylation factor like GTPase 11 (*ARL11*) is also a tumor suppressor gene that plays a role in several cell regulatory functions, such as cell survival, proliferation, and apoptosis [68]. Mutation in this gene is associated with BC [69]. Some studies associate *ARL11* mutations with poor BC prognosis [70]. Overexpression of mitogen-activated protein kinase 1 E3 ubiquitin-protein ligase (*MAP3K1*) is associated with BC, particularly the luminal subtype with poor prognosis [71]. *MDM2* overexpression is associated with poor prognosis in BC [72]. MDM2 proto-oncogene negatively regulates *TP53*, and overexpression of *MDM2* is associated with

increased risk of developing BC [73, 74]. Moreover, Estrogen Receptor 1 (ESR1) has been linked to a moderately increased risk of developing BC [75]. This mutation is found in hormone receptor-positive BCs and is associated with aromatase inhibitors [76]. Mutations in *ABRAXAS1* are associated with DNA repair defects along with *BRCA1* dysfunction, so there is an elevation in BC risk by impairing *BRCA1* function [77]. Germline mutations in the *PARP4* gene are associated with thyroid cancer as well as BC [78]. Additionally, studies also show that vascular endothelial growth factor (*VEGF*), fibroblast growth factor receptor 2 (*FGFR2*), caspase 8, Lymphocyte-specific protein 1, *TNRC9, H19, TOX* high mobility group box family member 3, are other low penetrant variants associated with BC [79].

The development of BC follows a multi-step process, with each stage linked to specific mutations in critical regulatory genes. The progression model differs between sporadic and hereditary BC. Figure 1 provides an overview of the key genes involved and their roles in both hereditary and sporadic BCs [80].

In conclusion, BC encompasses a wide array of pathological variants, adding to the complexity of the disease. These variants present promising targets for novel drugs, and also exploring new pathological variations can enhance screening initiatives. Moreover, such investigations are vital for unraveling drug resistance mechanisms in BC.

Significant Pathways in BC

BC development is influenced by complex genetic and molecular pathways. Besides, interactions among signaling pathways in cell metabolism have a crucial role in BC development as well. Therefore, concentrating therapeutic efforts on these altered biochemical pathways is essential, as it offers the potential to improve clinical outcomes and advance the creation of effective treatment strategies.

Gene	Locus	Role in Hereditary BC	Role in Sporadic BC
BRCA1	17q12-21	Germline mutation (HBOC syndrome)	Inactivation by hypermethylation of the BRCA1 promotor region
BRCA2	13q12-13	Germline mutation (HBOC syndrome)	Silenced via overexpressed EMSY
PTEN	10q.23-24	Germline mutation (Cowden Disease syndrome)	Rare
TP53	17p13.1	Germline mutation (Li-Fraumeni syndrome) TP53 mutations frequent in BRCA1 and BRCA2 mutant breast cancers	Rare
Rb1	13q14.1	No specific role	Late Event
CDH1	16q22.1	No specific role	Early event in lobular breast
CCND1	11q13	Frequently underexpressed in BRCA1 mutant breast cancers	Overexpressed in 30-40%
MYC	8q24	No specific role	Overexpressed in 25-30%
ERBB2/Her2/neu	17q21	Frequently underexpressed in BRCA1 mutant breast cancers	Overexpressed in 25-30%
ERα	6q25.1	Frequently underexpressed in BRCA1 mutant breast cancers	Underexpressed in 25%
ERβ	14q22-24	Not known	Not known

Figure 1. The key genes and their roles in both hereditary and sporadic BCs

Homologous Recombination Pathway in BC

The cellular genome is continuously exposed to a variety of mutagenic substances, such as oxidants, alkylating agents, ultraviolet light, and ionizing radiation. The maintenance of genomic integrity and DNA repair are ultimately made possible by DNA damage response pathways. Human DNA repair pathways include inter-strand crosslink repair, base excision repair, nucleotide excision repair, MMR, direct damage reversal, and the DSBs repair pathways as HR and NHEJ [81].

Some nucleases, such as the MRE11/RAD50/NBS1 complex, facilitate the formation of 3'-terminal single-stranded DNA (ssDNA) by cleaving the 5'ends of DSBs. The formation of the Rad51 nucleoprotein filament results from the initial binding to the ssDNA by replication protein A, which is later replaced by RAD51. BRCA2 and RAD52 are two important mediators in this process. The RAD51 filaments, with the assistance of PALB2 and RAD51AP1, interact with homologous double-stranded DNA to create a D-loop structure. The D-loop is then disassembled by FANCM, which ends in a non-crossover product. Furthermore, the double Holliday junction structure created during the DSB repair can be resolved by the Bloom syndrome protein (BLM)-Topoisomerase IIIα (TopoIIIα) helicase-topoisomerase complex, producing a non-crossover product [82].

HR deficiency (HRD) is caused by defects in DNA damage repair mechanisms, especially in the HR repair process, which is essential for the repair of DSB [83, 84]. Genomic instability brought on by HRD is a major contributing factor in the development of cancer [83]. Many different mechanisms, such as epigenetic modifications, mutations in genes associated with HR, and indirect interactions between BRCA proteins and other DNA repair proteins, can also cause HRD [85]. HRD is found in various subtypes of primary BC, though its prevalence varies among BC subtypes. In TNBC, HRD is estimated to occur in 50-60% of cases [86]. HRD is less common, but still significant, in hormone receptor-positive (ER-positive/HER2-negative) BCs, ranging from 14–20% [86]. Notably, defects in BRCA1/2 and elevated HRD scores are observed across all BC subtypes, including ER-positive/HER2-negative, ER-negative/HER2-positive, and ER-positive/HER2-positive BC [87]. This finding suggests that HR defects in genes other than *BRCA1/2* are present across all BC subtypes. However, the specific genetic causes of HRD vary by cancer type [83]. For example, almost all triple-negative tumors have methylation in the *BRCA1* promoter region [87]. In conclusion, all other BC subtypes exhibit HRD to varied degrees, although TNBC exhibits the highest frequency of HRD. This finding has important treatment implications. Independent from their BC subtype, patients with HRD tumors may benefit from treatments which target this deficiency, such as PARP inhibitors or platinum-based chemotherapy.

HRD has significant importance in BC treatment, especially for patients with *BRCA1/2* mutations or other defects in the HR repair pathway [88, 89]. Since HRD is linked to sensitivity to DNA-damaging substances like platinum salts and PARP inhibitors, it is an essential biomarker for treatment choices [88, 90]. Remarkably, patients with BC who do not have germline or somatic mutations in *BRCA1/2* or other known HR-related genes can still have HRD. High HRD scores have been associated with mutations in genes, such as *LRP1B, NOTCH3, GATA2,* and *CARD11*, which may increase the number of patients who could benefit from PARP inhibitors and platinum-based chemotherapy [91]. Additionally, the overexpression of certain DNA helicase genes correlates with high HRD scores in both *BRCA*-mutated and *BRCA* wild-type BCs [92].

The phosphatidylinositol 3-kinase (PI3K)/ protein kinase B (AKT)/mammalian target of rapamycin (mTOR) Pathway

One important signaling pathway connected to BC is the PI3K/AKT/mTOR pathway, which is often deregulated in luminal BC [93]. This pathway participates in cell proliferation, migration, apoptotic cell death, DNA repair mechanism and glucose metabolism. It increases angiogenesis, survival, growth, and proliferation of BC cells [94]. Even in normoxic settings, the altered PI3K/AKT/mTOR pathway in BC cells are able to increase hypoxia-inducible factor 1 alpha (HIF-1α), which activates genes related to glycolysis and glucose uptake. Further, tumor development and carcinogenesis are influenced by HIF-1α [95]. Additionally, Hexokinase II, which is essential for cancer cells to survive and adjust to the varying cellular environment, is upregulated by PI3K/AKT/mTOR pathway [96]. AKT phosphorylates numerous cellular proteins, such as MDM2, FOXO, BCL2-interacting mediator of cell death, BCL2-associated

agonist of cell death, and glycogen synthase kinases 3α (GSK3α) and 3β (GSK3β), in order foster cell survival and promote cell cycle progression [97]. Additionally, the PI3K/AKT/mTOR pathway is a major contributor to resistance against standard therapies in BC. It has emerged as a novel target for overcoming drug resistance in recent years [98].

Wnt Signaling Pathway

The Wnt signaling pathway controls the capacity of self-renewal and differentiation potential of stem cells in humans [99]. There are two types of Wnt signaling pathways: canonical and noncanonical. β-catenin is the main effector molecule in the canonical Wnt signaling pathway. β-catenin interacts with transcription factors belonging to the T cell factor/lymphoid-enhanced binding factor 1 (TCF/LEF1) family. The key regulator steps in this pathway are the stabilization and presence of β-catenin in the cytoplasm, and then its translocation into the cell nucleus, so it can bind to TCF/LEF1 and triggers target gene expression [100]. Without the Wnt signal, the axin-APC complex anchors β-catenin, which is subsequently phosphorylated by casein kinase Iα (CKIα) and GSK3β. The 26S proteasome degrades β-catenin as a result of this phosphorylation, which prepares it for ubiquitination by the SKP1–cullin1–F-box (SCF-β-TRCP) E3 ubiquitin ligase. Wnt inactivates the axin-APC destruction complex by recruiting the intracellular signaling protein dishevelled (DVL) after binding to the frizzled (FZD) and LRP5/6 coreceptors. This mechanism prevents β-catenin from degrading, enabling it to enter the nucleus and initiate transcription [101, 102]. Noncanonical Wnt signaling pathways are independent of β-catenin. The PCP pathway and the Ca^{2+} pathway are the two primary types of these pathways. In order to initiate non-canonical Wnt signaling, Wnt5a and Wnt11 bind to different receptors such as RYK, ROR2, ROR1, or the Fzd family [103, 104].

Dysregulation of the Wnt signaling pathway is common in various cancer types, and it is involved in BC development and progression like other cancers [105]. Each of the Wnt/β-Catenin, Wnt-PCP, and Wnt-Ca^{2+} signaling pathways contribute differently to the development of BC and share overlapping components [106].

Genome-wide sequencing and gene expression profile analysis has demonstrated that the Wnt signaling pathway has an important part in BC metastasis and proliferation [106]. Wnt signaling is also crucial for maintaining stemness, regulating the immune microenvironment of BC, producing treatment resistance, and developing cancer phenotypes, according to recent research [106]. Furthermore, the WNT/β-Catenin pathway has a role in the development of TNBC [107, 108].

WNT signaling causes the shifting to Warburg phenotype in BC cells by upregulating phosphofructokinase platelets (PFKP). Furthermore, WNT3A triggers the activation of the epidermal growth factor receptor (EGFR), which in turn activates the PI3K/Akt pathway. This activation enhances the glycolytic phenotype, cell division, and migration potential of cancer cells by phosphorylating and stabilizing PFKP [109, 110]. Studies show that the WNT β-catenin pathway increases the M2 isoform of pyruvate kinase in BC cells, which increases glycolysis and stemness in BC cells [111]. Additionally, the canonical WNT/β-catenin signaling pathway suppresses mitochondrial respiration by reducing the ATP synthase subunit expression, cytochrome c oxidase, and cytochrome c1. As a result, aerobic glycolysis increases [112, 113].

The Wnt signaling pathway interacts with a variety of proteins. The adenomatous polyposis coli (APC) gene serves as a vital regulator within the Wnt pathway, functioning as a tumor suppressor gene [106]. A transcription factor called ΔNp63 increases the expression of the Wnt receptor Frizzled Class Receptor 7 (Fzd7), which in turn increases the activities of mammary stem cells. BC stem cells (BCSCs) use this certain mechanism as well, to facilitate tumor growth in TNBC [114].

The Wnt signaling pathway can also be controlled by micro-RNAs (miRNAs). The levels of Lethal-7 (let-7) miRNAs are dramatically reduced in the MCF-7 BC cell line and reintroducing them can suppress the proliferation of BC cells [115]. Stearoyl-Coenzyme A desaturase 1, an enzyme necessary for Wnt signaling activation, is the direct target of miR-600. Inhibiting miR-600 results in the proliferation of BCSCs, while increasing its expression might reduce BCSC self-renewal [116, 117]. In addition, BCSCs go into a quiescent state when Wnt signaling becomes inactivated, which makes them drug-insensitive and leads to multidrug resistance in BC [118].

Moreover, AF1q, a protein associated with poor prognosis in various cancers, especially BC, has been linked to the activation of the Wnt signaling pathway. Protein AF1q increases BC cells' ability to form spheres by promoting the development of stem-like populations via the activation of the Wnt pathway [119]. This finding suggests the relationship between cancer stem cells, Wnt signaling, and the development of BC.

In summary, the Wnt signaling pathway exerts a significant role in BC development and affects many aspects of tumor biology. It may be achievable to improve treatment options by comprehending the mechanisms of Wnt signaling in BC [106]. One possible treatment strategy for BC is to target particular Wnt pathway components, such as CDK14, which is upregulated in TNBC [120].

Nuclear factor κ-B (NF-κB) Pathway

The non-canonical NF-κB pathway increases the expression of Indoleamine 2,3-dioxygenase (IDO). Higher IDO activity contributes to immunosuppression, tumor metastasis, and is associated with poor prognosis [121, 122].

Lactic acid, formed as a result of anaerobic respiration in cancer cells, is released outside the cell via MCT4 and taken into endothelial cells via MCT1, which causes tumor angiogenesis via the NF-κB/IL-8 pathway [123]. In BCs with BCL2 overexpression, the anti-apoptotic effect of BCL2 is enhanced by NF-κB [124].

Notch Signaling Pathway

The Notch pathway is a highly conserved cell signaling pathway in eukaryotes. The Notch signaling pathway is activated in both malignant and normal stem cells, and it is essential for stem cell maintenance, differentiation, proliferation, and cell fate determination. Normal stem cells are able to maintain a balance between self-renewal, differentiation, and proliferation through interactions with various signaling networks, including the JAK-STAT pathway [125]. Likewise, the abnormal stimulation of Notch signaling pathways facilitates the self-renewal, cell proliferation, and metastasis of BCSCs [126]. Therefore, it is considered that the Notch signaling pathway is essential for determining the destiny of BCSCs [127]. The invasion, mesenchymal-like characteristics, and drug resistance of BCSCs can be stimulated and maintained via the Notch pathway via JAG-1 and NOTCH-4 [128, 129]. MAP 17 (PDZKIP1) stimulates the Notch pathway, inhibits NUMB activity, and encourages BCSC maintenance [130]. The NUMB protein suppresses the Notch pathway and blocks the Notch intracellular domain (NICD) in the cytoplasm of non-cancerous cells. miR-146a stimulates the Notch pathway, inhibits NUMB activity, and causes BCSCs to proliferate [131]. Notch signaling induces stemness by promoting the deacetylation and subsequent activation of ALDH1A1 [132]. Furthermore, there is a high correlation between the Notch signal and BCSC Ki-67 expression [133]. The normal epithelial cell transition into malignant BC cells is also induced by the Notch pathway [134]. The pathway's ability to crosstalk with other signaling systems, such as PI3K/AKT, NF-κB,, and miRNAs, further emphasizes its importance in precisely regulating cell fate [135]. In addition, a study suggests that Notch signaling regulates NF-κB activity and mitochondrial metabolism in TNBC cells through IKKα-Dependent Non-Canonical pathways. [136]. Since utilizing inhibitors that target the Notch signaling pathway has demonstrated effectiveness in reducing the BSCS population, BC treatment responsiveness may be enhanced by inhibitors of the Notch signaling [137]. Besides, in TNBC cases with mutated *Notch1* and wild-type *PTEN* expression, combination therapies that target the intersection of the Notch, AKT, and NF-κB pathways may also have therapeutic uses in regard to BCSCs [136].

HIF-1 Alfa Pathway

HIFs-mediated downstream pathways, mainly VEGF, can trigger angiogenesis in BC [138]. It is shown that proline residues P402 and P564 of the human HIF-1α ODD domain are hydroxylated by prolyl hydroxylase domain proteins (PHDs), under normoxic conditions [139]. This hydroxylation process is essential for the HIF-1α protein to bind the von Hippel-Lindau protein (pVHL) [140]. As the recognition subunit of an E3 ubiquitin ligase, VHL attaches a poly-ubiquitin chain to HIF-1α, directing the proteasome to degrade HIF-1α [141]. Transactivation function of HIF-1α under normoxic conditions is also inhibited by Factor İnhibiting HIF-1 (FIH-1)'s oxygen-dependent hydroxylation of the asparagine residue N803 in HIF-1α, which also prevents HIF-1α interactions with the coactivators p300 and CBP (CREB binding protein) [142].

HIF-1α can reduce the expression of the tricarboxylic acid (TCA) enzymes, accelerate glycolysis and lactic acid accumulation, and result in immunosuppression and angiogenesis [143]. HIF-1α increases glucose uptake by cancer cells through increasing the expression of glucose transporter 1 (GLUT1) [144]. Moreover, HIF-1α elevates pyruvate dehydrogenase kinase (PDK) activity, which suppresses pyruvate dehydrogenase (PDH). This inhibition leads to a decreased flux of pyruvate into TCA. In addition, HIF-1α raises lactate dehydrogenase (LDH) activity, which converts pyruvate to lactate [145].

α-Ketoglutarate (αKG) Signaling

Within tumor cells bearing Isocitrate dehydrogenase mutations, there is a reduction in α-KG levels, resulting in heightened levels of HIF-1α and a greater recurrence rate [146]. Elevated α-KG levels are linked to reduced tumor metastasis as a result of augmented DNA demethylation, hindered cell migration, and the downregulation of Zeb1 [147]. Despite indications of the potential tumor-suppressive effects of αKG, its regulatory impact on BC is not yet fully understood, emphasizing the necessity for further research to validate this role.

STAT3 Pathway

Signal transducer and activator of transcription 3 (STAT3) is a tumor diagnostic marker and is known to increase BC malignancy [148]. The activation of STAT3 is triggered by different receptors, including the IL-6 receptor, tyrosine kinase receptors, fibroblast growth factor receptors, and platelet-derived growth factor receptors. In addition, toll-like receptors, G protein-coupled receptors, and receptors like EGFR, SRC, and ABL are involved in this process [149].

It is known that the increased activity of the STAT3 pathway is linked to increased BC progression, proliferation, metastasis, and chemoresistance with decreased apoptosis [148]. Upregulation of STAT3 increases IDO expression through the non-canonical NF-κB pathway, leading to tumor metastasis [150]. In cancer cells, STAT proteins promote aerobic glycolysis via upregulating the expression of MYC and HIFs [151]. These factors are important drivers of the Warburg effect, enhancing the expression of genes that encode main glycolytic enzymes and proteins which are responsible for glucose uptake. Additionally, STAT3 specifically regulates several glycolysis-related genes, including *HK2, PKM, SLC2A1* (which encodes GLUT1), *SLC2A3* (which encodes GLUT3) and enolase 1 (*ENO1)* [152]. Furthermore, in mitochondria, STAT3 is involved in controlling the activity of the electron transport chain, which produces reactive oxygen species (ROS) [149]. As a result, treatment with STAT3 inhibitors alone or combined with other therapeutic medications may have more encouraging results when it comes to reducing or eliminating chemoresistance in BC.

RHOA/ROCK/GLUT1 pathway

TP53, can induce cell cycle arrest, apoptosis, and control tumor cell metabolism by inhibiting the effect of *TP53* on glycolysis through the suppression of GLUT1, GLUT3, and GLUT4 expression and the regulation of the enzymatic expression of HK2, PFK1, PDH, PDK2, phosphoglycerate mutase, and parkin 2 [153]. Mutated *TP53* contributes to tumorigenesis through increasing glycolysis via activating the RhoA/ROCK/GLUT1 signaling pathway, since this pathway causes the GLUT1 translocation to the plasma membrane [154].

SNAIL/E-Cadherin Pathway

The transcription factor SNAIL induces epithelial-to-mesenchymal transition (EMT), and its inhibition promotes mesenchymal-to-epithelial transition breast epithelial cells, enhancing cancer stem cell-like characteristics [155]. Phosphoglucoisomerase (PGI)/Autocrine motility factor (AMF) is linked to the downregulation of epithelial markers, such as E-cadherin, through the SNAIL/E-Cadherin pathway [156]. Moreover, the high expression of Snail and low expression of E-cadherin is found in adriamycin-resistant human BC MCF-7/ADM cells [157]. These point towards a promising research direction for targeted drug-resistant BC therapy, which could potentially provide valuable clinical guidance for BC therapy and prognosis evaluation.

As a summary, we highlighted the key genetic pathways in BC in Table 1.

Metabolic Alterations in BC

In recent years, extensive focus in cancer research has shifted towards understanding the dysregulation of cellular metabolism within cancer cells, as it is now recognized as a key hallmark of cancer. Growing evidence suggests that the disrupted cellular metabolism could significantly

Table 1. Key genetic and molecular pathways in BC

Pathway	Role in Cancer
HER2/ERBB2 Pathway	Overexpression or amplification of the HER2/ERBB2 gene leads to aggressive tumor growth and resistance to apoptosis.
Hormone Receptor (ER/PR) Pathway	Mutations or overexpression can drive hormone-dependent BC proliferation.
PI3K/AKT/mTOR Pathway	Mutations in PIK3CA or loss of tumor suppressor PTEN activate this pathway, promoting growth and therapy resistance.
TP53 Pathway	Mutations in TP53 are common in aggressive BCs, particularly triple-negative subtypes.
BRCA1/BRCA2 Pathway	Mutations increase the risk of breast and ovarian cancers by impairing DNA repair.
Wnt/β-Catenin Pathway	Dysregulation, often through mutations or overexpression, contributes to tumor progression and metastasis.
Notch Pathway	Overactivation promotes tumorigenesis, stemness, and therapy resistance.
NF-κB Pathway	Chronic activation supports cell survival, proliferation, and angiogenesis.
MYC Pathway	Amplification or overexpression leads to uncontrolled proliferation and metabolic reprogramming.

contribute to the development of drug resistance in cancer patients. According to the principles of the Warburg effect, cancer cells exhibit a preference for glycolysis whether there is oxygen availability or not, indicating the presence of mitochondrial dysfunction [7]. This metabolic shift is illustrated in Figure 2. The other theory, "the reverse Warburg effect" indicates that cancer cells enhance aerobic glycolysis in tumor-associated fibroblasts, and lactate and pyruvate produced by these cells promote tumor growth and development [158]. This concept of metabolic reprogramming encompasses not only glucose metabolism but also extends to lipid and amino acid metabolism [6]. The observed metabolic reprogramming in resistant BC cells holds substantial therapeutic promise. This highlights the opportunity to exploit metabolic vulnerabilities for therapeutic advantages in BC management.

Altered Glucose Metabolism in BC

The reprogramming of glucose metabolism in cancers facilitates the energy needs of rapidly growing cancer cells. Abnormal expressions of glycolytic-related enzymes can promote oncogenesis, support tumor growth, and contribute to treatment resistance. Studies have shown that key glycolytic enzymes such as HK, PFK, ENO, PK, and LDH are upregulated in BC, as well as GLUTs [159-162]. However, molecular and metabolic heterogeneity are characteristics of BC. While TNBC is linked to the Warburg effect and mixed types, the luminal-A subtype often displays the reverse Warburg effect [163]. Studies also show that wild-type *TP53* inhibits glycolytic activity and enhances oxidative phosphorylation by reducing the expression of glycolytic enzymes and increasing the levels of mitochondrial proteins. Accordingly, cancer cells lacking functional p53 tend to exhibit

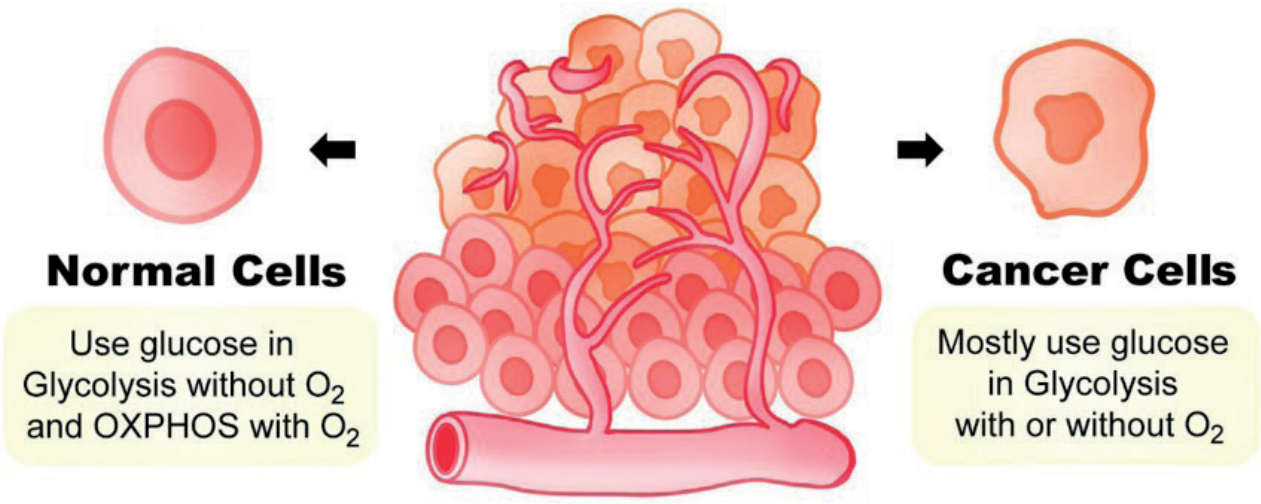

Figure 2. The warburg effect in cancer cell metabolism

metabolic reprogramming towards glycolysis, leading to an increased reliance on this pathway for energy production. This highlights the significance of the diverse molecular features present in various subtypes of BC, which contribute to the metabolic diversity observed within the disease [164].

It is known that GLUT1-mediated glucose uptake is a pivotal component in the development of BC, as the loss of a single copy of SLCA2A1, which encodes GLUT1, is adequate to prevent the neoplastic process of the Neu-induced breast tumor *in vivo* [165]. Moreover, ectopic overexpression of GLUT1 and GLUT3 has been reported to be associated with chemotherapy resistance in BC cells [166]. In line with this, TNBC which is known as the most aggressive subtype of BC, demonstrates elevated expression of GLUT1 compared to non-TNBC [167]. Compared to other subtypes, ER-positive BCs depend less on glucose uptake, favoring the consumption of lactate produced by neighboring cancer-associated fibroblasts (CAFs) [9]. Moreover, HIF-1 can also accelerate glycolysis by regulating glycolytic pathway enzymes, including HK2, LDHA, and GLUT1 as well as by reducing the expression of TCA enzymes [143].

The Pentose Phosphate Pathway (PPP) is an alternative pathway for glucose oxidation in addition to glycolysis. Due to the critical role of the PPP in facilitating tumor proliferation and enabling cancer cells to endure the impacts of ROS, elevated levels of certain PPP enzymes, like glucose 6-phosphate dehydrogenase and transketolase, are also correlated with poor outcomes in BC [168]. Some PPP enzymes, however, are primarily expressed in HER2-positive tumors, indicating that activation of PPP is fundamental in this intrinsic subtype of BC [169].

Glucose not only participates in glycolysis or the PPP but also contributes to the hexosamine biosynthetic pathway (HBP). The HBP ultimately leads to the synthesis of UDP-GlcNAc, an amino sugar that, along with other nucleotide sugars, forms the foundation for glycoprotein and glycoconjugate biosynthesis [170]. Additionally, O-GlcNAc can indirectly regulate transcription by impacting cancer metabolism. In BC cells, increased O-GlcNAcylation leads to a decrease in the TCA metabolite α-KG, resulting in reduced hydroxylation of HIF-1α and its interaction with the pVHL. As a consequence, HIF-1α is stabilized, leading to enhanced expression of its transcriptional targets, such as GLUT1, and it contributes significantly to the survival of BC cells under metabolic stress [171]. Overall metabolic alterations in different BC subtypes are summarized in Figure 3 [9]. Consequently, the comprehensive metabolic reprogramming in different BC subtypes remains to be fully revealed.

Altered Lipid Metabolism in BC Tumors

The *de novo* synthesis of fatty acids is a crucial metabolic characteristic that sets cancer cells apart from normal cells. Even though it is seen in normal cells, it is restricted to the liver, adipose tissue, and breast during lactation. Meeting the increased need for membrane production, the metabolism of fatty acids (FAs) and lipids plays a significant role in promoting the growth and progression of BC [172]. Research has demonstrated that several key enzymes involved in lipid metabolism in breast tumors, including acetyl-CoA carboxylase (ACC),

	Breast Cancer Subtypes		
Metabolic alterations	**ER+ (Luminal A, Luminal B)**	**HER+**	**TNBC**
Glycolytic Flux	Context dependent	Increased	Increased
Glutamine Catabolism	Decreased	Increased	Increased
Lipid Metabolism	Increased cholesterol biosynthesis	Increased Fatty acid biosynthesis	Increased cholesterol uptake

Figure 3. Overall metabolic alterations in BC subtypes

ATP citrate lyase, monoacylglycerol lipase (MAGL), and fatty acid synthase (FASN), are upregulated [153]. Inhibition of these enzymes can hinder tumor growth and metastasis. Notably, ACC, the enzyme that governs the rate of fatty acid synthesis, is highly expressed in BC, and inhibition of ACC results in increased cell apoptosis [173]. Furthermore, a study has reported an interaction between BRCA1 and ACC-alpha (ACCα) through the BRCA1 C-Terminal domain. Variations in the *BRCA1* gene may cause a disruption of the BRCA1-ACCα complex, which leads to increase in ACCα release and lipogenesis in breast tumor cells [174].

Additionally, the dysregulation of Acyl-coenzyme A synthetase short-chain family member 2 (ACSS2) in cancer, particularly BC, has been associated with a poorer prognosis. ACSS2 is often highly expressed in BC and acts as a metabolic immunomodulator, thereby influencing cancer progression [175].

Another enzyme found to have a role in BC pathogenesis is MAGL. MAGL is an enzyme that has shown involvement in tumor progression through energy supply by fatty acid oxidation and increased oncogenic signaling lipids like free fatty acids, monoacylglycerol, and secondary lipid metabolites. These promote migration, invasion, survival, and in vivo tumor growth, leading to increased malignancy of cancer cells [176].

The FASN enzyme can be directly activated by HER2, leading to the expression of FASN in BC cells [177]. In contrast, TNBCs demonstrate lower levels of FASN expression. As a result, HER2-positive BCs increase the *de novo* production of lipids, while TNBCs increase their lipid uptake [178]. The differences in lipid metabolism in BC subtypes are summarized in Figure 3 [9].

In BC, disruptions in lipid metabolism can result in the accumulation of free fatty acids and cholesterol within the tumor microenvironment. This accumulation has been observed to negatively impact the activation and function of immune cells. Elevated levels of free fatty acids have been linked to impaired immune function in CD8+ T cells, while increased cholesterol levels have been shown to inhibit T cell receptor signaling, causing impaired T cell proliferation and cytokine production. These effects eventually contribute to a weakened anti-tumor immune response. Moreover, increased free fatty acid levels may stimulate the production of myeloid-derived suppressor cells and immunosuppressive regulatory T cells, which efficiently inhibit the activity of effector immune cells and impede immune responses against cancer [179].

Therefore, investigating the regulatory mechanism of fatty acid synthesis and its effect on various tumor subtypes can be helpful for an accurate understanding of tumor pathogenesis and the development of more effective strategies for treatment.

Amino Acid Metabolism Alterations in BC

In BC, glutamine metabolism is significantly altered, which has a significant impact on the metabolism of amino acids. A nonessential amino acid, glutamine is necessary for many metabolic processes, including nucleotide biosynthesis and protein synthesis [180]. Glutamate dehydrogenase, cell-surface glutamine transporter ASCT2, and glutaminase-1 are among the proteins linked to glutamine metabolism that have been found to express more in HER2-positive BC than in other subtypes. This implies that there is increased glutamine metabolism activity in HER2-positive BC [181]. Compared to HER2-positive and luminal subtypes, TNBC tumors exhibit significantly higher expression of the glutaminase enzyme, which transforms glutamine into glutamic acid [181]. Therefore, exogenous glutamine is necessary for the TNBC cells to survive [182]. Not because they proliferate less, but rather because the luminal tumors themselves can synthesize glutamine through the expression of a glutamine-synthetase enzyme, these subtypes are less reliant on exogenous glutamine [54]. The differences between glutamine metabolism across different BC subtypes are shown in Figure 3.

Serine plays a vital role in providing one-carbon units crucial for DNA synthesis for cellular proliferation. Alongside the upregulation of glutamine metabolism, the increased activity in serine metabolism is associated with the heightened proliferation of tumor cells and is indicative of a poor prognosis for patients. 3-phospho-glycerate-dehydrogenase, the initial enzyme involved in serine synthesis, is fundamentally overexpressed in BC, particularly in subtypes characterized by higher proliferation rates, such as ER-negative

tumors [183, 184]. Nevertheless, these amino acids do not only participate in biosynthesis but also communicate with signaling pathways. For instance, glutamine activates mTORC1 signaling and leads to tumor proliferation [185]. Overall, these findings underscore that understanding the interplay between metabolic pathways and the distinct metabolic reprogramming across different subtypes is essential for more efficient BC therapies.

BC Heterogeneity and Immunotherapy

Tumors are recognized to adopt diverse strategies to avoid immune detection and clearance by the immune system, such as activating inhibitory pathways controlled by immune checkpoints. The administration of immune checkpoint inhibitors (ICIs) disrupts these inhibitory signals, revitalizing the anti-tumor immune response, as validated by a multitude of studies and clinical trials utilizing monoclonal antibodies targeting programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) [186].

The heterogeneity of breast tumors prompts the question of whether specific types of breast tumors may derive greater benefit from immune-based treatments, and what cellular or environmental factors within the cancer cells contribute to the likelihood of eliciting a strong and lasting anti-tumor immune response [187]. It has been suggested that BC is an immune-silent type of cancer that is less responsive to immunotherapy. Yet, mounting evidence suggests that BC encompasses a diverse range of tumors with varying levels of immunogenicity. In this spectrum, TNBC is thought to represent a particularly immunogenic subtype, and treatment with ICI has been shown to enhance clinical outcomes [188, 189]. Currently, a significant portion of BC research is dedicated to inhibiting the PD1/PD-L1 axis. A study delving into the concurrent use of PD1/PD-L1 and CTLA-4 inhibitors demonstrated a noteworthy tumor size reduction in metastatic TNBC patients with a %43 objective response rate. Intriguingly, individuals with HR-positive BC did not exhibit any responses to this combination treatment [190]. Moving forward, combining ICIs with chemotherapy, PARP inhibitors, or other therapies shows promising potential for enhancing the clinical efficacy in TNBC. However, to maximize the benefits of these treatments, it will be essential to identify reliable predictive biomarkers for patient selection. This emphasis on predictive biomarkers and understanding the tumor microenvironment paves the way for more precise and effective interventions in the future.

Conclusions

In conclusion, a comprehensive understanding of BC's genetic and metabolic features is essential for developing more effective treatment strategies. As research continues to elucidate the complex interactions among these molecular factors, the development of personalized and targeted therapies will be crucial in addressing the challenges posed by this heterogeneous disease. Integrating insights from genetic studies, signaling pathways, and metabolic reprogramming will pave the way for more precise and effective interventions, ultimately improving survival rates and quality of life for BC patients. The highlighted molecular pathways in this review can help us discover novel diagnostic and prognostic biomarkers and hopefully, new therapy targets to overcome drug resistance and off-target side effects. By using these biomarkers, eventually, we will also maximize the efficacy of current treatments and minimize their toxicities.

Author contribution

Study conception and design: YD, AB, and BC; draft manuscript preparation: YD, AB, and BC. All authors reviewed the results and approved the final version of the manuscript.

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