

Review

Metabolic and Genetic Characteristics of Different Breast Cancer Phenotypes

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Academic Editor: Kishu Ranjan

Submitted: 6 March 2026 Revised: 24 April 2026 Accepted: 11 May 2026 Published: 28 October 2026

Abstract

This review systematizes data on the characteristics of glucose, amino acid, and lipid metabolism, as well as proteomic and genetic alterations in different breast cancer phenotypes. Specifically, triple-negative breast cancer has increased aerobic glycolysis and serine metabolism, and shows glutamine dependence; estrogen-positive breast cancer has a decreased role in glucose and glutamine uptake, as the tumor prefers to consume lactate produced by adjacent cancer-associated fibroblasts; and human epidermal growth factor receptor type 2 (HER2)-enriched breast cancer has increased fatty acid synthesis, with increased glucose and glutamine uptake. However, existing breast cancer phenotyping does not always allow for the classification of samples based on their metabolic characteristics. This requires the introduction of new classification methods that will have clinical relevance. Future developments in personalized medicine may benefit from the integration of both clinical protein markers and molecular subtypes to optimize treatment selection.

Keywords: breast cancer; phenotype; metabolome; genome; amino acids; lipids; glycolysis

1. Introduction

Breast cancer (BC) is the most common cancer in women [1]. Approximately 1.7 million new cases of BC are registered worldwide annually, posing a social and medical problem due to its high mortality rate among the female population [2]. Phenotyping of BC is important for determining the prognosis and clinical course of the disease, as well as for choosing effective treatment tactics. In practical healthcare, the molecular genetic characteristics of BC are assessed using a surrogate method, through immunohistochemical testing of key biological markers of BC, such as estrogen receptors (ER) and progesterone receptors (PR) [3], human epidermal growth factor receptor type 2 (HER2) [4], and Ki-67 [5]. Based on the expression level of these biomarkers, BC tumors are divided into luminal A, luminal B HER2-negative, luminal B HER2-positive, non-luminal HER2-positive and triple-negative breast cancer (TNBC) subtypes [6,7]. Subtyping of BC can be carried out based on the expression of specific genes—Prediction Analysis of Microarray 50 (PAM50) [8]. The test helps classify tumors into four subtypes: Luminal A, Luminal B, Basal-Like, and HER2-enriched. The “normal-like” subtype of tumors is thought to be an artifact due to an excessive number of normal breast cells in the sample. This subtype is established when the volume of tumor tissue is insufficient to determine the tumor subtype [9]. The presence of “normal” tissue can lead to misclassification, which most often occurs with luminal B subtypes, which are disguised as luminal A due to “normal” tissue [10]. There is also a suggestion that some “normal-like” tumors may be classified as tumors with low claudin levels [11,12]. The correlation between molecular biological and genetic BC subtypes is shown in Fig. 1.

The clinical manifestations and molecular profiles of BC are so heterogeneous that the response to the same therapy can vary significantly. Analysis of large collections of tumor cell lines has revealed a correlation between genetic alterations and protein expression [13]. Alterations in genes responsible for metabolism are common and determine BC aggressiveness and response to therapy [14,15]. By analyzing the global metabolic profile of BC cells or tissues, it is possible to gain insight into the underlying disrupted metabolic pathways and potentially discover biomarkers for the early diagnosis and prognosis of BC [16,17,18,19]. Dysregulation of glucose and lipid metabolism, as well as abnormalities in amino acid metabolism, are known to be common pathophysiological hallmarks of BC [20]. Targeting these metabolic pathways and their associated metabolites may offer new therapeutic strategies aimed at eliminating metabolic dysregulation [20,21].

This review systematizes data on the characteristics of glucose, amino acid, and lipid metabolism, as well as proteomic and genetic alterations in different BC phenotypes.

2. Metabolic Features of BC Depending on Tumor Phenotype

Metabolomic profiles of BC molecular subtypes typically describe metabolite concentrations depending on HER2 expression and hormonal status [22,23]. Most studies have focused on the characteristics of basal-like and luminal tumors [24]. For example, the metabolic profile with positive HER2 expression is characterized by increased glycolysis, fatty acid (FA) biosynthesis, and gluconeogenesis [25]. Phenotype-specific differences have been shown depending on the response to neoadjuvant treatment [26]. In



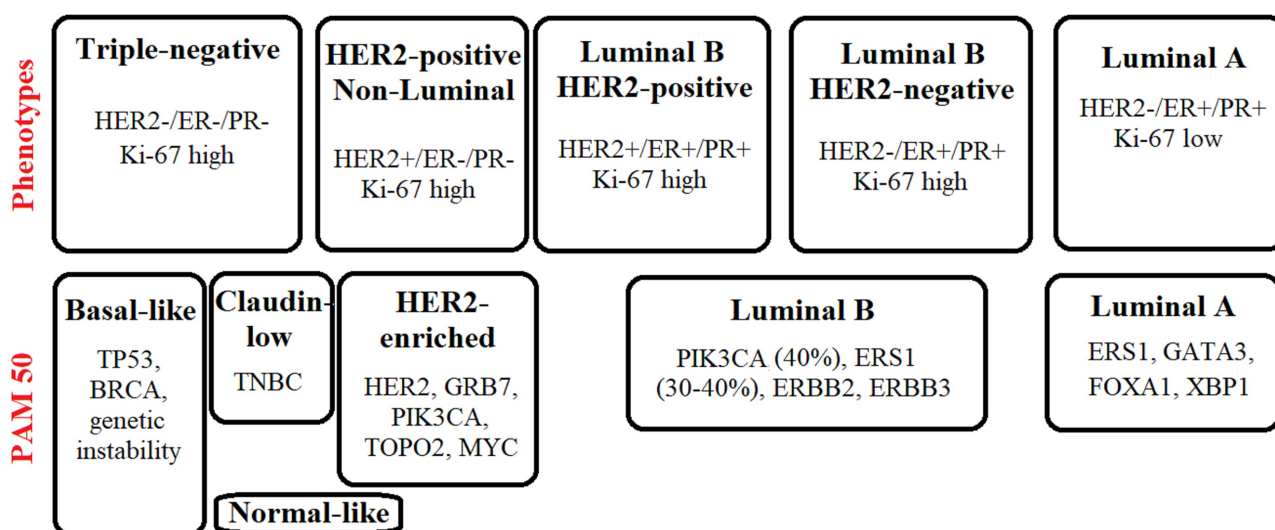


Fig. 1. Correlation of molecular biological and Prediction Analysis of Microarray 50 (PAM50) subtypes of breast cancer (BC). HER2, human epidermal growth factor receptor type 2; ER, estrogen receptors; PR, progesterone receptors; BRCA, breast cancer gene; TNBC, triple-negative breast cancer; GRB7, growth factor receptor-bound protein 7; PIK3CA, catalytic subunit of phosphatidylinositol 3-kinase alpha; TOPO2, topoisomerase II; MYC, proto-oncogene c-MYC; ERS1, estrogen receptor 1; ERBB2, growth factor receptor erbB-2; GATA3, GATA-binding protein 3; FOXA1, Forkhead box A1; XBP1, X-box binding protein 1.

particular, for patients with HER2-enriched BC, subgroups with different pathological responses showed differences in metabolites associated with amino acid and carbohydrate pathways. For TNBC, differences in metabolites associated with the long-chain FA pathway were shown, whereas for luminal B BC, differences with acylcarnitine pathways were demonstrated. Thus, specific differences have been identified for each BC phenotype (Fig. 2) [27,28,29,30,31].

Table 1 (Ref. [32,33,34,35,36,37,38]) summarizes the main metabolic features associated with BC subtypes.

2.1 Glucose Metabolism in Different BC Phenotypes

Barupal D.K. et al. [39] established a relationship between changes in glycolysis, the pentose phosphate pathway (PPP), the tricarboxylic acid cycle (TCA), nucleotide salvage, glutathione conjugation, steroid metabolism, fatty acyl-CoA biosynthesis, Ser and aromatic amino acid metabolism with ER expression status in BC. Increased levels of intermediates (ribose-5-phosphate and ribulose-5-phosphate) indicate increased PPP activity and provide metabolites for nucleotide and fatty acid synthesis during cell division and tumor proliferation (Fig. 2) [40]. Consistent with PPP activation, increased levels of five purine metabolites were observed. Levels of β -Ala (an intermediate in the pyrimidine salvage pathway), as well as uracil, pseudouridine, uridine monophosphate, and cytidine monophosphate, were elevated in ER-negative BC [39], allowing for differentiation of tumors based on hormone receptor expression [41].

Increased glucose consumption correlates with increased tumor aggressiveness and poor prognosis in patients [42]. Elevated lactic acid levels, resulting from an en-

hanced Warburg effect, were detected in ER-negative compared to ER-positive cells, with minor differences between BC and normal cell lines [43].

Basal-like and HER2-enriched BC tissues have increased glucose utilization compared to the luminal A phenotype [44,45]. Glucose transporter type 1 (GLUT-1) expression in TNBC is highest compared to other BC subtypes [46]. In these same subgroups, an increase in the activity of glycolytic enzymes (hexokinase, lactate dehydrogenase A) was observed [47,48]. Analysis of TCA cycle metabolites showed that increased fumarate and malate levels correlated with subtype-specific aggressiveness. In particular, more aggressive TNBC had elevated fumarate and 2-hydroxyglutarate (2-HG) concentrations compared to luminal forms, which was mediated by proto-oncogenic protein Myc (MYC) activation and associated with a DNA hypermethylation phenotype [49,50].

hypoxia-inducible factor 1-alpha (HIF-1 α) acts to enhance glycolysis in BC [51]. HIF-1 α targets mRNAs encoding glucose transporters, glycolytic enzymes [52], and the plasma membrane lactate transporter monocarboxylate transporter 4 (MCT4) [53], resulting in increased lactic acid production. Basal-like BC cell lines exhibit higher HIF-1 α mRNA levels compared to luminal BC lines [54]. In BC cells, PPP activity is often elevated due to the increasing demand for nucleotide and fatty acid synthesis and the need to mitigate oxidative stress. Inhibition of key PPP enzymes (G6PD and 6-phosphogluconate dehydrogenase) is observed, alongside elevated levels of ribose-5-phosphate and other PPP intermediates, as DNA synthesis intensifies and the cell cycle progresses [55]. Pyruvic acid levels were significantly elevated in BC cell lines compared

Table 1. Metabolic features of BC phenotyping.

Authors, reference	Luminal A	Luminal B HER2-negative	Non-luminal	Luminal B HER2-positive	TNBC
Díaz-Beltrán L. et al. [32]	↑L-Trp, ↑LysoPC 14:0, ↑LysoPE 18:2, ↑Glycoursodeoxycholic acid	↑LysoPE 16:0, ↑LysoPE 18:2, ↑LysoPE 18:1, ↑LysoPC 20:3, ↑Biliverdin	↑L-Trp, ↑LysoPE 18:1, ↑LysoPE 18:2, ↑LysoPC 0:0/16:0, ↑Biliverdin		↑L-Trp, ↑LysoPC 16:0/0:0, ↑LysoPE 18:1
Cappelletti V. et al. [33]	-	↑Oleate (18:1n9), ↑Palmitate (16:0), ↑Linoleate (18:2n6), ↑Glycerol, ↑1-Palmitoylglycerol, ↑1-Stearoylglycerol, ↑1-Oleoylglycerol, ↑1-Linoleoylglycerol	↑Glucose-6-phosphate, ↑Fructose-6-phosphate, ↑Fructose-1,6-bisphosphate, ↑Lactate, ↑Ribulose 5-phosphate, ↑Xylulose 5-phosphate, ↑Adenosine, ↑Guanine, ↑Fumarate, ↑Malate, ↑2-HG, ↑Oleate (18:1n9), ↑Palmitate (16:0), ↑Linoleate (18:2n6), ↑Glycerol, ↑1, 2-Dipalmitoylglycerol, ↑Sphingolipids		↑Glucose-6-phosphate, ↑Fructose-6-phosphate, ↑Fructose-1,6-bisphosphate, ↑Lactate, ↑Adenosine, ↑Guanine, ↑Fumarate, ↑Malate, ↑2-HG, ↓Gln, ↑Glu, ↑Glu/Gln, ↑Kynurenine, ↑Oleate (18:1n9), ↑Palmitate (16:0), ↑Linoleate (18:2n6), ↑Glycerol, ↑1-Palmitoylglycerol, ↑1-Stearoylglycerol, ↑Sphingolipids
Shahnazari P. [34]	↑2-Aminoadipic acid, ↑PC 38:2, ↑Creatinine, ↑Thr, ↑Tyr, ↑Ser, ↓β-Ala, ↓TAG 60:2, ↓TAG 58:1, ↓PC 32:1, ↓PC 32:2, ↓PC 30:1		↑PC 30:1, ↑PC 32:1, ↑PC 32:2, ↑PE 32:1, ↑N-acetyl-D-mannosamine, ↑Aminobutyrate, ↑Aminoisobutyrate, ↑Tau, ↑Gln, ↓Thr, ↓Tyr, ↓Leu, ↑Asp, ↓TAG 55:1, ↓TAG 52:2, ↓TAG 56:9	↑Tyr, ↑Ile, ↑Leu, ↑Trp, ↑Thr, ↑Ser, ↑Cit, ↑Homoserine, ↑PC 34:2, ↑Cholate, ↓Ribose 5-phosphate, ↓Xanthine, ↓TAG 58:1, ↓Uridine-5-monophosphate, ↓Malate	↑TAG 58:1, ↑TAG 60:2, ↑TAG 58:10, ↑TAG 56:9, ↑Xanthine, ↑Uridine 5-monophosphate, ↑Citric acid, ↑Alpha-ketoglutaric acid, ↑Maltotriose, ↑Ribose 5-phosphate, ↑Uracil, ↑Malate, ↑Glu, ↓β-Ala, ↑Tau, ↓Thr, ↓Trp, ↓PC 36:2, ↓PC 38:2
León-Carreño L. et al. [35]	↓Ser, ↑Asp, ↑Nicotinic acid, ↑LPG 16:0, ↓DG 27:0	↓Trp, ↓Ile, ↓Leu, ↑Gly, ↓Asp, ↑Creatine, ↑Lauric acid, ↑Araabitol, ↑Myristic acid, ↑Erythritol, ↑Palmitic acid, ↑Glycerol, ↑Succinic acid, ↑Capric acid, ↑Stearic acid, ↑Glucose, ↑Mannose, ↑Malic acid, ↑Galacturonic acid, ↑Oleic acid, ↑3-hydroxybutyric acid, ↑Glucuronic acid, ↑Palmitoleic acid, ↓LPC 20:2, ↑SM d34:1, ↑Arachidonic acid, ↑Biliverdin, ↑SM d34:0, ↑Betaine, ↑PC 36:6, ↑Carnitines, ↑PC 38:7, ↑PC 36:5,	↓Met, ↑Trp, ↑Gly, ↑Creatine, ↑Glu, ↑Asp, ↑Malic acid, ↑Bilirubin, ↓Glycochenodeoxycholic acid, ↓L-carnitine, ↓LPC 20:5, ↑LPC 20:0, ↑LPC 0–20:1		↑Gly, ↑Ser, ↑Trp, ↑Met, ↑Leu, ↑Gluconic acid lactone, ↑Citric acid, ↑Glycerol, ↑Succinic acid, ↑Glycochenodeoxycholic acid, ↑Glycocholic acid, ↑LPC 20:5, ↑PCP 40:6, ↑LPC 0–18:2, ↑SM d34:2, ↑SM d32:1, ↑LPC 20:0, ↓Palmitoylcarnitine
Willmann L. et al. [36]		-	↑Gly, ↑Ala, ↑Lactate	↓Lactate	↑Phe, ↑Tyr, ↑Pro, ↑Thr, ↑Trp, ↑Val, ↑Tau, ↑Lactate, ↑HIF-1α, ↑Ribose-5-phosphate

Table 1. Continued.

Authors, reference	Luminal A	Luminal B HER2-negative	Non-luminal	Luminal B HER2-positive	TNBC
Gallo M. et al. [37]	↑O-phosphocholine		↑O-phosphocholine	-	↑Myo-inositol, ↑Taurine, ↑Lactate, ↑Glu/Gln
Tyanova S. et al. [38]	↑NDUFAB1, ↑FOXA1, ↑MAPK3 (Erk1), ↓EEF1G		↑Her2, ↑Grb7, ↑CDK12, ↑DNAJA1,2, ↑FUT8, ↑COG3		↑MCM3, ↑MCM5, ↑RCL1, ↑MRPS27, ↑EIF2S2, ↑EEF1G, ↑STMN1, ↑GLS, ↑C9ORF114, ↑ENO1

Note. ↑, the concentration of the metabolite increases; ↓, the concentration of the metabolite decreases in the corresponding subgroup. BRCA, breast cancer gene; TNBC, triple-negative breast cancer; GRB7, growth factor receptor-bound protein 7; PIK3CA, catalytic subunit of phosphatidylinositol 3-kinase alpha; TOPO2, topoisomerase II; MYC, proto-oncogene c-MYC; ERS1, estrogen receptor 1; ERBB2, growth factor receptor erbB-2; GATA3, GATA-binding protein 3; FOXA1, Forkhead box A1; XBP1, X-box binding protein 1.

in the Glu level were observed [69]. Increased c-MYC transcriptional activity, leading to alterations in glutaminergic metabolism, is known to be a hallmark of TNBC [70,71]. The Glu/Gln-ratio varied significantly with the highest increase in the basal-like subtype. Low levels of glutamine synthetase (GLUL) are observed in TNBC [72]. Gln deprivation suppresses the growth of basal-like and low-claudin triple-negative tumors [59]. In contrast, luminal tumor cells express GLUL and are resistant to Gln deficiency [73]. The glutaminase isoenzyme GLS2 is activated and plays a significant role in luminal BC subtypes [74].

Elevated glycine levels have been found in HER2-positive tumors, supporting the potential of Gly as a marker of tumor aggressiveness [69].

Preoperative free amino acid levels were shown to be significantly increased in basal-like BC compared to luminal A tumors, with the exception of Asp, Gln, and Glu [75].

Negative estrogen and progesterone receptor expression status was associated with decreased Trp concentrations and increased plasma kynurenine to Trp ratio [76] due to increased tryptophan 2,3-dioxygenase activity [77]. In basal-like BC, kynurenine levels were increased by IDO activation [78].

ER-positive BC is characterized by increased plasma Pro, Ala, and Val concentrations [22]. TNBC and non-TNBC differed in serum Gln and Orn levels [79]. A diagnostic panel (Gln, Orn, D-dimer, CA15-3, CEA, L5CH) [80] and decreased serum N-acetyltransferase (NAT) levels [81] was proposed to differentiate TNBC and non-TNBC with high diagnostic accuracy. Increased Gln demand provides intermediates such as Glu and Orn [82,83].

Metabolomics and lipidomics studies in large cohorts have shown that the BC metabolome is strongly influenced by hormone expression status and tumor grade, but to a much lesser extent by HER2 status [41,84]. Low 4-aminobutyrate aminotransferase expression has been associated with β -Ala accumulation and reduced recurrence-free survival in all BC subtypes. An increase in β -Ala and xanthine levels and changes in three metabolites of Gln metabolism ($\uparrow$ glutamate, $\downarrow$ glutamine, $\uparrow$ 2-HG) were observed in hormone receptor-negative BC cells [85]. 2-HG levels were higher in hormone receptor-negative tumors and reached the highest values in TNBC [86]. To quantify the disturbances of Gln metabolism, the Glu/Gln-ratio was introduced, which also increased maximally in TNBC. The results of Glu/Gln-ratio studies in BC support the idea of the need to evaluate the efficacy of glutaminase inhibitors in ER/PR-negative tumors and in selected ER/PR-positive tumors.

The content of betaine, palmitic acid, Asn, 2,3-dihydroxybenzoic acid, 3-indoxylsulfate, indole-3-acetic acid, hypoxanthine, gentisic acid, stearic acid, Tau, and 5-aminolevulinic acid was higher in ER-positive BC. The content of indole-3-acetic acid, Pro, and cytidine was higher in HER2-enriched BC [87].

2.3 Lipid Metabolism in BC of Different Phenotypes

A significant increase in lipid content, including phospholipids, has been shown with ER/PR-negative BC [84,86].

The accumulation of free FA, including linoleate, palmitate, and oleate, is accompanied by an increase in the level of triacylglycerol catabolites, such as glycerol and monoacylglycerols (MAGs). MAGs include unsaturated palmitic and stearic acyl chains. In the process of *de novo* synthesis, monoacylglycerol lipases (MAGL), glycerol-3-phosphate acyltransferases and diacylglycerol lipases regulate the concentration of glycerolipids. Increased MAGL expression has been shown in aggressive tumor cell lines [88]. Significant accumulation of 1-MAG was observed in luminal B BC tissues, indicating the ability to regulate the complex network of FA (prostaglandins, lysophospholipids, and ether lipids) involved in inflammation and BC progression. In addition to *de novo* lipid synthesis (potentially from citrate), lipolysis may promote higher tissue FA levels. As a critical energy source, FA fuel oxidative metabolism and promote ATP production. In luminal B, basal-like, and HER2-enriched BC, accumulation of palmitoylcarnitine, stearoylcarnitine, and oleoylcarnitine was observed alongside elevated FA levels.

An accumulation of 3-hydroxybutyrate (indicator of lipid oxidation and mitochondrial dysfunction), which is formed from excess acetyl-CoA through the oxidation of some FA, is observed. FA oxidation did not differ between molecular subtypes of BC. Thus, basal-like and HER2-positive BC were characterized by increased lipolysis and membrane biogenesis, which correlates with the fact that excessive FA production contributes to BC progression [89,90]. It should be noted that altered FA metabolism is observed for luminal B tumors, whereas changes in glucose/Gln metabolism are also observed for HER2-enriched and basal-like BC. Tumor-associated metabolic changes support theories of *de novo* lipogenesis in tumor tissue and the role of stromal tissue in tumor growth and development, as well as in the overall prognosis of the disease [91].

Elevated FA levels and phospholipid metabolism may be interrelated. Levels of glycerolphospholipids and sphingolipids indicate differential cell membrane remodeling depending on the BC subtype and are maximal in basal-like and HER2-enriched BC, reflecting the greater growth potential of such tumors. Oncogene-induced cell signaling is interconnected with phospholipid metabolism. For example, phosphatidylinositol-4-phosphate 5-kinase I γ (PIP-KI γ) is overexpressed in TNBC, and its loss impairs phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) activation in TNBC cells [92]. Increased EGF expression is associated with phosphatidylcholine cycle enzymes (ChoK and PtdCho-specific phospholipase C) and is observed in TNBC [93,94]. Thus, key regulators of BC progression are enzymes involved in the biosynthesis and catabolism of phospholipids.

In ER-positive tumors, levels of LysoPC 16:1 and 2-octendioic acid were decreased, but levels of octanoylcarnitine in plasma were increased. In HER2-enriched BC, levels of lysoPC 20:4, carnitine, which is associated with the transport of fatty acids for mitochondrial β -oxidation, and 2-octendioic acid were increased [95]. According to Wang R. et al. [96], BC subtyping can be performed based on phosphatidylcholine (PC) concentration. The content of many phospholipids (PC, PE, and PI) was increased in ER/PR-negative compared to ER/PR-positive expression, while triglyceride content did not differ [97].

HER2-positive BC cells are dependent on FA synthesis and exhibit significantly elevated levels of accumulated lipids, with impairment of synthesis leading to apoptosis [98]. The growth of HER2-normal cells is not affected by palmitate supplementation, whereas HER2-positive cells exhibit unchanged neutral lipid levels, activation of AMP-activated protein kinase, inhibition of FA synthesis, and significantly altered Gln, glucose, and Ser/Gly metabolism. Levels of the bioactive lipid N-palmitoylglycine, which is nontoxic to these cells, are significantly increased. HER2 overexpression has a prolipogenic effect by increasing the expression of acetyl-CoA carboxylase alpha and FA synthase [99]. HER2-positive BC cells have higher levels of stored triacylglycerides and saturated FA compared to other cell types [100,101,102]. Genetic alterations in these cells allow for the constitutive production of FA as a means of regenerating reducing equivalents for glycolysis through the concerted action of malate dehydrogenase, while peroxisome proliferator-activated receptor gamma (PPAR γ) coordinates the binding of FA to neutral lipids to avoid lipotoxicity [103].

Basal-like BC is characterized by an increased glycerophosphocholine (GPC) to phosphocholine (PCho) ratio and Gly concentrations, which are due to lower choline kinase (CHKA, CHKB) expression and higher phosphatidylcholine degradation mediated by overexpression of phospholipase A2 group 4A and phospholipase B1 [104]. A metabolic shift from phosphatidylcholine synthesis to Gly formation is characteristic, mediated by the expression of choline and sarcosine dehydrogenase [105]. Furthermore, lower Gly concentrations were observed in BC patients with a better prognosis [106]. Grinde M.T. et al. [107] found a higher PCho/GPC-ratio in luminal B compared to basal-like BC. Overall, heterogeneity in choline metabolism was observed across different molecular subtypes of BC [108,109].

Metabolomics has the potential to assess prognostic factors in BC [110]. Choi J.S. et al. [111] found that higher choline levels correlated with hormone receptor-negative tumors. Furthermore, TNBC was associated with higher total choline to creatine ratios. Higher choline levels but lower creatine and Gln levels, along with higher levels of Glu, Gly, and lactate, were noted in TNBC [69]. HER2-positive tumors were significantly associated with higher levels of Tau, scyllo-inositol, myo-inositol, creatine, suc-

cinatate, Gly, and Gln, and lower Ala concentrations. Tang X. et al. [112] showed a correlation between differences in lipolysis and FA oxidation (FAO) and ER/PR expression, specifically an increase in eight metabolites in ER-positive BC (carnitine derivatives, short- and medium-chain FA) and an increase in long-chain FA and monoacylglycerols in ER-negative BC. Furthermore, a FAO-related metabolites were associated with higher levels of BRCA1 expression. Inhibition of FAO is a promising therapeutic strategy because FAO-related genes promote BC cell proliferation and survival [113,114].

2.4 Other Metabolic Biomarkers Depending on BC Phenotype

In ER-positive BC, glycodeoxycholic acid (GDCA) concentrations were elevated in plasma [22].

Gonzalez R.M. et al. [115] found that ten analytes (AmR, EGF, HB-EGF, MMP1, MMP9, PDGF, RANTES, TGF- α , TNF- α , and VEGF) were significantly altered in at least one of four BC subtypes, as determined by tumor ER and HER2 expression levels.

For basal-like BC, IFN- γ has been shown to have independent prognostic value [116]. In luminal B, HER2-positive, and basal-like BC, the prognostic effect of the IFN- γ gene signature was more pronounced than in luminal A subtypes.

Seven metabolites were identified to differentiate luminal A and B BC from healthy controls (choline, acetoacetate, Ala, lactate, His, 3-hydroxybutyrate, and Tyr). Three metabolites were not common to the tested subgroup comparisons: citrate for the Luminal B group, and Glu and O-phosphocholine for Luminal A [117].

Schweinsberg P.D. et al. [118] identified metabolites of the antitumor tricyclic nucleoside NSC-154020 that may have implications for targeted therapy of BC [119].

2.5 Metabolic Features of BC Cell Lines

The metabolite profile of seven BC cell lines with different subtypes was characterized: five cell lines (SK-Br-3, T-47D, MCF-7, MDA-MB-436, MDA-MB-231) and two patient-derived xenografts (Hbcx39, Hbcx9) [37]. It was shown that the metabolite profiles differed mainly not in the list of metabolites, but in their differential accumulation. All BC cell lines exhibited high concentrations of Gly, Glu, lactate, and formate, which promote invasion and metastasis. Unique metabolites were identified for some cell lines: xanthine and 2-oxoglutarate (SK-Br-3), 2-oxobutyrate (T-47D), cystathionine and glucose-1-phosphate (MCF-7), NAD $^{+}$ (MDA-MB-436), isocitrate (MDA-MB-231) and NADP $^{+}$ (Hbcx9).

Major differences in the biochemical pathways of central metabolism were found in BC cell lines (MDA-MB-231, MDA-MB-453, BT-474) compared with the MCF-10A breast epithelial cell line [36]. Significant differences were identified, particularly in amino acid metabolism, the TCA cycle, and glycolysis. Characteristics of BC subtypes

can be correlated with their individual metabolic profiles. Dubuis S. et al. [120] analyzed the intracellular metabolism of 18 BC cell lines and demonstrated extensive heterogeneity across all metabolic pathways. A comparison of specific metabolomic profiles of BC cell lines was conducted, demonstrating that they are more significant than patterns associated with malignancy or subtyping. The authors developed an unsupervised metabotyping procedure that automatically recognized metabolic types for each pathway from metabolomic data and assigned cell lines. The data obtained allow us to assess how metabolic types correlate with differences in basal fluxes and different sensitivities to gene knockdown or pharmacological inhibition.

BC cell lines also exhibited metabolic differences depending on the presence of BRCA1 mutation depending on the presence of BRCA1 mutation [121]. The distribution of nine metabolites differed significantly between clusters. Metabolite levels were significantly lower in BRCA1-mutated compared to non-mutated BC cell lines. TNBC with and without BRCA1 mutation differed in plasma concentrations of adenine, N6-methyladenosine, and 1-methylguanine. Adenine is an indicator of abnormal cancer cell proliferation and is a potential prognostic marker for BC metastasis [122]. 1-methylguanine is a marker of DNA damage [123]. N6-methyladenosine as the most frequently methylated nucleoside is suggested to be a marker of RNA methylation involved in transcriptional regulation [124,125,126].

Ziegler et al. [127] compared glycolytic proteins in the conditioned medium (CM) of TNBC cell lines and normal cells. Eleven glycolytic proteins were expressed at elevated levels in at least one TNBC cell line, of which 4 (ENO1, GAPDH, LDHA, and LDHB) showed higher expression levels, on average, in TNBC CM compared to CM from MCF-7 cells [127]. Extracellular vesicles are characterized by elevated levels of these enzymes, which mediate processes such as angiogenesis, immune evasion, drug resistance, and activation of macrophages and fibroblasts, which promote invasion and metastasis [128].

The stage of studying the metabolic properties of cell lines is critical, and the understanding of cell line analysis should be transferred to human body fluids, such as blood or urine, in the next step.

2.6 Metabolic Reprogramming and BC Phenotypes

Metabolic reprogramming is a key mechanism that allows cancer cells to adapt to their microenvironment, grow rapidly, survive nutrient deficiencies, and develop resistance to therapy [129]. In the context of BC, this reprogramming leads to the formation of various metabolic phenotypes that influence tumor aggressiveness, progression, and response to treatment [130].

The main metabolic phenotypes in BC include:

1. *Glycolytic phenotype*. Characterized by increased glucose consumption and active lactate production even in the presence of oxygen (Warburg effect), which en-

sures the rapid synthesis of macromolecules necessary for tumor proliferation. The glycolytic phenotype is often found in aggressive forms of BC, such as nonluminal and TNBC. Drivers include increased expression of glucose transporters (GLUT1) and key glycolytic enzymes (HK2, LDHA), as well as activation of HIF during hypoxia.

2. *OXPHOS-dependent phenotype*. Unlike the glycolytic phenotype, these cells retain or increase their dependence on mitochondrial respiration. They are characterized by high mitochondrial mass and stable electron transport chain activity. OXPHOS-dependent tumors are often less aggressive but more resistant to prooxidant therapy and some chemotherapy agents. This is characteristic of luminal A and B HER2-negative BC subtypes.

3. *Lipid phenotype*. Associated with the active utilization of fatty acids as an energy source. Observed in the luminal B HER2-positive BC phenotype. These tumors are characterized by increased expression of enzymes involved in FAO and lipogenesis (fatty acid synthase (FASN), ACC, SREBP1, carnitine palmitoyltransferase 1a (CPT1A)).

4. *Mixed phenotypes*. Most clinical cases represent hybrid phenotypes, combining two or more dominant pathways (e.g., glycolytic and OXPHOS-dependent or glycolytic and glutaminolytic). Metabolic hybridity leads to multiresistance and may reduce the effectiveness of standard chemotherapy.

The results in Table 1 demonstrate that despite the wide diversity of metabolites, they can be grouped based on their involvement in specific metabolic processes (Fig. 2). Most metabolites were identified in isolated studies and are not systematically reproduced (Table 1). However, therapeutic interventions for a limited number of metabolites have been demonstrated, highlighting the need for a further targeted, systematic approach to identifying potential therapeutic targets for BC.

3. Genetic and Proteomic Features of Different BC Phenotypes

Mutations in key driver genes (e.g., TP53, PIK3CA, MYC) in BC are known to result in specific metabolic phenotypes through associated signaling pathways [131].

Mutations in the TP53 gene lead to disruptions in cell cycle control, apoptosis, DNA repair, and angiogenesis [132]. Mutant p53 can exert oncogenic functions by regulating cancer metabolism. TP53 mutations are associated with alterations in metabolic genes involved in glycolysis/gluconeogenesis, TRp and glutathione metabolism, glycosphingolipid and purine biosynthesis. This may contribute to BC progression by increasing demands for energy, biomass, and nutrients. TP53 mutations may promote the expression of metastasis-associated transcription factors (ZEB1, SLUG, TWIST1) through transcriptional, post-translational, and epigenetic modifications.

Mutations in the PIK3CA gene activate the PI3K/Akt/mTOR signaling pathway [133,134]. Its activity enhances cell proliferation and suppresses apop-

tosis, thereby ensuring tumor growth and survival. In addition, this pathway is involved in the regulation of cell migration, epithelial-mesenchymal transition, autophagy, and chemoresistance [135]. Molecular genetic alterations in the PI3K/AKT/mTOR signaling pathway are associated with resistance to endocrine therapy in BC [136]. Some consequences of mutations include increased aerobic glycolysis. Among BC subtypes, activating variants of PIK3CA are most often detected in luminal subtype A (59.8%). In luminal B and HER2-positive BC, the frequencies of PIK3CA mutations are similar and amount to approximately 38%. The lowest frequency of 23.3% is observed in TNBC [137].

Carcinogenic levels of MYC reprogram cellular metabolism, promoting cancer cell growth and proliferation [138,139]. Some mechanisms include direct regulation of glycolytic genes that regulate glucose metabolism, as well as indirect regulation of the expression of genes that increase glutamine metabolism. Ectopic MYC expression in cancer leads to aerobic glycolysis and oxidative phosphorylation. MYC amplification is detected in 8–73% of BC cases. It is more common in ductal tumors and may be associated with larger tumor size. MYC gene amplification is observed in 30–50% of high-grade BC cases [140].

In addition to those listed, the following genes may influence metabolism in BC: *BRCA1* and *BRCA2*, *CYP11A1* and *CYP11B1*, *CYP19*, *COMT*, *MTHFR*, *MTR*, and *MTRR* [141,142,143]. The *BRCA1* and *BRCA2* genes are involved in the regulation of many cellular processes, maintaining genome stability and homologous recombination during the repair of double-stranded DNA breaks [142]. *CYP11A1* and *CYP11B1* control the synthesis of 2-, 4-hydroxylases and, as a consequence, the formation of 2-OH and 4-OH estrogens [143]. Aromatase (*CYP19*) encodes cytochrome P450, an enzyme that catalyzes the conversion of androgens to estrogens [143]. The catechol-O-methyltransferase (*COMT*) gene is also responsible for ER metabolism [143]. Polymorphic variants of the *MTHFR*, *MTR* and *MTRR* genes affect the increase in homocysteine levels in the blood, which may affect the regulation of the activity of many genes and the development of BC [141].

Thus, BC phenotypes contain different classes of mutations (Fig. 3) [144], which is of significant interest for further understanding of BC biology. Tumor mutational burden depends on the breast cancer phenotype, with basal-like tumors having the highest rate [145]. Mutations in the TP53 gene are more common in patients with the basal-like and HER2-positive subtypes, while mutations in the PIK3CA gene are frequently found in luminal A BC [146]. This demonstrates an association between mutations in tumor genes and molecular subtypes; however, this is not sufficient for creating a more precise classification. To overcome this problem and achieve a more precise classification based on gene expression, approaches are being developed that improve the reliability of tumor classification.

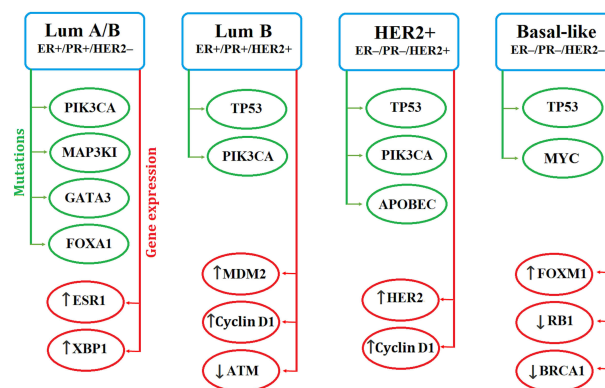


Fig. 3. Associations of genetic mutations with BC phenotype. MAP3K1, Mitogen-Activated Protein Kinase Kinase 1; TP53, tumor protein p53; MDM2, Mouse Double Minute 2 Homolog; ATM, Ataxia Telangiectasia Mutated; APOBEC, Apolipoprotein B mRNA Editing Catalytic Polypeptide-like; FOXM1, Forkhead Box M1; RB1, Retinoblastoma 1; ↑, mutation rate increases. ↓, mutation rate decreases.

Research in the field of molecular oncology of BC is enabling the discovery of new genes involved in carcinogenesis. Table 2 (Ref. [147,148,149,150,151]) shows a comparison of genetic signatures depending on the classification of BC into one of the groups according to the RAM50 classification.

Luminal A and B subtypes were characterized by a decrease in the expression of several genes encoding polypeptides that bind glycosyl structures (*VCAM1*, *ICAM1*, *ICAM2*, *PECAM1*, and *SELP*) [148] (Table 2). In contrast, in basal-like BC, an increase in the expression of such genes (*ICAM1*, *ICAM2*, *LGALS7*, *SELE*, and *VCAM1*) was observed. HER2-enriched BC were characterized by an increase in the expression of the *FUT3* gene, which is a fucosyltransferase involved in the biosynthesis of glycosphingolipids and fucosylation of Lewis antigens.

Yu F. et al. [147] identified specific gene signatures for BC prognosis. The prognostic signature specific for basal-like BC contains six genes. The transcription factor *LMO2* promotes invasion and metastasis of BC tumor cells [152]. A five-gene signature has been identified for HER2-enriched BC, with the *ABCC5* gene being associated with bone metastasis [153]. The prognostic signature of luminal subtype A includes three genes (*PTGIS*, *ST3GAL1*, and *PGAP1*) involved in the metabolic pathway and two genes (*ILIR1* and *LONRF1*) involved in cytokine signaling in the immune system. The prognostic signature of luminal B subtype contains 10 genes, including the *FBXO4* gene [154].

Subtype-specific epigenetic landscapes have been demonstrated in BC [155]. In particular, key histone biomarkers (H3K9me2, H3K36me2, and H3K79me) showed differential expression depending on the BC phenotype. Increased H3K9me2 expression correlates with higher grade and stage in TNBC. Cell prolifera-

Table 2. Differential gene expression depending on the molecular biological subtype of BC.

Features	Luminal A HER2-negative	Luminal B HER2-negative	HER2-enriched	Basal-like	Normal-like
Predictive gene signatures [147]	<i>PTGIS</i> , <i>ST3GAL1</i> , <i>PGAP1</i> , <i>IL1R1</i> , <i>LONRF1</i>	<i>FBXO4</i>	<i>ABCC5</i>	<i>LMO2</i>	-
Glycan related gene expression signatures [148]	↑ <i>CLGN</i> , ↑ <i>EDEM3</i> , ↑ <i>FUCA1</i> , ↑ <i>GALNT7</i> , ↑ <i>LMAN2L</i> , ↓ <i>B3GNT5</i> , ↓ <i>B4GALT5</i> , ↓ <i>CALR</i> , ↓ <i>CHST12</i> , ↓ <i>RPN1</i> , ↓ <i>SLC35B1</i> , ↓ <i>ST8SIA1</i> , ↓ <i>VCAM1</i>	↓ <i>B3GNT5</i> , ↓ <i>CHST2</i> , ↓ <i>CHST3</i> , ↓ <i>FUT3</i> , ↓ <i>GALNT3</i> , ↓ <i>ICAM1</i> , ↓ <i>ICAM2</i> , ↓ <i>PECAM1</i> , ↓ <i>SELP</i>	↑ <i>FUT3</i>	↑ <i>B3GNT5</i> , ↑ <i>B4GALT5</i> , ↑ <i>CALR</i> , ↑ <i>CHST2</i> , ↑ <i>GYLTL1B</i> , ↑ <i>HSPC159</i> , ↑ <i>ICAM1</i> , ↑ <i>ICAM2</i> , ↑ <i>LGALS7</i> , ↑ <i>SELE</i> , ↑ <i>VCAM1</i> , ↓ <i>CLGN</i> , ↓ <i>FUCA1</i> , ↓ <i>GALNT6</i> , ↓ <i>GALNT7</i> , ↓ <i>LMAN2L</i> , ↓ <i>MAN2B2</i> , ↓ <i>MPDU1</i> , ↓ <i>NEU1</i> , ↓ <i>PIGT</i> , ↓ <i>ST6GALNAC2</i>	-
Differentially expressed miRNAs [149]	↑miR-29c-5p, ↑miR-30a-3p, ↓miR-130b-3p, ↓miR-185-5p, ↓miR-362-5p, ↓miR-378-3p	↑miR-15b-5p, ↑miR-29c-5p, ↑miR-149-5p, ↑miR-193b-3p, ↑miR-342-3p/5p, ↓miR-31-5p/5p, ↓miR-99a-5p, ↓miR-125b-2-3p/5p, ↓miR-139-5p, ↓miR-140-3p, ↓miR-150-5p, ↓miR-204-5p, ↓miR-221-3p, ↓miR-223-3p, ↓miR-299-3p, ↓miR-376a-3p, ↓miR-377-3p, ↓miR-378-3p, ↓miR-381-3p, ↓miR-433-3p, ↓miR-505-3p	↓miR-30a/c-2-3p, ↓miR-139-5p, ↓miR-144-3p, ↓miR-204-5p, ↓miR-221-3p	↑miR-18a-5p, ↓miR-29c-5p, ↓miR-139-5p, ↓miR-193a-5p, ↓miR-375-3p, ↓miR-887-3p	↑miR-99a-5p, ↑miR-497-5p, ↑miR-100-5p, ↓miR-130b-3p, ↓miR-185-5p
Subtype-specific therapeutic genes [150]	<i>LTO1</i> , <i>CCND1</i> , <i>GATA3</i> , <i>ESR1</i> , <i>COXC6</i> , <i>MRPS30</i> , <i>ELP2</i> , <i>LMX1B</i> , <i>POTEI</i> , <i>NOS1AP</i> , <i>RMND1</i> , <i>PDZK1</i>		<i>PSMB3</i> , <i>RPL23</i> , <i>RPL19</i> , <i>RPL23A</i> , <i>PSMD3</i> , <i>MED1</i> , <i>MRPL45</i> , <i>ERBB2</i> , <i>CWC25</i> , <i>EPOP</i> , <i>CDK12</i> , <i>MALL</i> , <i>MIEN1</i> , <i>ALDOC</i> , <i>CACNB1</i> , <i>NEUROD2</i> , <i>ACACA</i> , <i>MED24</i>	<i>ATL2</i> , <i>SOX10</i> , <i>ANP32E</i> , <i>HORMAD1</i>	-
Subtype-associated hallmark genes [151]	<i>GRIA2</i> , <i>ROGDI</i> , <i>PLCD4</i> , <i>MAPK9</i> , <i>PCDH1</i>	<i>CNTNAP2</i> , <i>FOXMI</i> , <i>IGF2BP1</i> , <i>CLDN9</i> , <i>LTBP1</i>	-	-	-

↑, increase. ↓, decrease.

tion and modulation of the epithelial-mesenchymal transition pathway were dependent on G9a inhibition, particularly in TNBC, demonstrating its potential as a therapeutic target. Genes, including 8 mRNAs (*ALCAM*, *SPARCL1*, *CAMC2N1*, *DCTN4*, *DHRS2*, *EFHD1*, *GRP*, and *C19orf33*) and 9 microRNAs (*HS_239*, *has-miR-101*, *has-miR-184*, *has-miR-130b*, *has-miR-33b*, *has-miR-521*,

has-miR-135b, *has-miR-135a*, and *has-miR-411*), have been identified that may be key molecules differentiating BC subtypes [156]. A new marker, *FOXA1*, has been proposed for BC classification. A critical role of Notch signaling pathways in luminal HER2-negative tumors and cell cycle signaling in luminal HER2-positive tumors has been demonstrated.

Non-coding RNAs, proteins, transcription factors, and histone complexes may contribute to phenotype-specific dysregulation of lncRNAs [157]. Overexpression of the following lncRNAs has been shown in HER2-positive BC - HOTAIR [158], in basal-like BC - HOTAIRM1 [158], in luminal A - LINC160 [159] and in luminal B subtypes - DSCAM-AS1 [160]. The highest number of lncRNA changes were observed in luminal A and B HER2-negative BC. Comparable levels of differentially expressed lncRNAs were found in TNBC and luminal B HER2-positive BC. A unique lncRNA-mRNA pair specific to the ER-positive BC (SNHG12 and EPB41) was identified; decreased SNHG12 expression and increased EPB41 expression were observed.

Functional differences between BC phenotypes have been demonstrated using proteomic analysis, including energy metabolism, cell growth, mRNA translation, and intercellular communication. A signature of 19 proteins was obtained (luminal A and B - 2, HER2-enriched - 2, TNBC - 15). Among these proteins, Her2 and Grb7 were positive markers for HER2-positive tumors (with high expression); for ER/PR-positive tumors, MAPK3 (Erk1) and EEF1G were positive and negative markers, respectively; and positive markers for TNBC were MCM5, STMN1, GLS, RCL1, C9ORF114 and ENO1 [38].

A unique set of transcription factors (TF) regulates BC subtyping [161]. Understanding the interplay between DNA methylation (DNAm) and copy number alterations (CNAs) contributes to a better understanding of the mechanism by which BC subtypes arise. Luminal A TFs tended to have DNA hypomethylation, whereas basal-like TFs tended to have CNA gain/decrease. Basal-like BC cells accumulate high amounts of CNA, which cause genomic instability, and therefore exhibit highly dynamic and complex phenotypes [162]. In luminal A BC, hypomethylation enhances luminal lineage differentiation at key lineage-specific markers (GATA3, ESR1, FOXA1) and largely extends to TF binding regions and enhancers of these lineage markers [163]. Transcription factor regulatory network analysis highlighted the importance of BHLHE40 in luminal BC and luminal mature cells, and KLF5 in basal-like tumors and luminal progenitor cells [164]. Key genes defining basal-like (SOX6 and KCNQ3) and luminal A/B (FAM155A and LRP1B) lineages were identified. Exhausted CD8⁺ T cells expressing CTLA4 were enriched in basal-like BC, suggesting an altered mechanism of immune dysfunction [164].

Elango R. et al. [150] identified 284 genes specific for ER/PR-positive BC, 92 genes for HER2-enriched BC, and 158 genes specific for TNBC. Twelve genes were identified for ER/PR-positive BC, eighteen genes for HER2-positive BC, and four core genes for TNBC (Table 2). The limited number of core genes for TNBC can be explained by the high similarity between TNBC and HER2-enriched BC. In addition, potentially effective subtype-specific therapeutic target genes were identified: for ER/PR-positive BC

(GATA3, CCND1, ESR1, ELP2), for HER2-enriched BC (ERBB2, CDK12), for TNBC (SOX9, HMGAI, ATP1A1, CAD, PPP1CB).

A higher correlation between the transcriptome and proteome was shown for highly proliferative (basal-like, luminal B, and HER2-enriched) compared to low proliferative BC subtypes (normal-like and luminal A) [165]. The proteomes of highly proliferating subtypes were enriched for E2F, MYC, and G2M checkpoint proteins, but basal-like tumors differed in the content of specific major histocompatibility complex (MHC) class proteins.

Oncogenes, such as c-Myc, play a central role in orchestrating proliferation, metabolism, and differentiation and initiate reprogramming of BC cellular metabolism. Human cytosolic branched-chain aminotransferase (hBCATc) is a target of c-Myc. There are two known main isoforms of hBCAT proteins: mitochondrial (hBCATm protein, BCAT2 gene), which is expressed in most tissues, and cytosolic (hBCATc protein, BCAT1 gene), expressed only by highly specialized tissues. Elevated hBCATc levels have been shown to enhance the proliferation and migration of ER-negative BC cells [166,167]. IDH enzymes also support the growth of BC cells [168]. IDH mutations result in the formation of the oncometabolite 2HG from α -ketoglutarate, which inhibits hBCATc expression [169]. Shafei M.A. et al. [170] found that hBCATm was associated with IDH1 expression. In luminal A BC, coexpression of IDH1 and hBCATm may be due to increased expression of the ER-activated transcription factor SREBP1. In contrast, hBCATc expression was significantly associated with the more aggressive HER2-enriched and luminal B subtypes.

The zinc transport network is also subtype-specifically dysregulated [171]. Malignant behavior in BC cells may be mediated by defects in the subcellular zinc microenvironment and is associated with alterations in apoptosis, oxidative stress, and/or cellular signaling.

ER-positive BC demonstrated abnormalities in keratinization, as well as in genes of the *RUNX3* and *AP2* families, which regulate transcription and metabolism [172]. In the absence of hormone receptor expression, tumors exhibited impairments in ubiquitination, FGFR signaling, extracellular matrix interactions and Notch signaling, as well as collagen and cellular signaling pathways.

Tyanova S. et al. [38] found a significant increase in “energy metabolism” in ER/PR-positive and a decrease in the activity of this pathway in HER2-enriched tumors. The protein-protein interaction network shows higher expression levels of multiple proteins in ER/PR-positive tumors. A moderate increase in multiple components of the electron transport chain (NDUF, UQCR, SDH, and COX subunits) and the ATP synthase complex (ATP5 and ATP6 subunits) was shown, associated with a marked increase in the level of cytosolic carbonic anhydrases 1 and 2, potentially for buffering intracellular acidification caused by increased oxidative phosphorylation. In contrast, the level of multiple proteins related to glycolysis, serine synthesis (PHGDH),

and GLS was lower in ER/PR-positive tumors. The most highly upregulated proteins in the entire network, FBP2 and FBP1, are key enzymes in gluconeogenesis, which counteracts glycolytic flux.

Decreased «amino acid and energy metabolism» is characteristic of HER2-enriched BC. These include amino acids themselves, proteins involved in the oxidation of amino acids, fatty acids, alcohols, etc. In HER2-enriched phenotypes, alcohol oxidation by alcohol dehydrogenase and subsequent reactions by aldehyde dehydrogenases, as well as fatty acid oxidation by acyl-CoA dehydrogenases, were decreased. Expression of Pro (PYCR1, 2, PYCR2, and PRODH), Met (HNMT), and Trp (KMO) metabolism enzymes was increased. In this BC subtype, changes in the «cell community» pathway were observed, including cytoskeletal proteins, extracellular matrix, and cell adhesion molecules. The activity of myosins (MYH), a family of extracellular proteins of the laminins, decreased, but there was an increase in the level of several collagens, fibronectin, thrombospondin (THBS1 and 2), which can mediate the interaction of cells with the extracellular matrix. In the HER2-enriched subtype, an increase in the activity of «glycan biosynthesis and metabolism» was observed, including proteins involved in glycosylation in the Golgi apparatus, such as fucosyltransferase (FUT8), acetylgalactosaminyltransferase (GALNT 2, 3, 6), as well as proteins involved in glycan degradation in lysosomes, such as hexosaminidase (HEXA, HEXB), mannosidases (MAN2B2, MAN1B1, MAN2A1).

TNBC, as rapidly growing tumors, has altered pathways associated with increased «replication and repair», «cell growth and death», and «translation» activities. Higher levels of ribosomal proteins, ribosome biogenesis proteins (RCL1), and translational support mechanisms such as tRNA synthetases (ARS family) and nuclear pore complex components are characteristic of the translation network. A significant increase in cell cycle regulators and DNA replication proteins, such as MCM complex proteins, DNA polymerases, DNA damage response proteins, CDK1, CDK2, CDK6, and PCNA, was noted. A decrease in activity was observed for the tumor suppressor PTEN, which maintains the activity of the oncogenic PI3K pathway, indicating the known increased proliferative capacity of TNBC [173].

TNBC samples showed greater immune cell infiltration in primary tumors compared to ER/PR-positive and HER2-enriched tumors [174]. Given the diversity of gene expression present in basal tumors, subtypes with differences in survival have been noted [175], with two basal-like (basal-like type 1 (BL1), BL2), mesenchymal (M), and luminal androgen receptor-positive (LAR) subtypes identified [176]. A large, comprehensive multi-omics study has identified new subtype-specific molecular features [177]. Gene expression patterns characteristic of and upregulated by subtypes were identified, ranging from *ESR1*, *GATA3*, *FOXA1*, *XBPI*, and *cMYB* in ER/PR-positive subtypes

to high expression of receptor tyrosine kinases such as *FGFR4*, *HER1/EGFR*, and loss of *PTEN* and *INPP4B* in the HER2-enriched BC [178]. Key pathways (Tyr and Phe metabolism, and glycolysis/gluconeogenesis) were identified, highlighting the complex biological landscape of TNBC that goes beyond simple genomic alterations. Notably, the analysis identified two differential metabolites (4-hydroxyphenylacetaldehyde and oxalic acid) and six differentially expressed genes (*MAOA*, *ADH1B*, *ADH1C*, *AOC3*, *TAT*, and *PCK1*) as integral components of these pathways [179]. TNBC-specific patterns of microRNA expression have been identified [180]. TNBC BL1 differed from basal-like type 2 by increased expression of miR-17-92 microRNA cluster members and downregulation of several known miR-17-92 targets, including inositol polyphosphate 4-phosphatase type II, *INPP4B*.

4. Features of the BC Microenvironment Depending on the Tumor Phenotype

The tumor microenvironment is closely linked to phenotype-specific metabolic reprogramming in BC. This interaction determines tumor cell adaptation to environmental conditions, their proliferation, invasion, metastasis, and resistance to therapy. For example, lactate can act as a metabolic fuel and signaling molecule, influencing proliferation, invasion, angiogenesis, and immune evasion [181]. A high correlation has been demonstrated between lactate metabolism parameters and HLA expression, intraepithelial lymphocyte infiltration, and interferon response in TNBC. Polarization of M1 macrophages promotes anti-tumor immunity, while lactate promotes polarization of tissue macrophages to the pro-tumor M2 phenotype [181].

Different BC subtypes have different tumor microenvironments [182]. Basal-like and HER2-enriched BC are associated with a high level of immune response, expression of most immunoregulatory targets and immune cell infiltration, the so-called “immunoactive” tumors, suitable for therapy with immune checkpoint inhibitors (Table 3, Ref. [182]). At the same time, the Luminal A and Luminal B subtypes are associated with a low level of immune cells and immune cell infiltration, i.e., they are “immunodeficient” tumors. However, high levels of expression of two immunosuppressive targets (CD39 and IFNAR1) were observed in Luminal A subtype tumors. The Luminal B subtype showed high levels of expression in terms of metabolism, and therefore it is a potential candidate for antimetabolite therapy. The “normal-like” subtype is characterized by high levels of both immune and stromal cells, meaning it can be treated with more diverse treatment strategies.

Prognostic cells were identified that are characteristic of the HER2-enriched, luminal A, and luminal B subtypes of BC (Table 3). In the HER2-enriched subtype, patients with high infiltration of B cells and natural killer T cells had longer overall survival. High infiltration of type 1 T

Table 3. Summary of TME features and therapy strategies in different subtypes [182].

Features	Luminal A HER2-negative	Luminal B HER2-negative	HER2-enriched	Basal-like	Normal-like
Specific Cells	Adipocytes, CMP, Endothelial cells, Neutrophils, Pericytes	CD4 memory T cells, Erythrocytes, GMP, MPP, Neurons, Osteoblasts	CD4 naive T cells, CD4 Tcm, CD8 Tem, Megakaryocytes, Memory B cells, MSC, naive B cells, Pericytes, pro B cells, Tregs	CD4 Tcm, CD8 Tem, Keratinocytes, Memory B cells, naive B cells, pro B cells	Fibroblasts, Megakaryocytes
Subtype-specific mutation	PIK3CA/GATA3/ MAP3K1/CBFB/CTCF	GPS2	MUC16/SMAD4	TP53/SYNE1/DNAH11 /AKAP9/ RB1	CDH1/JAK1
Therapy strategy	CD39 inhibitors/IFNAR1 inhibitors	Antimetabolite	Immune checkpoint blockers (ICB)/Antimetabolite/ VEGF inhibitors/hypoxia- CD39-CD73-A2aR pathway inhibitors	Immune checkpoint blockers (ICB)/Antimetabolite/ VEGF inhibitors	VEGF inhibitors/hypoxia- CD39-CD73-A2aR pathway inhibitors/CD47 inhibitor/IFNAR1 inhibitor

TME, Tumor Microenvironment; GMP, Granulocyte-Monocyte Progenitor; MPP, Multipotent Progenitor Cell; CMP, Common Myeloid Progenitor; VEGF, vascular endothelial growth factor; PIK3CA, Phosphatidylinositol-3-kinase catalytic subunit alpha; GATA3, GATA binding protein 3; MAP3K1, Mitogen-activated protein kinase kinase 1; BFB, Break Apart and Clone; CTCF, CCCTC-binding factor; GPS, G protein pathway suppressor 2; MUC16, mucin 16; SMAD4, Mothers against decapentaplegic homolog 4; TP53, Tumor protein 53; SYNE1, spectrin repeat containing nuclear envelope protein 1; DNAH11, dynein axonemal heavy chain 11; AKAP9, A-kinase-associated protein 9; RB1, retinoblastoma 1; CDH1, cadherin-1; JAK1, Janus kinase 1.

helper cells was associated with a better prognosis in the luminal A subtype. In the luminal B subtype, patients with high infiltration of central memory CD4 T cells had longer overall survival.

5. Microbiome of BC Depending on the Molecular Biological Subtype of the Tumor

Metabolic reprogramming and the microbiome can interact in numerous ways, influencing physiological and pathological responses during BC cancer progression [183]. For example, products of increased synthesis by tumor cells can reach the intestinal tract and affect microorganisms, promoting mucosal inflammation. In turn, microbial metabolites can be transported into the tumor microenvironment and participate in metabolic reprogramming [183].

The microbiome can influence tumor development and progression through various mechanisms [184]. In particular, some microorganisms can promote oncogenesis by inducing mutations, activating oncogenic signaling pathways (e.g., Wnt/ β -catenin), or inhibiting apoptosis in tumor cells (direct effects). The microbiome can modulate the immune response, influencing the local immune response and altering the tumor's response to chemotherapy and immunotherapy. Some microbial metabolites can be transported into the tumor microenvironment and participate in metabolic reprogramming. Chronic inflammation caused by the microbiota can promote malignant transformation of cells by creating an inflammatory environment. The microbiome can also alter the composition of the tumor stroma, influencing cell recruitment and their functional state.

Lactobacilli in benign and malignant breast tissues have been shown to be associated with metabolic pathways including Cys and Met metabolism, glycosyltransferases, and fatty acid biosynthesis [185]. *Cytophagaceae*, *Conexibacteraceae*, and *Flavobacteriaceae* modulate the BC immune microenvironment and induce an antitumor response via lipid pathways [184]. *Clostridiales* metabolite (trimethylamine N-oxide) induces pyroptosis by activating endoplasmic reticulum stress kinase PERK in TNBC [186]. Metabolites produced by gut microbiota can alter ER receptor activity and the response to endocrine therapy in ER-positive BC [187]. Increased levels of *Citrobacter* in the gut in BC are associated with increased biosynthesis of glycans and lipopolysaccharides [188]. A direct role of intestinal microbiota in hormonal dysregulation has been shown through its influence on β -glucuronidase expression [189]. Furthermore, patients with high *Campylobacter* counts and high inositol phosphate metabolic activity had the worst survival probabilities [190].

The BC tissue microbiome is also subtype-specific [191] (Table 4, Ref. [163,164,165,191]). *Arcanobacterium* were the most prevalent genera among TNBC tissue samples (75%). An additional nine genera had a spot prevalence of $\geq 50\%$, including *Brevundimonas* (73%), *Sphingobacteria* (67%), *Providencia* (67%), and *Prevotella* (67%) [192]. As a result of adaptation to the fatty acid-rich environment of mammary gland tissue or in response to environmental factors, a predominance of *Proteobacteria* and *Firmicutes* was observed.

Table 4. Subtype-associated features of the microbiome of BC tissues.

Authors, reference	Luminal A	Luminal B HER2-negative	Non-Luminal	Luminal B HER2-positive	TNBC
Komorowski A.S. and Pezo R.C. [191]	Flavobacterium [163] Methylobacterium [164] Arcanobacterium [164] Bifidobacterium Cardiobacterium Citrobacter Escherichia		Streptococcus	Bordetella Campylobacter Chlamydia Chlamydophila Legionella Pasteurella	Arcanobacterium [165] Actinomyces Brevundimonas Brucella Escherichia Prevotella Providencia Sphingobacteria Aerococcus Arcobacter Geobacillus Orientia Rothia

Different microbial signatures have been identified within each molecular subtype of BC [193]. Two clusters were identified among ER-positive, HER2-negative tumors: Cluster 1 had higher hybridization signals for *Propionibacteria*, *Arcanobacteria*, *Brucella*, *Brevundimonas*, and *Caulobacter*. No clusters were identified among ER/HER2-positive tumors, while two clusters were identified among HER2-enriched tumors: cluster 1 had lower hybridization signals for *Kingella*, *Brevundimonas*, *Eikenella*, *Bartonella*, and *Acinetobacter* [193,194].

Patients with HER2-enriched tumors had survival rates ranging from 75 to 86%, whereas ER/PR-positive tumors in cluster, which had a more diverse microbiome, had a lower mortality rate.

Gut microbiota has been shown to correlate with clinical phenotypes of BC [195]. A new BC subtyping system has been developed, and a subtype with more genetic mutations and a more complex immune environment (“complex BC”) has been identified. Activation of the TPK1-FOXP3-mediated Hedgehog signaling pathway and the TPK1-ITGAE-mediated mTOR signaling pathway was shown to be associated with poor prognosis in patients with “complex BC” [195].

Further research is needed to determine the role of the local mammary microbiome in breast carcinogenesis. Local dysbiosis may, for example, create or maintain a microenvironment favorable for tumor proliferation [193,194].

6. Clustering of BC Subtypes Based on Metabolomic and Genetic Studies

Several alternative classifications of BC tumors based on metabolomic and/or genetic studies have been proposed.

Tumors were stratified into two groups using unsupervised analysis of untargeted metabolite data [196]. One subgroup included normal breast tissue, ER-positive tumors, and some TNBC tumors and was designated the

“Lipid/Fatty Acid Rich” phenotype. The second subgroup included the majority of TNBC tumors and was designated the “Nucleotide/Carbohydrate Rich” phenotype. In TNBC tumors, an increase in the level of metabolites involved in the metabolism of glutamate and pyrimidines (glutamate, succinate, fumarate, etc.) was observed, which may contribute to cell proliferation.

All metabolic BC phenotypes can be classified into two heterogeneous clusters according to the energy metabolism classifier [197]. The two energy metabolic patterns included: (1) glycolysis- and PPP-dependent and (2) FA-enriched and glutaminolytically enriched. Cluster 1 consisted predominantly of HER2-enriched and basal-like BC, which was associated with lower survival, whereas cluster 2 predominantly included luminal A subtype. Luminal B and normal-like subtypes were evenly distributed across both clusters, confirming the metabolic heterogeneity of these BC phenotypes and its prognostic significance.

Shahnazari P. et al. [34] identified subtype-specific metabolic signatures. Group 1 (ER/PR-positive, HER2-negative) was characterized by increased amino acid metabolism, supporting nucleotide synthesis and redox balance (↑2-aminoadipic acid, ↑Thr, ↑Ser, ↑Tyr, and ↓β-Ala) [198,199,200]. Group 2 (ER/PR-positive, HER2-positive) demonstrated increased anaplerotic responses that promote rapid cell proliferation (↑homoserine, ↑citrulline) [75,201,202]. In group 3 (TNBC), a metabolic shift was observed towards energy production and biosynthesis to support aggressive proliferation (↑maltotriose, ↑β-Ala, ↑Glu, ↑α-ketoglutarate, ↑malate) [203]. Increased glycolytic and gluconeogenic activity (↑β-Ala, ↑maltotriose) have been demonstrated, further supporting glucose and energy metabolism required for rapid cell proliferation [204,205,206]. Important roles in maintaining this metabolic state are played by the enzymes glutaminase (GLS), which converts Gln to Glu to fuel the citric acid cycle, and malate dehydrogenase (MDH), which increases malate levels [207]. In TNBC, «Gln dependence» refers

to elevated levels of α -ketoglutarate and Glu. In group 4 (HER2-enriched), increased biosynthesis of monounsaturated phospholipids ($\uparrow$ PC 30:1, $\uparrow$ PC 32:1, $\uparrow$ PC 32:2, $\uparrow$ PE 32:1) and unique metabolic composition ($\uparrow$ N-acetyl-D-mannosamine, $\uparrow$ Gln, $\uparrow$ Asp, $\uparrow$ Tau) were observed. Increased membrane lipid synthesis was due to increased activity of the enzyme stearoyl-CoA desaturase 1, which promotes the formation of unsaturated phospholipids, increasing membrane fluidity and stability, which supports rapid proliferation and membrane adaptation, key features of HER2-positive BC cells [208,209]. Triacylglyceride accumulation is more pronounced in aggressive TNBC and HER2-enriched phenotypes [210,211].

Investigation of the metabolic landscape in BC has identified three subtypes with increasing degrees of metabolic deregulation [212]. Subtype M1 is dependent on bile acid biosynthesis, while M2 showed dependence on the methionine pathway, and M3 was involved in fatty acid, nucleotide, and glucose metabolism. The degree of metabolic alterations was closely correlated with tumor aggressiveness and patient outcome. Genomic characterization of metabolic subtypes revealed distinct oncogenic drivers, such as TP53 and PIK3CA mutations and MYC amplification.

Gong et al. [213] identified three heterogeneous subtypes of TNBC based on metabolic pathways with distinct metabolic features (lipogenic, glycolytic, and mixed subtypes). The lipogenic phenotype (MPS1) showed lipids accumulation ($\uparrow$ myristic, $\uparrow$ palmitoleic, $\uparrow$ oleic, $\uparrow$ arachidonic acids, $\uparrow$ acetyl-CoA carboxylase alpha, $\uparrow$ HMG-CoA reductase, $\uparrow$ FASN, and $\uparrow$ stearoyl-CoA desaturase). The MSP2 subtype exhibited increased expression of metabolic enzymes associated with glycolysis and nucleotide metabolism, as well as the glucose transporter GLUT, solute carrier family 2 member 1 (SLC2A1), and the lactate transporter SLC16A1. The MSP2 subtype also exhibited lower glucose levels and accumulation of glycolytic and nucleotide metabolic intermediates, including glucose-1-phosphate, dihydroxyacetone phosphate, lactate, and adenosine 3'-5'-diphosphate. MPS3, a mixed subtype, showed only partial dysregulation of metabolic pathways. The subtypes were characterized by different prognoses and genomic alterations. MPS1 subtype TNBC was more sensitive to metabolic inhibitors affecting fatty acid synthesis, while MPS2 subtype was more sensitive to inhibitors affecting glycolysis.

Haukaas T.H. et al. [214] applied hierarchical clustering and identified three distinct metabolic subgroups (MC1, MC2, and MC3). MC1 exhibited a lipidomic phenotype ($\uparrow$ GPC, $\uparrow$ PCho) with lower concentrations of acetate and Gln due to lower expression of aldehyde dehydrogenase and GLS enzymes. Cluster MC2 exhibited a low glycolytic profile with elevated glucose concentrations; and MC3 exhibited elevated levels of lactate and Ala. Genes related to collagens and the extracellular matrix were downregulated in cluster MC1 and upregulated in clusters MC2 and

MC3, respectively, explaining the differences in protein subtypes within the metabolic clusters. Genetic subtypes were evenly distributed across the three metabolic clusters and thus may provide an additional explanation for BC heterogeneity.

Proteomics and metabolomics allow TNBC to be classified into three subtypes: C1 ($\uparrow$ sphingolipids, $\uparrow$ long-chain and unsaturated FA), C2 ($\uparrow$ Glu and carbohydrate metabolism, $\uparrow$ oxidative reactions) and C3, whose metabolomics are more closely related to normal breast tissue [215]. Previously developed transcriptomic subtypes of TNBC were refined and subtype-specific metabolites were identified as potential therapeutic targets. The luminal androgen receptor (LAR) transcriptomic subtype overlapped with the C1 metabolomic subtype, while the basal-like immunosuppressive (BLIS), immunomodulatory (IM), and mesenchymal-like (M) subtypes belong to C2 and C3. Furthermore, LAR tumors are characterized by high ceramide pathway activation and sphingosine-1-phosphate levels, while BLIS tumors contain high levels of N-acetyl-aspartyl-glutamate.

Various protein signatures associated with different immune responses and clinical outcomes have been identified in BC [216]. Basal-like BC can be divided into two subgroups, including immunoactive (favorable prognosis) and immunoactive cold (unfavorable prognosis). HER2-enriched BC can be divided into three subgroups based on lipid metabolism, immune response, and extracellular matrix characteristics. Four proteomic clusters have been formed for TNBC: basal-immunoactive, basal-immunoactive cold, mesenchymal, and luminal.

Highly transcribed noncoding elements (HTNEs) are associated with subtype-specific transcriptional processes [217,218]. BC samples were classified into different clinical subtypes [219]. Class I (ER/PR-positive) included luminal A/B patterns, class II (ER/PR-negative) included HER2-enriched and basal-like patterns. A Th1 and Th2 cell differentiation pathway unique to class I and a hippo signaling pathway specific to class II were found. Numerous clinical reports have shown that estrogen induces a shift between Th1 and Th2 in a pathway termed Th1 and Th2 cell differentiation [220]. The hippo signaling pathway can regulate BC tumor growth, metastasis, and drug resistance and is not hormone-dependent [221].

Thus, numerous attempts have been made to alternatively classify BC into metabolically significant groups. However, the identified groupings are difficult to compare with the existing traditional classification or with each other. In all cases, a smaller number of subgroups (2–3) is observed, which is apparently due to a reduction to three basic metabolic phenotypes (glycolytic, OXPHOS-dependent, and lipid). We also believe that the existence of alternative classification options is due to the heterogeneity of subtypes identified based on immunohistochemical and genetic classification. However, to date, no advantage of alternative classification options over existing BC subtype-

Table 5. Some groups of metabolic inhibitors for breast cancer therapy.

Metabolic inhibitors	Purpose
Mitochondrial process inhibitors	Target oxidative phosphorylation in mitochondria. These include classic inhibitors (e.g., metformin, ME-344) and newly developed compounds (e.g., IACS010759) that are undergoing clinical trials [222].
AKT (protein kinase B) inhibitors	AKT is a key component of the PI3K/AKT/mTOR signaling pathway, which regulates cell proliferation, survival, and metabolism. AKT inhibitors (e.g., capivasertib and ipatasertib) have been tested in clinical trials, including in combination with chemotherapy for TNBC [223].
PI3K (phosphatidylinositol 3-kinase) inhibitors	The use is associated with mutations in the PIK3CA gene, which encodes the catalytic α -isoform of PI3K (p110 α). For example, alpelisib is a PI3K α -specific inhibitor. Its use may be accompanied by hyperglycemia, the most common side effect [224].
CDK4/6 inhibitors	They block cyclin-dependent kinases 4 and 6, which regulate the G1-to-S phase transition. CDK4/6 inhibitors are used in hormone-receptor-positive, HER2-negative advanced or metastatic BC [225]. CDK4/6 inhibitors may exhibit synergism when combined with endocrine therapy [226].
PARP (poly(ADP-ribose) polymerase) inhibitors	PARP inhibitors are used for BC with BRCA1/BRCA2 mutations. Olaparib is the first PARP inhibitor approved for the treatment of metastatic BC [227,228].
Inhibitors of fatty acid metabolism enzymes	Key enzymes of fatty acid metabolism, such as ATP citrate lyase, acetyl-CoA carboxylase, fatty acid synthase (FASN), carnitine palmitoyltransferase, and acyl-CoA dehydrogenases of various chain lengths, desaturases, and elongases, play an important role in maintaining lipid metabolism homeostasis [229]. For example, carnitine palmitoyltransferase 1a (Cpt1a) is a key enzyme in the oxidation of long-chain fatty acids in BC caused by the ErbB2 gene mutation. The combination of a ketogenic diet consisting of short-chain fatty acids or monoclonal antibodies against ErbB2 with Cpt1a deficiency significantly inhibits tumor growth, enhances apoptosis, and reduces lung metastasis [230].
Glycolysis inhibitors	Antiglycolytic drugs target key glycolytic enzymes in BC, including glucose transporters, hexokinase, phosphofructokinase, pyruvate kinase, and lactate dehydrogenase-A [231].

ing systems has been demonstrated in terms of prognosis and treatment decisions.

7. Prospects for the Use of Metabolic Therapy in BC

Metabolic inhibitors in BC therapy are drugs that target key metabolic pathways involved in tumor cell growth, proliferation, and survival. They can be used both as monotherapy and in combination with other treatments (Table 5, Ref. [222,223,224,225,226,227,228,229,230,231]).

Metabolic inhibitors should be selected according to the phenotypic features of BC (Fig. 4) [232].

A distinctive feature of the HER2-positive BC subtype is its ability to utilize aerobic glycolysis. HER2 protein activity increases glucose transporter expression, leading to increased glucose consumption and increased environmental acidity due to lactate production, which promotes BC progression [233]. Lipid metabolism is unique in HER2-positive tumors due to increased activity of enzymes involved in lipid biosynthesis. These enzymes are involved in the production of new cell membranes and the transmission of critical lipid signals necessary for cell growth and survival. Tumor cells enhance Gln metabolism, absorbing large amounts of it, which serves as an important resource for the synthesis of nucleotides and protein components.

Metabolic processes in TNBC tumors are not limited to glycolysis: FA synthesis is activated to generate energy and form cell membranes. TNBC cells require metabolic adaptation in conditions of nutrient and oxygen deprivation,

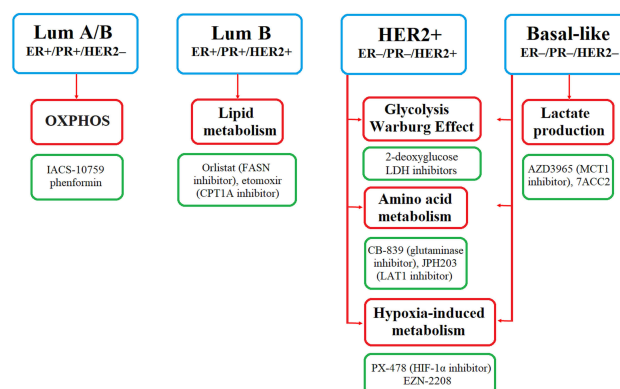


Fig. 4. Metabolic features of BC phenotypes as a potential for metabolic therapy. OXPHOS, oxidative phosphorylation; LDH, lactate dehydrogenase; LAT1, solute carrier family 7 member 5 (SLC7A5); HIF-1 α , hypoxia-inducible factor 1-alpha; MCT1, monocarboxylate transporter 1.

as they utilize FA as their primary energy source. TNBC tumors rely on Gln metabolism, as it is involved in the creation of intermediates that fuel the TCA cycle.

ER-positive BC possesses superior metabolic adaptability [131] due to a dual metabolic pathway involving glycolysis and oxidative phosphorylation. ER-positive tumors exhibit increased lipid biosynthesis, which is a fundamental metabolic feature. Cells utilize lipids to build membranes during cell division and to activate hormonal signals that stimulate tumor growth [234]. The survival of

ER-positive BC cells largely depends on lipid metabolism processes, particularly the amino acids Ser and Gly, which are the starting point for one-carbon metabolism. One-carbon metabolism enables the synthesis of nucleotides, which allows DNA replication, works in conjunction with DNA repair mechanisms, and controls epigenetic regulation through methylation.

Thus, in HER2-positive and TNBC, targeting glycolysis, Gln metabolism, and lipid biosynthesis pathways to arrest BC growth shows promise [235]. Combinations of therapeutic approaches targeting one or more metabolic pathways are being considered to develop more effective treatments for difficult-to-treat BC [130]. Methods targeting lipid biosynthesis, amino acid metabolism, and the transition from oxidative phosphorylation to glycolysis are being developed for the treatment of ER-positive BC [236]. Targeting the HIF signaling pathway may be a promising strategy for treating hypoxic BC, in particular TNBC [237]. Suppression of HIF-1 α protein accumulation is caused by topotecan (a topoisomerase I inhibitor), as well as the cardiac glycoside digoxin [237]. The combination of digoxin with paclitaxel or gemcitabine results in tumor regression in TNBC by blocking HIF-dependent transcriptional responses [237]. A number of metabolic inhibitors are in clinical trials (Fig. 4), including the glutaminase (GLS1) inhibitor CB-839 (Telaglenastat) (NCT03057600, Phase I/II, recruitment completed), the fatty acid synthase (FASN) inhibitor TVB-2640 (Denifanstat) (NCT03179904, Phase I/II, completed/ongoing), the OXPHOS complex I inhibitor metformin (NCT01101438, Phase II/III, completed/observational), the pyruvate dehydrogenase and α -ketoglutarate dehydrogenase inhibitor CPI-613 (Devimistat) (NCT03435289, Phase I/II, ongoing), the monocarboxylate transporter 1 (MCT1) inhibitor AZD3965 (NCT01791595, Phase I, limited enrollment), the mTOR signaling inhibitor Everolimus (NCT01698918, Phase III, approved for the treatment of endocrine resistance), the glycolysis inhibitor 2-DG (2-deoxyglucose) (NCT00096707, Phase I/II, completed), and others [232].

The development and use of metabolic inhibitors in oncology is a rapidly developing area that requires further study of the mechanisms of drug action and optimization of treatment regimens.

8. Conclusions

The existence of characteristic metabolic and genetic features of BC has been demonstrated. Specifically, TNBC exhibits increased aerobic glycolysis and serine metabolism, as well as glutamine dependence; ER-positive BC exhibits decreased glucose and glutamine uptake, as the tumor preferentially consumes lactate produced by adjacent cancer-associated fibroblasts; and HER2-enriched BC exhibits increased fatty acid synthesis, with increased glucose and glutamine uptake. However, existing BC phenotyping does not always allow for the classification of samples based on their metabolic characteristics. This requires the

introduction of new classification methods that will have clinical relevance. The intersection of these new groups, existing subtypes, and standard biomarkers already in use should facilitate more personalized treatment and improved outcomes in the future.

Author Contributions

LB designed the research study. The author contributed to editorial changes in the manuscript. The author read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Thanks to all the peer reviewers for their opinions and suggestions.

Funding

This research was funded by Russian Science Foundation, grant number 23-15-00188, <https://rscf.ru/project/23-15-00188/>.

Conflicts of Interest

The author declares no conflicts of interest.

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