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REVIEW

The Landscape of Potential Targeted Treatments and Chemotherapy Efficacy Biomarkers for TNBC

Yujuan Kang*, Yanqing Liu*, Zhi Liang*, Song Zhang*, Guangdong Qiao

Department of Breast Surgery, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Guangdong Qiao, Department of Breast Surgery, The Affiliated Yantai Yuhuangding Hospital of Qingdao University, Yantai, People's Republic of China, Email qiaoguangdong@ytyhdyy2.wecom.work

Abstract: Triple negative breast cancer (TNBC) is characterized as an estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor (HER-2) negative disease with an enhanced systemic metastatic incidence, chemotherapeutic insensitivity, and drug resistance. The internal characteristics of TNBC are extraordinary complex and are accompanied by numerous gene mutations and constitutively activated signaling networks, which, in turn, augment TNBC malignancy. There is an urgency to uncover new and potent therapeutic targets for TNBC. Herein, we discussed the historical as well as newly discovered subtypes and properties of TNBC. We also presented a systematic outline of the aberrant gene expression and abnormal activated signaling networks in TNBC. Subsequently, we summarized the corresponding targeted therapeutic drugs, and reviewed the current targeted TNBC therapies launched in clinical trials, thereby providing a direction for future TNBC therapy. We also provided a detailed list of coding genes involved in chemo-sensitive and chemo-resistance of TNBC, which can potentially serve as indicators of chemotherapeutic efficacy. Finally, we discussed the novel and future potential treatments of TNBC. This review highlighted the new era of TNBC treatment in the coming years and provided the gene expression profile of TNBC patients who may benefit from chemotherapy.

Keywords: TNBC, immunotherapy, PI3K-AKT-mTOR, BRCA, EGFR, FGFR, PD-L1, CDK, chemo-sensitive, chemo-resistance

Introduction

About 2.1 million women suffer from breast cancer (BC) in a given year, and BC is the largest contributor of cancer-linked deaths among women.[1] BC is immunohistochemically (IHC) stratified into five sub-cohorts, namely, Luminal A, Luminal B, HER2, TNBC, and Normal-Like BC.[2] TNBC, marked with no ER, PR, and HER2 contents, make up approximately 15–20% of all BC patients.[3] TNBC including six TNBC categories,[4,5] namely, two Basal-Like (BL1 and BL2), a mesenchymal (M), a mesenchymal stem-like (MSL), an immunomodulatory (IM), and a luminal androgen receptor (LAR).[5] Due to the poor response of TNBC patients to anti-HER2 monoclonal antibodies (mAb)-based and endocrine interventions, classic anticancer treatments, such as, surgery, radiotherapy, and chemotherapy remain the primary strategies for treating TNBC.[6] Among TNBC patients, disease progression and recurrence are common within the initial 3–5 years following diagnosis, and distant metastases frequently occur in the brain and lung.[7] The primary TNBC intervention is chemotherapy. Anthracyclines and Taxanes are the most effective drugs.[8] Even though 30% of TNBC patients respond adequately to chemotherapy and have good prognosis, presently, there are no available interventions for chemo-resistant patients.[9] Among an unselected TNBC population, BRCA mutation incidence is about 20%.[10] Emerging evidences revealed that platinum agent introduction in metastatic and neoadjuvant settings achieves satisfactory outcomes in patients with BRCA mutations.[11,12] Furthermore, others have successfully employed poly ADP-ribose polymerase (PARP) inhibitors to cure TNBCs with BRCA mutations.[13] With growing advancements in medicinal technology, immunotherapeutic agents have emerged as drugs with robust responses and enhancements in patient overall survival (OS).[14] TNBC exhibits excess tumor infiltrating lymphocytes (TILs),[15] relative to other subtypes, along with markedly enhanced PD-L1 expression[16] and OS strongly linked to the severity of immune cell

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invasion.[17] Hence, immune checkpoint blockade (ICB) therapies, such as, programmed death-1 (PD-1)- or programmed death-ligand 1 (PD-L1)-specific antibodies were shown to be highly efficacious in suppressing TNBC development.[18,19]

In addition, dysregulated gene expression and signaling networks are the most prominent feature of TNBC.[20] Presently, several molecular targeted drugs are recognized as crucial for the treatment of TNBC. Notably, even though some TNBC patients are responsive to chemotherapy, there is still a considerable need for novel targeted therapeutic strategy discovery.[21] In this review, we summarized the abnormal TNBC gene expression landscape, existing molecular targeted treatments, and chemotherapeutic efficacy biomarkers from the following four aspects: (1) The Molecular Subtypes of TNBC; (2) The Essential Characteristics and Potential Molecular Targeted Therapy of TNBC; (3) Coding Genes Involved in Chemo-Sensitive and Chemo-Resistance of TNBC; (4) Potential Novel Therapeutic Targets for TNBC.

Results

The Molecular Subtypes of TNBC

TNBC is a diverse disease that displays considerable differences in pathological characteristics, physiological activities, and genetic profiles.[5,22] The established TNBC subtypes are BL1, BL2, M, MSL, IM, and LAR,[5] and they are all unique in their features. The BL1 subtype is characterized by enhanced MYC, PI3K catalytic subunit α (PIK3CA), CDK6, AKT2, KRAS, FGFR1, IGF1R, CCNE1, and CDKN2A/B amplification, and augmented prevalence of heterozygous or homozygous deletion of DNA repair-associated genes (BRCA2, PTEN [phosphatase and tensin homolog], MDM2, RB1, and TP53). It is often combated with PARP inhibitors (PARPi) and genotoxic agents.[23] The BL2 subtype features aberrant activation of EGFR, MET, NGF, Wnt/β-catenin, and IGF-1R pathway activations, and it is treated with mTOR inhibitors and growth factor inhibitors.[23] The M subtype features constitutive stimulation of the cell migration-associated axis, extracellular matrix-receptor association network, and differentiation axes [Wnt, anaplastic lymphoma kinase, transforming growth factor (TGF)-β],[23] and it is targeted with mTOR inhibitors and drugs against the epithelial-mesenchymal-transition (EMT).[24] The MSL subtype exhibited markedly reduced cell proliferation-associated genes, with simultaneous elevations in the stemness-associated genes (ABCA8, PROCR, ENG, ALDHA1, PER1, ABCB1, TERT2IP, BCL2, BMP2, and THY), HOX genes (HOXA5, HOXA10, MEIS1, MEIS2, MEOX1, MEOX2, and MSX1), and mesenchymal stem cell (MSC) markers (BMP2, ENG, ITGAV, KDR, NGFR, NT5E, PDGFR, THY1, and VCAM1), and this is managed using PI3K inhibitors, v-src sarcoma viral oncogene homolog (Src) antagonists, or antiangiogenic drugs. A Src inhibitor (Dasatinib) may also be used to treat M and MSL TNBC.[23] Of note, the M and MSL categories are linked to an enhanced angiogenesis signature score.[25] The IM subtype is featured with abundant immune signaling networks, including, Th1/Th2, NK cell, B cell receptor, dendritic cell (DC), T cell receptor, interleukin (IL)-12, and IL-7 networks, and this category is treated with immune checkpoint inhibitor (ICI).[23] The LAR subtype have enhanced AR signaling, as is evidenced by IHC, which depicts upregulated AR, downstream genes, and auxiliary activators (DHCR24, ALCAM, FASN, FKBP5, APOD, PIP, SPDEF, and CLDN8).[26,27] LAR tumors also contain PI3KCA (55%), AKT1 (13%) and CDH1 (13%) gene mutations.[25] LAR responds to anti-AR therapy.[5]

With advancements in medical technology, there have emerged certain modification to TNBC stratification. Burstein et al proposed a four subtypes classification of TNBC, including, LAR, mesenchymal (MES), basal-like immunosuppressed (BLIS), and basal-like immune activated (BLIA).[28] The potential corresponding targets were also identified as follows: (i) LAR: AR and MUC1, (ii) MES: growth factor receptors, (iii) BLIS: an immunosuppressing molecule (VTCN1), and (iv) BLIA: STAT-related molecules and cytokines.[28] Alternatively, Zhao et al identified AR, CD8, FOXC1, and DCLK1 as TNBC bioindicators, and stratified TNBCs into five categories, based on IHC: (a) IHC-based LAR (IHC-LAR; AR-positive [+]), (b) IHC-based immunomodulatory (IHC-IM; AR-negative [−], CD8+), (c) IHC-based basal-like immune-suppressed (IHC-BLIS; AR−, CD8−, FOXC1+), (d) IHC-based mesenchymal (IHC-MES; AR−, CD8−, FOXC1−, DCLK1+), and (e) IHC-based unclassifiable (AR−, CD8−, FOXC1−, DCLK1−). The IHC-LAR category is marked with a strongly activated HER2 network. The IHC-IM category has $CD8^+$ T cell invasion into the tumor parenchyma. The IHC-BLIS category has an enhanced VEGF expression. The IHC-MES category is featured by active JAK/STAT3 axis.[29] *He* et al stratified TNBC according to immune profiles as follows: High (Immunity_H), Medium (Immunity_M), and Low (Immunity_L). Immunity_H displays a vast immune cell invasion and anti-tumor

immunologic activity. Among its immune signatures are excess cellular apoptosis, as well as calcium, MAPK, PI3K–Akt, and RAS networks. Alternatively, Immunity_L presents with a diminished immune profile and enhanced cellular cycle, Hippo axis, DNA replication, mismatch repair, cell adhesion molecule interaction, spliceosome, adherens junction activity, pyrimidine metabolism, glycosylphosphatidylinositol-anchor biosynthesis, and RNA polymerase networks. There are five transcription factor (TF) genes that are specific to the Immunity_H category, namely, CORO1A, STAT4, BCL11B, ZNF831, and EOMES, and two that are specific to the Immunity_L category, namely, IRF8 and SPI1.[30] These TNBC classifications facilitate an elevated level of understanding of TNBC (Table 1).

The Essential Characteristics and Potential Molecular Targeted Therapy of TNBC

TNBC prognosis is generally worse than non-TNBC.[8,31,32] Although chemotherapy is the primary intervention for TNBC, it often produces rather disappointing outcomes. Due to the lack of precision therapeutic targets, TNBC is often aggressive in BC patients.[33,34] TNBC is a heterogeneous tumor, accompanied by dysregulated gene expression and constitutively activated signaling networks. In this report, we provide a detailed list of gene mutations and aberrantly activated signaling networks in TNBC, as well as corresponding treatment methods for TNBC, based on the following aspects: (a) DNA Damage Response (DDR)-Related BRCA Loss-Function Mutation; (b) PI3K Signaling Network; (c) NOTCH Signaling Network;

Table 1 The Subgroups and Properties of TNBC

TNBC	ER (-)	PR (-)	HER2 (-)	Properties	Therapy	Ref
Lehmann et al	Basal-Like 1 (BL1)			(a) High expression of MYC, PIK3CA, CDK6, AKT2, KRAS, FGFR1, IGF1R, CCNE1, CDKN2A/B; (b)Augmented prevalence of heterozygous or homozygous deletion of DNA repair-associated genes (BRCA2, PTEN, MDM2, RB1, and TP53)	PARPi; Genotoxic Agents	[5, 23]
	Basal-Like 2 (BL2)			(a) Activation of EGFR, MET, NGF, Wnt/β-catenin, IGF-1R pathways	mTOR Inhibitors; Growth Factor Inhibitors	[5, 23]
	Mesenchymal (M)			a. Activated cell migration- associated axis, extracellular matrix–receptor network, and differentiation axes (Wnt, anaplastic lymphoma kinase, TGF-β); (b) Higher signature score for angiogenesis	mTOR Inhibitors; Drugs against EMT; Src Inhibitor	[5, 23–25]
	Mesenchymal stem-like (MSL)			a. Reduced cell proliferation-related genes; b. Elevation in the stemness-related genes (ABCA8, PROCR, ENG, ALDHA1, PER1, ABCB1, TERT2IP, BCL2, BMP2, and THY); c. Elevation in the HOX genes (HOXA5, HOXA10, MEIS1, MEIS2, MEOX1, MEOX2, and MSX1); d. Elevation in the MSC-specific markers (BMP2, ENG, ITGAV, KDR, NGFR, NT5E, PDGFR, THY1, and VCAM1); e. Higher signature score for angiogenesis;	PI3K Inhibitors; Src Inhibitor; Antiangiogenic drugs	[5, 23, 25]
	Immunomodulatory (IM)			a. Enriched immune related signaling networks, including, Th1/Th2, NK cell, B cell receptor, dendritic cell (DC), T cell receptor, interleukin (IL)-12, and IL-7 networks	ICI	[5, 23]
	Luminal Androgen Receptor (LAR)			a. Enhanced AR signaling, downstream genes, and auxiliary activators (DHCR24, ALCAM, FASN, FKBP5, APOD, PIP, SPDEF, and CLDN8) (b) Contain PI3KCA (55%), AKT1 (13%) and CDH1 (13%) gene mutations	AR Antagonist (Bicalutamide)	[5, 25–27]
Burstein et al	Luminal androgen receptor (LAR)			AR and MUC1		[28]
	Mesenchymal (MES)			Growth factor receptors		
	Basal-like immunosuppressed (BLIS)			Immunosuppressing molecule (VTCN1)		
	Basal-like immune activated (BLIA)			STAT-related molecules and cytokines		

(*Continued*)

Table 1 (Continued).

TNBC	ER (-)	PR (-)	HER2 (-)	Properties	Therapy	Ref
Zhao et al	IHC-based LAR (IHC-LAR; AR-positive [+])			Activation of HER2 network		[29]
	IHC-based immunomodulatory (IHC-IM; AR-negative [−], CD8+)			$CD8^+$ T cell invasion into the tumor parenchyma		
	IHC-based basal-like immune-suppressed (IHC-BLIS; AR−, CD8−, FOXC1+)			Enhanced VEGF expression		
	IHC-based mesenchymal (IHC-MES; AR−, CD8−, FOXC1−, DCLK1+)			Active JAK/STAT3 axis		
	IHC-based unclassifiable (AR−, CD8 −,FOXC1−, DCLK1−)			Unknown		
He et al	Immunity High (Immunity_H)			(a) Excess cellular apoptosis, as well as calcium, MAPK, PI3K–Akt, and RAS networks; (b) Express five TF genes (CORO1A, STAT4, BCL11B, ZNF831, and EOMES)		[30]
	Immunity Medium (Immunity_M)			In the middle		
	Immunity Low (Immunity_L)			(a) Diminished immune profile and enhanced cellular cycle, Hippo axis, DNA replication, mismatch repair, cell adhesion molecule interaction, spliceosome, adherens junction activity, pyrimidine metabolism, glycosylphosphatidylinositol-anchor biosynthesis, and RNA polymerase networks		

(d) CDK-Rb Signaling Network; (e) EGFR Activation; (f) Angiogenesis Signaling Network; (g) HER2-Low TNBC; (h) DDR Signaling Network (i) Immunotherapy, and (j) Androgen Receptor (AR) (Figure 1 and Table 2).

DDR-Related BRCA Loss-Function Mutation

Among the cancer features are DNA damage and impaired repair.[98] Prior reports demonstrated loss-of-function mutations in two essential BC susceptibility genes (BRCA1 and BRCA2) that modulate DDR, in 5% of BC patients.[99–101] BRCA1 and BRCA2 proteins modulate DNA replication for stabilization and homologous recombination (HR).[102] Based on one report, 70% of the inherited BRCA1 mutation-harboring BC patients and 16~23% of BRCA2 mutation-harboring BC patients are TNBC.[103] TNBC PARP enzymes are essential to the base excision repair mechanism, and PARP1 and PARP2 modulate DDR process.[104] BRCA1/2-mutated tumors tend to possess extra sensitivity toward PARP1 inhibition induced synthetic lethality. Thus, PARP1 inhibitors are promising for BRCA1/2 mutated patients.[105] The PARPi Olaparib is highly potent as a monotherapy in BC patients.[106] Presently, there are five BC-combating PARPi are under clinical validation: Olaparib, Rucaparib, Niraparib, Talazoparib, and Veliparib.[35] Additionally, emerging preclinical and clinical investigations demonstrated strong efficacy of platinum-based chemotherapy among TNBC patients.[107] Moreover, relevant clinical investigations were launched to accurately access the therapeutic effect of PARPi in TNBC and BC (https://clinicaltrials.gov/) (Supplemental Table 1).

PI3K Signaling Network

Dysregulated phosphoinositide 3-kinase (PI3K)/AKT/mTOR is a hallmark of cancerous development.[105] This axis is essential for the receptor tyrosine kinase (RTK) signaling and tumor growth in BC.[108] In fact, PI3K pathway mutations form a special subgroup among TNBC patients.[20] In TNBC, the aberrant PI3K/AKT/mTOR axis activation is regulated by upstream regulator, activating PIK3CA mutations, PTEN loss of function or expression mutation, and proline-rich inositol poly-phosphatase (negative PI3K modulator) downregulation.[109,110] Herein, we summarized the underlying mechanisms and PI3K signaling-targeted drugs associated with TNBC.

PI3K Inhibitors

In a previous report, it was revealed that pan-PI3K inhibitor (Buparlisib), combined with Buparlisib and Olaparib, diminishes

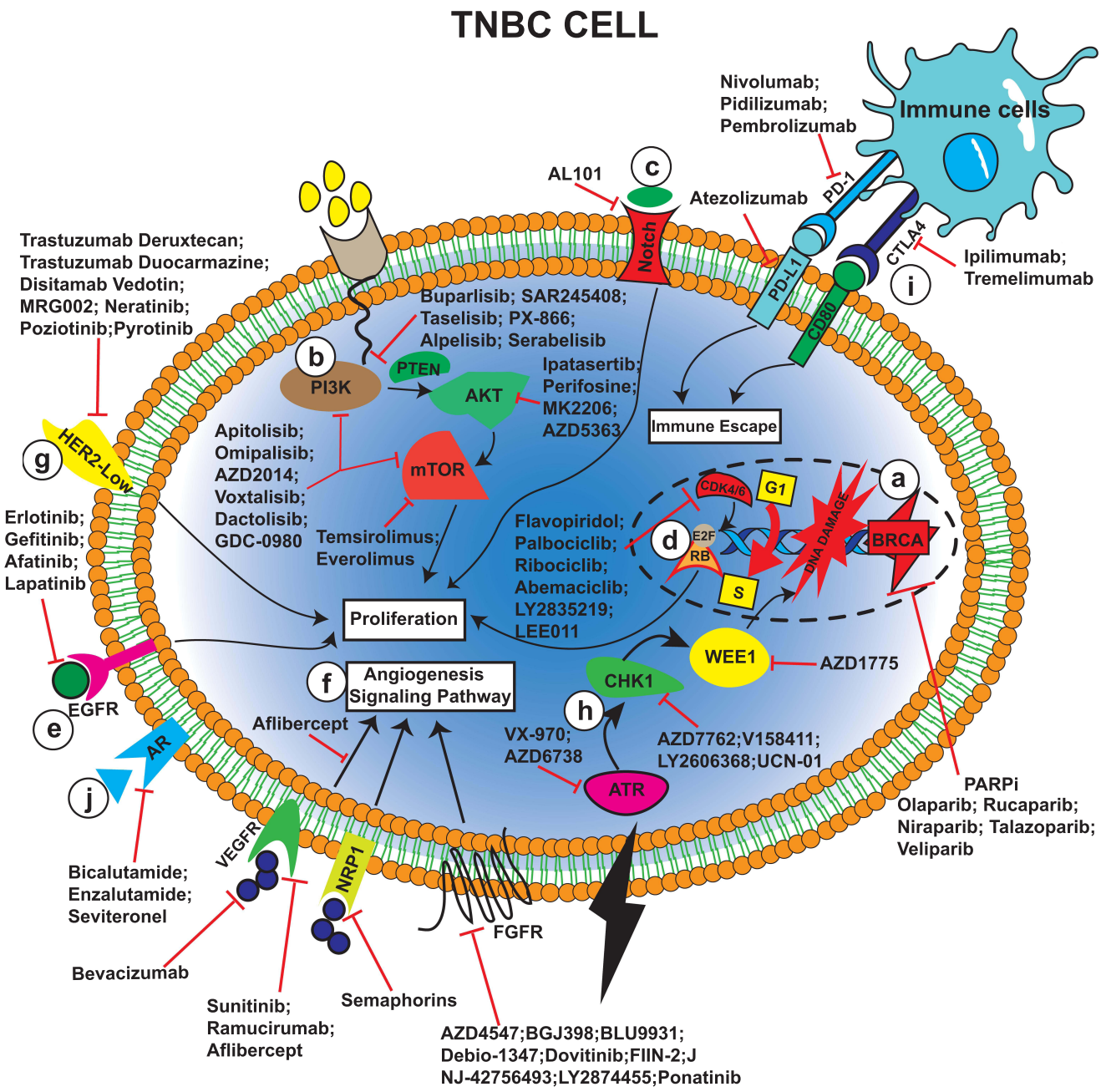

Figure 1 The abnormal gene and cell signal transduction profiles, as well as corresponding targeted TNBC therapy. (**a**) DNA Damage Response (DDR)-Related BRCA Loss-Function Mutation; (**b**) PI3K Signaling Network; (**c**) NOTCH Signaling Network; (**d**) CDK-Rb Signaling Network; (**e**) EGFR Activation; (**f**) Angiogenesis Signaling Network; (**g**) HER2-Low TNBC; (**h**) DDR Signaling Network (**i**) Immunotherapy, and (**j**) Androgen Receptor (AR).

BRCA1/2 content and encourages HR deficiency in BRCA1 WT TNBC patients.[36] In addition, the pan-PI3K inhibitors (SAR245408, Taselisib, and PX-866) are undergoing studied for HER2$^+$ and HR$^+$ BC.[37–39] Alpelisib is an isoform-specific PI3K inhibitor under examination in clinical trials.[40] Moreover, there is ongoing development of Serabelisib, a robust and targeted PIK3CA inhibitor for management of solid tumors.[41] The relevant clinical trials are listed in Supplemental Table 1.

AKT Inhibitors

Ipatasertib inhibits AKT which is downstream of PI3K.[42] Early AKT inhibitors, namely, Perifosine and MK2206, exhibited no clinical significance in Phase II trials,[43] however, novel AKT inhibitors appear to be highly promising in Phase I trials.[44,45]

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Table 2 The Molecular Targeted Medicines of TNBC

Drug Type	Drugs Name	Targeted Gene/Signaling Pathway	Ref
PARP Inhibitors	Olaparib; Rucaparib; Niraparib; Talazoparib; Veliparib	BRCA1/2	[35]
PI3K Inhibitors	Buparlisib; SAR245408; Taselisib; PX-866; Alpelisib; Serabelisib	PI3K	[36–41]
AKT Inhibitors	Ipatasertib; Perifosine; MK2206; AZD5363	AKT	[42–46]
mTOR Inhibitors	Temsirolimus; Everolimus	mTOR	[47]
Dual PI3K/AKT/mTOR Inhibitors	Apitolisib; Omipalisib; AZD2014; Voxtalisib; Dactolisib; GDC-0980	PI3K/AKT/mTOR	[48–53]
Notch Inhibitors	AL101	Notch	[54, 55]
CDK4/6 Inhibitors	Flavopiridol; Palbociclib; Ribociclib, Abemaciclib; LEE011; LY2835219	CDK-Rb Pathway	[56–58]
EGFR TKI	Erlotinib; Gefitinib	EGFR	[59]
Anti-EGFR mAb	Afatinib; Lapatinib	EGFR and ERBB2	[59]
VEGFR mAb	Bevacizumab; Sunitinib; Ramucirumab	VEGF-A and VEGFR	[60–62]
Anti-angiogenic	Semaphorins	NRP1 and NRP2	[63]
VEGF decoy receptor	Aflibercept	VEGFR	[64]
FGFR Inhibitors	AZD4547; BGJ398; BLU9931; Debio-1347; Dovitinib; FIIN-2; JNJ-42756493; LY2874455; Ponatinib	FGFR	[65–74]
Anti-HER2 ADC	Trastuzumab Deruxtecan; Trastuzumab Duocarmazine; Disitamab Vedotin; MRG002	HER2	[75]
Anti-HER2 TKIs	Neratinib; Poziotinib; Pyrotinib	HER2	[76]
ATR Inhibitors	VX-970; AZD6738	ATR-CHK1-WEE1	[35]
CHK1 Inhibitors	AZD7762; V158411; LY2606368; UCN-01	ATR-CHK1-WEE1	[77–80]
WEE Inhibitors	AZD1775	ATR-CHK1-WEE1	[81]
CTLA-4 Inhibitors	Ipilimumab; Tremelimumab	CTLA-4	[82]
PD-1 Inhibitors	Pembrolizumab; Pidilizumab; Nivolumab	PD-1	[83]
PD-L1 Inhibitors	Atezolizumab	PD-L1	[83]
AR Inhibitors	Bicalutamide; Enzalutamide; Seviteronel	AR	[84]
Ferroptosis related drugs	1-methyl-3-isobutylxanthine; Rosiglitazone	Ferroptosis Pathway	[85]
Targeted ADC bioindicators	Sacituzumab Govitecan (IMMU-132); Ladiratuzumab vedotin (SGN-LIV1A); Glembatumumab Vedotin (CDX-011); AVID100; U3-1402; CAB-ROR2-ADC; SAR566658	Trop-2; LIV1; EGFR; gpNMB; EGFR; HER3; ROR2; DS6	[86–89]
Ceritinib	Ceritinib	RTK-ACK1/FAK-AR	[90, 91]
Src Inhibitor	Dasatinib	Src	[92–96]
CDK12/CDK13 Inhibitor	SR-4835	CDK12/CDK13	[97]

Other AKT inhibitors (AZD5363) are under clinical development either as a mono- or chemo-combined therapy or as targeted agents for TNBC therapy.[43,46] Supplemental Table 1 summarizes the related clinical trials.

mTOR Inhibitors

A phase I investigation explored the synergistic effect of the chemotherapeutic doxorubicin, antiangiogenic bevacizumab, and mTOR inhibitors (Temsirolimus, Everolimus) in TNBC patients.[47] Clinical trials related with them are provided Supplemental Table 1.

Dual PI3K/AKT/mTOR Inhibitors

Apitolisib is a PI3K inhibitor that also targets mTORC.[48] Omipalisib is reported to have strong pan-PI3K and mTORC suppression abilities in a $HER2^+$ model.[49] Preclinical information confirmed the mTORC1/2 inhibitor AZD2014-based inhibition of p-AKT, relative to everolimus in TNBC patient-based xerograph models.[50] Voxtalisib is another PI3K and mTOR inhibitor that is presently under investigation in clinical trials as a potential HR^+ tumor treatment.[51] Dual PI3K/AKT/mTOR inhibitors are often administered alongside other drugs. Dactolisib is a potential PI3K and mTOR inhibitor that will supplement MEK162 (a MEK inhibitor) therapy in treated TNBC.[52] *De* et al also reported that the synergistic effect of GDC-0980 (pan-PI3K and mTOR inhibitor) and ABT888 (a PARPi) significantly suppressed tumor development in a PTEN-null TNBC model.[53] Clinical trials are summarized in Supplemental Table 1.

NOTCH Signaling Network

The NOTCH axis is a robust bioindicator of TNBC. Notch gain of function mutations occured in 10% of TNBC patients. The NOTCH signaling pathway utilizes four distinct receptor types (Notch-1 through Notch-4) which interact with five specific ligand molecules (Delta-like 1, 3, and 4 along with Jagged proteins 1 and 2).[54] AL101 is currently being developed as a pan-Notch inhibitor of the NOTCH network.[55] Relevant clinical trials are summarized in Supplemental Table 1.

CDK-Rb Signaling Network

The cyclin-dependent kinases 4 and 6 (CDK4/6)–RB1 axis modulates the G1 phase restriction point of the cell cycle, and cancers often impair this signal transduction to initiate constitutively active cell proliferation.[111,112] Mutations and aberrations impacting the Rb axis are another hallmark of TNBC etiology.[4,113] Pharmaceutics-based CDK4/6 inhibition (CDK4/6i) generally abrogates RB phosphorylation, thereby affecting the G1/S checkpoint.[114] More recently, it was revealed that RB-harboring TNBC are highly responsive to CDK4/6 inhibition, thereby providing ample evidence of the strong potential of CDK4/6i as a successful TNBC therapy.[21,115–117] Flavopiridol became the first broad-spectrum CDK inhibitor examined in clinical trials.[56] Palbociclib, a specific CDK4/6 inhibitor, has been approved by the FDA for the treatment of ER-positive advanced BC[57,58] and is expected to provide new treatment strategies for TNBC patients, especially the LAR subtype of TNBC.[21] At present, there are three FDA-approved CDK4/6i: Palbociclib, Ribociclib, and Abemaciclib for BC patients. Two other CDK4/6i (LEE011 and LY2835219) are under examination in dose-screening Phase I investigations. Relevant clinical trials are presented in Supplemental Table 1.

EGFR Activation

Unlike non-TNBC,[118,119] TNBCs exhibited close to 78% EGFR overexpression,[118,120–123] indicating the possibility of using EGFR as a target for TNBC therapy. Among the reasons for EGFR overexpression in TNBC is EGFR gene amplification, which is highly variable and present in close to 24% TNBC patients,[124–126] and EGFR gene mutation.[124,126] Given these evidences, EGFR tyrosine kinase inhibitors (TKI) and anti-EGFR mAb have been examined alone and alongside chemotherapy in the early[127,128] and metastatic stage of disease.[129,130] TKIs like Erlotinib and Gefitinib target EGFR; anti-EGFR mAb, which include Afatinib and Lapatinib target EGFR and ERBB2[59] in TNBC therapy. The available clinical information involving Erlotinib, Afatinib, and Lapatinib usage are presented in Supplemental Table 1.

Angiogenesis Signaling Network

Angiogenesis critically modulates tumor growth.[131] Vascular endothelial growth factor (VEGF) is the primary angiogenic modulator, and it is synthesized during BC.[131] Angiogenic homeostasis is maintained via an intricate

balance of pro- angiogenic agents (VEGF, FGF and PDGF, HIFs) and anti-angiogenic agents (thrombospondin, angiostatin and endostatin).[132] VEGF are expressed in 30–60% of TNBC,[133] thereby raising the possibility of an anti-VEGF based therapy for TNBC. Herein, we summarized relevant and potential therapies targeting angiogenesis in TNBC.

VEGFR

TNBC patients exhibit markedly elevated intra-tumoral VEGF rates, relative to non-TNBC patients.[134] VEGF family includes five ligands (VEGFA, VEGFB, VEGFC, VEGFD, and placental growth factor), five receptors (VEGFR1, VEGFR2, VEGFR3, NRP1 and NRP2).[132] Since angiogenesis is critical for tumor cell proliferation, Bevacizumab, a VEGF-A-binding mAb, has gained much attention as a potential TNBC therapeutic target.[60] Under a neoadjuvant situation, bevacizumab is reported to strongly enhance pathological complete response (pCR).[135] In addition, the VEGF axis-targeting interaction efficacy can potentially be modified using other ligands, such as, Semaphorins, that associate with both NRP1 and NRP2, suggesting that Semaphorins a potential may be new anti-angiogenic therapeutic target.[63] Small molecule TKIs have been developed to prohibit angiogenesis through binding receptors.[136] Sunitinib represents one such agent, binding multiple moieties including VEGFR1, VEGFR2, PDGFR and KIT.[61] IMC-1121 (Ramucirumab) is a fully humanized mAb of VEGFR, and it is reported to demonstrate strong efficacy against BC.[62] VEGF-Trap (Aflibercept) is a decoy VEGFR that potentially sequesters VEGF to disrupt its association with its true receptor.[64] Ongoing clinical investigations evaluating the effectiveness of the aforementioned drugs are summarized in Supplemental Table 1.

Fibroblast Growth Factor Receptors (FGFR)

FGFRs belong to the trans-membranal receptor family that are crucial for angiogenic regulation.[55] Tumor-based fibroblasts are ubiquitous present in BC, whereby they generate a myriad of growth factors, namely, basic fibroblast growth factor (bFGF).[137] The bFGF-FGFR axis activation is a hallmark of carcinogenesis.[138] FGFR1, FGFR2, FGFR3, and FGFR4 make up the FGFR family of RTKs.[139–141] FGFR1 over-expression is typically found in 18% of TNBC patients, with the FGFR1 gene amplification accounting for 33% of cases,[142] and FGFR2 amplification in <5% of cases.[143] Clinical trials have reported favorable outcomes for both multi-targeted TKIs[144] and FGFR-specific TKIs.[145] Unlike TKIs, anti-FGFR isoform antibodies[146] and FGF ligand inhibitors were also shown to have strong anti-TNBC efficacies.[147] AZD4547,[65,66] BGJ398 (Infigratinib),[67] BLU9931,[68] Debio-1347,[69] Dovitinib (TKI258),[70] FIIN-2,[71] JNJ-42756493,[72] LY2874455[73] and Ponatinib[74] are small but robust molecular compounds that suppress FGFRs at reduced concentrations. Relevant clinical trials were hoped to develop in the future.

HER2-Low TNBC

A new stratification was proposed for BC with reduced HER2 content and undetectable gene amplification (IHC) 1+ or IHC 2+ with negative in situ hybridization (ISH). This is termed as HER2-low.[55] Anti-HER2 agent technology has also been transformed from the classical binary stratification to the "HER2-low" BC classification.[75] Antibody-drug conjugates (ADCs) are a relatively new anticancer therapy that facilitates the specific deployment of a robust cytotoxic "payload" to cancer cells via targeted association between antibody and cancer cell surface molecule.[148] At present, multiple ADCs are being examined for drug efficacy and safety.[149] Till now, four anti-HER2 ADCs were reported to produce strong anti-cancer activity among HER2-low BC patients: Trastuzumab Deruxtecan (DXd), Trastuzumab Duocarmazine, Disitamab Vedotin, and MRG002.[75] The anti-HER2 ADC Dxd (DS-8201a) demonstrated satisfactory outcome in a Phase 1 investigation involving advanced HER2-low solid tumors, which including BC (NCT02564900). Trastuzumab Duocarmazine (SYD985) comprises an anti-HER2 antibody attached to a DNA-alkylating duocarmycin payload via a cleavable linker.[75] Disitamab Vedotin (RC48-ADC) is an ADC made up of a new anti-HER2 humanized antibody, hertuzumab, which is attached to a microtubular inhibitor monomethyl auristatin E (MMAE) payload via a cleavable linker.[75] MRG002 is a newly designed HER2-targeted ADC made up of modified trastuzumab linked with a cleavable linker to a MMAE payload.[75] Several anti-HER2 vaccines are currently being examined among HER2-low BC population, among them, some displayed good outcome among TNBC patients.[149,150] Anti-HER2 TKIs, Neratinib,[76]

and other anti-HER2 TKIs, namely, Poziotinib and Pyrotinib, are also under investigation as potential anti-cancer agents. Relevant clinical trials are provided in Supplemental Table 1.

DDR Signaling Network

TNBC patients exhibited a high frequency of distinctive DDR alterations.[4,151–153] The DDR axis, which modulates damaged DNA repair and genomic stability maintenance, is, in turn, regulated by DNA damage sensors, cell cycle checkpoints, diverse DNA repair signals and cellular apoptosis.[154,155] The ATR-CHK1-WEE1 axis is most targeted among all the DDR networks. VX-970 (VE-822 or Berzosertib) is a robust and specific ATR inhibitor, and the first ATR inhibitor to be examined in clinical trials. In another clinical trial, AZD6738 (Ceralasertib), a targeted ATR inhibitor, was employed as a second ATR inhibitor.[35] The CHK1 inhibitor AZD7762 is an ATP-competitive dual CHK1/2 inhibitor, which exerts its primary antitumor property via CHK1 suppression.[77] TNBC sensitivity to AZD7762 is substantially augmented by RB deficiency in vitro and *in xenografts* likely due to the non-existent RB enhanced DNA replication stress.[78] V158411, another ATP-competitive CHK1/2 inhibitor, demonstrated marked cytotoxicity in TNBC versus HR^+ BC. LY2606368 (Prexasertib) is a second-generation CHK1/2 dual inhibitor that selectively targets CHK1. LY2606368 monotherapy was proven to be safe and efficacious among high-grade ovarian carcinoma patients, who have numerous commonalities with TNBC patients.[79] UCN-01 was the first proposed CHK1 inhibitor, and its synergistic effect with gemcitabine inhibits TNBC as UCN-01 drives the gemcitabine-induced S-phase cell arrest the through G2/M checkpoints, thereby augmenting DNA damage, and accelerating cellular death.[80] Despite the recent emergence of several small-molecule WEE1 inhibitors, AZD1775 (Adavosertib) is the most studied, and only molecule to enter clinical trials till date.[81] Relevant clinical trials are provided in Supplemental Table 1.

Immunotherapy

TNBC have strongly upregulated PD-1/PD-L1 levels. Consequently, scientists examined the efficacies of these checkpoint inhibitors in mono- and combined therapies, with modest outcome.[156] CTLA-4, PD-1, and PD-L1 inhibitors are the extensively examined immune checkpoint blockers (ICB). CTLA-4/CD152, found on $CD8^+$ and $CD4^+$ T cells,[157] critically activates or inhibits T cell-induced immune response. Among the current CTLA-4 inhibitors are Ipilimumab and Tremelimumab.[82] PD-1/CD279 functions as a single-chain glycoprotein[158] predominantly expressed on the membranes of various immune cells including T lymphocytes, B lymphocytes, NK cells, monocytic cells, DCs and tumor tissues.[159] PD-1 is a major activated T cell immune checkpoint receptor, and it strongly modulates immune suppression. The current PD-1 inhibitors are Pembrolizumab, Pidilizumab, and Nivolumab. Among them, nivolumab is a fully humanized IgG4 mAb[83] with remarkable clinical outcome. PD-L1 inhibits and inactivates T-cell via its association with the PD-1 and B7-1 receptors on stimulated T cells.[160] Atezolizumab, a humanized anti-PD-L1 IgG-1 mAb,[83] also enhances median OS and ORR among lung cancer patients.[161] Relevant clinical trials are summarized in Supplemental Table 1.

Androgen Receptor (AR)

Approximately, 25–75% TNBC patients have enhanced AR expression level, among whom, the strongest expression is seen among patients with the LAR subtype.[162] Using both in vitro and in vivo investigations, AR^+ TNBCs were shown to respond well to AR antagonist therapy.[163,164] Currently, three anti-AR drugs, Bicalutamide, Enzalutamide, and Seviteronel, are under clinical investigation.[84] All available anti-androgen therapy-based clinical information are provided in Supplemental Table 1.

Coding Genes Involved in Chemo-Sensitive and Chemo-Resistance of TNBC

Unlike non-TNBC, TNBC are generally larger, of enhanced grade, and node positive. Hence, for TNBC, chemotherapy is the best treatment option.[7] Among the recommended interventions are taxanes and anthracyclines, however, platinum-based regimens could be employed in neo-adjuvant settings.[165] Taxanes are the primary constituents of neoadjuvant chemotherapy. Mechanically, they suppress microtubule depolymerization to repress cancer cell proliferation.[166] TNBC patients are typically more responsive to neoadjuvant therapy than ER^+ BC. They also have considerably worse OS, relative to non-TNBC tumor patients despite having better pCR rates; thus, this is known as the "triple negative paradox".[167] Given that chemotherapy is the main form of TNBC treatment, chemoresistance is the primary contributor of TNBC recurrence and metastasis. Currently,

there is a lack of clinically employed bioindicators for sensitive or resistant tumor classification. Moreover, there are no treatment approaches geared toward the chemo-refractory cases.[168] In this report, we first discussed the TNBC-associated chemotherapy-sensitivity and chemotherapy-resistance coding genes. The chemo-sensitive genes are strongly diminished in chemo-resistant TNBCs. It is speculated that future TNBC treatment may utilize overexpression of the chemo-sensitive genes (Figure 2 and Table 3). Alternatively, the chemo-resistant genes are ubiquitously expressed in chemo-resistant TNBC. Thus, future research may entail suppression of the aforementioned genes in TNBC (Figure 3 and Table 4). Due to the strongly altered states of these genes, they are served as strong candidates for estimating the chemotherapeutic response of TNBC patients, which, in turn, can assist in enhancing patient care and prognosis. However, whether these genes can become indicators of drug resistance in patients still has a long way to go.

Chemotherapy-Sensitivity Genes of TNBC

CLDN1

Approximately 77% TNBC display little to no claudin-1 (CLDN1) expression, and this deficiency is strongly associated with worse outcome. One study reported that CLDN1 enhances TNBC cell line sensitivity to chemotherapeutic agents (paclitaxel, abbreviated as PTX) for BC therapy. These evidences confirm CLDN1 as a chemotherapeutic response indicator for TNBC patients.[169]

DAB2IP

DAB2IP abrogates TNBC chemoresistance (Docetaxel) by suppressing the RAC1-triggered nuclear β-catenin transfer. Decitabine treatment re-expresses DAB2IP by preventing DNA methylation, thereby enhancing its potential in the management of TNBC.[170]

Thioredoxin-Interacting Protein (TXNIP)

TXNIP originates from the α-arrestin family of proteins,[171] which tightly modulate various physiological activities via interaction with other proteins.[172] TXNIP accelerates cellular apoptosis, and inhibits chemo-resistant TNBC cellular growth both in vitro and in vivo by enhancing ROS-based DNA damage. The small molecular c-Myc inhibitor 10058-F4 enhances TXNIP content and augments intracellular ROS production to downregulate DOX-stimulated chemoresistance in TNBC. Combination with DOX further enhances the chemotherapeutic cytotoxic properties of 10058-F4.[173]

C/EBP-β LIP

Doxorubicin effectiveness depends on the number of drug efflux transporters like P-glycoprotein (Pgp) present within tumor cells.[174] One report revealed that blocking C/EBP-β LIP degradation strongly enhances nitric oxide content, while reducing Pgp expression and activity, which, in turn, restores ER stress-dependent apoptosis and Doxorubicin-induced immunogenic cell apoptosis. This, in turn, rescues the anthracycline therapeutic activity in Pgp-positive TNBC.[175]

cAMP Response Element Binding Protein 3-Like 1 (CREB3L1)

Researchers reported high CREB3L1 levels in chemotherapeutic sensitive cancers than chemotherapeutic resistant cancers. Similarly, high CREB3L1-harboring TNBC responds better to doxorubicin-based chemotherapy than low CREB3L1-harboring TNBC.[176]

Atractylenolide-I (ATL-I)

ATL-I exerts strong anti-tumor influences against BC.[177] In particular, ATL-I reduces the CTGF transcript levels in TNBC, which reduces TNBC cell migration, diminishes the fibroblast to cancer-associated fibroblasts (CAFs) transformation, and enhances TNBC cell sensitivity to PTX.[178]

SLFN12

SLFN12 is a newly discovered protein, with strong association with TNBC patient prognosis.[179] SLFN12 was shown to enhance TNBC cell sensitivity to radiation and cytotoxic drugs via reduction of CHK1 and CHK2 phosphorylation, which may be responsible for the OS differences between high and low SLFN12 tumor patients.[180]

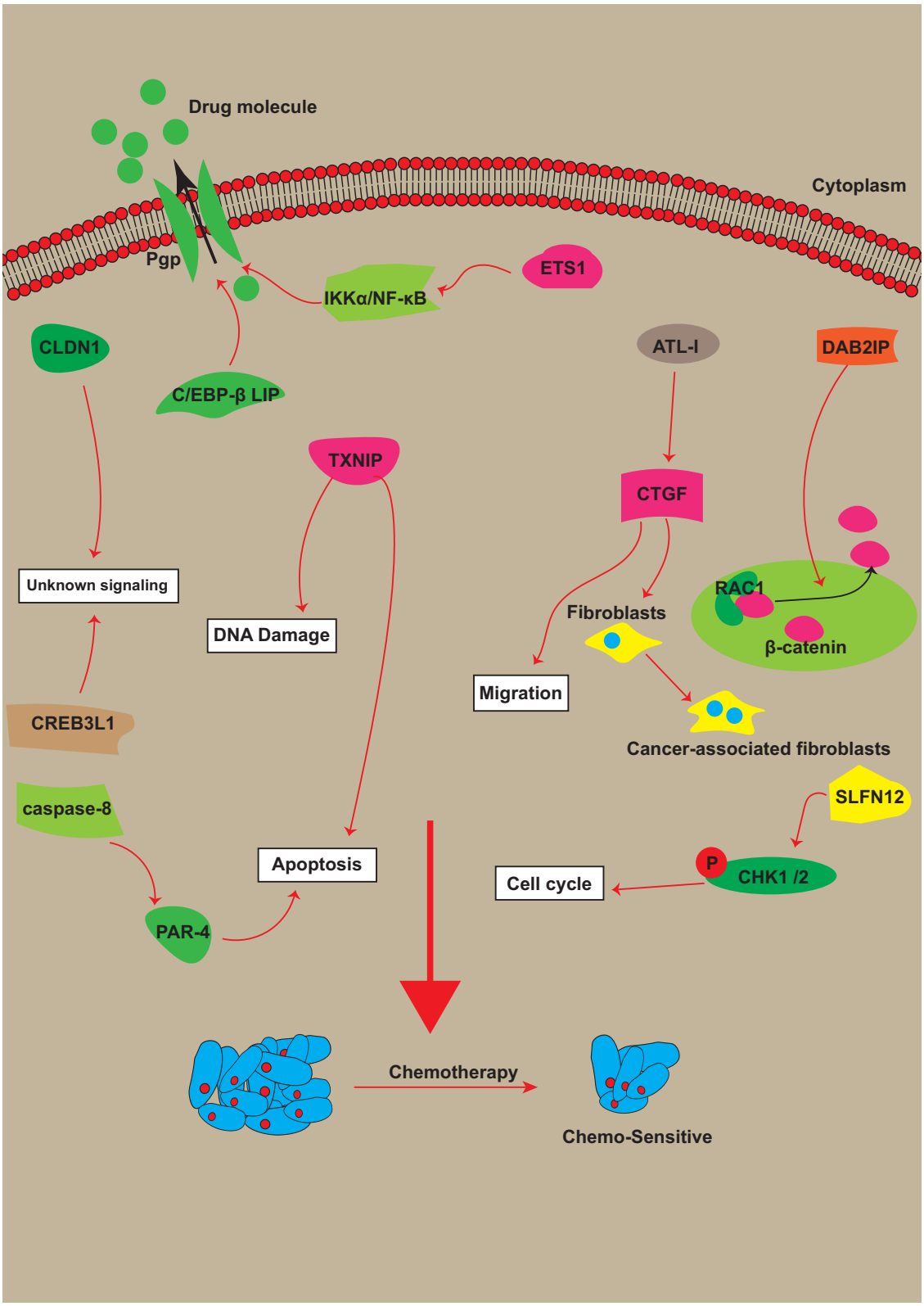

Figure 2 Genes promoting chemotherapeutic sensitivity in TNBC.

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Table 3 Chemotherapy-Sensitive Genes of TNBC

Genes	Target Gene	Medication	Refs.
CLDN1	Unknown pathway	PTX	[169]
DAB2IP	RAC1-mediated β-catenin nuclear accumulation	Docetaxel	[170]
TXNIP	ROS-based DNA damage	DOX	[171–173]
C/EBP-β LIP	Pgp	Anthracycline	[174, 175]
CREB3L1	Unknown pathway	Doxorubicin	[176]
ATL-1	CTGF	PTX	[177, 178]
SLFN12	CHK1 and CHK2	PTX	[179, 180]
PAR-4	Caspase-8	Doxorubicin	[181]
ETS-1	IKKα/NF-κB pathway	Cisplatin	[182]

Prostate Apoptosis Response-4 (PAR-4)

PAR-4 deficiency in TNBC facilitates resistance to DNA damage-driven apoptosis, while simultaneously preventing caspase-8 activation. PAR-4 is downstream of caspase-8, and it functions by cleavage-triggered nuclear transfer of the C-terminal. Herein, researchers demonstrated that the nuclear transfer of the C-terminal PAR-4 fragment strongly depletes cIAP1, then activates caspase-8.[181]

ETS1

Strong evidence suggests that the ETS1 dysregulation is behind the cisplatin resistance of TNBC. This indicates that ETS1 overexpression can potentially enhance cisplatin chemosensitivity by augmenting ABC transporters via the IKKα/NF-κB axis.[182]

Chemotherapy-Resistance Genes of TNBC

Autophagy-Related Genes

SERCA2. SERCA2 is intricately linked to TNBC progression, and it enhances TNBC cell chemoresistance. SERCA2 was shown to interact with LC3B via the LIR motif in order to augment WIPI2-independent autophagosome production, which promotes autophagy.[183]

HORMA Domain-containing Protein 1 (HORMAD1). HORMAD1 is a CTA with normal testicular expression, whereby it is engaged in essential physiological activities.[184] In TNBC, however, it is expressed in substantially elevated levels.[185,186] HORMAD1 modulates autophagy, and autophagic partially augments docetaxel-induced cellular apoptosis.[187]

TNFSF13. TNFSF13 accelerates autophagy and desensitizes TNBC cells to chemotherapy by inhibiting the AKT-mTOR axis. Hence, the TNFSF13-autophagy network is an excellent target for reversing TNBC chemoresistance.[188]

Cell Cycle-Related Genes

Protein Phosphatase 1 Regulatory Subunit 14B (PPP1R14B). PPP1R14B belongs to the protein phosphatase 1 family of modulatory subunits, and it is strongly elevated in TNBC tissues. PPP1R14B augments STMN1-based α-tubulin acetylation, microtubular stability, and cell-cycle progression, which, in turn, facilitates TNBC cell resistance to PTX.[189]

CENPF. CENPF expression is strongly elevated in TNBC, and it is linked to worse outcome in patients undergoing chemotherapy.[190,191] In vitro CENPF deficiency strongly enhances adriamycin (ADR)-driven cytotoxicity in MDA-MB-231 and ADR-resistant cells (MDA-MB-231/ADR). CENPF also modulates the Chk1-based G2/M phase

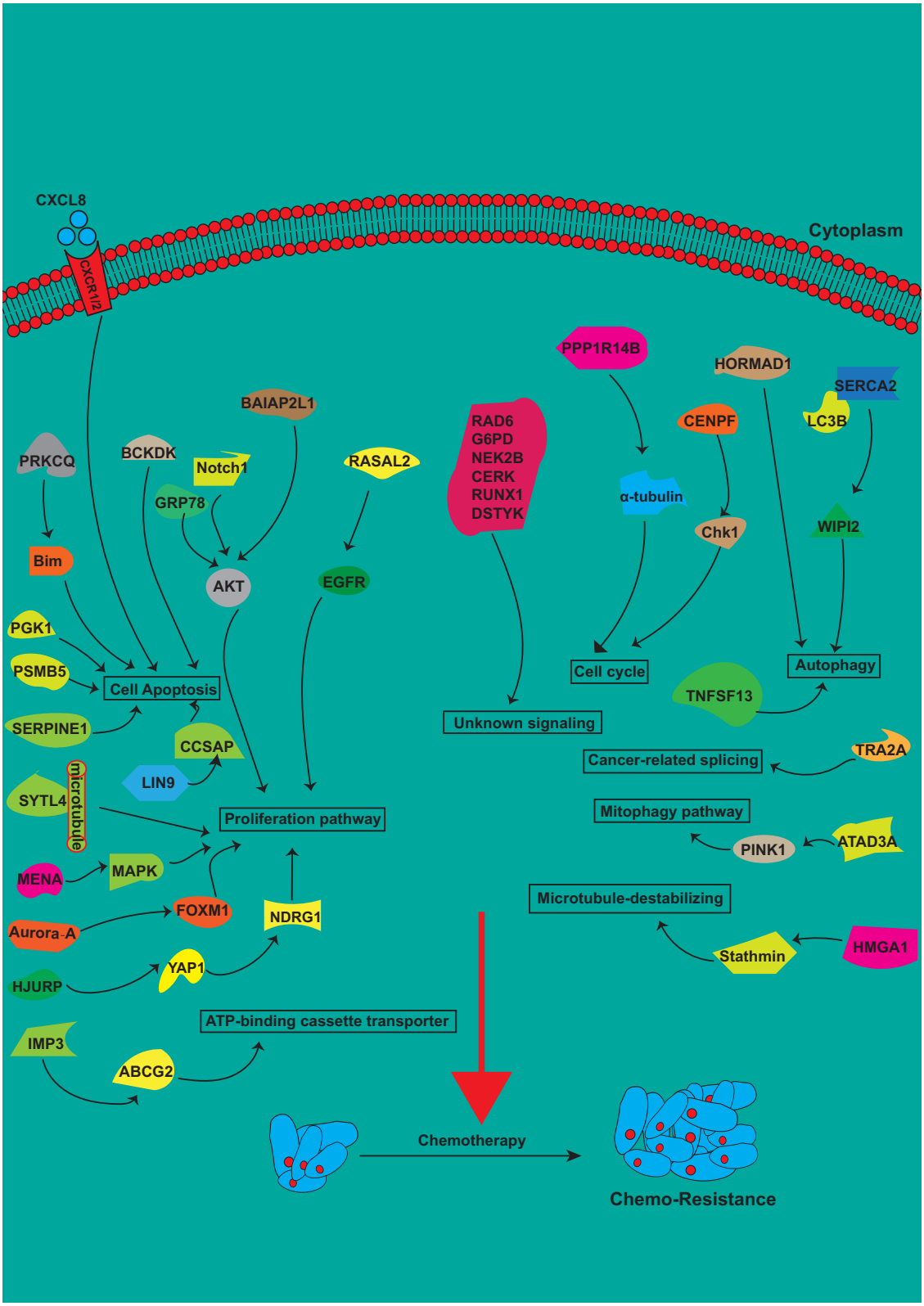

Figure 3 Genes promoting chemotherapeutic resistance in TNBC.

https://doi.org/10.2147/BCTT.S553421

Table 4 Chemotherapy-Resistant Genes of TNBC

Genes	Target Gene/Signaling Pathway	Medicine	Ref.
SERCA2	LC3B	PTX	[183]
HORMAD1	Apoptosis and Autophagy	Docetaxel	[184–187]
TNFSF13	AKT-mTOR	PTX	[188]
PPP1R14B	STMN1	Paclitaxel	[189]
CENPF	Chk1	Adriamycin	[190–192]
Notch1	MVP/AKT	Cisplatin	[193]
HJURP	HJURP/YAP1/NDRG1 axis	Doxorubicin	[194]
BAIAP2L1	RPL3/AKT	Docetaxel	[195]
RASAL2	MEK/EGFR	Cisplatin	[168]
SYTL4	C2A domain	PTX	[196]
MENA	MAPK signaling	PTX	[197]
Aurora-A	FOXM1	PTX	[198]
GRP78	p-AKT/mTOR pathway	Pirarubicin	[199, 200]
CXCL8	Apoptosis signaling	PTX	[201, 202]
BCKDK	BCAA flux	DOX	[203]
PRKCQ	Bim	PTX; doxorubicin	[204]
PSMB5	Apoptosis	PTX	[205]
LIN9	CCSAP	PTX	[206]
PGK1	XAF1	PTX	[207]
SERPINE1	VEGFA	PTX	[208]
ATAD3A	PINK1	PTX	[209]
TRA2A	Splicing factors	PTX	[210]
HMGA1	HMGA1/p27/stathmin	Paclitaxel	[211, 212]
IMP3	ABCG2	Doxorubicin	[213]
RAD6	Microtubule dynamics	PTX	[214]
G6PD	Unknown signaling	DOX	[215]
NEK2B	β-catenin	PTX	[216, 217]
CERK	Unknown signaling	Paclitaxel; Cisplatin	[218]
RUNX1	Unknown signaling	Paclitaxel	[219]
DSTYK	Unknown signaling	DOX	[220]

arrest, and associates with Rb to sequester E2F1 in TNBC. Given the critical E2F1 role in DNA damage response and repair, discovery of a new signal transduction whereby CENPF modulates the Rb-E2F1 network will enable a novel approach to overcoming chemoresistance in TNBC.[192]

Proliferation-Related Genes

Notch1. Notch1 and major vault protein (MVP) are robust regulators of TNBC cell chemoresistance. It does so by modulating MVP expression to stimulate the AKT and EMT axes. Notch1 deficiency increases TNBC cell sensitivity to cisplatin-based chemotherapy.[193]

HJURP. HJURP modulates Yes-Associated Protein (YAP1) protein ubiquitination to control its downstream transcriptional activity. In addition, YAP1 associated with the NDRG1 gene promoter to enhance gene transcription. Subsequently, the HJURP/YAP1/NDRG1 network modulates cell proliferation and doxorubicin resistance in TNBC. Together, these evidences indicate that the HJURP/YAP1/NDRG1 network modulation is essential in TNBC progression and therapeutic response.[194]

BAI-Associated Protein 2-Like 1 (BAIAP2L1). Excess BAIAP2L1 expression markedly induces BC proliferation potentially via AKT activation. Conversely, exposure to AKT inhibitor LY294002 diminishes BAIAP2L1 expression in BC cells. BAIAP2L1 interacts with the AA202-288 of ribosomal protein L3 (RPL3) within its SRC homology 3 (SH3) domain. In contrast, its deficiency abolishes AKT signaling to enhance PIK3CA degradation. Additionally, BAIAP2L1 overexpression enhances docetaxel resistance.[195]

RASAL2. Emerging evidences revealed that excess RASAL2 forms a chemotherapy-unresponsive TNBC subset. RASAL2 GAP function is critical for kinase inhibitor sensitivity, and RASAL2-high TNBCs maintain basal RAS activity via inhibition of negative feedback modulators SPRY1/2, along with EGFR elevation. As a result, RASAL2 expression reduces feedback compensation following MEK1/2 and EGFR co-suppression thereby inducing synergistic apoptosis in vitro and in vivo. Among TNBC patients, elevated RASAL2 contents indicate clinical chemotherapeutic response (Cisplatin).[168]

Synaptotagmin-Like 4 (SYTL4). SYTL4 is a relatively new chemo-resistant gene in TNBC. SYTL4 downregulation stabilizes the microtubular network by decelerating microtubular growth rate. Additionally, SYTL4 expresses alongside microtubules and interacts with the middle region of microtubules via a linker and C2A domain. SYTL4 also induces PTX resistance in TNBC in vitro and in vivo.[196]

MENA. The MENA isoform disrupts the balance between dynamic and stable microtubules in PTX-exposed cells. Following PTX exposure, MENA activates MAPK. Conversely, following MEK inhibitor co-treatment, reduced ERK phosphorylation restores PTX sensitivity by enhancing microtubule stabilization in MENA isoform-harboring cells.[197]

Aurora Kinase A (Aurora-A). Aurora-A modulates FOXM1 in TNBC. Aurora-A-induced FOXM1 stabilization represents its kinase-independent induction of augmented TNBC cell proliferative capacity. Even though Aurora-A kinase inhibition is a potentially potent TNBC treatment regimen, the report indicated that the antibiotic drug thiostrepton usage, which downregulates Aurora-A and FOXM1 contents, can work together with PTX to revert PTX chemoresistance in TNBC.[198]

GRP78. GRP78 is intricately linked to apoptosis, and GRP78 deficiency enhances BC apoptosis.[199] GRP78 silencing strongly reduces MDR1 levels by negatively modulating the Akt/mTOR network in MDA-MB-231R cells.[200] Furthermore, it reverts pirarubicin resistance of TNBC using miR-495-3p mimics and the p-AKT/mTOR axis.[200]

Apoptosis-Related Genes

Cxcl8. CXCL8, otherwise called IL-8, originates from the proangiogenic chemokine family, and it is strongly linked to CXCR1/2.[201] CXCL8 is ubiquitously present in PTX-resistant TNBC cells. In contrast, CXCL8 deficiency enhances TNBC cell sensitivity to PTX via regulation of the cell apoptosis network.[202]

Branched-Chain Ketoacid Dehydrogenase Kinase (BCKDK). Based on transcriptome analysis, BCKDK silencing dysregulates mitochondrial metabolic axes and upregulates the apoptotic axis. BCKDK suppression and simultaneous DOX exposure exacerbate apoptosis, caspase activity, and inhibition of TNBC proliferation. Collectively, BCKDK inactivity in TNBC alters BCAA flux, diminishes protein translation, thereby accelerating cell apoptosis, ATP insufficiency, and susceptibility toward genotoxic stress.[203]

PRKCQ. Excess PRKCQ content strongly suppresses PTX- or doxorubicin-induced cell apoptosis. Conversely, PRKCQ deficiency enhances chemotherapy-induced TNBC cell apoptosis. PRKCQ modulates chemotherapy responsiveness by regulating Bim (a pro-apoptotic Bcl2 family member) content. Bim suppression abrogates the simultaneous PRKCQ deficiency- and chemotherapy treatment-induced cell apoptosis.[204]

Proteasome Subunit Beta 5 (PSMB5). Excess PSMB5 expression is strongly associated with worse TNBC patent outcome. In contrast, PSMB5 deficiency enhances TBNC cell apoptosis and augments chemotherapeutic sensitivity to PTX.[205]

LIN9. PTX-resistant TNBC cells have strongly elevated LIN9 content, relative to corresponding parental cells. LIN9 knockdown or PTX-resistant TNBC cell exposure to a bromo- and extra-terminal domain inhibitor (BETi) JQ1 substantially diminished LIN9 levels while enhancing PTX-resistant TNBC cell sensitivity to PTX. LIN9 suppression in resistant cell lines visibly reduces tumor cell survivability, increases multinucleated cell production, and enhances tumor cell apoptosis via direct regulation of CCSAP.[206]

PGK1. PGK1 silencing markedly increased TNBC cell line sensitivity to PTX therapy by enhancing drug-induced apoptosis. Moreover, PGK1-knockdown cells display excess XAF1, as well as apoptotic proteins cleaved caspase-3 and Bax expressions.[207]

SERPINE1. Enhanced SERPINE1 expression confers BC resistance to PTX treatment via elevation of VEGFA, and inhibition of cell apoptosis.[208]

Mitophagy-Related Genes

ATAD3A. PINK1 transports PD-L1 to the mitochondria for mitophagy-mediated destruction. PTX also increases ATAD3A content to impair PD-L1 proteostasis via modulation of PINK1-reliant mitophagy. In the clinics, tumor patients who have elevated ATAD3A levels prior to ICI and PTX co-treatment experienced substantially reduced PFS relative to those with ATAD3A-low tumors.[209]

Cancer-Related Splicing Genes

Transformer2A (TRA2A). TRA2A promotes TNBC cell proliferation, survival, migration, and invasion. Additionally, TRA2A induces PTX resistance of TNBC cells via specific regulation of cancer-associated splicing, independent of other splicing factors.[210]

Microtubule-Destabilizing-Related Splicing Genes

High Mobility Group A1 (HMGA1). HMGA1 is typically ubiquitously expressed during embryogenesis, and it declines to little or no expression in adults. However, it is strongly expressed in multiple tumors.[211] The HMGA1/p27/stathmin network regulates TNBC cell motility. Therefore, HMGA1 silencing in TNBC cells strongly diminishes in stathmin content and action on microtubules. This, in turn, impairs cell motility in a p27-reliant fashion. Additionally, in a xenograft mouse model, HMGA1-depleted TNBC cells are more responsive to PTX treatment.[212]

ATP-Binding Cassette Transporter-Related Genes

IMP3. BC resistance protein (BCRP), otherwise called ABCG2, belongs to the ATP-binding cassette transporter family. The IMP3 protein is reported to enhance chemoresistance (Doxorubicin) of BC cells via modulating ABCG2 levels.[213]

Unknown Signaling-Related Genes

RAD6. SMI#9 (a RAD6 inhibitor) and PTX share the same mechanism of microtubular modulation. Therefore, the synergistic effect of both PTX and RAD6 inhibitor has potential advantages on enhancing TNBC sensitivities to PTX

while eliminating toxicity. The aforementioned investigations were the first to uncover a role for RAD6 in modulating microtubule dynamics.[214]

Glucose-6-Phosphate Dehydrogenase (G6PD). Metastatic TNBC cells exhibit markedly elevated G6PD levels once DOX resistance form following lung metastasis. Moreover, G6PD suppression abrogates DOX resistance in the same mTNBC cells, while enhancing parental TNBC cell responsiveness to DOX.[215]

NEK2B. Elevated Nek2B expression is intricately linked to worse disease-free survival (DFS) and OS in TNBC.[216] Nek2B interacts with β-catenin to negatively regulate TNBC patient prognosis. Their synergistic action enhances TNBC chemo-resistance to PTX.[217]

Ceramide Kinase (CERK). Upregulated CERK activates numerous oncogenic networks to promote chemo-resistance in TNBC cells. Additionally, excess CERK expression heavily influences chemo-sensitivity (PTX and cisplatin), and therefore serve as a potential bioindicator of chemo-resistance risk classification in newly diagnosed TNBC patients.[218]

RUNX1. Suppression of RUNX1 transcriptional activity strongly enhances chemotherapy sensitivity in (AR^+) TNBC cell lines both in culture and forced suspension. Pharmacologic RUNX1 suppression also augments the effects of the aforementioned combinational treatments (PTX).[219]

DSTYK. One investigation knocked out DSTYK using the CRISPR/Cas9 method, and revealed considerable chemo-resistant cell death following drug intervention. In addition, DSTYK knockout enhances the chemotherapeutic drug-driven tumor cell apoptosis in an orthotopic mouse model. Collectively, these results indicate that DSTYK is essential for DOX chemoresistance.[220]

Potential Novel Therapeutic Targets for TNBC

Considering the aforementioned TNBC-based evidences, a detailed and extensive list of chemotherapy, as well as existing and ongoing targeted molecular therapy including the following: (1) chemotherapy; (2) DRR axis inhibitors (targeting BRCA, ATR-CHK1-WEE1); (3) proliferation-associated network inhibitors (targeting PI3K-AKT-mTOR; NOTCH; RB; EGFR); (4) ICBs (targeting PD-L1/PD-1); (5) AR inhibitor. With emerging investigations, more researchers have proposed additional approaches to treating TNBC. Here, we have summarized the most current potential TNBC therapies, namely, ferroptosis-associated network; potential targeted ADC markers; Ceritinib; Src Inhibitor; CDK12/CDK13 inhibitor. All TNBC-related therapies and medications are presented in Figure 4 and Table 2.

Ferroptosis-Associated Network

Twelve genes linked to ferroptosis were analyzed for prognostic evaluation in TNBC cases, with seven genetic markers (ASNS, LAMP2, CAV1, DPP4, HELLS, TF, ZFP69B) emerging as viable therapeutic candidates. Additionally, two pharmaceutical compounds (1-methyl-3-isobutylxanthine and rosiglitazone) demonstrated potential efficacy in TNBC treatment scenarios.[85]

Potential Targeted ADC Bioindicators

ADC enhances high cytotoxic drug concentration delivery to ADC-containing cells.[86] Sacituzumab govitecan (IMMU-132) is an SN-38 conjugate Trop-2-targeting antibody. Trop-2 is present in approximately 90% of all TNBCs.[87] Ladiratuzumab Vedotin (SGN-LIV1A), with monomethyl-auristatin-E (MMAE) as the payload, achieves a 25% ORR and median PFS of 11 months among TNBC patients. Excess glycoprotein-NMB (gpNMB) expression, indicated by ≥25% of tumor epithelial cell staining, occurs in about 40% of TNBCs, and in this subgroup, glembatumumab vedotin (CDX-011, an ADC that interacts with gpNMB to deploy MMAE) achieves 40% ORR versus 0% with the author´s therapy of choice.[88] Some new ADC medicines have also been created and engaged in clinical trials. AVID100 is an anti-EGFR ADC that targets EGFR and is conjugated with DM1.[89] U3-1402 is an anti-HER3 ADC that is conjugated with a topoisomerase I inhibitor exatecan derivative via a peptidyllinker.[221] CAB-ROR2-ADC is an ADC composed of a conditionally active biologic antibody directing receptor tyrosine kinase-like orphan receptor 2 (ROR2) conjugated to an undisclosed payload.[89] Anti-CA6-DM4 immunoconjugate (SAR566658) is a humanized DS6 antibody directed against CA6 conjugated to DM4.[89] New targeted for ADC drug development is the most potential direction for TNBC therapy.

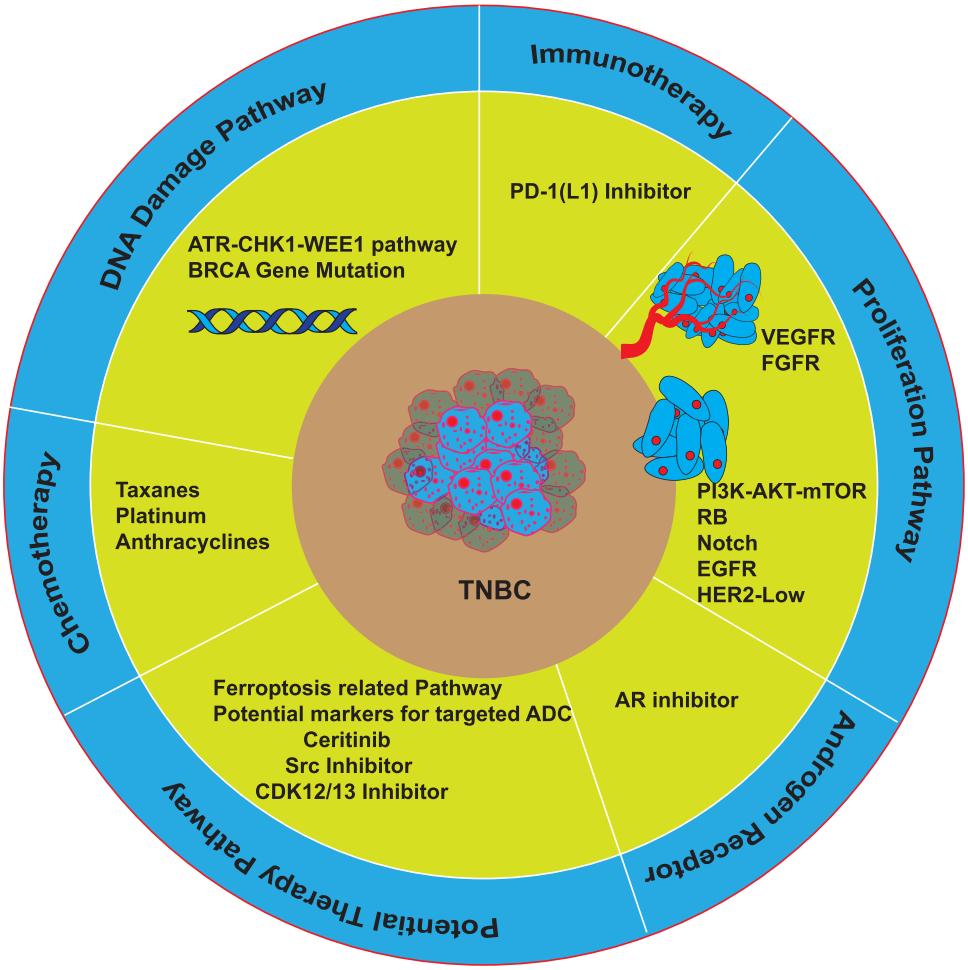

Figure 4 An illustration of all available therapeutic means of TNBC including the DNA damage pathway, immunotherapy, chemotherapy, proliferation pathway, androgen receptor, potential therapeutic pathway.

Ceritinib

Ceritinib, an FDA-approved anti-lung cancer medication,[90] significantly inhibits LAR TNBC development. Additionally, Activated CDC42 Kinase 1 (ACK1) is a strong ceritinib target in LAR TNBC cells, whereby ceritinib inactivates the RTK-ACK1/FAK-AR network in LAR TNBC cells. Lastly, this investigation established a new treatment approach for AR^+ TNBC tumors involving a combinational therapy for AR^- or AR low TNBCs.[91]

Src Inhibitor

Src is a specific tyrosine kinase that has gained recognition as a possible target for multi-cancer treatment.[92,93] Prior investigations by *Finn* et al[94] reported that TNBC cell lines are especially responsive to dasatinib, whereas, *Huang* et al demonstrated that a BC subgroup harboring the dasatinib-responsive signature includes patients with TNBC.[95] It was also revealed that dasatinib suppresses different TNBC cellular growth in culture. However, Src content or phosphorylation failed to indicate dasatinib responsiveness in vitro.[96]

CDK12/CDK13 Inhibitor

CDKs are serine/threonine kinase activities are heavily reliant on their association with the cyclin modulatory subunit.[222] The CDK enzyme family modulates the cell cycle and transcription processes.[223] *Quereda* et al established a targeted dual CDK12/CDK13 inhibitor (SR-4835) that diminishes core DNA damage response gene expressions by upregulating intronic polyadenylation site cleavage, which results in impaired DNA damage repair, thereby increasing cellular responsiveness to DNA-damaging agents and PARP inhibitors.[97]

Conclusion and Future Perspective

TNBC is a disease marked by enhanced heterogeneity and poor prognosis. Unlike HR-positive BC, TNBC is correlated with a younger patient age, increased visceral metastases risk, enhanced early recurrence risk, and extremely poor outcome.[9,224,225] Therapy for TNBC patients, who lack ER and PR expressions as well as HER2 amplification, is quite challenging due to the heterogenic characteristic of this disease, as well as the lack of well-established molecular targets.[167,226,227] Gene expression profiling-related molecular TNBC subtyping is critical for elucidating the underlying mechanisms of this disease, which, in turn, will benefit personalized treatment.[29] Hence, an extensive exploration of all subtypes and properties is crucial. Additionally, newly discovered subtype stratification enables clinicians to better manage TNBC. As a result, given the poor outcome of TNBC patients, it is essential to gain an extensive comprehension of the disease, particularly, in relation to the following aspects: (a) DDR-associated BRCA Loss-Function Mutation; (b) PI3K axis; (c) NOTCH network; (d) CDK-Rb axis; (e) EGFR Activation; (f) Angiogenesis network; (g) HER2-Low; (h) DDR signal transduction; (i) Immunotherapy and (j) AR signaling. Based on the aforementioned genes and aberrant signal networks, scientists have developed potential targeted therapies, as is presented in Table 2. The relevant clinical trials are summarized in Supplemental Table 1. It is our hope and speculation that the mentioned medications will be incredibly advantageous to TNBC therapy in near future. Notably, with the emergence of the HER2-low concept, drugs targeting HER2-low are being proposed and placed in clinical trials. Furthermore, given that chemotherapy is the standard intervention for TNBC, herein, we summarized the coding genes associated with TNBC chemoresistance, which may eventually be targets of future TNBC therapy. Additionally, we also listed the known chemo-sensitive and chemo-resistance genes associated with TNBC. Moreover, the CLDN1, DAB2IP, TXNIP, C/EBP-β LIP, CREB3L1, ATL-1, SLFN12, PAR-4, and ETS-1 genes may can be used to predict patient sensitivity to chemotherapy or neoadjuvant-chemotherapy in the clinic. Similarly, the HJURP, CXCL8, SERCA2, PPP1R14B, HORMAD1, DSTYK, Notch1, and CENPF genes serve as indicators of patient resistance to chemotherapy in the clinic. We speculate that the aforementioned chemo-sensitive and chemo-resistant genes will be examined further in coming years for the development of better anti-TNBC therapy. We also discussed the emergence of new treatments for TNBC, namely, the ferroptosis-associated network, ADC, Ceritinib, Src inhibitor, and CDK12/CDK13 inhibitor. Considering that the aforementioned drugs continue to show benefit against TNBC, they may enter clinical trials relatively soon, and be administered to TNBC patients in the clinic.

In summary, this review presents an extensive overview of the gene mutation profile of TNBC, as well as the corresponding targeted immune- and chemotherapies. This will provide a direction and beacon for the development of highly efficacious future TNBC therapy.

Abbreviations

ACK1, Activated CDC42 Kinase 1; ADCs, Antibody-drug conjugates; ADR, Adriamycin; Aurora-A, Aurora kinase A; AR, Androgen Receptor; ATL-I, Atractylenolide-I; BAIAP2L1, BAI-associated protein 2- like 1; BC, Breast Cancer; BCKDK, Branched-chain ketoacid dehydrogenase kinase; BCRP, Breast cancer Resistance Protein; BETi, bromo- and extra-terminal domain inhibitor; bFGF, Basic Fibroblast Growth Factor; BLIA, Basal-like Immune activated; BLIS, Basal-like Immunosuppressed; CAFs, Cancer-Associated Fibroblasts; CDK 4/6, Cyclin-Dependent Kinases 4 and 6; CDK4/6i, CDK4/6 inhibitor; CERK, Ceramide Kinase; CLDN1, Claudin-1; CREB3L1, cAMP response element binding protein 3-like 1; DC, Dendritic Cell; DDR, DNA Damage Response; DFS, Disease-Free Survival; ER, Estrogen Receptor; EMT, Epithelial–Mesenchymal Transition; FGFR, Fibroblast Growth Factor Receptors; G6PD, Glucose-6-phosphate Dehydrogenase; gpNMB, Glycoprotein-NMB; HER-2, Human Epidermal Growth Factor Receptor; HMGA1, High Mobility Group A1; HORMAD1, HORMA domain-containing protein 1; HR, Homologous Recombination; ICB, Immune Checkpoint Blockade; ICI, Immune checkpoint inhibitor; IHC, Immunohistochemical; IHC-BLIS, IHC-based basal-like immune-suppressed; IHC-LAR, IHC-based luminal androgen receptor; IHC-IM, IHC-based immunomodulatory; IHC-MES, IHC-based mesenchymal; IL-8, Interleukin-8; IM, Immunomodulatory; ISH, In Situ Hybridization; LAR, Luminal Androgen Receptor; mAb, Monoclonal Antibodies; MES, Mesenchymal; MSC, Mesenchymal Stem Cell; MSL, Mesenchymal stem-like; MMAE, Monomethyl-Auristatin-E; MVP, Major Vault Protein; OS, Overall Survival; PAR-4, Prostate apoptosis response-4; PARP, Poly ADP-ribose Polymerase; PARPi, Poly ADP-ribose Polymerase Inhibitor; pCR, Pathological

Complete Response; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PIK3CA, PI3K catalytic subunit α; Pgp, P-glycoprotein; PI3K, Phosphoinositide 3-kinase; PPP1R14B, Protein phosphatase 1 regulatory subunit; PR, Progesterone Receptor; PSMB5, Proteasome Subunit Beta 5; PTEN, Phosphatase And Tensin Homolog; PTX, Paclitaxel; ROR2, Receptor Tyrosine Kinase-Like Orphan Receptor 2; RPL3, ribosomal protein L3; RTK, Receptor Tyrosine Kinase; SH3, SRC homology 3; Src, v-src Sarcoma Viral Oncogene Homolog; SYTL4, Synaptotagmin-like 4; TF, Transcription Factor; TGF, transforming growth factor; TNBC, Triple Negative Breast Cancer; TILs, Tumor Infiltrating Lymphocytes; TKI, Tyrosine kinase inhibitors; TRA2A, Transformer2A; TXNIP, Thioredoxin-interacting protein; VEGF, Vascular endothelial growth factor; YAP1, Yes-Associated Protein.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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