Precision medicine based on tumorigenic signaling pathways for triple-negative breast cancer (Review)

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Abstract. As a clinically heterogeneous subtype of breast cancer, triple-negative breast cancer (TNBC) is associated with a poor clinical outcome and a high relapse rate. Conventional chemotherapy and radiotherapy are effective treatments for patients with TNBC. However, the prognosis of TNBC remains unsatisfactory. Therefore, a large volume of research has explored the molecular markers and oncogenic signaling pathways associated with TNBC, including the cell cycle, DNA damage response and androgen receptor (AR) signaling pathways, to identify more efficient targeted therapies. However, whether these predicted pathways are effective targets has yet to be confirmed. In the present review, potentially carcinogenic signaling pathways in TNBCs from previous reports were considered, and ultimately five tumorigenic signaling pathways were selected, specifically receptor tyrosine kinases and downstream signaling pathways, the epithelial-to-mesenchymal transition and associated pathways, the immunoregulatory tumor microenvironment, DNA damage repair pathways, and AR and coordinating pathways. The conclusions of the preclinical and clinical trials of each pathway were then consolidated. Although a number of signaling pathways in TNBC have been considered in preclinical and clinical trials, the aforementioned pathways account for the majority of the malignant behaviors of TNBC. Identifying the alterations to different carcinogenic signaling pathways and their association with the heterogeneity of TNBC may facilitate the development of optimal precision medical approaches for patients with TNBC, potentially improving the efficiency of anticancer therapy.

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Abbreviations: ALDH1, aldehyde dehydrogenase 1; AR, androgen receptor; BRCA, breast cancer-associated; Co-Smads, common mediator Smads; DSB, DNA double-strand break; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; ER, estrogen receptor; Erk, extracellular signal-regulated kinase; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; I-Smads, inhibitory Smads; IGFR, insulin-like growth factor receptor; LRP5/6, low-density lipoprotein receptor-related 5/6; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase 1; mTOR, mechanistic target of rapamycin; PARP, poly(ADP-ribose) polymerase; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinase; PIP_2, phosphatidylinositol-4,5-diphosphate; PIP_3, phosphatidylinositol-3,4,5-triphosphate; PR, progesterone receptor; PTEN, phosphatase and tensin homolog; R-Smads, receptor-regulated Smads; RTKs, Receptor tyrosine kinases; SHP2, Src homology phosphotyrosyl phosphatase 2; TGFR-β, transforming growth factor receptor-β; TNBC, triple-negative breast cancer

Key words: triple-negative breast cancer, precision medicine, carcinogenic pathway, targeted therapy, clinical treatment

Contents

1. Introduction

Breast cancer is the leading cause of cancer-associated mortality for women. In 2012, 1.7 million people were diagnosed with breast cancer worldwide, and 521,900 succumbed to the complications (1). Given the varied prognosis and response to treatment of patients with breast cancer, the molecular classification of breast cancer has been examined to improve the understanding of this disease. Triple-negative breast cancer (TNBC), which was first reported in the literature in 2005, is a molecular subset of breast cancer. TNBC is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) expression (2), and accounts for 16% of all breast cancer cases (3). Although TNBC tumors display relatively simple molecular phenotypes, they are inherently heterogeneous. In particular, TNBCs exhibit varying morphology, gene expression and signaling pathway activity (4); thus, they have complicated clinicopathological features, to the detriment of the prognosis of patients with TNBC. TNBC was compared with other breast cancer subtypes in a retrospective analysis; increased risks of distant relapse [hazard ratio (HR), 2.6; P<0.0001] and mortality (HR, 3.2; P<0.001) in the first five years were identified (5). As established endocrine and targeted therapies are ineffective against TNBC, chemotherapy remains the primary regimen for TNBC treatment (6). TNBC is highly sensitive to cytotoxic chemotherapy (7), but this treatment is associated with relatively low rates of pathological response (8,9). Thus, developing a more effective therapeutic method for patients with TNBC is necessary.

With this objective, a number of studies have investigated the molecular classification of TNBC to determine optimal individualized therapy strategies for TNBC. Lehmann et al (4) indicated that TNBCs could be classified into the following subtypes according to gene expression profiles: Basal-like subtypes 1 and 2, immunomodulatory subtype, mesenchymal subtype, mesenchymal stem-like subtype, and luminal androgen receptor (AR) subtype. Alternatively, Burstein et al (10) reported that TNBCs could be divided into four subtypes: Basal-like/immune-suppressed subtype, basal-like/immune-activated subtype, mesenchymal subtype and luminal/AR subtype. Patients with specific tumor molecular abnormalities treated with molecularly matched targeted therapy respond better to therapy compared with those treated with non-matched targeted therapy (11). In the present review, the molecular markers and signaling pathways frequently dysregulated in TNBCs, and the targeted therapies in clinical trials and preclinical studies, will be summarized.

2. Receptor tyrosine kinases and downstream signaling pathways

RTKs are important components of signal transduction pathways in the regulation of proliferation, and are associated with two downstream signaling pathways in particular: The Ras/mitogen-activated protein kinase (MAPK) pathway, and the phosphoinositide 3-kinase (PI3K)/AKT/mechanistic target of rapamycin (mTOR) pathway. The RTKs include epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR) 1-3, platelet-derived growth factor receptor (PDGFR) α/β, insulin-like growth factor receptor (IGFR), fibroblast growth factor receptor (FGFR), c-Met, and transforming growth factor receptor-β (TGFR-β), all of which are potential targets for TNBC therapy (4,12-16). EGFR dysregulation is the most commonly identified in TNBC tumors; 60-80% of TNBC tumors demonstrate EFGR overexpression (17,18). However, the applicability of anti-RTK drugs against TNBC are limited on account of biochemical multiplicity and toxicity (19). For example, lapatinib, a dual EGFR and HER2 TK inhibitor, is ineffective in patients with TNBC, although it is clinically effective against HER2-positive breast cancer. The mechanism of lapatinib resistance in TNBC may be associated with interleukin-6 expression (20). The inhibition of Src homology phosphotyrosyl phosphatase 2 (SHP2), an important molecule in EGFR/FGFR1/c-Met signaling (21), was reported to suppress TNBC tumorigenesis and metastasis in vitro (22), indicating the potential anti-tumor efficiency of RTK inhibitors in TNBC treatment. A number of RTK inhibitors have also exhibited promising anticancer therapeutic efficacy in a clinical setting. For example, bevacizumab is an anti-VEGF monoclonal antibody. In a single-arm and phase II multicenter study of bevacizumab, docetaxel, and carboplatin-based neoadjuvant treatment for patients with stage II/III TNBC, the results demonstrated a relatively high pathological complete response rate (42%) with a low risk of adverse events (23); additionally, adding bevacizumab to neoadjuvant chemotherapy regimens improved the pathological complete response rate among patients with TNBC (39.3 vs. 27.9%; P=0.003) (24).

Ras/MAPK pathway. The Ras/MAPK pathway promotes cell proliferation, cell differentiation and angiogenesis (25). Ras family members, including H-Ras, K-Ras and N-Ras, can be activated by RTKs to transmit growth signals from the cell membrane to the nucleus via a series of phosphorylated proteins, including Raf, MAPK kinase 1 (MEK) and extracellular signal-regulated kinases (ERK) 1/2 (26). Although the frequency of mutations in the Ras/MAPK signaling pathway is <2% in TNBC, copy number variations of certain genes from the Ras/MAPK pathway have been demonstrated to be associated with TNBC (26). For example, the overexpression of ERK is associated with a higher mortality rate in patients with TNBC (27). The MEK inhibitor selumetinib inhibited the motility and invasiveness of the MDA-MB-231 and SUM149 TNBC cell lines in vitro. In addition, selumetinib had a significant effect on the prevention of lung metastasis in a TNBC-bearing mouse xenograft model (25). These findings may provide evidence of the applicability of MEK inhibitors in TNBC treatment. However, certain genetic defects along the Ras/MAPK pathway, including the loss of negative regulators of MAPK signaling, such as phosphatase and tensin homolog (PTEN) and certain regulatory micro (mi)RNAs, such as the let-7 family, are also proposed to serve an important role in TNBC development (26). The Ras/MAPK pathway negatively regulates tumor immunogenicity by affecting the process of tumor antigen presentation in TNBC cells; compared with solo therapy, combining MEK inhibition and programmed death-1 (PD-1)/programmed death ligand 1 (PD-L1) immune checkpoint inhibitors increased the therapeutic efficiency in a murine syngeneic TNBC model (28).

PI3K/AKT/mTOR pathway. PI3K family members are activated by RTKs. Activated PI3Ks phosphorylate phosphatidylinositol-4,5-diphosphate (PIP_2) to phosphatidylinositol-3,4,5-triphosphate (PIP_3), resulting in the downstream phosphorylation of AKT (29). Phosphorylated AKT then activates mTOR, a serine/threonine protein kinase, through the intermediary tuberous sclerosis complex 1/2 to promote protein synthesis and cell growth (30,31). PTEN serves an important tumor suppressor role in the process by inhibiting the dephosphorylation of PIP_3 to PIP_2 (32). The PI3K/AKT/mTOR pathway mediates a range of processes, including cell growth, survival and migration, and tumor formation and angiogenesis (33). The dysregulation of the PI3K/AKT/mTOR pathway occurs frequently in TNBC. PI3KCα-activating mutations are observed in 23.7% of TNBC patients (34), and PTEN loss mutations, including promoter silencing and functional suppression, are detected in 25-30% of TNBC cases (32,35,36). With regards to outcome, the hyperactivation of AKT and mTOR are associated with the poor prognosis of patients with TNBC, and based on success in preclinical experiments, dual inhibition of these molecules may represent a promising strategy for TNBC treatment (37-39).

The mTOR inhibitor everolimus has been approved by the US Food and Drug Administration (FDA), and can be combined with the aromatase inhibitor exemestane for patients with metastatic homologous recombination (HR)-positive breast cancer (40). The therapeutic effect of everolimus has been confirmed for patients with TNBC; mTOR activation may lead to platinum therapy resistance (41), and so everolimus combined with carboplatin has been proposed as an effective therapy for patients with metastatic TNBC (42). Phase I trials have also demonstrated that patients with metastatic TNBC who received a combination of chemotherapy and PI3K/AKT/mTOR inhibitor-based targeted therapy had a significantly prolonged median PFS time compared with patients who did not receive the targeted therapy (43). Another study reported that PI3K inhibition causes HR impairment and increased sensitivity to poly(ADP-ribose) polymerase (PARP) inhibition in TNBC without breast cancer associated (BRCA) 1/2 mutations. Therefore, PI3K inhibition can improve the therapeutic efficiency of PARP inhibition in BRCA-wild type TNBC (44). Based on this observation, a clinical trial with BKM120 (buparlisib) and olaparib was initiated, as presented in Table I (45-67).

A high level of crosstalk between the Ras/MAPK and PI3K/AKT/mTOR pathways has been detected in basal-like breast cancer models (68), and an approach that inhibits both pathways may be feasible. However, the high toxicity levels of such an approach are concerning (69), so a greater understanding of the cross-talk mechanisms between pathways is required before effective targeted therapy of this type with improved tolerability can be developed.

3. Epithelial-to-mesenchymal transition and associated pathways

EMT is an essential biological process that also assists the migration and invasion of malignant tumor cells. Thus, elucidating the molecular mechanism of the EMT process and its association with the occurrence, development and metastasis of cancer is of great significance.

During EMT, epithelial cells lose the expression of E-cadherin and acquire mesenchymal markers, including vimentin (70). There is evidence to indicate that a number of RTKs, including EGFR, IGF1R, hepatocyte growth factor receptor and c-Met, non-RTKs, including Src, and embryonic transcription factors, including Twist and Slug (71-77), can induce EMT. Diverse signaling pathways, including MAPKs, PI3K and nuclear factor-κB, also promote EMT (76,78). Other pathways, including Notch and Wnt/β-catenin signaling pathways, are also associated with EMT (79). Tumor cells undergoing EMT may acquire stem cell-like phenotypes and migratory abilities (80). Previous studies have indicated that the genes involved in EMT and conversion to the cancer stem cell phenotype are activated in TNBC (4,81). Additional studies have demonstrated that EMT may induce the resistance to chemotherapy and radiotherapy (82), and may thus have potential as a therapeutic target in TNBC.

In preclinical trials, miRNAs have been demonstrated to regulate tumor EMT and metastasis by inhibiting the expression of certain genes (83). For example, a previous study indicated that miR-200b-3p and miR-200b-5p synergize to suppress TNBC cell migration by inhibiting EMT (84). This finding may provide a novel strategy for clinical treatment. Furthermore, protein tyrosine kinase 6 (PTK6) is an intracellular non-receptor kinase that can promote EMT and regulate the metastasis of TNBC cells by modulating E-cadherin expression. PTK6 inhibition may prevent the metastasis of TNBC cells, and thus exhibits clinical potential for improving the treatment strategies for patients with mesenchymal TNBC (85). Considering the association of EMT with breast cancer stem cells (80), aldehyde dehydrogenase 1 (ALDH1) inhibitors were proposed as a therapeutic alternative in TNBC therapy, targeting the characteristic ALDH1 phenotypic marker of breast cancer stem cells (86,87). A preclinical study confirmed that LBH589, a histone deacetylase inhibitor, could inhibit the metastasis of TNBC cells by partially reversing EMT (88).

Wnt/β-catenin pathway. Aberrant regulation of the Wnt signaling pathway serves an important role in tumorigenesis (89). This regulation is associated with EMT and self-renewal in breast cancer, as it regulates the transcription factors Twist and Slug (90,91).

During tumorigenesis, the Wnt ligand binds to Frizzled (Fz), a seven-pass transmembrane surface receptor, and its co-receptor, low-density lipoprotein receptor-related 5/6 (LRP5/6), to form a Wnt-Fz-LRP6 complex. The combination of this complex with the protein Dishevelled can elicit the phosphorylation of LRP6 and the recruitment of the axin complex, which is composed of axin, anaphase-promoting complex, casein kinase 1 and glycogen synthase kinase 3. These events ultimately stabilize β-catenin, which is degraded by the axin complex without Wnt. The β-catenin protein is transferred to the nucleus where it activates the transcription of Wnt target genes (92).

Lehmann *et al* (4) demonstrated that TNBC has a unique Wnt/β-catenin pathway gene expression. Other studies have indicated that the activation of the Wnt pathway is

Table I. Current clinical trials regarding potential targets in triple-negative breast cancer.

Target pathway/molecules	Chemical agent	Drug class	Combinatorial agents	Clinical trials	Phase	Side effect	(Refs.)
EGFR	Afatinib	EGFR-TKI	Paclitaxel	NCT02511847	II	Gastrointestinal and skin-related side effects	(45)
	Gefitinib	EGFR-TKI		NCT01732276	II	Hematological toxicity	(46)
	Lapatinib	EGFR-TKI	Veliparib (PARPi)	NCT02158507	II	-	
	Panitumumab	EGFR mA	Gemcitabine, carboplatin	NCT00894504	II	-	
VEGFR	Bevacizumab	VEGFR mA	Carboplatin/cyclophosphamide or paclitaxel	NCT01898117	II	Hypertension, proteinuria, mild to moderate bleeding, delayed wound healing, thromboembolic events, nasal septum perforation	(47)
	Apatinib	VEGFR2		NCT01176669	II	A favourable side effect profile	(48)
	Cediranib maleate	pan-VEGFR	Olaparib (PARPi)	NCT01116648	I/II	Chest pain, fatigue, thrombocytopenia, hypertension, hemoptysis	(49)
HGFR/c-MET	Tivantinib	c-MET-TKI		NCT01575522	II	Toxicity was minimal with anemia, fatigue and grade 3/4 neutropenia	(50)
RTKs	Cabozantinib	VEGFR-MET		NCT01738438	II	Fatigue, diarrhea, mucositis, and palmar-plantar erythrodysesthesia	(51)
	Lucitanib	VEGFR-FGFR-PDGFR		NCT02202746	II	Hypertension, asthenia, proteinuria and thrombotic microangiopathy	(52)
PI3K/AKT/mTOR pathway	BKM120	pan-PI3K	Capecitabine	NCT02000882	II	Hyperglycemia, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyltransferase increase	(53)
	BKM120	pan-PI3K		NCT01629615	II	Hyperglycemia, alanine aminotransferase, aspartate aminotransferase and γ-glutamyltransferase increase	(53)
	BKM120/BYL719	PI3K	Olaparib (PARPi)	NCT01623349	I	Hyperglycemia, alanine aminotransferase, aspartate aminotransferase and γ-glutamyltransferase increase	(53)
	Taselisib	PIK3CA	Enzalutamide (ARi)	NCT02457910	I/II	Diarrhea, hyperglycemia, decreased appetite, nausea, rash, stomatitis and vomiting	(54)
	AZD8186	PI3K	AZD2014 (EGFR-TKI), abiraterone acetate	NCT01884285	I	-	
	ARQ 092	pan-AKT	Carboplatin, paclitaxel	NCT02476955	I	-	
	AZD5363	AKT	Paclitaxel	NCT02423603	II	Diarrhea, hyperglycemia, nausea and maculopapular rash	(55)
	MK2206	AKT		NCT01319539	II	Dose-limiting toxicities: Mucosal inflammation, hyponatremia, face edema, erythema multiforme and hyperglycemia. Common adverse events: Rash, an elevated insulin c-peptide level, stomatitis, pyrexia, eosinophilia, leukopenia and hyperglycemia	(56)
	Ipatasertib	pan-AKT	Paclitaxel	NCT02162719	II	Gastrointestinal adverse events	(57)

Table I. Continued.

Target pathway/ molecules	Chemical agent	Drug class	Combinatorial agents	Clinical trials	Phase	Side effect	(Refs.)
	Everolimus	mTOR	Eribulin	NCT02616848	I	Mucositis, hyperglycemia, non-infectious pneumonitis and hematological toxicity	(58)
	Temsirolimus	mTOR	Neratinib (EGFRi)	NCT01111825	I/II	Fatigue, edema, anorexia, nausea, rash, mucositis and lymphopenia	(59)
AR	GTx-024	AR		NCT02368691	II	-	
	Bicalutamide	AR		NCT02348281/ NCT02353988	II	Well tolerated	
	Enzalutamide	AR	Paclitaxel	NCT02689427	II	Well tolerated	(60)
BRCA mutation	Rucaparib	PARP	Cisplatin	NCT01074970	II	Well tolerated	(61)
	E7449	PARP	Temozolomide/ carboplatin, paclitaxel	NCT01618136	I/II	-	
	Iniparib	PARP	Gemcitabine, carboplatin	NCT01045304	II	Well tolerated	(62)
	Iniparib	PARP1	Paclitaxel	NCT01204125	II	Well tolerated	(62)
	Veliparib	PARP	Cyclophosphamide	NCT01306032	II	Nausea and vomiting, decreased appetite, abdominal pain, diarrhea and malaise	(63)
	Talazoparib	PARP	AT13387	NCT02627430	I	Fatigue, anemia and thrombocytopenia	(64)
	Olaparib	PARP	Paclitaxel	NCT00679783	II	Anemia, nausea, vomiting, fatigue, headache and cough	(65)
	Veliparib	PARP	Cisplatin	NCT02595905	II	Nausea and vomiting, decreased appetite, abdominal pain, diarrhea and malaise	(63)
	Olaparib	PARP	Radiotherapy	NCT02227082	I	Anemia, nausea, vomiting, fatigue, headache and cough	(65)
	Olaparib	PARP	Paclitaxel, carboplatin	NCT00516724	I	Anemia, nausea, vomiting, fatigue, headache and cough	(65)
	Talazoparib	PARP		NCT02401347	II	Fatigue, anemia and thrombocytopenia	(64)
PD-1	PDR001	PD-1		NCT02404441	I/II	-	
	Pembrolizumab	PD-1	PLX3397 (CSF1)	NCT02452424	I/II	Arthralgia, fatigue, myalgia and nausea	(66)
	Pembrolizumab	PD-1	Nab-paclitaxel, anthracycline, cyclophosphamide, carboplatin	NCT02622074	I	Arthralgia, fatigue, myalgia and nausea	(66)
	Pembrolizumab	PD-1	Compared with capecitabine, eribulin, gemcitaine and vinorelbine	NCT02555657	III	Arthralgia, fatigue, myalgia and nausea	(66)
	Pembrolizumab	PD-1		NCT02447003	II	Arthralgia, fatigue, myalgia and nausea	(66)
	Durvalumab	PD-1	Paclitaxel	NCT02628132	I/II	low grade skin and gastrointestinal tract which were well-tolerated	(67)

Table I. Continued.

Target pathway/molecules	Chemical agent	Drug class	Combinatorial agents	Clinical trials	Phase	Side effect	(Refs.)
	Pembrolizumab	PD-1	Niraparib	NCT02657889	I/II	Arthralgia, fatigue, myalgia and nausea	(66)
	Pembrolizumab	PD-1	INCB039110 (JAKi)/INCB050465 (PI3Ki)	NCT02646748	I	Arthralgia, fatigue, myalgia and nausea	(66)

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PARP, poly(ADP-ribose) polymerase; i, inhibitor; mA, monoclonal antibody; VEGFR, vascular endothelial growth factor receptor; HGFR, hepatocyte growth factor receptor; RTK, receptor tyrosine kinase; MET, mitogen-activated protein kinase kinase 1; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; PI3K, phosphoinositide 3-kinase; mTOR, mechanistic target of rapamycin; PIK3CA, phosphoinositide 3-kinase catalytic subunit α; AR, androgen receptor; PD-1, programmed death-1; CSF1, colony stimulating factor 1; JAK1, Janus kinase 1.

associated with poor prognosis and metastasis in patients with TNBC (93). Thus, the Wnt/β-catenin pathway could be utilized as a target for TNBC therapy. Substantial efforts targeting the Wnt pathway have been made, but few have reached the clinical trial stage thus far. LGK974, a molecular inhibitor of Wnt secretion, has been evaluated in stage I trials in several types of cancer, including TNBC (http://www.clinicaltrials.gov). In preclinical trials, a previously FDA-approved anti-helminthic drug niclosamide, which can reduce LRP6 and β-catenin levels *in vitro*, was reported to suppress the growth of basal breast cancer xenografts *in vivo* (94,95). Thus, niclosamide may be a promising drug for clinical trials. Another FDA-approved, anti-leprosy drug, clofazimine, was observed to suppress the growth of TNBC cells through the inhibition of the Wnt/β-catenin pathway (94). Notably, the multipurpose drug suramin can inhibit the Wnt signaling pathway and the proliferation of TNBC cells *in vitro* and *in vivo*. Such findings may pave the way for the discovery of novel targeted therapies against Wnt-dependent TNBC tumors (96).

TGF-β/Smad pathway. In addition to the Wnt pathway, the TGF-β/Smad pathway can also regulate cell proliferation, invasion, apoptosis and metastasis, and induce EMT, and thus has potential in targeted strategies against TNBC (97). When secreted from cells, TGF-β remains as an inactive, latent homodimeric polypeptide (98). TGF-β can be activated by hydrolyzing the latent complex. The TGF-β then binds to and activates its receptors, TGF-β receptor type II (TβRII) and I (TβRI), which are transmembrane serine/threonine kinases. This induces two TβRI and two TβRII molecules to form a heterotetramer, and TβRII triggers the cross-phosphorylation of TβRI, allowing the activation of substrate Smad proteins (99). Smads include receptor-regulated Smads (R-Smads), common mediator Smads (Co-Smads) and inhibitory Smads (I-Smads). Among the Smad types, Smad-2 and Smad-3, as R-Smads, are the direct substrates of TβRI. The activated R-Smads combine with Smad-4, a Co-Smad, where they induce the activation of specific genes. Inversely, Smad-7, as an I-Smad, can inactivate the TGF-β/Smad pathway by disrupting the combination of R-Smad with TβRI (100).

Smad-2 or Smad-3 overexpression, when combined with Smad-4, can induce EMT. Inversely, the reduced expression of Smad-2, Smad-3 and Smad-4, or the overexpression of Smad-7, can constrain EMT (101). Clinical evidence suggests that ~40% of human breast cancer tumors have high TGFβ1, TGFβ2, Smad-3 and Smad-4 expression levels, although the positive TGFβ gene signature occurs primarily in ER-positive breast tumors and lung metastases (102). In addition, a high TGF-β1 expression level was detected in TNBC cells (MDA231, Hs578T, HCC1806) compared with non-TNBC (BT474, ZR75-1, SKBR3) (103). Treatment with zerumbone may inhibit the tumorigenicity of TNBC cells by suppressing the TGFβ/Smad pathway, and thus has a potential as a targeted drug for TNBC. LY2109761, another selective TβRI/II dual inhibitor, can also suppress the invasion and motility of TNBC cells (103). The antidiabetic agent metformin can hinder the TGF-β/Smad pathway by disrupting the activation of Smad-2 and Smad-3 in TNBC (104). This finding may offer a novel perspective for the clinical treatment of TNBC patients.

Although chemotherapy is the central treatment methodology against TNBC, patients with TNBC are likely to eventually develop drug resistance and disease recurrence, which is contributed to by cancer stem-like cells. The TβRI inhibitor LY2157299 can constrain the development of stem-like cells, indicating the potential combination of chemotherapy and TGF-β targeted drugs in clinical trials (105).

4. Androgen receptor and coordinating pathways

ER and PR are widely accepted molecular markers in the occurrence, development and prognosis of breast cancer. TNBC tumors lack ER and PR expression. An association between TNBC and AR, another hormone receptor, has been observed (4). Lehmann et al (4) classified cases of TNBC according to gene expression profiling, in which a luminal AR subtype, featuring increased gene expression in the AR signaling pathway, was identified. In another study of 593 TNBC cases, a luminal AR subtype was also identified based on the expression profiles and histopathological features of primary TNBC tumors (106).

As a member of the steroid hormone receptor family, AR is expressed in ~77% of breast cancer tumors (107), and serves an important role in regulating cell proliferation (108). Testosterone, particularly dihydrotestosterone, is the main activator of AR (109). Subsequent to ligand binding, AR is usually bound to chaperone proteins, including heat shock proteins, before forming a homodimer. The homodimer translocates to the nucleus and promotes the transcription of target genes (110).

Anti-androgens are the most common drugs for treating AR-positive cancer, including AR-positive TNBC. In recent research, bicalutamide (150 mg daily) was prescribed to 424 patients with AR-positive, ER and PR-negative metastatic breast cancer. The six-month clinical beneficial rate was 19% [95% confidence interval (CI), 7-39%], and the median progression-free survival time was 12 weeks (95% CI, 11-22 weeks). These findings provided evidence in favor of the application of anti-androgen therapy in ER/PR-negative and AR-positive breast cancer (111). In a phase II clinical trial of enzalutamide, another AR antagonist, considerable beneficial therapeutic efficiency was demonstrated in AR-positive TNBC patients, indicating the potential efficacy of anti-AR therapy in clinical settings (clinicaltrials.gov: NCT01889238).

A previous study indicated that the concomitant administration of the anti-androgen bicalutamide with a EGFR, PDGFRβ or Erk1/2 inhibitor significantly decreased the AR expression level when compared with the single administration of the inhibitors (112). Another study reported that activating PIK3CA mutations are enriched in AR-positive TNBCs, potentially providing a basis for the concomitant use of AR antagonists with PI3K/mTOR inhibitors (4). In addition, enhanced therapeutic effects of bicalutamide combined with the PI3K inhibitor GDC-0941 (pictilisib) or the mTOR inhibitor GDC-0980 (apitolisib) have also been also observed in MDA-MB-453 and CAL-148 luminal AR subtype cell xenografts, indicating that the inhibitors targeting the PI3K/mTOR signaling pathway also notably decrease the amount of AR protein (113). It was concluded that AR expression can be regulated post-transcriptionally by activating the RTK, PI3K or Erk1/2 signaling pathways (113). The combination of anti-androgen therapy with targeted therapy against the RTK, PI3K and Erk1/2 signaling pathways may be a promising alternative treatment for AR-positive TNBC.

5. DNA damage repair pathways

The DNA damage response has recently attracted considerable attention in cancer research. Three major pathways operate in this process: DNA repair mechanisms that remove DNA lesions, cell cycle checkpoints that prevent the growth of cells with DNA damage and apoptotic pathways that eliminate cells with irreparable DNA lesions (114). Among the various types of DNA damage, DNA double-strand breaks (DSB) are of particular interest on account of their function in genomic instability, which promotes tumorigenesis (115). DSB repair is accomplished through the HR or non-homologous end-joining pathways (116). BRCA1 and BRCA2 are critical genes modulating DSB repair through HR (117).

TNBC is commonly associated with BRCA1/2 mutations. A germline mutation in BRCA1 or BRCA2 is present in ~15% of patients with TNBC; TNBC cases account for 70% of cases of breast cancer with BRCA1 mutation, and 16-23% of those with BRCA2 mutation (118). TNBC also has similar clinical and pathological features as breast cancer with a BRCA1/2 mutation. For instance, the patients are more likely to be young and present with a high grade and lymph node invasion ratio (119,120). In addition, BRCA1/2 mutations have been confirmed to be indicators of a poor TNBC prognosis (121). In a study of 182 women with TNBC, >50% were carrying inherited BRCA1 mutations, thus demonstrating the close association between TNBC and BRCA1 (122).

Polyadenosine 5'-diphosphoribose produced by PARP enzymes serves an important role in the repair of DNA damage (123). Where there is a defect in DNA repair genes, such as BRCA in TNBC, a PARP inhibitor may be a desirable choice for therapy. In an open-label phase II clinical study, results indicated that the combination of PARP inhibitor iniparib and conventional chemotherapy drugs, including gemcitabine and carboplatin, could produce significant clinical benefit rates (from 34 to 56%; P=0.01) and a high overall response rate (from 32 to 52%; P=0.02) in patients with TNBC. The median progression-free and overall survival times were also prolonged, with an extension from 3.6 to 5.9 months (progression HR, 0.59; P=0.01) and from 7.7 to 12.3 months (mortality HR, 0.57; P=0.01), respectively (124). In addition, in a phase I trial of the oral PARP inhibitor olaparib for metastatic TNBC, 7 (37%) out of 19 patients receiving olaparib in combination with weekly paclitaxel had confirmed partial responses (125). Data regarding the safety of PARP inhibitor treatment for advanced TNBC and/or BRCA-mutated breast cancer from clinical trials is summarized in Table I; the side effects of PARP inhibitors are well tolerated. Interestingly, in the TNBC patients with BRCA downregulation, the sensitivity to PARP inhibitor treatment was enhanced when combined with PI3K inhibition, as the blockade of PI3K impaired HR, inducing sensitization to PARP inhibitors (44), providing a theoretical basis for the combination of PI3K with PARP inhibitors for these patients.

In addition to the aforementioned BRCA1/2 genes, other breast cancer predisposition genes, including RAD51D,
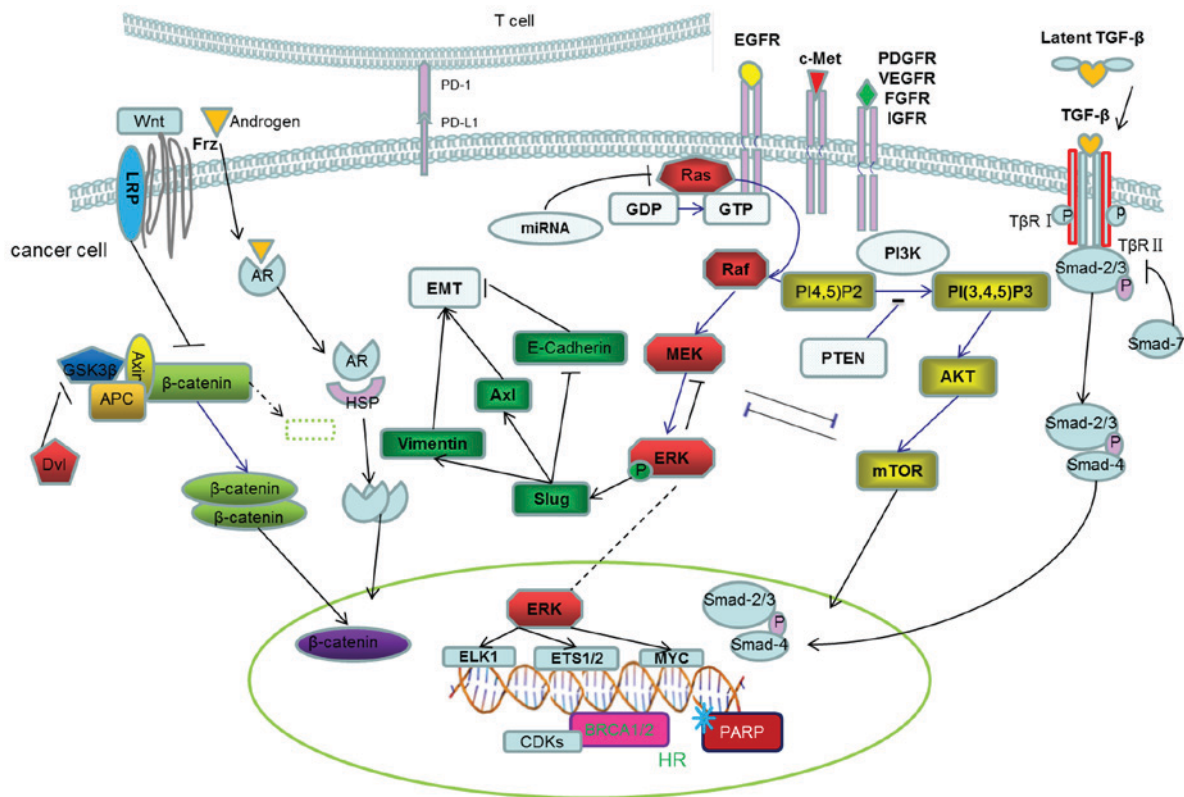
Figure 1. Molecular mechanisms of TNBC. RTKs promote tumorigenesis through the Ras/mitogen-activated protein kinase and PI3K/Akt/mTOR pathways. The phosphorylation of ERK, the Wnt/β-catenin pathway and the TGF-β/Smad pathway activates EMT, and regulates the migration and invasion of tumor cells. In the AR pathway, AR can bind to chaperone proteins to promote the transcription of target genes in the nucleus. At the genetic level, BRCA1/2 mutations can also promote the development of TNBCs. In the tumor microenvironment, tumor-infiltrating lymphocytes and the immune checkpoint system can allow evasion from recognition by the host immune system. TNBC, triple negative breast cancer; RTK, receptor tyrosine kinase; PI3K, phosphoinositide 3-kinase; mTOR, mechanistic target of rapamycin; ERK, extracellular signal-regulated kinase; TGF, transforming growth factor, EMT, epithelial-mesenchymal transition; AR, androgen receptor; BRCA, breast cancer-associated; PD-(L)1, programmed death (ligand) 1; EGFR, epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor; IGFR, insulin-like growth factor receptor; LRP, LDL receptor-related protein; Frz, Frizzled; TβR, transforming growth factor β receptor; miRNA, microRNA; GSK3β, glycogen synthase kinase 3β; HSP, heat shock protein; MEK, mitogen-activated protein kinase kinase 1; PIP₂, phosphatidylinositol 4,5-bisphosphate; PTEN, phosphatase and tensin homolog; Dvl, Dishevelled; CDKs, cyclin-dependent kinase; HR, homologous recombination; PARP, poly(ADP-ribose) polymerase.

MRE11A, checkpoint kinase 2, mutL homolog 1, mutS homolog 6 and partner and localizer of BRCA2, have been confirmed to be associated with the development and progression of TNBC (126). It was previously reported that the cytoplasmic expression and lack of nuclear expression of RAD51 were associated with TN phenotypes, the aberrant expression of BRCA1 and a poor prognosis for patients (127), indicating that RAD51 may be a promising biomarker for selecting patients who are suitable for treatment with DNA-damaging agents.

6. Immunoregulatory tumor microenvironment

An increasing number of studies have demonstrated that the tumor microenvironment, particularly the immune microenvironment, is associated with the development and progression of breast cancer (128). Lehmann *et al* (4) and Burstein *et al* (10) reported that a subtype of TNBC displayed upregulated immunological responses, immune cell markers and immune transcription factors, implying the dysregulation of immune pathways in TNBC, and that the immunotherapeutic approach may be a valuable treatment strategy for patients with TNBC (4,10).

Tumor infiltrating lymphocytes. High levels of stromal lymphocytic infiltration was confirmed to be associated with improved TNBC prognosis in two adjuvant phase III trials. Results of one trial indicated that compared with the patients who had a lower level of stromal lymphocytic infiltration, patients with high lymphocytic infiltration had a 14% reduced risk of recurrence (P=0.02), an 18% reduced risk of distant recurrence (P=0.04) and a 19% reduced risk of mortality (P=0.01) for every 10% increase in stromal lymphocytic infiltration (129). Another phase III randomized adjuvant breast cancer trial reported similar results, indicating that an increase in lymphocytic infiltration was associated with an improved prognosis in node-positive and ER-negative/HER2-negative breast cancer, regardless of chemotherapy (130). In addition, the presence of tumor-infiltrating lymphocytes predicted a better clinical response to neoadjuvant chemotherapy (131). Therefore, the existence of tumor-infiltrating lymphocytes can be regarded as a prognostic parameter for the prediction of the response to clinical treatment of patients with TNBC.

Immune checkpoint system. Tumor cells can evade the recognition and destruction by the host immune system through the immune checkpoint system; blocking the immune

checkpoint system is a promising treatment for achieving effective antitumor immunity. PD-1 is a well-established immune checkpoint protein and cell-surface receptor that disrupts the T-cell response by triggering inhibitory pathways (132). Notably, PD-1 is expressed in 20% of TNBC tumors (133). PD-L1 is the ligand of PD-1, and is expressed in 58.6% of TNBC tumors (66,134). PD-L2 is expressed on the surface of dendritic cells, macrophages, mast cells and B cells (135). Antibodies to inhibit PD-1 signaling are currently being assessed for clinical use. For example, pembrolizumab, a monoclonal antibody against PD-1, has demonstrated an overall response rate of 18.5% in a phase Ib study (n=32) of patients with PD-L1-positive TNBCs (66). Furthermore, a preliminary phase I trial study suggested that the monoclonal anti-PD-L1 antibody MPDL3280A prolonged progression-free survival time and produced durable therapeutic effects in certain patients with TNBC (136).

In addition, there is an association between the immune response and the Ras/MAPK pathway in TNBC. A study has indicated that the Ras/MAPK pathway negatively regulated antitumor immunity by affecting antigen presentation, including that of MHC-I, MHC-II and PD-1, and it was verified that a combination of MEK inhibition and PD-1/PD-L1 antibodies increased the effect of treatment in murine syngeneic tumor models (26). An additional study identified that an oncolytic viral therapy (NV1066) eliminated >70% of the cells from all the TNBC cell lines tested by day 7, and effectively reduced the tumor size compared with control treatment groups (57 vs. 438 mm; P=0.002) through downregulating the Ras/MAPK pathway (137).

7. Conclusion

TNBC is attracting increasing attention on account of its unique clinical pathology and molecular features. Chemotherapy remains the exclusive effective systemic treatment for patients with TNBC. These patients exhibit varied therapeutic responses and prognoses. Thus, individualized treatment and prognostic analysis in patients with TNBC can be difficult, particularly when this depends on conventional clinical and pathological features, including the histological grade, primary tumor size, lymph node metastasis status and ER/PR/HER2 expression. With the emergence of targeted therapy, screening more reliable molecular markers is imperative, and comprehensively understanding the signaling pathways that regulate biological behaviors may facilitate the establishment of a precise molecular classification for TNBC and effective therapeutic regimens.

In the present review, TNBC-associated tumorigenic signaling pathways were summarized in five categories, specifically RTKs and downstream signaling pathways, epithelial-to-mesenchymal transition and associated pathways, immunoregulatory tumor microenvironment, DNA damage repair pathways, and AR and coordinating pathways. These pathways are illustrated in Fig. 1 to demonstrate the interactions across the entire network, and the relevant drugs against specific pathways are summarized in Table I. Enhancing the understanding of the molecular heterogeneity of TNBCs can lay the foundation for the individualized treatment of patients with TNBC.

It is worth noting that a study concerning the efficacy of a number of biological agents, including bevacizumab, sunitinib, sorafenib, lapatinib, iniparib and cetuximab, in metastatic TNBCs indicated that a significant PFS improvement was obtained following treatment with bevacizumab or cetuximab, indicating the importance of targeted therapy. Regrettably, the impact of the other agents in the study on patient survival was not significant (138), possibly due to concurrent abnormalities occurring in a number of the patients. If that is correct, the concurrent inhibition of tumorigenic pathways may inhibit the cancer process (45). Therefore, the understanding of the signaling crosstalk and feedback among the TNBC-associated tumorigenic signaling pathways needs to be improved to allow effective treatments with tolerable side effects to be developed.

Availability of data and materials

Not applicable.

Authors' contributions

NW led the review's designing, consulting and writing. JL and JY led the conception and review of the paper. JZhang, JZhao, KM, JuZ, and ZJ made contributions to the collection of relevant literature. All authors have read and approved the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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