Journal of Research High School

Vol. 2025 (9) 675 – 687
ISSN 2688-3651 [online]

Novel Targeted Therapies for Triple Negative Breast Cancer with Basal-like Features

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Received November 17, 2024; Revised April 1, 2025; Accepted May 29, 2025

Abstract

Triple-negative breast cancer (TNBC) with basal-like features is a highly aggressive subtype of breast cancer, with the worst prognosis of all subtypes. TNBC has limited treatment options because it does not respond to hormonal or other targeted therapies due to the absence of estrogen receptors, progesterone receptors and human epidermal growth factor receptor 2 expression. Current treatment modalities include chemotherapy, PARP inhibitors, EGFR inhibitors, and mTOR inhibitors. However, the results of these treatments are variable across patients due to drug resistance from mutations and tumor heterogeneity. Oncogenic transcription factors, including ID4 and FOXC1, have been identified in previous studies as novel targets due to their involvement in the progression and aggressiveness of basal-like TNBC. Since these transcriptional factors cannot be targeted using conventional small molecule inhibitors due to a lack of active site, PROTAC (PROteolysis TArgeting Chimeras) technology is proposed as a novel alternative, which works by degrading the protein of interest. Over the past few years, PROTACs have emerged as a novel strategy for targeted protein degradation because they have a better target selectivity compared to traditional small molecule inhibitors and lower toxic side effects. A literature search was conducted using PubMed for articles published within the past 15 years, focusing on targeted therapies, clinical trial outcomes, and emerging treatments within this field. Findings suggest that current therapies face challenges in efficacy, while PROTACs can potentially overcome the issue of drug resistance and lack of specificity in targeting oncogenic proteins.

Keywords: Triple Negative Breast Cancer (TNBC), Basal-like, Hormone therapies, Targeted therapies, PROTAC technology, Transcription factors

1. Introduction

Breast cancer affects women globally, accounting for 15.5% of female deaths (Kalaba et al., 2024). In 2020, 2.3 million new cases were estimated and more than 685,000 deaths were reported (Nolan et al., 2023). Breast cancers can be classified into four subtypes based on hormonal receptor expression: luminal A, luminal B, HER2-positive (HER2+), and triple-negative breast cancer (TNBC) (Kalaba et al., 2024). Despite being a small percentage of all types of breast cancers, TNBC is responsible for a disproportionate number of deaths due to its aggressive nature and limited treatment options (Dogra et al., 2020). Furthermore, TNBC has the lowest 5-year survival rate (77.1%), compared to luminal A (94.4%), luminal B (90.7%), and HER2+ (84.8%) subtypes (Kalaba et al., 2024; Table 1). There is a disproportionate prevalence of TNBC in African women and women under 40 years old undergoing premenopause (Alluri & Newman, 2014; Yin et al., 2020). Therefore, there is an urgent need to develop more effective therapeutic strategies for TNBC to narrow the gap in healthcare equity.

The poor prognosis of TNBC is due to its negative expression of estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor 2 (HER-2) (Table 1). The negative expression of these receptors makes it unresponsive to FDA-approved endocrine and molecular targeted therapies that other subtypes respond to (Yin et al., 2020). Due to the absence of specific and well-established targets, non-targeted treatments including chemotherapy, radiation and surgery remain as the main approaches (Cao & Niu, 2020). However, non-targeted

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ISSN 2688-3651 [online]

approaches are less effective because there is large variability within a tumor genetically and molecularly, reducing the treatment specificity and increasing the toxic side effects.

Table 1. Breast Cancer Subtypes and Survival Rates (Thakur et al., 2022)

Molecular Subtypes	Frequency	Biomarkers	5-year survival rate (Kalaba et al., 2024)	Histological Grade	Effective therapies
Luminal A	40-50%	HR+, ER+, HER2-, PR+, Ki67 low	94.4%	Well-differentiated (Grade 1)	Endocrine
Luminal B (HER 2+)	20-30%	HR+, ER+, HER2+, PR+/-, Ki67 low/high	90.7%	Moderately Differentiated (Grade 2)	Endocrine, Chemotherapy, Target therapy
Luminal B (HER 2-)		HR+, ER+, HER-, PR-, Ki67 high			Endocrine, Chemotherapy
HER2+	15-20%	HR-, ER-, HER2+, PR-, Ki67 high	84.8%	Poorly Differentiated (Grade 3)	Chemotherapy, Target therapy
TNBC	10-20%	HR-, ER-, HER2-, PR-, Ki67 high	77.1%	Poorly Differentiated (Grade 3)	Chemotherapy, PARP inhibitor

Approximately 20% of TNBC patients respond well to the standard therapy; while the other 80% will develop a metastatic disease where cancer spreads to vital organs, making it more difficult to eradicate the cancer (Wang et al. 2019). TNBC patients still experience the highest rates of distant recurrence and poorer prognosis (Cao & Niu, 2020), while some patients do not see any clinical improvements at all (Zhu et al., 2023). The median overall survival of patients with advanced TNBC being treated with chemotherapy rarely exceeds 12-18 months (Zhang et al., 2024), while the mortality rate within 5 years of diagnosis is 40% (Yin et al., 2020).

Targeted therapies only interfere with the specific biomolecule, directing its target to a molecular characteristic of the cancer cell, such as an overexpressed protein (de Ruijter et al., 2010). Finding effective targets without adverse side effects remains a clinical challenge in the treatment of TNBC. Developing targeted therapies will hopefully raise survival rates to comparable levels to other breast cancer subtypes.

This paper provides an overview of the molecular characteristics of TNBC and discusses existing and emerging therapeutic approaches for the TNBC subtype. This review proposes targeted protein degradation as a potential strategy that addresses resistance mechanisms in cancer treatment, which work by inhibiting the activity of overexpressed proteins through degradation within the cell.

2. Methods

A literary search was conducted using PubMed for articles published from 2009-2024 to ensure a comprehensive coverage and sufficient relevancy. Keywords for advance search included: “TNBC”, "BLBC", "targeted therapies”, "EGFR inhibitors", "PARP inhibitors", "chemotherapy efficacy in TNBC”, "PROTAC cancer". Boolean operators were used to refine search results. Data extraction was focused on the treatment outcomes, clinical trials, and the challenges and limitations of the targeted therapies and developments. Each article was read after an initial screening of the abstract and title if they addressed those topics.

3. TNBC Molecular Subtypes

TNBC can be classified into six subtypes based on molecular heterogeneity: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), mesenchymal stem-like (MSL), immunomodulatory (IM), and luminal androgen receptor (LAR) (Yin et al., 2020) (Figure 1). The presence of distinct genetic profiles within TNBC makes finding targeted treatment more difficult as the different subtypes may respond differently to therapies. The majority of TNBC are basal-like (Badowska-Kozakiewicz & Budzik, 2016), exhibiting poor differentiation (Bando et al., 2021), with tumor cells abnormal in behavior and appearance. Basal-like tumors have high proliferative rates (Bando et al., 2021), dividing rapidly, making them highly aggressive and more prone to drug resistance.

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The basal-like tumors in TNBC include the BL1 and BL2 subtypes (Yin et al., 2020). BL1 is associated with genomic abnormalities in cell cycle gene expression, DNA repair, and cell proliferation (Figure 1). BL2 is associated with abnormalities in growth factor signaling, glycolysis, gluconeogenesis, and myoepithelial markers (Yin et al., 2020; Figure 1). Together, they are referred to as Triple Negative Basal Breast Cancer. BL1 and BL2 will be referred to as basal breast cancer (BLBC) when mentioning both in this paper.

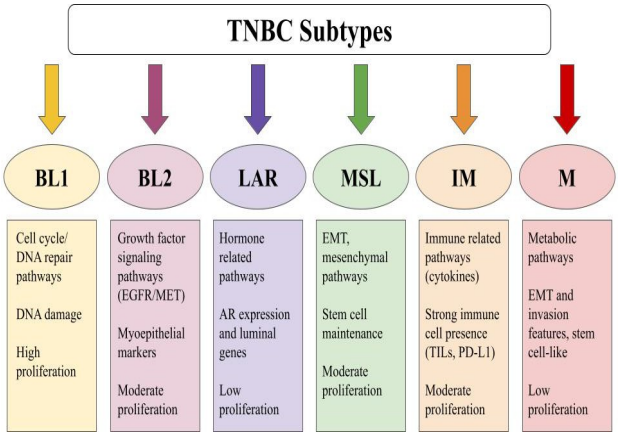

Figure 1. Six molecular subtypes of triple negative breast cancer (TNBC) and their key characteristics.

4. Therapeutic Approaches to Treating Basal-like TNBC

There are several therapeutic approaches for TNBC that target distinct molecular pathways to combat tumor growth and progression. This section explores the efficacy and mechanisms of these strategies including: chemotherapy, PARP inhibitors, EGFR inhibitors, and mTOR inhibitors. Despite their potential benefits, these therapies face significant challenges and are often insufficient on their own, necessitating the need for continued research and development of more effective treatment strategies.

Table 2. Drug types and mechanism of action for TNBC basal treatments (Yin et al. (2020))

Drug type	TNBC basal subtype	Drug names	Mechanism of Action	Limitations
Cytostatics	BL1, BL2	Taxane, Anthracycline, Cyclophosphamide, Fluorouracil, Cisplatin, Carboplatin	Halts rapidly dividing cells by disrupting DNA replication	Adverse side effects.
PARP inhibitor	BL1	Olaparib, Rucaparib, Talazoparib and Niraparib	Suppresses BRCA activity and blocks DNA damage repair	Limited to patients with BRCA mutations.
Growth Factor Inhibitors	BL2	Pertuzumab, Cetuximab, Lapatinib, Gefitinib	Prevents cancer cells from receiving signals that promote cell proliferation	Induces tumor resistance through activation of alternative pathways.
mTOR inhibitors	BL2	Rapamycin, Everolimus, RapaLink-1	Inhibits the mTOR pathway responsible for regulating cell growth and proliferation	Induces negative feedback mechanisms that reduce drug efficacy and promote tumor progression.
DNA synthetic inhibitors	BL1	Topotecan, Irinotecan, Camptothecin, Doxorubicin, Daunorubicin, Mitomycin	Modifies the composition and structure of the nucleic acid substrate, inhibit DNA polymerase activity	Limited by tumor heterogeneity, with varying responses among tumor populations.
Mitosis inhibitors	BL1	Paclitaxel, Docetaxel, Ixabepilone, Nab-Paclitaxel, Vinorelbine	Inhibits cancer cell division by targeting microtubules that forms mitotic spindle	Limited effectiveness against tumors less reliant on rapid cell division.

4.1 Chemotherapy efficacy and resistance in TNBC treatment

Chemotherapy is the standard treatment for TNBCs, with taxanes and anthracycline being the most commonly used (Ferrari et al., 2022; Table 2). These chemotherapy drugs work by inhibiting cell proliferation, interfering with DNA, RNA, or protein synthesis, leading to cell apoptosis (Amjad et al., 2023; Table 2). Only 20% of TNBC patients achieve a higher pathologic complete response (pCR) after neoadjuvant chemotherapy (before surgery). Achieving a pCR means that there are no detectable cancer cells remaining in the body. Patients who do not achieve pCR are likely to experience early recurrence and die from metastasis (Ferrari et al., 2022). This suggests that a small subset of triple-negative tumors respond to chemotherapy, while most develop chemoresistance, when the tumor becomes resistant to

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chemotherapy drugs (Ferrari et al., 2022). The median progression free survival is 1.2-3.7 months before cancer cells come back, while the median overall survival after metastasis is 10-13 months under chemotherapy regimen (Won & Spruck, 2020).

Chemoresistance happens when cells within a tumor undergo molecular changes, allowing them to escape the effects of chemotherapy drugs. Molecular alterations can be intrinsic, where a tumor contains cancer cells that have a variety of molecular characteristics, or acquired, where cancer cells acquire mutations after chemotherapy is being administered (National Cancer Institute, 2016). Molecular alterations can include the mutation of the drug's molecular target, changes in the tumor microenvironment, and changes in the way the drug interacts with the tumor. All of these factors contribute to the ineffectiveness of chemotherapy drugs.

Chemoresistance is the main challenge of the cytotoxic treatment for TNBC, and accounts for 90% of therapy failure during metastasis. Mechanisms like cancer stem cells (CSC) and ATP-binding cassette (ABC) transporters contribute to chemoresistance. For example, ABC transporters are membrane proteins that translocate compounds – including chemotherapy drugs – across cellular membranes through ATP transport, leading to failure of drug penetration. In TNBC, many drug resistant proteins are overexpressed including ABCC1/MRP1 and ABCG2/BCRP (Ferrari et al., 2022). Chemotherapy has been found to increase ABCC1 protein expression, while TNBC cell activation of the hedgehog pathway – which is a crucial pathway for tissue regeneration – can increase drug resistance through upregulation of ABC transporters (Ferrari et al., 2022).

Although chemotherapy is the standard treatment for TNBC, prognosis remains poor due to high likelihood of relapses among patients caused by chemoresistance. The minimal efficacy of chemotherapy is still a clinical challenge that needs to be addressed, though targeted therapies may offer more selectivity with less side effects.

4.2 PARP inhibitors in BRCA-deficient TNBC

Poly (ADP-ribose) polymerase (PARP) is an enzyme that helps repair DNA damage in cells during oxidative stress, inflammation, and ischemia (Uscanga-Perales et al., 2016; Table 2). Triple Negative Basal Breast Cancer patients often have a reduced expression of BRCA1/2 (Singh & Yadav, 2021), which are tumor suppressors that ensure cells do not grow uncontrollably. Patients with BRCA mutations have an increased lifetime risk of developing breast cancer. Specifically, those with BRCA1 mutations have a 60% lifetime risk of developing breast cancer, and patients with the BRCA2 mutation have a 26% lifetime risk (Rose et al., 2020). In tumors with BRCA mutations, PARP inhibition leads to cell death by apoptosis (Uscanga-Perales et al., 2016; Table 2).

PARP repairs DNA single strand breaks (SSBs) (Alluri & Newman, 2014) through the base excision repair (BER) pathway. In the BER pathway, PARP1 attaches to the ends of the damaged DNA strand and attracts necessary enzymes in order to repair SSBs (de Ruijter et al., 2010). When PARP1 is inhibited, SSBs do not get repaired due to the BER pathway being disrupted, leading to an accumulation of SSBs. This halts cell replication, resulting in DNA double-strand break (DSB), and ultimately causes cell death through apoptosis. PARP inhibitors have been used for neoadjuvant and preventive therapy for patients with BRCA mutations. Currently FDA-approved PARP inhibitors include olaparib, talazoparib, rucaparib, and niraparib (Rose et al., 2020).

Although PARP inhibitors have demonstrated prolonged overall survival in patients with TNBC based on several clinical trials, the difference was not significant. For example, in the OlympiAD phase 3 clinical trial, the overall survival was 19.3 months with olaparib, a PARP inhibitor, and 17.1 months for patients not receiving PARP inhibitors (Won & Spruck, 2020). Olaparib is ineffective against metastatic TNBC (Zhu et al., 2023) because cancer cells are reliant on alternative pathways to repair DNA damage that do not lead to cell death when PARP is inhibited. Additionally, cancer cells may undergo molecular alterations which activate their repair processes, helping them to survive (Trenner & Satori, 2019; Garrido-Castro et al., 2019). As an example, point mutations in *PARP1* can affect how well PARP inhibitor drugs trap the protein, reducing their efficacy (Garrido-Castro et al., 2019). Due to the development of this PARP resistance in tumor cells, it is necessary to explore other targets that can be more effective.

4.3 EGFR inhibitors

Triple-negative tumors are characterized by the overexpression of EGFR, found in 13-76% of the tumors (Ferrari

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et al., 2022). EGFR is a transmembrane receptor that stimulates growth factor signaling pathways, involved in cell cycle regulation, differentiation, proliferation and survival (Singh & Yadav, 2021). EGFR gene amplification leads to the overexpression of EGFR protein, which is highly associated with aggressiveness (Kato et al., 2019). It is linked to drug resistance and tumor growth; therefore, inhibiting it can halt the spread of cancer cells, making it an effective target (Kato et al., 2019). There are several EGFR inhibitors – including gefitinib, afatinib, dacomitinib, erlotinib, and osimertinib – that have been FDA approved for advanced non-small-cell lung cancer. Two EGFR-inhibitors – lapatinib and neratinib – were approved for HER2+ breast cancer (Zubair & Bandyopadhyay, 2023). EGFR has been reported as an efficient therapeutic target in 89% of TNBC, and especially the BL2 subtype that harbors amplification of EGFR (Zhu et al., 2023).

The activation of EGFR leads to MAPK and PI3K downstream signaling pathways that promote cell proliferation and survival (Kato et al., 2019). EGFR receptors stimulate cell replication, and when targeted, cells halt replication resulting in tumor growth arrest and tumor regression. Mutated EGFR can make these receptors overly active. EGFR therapies utilize two main agents: tyrosine kinase inhibitors (TKIs) and monoclonal antibodies. Monoclonal antibodies against EGFR target the extracellular part of the receptor by blocking ligand binding, to inhibit the receptor from interacting with growth signals. This can induce an immune response against cells that express the EGFR protein. TKIs target the intracellular part of the receptor, blocking the receptor from activating downstream signaling pathways, hindering cell proliferation (de Ruijter et al., 2010).

Although anti-EGFR monoclonal antibodies have been evaluated as a monotherapy and in combination, results have indicated limited efficacy based on several clinical trials, including the randomized phase II study of cetuximab in combination with carboplatin in TNBC (Uscanga-Perales et al., 2016). In this study, 120 TNBC patients were tested, and they found monotherapy of cetuximab had a response rate of <6% alone, and 17% in combination with chemotherapy (Yin et al., 2020). Although preclinical studies strongly suggested EGFR as an effective target for TNBC treatment, the clinical data did not show promising results (Yin et al., 2020). This is because tumor heterogeneity and genomic instability leads to resistance against EGFR inhibitors, and it has been found that patients administered with gefitinib, an EGFR inhibitor, develop chemo-resistance within 9-15 months of progression free survival (Singh & Sonawane, 2023). These findings also show that EGFR-targeted therapy alone cannot achieve significant efficacy, finding novel targets involved in growth signaling pathways may yield more favorable outcomes.

4.4 mTOR inhibitors to target PI3K/AKT/mTOR signaling pathways

The PI3K/AKT/mTOR signaling pathway is highly activated in TNBC, contributing to tumor survival and drug resistance (Mao et al., 2024). Mutations in the PI3K/AKT/mTOR pathway occur in the majority of breast cancers (70%), and 25% of primary TNBCs (Mao et al., 2024; Lee & Yuan, 2020). This pathway promotes cell growth and survival, leading to increased cell proliferation, apoptosis inhibition, and abnormal cell differentiation, which leads to metastasis (Mao et al., 2024).

mTOR exists in two complexes: mTORC1, which regulates protein synthesis, and mTORC2, involved in regulating AGC family kinases (Hare & Harvey, 2017). Alterations in the PI3K pathway, often due to PIK3CA mutations common in many BC patients, lead to increased mTOR activation via AKT. PI3K activation is initiated by growth factors binding to cell membrane receptors, catalyzing the conversion of PIP2 to PIP3. PIP3 recruits AKT and PDK1 to the membrane, where AKT is phosphorylated by mTORC2 and PDK1, fully activating it. Activated AKT then phosphorylates various target proteins, stimulating cell proliferation and survival (Miricescu et al., 2020).

Everolimus, a rapamycin analog approved in 2012 for advanced HR+, HER2-negative breast cancer, targets the serine-threonine kinase which stimulates cell proliferation, showed improved progression-free survival when combined with aromatase inhibitors (Table 2; Hare & Harvey, 2017). However, a small phase II study found no significant efficacy in TNBC when combined with paclitaxel and bevacizumab. Resistance to mTOR inhibitors can develop, as rapalogues may activate alternative pathways like AKT, alongside factors such as EMT markers, MYC upregulation, and mutations in mTOR.

Identifying new targets is crucial due to the limitations observed with current treatments and the emergence of resistance mechanisms in mTOR inhibitors. Understanding the complexities of the PI3K/AKT/mTOR pathway and

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its interactions can help researchers discover novel targets that may lead to more effective therapies.

5. Suggested Targets

5.1 Inhibitor DNA binding 4

Inhibitor DNA binding 4 (ID4) is highly expressed in TNBC and has been identified as a molecular signature for basal-like tumors (Donzelli et al., 2018). ID4 protein is associated with cancer aggressiveness through dominant-negative regulation of basic HLH transcription factors that lead to inhibition of cell differentiation, survival, growth, and metastasis (Baker et al., 2020; Benedetti et al., 2024). ID4 overexpression is associated with hormone receptor negative tumors (HER2+ and TNBC) (Garcia-Escolano et al., 2021).

In vitro data indicates that ID4 expression is higher in tumor cell lines than in the healthy breast epithelial cell lines (Garcia-Escolano et al., 2021), and is overexpressed in a subset of BLBC patients (Baker et al., 2020). High levels of ID4 are associated with larger tumor size, abnormal cell appearance, and invasion (Garcia-Escolano et al., 2021). Molecularly, ID4 has been shown to be responsible for the downregulation of BRCA1 (Donzelli et al., 2018), which consequently affects DNA repair, associated with chemoresistance and cell apoptosis. ID4 expression correlates with certain breast cancer biomarkers, including ER and PR, and chemo-resistance related proteins (Zhang et al., 2020). Reducing ID4 levels in breast cancer cell lines decreased cell proliferation and invasion, increasing the sensitivity of cancer cells to a chemotherapy drug (Zhang et al., 2020). This suggests that ID4 drives cancer growth and contributes to chemoresistance.

ID4 is implicated in other non-breast cancer types as well, including NSCLC (non-small cell lung cancer) and glioma stem cells (Zhang et al., 2020). In NSCLC, ID4 inhibits platinum-based chemotherapy drugs, and in glioma stem cells, low levels of ID4 makes cancer cells more sensitive to drugs. In clinical samples, ID4 was more frequently overexpressed in BRCA1-mutant BLBC compared to sporadic cases, indicating that there is a link between ID4 and DNA damage repair deficiencies (Baker et al., 2020). These findings highlight the role of ID4 in promoting cancer and drug resistance, making it a promising target.

However, the mechanism and role of how ID4 contributes to breast cancer aggressiveness is largely unexplored and unknown due to ID4 being a newly discovered member of the ID family (Garcia-Escolano 2021; Baker et al., 2020). Exploration of ID4's role in chemotherapy sensitivity in breast cancers are not yet investigated (Zhang et al., 2020). A review of published literature suggests that a strategy to target ID4 has not yet been established, with limited pre-clinical data for analysis, making this gene a new area for scientific exploration.

5.2 FOXC1

The Forkhead box C1 (FOXC1) gene is a member of the forkhead box (FOX) transcription factors, a crucial transcription regulator of key proteins linked to cancer. An altered expression of FOXC1 can lead to cancer stem cell maintenance, migration, and angiogenesis. FOXs are involved in proliferation, differentiation, apoptosis metastasis and invasion; therefore, mutations in this gene can result in cancer growth. In addition, dysregulation in FOXC1 was evaluated to play a role in chemotherapy resistance in breast cancer. Breast cancer studies have shown that FOXC1 is oncogenic, and the ectopic FOXC1 overexpression in BLBC cells contributed to increased tumor cell proliferation (Yang et al., 2017).

The oncogenic function of FOXC1 was first revealed in BLBCs, and since then, many studies have been investigating FOXC1 as a transcription regulator in cancers. Therefore, the expression of FOXC1 has been proposed as a biomarker and indicator of poor prognosis in many cancers (Yang et al., 2024).

Many studies have demonstrated the effectiveness of targeting FOXC1, however, knowledge of FOXC1 is still extremely limited and minimally explored. Potential gaps include understanding its regulatory mechanisms, role in phosphorylation processes, functions, and the pathways involved in promoting tumor cell growth. Due to FOXC1's various roles in promoting the development of tumor, targeting it could lead to better treatment outcomes for TNBC patients.

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6. Novel Strategy for targeting TNBC

This section discusses the factors influencing the efficacy of traditional small molecule inhibitors utilized in existing targeted therapies and the potential of proteolysis-targeting chimeras (PROTACs) as an alternative therapeutic modality to improve the precision and effectiveness of TNBC therapies. Lastly, we address key limitations and challenges of PROTACs, compare them with other new emerging therapeutic modalities, and outline future directions of PROTACs in advancing TNBC-targeted therapies.

6.1 Factors affecting efficacy of small-molecule inhibitors

Small molecule inhibitors are the main targeted strategy towards intracellular proteins, making up 90% of pharmaceutical drugs (Govardhanagiri et al., 2019). They are cell permeable and inhibit the activity of intracellular proteins by binding to a single target, interfering with the downstream signaling pathways (An & Fu, 2018), leading to decreased proliferation and tumor development. Small molecule inhibitors are compounds <500 Da in size, and include biological molecules such as fatty acids and glucose, and secondary metabolites such as lipids and glycosides (Megino-Luque et al., 2020; Govardhanagiri et al., 2019). Small molecule inhibitors are administered orally, and they are developed to target any portion of a molecule (Megino-Luque et al., 2020).

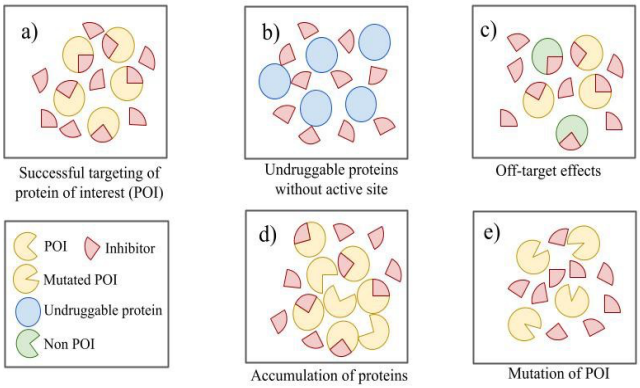

Figure 2. Adapted from (An & Fu, 2018), illustrating the limitations of small molecule inhibitors. (a) successful inhibition of the POI, (b) undruggable proteins without an active site for small molecule inhibitors to bind to, (c) off-target effects where small molecule inhibits proteins other than the POIs, (d) accumulation of proteins leading to incomplete inhibition, (e) drug resistance due to mutations where POI develops conformational changes

However, small molecule inhibitors have many limitations including undesired toxicities and side effects, due to needing to maintain high drug level for therapeutic efficacy (An & Fu, 2018), as well as off-target effects on proteins other than the protein of interest (POI) (Li & Song, 2020; Figure 2). Drug resistance may also occur because oncogenes are commonly mutated (An & Fu, 2018), which causes the overexpression of POI or an adaptation to an alternative signaling pathway that promotes tumor growth (Li & Song, 2020; Figure 2). Furthermore, small molecule inhibitors only target enzymes or receptors that have active sites (Figure 2). 75% of human proteins lack an active site including significant transcription factors that play a role in the development of breast cancers. Due to these limitations, small molecule inhibitors are not ideal for targeting oncogenic transcription factors as identified in the previous section.

6.2 PROTAC as an alternative to small molecule inhibitors

PROTACs are small molecules that consist of one ligand that binds to a POI, and another that binds to an E3 ubiquitin ligase, joined by a linker. The simultaneous binding of the POI and E3 ligase induces ubiquitylation of the POI and degrades by ubiquitin-proteasome system (UPS), while the PROTAC is recycled to target more POIs. (Békés et al., 2022; Figure 3). The UPS is a network of proteins that maintain intracellular protein homeostasis, and the degradation of UPS would lead to unsuccessful

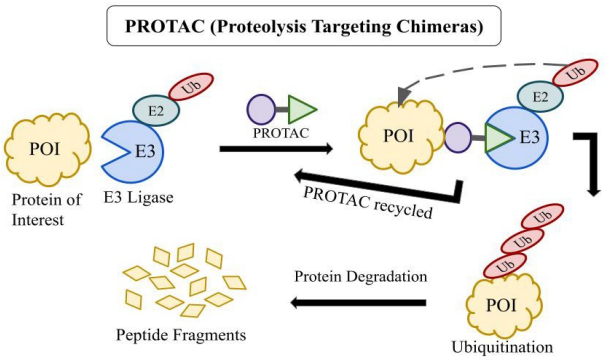

Figure 3. Mechanism of proteolysis targeting chimeras (PROTAC), which utilizes a bifunctional molecule to target specific proteins of interest for degradation via the ubiquitin-proteasome system.

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attempts of the cell to maintain a healthy intracellular environment (Sincere et al., 2023) causing oncogenic protein to degrade.

PROTAC technology is advantageous compared to traditional small molecule inhibitors because they reduce chances of off-target effects. PROTACs can be delivered at lower doses for longer dosing intervals, because they do not need to continuously bind to the POI, but can be recycled to degrade other additional POIs after the initial one degrades. Low amounts of PROTAC concentrations are sufficient to degrade proteins and have less chance of targeting healthy proteins. Secondly, PROTAC are highly specific, as they ensure the correct protein-protein interaction between E3 ligase and the target protein in order for the complex to be stable prior to degradation (Liu et al., 2022).

6.3 Utilizing PROTACs to target Transcription Factors

For decades, researchers have thought that transcription factors were undruggable by small molecule inhibitors due to their lack of active sites. However, transcription factors such as ID4 and FOXC1 are crucial in regulating cellular processes including proliferation, differentiation and apoptosis (Liu et al., 2022). PROTAC technology can be a way to target these oncogenic transcription factors through UPS-mediated protein degradation, which specifically degrades FOXC1 and ID4. These oncogenic transcription factors are responsible for tumor growth through regulation of transcription of multiple pathways and target genes. Thus, degrading a POI can modulate a network of oncogenes and downregulate TNBC-related pathways. Cancer cells that rely on transcription factors signaling may also die.

No studies so far have focused on targeting ID4 and FOXC1 using PROTACs. However, it is valuable to discuss other examples where PROTACs have been successfully developed. An example of this is the targeting of STAT3, a nuclear transcription factor that mediates signal transduction from a cell surface receptor to the nucleus (Li & Song, 2020). STAT3 is overexpressed in breast cancers, and integrates signaling from cytokines and growth factors, regulating cellular processes (Li & Song, 2020; Liu et al., 2022). Small-molecule inhibitors do not fully suppress STAT3 due to the lack of specificity between STAT family members (Liu et al., 2022). Wang et al. developed a STAT3 inhibitor, SI-109, and then used it to develop a STAT3 PROTAC SD-36 that solved the lack of selectivity, where the drug showed antiproliferative activity in leukemia and lymphoma cell lines even in low concentrations (Li & Song, 2020; Liu et al., 2022). This highlights the viability of PROTACs as a promising cancer therapeutic that can effectively target specific proteins while minimizing toxicity (Li & Song, 2020). SD-36 yielded promising clinical results, and is an example of how PROTACs can be applied to target challenging transcription factors that show limited response to conventional small-molecule inhibitors (Liu et al., 2022).

6.4 Limitations & Challenges of PROTAC-based Targeted Protein Degradation

There are still significant clinical challenges to be overcome in the drug development process of PROTAC degraders. Firstly, small-molecule PROTAC are large in size, making it a challenge for oral administration, affecting its drug-like properties including its ability to be absorbed into the bloodstream when taken orally. Secondly, off-target effects and undesirable toxicity were seen in some studies despite its enhanced target selectivity, where the off-target proteins may be the target of the target ligands or the immunomodulatory-based cereblon binding ligands (An & Fu, 2018).

In addition, PROTAC technology requires large amounts of studies to validate the site of linkage, the linker, and the E3 ligand of the PROTAC. Approximately 50 POI-PROTACs have been established, even when there are available ligands or inhibitors of the POI. Fourthly, predicting the clinical outcomes of a PROTAC based on the POI inhibitor it contains is unreliable because the biological activities of a PROTAC that reduces the POI may be different than pharmacological inhibition. Lastly, PROTAC's activity is dependent on its associated E3, whose expression may vary in different cell types and tissues. In many cancers, mutations in genes encoding E3 ligases lead to an altered expression of these ligases. If the ligases are mutated or not expressed sufficiently in a specific tissue region, then PROTACs cannot tag proteins for degradation (Li & Song, 2020).

6.5 PROTAC Clinical Trials

To date, PROTACs have successfully degraded many types of proteins including BTK, BRD4, AR, ER, STAT3,

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IRAK4 (Liu et al., 2022). One example is ARV-110 (ER degrader), which is used to treat metastatic castration-resistant prostate cancer, while ARV-471 (AR degrader) treats ER+/HER2− metastatic breast cancer (Liu et al., 2022). Based on clinical data, ARV-110 has been designated as safe to consume orally, and phase I trials have shown that the drug reduced prostate-specific antigen levels by more than 50% in 40% of patients with mCRPC. ARV-110 has also been proven to be effective as biopsy data of a patient showed a 70-90% decrease in AR levels after administration of this drug. Additionally, in phase 1 clinical study of ARV-471 for ER+ and HER2- breast cancer patients, a high reduction in ER expression of the tumors was found, with 89% observed at 30-700 mg doses (Liu et al., 2022). These degraders were well tolerated and highly effective for patients in both studies, with desirable safety and clinical efficacy, making them a viable modality for anticancer drugs.

6.6 Comparison of PROTACs with Other Emerging TNBC Therapies

Although PROTACs is a highly promising method for treating TNBC, there are other new experimental therapies that show potential for improving TNBC treatment outcomes.

An emerging therapy includes antibody-drug conjugates (ADCs), which work by binding to the antigens of a target cell surface and triggering the cell to absorb it. Once inside, the ADC breaks down, releasing its cytotoxic payload, killing the tumor cell. A major challenge is that the tumor marker, antibody, cytotoxic payload, and linkage strategy must be precisely selected in order for the process to be successful. Due to these requirements, antigen heterogeneity, low internalization, and off-target effects, may occur when the criterias are not met (Nejadmoghaddam et al., 2019). ADC therapy can cause adverse side effects because the process relies on a cytotoxic payload release, while PROTACs are able to degrade proteins without releasing toxic agents.

CAR-T cell therapy is another modality that has made progress in hematologic malignancies. This therapy is now being adapted for solid tumors including TNBC. CAR-T cell therapy works by engineering a patient's T cells to express a chimeric antigen receptor (CAR) and then infusing it back into the body to bind and destroy the specific cancer cell expressing the antigen. However, its efficacy in treating solid tumors is limited due to intratumor antigen heterogeneity, where tumor cells express variable levels of a CAR-redirected target antigen on their surface, leading to failure of detecting all tumor cells (Nasiri et al., 2022). In addition, TNBC has a immunosuppressive tumor microenvironment, which can create a hostile environment for CAR-T cell survival (Chen et al., 2024). Unlike CAR T cells and ADC therapy, which are limited to surface antigens, PROTACs do not rely on antigen expression and can target intracellular proteins. PROTACs are also easier to produce compared to CAR T cells that need to be patient-specific when engineered.

In recent years, nucleic acid based methods have gained prominence in treating genetically mediated diseases. Particularly, RNA interference (RNAi) induces gene silencing by knocking down mRNA at the transcriptional level and degrading them. One weakness of this approach is that nucleic acid-based molecules cannot passively penetrate into cells. These molecules are also prone to rapid enzyme-mediated hydrolysis, where drugs are unable to enter cells on their own and are broken down by enzymes in the body (Li, X., & Song, Y., 2020). Additionally, RNAi only reduces mRNA levels, which can lead to incomplete protein knockdown, whereas PROTACs completely degrades the protein. RNAi is also limited to genes that can be silenced at the mRNA level, not including non-enzymatic and undruggable proteins involved in the TNBC pathway.

Compared to these therapies, PROTACs are advantageous because they do not rely on a cell's antigen expression for degradation, reduce off-target toxicity associated with cytotoxic payloads, and offer high specificity.

6.7 Future Directions

PROTACs could be used in combination with existing therapies like chemotherapy, EGFR inhibitors, PARP inhibitors, and mTOR inhibitors, to improve treatment effectiveness. Chemotherapy and targeted inhibitors primarily work by initiating cancer cell apoptosis and blocking specific oncogenic pathways respectively. PROTACs can be administered concurrently to overcome the limitation of drug resistance that these therapies face by selectively degrading target proteins, improving the specificity of targeting tumor cells and leading to a reduced relapse rate in

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patients. Traditional therapies require high drug doses to achieve the desired effects, but this can lead to toxicity. PROTACs on the other hand function catalytically, and can therefore degrade proteins at lower doses. When these therapies are used in conjunction with PROTACs, high levels of drug doses would not be necessary, which minimizes their adverse side effects. The next step includes studies to evaluate the optimal combinations of these therapies with PROTACs to provide the most efficient dosing.

A single PROTAC can degrade multiple POIs, leading to longer-lasting effects compared to small molecule inhibitors, which can reduce toxicity and increase drug effectiveness (Sincere et al., 2023). However, PROTACs are not well explored yet, and current gaps include designing it to be more selective (Li & Song, 2020), identifying the targets suitable for PROTAC, and designing PROTACs so that it can be administered orally (Liu et al., 2022). There are more than 600 E3 ubiquitin ligases in humans which can be used in the context of PROTAC (Li & Song, 2020), making it a promising technology for various types of cancer. PROTAC technology has already shown great clinical efficacy and potential for anticancer therapy treatments based on clinical trials (Liu et al., 2022).

7. Conclusion

TNBC is an extremely challenging disease to treat that disproportionately affects young women of African descent, due to its heterogeneity, aggressiveness, and lack of targeted therapies. This review examined the standard of care, as well as existing therapies including EGFR, PARP, and mTOR inhibitors. Although these targeted therapies have some clinical efficacy, the results have been inconsistent. Many challenges of these therapies have arisen due to acquiring drug resistance, limited target population, and alternative signaling pathways being activated, making it urgent to identify potential targets for basal-like TNBCs.

PROTAC technology has been proposed in this paper as a novel modality for targeting these oncogenic transcription factors through the degradation of target protein rather than only inhibiting its expression as seen in traditional small molecule inhibitors. Multiple studies have shown its reduced toxicity, off-target effects, and maximized selectivity of target proteins. However, some limitations include difficulty of oral administration due to its large size, unpredictable clinical outcomes, limited knowledge of the site of linkers, and unintended off target effects. Despite the limitations, ER and AR degraders have proven successful results in clinical phase II to degrade ER and AR protein, indicating a promising area of drug development. Since PROTACs can degrade targets without an active site, oncogenic transcription factors can finally be targeted. Other emerging therapies, including antibody drug conjugates, RNA interference, and CAR-T cell therapy, offer unique advantages but face significant challenges because TNBC lacks well defined antigens and has an immunosuppressive tumor microenvironment. PROTAC technology can better advance TNBC therapeutics and overcome the limitations of traditional small molecule inhibitors.

Acknowledgements

I would like to thank my mentor, Rebecca Rodell, for her invaluable guidance and mentorship throughout the development of this review article.

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